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Process intensification using a semi-continuous mini-blender to support continuous direct compression processing

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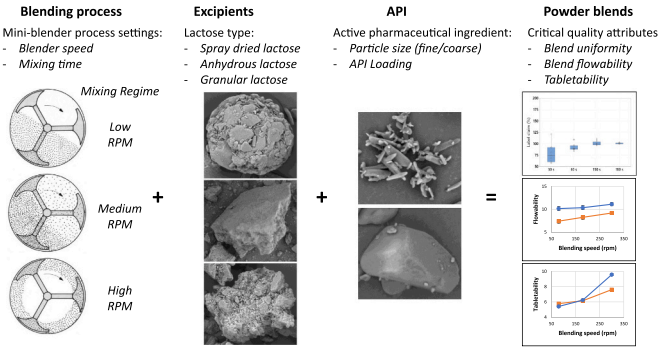
HIGHLIGHTS

- Demonstration of a semi-continuous powder mini-blender for process intensification.
- Mini-blender design supports continuous direct compression of low drug loads.
- Extend of process intensification is impacted by blending regime.
- Powder flow and tablet properties are affected by blending process and excipients.
- Mixing process intensification allows product optimization to focus on other CQA's.

GRAPHICAL ABSTRACT



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ABSTRACT

The production of pharmaceutical tablets is shifting towards continuous manufacturing. Therefore, individual unit operations such as powder blending need to be re-designed. Continuous powder blending has been implemented successfully, but for low-dose formulations this is challenging due to difficulties with continuously dosing small amounts of powder. To overcome such challenges, a semi-continuous mini-blending operation combined with batch-wise dosing can be introduced in a continuous process. The objective of this study is to investigate key factors that affect blending performance of a novel, semi-continuous mini-blending process. A design of experiments is performed, varying both process settings and blend formulations. This reveals that blending performance of the mini-blending process is largely controlled by process settings. These results show that the mini-blender design, with high mixing intensity and short mixing times, supports process intensification of powder blending. The results obtained can be used for Quality by Design-based formulation development for continuous direct compression.

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1. Introduction

Continuous manufacturing of oral solid dosage forms is currently being implemented in the pharmaceutical industry. Advances in the development of novel excipients, equipment design and process analytical technology are facilitating the transition from batch to continuous manufacturing [1]. This is driven by multiple benefits, including a smaller production footprint, reduced scale-up activities, more consistent product quality and cost reduction [2–4]. The implementation of continuous manufacturing provides a need for an advanced understanding of the relationship between powder material properties and process settings, as the process requires a consistent flow of materials through multiple unit operations. Such an advanced understanding of the interaction between material properties and process operations is in line with Quality by Design (QbD) for pharmaceutical development [5].

With the transition from batch to continuous manufacturing, the blending of an active pharmaceutical ingredient (API) with excipients needs to be re-designed. In a conventional batch process, API and excipients are loaded in a large vessel and blended for a fixed amount of time before discharging. In a continuous blending process on the other hand, API and excipients are continuously fed into the blender and the powder blend is continuously removed from the process. Because of the increasing interest in continuous manufacturing, continuous powder blending has been studied extensively in recent years [6–8]. Studies on directly comparing batch versus continuous powder blending have indicated an improved mixing efficiency and reduced segregation potential for continuous blending [9–11]. Continuous powder blending also suffers from some critical limitations, however, as inconsistencies in feeding of ingredients can affect blend uniformity [12,13]. Especially for formulations with low API dosage, such fluctuations can result in poor content uniformity of tablets produced in a continuous process [14,15]. Optimizing the continuous blending process can only partly resolve these issues, as there is always a tradeoff between the high shear (increased impellor speed) required for increased micro-mixing and reduced residence time that results from increased impellor speed. Thus micro-mixing and the fluctuation damping required for handling feeding fluctuations are inherently coupled and cannot be independently adjusted.

To overcome the challenges with continuous processing of low-dose formulations, a semi-continuous mini-blending operation can be introduced. In this novel mini-blending process, batch-wise blending of API and excipients is performed at small scale of a few kilograms and short mixing times in the order of seconds or minutes. The short mixing time requires a process intensification and high mixing efficiency. The small scale of mixing leads to low segregation potential, similar to a continuous blending process. In the mini-blending process, shear forces can be adjusted independently of mixing time, as blender speed does not affect residence time. And since raw materials are dosed batch-wise, short-term fluctuations in dosing over time are averaged out, making this process especially suitable for low-dose formulations. The small scale of the process allows for close coupling to a tablet press. This reduces the risk of segregation, allowing for direct compression (DC) of low-dose formulations that are generally processed by granulation. Such a DC process for low-dose formulations requires a highly efficient blender that can produce a uniform blend of API and excipients with varying material properties in very short timescales.

For any pharmaceutical blending process, blend uniformity is a critical quality attribute (CQA) as it determines uniformity of the API in the final dosage form. Blend uniformity is generally determined by a combination of process settings and material properties of excipients and API. For continuous powder blending, process settings such as mass flow rate, rotational speed and design of the impeller configuration have been shown to affect blend uniformity [16–19], which requires additional development work to understand this design space. For the semi-continuous mini-blender used in the current study, impeller rotational speed is also a potentially important factor as the mixing regime is determined by the Froude number (*Fr*, Fig. 1). At low Fr (<2.5), mixing takes place primarily within the powder bed through a push mixing mechanism and strongly cohesive particles may not fully deagglomerate (Fig. 1a) [20]. Upon increasing rotational speed, partial fluidization of the powder occurs and mixing pre-dominantly occurs in the mechanically generated fluidized bed (Fig. 1b). In this mixing regime, it is expected that particle deagglomeration occurs due to significantly higher shear forces. A further increase in blender speed to *Fr* above 11 results in complete fluidization and circulation of the powder as a rotating material ring (Fig. 1c). Such a centrifugal mixing mechanism could cause high frictional forces between the powder and the blender walls [20]. As running the mini-blender at conditions to promote micro-mixing does not have a negative impact on residence time distribution (RTD) or feeder fluctuation damping, a more generic operating space is expected for this technology. This is explored in the current study.

Besides process settings, also material properties of excipients and API can affect blending performance. In a batch mixing process the impact of material properties can be large, as differences in particle size and density can cause segregation and thereby reduce blend uniformity [9,11,21]. The effect of material properties on blend uniformity is less pronounced in a continuous process, although powder flow properties have been shown to impact mixing performance [10,22]. How the material properties of API and excipients affect blending performance of the semi-continuous mini-blending process is part of the current study. In general, the relative particle size of API and excipients is an important factor in powder mixing, as it determines the type of mixture obtained. If particle size of the API and excipients is similar, a random mixture is obtained without inter-particle interactions. For many pharmaceutical formulations, however, the API particles are much smaller than the excipients. The blending of such formulations can cause adhesion of the API particles to the surface of the coarser excipients, resulting in an adhesive mixture [23,24]. For a random mixture, blending of API and excipient particles can be considered as a random statistical process

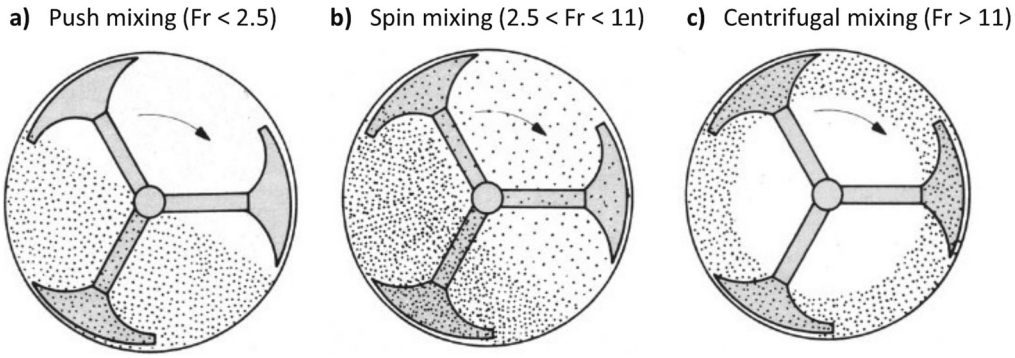

Fig. 1. Schematic representation of the mixing regimes obtained at increasing blender rotational speeds, expressed by the Froude number (*Fr*) [20].

Table 1
Multi-level factorial design used in the current study.

Factor	Level 1	Level 2	Level 3	Level 4
Blending speed	80 rpm (*Fr* = 0.8)	180 rpm (*Fr* = 4.2)	300 rpm (*Fr* = 11.6)	–
Blending time	30 s	60 s	150 s	180 s
API dosage	1% w/w	5% w/w	10% w/w	–
Lactose type	Spray dried	Anhydrous	Granular	–
API particle size (x50)	20 μm	183 μm	–	–

[25]. For an adhesive mixture on the other hand, blending involves multiple mechanisms including random mixing, particle deagglomeration, adhesion and redistribution of adhered particles [26]. The effect of process settings and material properties on mixing performance is therefore expected to be different for an adhesive mixture compared to a random mixture.

The objective of the current study is to identify the key factors that determine blending performance of a semi-continuous mini-blending process, with a focus on how the mini-blender design supports process intensification for the blending of API and excipients. To this end, a design of experiments (DoE) is performed according to a multi-level factorial design, which includes both process settings and variations in the blend formulation. The factors included in the DoE are blending speed, blending time, API dosage, type of lactose and API particle size (Table 1). This DoE includes formulations that are difficult to process continuously, due to the low API dosage and cohesiveness of the API used. The CQA's of the powder blends that are analyzed are blend uniformity, flowability and tabletability. The results of this study show that the mini-blender design supports process intensification and introduces a generic simplicity in optimizing blending of API and excipients, with only a minor dependence on powder material properties.

2. Materials and methods

2.1. Materials

Anhydrous lactose (SuperTab® 21AN), spray dried lactose (SuperTab® 11SD), agglomerated lactose (SuperTab® 30GR), microcrystalline cellulose (Pharmacel® 102) and croscarmellose sodium (Primellose®) were obtained from DFE Pharma (Goch, Germany). Paracetamol dense powder (referred to as coarse API grade in this manuscript) and fine powder (referred to as fine API grade in this manuscript) were purchased from Mallinckrodt Inc. (Raleigh, NC, USA). Magnesium Stearate was purchased from Sigma Aldrich (*St.* Louis, MO, USA).

2.2. Powder characterization

Particle size distributions of the excipients and APIs were determined ($n = 3$) by dry laser diffraction (Helos/KR, Sympatec, Germany) using a vibratory dispersion unit and an air pressure of 1.5 bar. The specific surface area (SSA) of the excipients and paracetamol was measured ($n = 2$) using a physisorption instrument (Tristar II, Micromeritics, GA, USA), which is based on static volumetric technology. Before the measurement, powder samples of approximately 1–2 g were degassed under nitrogen flow at a temperature of 40 °C for 2 h. Krypton was used as the adsorptive gas, at a pressure range of P/P0 = 0.05–0.3. Bulk and tapped densities were measured ($n = 2$) according to USP method <616>, method I. The Hausner ratio (HR) was calculated as the quotient of the tapped density (TD) and the bulk density (BD).

2.3. Blending

Lactose, microcrystalline cellulose (MCC), croscarmellose sodium (CCS) and paracetamol were pre-weighed and added to the mini-blender with a volume of 10 l (GBM 10-P, Gericke AG, Regensdorf, Switzerland). The powders were added to the blender in the same order for all blends. The lactose was added to the blender first, followed by the paracetamol, then MCC and finally CCS. The total weight of the powder in the blender was 3.98 kg and the relative amounts of the API and excipients in the formulations are shown in Table 2. The powders were mixed at 80, 180 or 300 rpm, corresponding to calculated Froude numbers of 0.8, 4.2 and 11.6 respectively. After 30, 60 and 150 s the blender was paused for sampling powder for blend uniformity analysis. A sample thief was used to sample between 0.3 and 0.9 g of powder from five locations of the top of the blend and four locations of the bottom of the blend, as shown in Fig. 2. Subsequently, 20 g of magnesium stearate was added and blending was performed for an additional 30 s before taking the final samples.

Table 2
Formulations of the API-excipient blends prepared in the current study.

Material	Very low-dose formulation (% *w*/w)	Low-dose formulation (% w/w)	Medium-dose formulation (% w/w)
Paracetamol (API)	1	5	10
Lactose	74.86	71.82	68.02
Microcrystalline cellulose	19.7	18.9	17.9
Croscarmellose sodium	3.94	3.78	3.58
Magnesium stearate	0.5	0.5	0.5

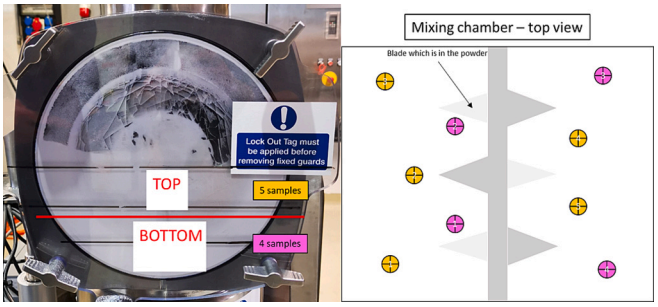

Fig. 2. Sampling plan for blend uniformity analysis, showing a picture of the mini-blender with the distinction between the top and bottom of the powder blend and a schematic top view of the mixing chamber with the exact sampling locations.

2.4. Blend uniformity analysis

The powder samples were dissolved in MilliQ water by sonication for 15 min at 35 °C. The solutions were subsequently diluted to paracetamol concentrations in the range of 10^{-3} –10^{-2} g L^{-1}. The diluted solutions were filtered over a 0.45 μm porous filter to remove the insoluble components. UV absorbance of the filtered solutions was measured at a wavelength of 243 nm using a UV/VIS spectrophotometer (Lambda 25, Perkin Elmer, MA, USA). The UV absorbance was translated to paracetamol concentration by using a calibration line. The uniformity of a blend is represented by the relative standard deviation (RSD), which is the ratio of standard deviation and average paracetamol concentration of nine samples taken from each blend.

2.5. Powder flow characterization

Flow analysis was performed for the blends containing magnesium stearate, after 180 s of mixing. A ring shear tester (RST-XS, Dietmar Schulze, Wolfenbuttel, Germany) was used to measure the flow function coefficient (FFC, $n = 2$). The FFC is defined as the ratio of the

Table 3
Overview of particle size, surface area, bulk density and flow properties of the excipients and APIs used in the mini-blend process.

Material	X10 (μm)	X50 (μm)	X90 (μm)	SSA (m^2/g)	Bulk density (g/cm^3)	HR (−)	FFC (−)
Anhydrous lactose (SuperTab® 21AN)	10	147	307	0.41	0.72	1.25	8.6
Granular lactose (SuperTab® 30GR)	30	128	282	0.39	0.56	1.22	18
Spray dried lactose (SuperTab® 11SD)	43	109	199	0.14	0.61	1.20	17
Microcrystalline cellulose (Pharmacel® 102)	29	92	197	1.16	0.33	1.42	8.3
Croscarmellose sodium (Primellose®)	23	55	124	0.27	0.55	1.35	7.4
Paracetamol fine grade	3.4	20	79	0.51	0.27	1.56	1.1
Paracetamol coarse grade	27	183	373	0.07	0.65	1.35	5.0

consolidation stress and the unconfined yield strength. Powder blends were measured at a pre-consolidation stress (σ_{pre}) of 4 kPa and normal stresses of 1, 2 and 3 kPa were used for shear to failure.

2.6. Tableting

Tableting was performed for the blends containing magnesium stearate, after 180 s of mixing. The blends were tableted using a rotary tableting press (Luxner RoTab T, Germany). Flat beveled punches (iHollland, United Kingdom) with a diameter of 9 mm were used to compact tablets of 250 mg at a rotating frequency of 25 rpm, resulting in a dwell time of 60 ms. The compression force was adjusted for each individual blend formulation to target a tablet tensile strength of 1 MPa.

Tablets were analyzed on tablet crushing force, weight, diameter and thickness ($n = 20$) using an automated tablet tester (Sotax AT50, Switzerland). Force to break the tablet was measured at a constant speed of 2 mm/s. The maximum force required to break the tablets is used as tablet crushing force. The tablet tensile strength (TTS) is derived from the tablet crushing force (TCF), diameter (D) and tablet height (H) for flat beveled tablets [27]:

$$TTS = \frac{2^*TCF}{\pi^*D^*H} \quad (1)$$

2.7. Scanning electron microscopy

Scanning electron microscopy (SEM) images were recorded using a Phenom Pro scanning electron microscope (Thermo Fischer Scientific, MA, USA) with a backscattered electron detector. Images were recorded at an acceleration voltage of 10 kV and at a magnification of 3000 times. Prior to the measurements, samples were coated with a gold layer with a thickness of 6 nm.

3. Results and discussion

3.1. Material properties of excipients and APIs

To test how mixing performance of the mini-blender depends on API and excipient properties, varying grades of lactose and paracetamol were used. An overview of the excipients and APIs used in this study and key material properties that are relevant for mixing performance are shown in Table 3. As lactose is the major component of the blends, this excipient was varied between three different grades: spray dried, anhydrous or granular. These three lactose grades show similar median particle sizes, with x50 varying from 110 to 150 μm. The particle size distribution (PSD), however differs among the lactose grades (Table 3). Anhydrous lactose shows the widest PSD (lowest x10 and highest x90), whereas the spray dried grade shows the narrowest distribution. Besides the PSD, particle shape and surface morphology are also vastly different for the three lactose grades, as shown by SEM in Fig. 3. The different morphologies are also reflected by the specific surface area (SSA) of the three lactose grades. Spray dried lactose consists of spherical particles with a relatively smooth surface, resulting in the lowest SSA. Granular lactose shows a more irregular particle shape with cavities in the surface, resulting in a higher SSA. Anhydrous lactose shows the highest SSA

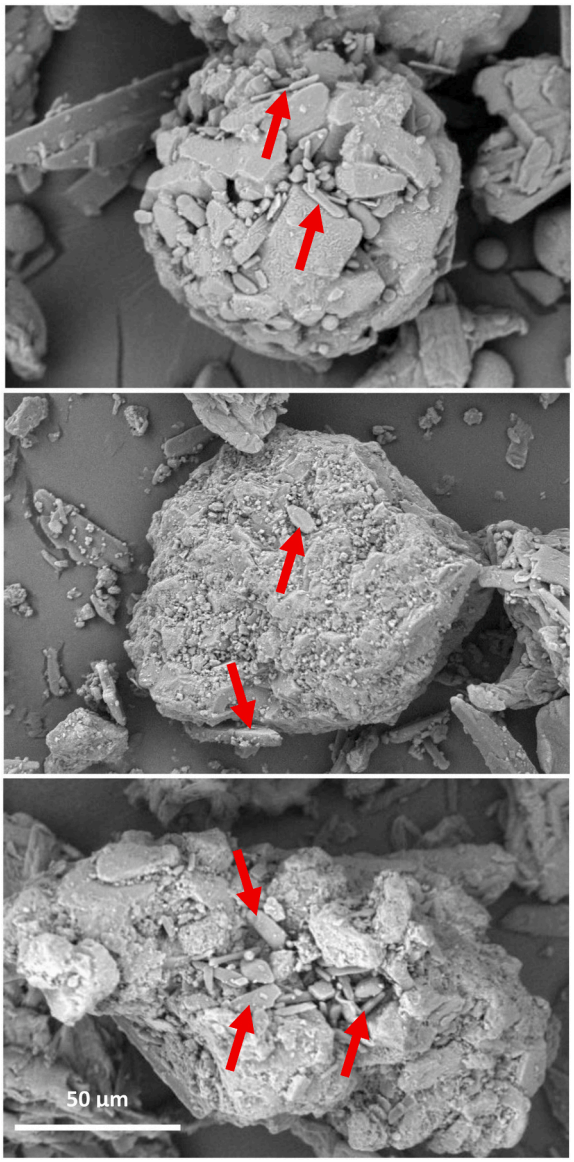

Fig. 3. Scanning electron microscopy images of lactose particles after blending with 10% *w*/w of the fine API grade. The images show adhesion of fine API particles to the coarser lactose particles, as indicated by the arrows. The API can be identified as particles with a high aspect ratio and smoother surface compared to lactose. The top image shows a spray dried lactose particle with spherical morphology, and API particles adhered to the cavities in the spherical surface. The middle image shows anhydrous lactose with a more irregular morphology. For the granular lactose shown in the bottom image, adhesion of API particles occurs primarily in the surface cavities of the granules.

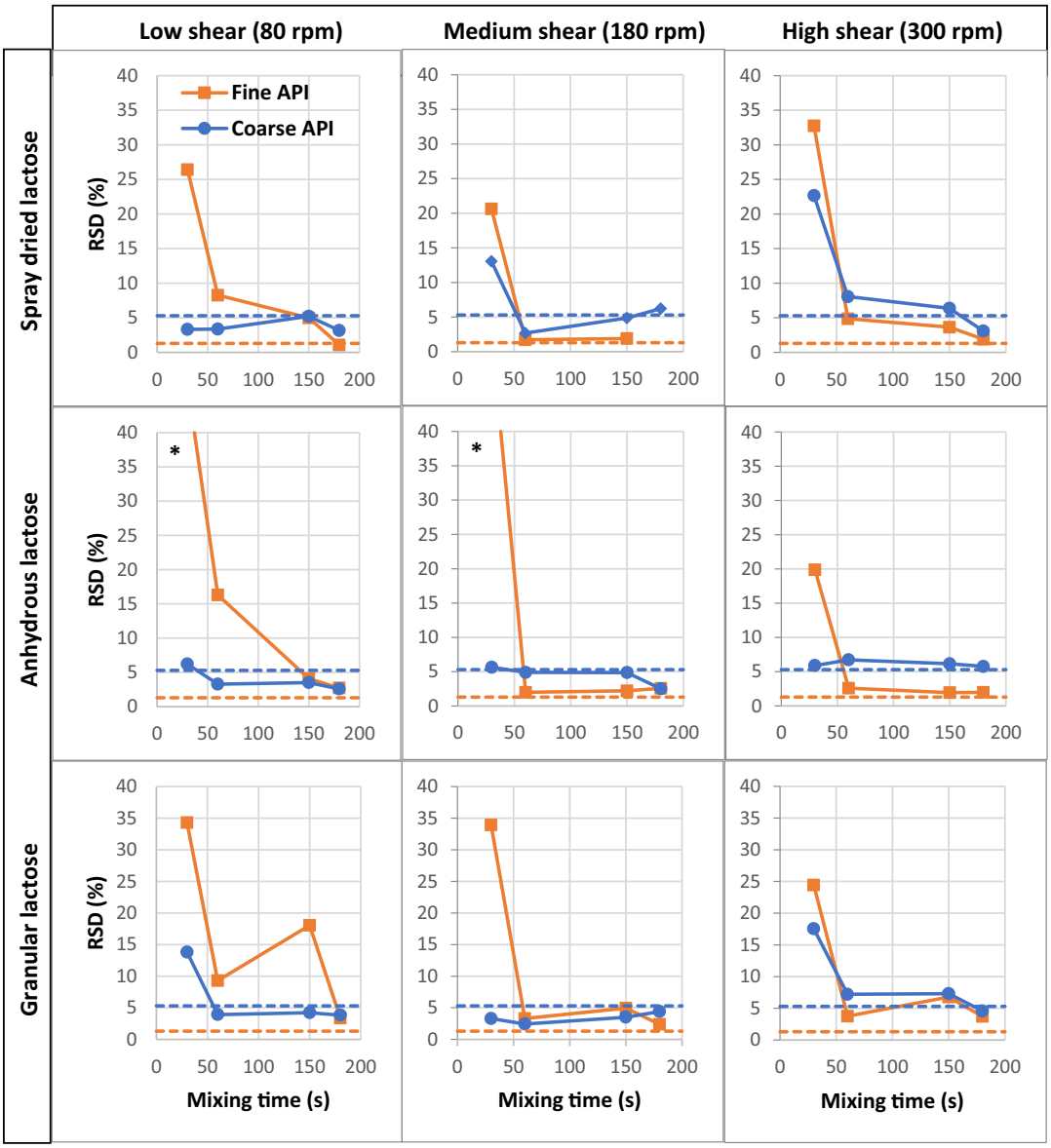

Fig. 4. Blend uniformity of blends with 1% w/w API dosage, prepared at three different mixing speeds and with three different lactose grades. Blend uniformity is represented by the RSD of the API concentration. Dotted lines represent calculated RSD values for the fine and coarse API grade based on the model by Yalkowsky [28]. *Blends of anhydrous lactose with fine API at 30 s mixing time show RSD > 40%.

due to the presence of more fine particles, which is also reflected by a lower x10 value (Table 3). This higher amount of fines also results in reduced flowability of anhydrous lactose compared to the spray dried and granular grades, reflected by a lower flow function coefficient (FFC) and higher Hausner ratio (HR) for anhydrous lactose. All three lactose grades show acceptable flowability for usage in a DC process.

A fine and a coarse paracetamol grade, with x50 values of 20 μm and 183 μm respectively, were used as model API in the current study. Because of the large difference in particle size between the fine API and lactose grades used, adhesion of the API particles to the larger lactose particles occurs during blending. This is also observed in the SEM images shown in Fig. 3, which show API particles with a high aspect ratio (marked by the arrows in Fig. 3) adhered to the surface of the larger lactose particles. For spray dried and granular lactose, API particles primarily adhere to the lactose surface cavities, where multiple contact points between the particles result in stronger adhesion. Anhydrous lactose shows a smoother surface without cavities, which results in weaker adhesive interactions and less adhered API particles. The coarse paracetamol grade shows a similar particle size distribution as the excipients used in the blends. Therefore, a random mixture without adhesive interactions can be expected for the blends with the coarse API grade. Besides API and lactose as the major excipient, a fixed amount of microcrystalline cellulose (MCC) and croscarmellose sodium (CCS) was included in all blend formulations (Table 3). MCC was included to optimize the strength of the tablets produced from the blend formulations and CCS was included as a tablet disintegrant. Both MCC and CCS are not shown in the SEM images in Fig. 3.

3.2. Blend uniformity results

Blend uniformity was analyzed for the blends prepared according to the factorial design in Table 1. Here, blend uniformity is quantified by the relative standard deviation (RSD) of the API concentration of nine powder samples. RSD values are shown in Fig. 4 for blends with an API dosage of 1% *w*/w. Both mixing time and API particle size have a strong effect on blend uniformity. At a mixing time of 30 s, uniformity of the blends with the fine API grade is generally very poor. This indicates incomplete deagglomeration of the fine, cohesive API particles, resulting

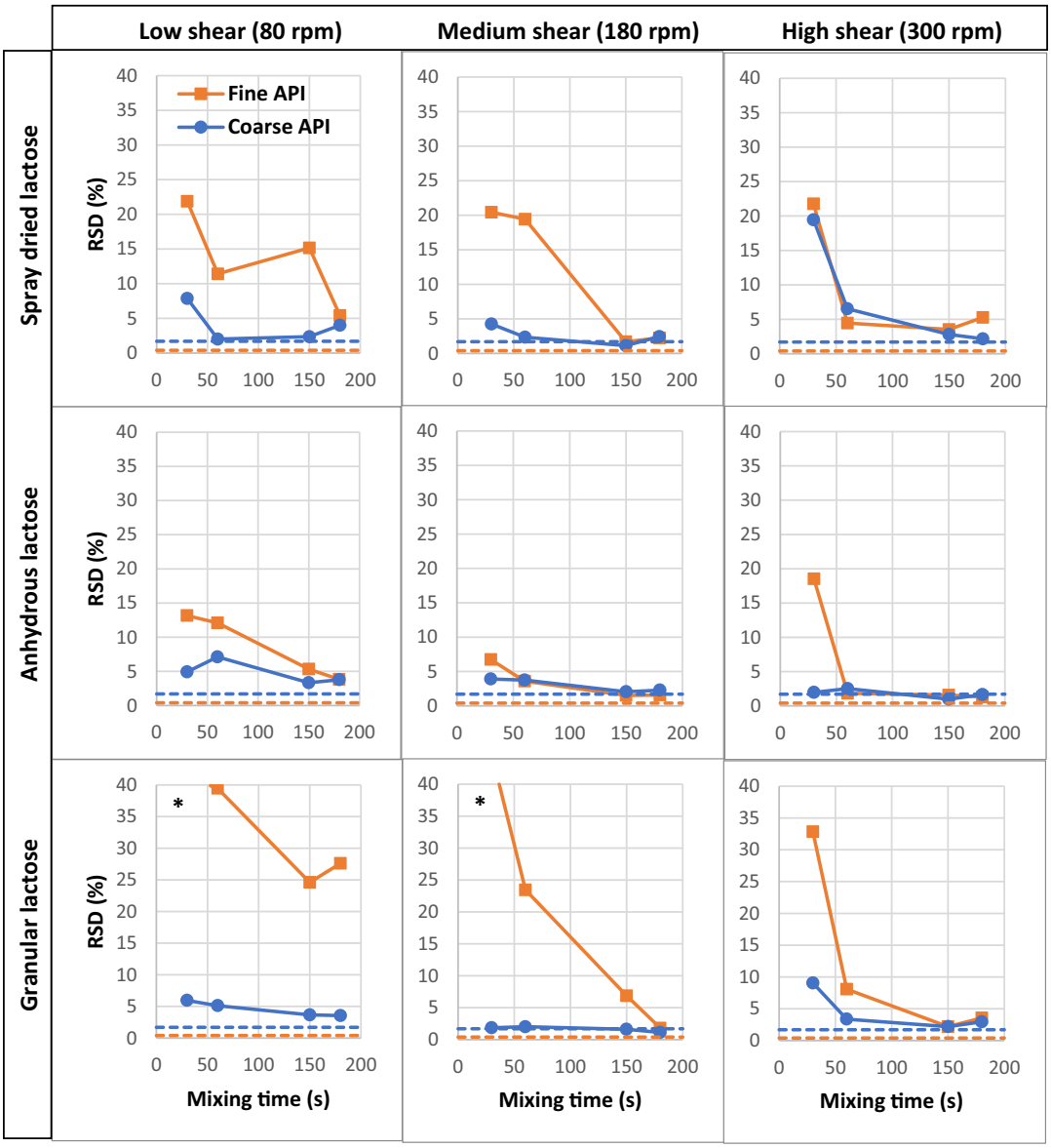

Fig. 5. Blend uniformity of blends with 10% w/w API dosage, prepared at three different mixing speeds and with three different lactose grades. Blend uniformity is represented by the RSD of the API concentration. Dotted lines represent calculated RSD values for the fine and coarse API grade based on the model by Yalkowsky [28]. *Blends of granular lactose with fine API at 30 s mixing time show RSD > 40%.

in hotspots of agglomerated API within the powder blend. When these hotspots are sampled for blend uniformity analysis, strong variation in API content of the samples is observed, resulting in very high RSD values. For the coarse API grade, RSD values obtained after 30 s are generally lower, indicating a faster mixing process due to the less cohesive nature of the coarse paracetamol grade. This makes agglomeration of the coarse API grade less likely, resulting in a more random distribution of the API through the powder blend. Increasing mixing time generally improves blend uniformity, but the effect of mixing time is stronger for the fine API grade. For the coarse API grade, blend uniformity does not change significantly anymore after 60 s of mixing. For these blends a random statistical mixture without inter-particle interactions is obtained relatively fast. For the fine API grade, longer mixing times are required to deagglomerate the particles. The final blend uniformity after 180 s, however, is similar for both API grades and all blends show good uniformity with RSD values below 5%.

The blender speed also has an effect on blend uniformity (Fig. 4), and this effect is dependent on the particle size of the API used. For the fine API grade, a low mixing speed of 80 rpm results in less efficient mixing and longer mixing times are required to reach uniform blends. At medium (180 rpm) and high (300 rpm) speed, mixing is faster and homogeneous blends are obtained within 60 s. The improved mixing efficiency at higher speeds can be explained by faster deagglomeration of the cohesive fine API particles, which is dependent on the shear forces generated during blending. For the coarse API, the effect of blending speed on blend uniformity is less pronounced. At the highest mixing speed of 300 rpm, however, slightly higher RSD values are obtained, especially at short mixing time. This may indicate that the centrifugal mixing regime results in less efficient mixing. The type of lactose in the blend formulation has little effect on blend uniformity, with all formulations reaching a similar RSD value after 180 s of mixing. At a low mixing time of 30 s, however, the type of lactose may affect the RSD value obtained, especially for the blends with the fine API grade (Fig. 4). Here the blends of anhydrous lactose show higher RSD values compared to the granular and spray dried lactose grades, but due to the incomplete mixing process at this early timepoint there is greater uncertainty in blend RSD. By increasing blending time, the differences observed between the different formulations are reduced and homogeneous blend

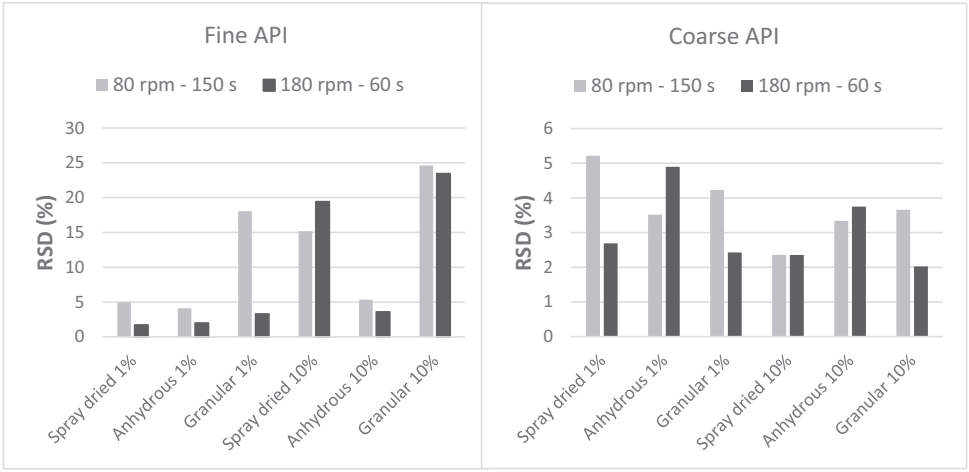

Fig. 6. Comparison of blend uniformity results for 150 s mixing at 80 rpm (200 revolutions) and 60 s mixing at 180 rpm (180 revolutions). The equal or improved blend uniformity obtained by mixing for shorter time at higher mixing speed shows intensification of the mini-blending process.

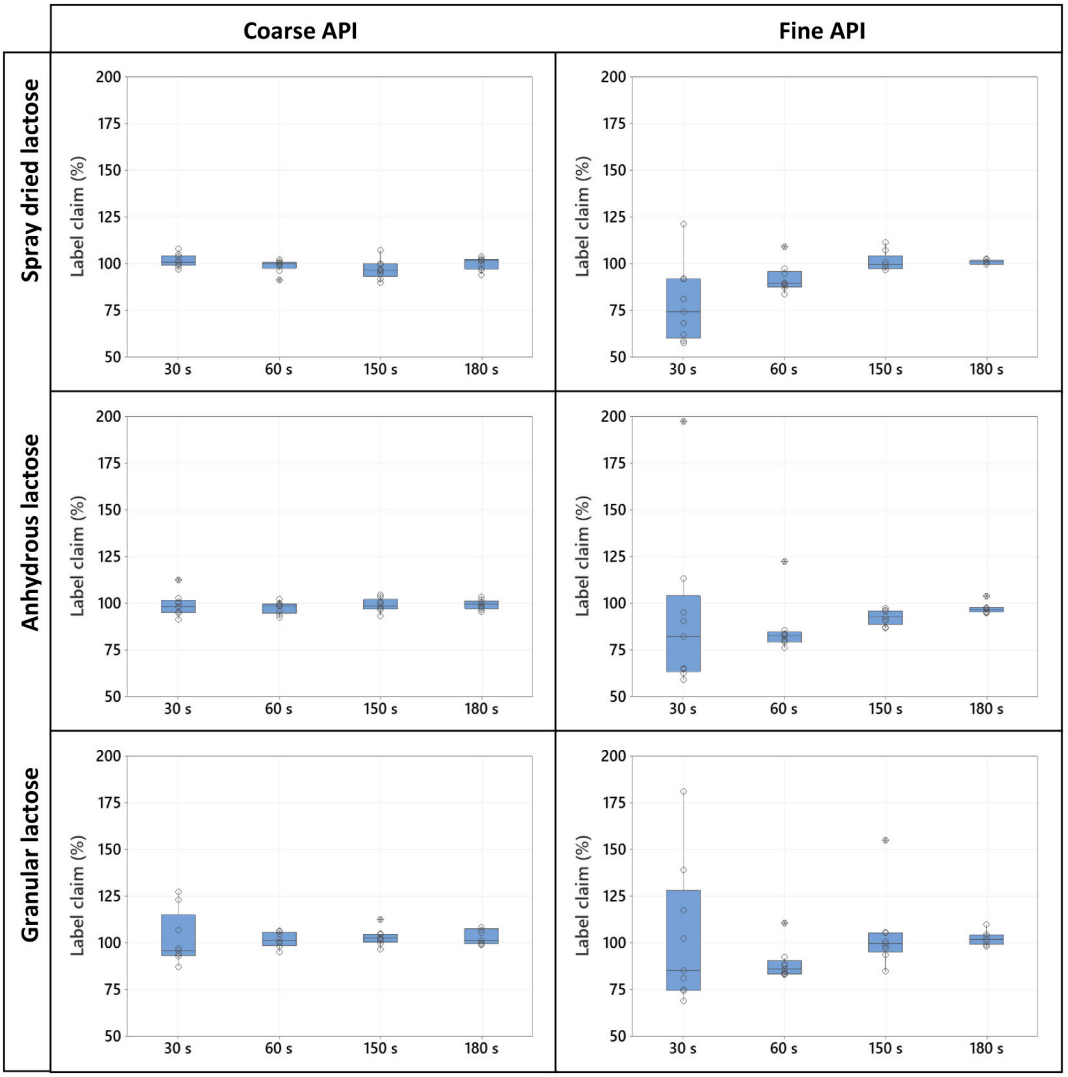

Fig. 7. Box plots showing the API label claims of the individual samples used for blend uniformity analysis. Data is shown for blends with 1% w/w API dosage at low blender speed.

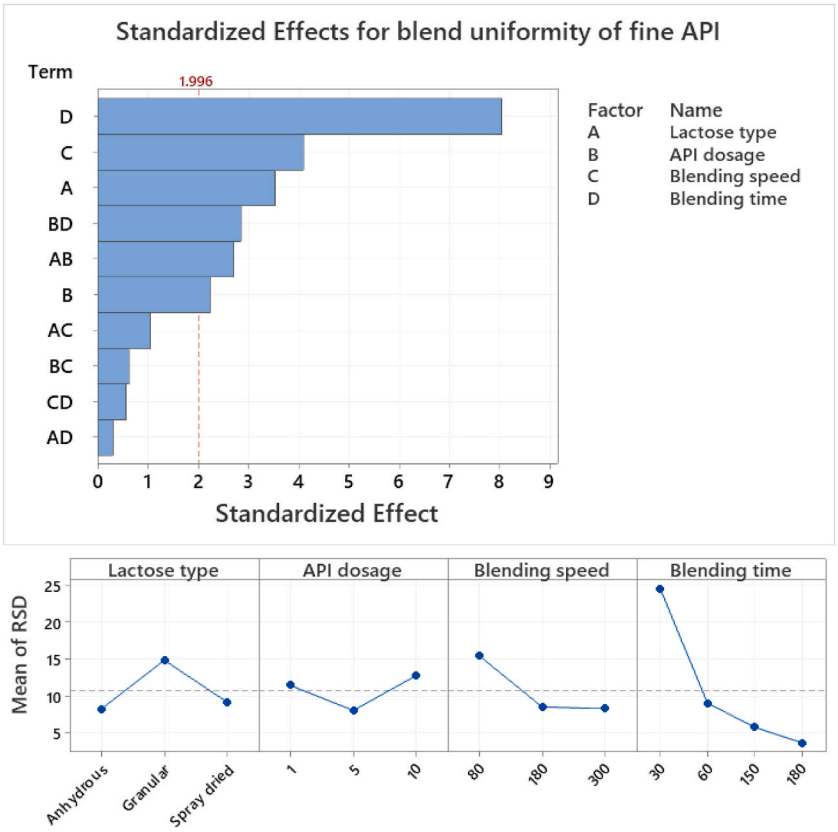

Fig. 8. Results of factorial regression analysis of blend uniformity for mixtures of the fine API grade. The pareto chart (top) shows the significant factors and interactions that determine blend uniformity. The main effects plots (bottom) show how blend uniformity is affected by each factor included in the analysis.

are obtained for all formulations. Mixing performance of the mini-blender is thus mainly determined by process settings (time and speed). A potential effect of excipient material properties on blend uniformity is only observed during initial blending stages.

Blend uniformity of the API-excipient blends was compared to a calculated RSD value, based on a statistical model developed by Yalkowsky and Bolton [28]. This model describes content uniformity of a pharmaceutical formulation based on the particle size distribution and dosage of the API (from drug loading and nominal sampled quantities), assuming spherical particles with a log normal size distribution. From this model, calculated RSD values of 5.3% for the coarse API grade and 1.3% for the fine API grade are obtained for 1% drug load (dotted lines in Fig. 4). These values generally agree well with the plateau experimental RSD values obtained, indicating that the API is well dispersed in the powder blends. For the fine API grade, experimental RSD values are slightly higher than the calculated values for most blends. This could be due to incomplete deagglomeration of the API particles or reflect an error contribution from the sampling or analysis process, resulting in slightly higher RSD values than expected based on theory.

Fig. 5 shows the blend uniformity results for formulations with an API dosage of 10% *w*/w. A similar trend is observed as for the blends with 1% API dosage, where the fine API grade requires longer mixing times to deagglomerate and disperse. Plateau values may not be achieved within the time frame tested at low speed suggesting incomplete dispersion and deagglomeration of the fine API particles. Mixtures of the coarse API grade again show less dependence of blend uniformity on mixing time, with plateau values typically reached after 60 s. This suggests that at higher API dosage of 10% w/w, a fully adhesive mixture is not obtained for the fine API as not all API particles can adhere to the excipients. Calculated RSD values based on the model by Yalkowsky [28] are lower at 10% API dosage compared to 1% dosage, with values of 1.7% for the coarse API and 0.4% for the fine API grade (dotted lines in Fig. 5). The experimental values obtained for the coarse API grade are similar to the calculated RSD. For the fine API grade, the experimental values are above the calculated RSD of 0.4%. Although due to the low theoretical RSD limit there may be increased relative contribution due to sampling and analytical uncertainty, this supports incomplete dispersion of the fine API particles within the powder blend, especially at low blending speed.

At 10% API dosage, longer mixing times are required to deagglomerate the fine API particles compared to 1% dosage. Blending speed strongly affects the time required to obtain a uniform blend (Fig. 5). At the highest speed of 300 rpm, deagglomeration is fast and uniform mixtures are obtained after 60 s. At medium speed, 150 s are required to obtain a uniform mixture. At low speed however, 180 s of mixing is not sufficient to obtain a uniform blend of the fine API grade. This indicates that the API particles are not fully deagglomerated and dispersed. For the coarse API grade, the effect of blending speed is limited, and uniform blends are obtained after 60 s at both low and high speed. At high speed however, the higher RSD observed for the initial time point suggests that blending is not complete. This may indicate the edge of process intensification achievable, as a medium speed of 180 rpm shows better short-time blending kinetics. To show the process intensification from low to medium blending speed, blend uniformity at both blender speeds are directly compared in Fig. 6. Here data is shown for 150 s mixing at 80 rpm versus 60 s mixing at 180 rpm, corresponding to 200 and 180 blender revolutions respectively. For the coarse API, similar blend uniformity is obtained for both settings, thus allowing intensification of the process in time. For the fine API, there is evidence for 1% drug load that mixing at 180 rpm for a shorter time results in improved uniformity compared to a longer mixing time at 80 rpm, although this is not so evident at 10% drug load. So for the fine API blends there may be a double benefit of both shorter mixing time and improved blending kinetics per blender revolution upon increasing blending speed.

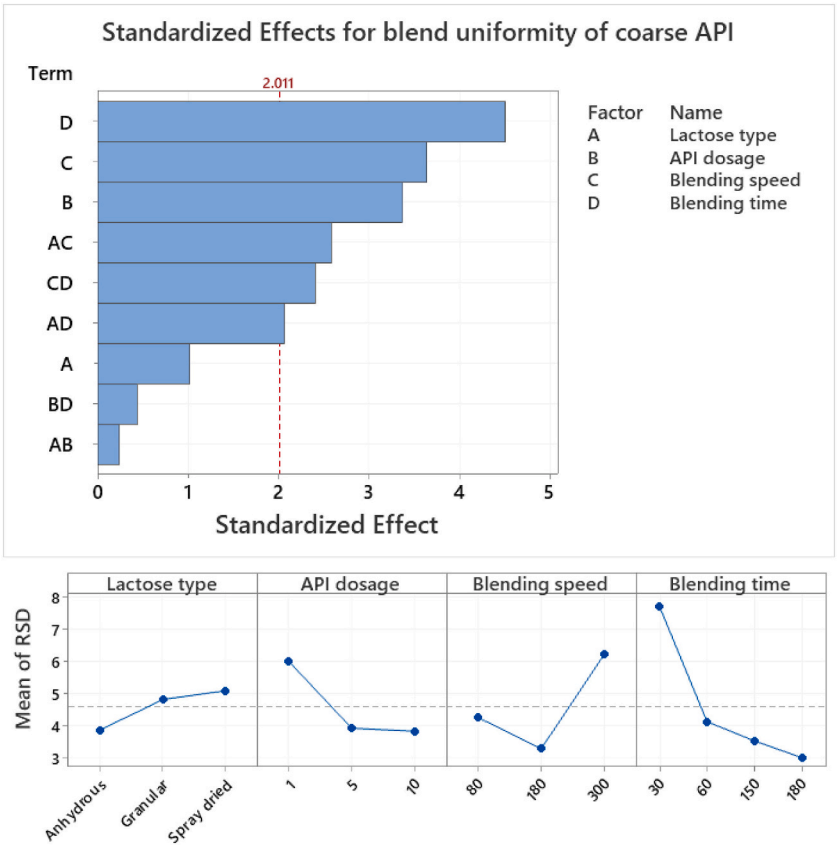

Fig. 9. Results of factorial regression analysis of blend uniformity for mixtures of the coarse API grade.

To illustrate the different mixing mechanisms of the two API grades in more detail, API label claim of the individual samples used for blend uniformity analysis is shown in Fig. 7. Here, blends with 1% *w*/w API dosage at low blending speed are used as an example. For the coarse API grade, API label claim of the individual samples is randomly distributed around a median value of approximately 100%. Samples with label claims above and below 100% are present equally, as would be expected for a random mixture. For blends of the fine API grade, the majority of the samples shows an API label claim below 100%, resulting in a median value lower than 100%. The presence of several individual samples with a very high API label claim up to 200% indicates the presence of hotspots in the blend due to incomplete deagglomeration of the cohesive API particles. This results in high RSD values obtained at short mixing time, but also increases the uncertainty of the true blend RSD values as the sampling of API hotspots has a very large effect on the RSD value. This failure mode can be detected by generally lowered assay values, rather than requiring the sampling of enriched areas. Longer mixing times result in an increase in API label claim of the majority of the samples and the median value approaches 100% after 150 s of mixing. This indicates deagglomeration of the API particles upon increasing mixing time. The different effect of mixing time highlights the different mixing mechanisms for the two API grades.

To analyze the factors that affect blend uniformity of the mini-blending process, factorial regression analysis of the DoE was performed. Since the two API grades show different mixing mechanisms, regression analysis was performed separately for each API grade. Factors included in the analysis were the type of lactose, API dosage, blending speed and time. RSD values were used as the response for blend uniformity. As discussed above, there is increased uncertainty in higher RSD values used as the response in this analysis, due to incomplete API deagglomeration and the probability of sampling API enriched zones. Two-way interaction terms between all factors were included in the factorial regression analysis as well. Fig. 8 shows the results of factorial regression analysis for blends of the fine API grade. The factor that has by far the most significant effect on blend uniformity is blending time. Furthermore, blending speed, lactose type and API dosage also significantly affect blend uniformity. Regarding the interaction terms, the interaction API dosage-blending time and the interaction API dosage-lactose type significantly affect blend uniformity.

The results of factorial regression analysis reveal that process settings (blending time and speed) have a more pronounced effect on blend uniformity than factors related to the blend formulation (lactose type and API dosage). An increase in either speed or time improves blend uniformity, as the cohesive API particles deagglomerate upon increasing the energy input in the blending process. A significant improvement in uniformity is observed upon increasing from low to medium speed (Fig. 8), in line with process intensification. But a further increase to high mixing speed has little effect on blend uniformity, indicating no further process intensification. The type of lactose used also affects blend uniformity, where the granular lactose grade shows reduced blending performance compared to the spray dried and anhydrous grades, especially at low shear conditions. This can be rationalized by the irregular morphology of the granulated lactose particles. Aggregates of fine API particles primarily adhere to the surface cavities of the granular lactose, also known as active sites [29,30]. This can result in incomplete dispersion of the API particles at low shear blending conditions, thereby reducing blend uniformity.

Factorial regression analysis of the blend uniformity data for the coarse API grade reveals that blending time and speed again have the most significant effect on mixing performance (Fig. 9). In contrast to the fine API blends, however, the type of lactose in the formulation does not significantly affect blend uniformity. This indicates no specific interaction between excipient and API particles, as would be expected for a purely random mixture. Increasing API dosage results in improved blend

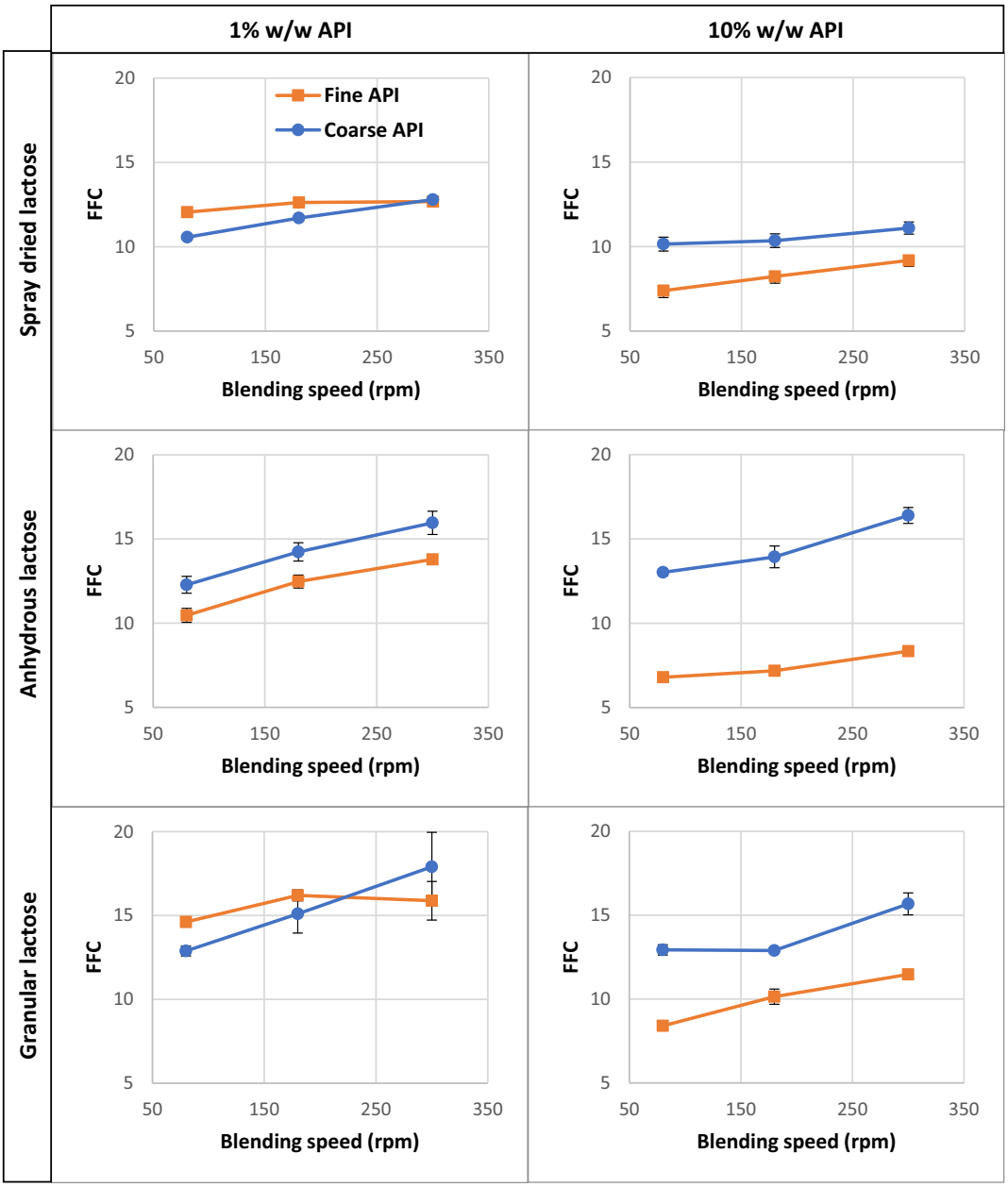

Fig. 10. Flowability of the powder blends, represented by the FFC of the blends prepared at increasing blending speeds.

uniformity, in line with predictions for random powder mixtures [31]. This improvement in blend uniformity upon increasing dosage was not observed for the fine API blends. Another difference between the fine and coarse API mixtures is the effect of blending speed. Where the uniformity of the fine API blends is improved upon increasing blender speed, the coarse API blends show apparent reduced blend uniformity at the highest blending speed. This effect is driven by the short-time blending kinetics, which are reduced at the highest blending speed. This may be related to the particles being pushed against the blender wall hindering dispersion. Upon longer blending times, uniformity reaches a plateau value which is unaffected by blender speed (Figs. 4, 5). This means that same blend uniformity can be obtained at different speeds, but the plateau value is not reached quicker at the highest speed. So blending at 300 rpm does not yield intensification of the process compared to 180 rpm blending. For all conditions studied, once the uniformity plateau is reached, there is no sign of de-mixing upon further blending. In general, regression analysis of the blend uniformity data reveals that blending efficiency of the mini-blender is largely dependent on process settings, with limited impact of excipient material properties. There is a limit to time process intensification that can be achieved, with little difference between medium and high speeds although these flow regimes allow significant time reduction compared to low speed push mixing. The small scale of the mini-blender combined with high shear applied results in high mixing efficiency, independent of powder characteristics and with a short cycle time.

3.3. *Powder flowability*

In a tableting process, powder flow is a critical material attribute as powder must flow uniformly into the tablet dies. Poor flow can result in large variations in weight and dosage of the final tablets. The flowability of a powder blend is determined by both the flow properties of individual components and interactions between the components introduced by the blending process. To determine how the mini-blending process affects powder flow properties, the flow function coefficient (FFC) of the blends was measured after 180 s of mixing, including

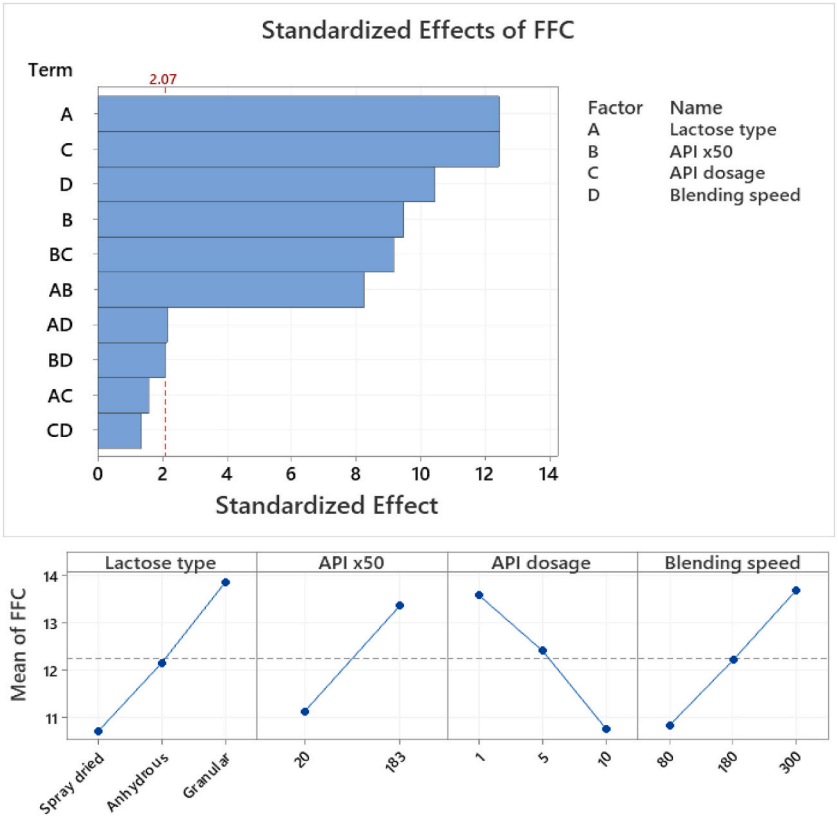

Fig. 11. Results of the factorial regression analysis of the flow function coefficient. The pareto chart (top) shows the significant factors and interactions that determine blend flowability.

lubrication. Fig. 10 shows how FFC depends on blending speed of the mini-blender for varying formulations. For all blends, an increase in FFC upon increasing blending speed is observed. This indicates improved blend flowability at higher mixing speed, which can be attributed to lubrication of API and excipients. Lubrication with magnesium stearate decreases the frictional and cohesive forces between particles, thereby improving powder flowability [32].

The particle size and dosage of the API also affect flowability of the blends. At an API dosage of 10% *w*/w, blends with the coarse API grade show a significantly higher FFC than blends with the fine API grade (Fig. 10). This can be explained by the very cohesive nature and poor flow properties of the fine API particles, which reduces flowability of the resulting mixtures. As would be expected at an API dosage of 1% w/w, all blends are free-flowing with FFC values well above 10 and no practically significant difference between fine and coarse API. Factorial regression analysis was performed to reveal the factors that significantly affect blend flowability in the mini-blending process. The factors included were the type of lactose, API particle size, API dosage and blending speed, as well as all two-way interactions. The results reveal that all four factors have a significant effect on flowability (Fig. 11). The largest standardized effects are found for the type of lactose and API dosage. Lactose is the major component of the blends and therefore strongly affects flowability. But since the APIs show significantly lower flowability compared to lactose, increasing API dosage also has a strong effect on blend flowability. Also the blending speed and API particle size have a significant effect on FFC. For the interaction terms, the most significant effect is found for the interaction between API particle size and dosage. This effect is also clear from Fig. 10, where increasing the dosage has a much larger effect on FFC for the fine API than for the coarse API. There is also a significant interaction between the type of lactose and type of API used in the formulation. This can be related to differences in adhesive interactions between the fine API particles and the different lactose grades with varying surface morphologies. The factorial regression analysis shows that blend flowability is largely determined by the material properties of the excipients and API, and the interactions between them. The blending process also affects flowability, as the FFC increases with increasing blending speed due to a lubrication effect. This dependence on blending speed presents an alternative approach to optimize blend flowability prior to tableting. Improving flowability through enhanced lubrication, however, also leads to other, undesired effects such as increased hydrophobicity and reduced tabletability of the powders. The effect of lubricant blending on tabletability of the blends is discussed further in Section 3.4.

3.4. *Tabletability of the powder blends*

To investigate how tabletability is affected by the mini-blending process, tablets were compressed from the blends prepared at varying blending speeds. Tablets were compressed at a target tensile strength of 1 MPa and the compression force required to reach this target was analyzed for the blends with 1% and 10% *w*/w API dosage. Fig. 12 shows how the compression force increases with blending speed for blends with different lactose and API grades. For all blends, the compression force required to meet the target tablet strength increases at higher blending speed. This indicates a reduction in tabletability of the blends upon increasing blending speed. Similar to the improved flowability, the reduced tabletability can be attributed to lubrication. At higher blending speed, the lubricant is distributed more homogeneously over the API and excipient particles. This results in a higher degree of dispersion of lubricant, which has a negative effect on tabletability. As would be expected, the effect is more marked for coarse API with its lower surface area resulting in a higher effective magnesium stearate contribution.

As tabletability of the blends is largely determined by the excipients, lubrication of the excipient particles is the primary cause of the observed

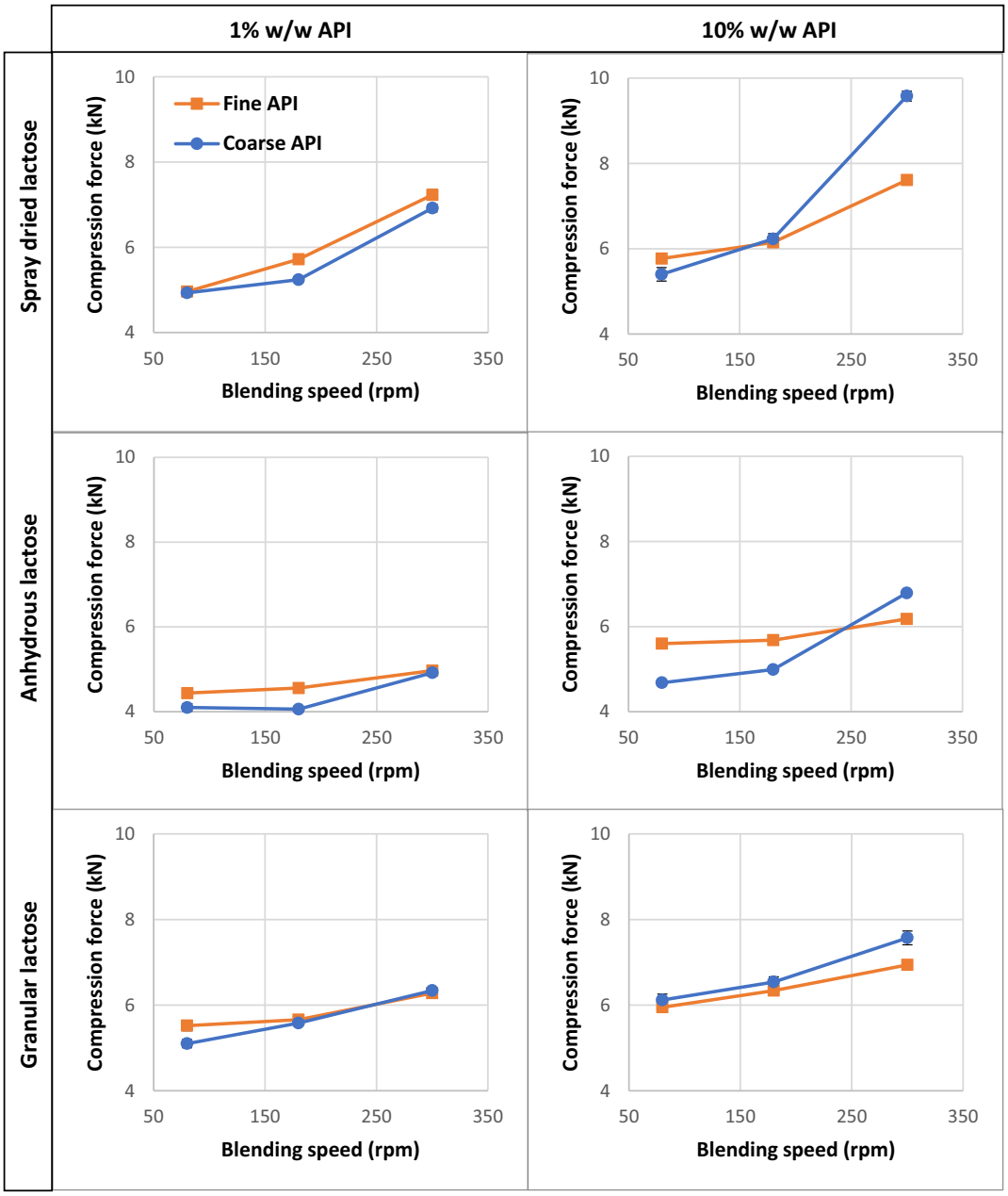

Fig. 12. Tabletability of the powder blends, represented by the compression force required to reach the target tablet strength. The compression force increases at higher blending speeds, indicating reduced tabletability of the blends prepared at higher speed.

effect of blending speed. It is known that plastically deforming excipients such as MCC are more sensitive to lubrication than brittle excipients such as lactose [33]. Increased lubrication of the MCC particles during blending will therefore result in reduced tabletability of the formulations. The type of lactose used, however, also strongly affects how the tablet compression force increases with blending speed (Fig. 12). For spray dried lactose, the increase in compression force with blending speed is much more pronounced than for anhydrous and granular lactose. The spray dried grade is not fully crystalline but partly consists of amorphous lactose. This amorphous lactose results in more plastic deformation behavior, making spray dried lactose more sensitive to lubrication than crystalline lactose grades. The anhydrous and granular lactose grades show brittle deformation behavior and are less sensitive to lubrication. This results in the reduced effect of blending speed on tabletability for these lactose grades. Furthermore, spray dried lactose has a lower surface area compared to the other two lactose grades. Therefore, a smaller fraction of the lubricant is adhered to the lactose particles and a larger fraction is available for lubrication of MCC. Since tabletability of MCC is more affected by lubrication, a more pronounced effect of blending speed on tabletability is observed for spray dried lactose.

Factorial regression analysis reveals that blending speed is the most significant factor that determines the tabletability of the blends (Fig. 13). Other significant factors are the lactose type and API dosage. This indicates that the blending process has a stronger effect on tablet strength than the type of lactose and API used in these formulations. The interaction between the lactose grade and blending speed also significantly affects tabletability, as tabletability of spray dried lactose is more affected by blending speed than the other two lactose grades. These results highlight that the effect of lubrication should be taken into account when optimizing the blending process of pharmaceutical formulations. A higher blending speed during lubrication of a pharmaceutical

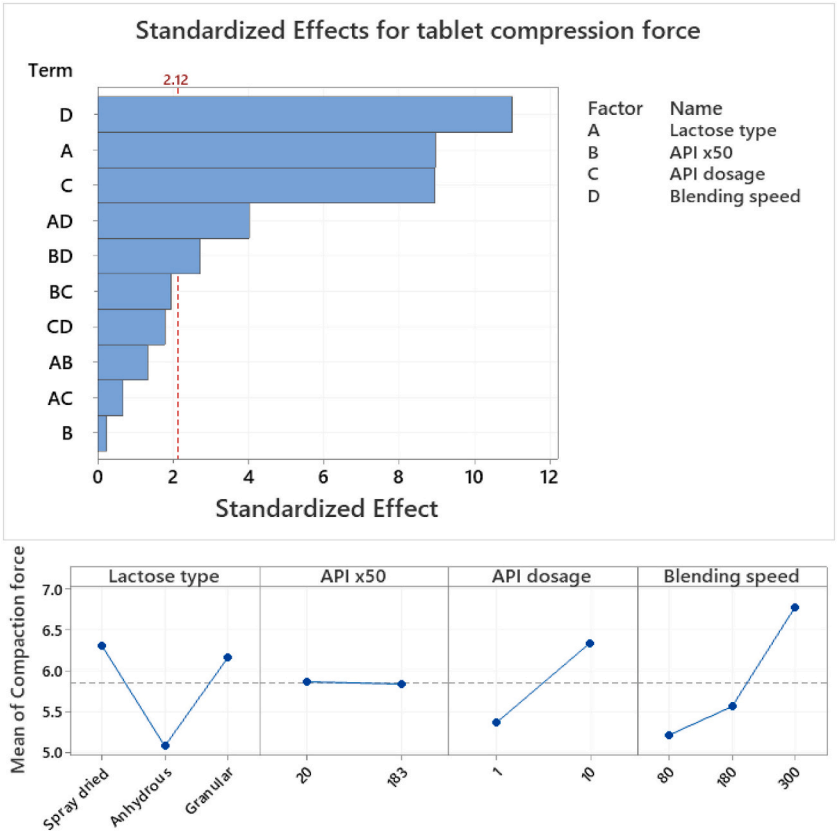

Fig. 13. Results of factorial regression analysis of the tablet compression force. The pareto chart (top) shows the significant factors and interactions that determine tabletability of the powder blends.

formulation can have a negative effect on tablet strength. For blend uniformity on the other hand, a higher blending speed can be beneficial, especially in the case of cohesive particles. To optimize the blending process in terms of both blend uniformity and tablet properties, using different blending speeds before and after the addition of lubricant can be an option. A two-step blending process with mixing at high speed to achieve good uniformity of API and excipients followed by mixing at low speed during lubrication to minimize the loss of tabletability is therefore proposed. If the goal of lubrication, however is to improve flowability of the blend, a higher blending speed is optimal. In this way, the blending process can be used to optimize CQA's of API-excipient blends such as flowability and tabletability.

4. Conclusions

The novel semi-continuous mini-blender used in this study combines the small scale and high mixing efficiency of a continuous powder blender with batch-wise dosing of ingredients to support dosing of low level components. The results presented here show that operating this blender design in spin and centrifugal mixing regimes allows process intensification of the blending of API and excipients to yield a short cycle time. A significant improvement in uniformity is observed from low speed push mixing to medium speed spin mixing. A further increase to high speed centrifugal mixing shows no further process intensification. Even at low dosage, a uniform blend is obtained within one to three minutes at medium or high speeds. Once a uniformity plateau is reached, there is no sign of de-mixing upon further blending within the time ranges studied. This potentially expands the boundaries of continuous direct compression to low-dose formulations. The optimal blender speed depends on the type of mixture, where cohesive API particles require a higher speed than a random powder mixture to achieve uniformity at short cycle times. However, operation at spin and centrifugal blending conditions showed similar performance and thereby potential for simplified process development operating at these conditions. The short blending times required for achieving uniformity (60 to 180 s) in these conditions are in line with process intensification and allow integration of the mini-blending process into a continuous DC line. Limited impact of excipient material properties on blend uniformity is observed after blending for at least 60 s, with all blends reaching a similar RSD plateau value showing that process intensification has been achieved. Only at short mixing times where a uniformity plateau is not reached, the type of excipient affects blend uniformity of the mini-blending process. The batch-wise dosing of ingredients makes this mini-blending process especially suitable for low-dose formulations that are generally difficult to process continuously. Formulation optimization for continuous DC in this format can thus be focused on CQA's other than uniformity.

Lubrication of the powders in the mini-blender is strongly dependent on energy input of the blending process. CQA's of the powder blends can be controlled by optimizing the process settings of the lubrication step. An increase in blending speed during lubrication affects both flowability and tabletability of the powder blends. This interdependence of material properties on process settings presents a new approach to optimize CQA's of powder blends. Flowability and tabletability of a pharmaceutical formulation are generally controlled by varying the ratio of the components used in the formulation, for example by varying the relative amount of lubricant. The results of this study show that control of these quality attributes can also be achieved to some extend by varying blending process settings, while using a fixed formulation. Such an enhanced understanding of the effect of process settings on product CQA's is in line with the Quality by Design approach for continuous pharmaceutical manufacturing.

CRediT authorship contribution statement

Maarten Jaspers: Writing – original draft, Investigation, Formal analysis, Visualization. **Timo P. Roelofs:** Methodology, Investigation, Formal analysis. **Alexandra Lohrmann:** Methodology, Investigation. **Florian Tegel:** Methodology, Investigation. **Muhammad Khalid Maqsood:** Methodology, Formal analysis. **Yunfei Li Song:** Writing – review & editing. **Bernhard Meir:** Writing – review & editing, Supervision. **Richard Elkes:** Methodology, Writing – review & editing, Supervision. **Bastiaan H.J. Dickhoff:** Writing – review & editing, Supervision.

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.

Data availability

Data will be made available on request.

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