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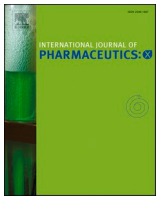

Process intensification of pharmaceutical powder blending at commercial throughputs by utilizing semi-continuous mini-blending

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ABSTRACT

Process intensification involves the miniaturization of equipment while retaining process throughput and performance. The pharmaceutical industry can benefit from this approach especially during drug product development, where the availability of active pharmaceutical ingredients (API) is often limited. It reduces the need for process scale up, as equipment used during product development and commercial production is identical. However, applications of process intensification for processing pharmaceutical powders are limited so far. Here we show that semi-continuous mini-blending can be utilized for process intensification of blending of API and excipients. Uniform blending at commercially relevant throughputs was achieved through mini-blends with a volume of less than ten liters. Our results demonstrate that blending speed, cycle time and blender fill level can be optimized without compromising blending performance. Acceptable blend uniformity is obtained over a broad range of operating parameters, by choosing the right excipients. The optimized throughput of the mini-blending process is in line with the desired throughput of a commercial Continuous Direct Compression (CDC) process.

1. Introduction

Process intensification (PI) traditionally involves the physical miniaturization of process equipment or reduction of the number of unit operations, while retaining process throughput and performance (Reay et al., 2013; Zhang et al., 2021). Its fundamental concept is based on process volume reduction, resulting in enhanced mixing and heat/mass transfer. Industrial development in PI has resulted in novel equipment with higher production capacity per unit vessel volume (Wang et al., 2017). Such equipment includes both reactive equipment, such as microreactors or oscillatory baffled reactors, as well as non-reactive processing equipment, such as mixing devices.

The focus of PI has mainly been on processes involving liquids and gases. PI applications for the processing of solids are limited, as fouling and equipment blockages can occur due to the presence of solids in comparably small confinements (Wang et al., 2017). Appropriately designed equipment is therefore key for intensifying industrially-relevant solid processes. The handling of solids, and powders in particular, is an important process in many industries such as the pharmaceutical and food industry. In these sectors, powder processing involves a variety of unit operations including dosing, blending, granulation, filling and compression. These unit operations are generally performed in batch-wise processes at large scale of production in the order of tens to hundreds of kilograms. PI of such operations can greatly reduce the production footprint, improve flexibility in scale of manufacturing and support rapid, material sparing development of new products by reducing scale up needs to deliver commercial throughputs.

Generally, the objective of PI in powder processing is transforming traditional batch processes to continuous ones. This reduces processing times and improves energy efficiency (Wang et al., 2017). Powder blending is a unit operation that is conventionally carried out in a large scale tumble blending process. This results in limited flexibility in terms of the scale of production as the batch size is determined by blender dimensions (Roth et al., 2017). In the pharmaceutical industry, the main goal of a powder blending process is to generate a uniform blend of the active pharmaceutical ingredient (API) and excipients. Uniformity of the

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powder blend is crucial to ensure accurate and consistent dosing of the API in the final dosage form. Achieving uniform blending can be challenging, as differences in powder material properties (e.g. particle size) can cause segregation during blending (Alexander et al., 2003; Shenoy et al., 2015; Tang and Puri, 2007). This results in poor content uniformity and drives the need for scale up trials. Process intensification of a powder blending process could reduce segregation potential by minimizing the scale of mixing and reducing the number of scale up steps to allow commercial manufacturing throughput.

Continuous powder blenders have been developed as a small-scale alternative for traditional batch blenders (Pernenkil and Cooney, 2006). With a volume in the order of several liters and residence times in the order of seconds to minutes, they are an excellent example of PI. It has indeed been shown that the segregation potential is greatly reduced in continuous powder blending compared to batch blending (Lakio et al., 2017; Oka et al., 2017). Furthermore, continuous blending has also been shown effective in producing uniform blends of API's and pharmaceutical excipients (Jaspers et al., 2022, 2021; Lakio et al., 2017). However, implementation of continuous powder blending, and continuous processing in general, in the pharmaceutical industry is still limited due to both regulatory and technical challenges (Vanhoorne and Vervaet, 2020). The technical limitations include management of fluctuations in feeding of individual ingredients (Bostijn et al., 2019; Jaspers et al., 2021), build-up of material in process equipment (Kauppinen et al., 2019) and challenges with content uniformity of formulations with low API dosage (Karttunen et al., 2019; Van Snick et al., 2017). Furthermore, a drawback of fully continuous processing in product development is the product consumption during start-up and ramp down of the system. This is especially an issue when commercial production volumes are small, as well as during product and process development where the availability of API is limited. A continuous process also requires the development of complex full line disturbance tracking and rejection strategies, as disturbances are guaranteed during refill of feeders.

To overcome the challenges of continuous powder blending while maintaining the advantages of PI, a semi-continuous mini-blender can be implemented. This mini-blender consists of a small-scale batch blender with a volume of approximately 10 l, combined with gravimetric feeders for dosing of API and excipients. The small volume of the mini-blender allows for process intensification of the blending process through enhanced mixing efficiency, resulting in reduced blending times (Bautista et al., 2022). The enhanced mixing efficiency is achieved by applying high rotational speeds of up to 300 rpm, equivalent to a Froude number up to 12. This is much higher than what can be achieved in a conventional batch powder blending process, where typical Froude numbers are below 1.0 (Muzzio and Alexander, 2005). In a semi-continuous mini-blending process, feeding, blending and discharge of the blend are carried out repeatedly at a set frequency, which allows continuous compression of the blend into tablets (Bautista et al., 2022). A major benefit of this semi-continuous approach is the averaging out of feeder fluctuations due to discrete dispensing of raw materials. The weight dispensed by each feeder exactly corresponds to the mass of each component in that particular mini-blend. Furthermore, refill of the feeders occurs during blending and therefore feeders are always dispensing under gravimetric control. This makes the process especially suitable for low-dose formulations which are sensitive to feeding fluctuations in a continuous process. Another benefit is the absence of a process start-up and ramp down phase, resulting in high yields and reduced amounts of API required during development. Finally, there is no need for scale up as the equipment used during development and commercial production is identical.

The objective of the current study is to demonstrate process intensification of the blending of API and excipients using a semi-continuous mini-blender. To this end, potentially critical process parameters; blending speed and blender fill level, are varied and blend uniformity of the resulting powder blends is tested. Blending is performed for formulations with low and medium API dosage and varying direct compression (DC) grades of lactose as the major excipient. The results of this study reveal the critical parameters that determine performance of the mini-blending operation. It is found that uniform blends of API and excipients are obtained over a broad range of process settings, indicating a robust blending process of the API with DC-grade excipients. By optimizing blending speed, the time required per blending cycle can be reduced, which results in an intensification of the blending process. Together with a tailored blender fill level and optimized excipient selection, this leads to a maximized throughput of the mini-blending process. This optimized throughput is in line with the throughput required for a commercial CDC process. These results show the potential of semi-continuous mini-blending for blending of API and excipients at small scale, while achieving a commercially relevant process throughput.

2. Materials and methods

2.1. Materials

Spray dried lactose (SuperTab® 11SD), anhydrous lactose (SuperTab® 21AN), agglomerated lactose (SuperTab® 30GR), microcrystalline cellulose (MCC, Pharmacel® 102) and croscarmellose sodium (CCS, Primellose®) were obtained from DFE Pharma (Goch, Germany). Paracetamol fine powder grade was purchased from Mallinckrodt Inc. (Raleigh, NC, USA).

2.2. Powder blending

API and excipients were blended in a Gericke Mini-Blender with a volume of approximately 10 l (GBM 10-P, Gericke AG, Regensdorf, Switzerland). The order of addition of the components into the blender was fixed for all blends, starting with lactose, followed by paracetamol, MCC and CCS. The total weight of the powder to be blended was varied between 0.5 and 5.0 kg, resulting in blender fill levels ranging from approximately 10% to 100% *v*/v. The relative amounts of API and excipients used in the blend formulations are shown in Table 1. Blending was performed at varying blender speeds, ranging from 80 to 260 rpm, corresponding to a Froude number ranging from 0.8 to 8.7. Sampling of the blends was performed after a fixed number of blender revolutions (90, 200, 450 and 750 revolutions), resulting in variable blending times depending on the rotational speed used. An overview of the dependency between blending speed, number of revolutions and blending times is given in Table 2. A stainless steel sample thief (PowderThief, Sampling Systems, Coleshill, United Kingdom) with a length of 600 mm and a diameter of 12.5 mm was used to extract between 0.3 and 0.9 g of powder from nine distinct locations of the powder blender. A schematic overview of the sampling plan used is shown in Fig. 1. Sampling tips with a volume of 1 mL were used for sampling the powder blends. The closed sample thief was manually inserted in the mini-blender at fixed sampling positions, according to Fig. 1. The outer tube of the sampling thief was retracted to collect the sample in the sampling tip. The collected sample was fully transferred into a glass vial, which was used for subsequent blend uniformity analysis.

Table 1
Formulations of the model API-excipient blends prepared in the mini-blending process. The type of lactose used in the formulations is varied between spray dried, anhydrous and granular lactose.

Material	Low-dose formulation (% *w*/w)	Medium-dose formulation (% w/w)
Paracetamol	1.0	10.0
Lactose	75.24	68.4
Microcrystalline cellulose	19.8	18.0
Croscarmellose sodium	3.96	3.6

Table 2
Overview of the blending time required in seconds to obtain the number of blender revolutions at each of the rotational speeds tested in the current study.

No. of revolutions	80 rpm	130 rpm	155 rpm	180 rpm	220 rpm	260 rpm
90	68 s	42 s	35 s	30 s	25 s	21 s
200	150 s	92 s	77 s	67 s	55 s	46 s
450	338 s	208 s	174 s	150 s	123 s	104 s
750	563 s	346 s	290 s	250 s	205 s	173 s

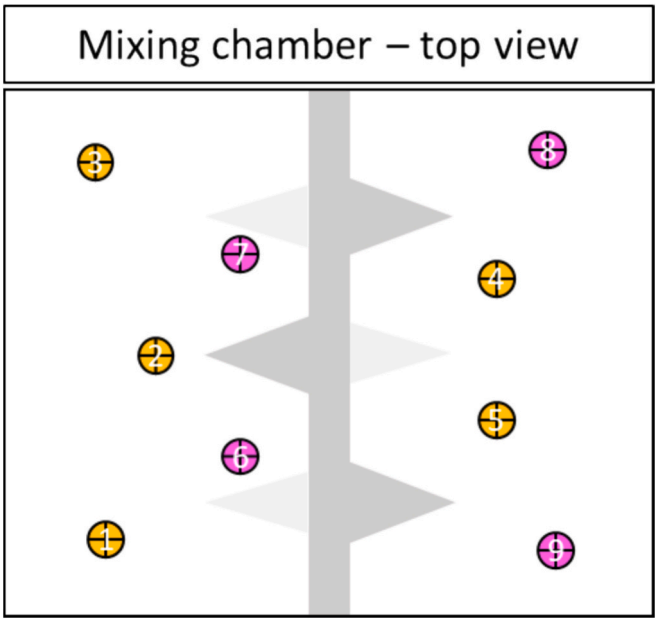

Fig. 1. Schematic overview of the sampling plan used for extracting samples from the mini-blender for blend uniformity analysis. The yellow dots represent sampling spots from the top half of the powder bed and purple dots represent sampling spots from the bottom half of the powder bed. Gray triangles represent the mixing blades of the mini-blender. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.3. Blend uniformity analysis

The whole powder sample of 0.3 to 0.9 g was dissolved in MilliQ water through ultrasonication for 15 min at 35 °C. The resulting solutions were diluted to API 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 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 linear calibration line. The API content of each sample analyzed was corrected for the sample weight. Blend uniformity is represented by the average and relative standard deviation (RSD) of the API content, calculated over nine samples for each blend.

2.4. Calculations of process throughput

The throughput of the mini-blending process was calculated based on the number of blender revolutions required to obtain acceptable blend uniformity. Here, an acceptable blend uniformity is defined as an RSD value lower than 5% and an average API label claim between 90% and 110%. The number of blender revolutions required to reach acceptable uniformity at a given blender speed is used to calculate the process throughput, according to eq. 1:

$$Throughput = \frac{60}{t_{cycle}} \times fill\ level = \frac{60}{t_{feed} + t_{blend} + t_{lub} + t_{dis}} \times fill\ level = \frac{60}{t_{feed} + \frac{n}{v_{rot}} + t_{lub} + t_{dis}} \times fill\ level \quad (1)$$

The throughput in kilograms per hour is calculated from the blending cycle time (t_{cycle}) and the blender fill level in kg. The blending cycle time is defined as the sum of the time required for raw material feeding (t_{feed}), blending (t_{blend}), lubrication (t_{lub}) and blend discharge (t_{dis}). The lubrication step includes both feeding and blending of the lubricant in the mini-blender. For raw material feeding, lubrication and discharge, fixed processing times are assumed of 2.5 min, 1 min and 0.5 min respectively. The time required for blending is calculated from the number of blender revolutions (n) and the rotational speed of the mini-blender (v_{rot}). For calculating the process throughput, a constant blender fill level of 4 kg of the powder blend is assumed, corresponding to a relative blender fill level of approximately 65% v/v for the formulations according to Table 1.

3. Results and discussion

3.1. The effect of blending speed and time on process performance

It is hypothesized that the most critical process parameter for optimizing API-excipient mini-blending is the blender speed. Increasing speed results in improved convective mixing and generates higher shear forces, which can improve the dispersion of cohesive API particles within the powder blend (Bridgwater, 2012). Efficient dispersion of the API particles is the most important factor in obtaining a uniform blend of API and excipients (Scheibelhofer et al., 2013). Furthermore, increasing the blender speed reduces the time required to reach a certain number of blender revolutions. The combined effect of improved dispersion and reduced mixing time at higher speed can thereby intensify the mini-blending process and optimize process throughput, while maintaining a small scale of mixing. In this study we will show that mini-blending allows commercial throughput at small blender scale, without need for blender scale up.

Blending of API-excipient formulations with three different grades of lactose according to Table 1 was performed at varying blender speeds, ranging from 80 to 260 rpm. Blender speeds below 80 rpm did not provide sufficient mixing to obtain a uniform blend and were therefore not further investigated, whereas the maximal speed of 260 rpm is close to the upper limit of the mini-blender (300 rpm). At low blender speed, mixing occurs primarily within the powder bed through a push mixing mechanism. Increasing the blender speed results in higher shear forces and partial fluidization of the powder within the mini-blender (Jaspers et al., 2023). For each blending speed, uniformity of the powder blends was analyzed after fixed numbers of blender revolutions (and thus different mixing times), up to the endpoint of 750 revolutions. Fig. 2 shows the blend uniformity results, expressed as the RSD of the API concentration, for the various formulations. The blend uniformity is onsidered acceptable when the RSD is below 5% (red lines).

After 90 blender revolutions, the RSD values are well above 5% for all blends, independent of the blending speed used (Fig. 2). This indicates that 90 blender revolutions is not sufficient to prepare a uniform blend of the excipients and API. Increasing the number of revolutions generally decreases the RSD values, indicating an improvement in blend uniformity. The blending efficiency of the mini-blending process shows a clear dependency on the blending speed. At higher blending speed, the RSD values show a stronger decrease with increasing number of blender revolutions (Fig. 2). This indicates a more efficient blending process at higher speeds, resulting in a lower number of revolutions required to obtain RSD values below 5%. Furthermore, the mixing time required to reach a certain number of blender revolutions is reduced upon increasing blending speed. In this way, an increased blending speed

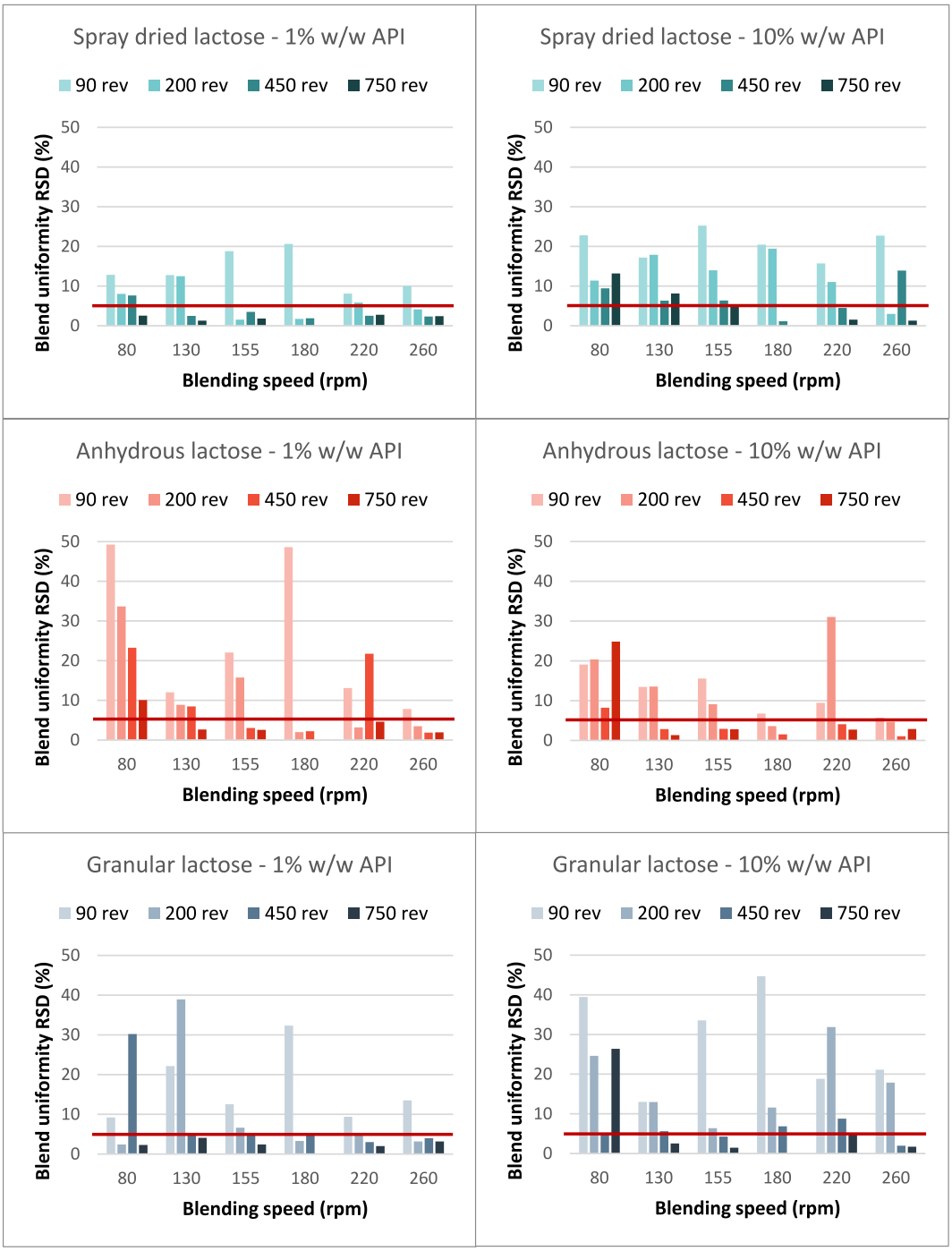

Fig. 2. Blend uniformity results for the six API-excpient blends based on three different lactose grades prepared at varying blender speeds at a fixed number of blender revolutions. Graphs show the relative standard deviation of the API concentration of the samples analyzed for each blend.

presents a double benefit in terms of the efficiency of the process, reducing both the number of revolutions and mixing time required to obtain a uniform blend.

The RSD values presented in Fig. 2 are used to quantify the uniformity of the powder blends. These values, however, are sensitive to deviations in the API content of individual samples taken from the powder blends. For the blends prepared at a low number of revolutions, it is generally observed that most individual samples are well below the expected API label claim of 100%, with one or several outliers showing an API label claim that is much higher than 100%. This indicates incomplete dispersion of the API particles within the powder blend, resulting in the presence of hotspots with very high API content. Since the chance of sampling such a hotspot is statistically low, the RSD values are strongly dependent on whether a hotspot is sampled or not. This results in some random variation observed in the RSD values. To further identify trends in blend uniformity at varying blender speeds, Fig. 3 shows the average API label claim of the samples analyzed from each powder blend. These results generally show that the average API label claim is well below 100% after 90 blender revolutions. This indicates incomplete mixing, in line with the high RSD values obtained after 90 revolutions. API label claim values consistently lower than 100% could also be related to sticking of the API to either the blender or the sampling thief. Increasing the number of revolutions at higher speeds, however, results in an increase in the average API label claim to values close to

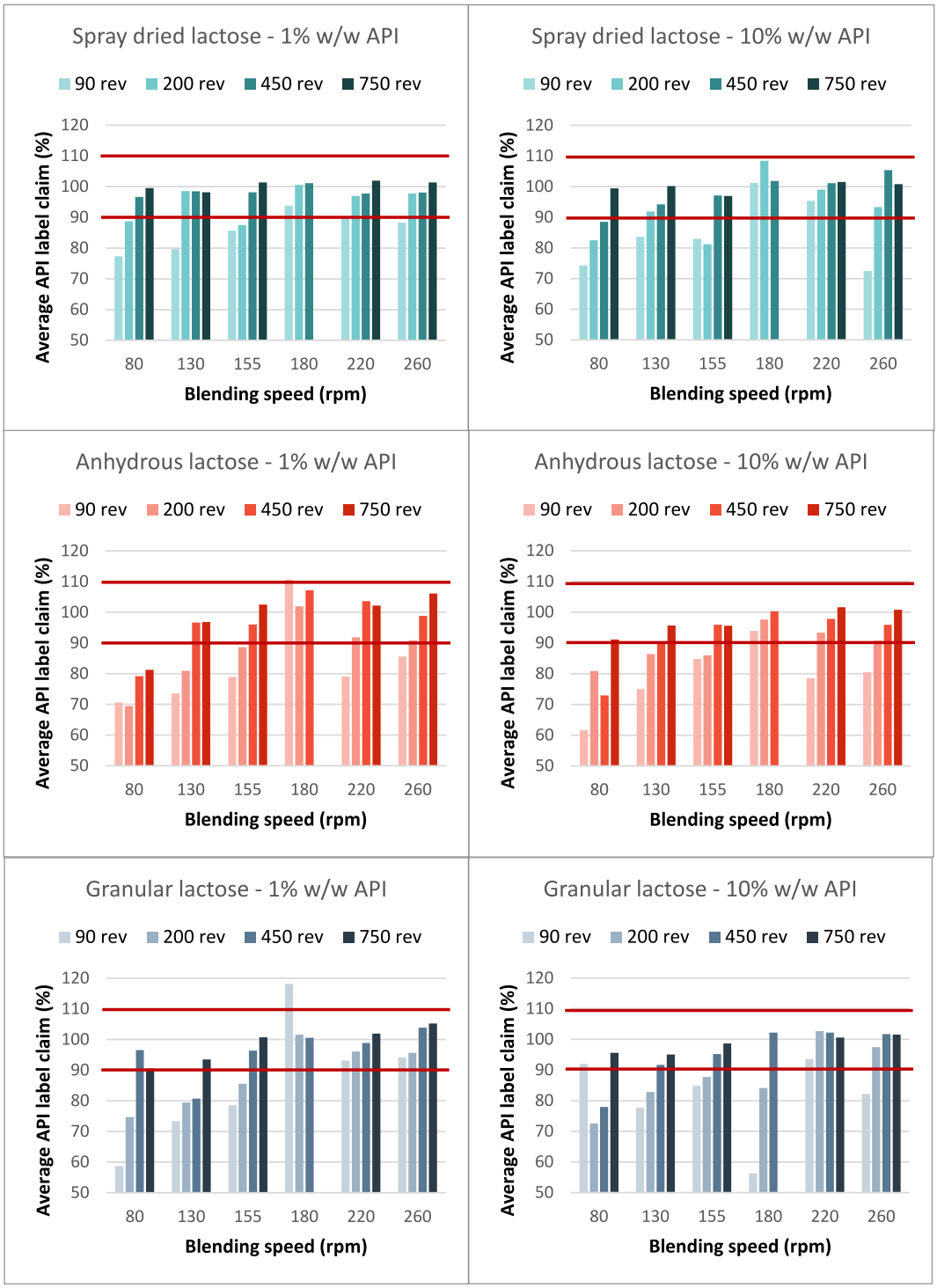

Fig. 3. Blend uniformity results for the six API-excpient blends based three different lactose grades prepared at varying blender speeds at a fixed number of blender revolutions. Graphs show the average API label claim of the samples analyzed for each blend.

100% and the absence of highly potent samples, as would be expected for a blend reaching uniformity. The overall trends in mean label claim and RSD with increased blending time are consistent with what would be expected from sampling across an evolving blending process, including the early stages of mixing where API distribution and dispersion is incomplete. If sticking of the API to the equipment would be an issue, average label claim values below 100% would also be expected after longer mixing. Only at the lowest blending speeds of 80 and 130 rpm, the average label claim does not reach 100% upon increasing number of revolutions. This indicates that the mixing is not complete after 750 revolutions, which is also in line with the respective RSD values. At increased blender speeds of 155 rpm and higher, the blends generally reach an average API label claim close to 100% within 450 blender revolutions (Fig. 3). This indicates that a uniform powder blend is obtained within 3 min mixing time (Table 2).

3.2. The effect of API concentration on process performance

The API dosage of the blend formulations also affects the performance of the mini-blending process (Fig. 2). Especially at low blending speeds, the blends with 1% *w*/w API dosage show a more pronounced decrease in RSD values upon increasing the number of blender revolutions compared to the blends with 10% w/w API dosage. At a mixing speed of 80 rpm, the blends with 1% w/w API generally reach lower RSD values upon increasing the number of revolutions, whereas the blends with 10% w/w API show high RSD values even after 750 revolutions. For a random mixture of particles, it would be expected that blends with a higher API dosage are more uniform (Rohrs et al., 2006). The fact that an opposite trend is observed, indicates challenges with dispersing of the API particles at low blender speeds. At higher blending speeds, similar blend uniformity for the formulations with 1% and 10% w/w API is obtained (Fig. 2). This indicates that the mixing performance of the mini-blending process is independent of API dosage, as long as sufficient shear force is applied to effectively disperse the API particles. If the shear forces applied during mixing are too low, blends with a higher dosage of API show incomplete disperison of the API particles, resulting in poor uniformity. The blends with 1% and 10% *w*/w API dosage also show a comparable increase in average API content upon blending (Fig. 3). This further supports that the mixing efficiency of the mini-blending process appears insensitive to the API concentration of the powder blend formulations, especially at higher blender speeds. It is only at low blending speeds, where lower shear forces cause inefficient dispersion of the API particles, that differences in API concentration affect mixing efficiency.

To verify that the blend uniformity results obtained experimentally are representative of the actual uniformity of the powder blends, the experimental RSD values are compared to theoretical calculations of blend uniformity for random powder mixtures. We used the model developed by Yalkowsky and Bolton (Yalkowsky and Bolton, 1990) to calculate blend uniformity RSD values expected for a random mixture based on particle size and API dose of the formulations used. This results in calculated RSD values of 1.3% and 0.4% for the formulations with 1% *w*/w and 10% w/w API dose respectively. Experimentally, we observe that RSD values in the range of 1% - 3% are obtained at the endpoint of the mini-blending process for both formulations (Fig. 4). This indicates that the experimental RSD values are in line with theoretical predictions for the formulation with 1% w/w API, but are slightly higher for the formulation with 10% w/w API dosage. This difference between the experimental data and theory could be related to additional errors introduced by the sampling process, the sample preparation or the analytical method used to characterize blend uniformity.

3.3. The effect of excipients on process performance

The type of lactose chosen as the major excipient in the blend formulations shows little effect on blend uniformity. Very similar behavior is observed for the blends based on spray dried, anhydrous or granular

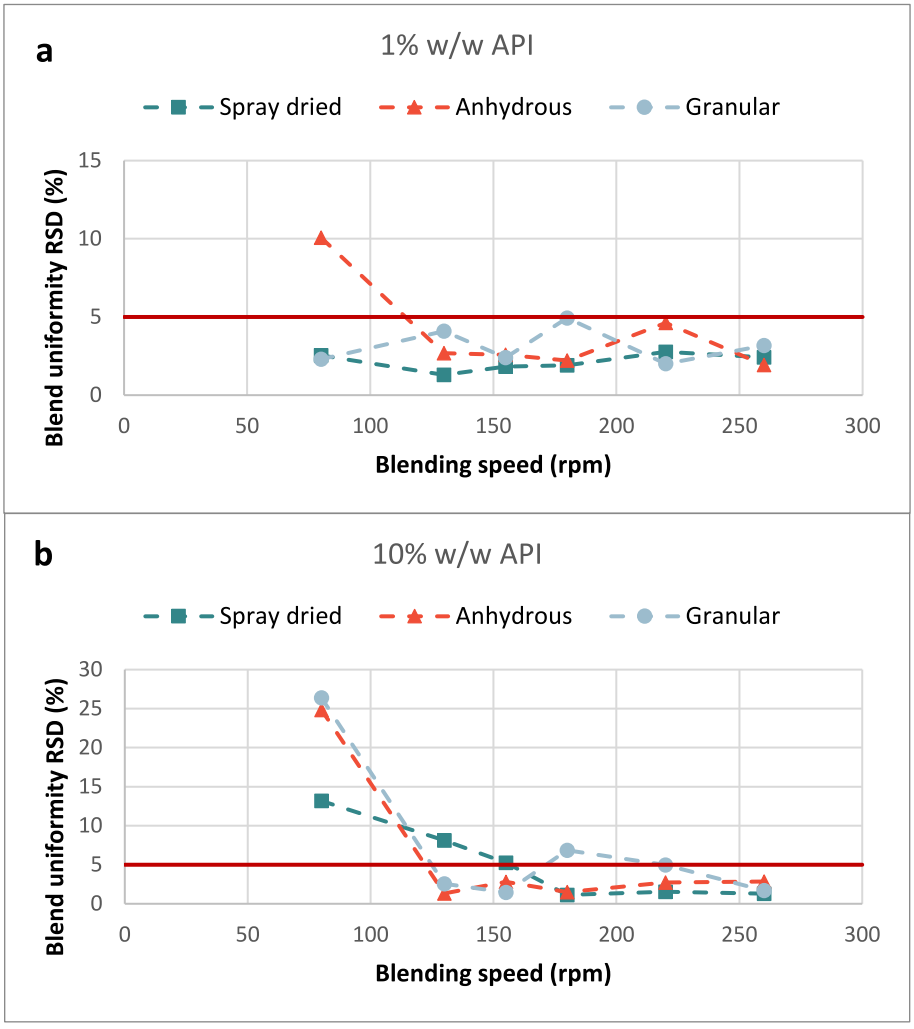

Fig. 4. Blend uniformity results of the API-excipient blends at the endpoint of the mini-blending process after 750 blender revolutions. (a) Blend uniformity results for the low-dose formulations with 1% *w*/w API and (b) blend uniformity results for the medium-dose formulations with 10% w/w API.

lactose, which are all excipients with optimized flowability properties suitable for DC. All three lactose grades show poor uniformity after 90 blender revolutions and a decrease in RSD values upon increasing the number of revolutions, at both 1% and 10% *w*/w API dosage (Fig. 2). This general trend indicates that blend uniformity in the mini-blending process is not sensitive to material properties of the excipients used. This simplifies the optimization of the blending process compared to other batch-wise blending operations, where blend uniformity has been shown to be dependent on powder characteristics (Jaspers et al., 2021; Oka et al., 2017). The robustness of the mini-blending process can be related to the small scale of mixing and the high shear forces generated during blending at high rotational speeds. This results in a high mixing efficiency, similar to a continuous powder blending process, but without the dependency on fluctuations in the continuous dosing of powders into the blender. The absence of feeding fluctuations makes the mini-blending process especially suitable for low-dose pharmaceutical formulations, where accurate dosing of very small amounts of powder is required (Fathollahi et al., 2020; Sacher et al., 2020). Similar to the RSD values, the average label claim values show little dependence on the type of lactose used in the powder blend formulation (Fig. 3).

To compare the effect of increasing blending speed for the three different excipients tested, Fig. 4 shows the blend uniformity RSD value obtained at the endpoint of the mini-blending process after 750 revolutions. For the blends with 1% *w*/w API dosage (Fig. 4a), all blends show an RSD value below 5% except for the anhydrous lactose-based blend prepared at the lowest blending speed. For the spray dried and granular lactose grades, the uniformity obtained at the endpoint shows no dependence on blending speed. The poor blending performance of anhydrous lactose at low blender speed is also indicated by the average API label claim of these blends, which is not close to 100% at 80 rpm (Fig. 3). The different behavior of the anhydrous lactose-based blends is in line with previous results showing shear thinning behavior for anhydrous lactose, whereas the other lactose grades show shear thickening (Janssen et al., 2021). This makes the anhydrous lactose more cohesive at low rotational speeds, resulting in reduced blending efficiency at low shear force. Increasing the blending speed results in similar performance for the three lactose grades, indicating a robust process at high blending speeds. At 10% *w*/w API dosage (Fig. 4b), poor uniformity is obtained at low blending speed for all three lactose grades. Upon increasing the blending speed, all formulations show an improvement in blend uniformity as a result of the increased shear forces generated during blending. At the highest blending speeds, all blends are uniform with RSD values well below 5%. These results highlight again that operating the mini-blender at high rotational speeds results in uniform blends for a variety of excipient formulations. Furthermore, the higher rotational speeds result in a shorter cycle time required to reach a certain number of revolutions. This improved blending efficiency obtained at shorter cycle times demonstrates process intensification of the blending of API and excipients.

3.4. The effect of blender fill level on process performance

An approach to support product development usage of the mini-blender is to vary the blender fill level to minimize material requirements. Due to the limited volume of the mini-blender (10*L*), optimization of both blender fill level and cycle time is crucial to support the commercial throughput of the process whilst minimizing development needs. In the experiments discussed previously, the amount of powder in the blender was kept constant at 4 kg, corresponding to a volume-based fill level of approximately 65%. Since the bulk density of the three lactose grades used is slightly different (Jaspers et al., 2023), the volume-based fill level is dependent on the formulation of the powder blend. Since the lactose grade used in the formulation only has very limited effect on blending performance, the effect of blender fill level was only investigated for formulations based on spray dried lactose with 1% and 10% w/w API dosage. The lowest fill level tested was 0.5 kg, corresponding to a volume-based fill level lower than 10% (Fig. 5a). The maximum fill level tested was 6 kg of material, which corresponds to a volume-based fill level > 95% (Fig. 5b).

Blend uniformity results of the blends prepared at varying fill levels are shown in Fig. 6. For these tests, the blending speed was kept constant at 180 rpm and blend uniformity was analyzed after fixed numbers of blender revolutions. The results indicate that the blending performance of the mini-blender is negatively affected when the blender fill level is too low. At the lowest fill level of 0.5 kg, the RSD values are consistently higher than 5%. Also, blend uniformity shows little improvement upon increasing the number of blender revolutions, indicating poor mixing efficiency. This poor blending performance at low fill level is likely due to the agitator not being able to pick up and move a sufficient amount of powder to have an efficient mixing process. At higher blender fill levels ranging from 1.0 kg to 6.0 kg, blend uniformity is improved. Little effect of the blender fill level on blend uniformity is observed in this range. Only for the blends with low API dosage, blends prepared at 1.0 kg fill level show slightly higher RSD values compared to the higher fill levels. Remarkably, no negative effect on blending performance is observed when the mini-blender is nearly fully filled with powder. At the maximum fill level of 6.0 kg, similar blend uniformity is obtained as at 4.0 kg fill level. The similar mixing performance obtained at fill levels of 1.0 to 6.0 kg indicate a broad operating range for the mini-blender in terms of blender fill level.

Blend uniformity obtained at the endpoint of the blending process is shown in Fig. 7 for the varying blender fill levels. These results clearly indicate an initial improvement in uniformity upon increasing the fill level from 0.5 to 1.0 kg. But further increasing the fill level has very little effect on blend uniformity, as RSD values consistently lower than 5% are obtained at both low and medium API dosage. These results show that the blender fill level can be varied significantly to optimize the throughput of the mini-blending process, without affecting mixing efficiency. This further demonstrates the robustness- of the mini-blending process for mixing API and excipients, which only shows reduced mixing efficiency at extreme process settings (very low fill level or blending speed). The observation that the mini-blending process can be operated close to the maximal blender fill level is also beneficial for the throughput of the process. Maximizing the process throughput can especially be important when the semi-continuous blending operation is combined with continuous downstream processing such as continuous direct compression.

3.5. Throughput calculations of the mini-blending process

Based on the number of blender revolutions required to obtain a uniform blend at a certain rotational speed, the cycle time of the mini-blending process can be calculated. Together with the blender fill

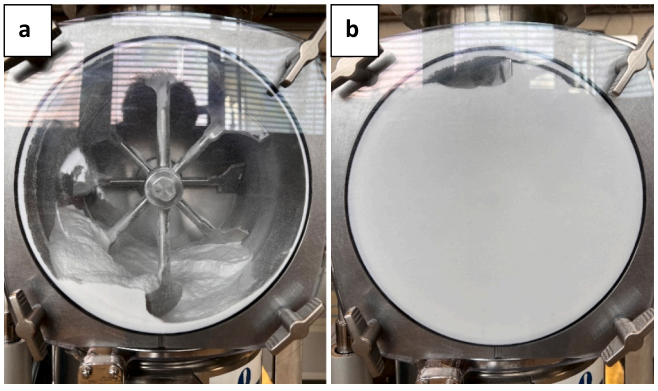

Fig. 5. Pictures showing the mini-blender after the preparation of blends based on spray dried lactose at minimal and maximal blender fill levels: (a) 0.5 kg fill level and (b) 6.0 kg fill level.

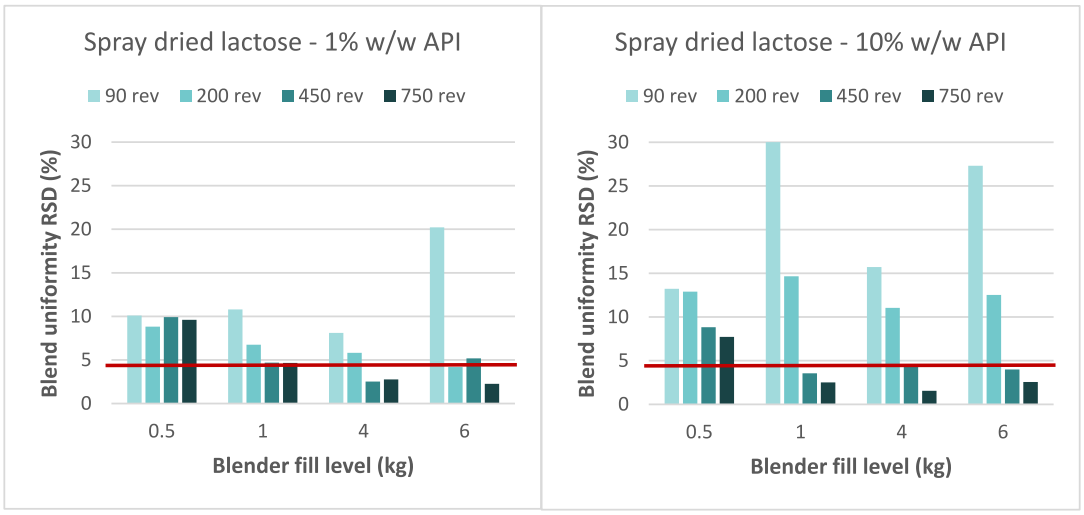

Fig. 6. Blend uniformity results for the API-excpient blends based on spray dried lactose prepared at varying blender fill levels at 180 rpm blender speed. Graphs show the relative standard deviation of the API concentration of the samples analyzed for each blend.

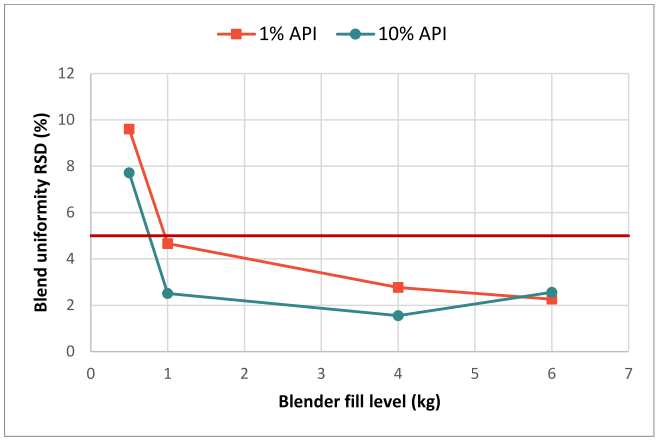

Fig. 7. Blend uniformity results of blends prepared at varying blender fill levels at the endpoint of the mini-blending process after 750 blender revolutions.

level, this cycle time determines the throughput of the mini-blending process when operating in a continuous direct compression line. A complete cycle of the mini-blending process does not only involve the blending step, but also includes the batch-wise feeding of API and excipients into the blender, feeding of a lubricant after the initial blending step, lubrication of the powders through a second blending step and discharging of the powder blend to a tablet press. For the throughput calculations in this study, a fixed time is assumed for the feeding, lubrication and discharging steps based on author's experience. The time required for the initial blending step of the API and excipients is calculated based on the number of revolutions required to obtain a uniform blend (Figs. 2 and 3) and the rotational speed of the mini-blender, according to eq. 1.

Figure 8 shows an overview of the calculated throughput of the process in kilograms per hour, based on the blend uniformity results obtained at varying blender speeds. For these throughput calculations, a blender fill level of 4 kg is assumed, as this was the fill level used in the blending trials performed at varying speeds. For all six formulations tested in this study, the throughput shows an increasing trend upon increasing blending speed. This is due to a reduced number of

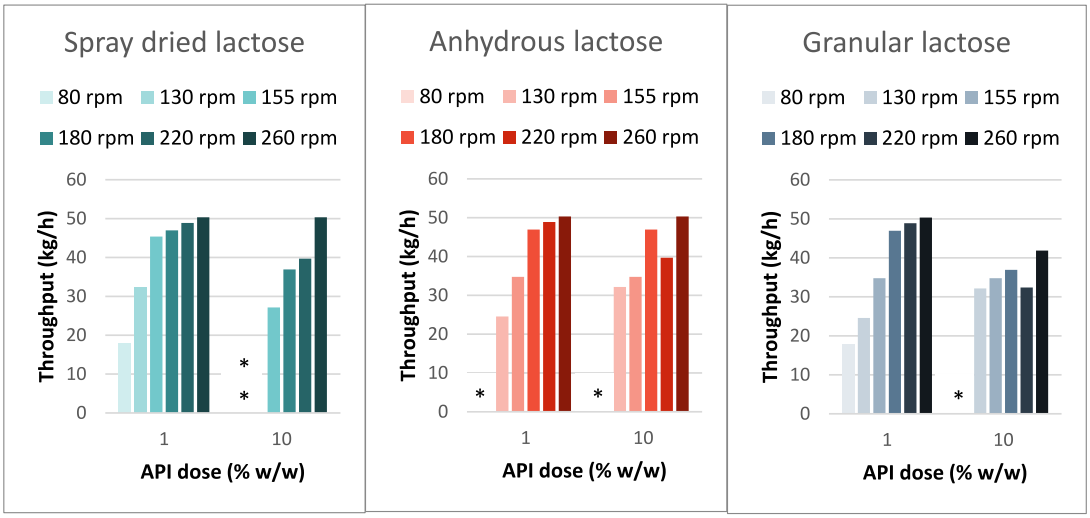

Fig. 8. Maximal throughput of the mini-blending process that can be achieved upon increasing blender speed, while maintaining acceptable blend uniformity. Throughput calculations are based on a blender fill level of 4 kg. * indicates that an acceptable blend uniformity is not obtained within 750 blender revolutions at low blending speed.

revolutions required to reach acceptable uniformity and less time required to reach a certain number of revolutions at higher blending speeds. At the highest blending speed, the throughput of the mini-blending process is close to 50 kg/h for most formulations, corresponding to about 12 blending cycles per hour or a cycle time of about 5 min. At lower blending speeds the throughput of the process gradually decreases. This effect is strongest for the blends with 10% *w*/w API dosage, as these blends require a higher number of revolutions to reach uniformity compared to the blends with 1% w/w API dosage. The throughput of the mini-blending process shows little dependence on the type of lactose used in the formulation, demonstrating the robustness of the process throughput for blends with varying formulations.

The calculated throughput of 30 to 50 kg/h, depending on blender speed, is in line with the common throughput of a continuous direct compression process for pharmaceutical tablets at typical commercial volumes (Holman et al., 2021; Van Snick et al., 2017). This makes the mini-blending process very suitable in combination with continuous tablet compression to support both product development and commercial manufacturing without need for any scale up of blending. Optimization of the mini-blending process in terms of blending speed can reduce the cycle time and thereby improve the throughput of the continuous tableting process. Fig. 9 shows an example of how optimization of the blending step affects the cycle time and resulting efficiency of the tablet compression process. The scenario in Fig. 9a assumes a blending time of three minutes, resulting in a cycle time of seven minutes including feeding, lubrication and blend discharge. Assuming a blender fill level of four kilograms per blending cycle, this results in a throughput of 34 kg/h. Intensification of the blending process by increasing the blender speed can reduce the blending time required to obtain a uniform blend to approximately one minute. The scenario depicted in Fig. 9b assumes a blending time of one minute and a corresponding cycle time of five minutes. This strongly improves the throughput of the process to 48 kg/h, and allows for an increased tableting speed. An alternative approach to reduce the cycle time and optimize process throughput would be reducing the time required to dispense the raw materials into the mini-blender. Optimizing feeding parameters of the gravimetric feeders used for dispensing API and excipients can further reduce cycle time and thereby increase throughput. Further optimization of the throughput of the combined mini-blending and direct compression process can be achieved by varying the blender fill level, which showed little effect on blending performance. By maximizing the fill level of the mini-blender, a maximal throughput of approximately 70 kg/h can be achieved. In this way the throughput of the semi-continuous mini-blending process can be exactly matched with the desired throughput of the continuous direct compression process.

4. Conclusions

The results presented in the current study demonstrate the potential of the mini-blending process for intensification of the blending process of API and excipients. It allows a single blender to support both product development and commercial requirements through a semi-continuous operation, removing the need for blending scale-up steps. In spite of a small blender volume, the short cycle times and high blender fill levels that can be used during operation result in a throughput that is in line with a continuous direct compression process for pharmaceutical tablets. Our results demonstrate that the cycle time and blender fill level can be optimized without compromising on blending performance, as acceptable blend uniformity is obtained over a broad range of blending speeds and blender fill levels. Furthermore, blending performance of the mini-blender is largely insensitive to a range of excipient formulations, when process settings are optimized. This makes the mini-blending process suitable for a variety of pharmaceutical formulations, with varying excipients and API dosage. The combination of semi-continuous mini-blending with continuous direct compression allows for continuous production of tablets with the further benefits of batch-wise dosing and blending of excipients and API. Therefore, the system is particularly suitable for low-dose formulations, where continuous dosing of ingredients is often challenging. The robustness of the mini-blending process, with little impact of the powder formulation on blend uniformity, allows for optimization of the API-excipient formulation for direct tablet compression. Excipient selection can be based on critical material attributes for direct compression processing, such as flowability and

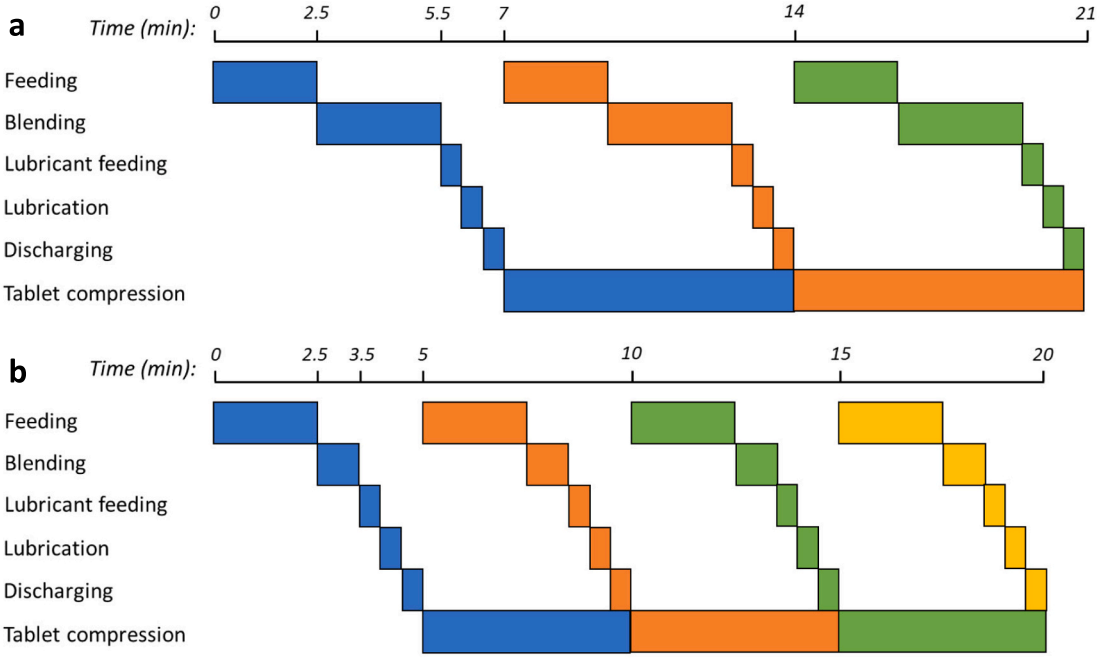

Fig. 9. Schematic overview of the semi-continuous mini-blending process in combination with continuous tablet compression, showing the effect of reducing blending time on process productivity. (a) A blending time of three minutes results in a cycle time of seven minutes for each mini-blend. (b) Optimization of the blending process reduces the mini-blend cycle time to 5 min, thereby increasing the throughput of the continuous direct compression process.

tabletability.

CRediT authorship contribution statement

Maarten Jaspers: Writing – original draft, Visualization, Investigation, Formal analysis, Data curation. **Florian Tegel:** Methodology, Investigation, Data curation. **Timo P. Roelofs:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Fabian Starsich:** Writing – review & editing, Investigation, Data curation. **Yunfei Li Song:** Writing – review & editing, Methodology, Conceptualization. **Bernhard Meir:** Writing – review & editing, Supervision. **Richard Elkes:** Writing – review & editing, Supervision. **Bastiaan H.J. Dickhoff:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

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

Florian Tegel, Fabian Starsich and Bernhard Meir are employees of Gericke, which is the manufacturer of the mini-blender used in this study. If there are other authors, they 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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