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Batch versus continuous blending of binary and ternary pharmaceutical powder mixtures

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ABSTRACT

The material properties of excipients and active pharmaceutical ingredients (API's) are important parameters that affect blend uniformity of pharmaceutical powder formulations. With the current shift from batch to continuous manufacturing in the pharmaceutical industry, blending of excipients and API is converted to a continuous process. The relation between material properties and blend homogeneity, however, is generally based on batch-wise blending trials. Limited information is available on how material properties affect blending performance in a continuous process. Here, blending of API and excipients is studied in both a batch and a continuous process. Homogeneity of the resulting mixtures is analyzed, which reveals that the impact of material properties is very different in a continuous process. Where parameters such as particle size, density and flowability have significant impact on blending performance in a traditional batch process, continuous blending is more robust resulting in uniform blends for a large variety of blend compositions.

1. Introduction

The production process of oral solid dosage (OSD) forms is shifting from traditional batch-wise manufacturing to continuous processing. In a continuous manufacturing process, starting materials are continuously fed while product is continuously removed from the process. If the feed rate and removal rate are equal and thus the mass within the system is constant, the process is in a so-called steady state (Lee et al., 2015). A conventional batch-wise production process consists of separate unit operations such as blending, granulation and tableting. After every unit operation, the product is discharged from the process and stored for off-line quality testing. In a continuous process on the other hand, all unit operations are integrated in one production line without the need to remove the product from the process in between unit operations. Quality testing can be performed in-line, which allows detecting variations in quality attributes in real-time. This can subsequently be used to adjust the process to keep critical quality attributes of the final product within defined specifications (Fonteyne et al., 2015; Vanhoorne and Vervaet, 2020). The drivers for shifting from batch-wise to continuous pharmaceutical manufacturing include an improvement in product quality, a more flexible supply chain and a reduction of scale-up activities, manufacturing costs and carbon footprint (Burcham et al., 2018; Byrn et al., 2015; Schaber et al., 2011; Vanhoorne and Vervaet, 2020).

Although several unit operations used in the production of oral solid dosage forms are inherently continuous, fully continuous production lines are not common yet. An integrated continuous production line for pharmaceutical tablets generally consists of multiple gravimetric powder feeders, a continuous powder blender, optionally a granulation unit, a second blender for lubrication and a rotary tablet press. The initial blending step is required to obtain a homogeneous mixture of the active pharmaceutical ingredient (API) with one or multiple excipients. The blending process of API and excipients is conventionally performed batch-wise by loading the powders in a large vessel, which is tumbled for a fixed amount of time before the blended material is discharged and processed further. It has been shown that particulate materials with large differences in physical properties are challenging to blend homogeneously in such a process. For example, differences in particle size or density can result in segregation and poor blend homogeneity in a batch process (Alexander et al., 2003; Arratia et al., 2006; Khakhar et al., 1997; Shenoy et al., 2015; Tang and Puri, 2007; Yang, 2006). In addition, even the discharge of powders from such a large blender may lead to segregation. In a continuous powder blender on the other hand, the

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residence time of powders in the blender is shorter since the radial and axial dimensions are much smaller. Therefore, mixing time is significantly shortened and components are less likely to separate due to differences in material properties such as particle size and bulk density (Jaspers et al., 2021; Oka et al., 2017). For the blending of API and excipients with varying material properties, this can result in better blend homogeneity and thus improved content uniformity of the active ingredient in the final dosage form. In addition, continuous blending may allow a direct compression (DC) process, where today a granulation step is often used for reasons of segregation.

With the increasing interest in continuous manufacturing for pharmaceutical dosage forms, continuous blending of powders is also gaining attention (Bhalode and Ierapetritou, 2020; Gao et al., 2013; Pernenkil and Cooney, 2006). Most studies on continuous powder blending so far have been focused on varying process parameters and the resulting effects on blending performance (Gao et al., 2011; Järvinen et al., 2013; Palmer et al., 2020; Roth et al., 2017; Van Snick et al., 2017; Vanarase and Muzzio, 2011). Furthermore, theoretical modeling and simulation of continuous powder blending has been a topic of increased interest in recent years (Galbraith et al., 2018; Gyürkés et al., 2020; Toson et al., 2018). The impact of powder material properties on continuous blending performance, however has not been included in most of these studies. Limited information is available on how the physical properties of powders such as particle size distribution, density and flowability affect a continuous blending process. Few studies that have included variations in particulate material properties, did show a significant effect on process performance. For example, the flow properties and bulk density of powders have been shown to affect a continuous mixing process of pharmaceutical excipients and API (Vanarase et al., 2013). Furthermore, the particle size of both excipients and API was shown to have a significant impact on product quality attributes such as content uniformity in a continuous DC process (Lakio et al., 2017).

Whereas the amount of research on continuous powder blending is increasing, blending of API and excipients in the pharmaceutical industry is still largely performed in a batch process. Quite remarkably, little has been published on directly comparing the performance of batch-wise and continuous blending of varying powder formulations. A recent example of such a study described the blending of binary powder mixtures that are prone to segregation due to large differences in particle size or bulk density of the individual components (Oka et al., 2017). It was shown that blends obtained from a continuous process exhibited a higher degree of homogeneity compared to the batch process. The homogeneity achieved in the batch process shows a relation to the difference in particle size and bulk density of the individual components. This relation between powder material properties and blend homogeneity was not observed for the continuous blends. From these results, it was concluded that batch blending is more dependent on the material properties of the components than continuous blending. In a second example, a batch process was directly compared to a continuous DC process for pharmaceutical formulations containing varying API dosages (Karttunen et al., 2019). The authors showed that the continuous process provides better content uniformity of the resulting tablets, except for a low-dose formulation which shows better uniformity in a batch process. A recent study, however suggested that content uniformity of tablets produced via a continuous DC process is not only dependent on the blending process of API and excipients, but additional mixing may occur in the feed frame of the tablet press (Sierra-Vega et al., 2019).

In a previous manuscript, batch and continuous blending were directly compared for binary API-excipient mixtures using three different functional excipients (Jaspers et al., 2021). The results of this study showed that batch-wise blending is more dependent on the type of excipient used, whereas continuous blending results in more homogeneous API-excipient blends for all three excipients investigated. The consistency of the continuous blending process over time, however was strongly dependent on the type of excipient used. Excipients with good flowability showed more consistent blend uniformity over time compared to poorly flowing excipients (Jaspers et al., 2021). In this current study, excipients with excellent flow properties and varying particle morphologies are investigated in both batch and continuous powder blending. Furthermore, the effect of material properties of the API is included in the current study, by making blends with both a poorly flowing, fine API grade and a coarser API grade with better flowability. Since actual pharmaceutical formulations generally contain multiple excipients, the blending of ternary powder blends containing lactose, microcrystalline cellulose (MCC) and API is also investigated here. By varying the material properties and ratios of the excipients used, the most important factors that determine blend homogeneity in batch and continuous blending processes are revealed. The results presented here can be used as guidance to optimize blending performance in both batch-wise and continuous processes, by choosing excipients with appropriate material properties for the desired blending process.

2. Materials and methods

2.1. Materials

Anhydrous lactose (SuperTab® 21AN), milled lactose monohydrate (Pharmatose® 200M), spray dried lactose (SuperTab® 11SD), agglomerated lactose (SuperTab® 30GR) and microcrystalline cellulose (Pharmacel® 101 and Pharmacel® 102) were obtained from DFE Pharma (Goch, Germany). Paracetamol standard powder and dense powder were purchased from Mallinckrodt Inc. (Raleigh, NC, USA) and are used as a model drug in the current study. The paracetamol standard powder was sieved using an oscillatory sieve with a 315 μm mesh before use to remove large agglomerates.

2.2. Powder characterization

Particle size distributions 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. Bulk and tapped density were measured according to Ph. Eur. ($n = 2$). Approximately 100 g of powder was poured into a 250 mL graduated cylinder which was mounted on a tapping device (Engelsmann, Ludwigshafen, Germany). The Hausner ratio was calculated as the ratio of the tapped density and the bulk density. The specific surface area (SSA) of the excipients 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 $P/P_0 = 0.05–0.3$. A ring shear tester (RST-XS, Dietmar Schulze, Wolfenbuttel, Germany) was used to measure the flow function coefficient (ffc, $n = 2$) and the effective angle of internal friction (ϕ_e, $n = 2$). The ffc is defined as the ratio of the consolidation stress and the unconfined yield strength. The effective angle of internal friction is calculated from the effective yield locus. Powders 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. Scanning electron microscopy (SEM) images were recorded using a Phenom ProX scanning electron microscope (Thermo Fischer Scientific, MA, USA). Prior to the measurements, samples were coated with a gold layer with a thickness of 4 nm. Images were recorded at an acceleration voltage of 10 kV and at a magnification of 1500 times.

2.3. Batch blending

Powders were loaded in glass jars with a volume of 2 L. For the binary API-excipient blends, paracetamol was sandwiched between the excipient. For the three-component blends, half of the MCC was loaded into the jar, followed by half of the lactose, paracetamol, half of the lactose and half of the MCC. The jars were filled up to approximately 40% of the total volume. The amount of paracetamol in the blends was

2%, 5%, 10% or 30% *w*/w. The exact composition of the binary and ternary API-excipient blends prepared in this study is given in Table 1. Powders were blended using a low-shear tumble blender (Turbula T2F, Willy A. Bachofen, Basel, Switzerland) at 96 rpm, with a blending time of 1, 5, 10 or 30 min. The corresponding tip speed of the batch blender is ~1.1 m s^{-1}, which is calculated from the distance between the rotational center and the corner of the jar and the rotational speed of the blender.

2.4. Continuous blending

Excipients and paracetamol were fed to a tubular continuous mixer (GCM 450, Gericke, Regensdorf, Switzerland) via separate funnels using gravimetric feeders (GZD 200.12 and GZD 200.22, Gericke, Regensdorf, Switzerland). The total powder feed rate was kept constant at 10 kg/h and the impeller rotation rate was 90 rpm for all blends. The blender impellers were oriented at a 10° forward angle. Product exited the blender over a weir placed at an angle of 90°. The feed rates of the gravimetric feeders were varied to obtain blends with 2%, 5%, 10% and 30% w/w of paracetamol. For the ternary blends, the feed rates of the lactose and MCC feeders were varied to obtain lactose:MCC weight ratios of 3:1, 1:1 and 1:3 (Table 1). The entire exit stream of the blender was sampled for approximately twenty to thirty seconds at four distinct time points, being 1, 5, 8 and 20 min after product started to come out of the blender. In this way, the amount of blended material collected is of similar order of magnitude as the amount of material prepared in the batch blending process. The mean residence time of the material in the continuous blender is in the order of 30 to 60 s, which is calculated based on the holdup mass of the powder inside the blender at steady state and the throughput of 10 kg/h. This residence time includes a certain degree of axial mixing, caused by axial dispersion of the particles within the blender, which dampens short time fluctuations in the feed rates of the powders. The entire powder stream exiting the blender was collected directly in pouches, which were packed tightly and free from air to prevent further mixing or de-mixing of the powders.

2.5. Blend uniformity analysis

Blend uniformity was quantified by determining the paracetamol content of fifteen samples for the binary API-excipient blends and twenty samples for the ternary blends. Samples of approximately 0.25 g, similar to the weight of a single tablet, were taken from distinct locations covering the top, middle and bottom of the bulk mixture as described previously (Jaspers et al., 2021). Individual samples were acquired using a volumetric sampling spoon with a volume of 0.5 mL for the lactose based blends and a volume of 1 mL for the MCC based blends. The sampling method used was the same for blends prepared by the batch process and by the continuous process, in order to avoid issues with differences observed between the two blending processes being related to the sampling process. For the binary API-excipient blends, each sample was dissolved in 100 mL MilliQ water and subsequently diluted to paracetamol concentrations in the range of 10^{-3}–10^{-2} g L^{-1}. For the diluted solutions, UV absorbance was measured at a wavelength of 243 nm using a UV/VIS spectrophotometer (Lambda 25, Perkin Elmer, MA, USA). Samples containing MCC were filtered over a 0.45 µm porous filter prior to measuring to remove insoluble MCC. The UV absorbance was translated to paracetamol concentration using a calibration line. For ternary API-excipient blends, each sample was dissolved in 50 mL MilliQ water. Samples were centrifuged and filtered over a 0.45 µm porous filter to remove MCC. The filtered solutions were measured by HPLC-UV (Zorbax, Agilent, CA, USA), using a mixture of water and methanol (90:10%*w*/w) as the eluent at a flow rate of 0.8 mL/min and a temperature of 30 °C. An injection volume of 5 µL was used for each sample. Content uniformity of a blend is represented by the relative standard deviation (RSD) over fifteen samples for the binary blends and over twenty samples for the ternary blends. The RSD is defined as the ratio of the standard deviation and average paracetamol concentration. The RSD thus represents the API uniformity of the blends collected at each distinct time point for the continuous process and of the blends prepared at different mixing times for the batch process.

Table 1
Composition of the binary and ternary mixtures of API and excipients prepared by batch and continuous blending in this study.

Binary mixtures		Ternary mixtures		
API (% w/w)	Excipient (% w/w)	API (% w/w)	Lactose (% w/w)	MCC (% w/w)
2%	98%	2%	73.5%	24.5%
5%	95%	2%	49%	49%
10%	90%	2%	24.5%	73.5%	
30%	70%	30%	52.5%	17.5%
		30%	35%	35%
		30%	17.5%	52.5%

3. Results and discussion

3.1. Material properties of excipients and API's

To investigate the impact of powder material properties on blending performance, a total of six different excipients and two grades of API are used in both a batch and a continuous blending process. The relevant physical material properties of the powders used in this study are given in Table 2. Four different grades of lactose showing large variations in particle size, particle morphology and flowability are used in this study. The anhydrous lactose grade SuperTab® 21AN is the lactose grade with the largest particle size and has the highest bulk density of all powders used. The milled lactose grade Pharmatose® 200M has a much smaller particle size and therefore shows poor flowability compared to the other lactose grades. SuperTab® 11SD and SuperTab® 30GR are spray dried and agglomerated lactose grades respectively, showing similar average particle sizes. These two lactose grades are specifically designed for a direct compression process and are considered to be free-flowing with ffc > 10. The main difference between the spray dried and granulated lactose grades is the particle morphology, which is spherical for spray dried lactose whereas granular particles are more irregularly shaped. The granular structure can be beneficial for blending with small API particles, as they can adhere to the surface cavities of the granules, preventing segregation. The spherical shape and relatively smooth surface of the spray dried lactose particles results in a much lower specific surface area (SSA) compared to the other lactose grades (Table 2). The different particle morphologies of the spray dried and granular lactose grades is also represented by a difference in the effective angle of internal friction (ϕ_e). The spray dried lactose shows a lower ϕ_e, indicating lower friction between sliding layers of powder due to the more spherical morphology of the particles. The varying morphologies of the excipients used in this study are depicted by SEM images in Fig. 1.

Besides lactose, also two grades of microcrystalline cellulose (MCC) with varying particle sizes are used for blending in this study. The finer MCC 101 grade (Pharmacel® 101) has a median particle size of 60 µm, whereas the coarser MCC 102 grade (Pharmacel® 102) has a median particle size of about 90 µm and therefore shows improved flowability. The bulk density of both MCC grades is much lower than the density of the varying lactose grades. The morphology of the MCC particles is very different from lactose, showing a fibrous structure with a high aspect ratio (Fig. 1e,f). This different morphology results in a larger surface area for MCC. Paracetamol is used as a model API for blending with these excipients. The standard paracetamol grade used here has a relatively small particle size, similar to the milled lactose grade, and shows very poor flowability with ffc = 1.9 and a high effective angle of internal friction. The bulk density of this API grade is similar to MCC and much lower than the different lactose grades. The second grade of paracetamol used has a particle size that is three times larger than the standard grade

Table 2
Physical material properties of the excipients and API used for blending in this study.

Material	Type	Particle sizex50 (μm)	Span (−)	Particle morphology	SSA (m^2/g)	Bulk density (g/cm^3)	Hausner ratio (−)	ffc (−)	ϕ_e (°)
SuperTab® 21AN	Anhydrous lactose	180	2.0	Shards	0.41	0.72	1.27	7.7	39
Pharmatose® 200M	Lactose monohydrate	38	2.8	Tomahawk/ fines	0.78	0.62	1.58	3.7	42
SuperTab® 11SD	Spray dried lactose	115	1.5	Spheres	0.14	0.62	1.21	17	35
SuperTab® 30GR	Granular lactose	106	2.1	Granules	0.39	0.57	1.23	17	41
Pharmacel® 101	MCC 101	60	1.7	Fibers	1.20	0.35	1.42	5.9	44
Pharmacel® 102	MCC 102	91	1.8	Fibers	1.16	0.36	1.31	7.5	40
Paracetamol	API	32	3.2	Needles/fines	–	0.34	1.66	1.9	52
Paracetamol dense	API coarse	96	2.9	Smooth crystals	–	0.63	1.36	4.5	36

and also shows a higher bulk density and improved flowability. The different morphologies of the two paracetamol grades are shown in Fig. 1g,h and the difference in morphology is also reflected by a large difference in ϕ_e. Overall, these grades of excipients and API represent a broad spectrum of physical material properties that are relevant for powders used in pharmaceutical OSD formulations.

The following three sections of this manuscript describe the blending of these excipients with API in both a batch and a continuous process. The first section describes blending of binary API-excipient mixtures of the standard paracetamol grade combined with excipients suitable for a DC process (spray dried lactose, granular lactose and MCC 102). These blends are prepared at varying API dosages and blending times. A similar blending study of binary API-excipient blends of anhydrous lactose, milled lactose monohydrate and MCC 101 has been described in a previous manuscript (Jaspers et al., 2021). The second section describes binary API-excipient blends of the coarser paracetamol grade with six different excipients. The results are compared to the blends of the standard API grade to investigate the impact of changing API particle size and density upon blending with varying excipients. The last section of this manuscript describes the batch versus continuous blending of ternary blends containing lactose, MCC and API. By varying the lactose grade, lactose-MCC ratio and API concentration, the effect of material properties of pharmaceutical formulations on blending efficiency is investigated.

3.2. Batch versus continuous powder blending of binary API-excipient mixtures

A previous study on blending of excipients and API revealed that a continuous process is less dependent on material properties than a batch process (Jaspers et al., 2021). The continuous blending of paracetamol with anhydrous lactose, lactose monohydrate or MCC 101 at varying API concentrations all resulted in good blend uniformity with RSD < 6%. In a batch process on the other hand, blend homogeneity was less consistent and showed a dependence on blending time and type of excipient. To widen the knowledge space in terms of material properties, this section describes the batch and continuous blending of paracetamol with three DC-grade excipients. Blend uniformity is represented by the RSD of the API concentration, as shown in Fig. 2. For all three excipients, blends have been prepared at four different API concentrations. For the batch process, blends have been prepared using four different blending times. For the continuous process the blended material was collected at four distinct time points during the process, but the mean residence time of the material within the blender is the same for the four blends.

For the spray dried lactose grade, very good blend uniformity is obtained in a batch process. All batch blends show an RSD < 4%, except for the blend with the highest API dosage and shortest mixing time of 1 min (Fig. 2a). At this high API dosage, longer mixing times improve blend uniformity as shown by a decrease in RSD. At lower API concentrations varying from 2% to 10% w/w, short mixing times are sufficient to obtain a homogeneous blend. At the lowest API concentration of 2%, no dependence of the RSD on blending time is observed and uniform blends are obtained already after 1 min of blending. This indicates that at this lowest API concentration, deagglomeration of the cohesive API particles is fast and already occurs within 1 min. The good flowability, low internal friction and spherical morphology of the spray dried lactose tends to set up a rolling motion inside the powder bed, which contributes to the de-agglomeration of the API particles. This results in a high number of particle collisions when the powders flow through the tumbling blender, resulting in fast API deagglomeration and efficient mixing. For the intermediate API concentrations of 5% and 10% w/w, a minor effect of varying blending time is observed, but all blends show acceptable homogeneity with RSD values below 4%. Continuous blending of spray dried lactose with paracetamol results in slightly higher RSD's compared to the batch process, both at low and high API dosage (Fig. 2b). This indicates that the batch process is more effective in making uniform blends of spray dried lactose and API than the continuous process used in the current study. These observations are remarkable, as previous blending trials showed a clear benefit of continuous blending for other excipients (Jaspers et al., 2021). It should be noted that optimizing process settings such as impeller speed and configuration could improve the uniformity of blends prepared by the continuous process. The excellent performance of spray dried lactose in a batch blending process is most likely related to the superior flow properties of this lactose grade compared to other excipients, as indicated by a low Hausner ratio, high flow function coefficient and low internal friction (Table 2). This good flowability is related to the spherical morphology of the spray dried particles and results in efficient mixing in the batch process, where the material flows through a tumbled jar. In the continuous blender on the other hand, the powders are mixed through contact forced by the impeller blades, which promotes mixing in a short period of time and shows less dependence on powder properties (Oka et al., 2017). Furthermore, mixing is more efficient due to the smaller scale of the continuous blending equipment, which has a volume of only 0.5 L. Therefore, the superior flow properties of spray dried lactose do not result in more efficient mixing in a continuous process. Even though the good flowability of a spray dried grade can be advantageous for continuous processing in general, this advantage is not observed upon blending with API in this study. The performance of the spray dried lactose grade in the continuous process could likely be improved by optimizing the design of the blender, for example by changing the blade angles or by including blades with a backwards orientation. In the current study, however, the blender design was kept constant for all mixtures with all blades oriented at a 10° forward angle.

The granular lactose grade does show a clear benefit for the continuous blending process (Fig. 2c,d). In batch-mode, several blends show poor uniformity with RSD's up to 10% whereas for the continuous process the RSD is consistently below 5%. Similar to what is observed for spray dried lactose, batch blending with the highest API content requires a longer blending time to obtain a uniform blend. For the batch blends with 30% *w*/w API and shorter blending times, high RSD's are observed due to several individual samples with a too high label claim. This indicates incomplete deagglomeration of API in the low shear batch blending process at this high API concentration. The less efficient

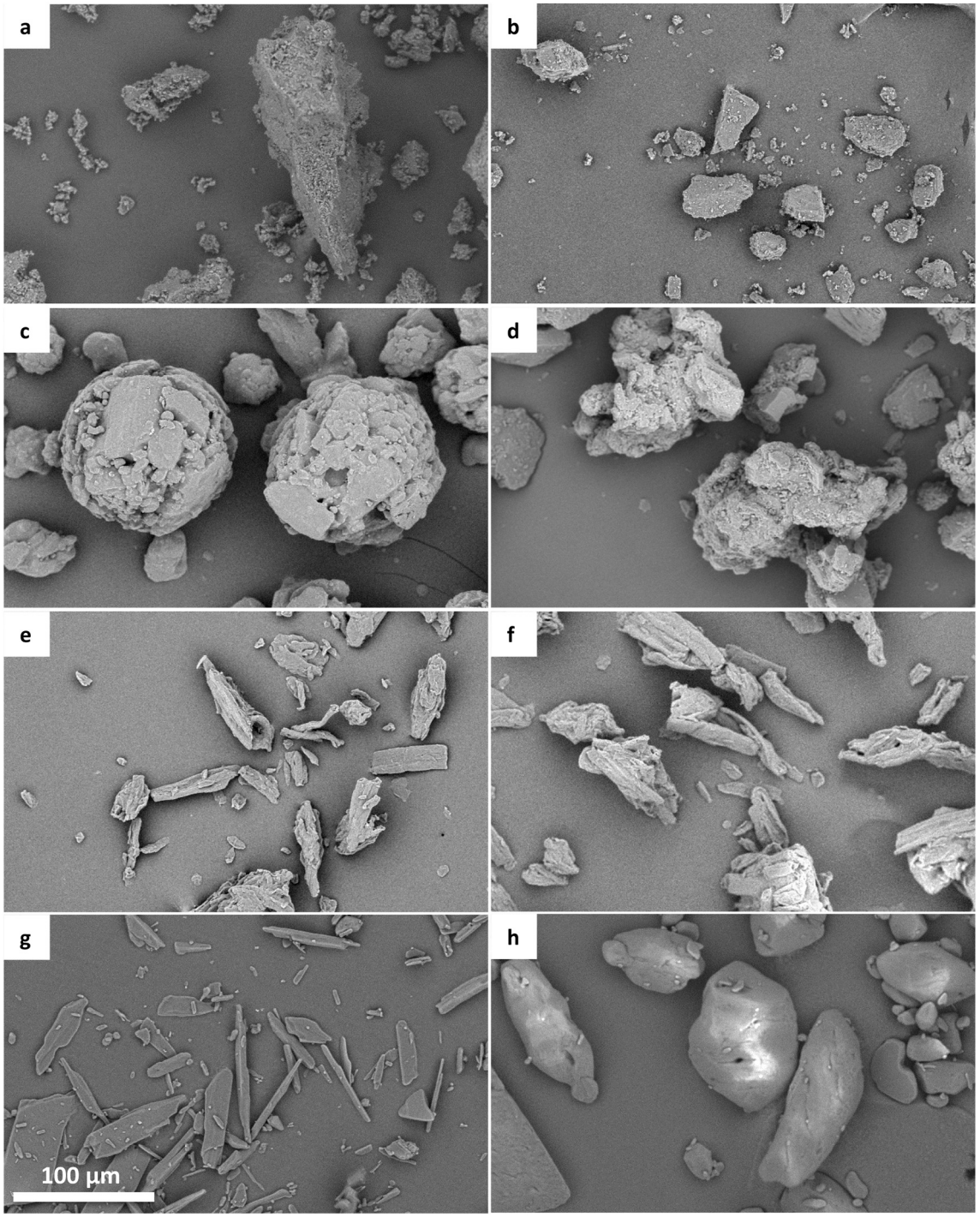

Fig. 1. Scanning electron micrographs of the six types of excipients and two API grades used in this study: a) anhydrous lactose, b) milled lactose monohydrate, c) spray dried lactose, d) granular lactose, e) MCC 101, f) MCC 102, g) paracetamol standard powder, h) paracetamol dense powder. The scale bar represents 100 µm.

deagglomeration of API particles in combination with granular lactose may be related to the irregular morphology and higher internal friction of the granular particles, which reduces the motion of the powder bed in the tumbling blender. For the blend of granular lactose with 2% *w*/w paracetamol on the other hand, the RSD increases for longer blending times. This could be due to adhesive interactions between granular lactose particles and fine API particles that are broken by shear forces during the batch blending process. Compared to the spray dried lactose particles, the granular lactose particles show a more irregular surface which is reflected by a higher SSA value in Table 2. These surface irregularities can promote the adhesion of fine API particles through the formation of multiple adhesive contact points. The formation or breakage of these adhesive interactions between excipient and API particles is dependent on blending time in the batch process. Therefore varying blending time likely has a stronger effect on the RSD for the granular lactose grade compared to the spray dried grade. Continuous blending of granular lactose shows no clear dependence on API concentration or time. For the highest API concentration, however, the RSD values are slightly lower than for lower API concentrations. Such a dependence of the RSD on API concentration would also be expected for ideal random mixtures, where lower concentrations of the minor ingredient will show higher RSD values. These results indicate that the

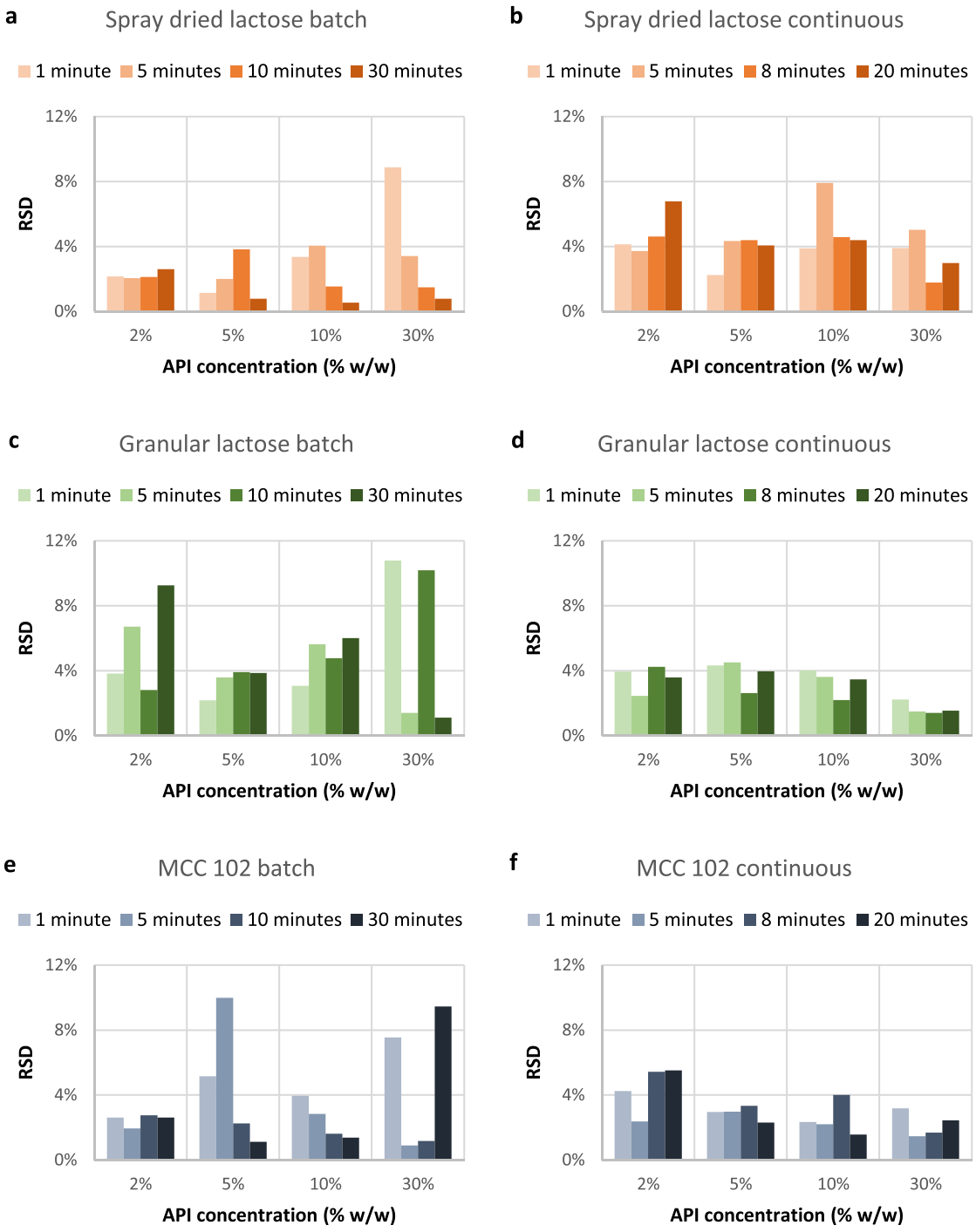

Fig. 2. Blend uniformity represented by the RSD ($n = 15$) for binary powder blends consisting of DC-grade excipients and paracetamol (2%, 5%, 10% or 30% *w*/w). The powder blends are prepared using both batch and continuous blending processes at varying mixing times.

continuous process is especially beneficial at high API content, but also at lower API contents down to 2% *w*/w the continuous process shows improved blend homogeneity compared to the batch process. It should be noted for API contents below 2% w/w, continuous processing may become more challenging due to issues with maintaining a consistent API feed rate. These issues are not observed, however, for the lowest API concentration of 2% w/w used in this study (Fig. S1).

The microcrystalline cellulose DC-grade (Pharmacel® 102) shows similar blending performance as the granular lactose grade (Fig. 2e,f). Batch blending of MCC with paracetamol results in several blends with a high RSD up to 10%. Especially at the highest API content of 30% w/w, several individual samples with a high label claim are observed. This causes high RSD values for the blends with the highest API content and indicates inefficient API deagglomeration in the batch process. The continuous blending is again more consistent with the RSD below 6% for all blends. At the lowest API concentration of 2% w/w, however, the batch process provides better blend uniformity than the continuous process. The continuous blending process again shows the best homogeneity at higher API dosages. These results are in line with a previous study that showed improved content uniformity for a continuous DC process at high API content, whereas a batch process achieved better content uniformity at low API dosage due to challenges with

maintaining a low API feed rate (Karttunen et al., 2019). When comparing the blending performance of the three excipients, the spray dried lactose grade stands out with very good blend uniformity in a batch process but relatively poor homogeneity in a continuous process. As discussed, the good performance in batch blending is likely related to the superior flow properties of spray dried lactose. The slightly higher RSD's observed for the continuous blending of spray dried lactose, however, are more difficult to relate to the excipient material properties. A possible explanation could be found in the lower surface area of spray dried lactose compared to the other excipients, which results in reduced particle-particle collisions during blending and thereby reduces blending efficiency. Alternatively, the large difference in morphology between the spherical spray dried lactose particles and the API particles showing a higher aspect ratio may result in reduced mixing efficiency. The different morphologies are highlighted by the large difference in ϕ_e for spray dried lactose and the API (Table 2). This issue, however, is not observed for the batch process and the reason for the relatively poor performance of the spray dried grade in the continuous blending process is not fully clear yet.

One of the main challenges in achieving good uniformity of content in a continuous process at low API dosage is to maintain a stable feed rate of the API and excipients over time. Previous results showed that the continuous blending of paracetamol with poorly flowing milled lactose (Pharmatose® 200M) resulted in large fluctuations in API content over time (Jaspers et al., 2021). Fig. 3 shows how the API content of the continuous blending process varies over time for the DC-grade excipients with varying API dosages. From this figure, it is clear that the API concentration has a large effect on the stability of the continuous process over time. At low API concentrations, relatively large fluctuations in API content are observed. At the highest API concentration, the API content is much more stable over time for all three excipients. The observed fluctuations in API content over time are likely related to the cohesiveness and poor flow properties of the paracetamol used in this study. This makes a consistent mass flow rate of the API through the continuous process challenging, especially at low dosage where the API feed rate is low. Quite surprisingly, the feed rate variability of the API over time shows very little dependence on API dosage (Table S1, Fig. S1). Even at the lowest API dosage of 2% *w*/w, the feed rate as a function of time is very consistent. For the continuous blending of MCC with the lowest API dosage, however, a small increase in API feed rate at the start of the process (Fig. S1) could be responsible for the high label claim observed for the first data point in Fig. 3. The type of excipient used has little effect on the consistency of the continuous blending process over time. All three excipients tested here show good flowability and also the feed rates used for the excipients are much higher than for the API, resulting in very low feed rate variabilities for the excipients (Table S1). The results presented in Fig. 3 demonstrate that even though a continuous process generally results in better blend uniformity than a batch process, consistent blending of low-dose formulations over time can be challenging in a continuous process.

3.3. Binary API-excipient blends with a coarse API grade

Besides the types and grades of excipients used in a pharmaceutical formulation, material properties of the API will also affect blending efficiency of a formulation. The blending experiments discussed so far were all conducted using the same paracetamol grade, which has a relatively small particle size and is quite cohesive resulting in very poor flowability (Table 2). A common approach to overcome issues with cohesiveness and flowability of an API is to increase its particle size. Therefore, batch and continuous blending trials were performed using a coarser paracetamol grade with an average particle size that is about three times larger than the paracetamol grade discussed so far. Due to its larger particle size, this coarser API grade also has a higher bulk density and improved flowability, as indicated by a higher ffc and lower ϕ_e (Table 2). Binary API-excipient blends with 10% w/w of this coarser API grade were prepared with all six types of excipients depicted in Table 2. Similar to the experiments described previously, blending was performed in a batch and a continuous process using four different mixing times. Blend uniformity represented by the RSD of the paracetamol concentration is shown in Fig. 4.

For batch blending of lactose with the coarse API grade, lower RSD's indicating better blend uniformity are observed compared to the standard paracetamol grade (Fig. 4a). Especially for the spray dried and granular lactose grades, very good blend homogeneity is obtained in a batch process. For the anhydrous lactose and milled lactose monohydrate grade, higher RSD's are observed. These results again highlight the importance of powder flowability in a batch blending process, where the combination of a coarse API with a free-flowing excipient results in optimal blending performance. Furthermore, the bulk density of the coarse API grade is very similar to the density of the varying lactose grades. This minimizes the chance of segregation of lactose and API in a batch process, resulting in good blend homogeneity independent of mixing time. Batch-wise blending of MCC with the coarse API grade on the other hand shows very poor uniformity with RSD's up to 35% (Fig. 4c). These values are much higher than the RSD's observed for

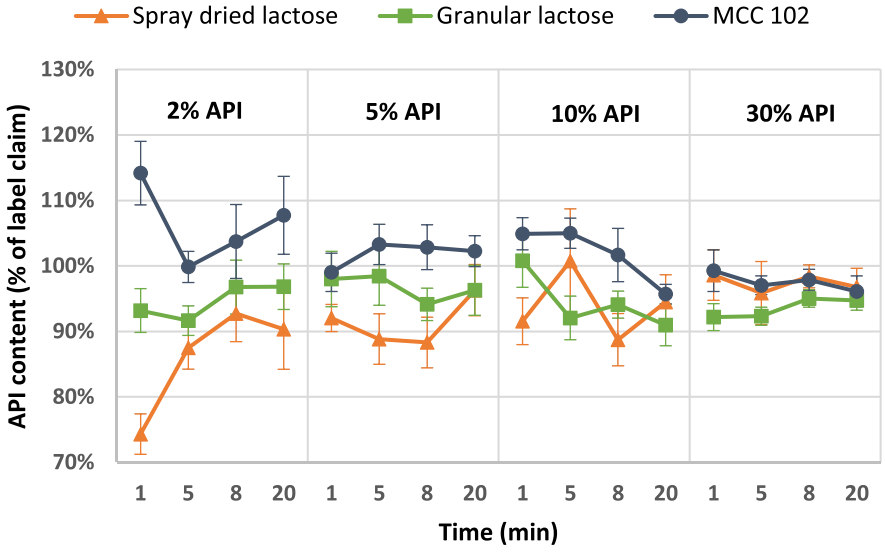

Fig. 3. API content plotted as a percentage of the label claim as a function of time for the continuous blending of DC-grade excipients with varying API dosages.

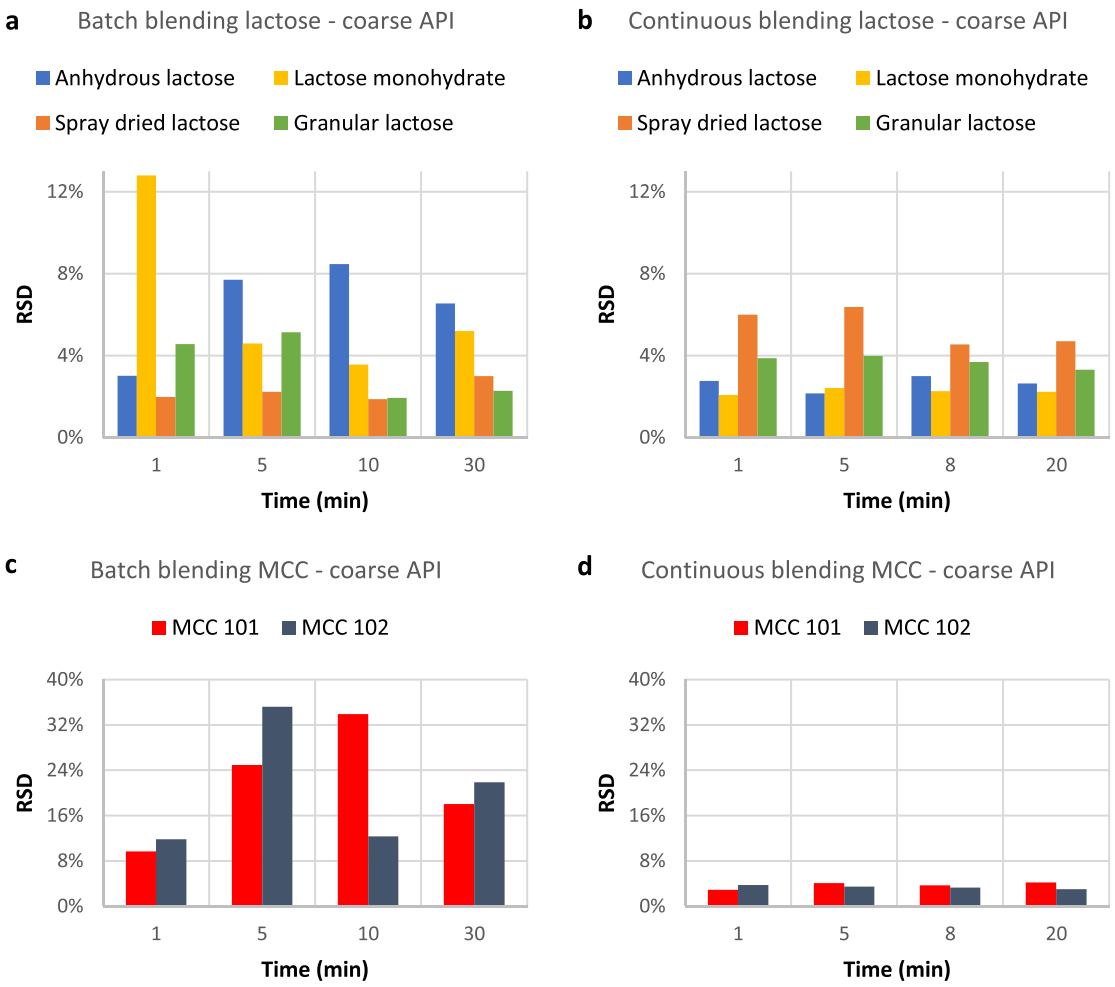

Fig. 4. Blend uniformity represented by the RSD ($n = 15$) for binary powder blends of a coarser paracetamol grade with six different excipient types. Blends were prepared in a batch-wise and continuous blending process at an API loading of 10% w/w.

MCC with the finer API grade (Fig. 2e). A likely explanation for the poor blending of MCC with the coarser API grade is the large difference in bulk density between excipient and API. Previous work on powder blending has shown that large differences in density can results in segregation of the components (Oka et al., 2017; Shenoy et al., 2015; Yang, 2006). The fact that the shortest mixing time of 1 min results in the best blend uniformity also indicates segregation of API and MCC during blending. For the blending of MCC with the finer API grade this effect of mixing time was not observed, since the components have similar bulk densities and therefore do not segregate. These results demonstrate the importance of matching bulk density of excipients and API when using a batch blending process, where random mixtures of materials with varying densities are prone to segregation.

Continuous blending of the coarser API grade with varying excipients results in low RSD's in the range of 2–4% for most excipients (Fig. 4b,d). These values are similar to the values obtained for continuous blending of the standard API grade with varying excipients. The feed rate variability data for the continuous blending of the coarse API grade with varying excipients is given in the supplementary information (Fig. S2, Table S2). The coarser API grade shows a lower variability in the feed rate over time compared to the finer grade, which is related to the difference in flowability between the two paracetamol grades. Compared to the batch process, much better blend uniformity is obtained in the continuous process for MCC in combination with the coarse API grade. Since the risk of segregation in a continuous blending process is much lower (Oka et al., 2017), the large density difference of excipient and API is no issue here. For lactose, the difference in blend uniformity between the two blending methods is much smaller than for MCC. This is mainly due to the lower RSD's obtained in a batch process for lactose in combination with the coarser API grade. Although variations in blend uniformity between the different grades of lactose are small in a continuous process, the spray dried lactose stands out with a consistently higher RSD (Fig. 4b). This observation is in line with the results of the standard API grade, where spray dried lactose also shows relatively poor blend uniformity in the continuous process (Fig. 2b). As discussed in the previous section, possible explanations for the different performance of spray dried lactose could be found in the spherical morphology and low surface area of the spray dried particles.

The blending results with a coarser API in combination with varying excipients reveal that improving flowability by increasing API particle size has a large effect on a batch blending process. Fig. 5 shows a direct comparison between the blend homogeneity obtained for the fine and coarse API grades, where a negative value corresponds to a decrease in RSD upon increasing API particle size. For the batch process, large differences are observed between the two API grades whereas differences are much smaller for the continuous process. This indicates that increasing the particle size of the API has little effect on blending performance in a continuous process. The small increase in RSD observed for coarser API particles in the continuous process is expected according to theory of random mixtures, where increasing particle size reduces the number of particles present of the minor component. Clearly no improvement in blend uniformity upon increasing API particle size is observed in the continuous blending process, except for one data point of lactose monohydrate which showed an unusually high RSD for the

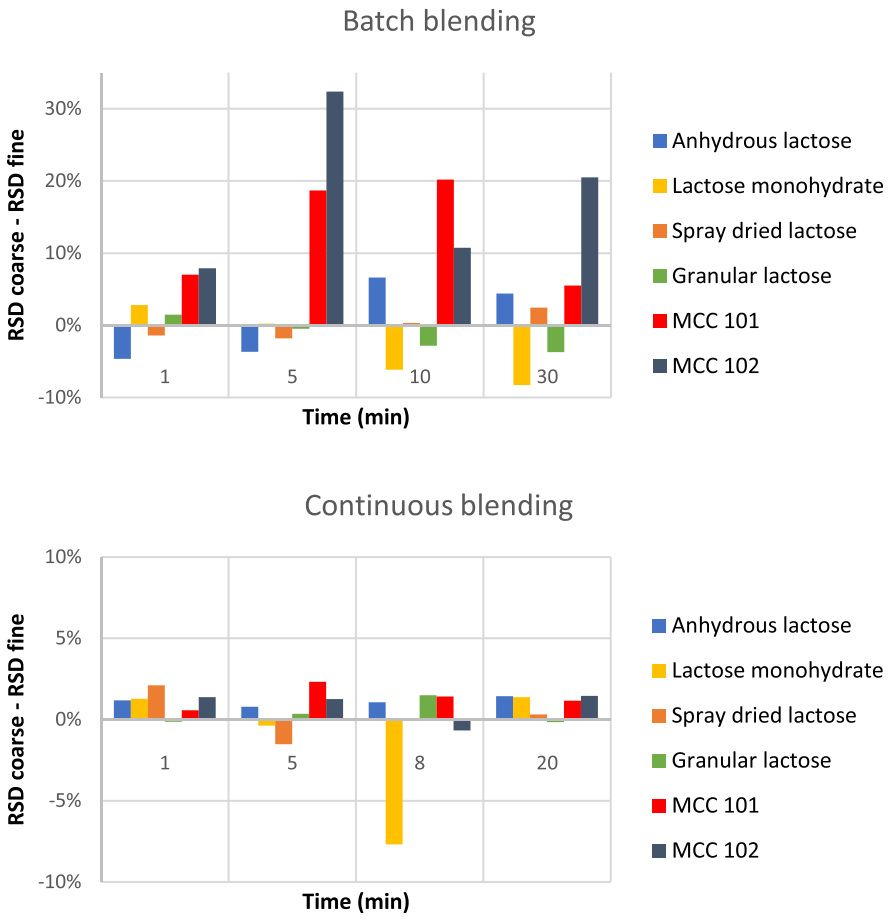

Fig. 5. Comparison of blend homogeneity for API-excipient blends with a coarse and a fine paracetamol grade. Values shown represent the difference in RSD obtained for blends prepared with both API grades, where a negative value corresponds to a decrease in RSD upon increasing API particle size. Results are shown for a batch blending process (top graph) and a continuous blending process (bottom graph).

fine API grade. For the batch process, the large differences observed for the two API grades can be related to the bulk density of the individual components. When the difference in density between API and excipients is large, a batch blending process results in segregation rather than mixing, as shown for the blending of MCC with the coarse API grade. For such combinations of materials with large density differences, a continuous blending process is much more efficient as it is less dependent on powder material properties. The type of excipient used, however does have some effect on blend uniformity in a continuous process, where especially the spray dried lactose grade shows a deviation from the other excipient grades studied here.

3.4. Batch versus continuous powder blending of three-component powder mixtures

The results presented in the previous sections provide insights in the effect of material properties on blending of API with a single excipient. In practice, however, pharmaceutical formulations for oral solid dosage forms generally contain multiple excipients. To optimize the compressibility of a tablet formulation, often a combination of brittle and plastically deforming excipients is used (Al-Ibraheemi et al., 2013; Govedarica et al., 2012). In order to mimic the blending of such a formulation, ternary blends containing lactose as a brittle excipient, MCC as plastic excipient and paracetamol are prepared. The lactose grade used in these ternary blends is varied between the four grades discussed previously: anhydrous, milled, spray dried and granular lactose, which all show different particle morphologies. The MCC grade used is MCC 101 for all blends and the paracetamol grade with an average particle size of 32 μm is used as API. Blends are prepared both at a low API dosage of 2% w/w and a high API dosage of 30% w/w. The lactose-MCC ratio is varied from 25% to 75% MCC of the total amount of excipient. As a comparison, also binary API-excipient blends with only lactose or MCC as the excipient are included in this section.

Fig. 6 shows how blend uniformity of three-component mixtures depends on its composition and the blending method. For the batch process, two different blending times of 1 min and 30 min were used. For the continuous process only one time point was evaluated, since no time-dependence was observed for the continuous blending of binary mixtures. Feed rate variability values for the lactose, MCC and API feeding are given in Table S3 in the supplementary information. But since the continuous blending of the ternary mixtures was only evaluated at a single time point, variations in feed rate will likely have little effect on blend uniformity. For batch blending of anhydrous lactose with MCC and API, very high RSD's are observed indicating poor blend homogeneity. Especially batch blends with low API dosage show poor uniformity, with an RSD of 68% for a 1:1 ratio of lactose and MCC and a blending time of one minute (Fig. 6a). Also at a higher API dosage of 30%, ternary blends of anhydrous lactose and MCC show higher RSD's than the binary blends (Fig. 6b). For the continuous process on the other hand, the ternary blends show very good homogeneity. The observed RSD's are even slightly lower than for the binary blends, both at low and high API dosage (Fig. 6a,b). A likely explanation for the poor uniformity of the batch blends is the large difference in material properties for anhydrous lactose and MCC. The bulk density of anhydrous lactose is more than two times higher than for MCC and the average particle size is three times higher. Previous research has shown that powders with large

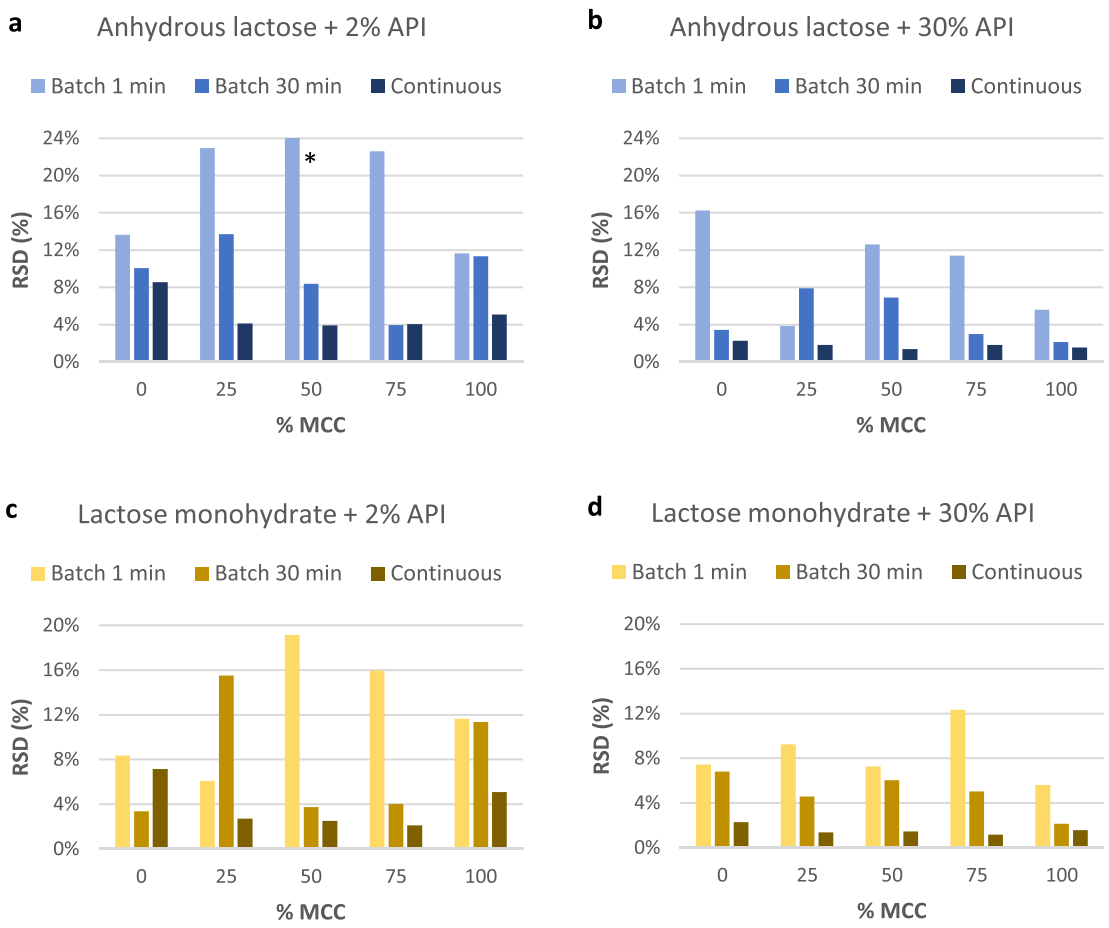

Fig. 6. Blend uniformity represented by the RSD ($n = 20$) for three-component powder blends of lactose (anhydrous or monohydrate), MCC and paracetamol (2% or 30% w/w). Blends are prepared by 1 min batch mixing, 30 min batch mixing and continuous mixing. The sample marked with * corresponds to an RSD of 68%.

differences in particle size and bulk density are challenging to blend in a batch process, whereas in a continuous process more uniform blends are obtained (Oka et al., 2017). So the mismatch in material properties between anhydrous lactose and MCC results in poor homogeneity in a batch process, whereas for a continuous process this is no issue. Ternary blends of milled lactose monohydrate, MCC and paracetamol show a similar difference between a batch and continuous blending process (Fig. 6c,d). For the batch process, relatively high RSD's are observed for ternary blends compared to binary blends. Homogeneity of blends with lactose monohydrate, however, is better than for blends with anhydrous lactose because of a smaller difference in particle size and bulk density between the two excipients. For the continuous process again very good blend uniformity is obtained at both low and high API dosage. These results highlight that the continuous process is less sensitive to the number of components to be blended and their material properties.

Blend uniformity of ternary mixtures containing spray dried lactose or granular lactose is depicted in Fig. 7. For these lactose grades, the difference between batch and continuous blending is not as pronounced. For the ternary blends of spray dried lactose with a low API dosage (Fig. 7a), the batch process results in more uniform blends than the continuous process. The batch blends show low RSD's, even at a blending time of 1 min. This indicates that batch blending is much more effective than for the ternary blends containing anhydrous lactose or milled lactose. The continuous blends with spray dried lactose consistently show an RSD of 5–6%, independent of MCC content. At high API content, both batch and continuous blending results in low RSD's (Fig. 7b). At a blending time of 1 min, higher RSD's are observed, but increasing the blending time resolves this issue. Again the RSD of the continuous blends is very consistent and independent of the lactose-MCC ratio. These results are in line with the binary API-excipient blends of spray dried lactose, which also show good homogeneity in a batch process and no advantage of using a continuous process. For the ternary blends containing granular lactose, the continuous process does show improved blend uniformity compared to the batch process (Fig. 7c,d). At low API dosage, the difference is relatively small but at higher dosage there is a clear benefit for the continuous process. For the batch process, increasing the number of excipients again results in an increase in RSD as was also observed for the anhydrous and milled lactose grades. For the continuous process, blend uniformity is independent of the number of excipients and also the lactose-MCC ratio has little effect on blend homogeneity.

These results demonstrate that blend uniformity in a batch process is highly dependent on the type and number of excipients in a formulation. Especially when material properties such as particle size and bulk density of the individual components are not matched, obtaining a homogeneous blend is challenging. For the continuous process on the other hand, increasing the number of excipients does not affect blend uniformity. Fig. 8 gives an overview of the continuous blending results of ternary API-excipient mixtures, showing the RSD (Fig. 8a,b) and the average label claim (Fig. 8c,d) for the different blend compositions. The RSD shows similar values for all lactose grades, but a clear difference is observed at low or high API concentration. For blends with 2% w/w API, the RSD is in the range of 3 to 8%, whereas at 30% API dosage all RSD's are below 3%. This indicates that a continuous blending process is especially beneficial at higher API dosages. The effect of the API concentration is further demonstrated by the average API content of the blends, shown as a percentage of the API label claim in Fig. 8c and d. At low API concentration, relatively large variations in API content are

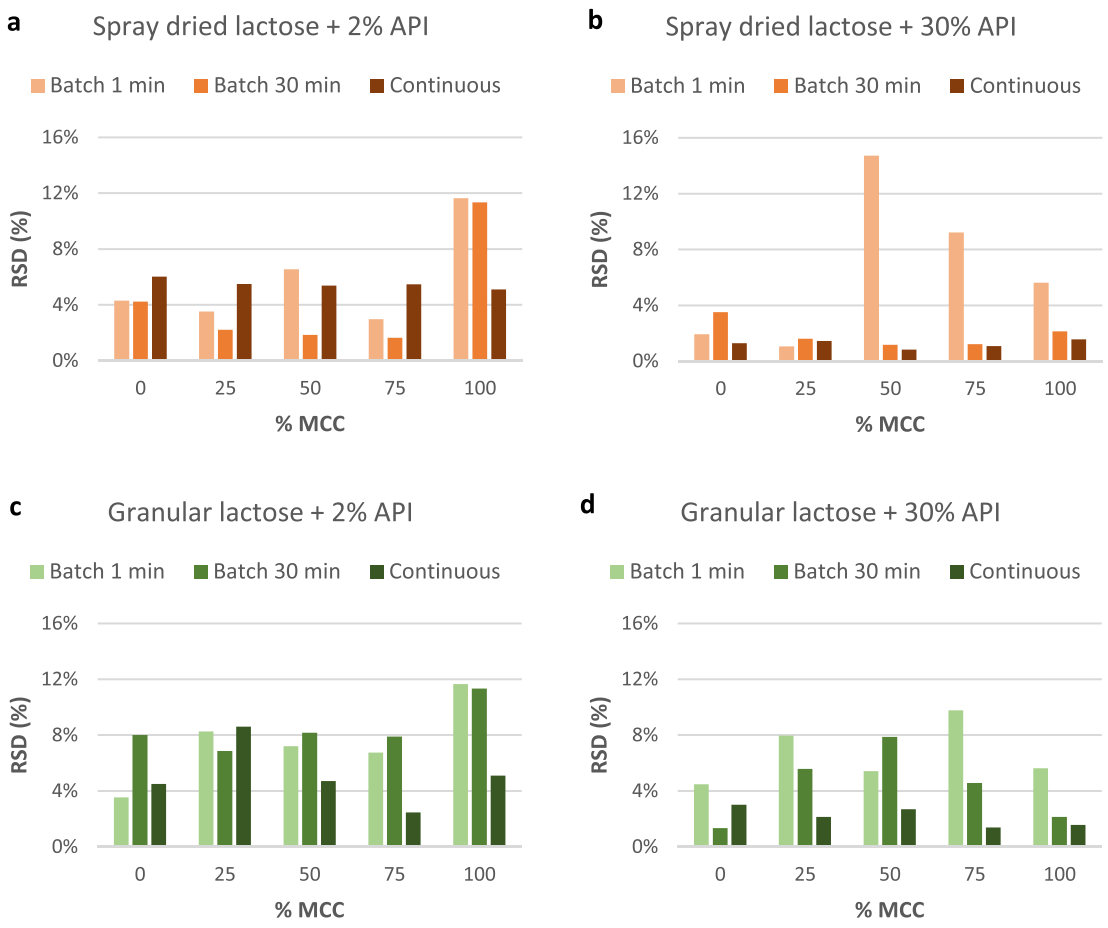

Fig. 7. Blend uniformity represented by the RSD ($n = 20$) for three-component powder blends of lactose (spray dried or granular), MCC and paracetamol (2% or 30% w/w). Blends are prepared by 1 min batch mixing, 30 min batch mixing and continuous mixing.

observed for the varying blends whereas at high dosage, API content is much more consistent. These variations in API content are related to the consistency of feeding of excipients and API over time. It has been shown that the feeding consistency of powders is dependent on powder flow properties, where good flowability results in more consistent feeding (Bostijn et al., 2019; Wang et al., 2017). Since the paracetamol grade used in these blends shows poor flowability, consistent dosing is challenging especially at low dosage where small variations in feeding accuracy have a large effect on API content of the resulting blends. At higher API content these variations have a relatively small effect, resulting in values close to 100% for the API label claim for all binary and ternary API-excipient blends. In combination with the low RSD's observed, this demonstrates the capability of a continuous process to accurately blend a variety of excipients with a high API dosage.

4. Conclusions

The shift from batch to continuous manufacturing of oral solid dosage forms requires redesigning the blending process of excipients and API. Where the factors that determine blend homogeneity and segregation in a batch process have been studied extensively, limited data is available on continuous powder blending of pharmaceutical powder formulations. The results presented in this manuscript show that the effect of excipient and API material properties on blend homogeneity cannot simply be translated from a batch process to a continuous process. In a batch process, matching the physical material properties of the individual components or reducing the number of components is required to optimize blending performance. Especially the bulk density of excipients and API should be similar, to prevent segregation resulting in poor blend uniformity. Furthermore, powder flow properties have a large impact on blending efficiency in a batch process, where excipients with improved flowability and lower internal friction result in better mixing. In general, careful selection of excipients based on API characteristics is required to produce a homogeneous batch blend. In a continuous blending process, however, these criteria for obtaining a homogeneous blend are not applicable as the impact of powder material properties is much smaller. The continuous blending of excipients and API with large differences in physical material properties is not problematic and the choice of excipients has relatively little effect on blending performance. Also increasing the number of excipients is no issue, with ternary blends showing similar uniformity as binary blends. The sensitivity to segregation for the batch process observed in this study, has been found in a relatively small laboratory scale blender. It can be assumed that for large commercial scale blenders with related intermediate storage of material, the overall sensitivity to segregation will even increase. The results of the continuous process on the other hand are already established at an industrial pharmaceutical scale. The limited effect of excipient material properties on blend uniformity presents a clear benefit for continuous processing. The choice of excipients in a formulation can therefore be focused on their functional properties such as compactability or flowability without significantly affecting blending performance.

Where the continuous process results in homogeneous blends for all types of excipients tested here, the spray dried lactose grade does stand out with a consistently lower degree of blend uniformity. Although the exact cause for this observation is not clear, it does show that there is some effect of material properties on continuous blending performance. This effect is most likely related to the morphology of the particles to be

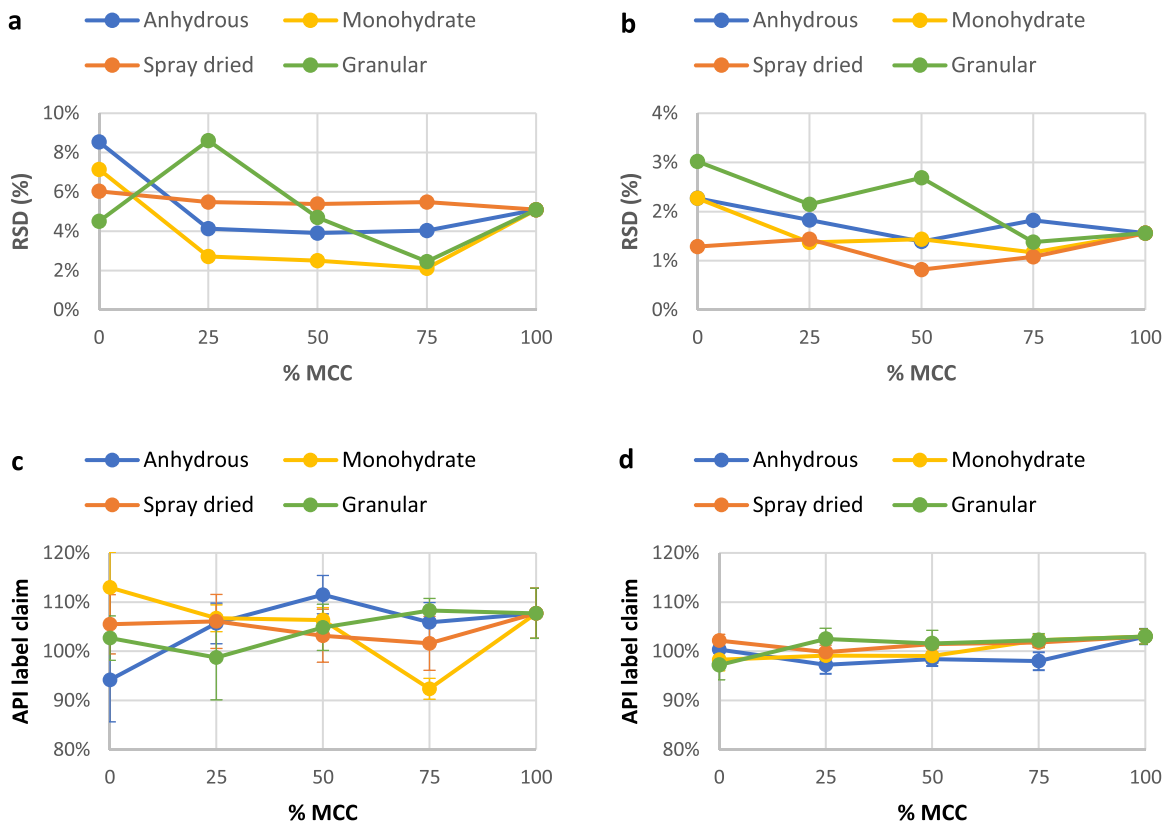

Fig. 8. Overview of blend uniformity for ternary blends with varying lactose/MCC ratios mixed in a continuous process. a) RSD for blends with 2% w/w API. b) RSD for blends with 30% w/w API. c) Average label claim for blends with 2% w/w API. d) Average label claim for blends with 30% w/w API.

blended, where the spherical shape of spray dried particles is very different from the morphology of the API particles used in this study. It has been shown previously that particle morphology has an effect on powder mixing and segregation, where more irregularly shaped particles are less likely to segregate than particles with a low specific surface area. (Wong and Pilpel, 1990) The spherical shape and low surface area of spray dried particles may therefore result in some segregation from the API particles upon collecting the material from the continuous blender. Besides the particle morphology, also the API content of the blends has an impact on continuous blending performance. At higher API concentrations, lower RSD values are obtained for both binary and ternary API-excipient mixtures. Furthermore, the blends with low API content show larger deviations from the expected label claim, which indicates that maintaining a consistent flow rate over time at low API dosage is more challenging. A possible way to overcome such challenges would be to make a pre-blend of the API with part of the excipient. This would, however require a combination of batch and continuous blending for low-dose formulations. Alternatively, improving API flowability by increasing its particle size results in a more controlled feeding process. For formulations with a higher API dosage this is not required, as the continuous process results in uniform blends with a consistent API content. Such high-dose formulations are often more difficult to handle in a batch process, due to the poor flow properties of most API's. Overall, the results presented here show that continuous powder blending is a very robust process that is suitable for a large variety of pharmaceutical excipients. This greatly reduces the complexity of excipient selection for the continuous manufacturing of oral solid dosage forms.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpx.2021.100111.

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