Effects of processing parameters and blade patterns on continuous pharmaceutical powder mixing

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Abstract

The present study summarizes the experimental characterization of a new continuous powder mixer (GCG-70 by Glatt®) using common pharmaceutical ingredients. The powder hold-up and residence time distribution were used to characterize the bulk behavior of the mixer as a function of impeller rotational speed, total throughput (mass flow rate) and blade configuration. The relative standard deviation (RSD), calculated from samples taken at the outlet of the blender, was used to characterize its mixing performance. The hold-up and the mean residence time decreased with increasing impeller rotational speed. The mean centered variance and the number of blade passes increased with increasing impeller rotational speed. The effect of the blade configuration on the mixing dynamics diminished as the rotation rate increased. The hold-up and mean residence time were sensitive enough to demonstrate the effects of blade configurations. The mixing performance, depending on the processing parameters, was found to be between 5% and 10% RSD for 5% w/w active pharmaceutical ingredient (API), and < 3% for 30% w/w API. These results showed improvements in the mixing performance when compared to studies of other continuous mixers using similar materials and analytical techniques for quantification.

Keywords: powders, continuous mixing, blade configuration, pharmaceuticals

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1. Introduction

Powder mixing is a critical manufacturing step in several industries, including pharmaceuticals, cosmetics, chemicals, food and minerals. Especially in the pharmaceutical industry, powder mixing is often carried out in batches. Therefore, batch powder mixing has been characterized more extensively than continuous powder mixing. In recent years, a strong initiative by the pharmaceutical industry and its regulatory agencies to understand, design and control more robust manufacturing processes, leading to high quality finished products, has led to growing interest in continuous processing [1].

Continuous processing offers several advantages over conventional batch processing [2,3]. These advantages include the opportunity for more meaningful implementation of process analytical technologies (PAT) and the use of modeling techniques for automated process control to maintain the required steady state and make finished products with sustained quality [4]. With continuous manufacturing, the same equipment used for process development can often be used in manufacturing. Therefore, the need for process scale up is reduced or eliminated, accelerating the introduction of new products to market. These advantages also include significant reductions in equipment size and the ability for integration with other continuous processes (e.g. tableting, capsule filling, roller compaction). Integration with an intrinsically continuous process would yield higher process efficiency and minimize segregation of the mixed materials. Moreover, because a continuous process can achieve a desired set point after a transient period of just a few minutes, entire sets of designed experiments can often be explored in a matter of just a few days, with great savings in materials, time and money. Overall, the advantages of continuous processing can significantly reduce costs during development and manufacturing of pharmaceuticals.

Continuous powder mixing equipment has been characterized both experimentally [5–11] and computationally [12–16] in the past few years. Such studies have described the mixing behavior and performance of continuous mixers as a function of design parameters, processing parameters and ingredient material properties. Design parameters include the impeller type and configuration [8,9,11], the outlet weir angle [8] and the mixer elevation angle [11]. Processing parameters include the impeller rotational speed and the total and individual flow rates (mass concentration) of the components [5,7–10]. However, only a few commercially available continuous powder mixers have been discussed in the literature. Marikh *et al.* studied and developed correlations for hold-up as a function of rotation rate for a continuous mixer (GCM-500 by Gericke with a length to diameter ratio (L:D) of 2.5) [10]. In a different study, using the same continuous mixer, Marikh *et al.* investigated the effect of impeller types on hold-up and mixing performance [9]. It was reported in both studies that mixing performance improved with increasing rotation rate and then worsened at higher rotation rates due to the change in mixing regimes (fluidization). Portillo *et al.* reported the characterization and comparison of two continuous mixers (GEA Buck Systems with L:Ds of 4.9 and 6.2) with the same design but different sizes [6,11]. In these studies, it was found that lower impeller rotation rates and a greater upward mixer elevation angle yielded enhanced mixing performance. Vanarase and Muzzio studied the effect of operating conditions and design parameters in a continuous powder mixer (GCM-250 by Gericke with an L:D of 3.0) [8]. It was found that the total strain that the powder experienced in the continuous mixer had a maximum at intermediate rotation rates also yielding better mixing efficiency. In our previous work, we examined the mixing behavior of the same continuous mixer (GC-250 by Gericke) using several pharmaceutical excipients differing

1 in particle size and flow properties. It was found that although the material properties affected
2 mixing behavior, the predominant variable was still the impeller rotation rate [7].

3 Most of the continuous powder mixers characterized and reported in the literature were not
4 designed for pharmaceutical applications, but rather for food applications. In an effort to advance
5 the understanding of continuous powder mixing and processing as a whole, a new commercial
6 continuous powder mixer (Glatt GCG-70) - designed for pharmaceutical processing - was
7 considered in this study. The main objective of this study was to characterize the mixing
8 dynamics and performance of a Glatt GCG-70 using pharmaceutical powders. Contrary to liquid
9 mixers such as stirred tanks, where dozens of impeller geometries have been studied, very few
10 studies of the effects of impeller geometry on mixer performance have been reported for powder
11 mixers. Thus, in this study, the effects of blade configurations on mixing dynamics and
12 performance were studied as well.

13 2. Materials and Methods

14 2.1. Materials

15 Materials used in these studies are listed in Table 1. Silicified microcrystalline cellulose
16 (Prosolv HD 90) was used for the mixing dynamics and performance characterization, presented
17 in subsection 5.1. Microcrystalline cellulose (Avicel® PH 200) was used for the blade
18 configuration studies, presented in subsection 5.2. Magnesium stearate (MgSt) was used as the
19 instantaneous pulse material to characterize residence time distributions. Semi-fine
20 acetaminophen (APAP) was used to characterize the continuous mixing performance.

2.2. Continuous Mixing

A new commercial continuous mixer (GCG-70, Glatt®), designed for pharmaceutical processing, was used in all the experiments presented in this article. The GCG-70 is 70 cm long and 8 cm in diameter (with an L:D of 8.75). The mixer and experimental set-up are shown in Figure 1. Two gravimetric feeders (Model AP300, Schenck Accurate) were used to feed the raw materials using the configurations described in Table 2. The selection of the screw type and nozzle size was based on previous experience, and it was dependent on the required flow rates and the cohesion of the individual components used, to minimize feeding variability.

2.3. Sampling and Near-Infrared Analysis

Stream sampling at the outlet of the continuous mixer was used. Samples were collected in 20-mL scintillation vials (Fisher Scientific) at different time intervals for the residence time distribution and blend uniformity measurements. Powder samples were analyzed in the vials using diffuse-reflectance near-infrared (NIR) spectroscopy. A Nicolet Antaris FT-NIR spectrometer (Thermo Electron) was used. The instrument measured the spectrum in the range of $4,000\text{ cm}^{-1}$ to $10,000\text{ cm}^{-1}$ wave numbers. Spectral data was collected using the software “Omnic.” Calibration samples were prepared in 20-mL scintillation vials in a vortex mixer (Fisher Scientific). The software “TQ Analyst” was used for calibration model development and quantification of the samples collected. Calibration samples were prepared by weighing 500 mg of mixture into the scintillation vials using an Ohaus Explorer analytical balance with an accuracy of $\pm 0.01\text{ mg}$. In all cases, the regression method used was partial least squares (PLS). The description, including the materials of interest and the concentration ranges, of the NIR calibration models used is summarized in Table 3.

3. Mixing Characterization

3.1. Hold-up

The powder hold-up (Equation 1) is the amount of mass accumulation in the continuous mixer. The hold-up was measured by monitoring the mass of the powder being fed to the mixer and the mass of powder collected at the outlet of the mixer. The difference between the amount of powder being fed and the amount of powder collected at the outlet of the blender after steady state flow through the mixer was reached determines the hold-up.

$$\text{Hold-up} = \text{accumulation} = \text{mass}_{in} - \text{mass}_{out} \quad (1)$$

3.2. Residence Time Distribution

The residence time distribution (RTD) and the calculated parameters from the RTD data describe the dispersion and the axial mixing behavior of continuous systems [17]. RTD in the continuous mixer was measured using the pulse experimental method. The main excipient (Avicel or Prosolv) was fed in the mixer until steady state mass flow (constant hold-up) was achieved. MgSt was used as the tracer and was introduced into the continuous mixer manually as an “instantaneous” pulse. The tracer amount (approximately 7-11 g depending on the flow rate and rotation rate) was chosen so that it could be detected using the analytical method (NIR spectroscopy) used in these studies. After the introduction of the tracer, samples were collected successively approximately every five seconds for two seconds from the outlet of the mixer in 20-mL scintillation glass vials, which were used to store and analyze the samples, for a total time of approximately 140 seconds. Samples were analyzed by NIR spectroscopy to determine the concentration of MgSt in them. Thus, for each experiment, the concentration of the tracer as a function of time $[c(t)]$ was determined. The RTD function $[E(t)]$, the mean residence time (MRT, τ) and the mean centered variance (MCV, σ_{τ}^2) were calculated. Mathematical expressions for the

RTD, the MRT and the MCV are described in equations 2, 3 and 4, respectively. The RTD describes the probability distribution of the time that a particle would spend inside the continuous mixer. The MRT, as its name implies, determines the average time that a tracer particle spends inside the continuous mixer. The MCV describes the width of the RTD curve and it is inversely related to the number of ideal stirred tanks in series that would describe the same RTD.

$$E(t) = \frac{c(t)}{\int_0^{\infty} c(t)dt} \quad (2)$$

$$\tau = \int_0^{\infty} tE(t)dt \quad (3)$$

$$\sigma_{\tau}^2 = \frac{\int_0^{\infty} (t-\tau)^2 E(t)dt}{\tau^2} \quad (4)$$

3.3. Number of blade passes (Strain)

The number of blade passes is an indirect measurement of the amount of strain, correlated to the energy input caused by the impeller, that the powder experiences inside a continuous mixer [6,8,11]. The number of blade passes (N_p) is proportional to the product of the rotation rate (ω) and the mean residence time (τ), shown in Equation 5.

$$N_p = \omega \cdot \tau \quad (5)$$

3.4. Blend Uniformity

The blend uniformity was determined using the relative standard deviation (RSD). Samples were collected successively approximately every 10 seconds for approximately three seconds from the outlet stream using 20-mL scintillation vials. The RSD, also known as the coefficient of

variability, is the most common mixing index used, and was calculated from the measured concentration of 20 samples for each experimental run. The acetaminophen concentration from each sample was quantified by using the NIR spectroscopy. The RSD is the ratio of the sample standard deviation (s) and the mean concentration ($\bar{C}$) of the material of interest (Equation 6).

$$RSD = \frac{s}{\bar{C}}, \text{ for } s = \sqrt{\frac{\sum_1^N (C_i - \bar{C})^2}{N-1}} \quad (6)$$

where C_i is the measured concentration of sample i and N is the total number of samples.

4. Experimental Conditions

4.1. Mixing characterization

The first part of this paper presents the characterization of the mixing dynamics and performance of the continuous mixer under investigation. A full factorial experimental design was performed using three flow rates (15, 30 and 45 kg/hr) and three rotation rates (112, 286 and 495 RPM). The mixing dynamics and performance were characterized by measuring hold-up, residence time distribution and blend uniformity. Prosolv HD90 was used as the main excipient, MgSt as the instantaneous pulse material for the RTD measurements, and semi-fine APAP was used as the active pharmaceutical ingredient (API), with a target concentration of 5% w/w, for the mixing performance characterization.

4.2. Blade Configurations

In the second part of this paper, the effect of blade configuration, varying in blade type (Figure 2 and Table 4) and orientation with respect to the horizontal axis, on the mixing dynamics and performance of the continuous mixer is summarized. All the blades, 24 in total, in

the impeller were at a 45° angle. The blade configurations are described as follows: (1) all-forward - all the blades convey the flow forward; (2) 1/2 all forward + 1/2 alternate – the first half of the blades convey the flow forward and the second half of the blades alternates, one blade conveying the flow forward and one blade conveying the flow backwards; and (3) 1/3 all-forward + 1/3 alternate + 1/3 all forward – the blades in the first third of the impeller convey the flow forward, the blades in the second third of the impeller alternates, one blade conveying the flow forward and one blade conveying the flow backwards, and the blades in the last third of the impeller convey the flow forward. For the blade configurations composed of more than one blade type, for example “Angled+Small” (Figure 2B), the angled blade was the first blade (closest to the inlet) in the impeller followed by a small blade followed an angled blade followed by a small blade and so on and so forth. For sake of brevity and to characterize the main effects of blade configurations, extreme operating conditions were investigated. Two flow rates (15 and 45 kg/hr) and two rotational speeds (112 and 495 RPM) for the five blade configurations described in Table 4 were used. The effect of blade configuration on hold-up, residence time and blend uniformity (RSD) was characterized. Avicel PH 200 was used as the main excipient, MgSt as the instantaneous pulse material for the RTD measurements, and semi-fine acetaminophen was used as the API (with a target concentrations of 5% and 30% w/w) for the mixing performance characterization.

5. Results and Discussion

5.1. Effect of process parameters on mixing dynamics and blend uniformity

In this subsection, the effects of process parameters (impeller rotation rate and flow rate) on the hold-up, RTD, MRT, MCV, and N_p are presented. The blend uniformity (RSD) of the

continuous mixer as a function of process parameters is presented as well. Experimental results in this section were performed using blade configuration #2 (Angled+Flat, all-forward).

5.1.1. Effect of process parameters on hold-up

The hold-up significantly decreased with increasing rotation rate for all feed rates used as shown in Figure 3. This change was statistically significant with *p-value* of 0.001. This trend was observed in other continuous mixers and was expected [8–10]. The rotation rate had the greatest effect on hold-up with an *F-value* of 50.11. In addition, the hold-up significantly increased (*p-value* = 0.023) with increasing flow rate. This was particularly true at lower rotation rates (112 RPM). At higher rotation rates, the hold-up was considerably lower for 15 kg/hr, while for 30 kg/hr and 45 kg/hr, the hold-up was very similar. A summary of the analysis of variance (ANOVA) for all responses, including hold-up, is shown in Table 5.

5.1.2. Effect of process parameters on residence time distribution

The residence time distribution (RTD) for flow rate at 30 kg/hr is shown in Figure 4. This results show a longer delay in the detection of the tracer for 112RPM followed by 286 RPM and 495 RPM. To better understand the meaning of and to summarize the RTD results, the mean residence time (MRT, τ) and the mean centered variance (MCV, σ_t^2) are described as a function of rotation rate and flow rate in Figure 5. The MRT significantly decreased (*p-value* < 0.05) with increasing rotation rate (Figure 5A). This means that the powder inside the continuous mixer spends more time at lower rotation rate. On the other hand, the MCV significantly increased (*p-value* < 0.05) with increasing rotational speed (Figure 5B), leading to a wider RTD at higher rotational speeds. The inverse of the mean centered variance yields the equivalent number of ideal stirred tanks in series that would provide a comparable RTD. The number of ideal stirred tanks in series indicates the degree of dispersion of the instantaneous pulse used. Fewer stirred

tanks in series (higher MCV) represent faster dispersion, and thus quicker axial mixing. For example at 15 kg/hr, the MRT at 112 RPM was 114 seconds while at 495 RPM it was 77 seconds. For these same values, the MCV increased from 0.204 to 0.414 which represent a decrease from 5 to ~2.5 stirred tanks in series. Although higher rotation rate gives rise to better axial mixing, it also decreases the amount of time available for mixing. The same trends were previously observed in a different continuous mixer (GCM-250 by Gericke) studied by Vanarase and Muzzio [8]. This confirms that this trade-off effect between the MRT and the MCV can be expected for cylindrical continuous mixers.

The RTD measurements for all three flow rates at 286 RPM is shown in Figure 6. The sharpest and narrower RTD was given by 45 kg/hr followed by 30 kg/hr and 15 kg/hr. The MRT significantly decreased ($p\text{-value} < 0$) with increasing flow rate (Figure 5A). This means that the amount of time that the powder spends inside the continuous mixer decreases with increasing flow rate. In another study, Vanarase and Muzzio obtained the same effect, in which the MRT decreased with increasing flow rate for 30 and 45 kg/hr [8]. In our study, the results show that the MRT values are more similar for 30 and 45 kg/hr than those obtained at 15 kg/hr. This is important to point out since as more powder is flowing through the blender, it is also spending less time and might not achieve efficient mixing. Therefore, at higher flow rates, it is recommended to operate at lower rotation rates. The effect of flow rate ($F\text{-value} = 226.71$) on the MRT was larger than the effect of rotation rate ($F\text{-value} = 55.49$). This means that flow rate had a greater influence on the MRT in the continuous mixer under investigation. Finally, the MCV did not display a clear trend due to variations in flow rate (Figure 5B). In addition, the flow rate did not generate a significant change on the MCV ($p\text{-value} = 0.357$).

5.1.3. Effect of process parameters on number of blade passes

A useful measurement obtained from the MRT is the number of blade passes (N_p), which can be used as an estimate of the mean strain that the powder experiences inside the continuous mixer. In this case, the number of blade passes substantially increased ($p\text{-value} < 0$) with increasing rotation rate (Figure 7). In previous work by Portillo *et al.*, the number of blade passes also increased with increasing rotation rate in a mixer of similar geometry [6,11]. In the work by Vanarase and Muzzio, which explored a wider range of rotation rates, the number of blade passes had a maximum at intermediate rotation rates [8]. In contrast, the mixer studied in this study does not display a maximum number of blade passes even though the rotational speeds are higher than in the cited works. This difference in trends can be attributed to the difference in geometrical dimensions of the continuous blenders, i.e. the length to diameter ratio (L:D) and the number of blades used in the mixer. The continuous mixers used by Portillo had L:Ds of 4.9 and 6.2 while the continuous mixer used by Vanarase had an L:D of 3.0. In this case, the continuous mixer used had an L:D of 8.75.

The number of blade passes (N_p) significantly decreased ($p\text{-value} < 0$) with increasing flow rate (Figure 7). The rate at which the number of blade passes decreased was lower at lower rotation rates. The largest difference in the number of blade passes was achieved at the highest rotation rate, 495 RPM (between 15 kg/hr and 30kg/hr). The interaction between the flow rate and the rotation rate on the number of blade passes was statistically significant ($p\text{-value} < 0$). Although rotation rate had a larger quantified contribution to the changes in the number of blade passes, these are similar with $F\text{-values}$ of 390.72 and 302.85 for rotation rate and flow rate, respectively.

5.1.4. Effect of process parameters on blend uniformity

1 The blend uniformity of the continuous mixer, as measured by the relative standard deviation
2 (RSD), is shown in Figure 8. A target concentration of 5% w/w APAP was used in this case. No
3 trends between the RSD and the rotation rate were found. In fact, the differences due to rotation
4 rate were not statistically significant ($p\text{-value} = 0.273$). For 15 and 30 kg/hr, a minimum RSD
5 was obtained at the intermediate rotation rate (286 RPM) but this was not true for 45 kg/hr. In
6 addition, there was no clear trend in the RSD due to flow rate, although the differences due to
7 flow rate were still statistically significant ($p\text{-value} = 0.082$).

8 The large error bars indicate that the true RSD can be anywhere between the specified
9 ranges. The errors bars were calculated using the results from Gao *et al.*, who studied the
10 determination of RSD confidence intervals using convolution [18]. The large error bars are
11 mainly a product of the small number of samples (20) used. This small number of samples is
12 typically used in the pharmaceutical industry when characterizing the blend uniformity and final
13 product (e.g. tablets) content uniformity. The RSD results obtained were in the range of 6% to
14 10%. Such RSD results were comparable to the results obtained by Portillo [6,11] and lower than
15 those obtained by Vanarase and Muzzio [8] in the characterization of different continuous mixers
16 using similar materials and the same analytical method (NIR spectroscopy). In addition, the
17 small amount of sample used and the analytical error occurring as a result of using NIR might
18 underrepresent the blend uniformity obtained in this and other studies. The root mean square
19 error of prediction (RMSEP) for the NIR calibration model was 0.297 in this case, which would
20 only allow for the lowest measurable RSD to be $\sim 5.9\%$ ($100\% * 0.297 \div 5$).

21 5.2. Effect of blade configuration on mixing dynamics and blend uniformity

22 5.2.1. Effect of blade configuration on hold-up

The hold-up was measured for five blade configurations at two flow rates (15 and 45 kg/hr) and two impeller rotation rates (112 and 495 RPM) using Avicel PH 200. The effect of blade configuration on hold-up is shown in Figure 9. For 15 kg/hr at impeller speed of 112 RPM (Figure 9A), the hold-up was the lowest for the all-forward with angled blades configuration (#1). The hold-up was slightly larger for the all-forward with angled and flat blades configuration (#2), followed by the 1/3 all-forward + 1/3 alternate + 1/3 all-forward blade configuration with the angled and flat blades (#3). On the other hand, the hold-up was largest for the blade configurations with the angled and small blades, having the second largest value for the all-forward blade configuration (#4) and the highest for the 1/2 all forward + 1/2 alternate blade configuration (#5). These changes in hold-up were statistically significant ($p\text{-value} = 0.040$). A summary of the ANOVA for the effect of blade configuration on all responses, including hold-up, is shown in Table 6.

The observed trend can be explained by the size variation (i.e. total area) of the blade types as well as the blade configuration and orientation of the blades (Figure 2). Blade configuration #1 was composed of the largest blade (angled) only, with all of them directing the powder flow forward. This configuration conveyed more powder when compared to the other blade configurations. Blade configuration #2 was composed of the angled and flat blades, in an alternating sequence, with all of them directing the flow forward. The flat blades are smaller in size than the angled blades. Therefore the hold-up increased due to a reduction in the total blade area available for powder transport when using this blade configuration. Blade configuration #3 was composed of the angled and flat blades, with a 1/3 blade configuration that alternated the orientation of the blades by directing the flow forward and then backwards. This alternating configuration, in the second third of the impeller, was expected to increase the recirculation of

the powder and, thus, the hold-up. For blade configurations #4 and #5, the use of the small blades in the impeller substantially decreased the amount of powder that could be transported through convection by the impeller. The alternating blade configuration in configuration #5 also created substantial recirculation in the second half of the impeller yielding the highest hold-up.

Two flow patterns can be easily identified when studying the effect of blade configuration on the hold-up [13]. These can be described as the “recirculation” (increasing dispersion) pattern and the “forward convection” pattern. The recirculation pattern determines the amount of powder that is held back in the blender by blades that direct the flow backwards. The convection pattern determines the amount of powder that is held in the blender as it is “pumped” forward by the blades. Smaller blades might also create larger stagnant regions in which the powder might not be flowing (conveyed) at all. Therefore blade configuration #5 was expected to yield the highest hold-up due to an increase in the recirculation created by the 1/2 alternating blade configuration as well as the reduction in the effective blade area available for powder convection.

The same trend in hold-up was obtained for 15 kg/hr at 495 RPM (Figure 9B). In this case, the hold-up decreased substantially with increasing rotation rate (expected) for all blade configurations except for blade configuration #5. In this case, the rotation rate had a minor effect on the hold-up. This further suggests the possibility of larger stagnant regions created by a less effective convective mechanism for this blade configuration even at higher rotational speeds. For 45 kg/hr at 112 RPM (Figure 9C) and 495 RPM (Figure 9D), the effect of the blade configuration was the same but the differences in hold-up values between blade configurations were substantially smaller. At 45 kg/hr, a strong interaction between the flow rate and the impeller rotational speed was observed causing the hold-up for all blade configurations to be similar to each other. This can be an indication that powder convection is stronger due to the

bulk flow while the effect of blade configuration is less significant at higher flow rates. A summary of the ANOVA (Table 6) shows that the flow rate and rotation rates have larger effects on the hold-up than the blade configurations with *F-values* of 18.63, 57.49, and 7.33, respectively.

5.2.2. Effect of blade configuration on mean residence time

The effect of blade configuration on the MRT (τ) for all experiments in this section are plotted in Figure 10. The MRT showed a clear trend, similar to the hold-up results as expected. In general, the MRT for blade configuration #5 was higher for all experimental conditions when compared to all the other blade configurations, as expected, followed by configurations #4 through #1, in that order. These differences in MRT caused by the blade configuration were statically significant (*p-value* = 0.022). For 45 kg/hr, the MRT was lower and almost identical for all blade configurations, especially at 495 RPM. The recirculation and the convective mechanisms previously described also explain the effect of blade configuration on the MRT. As the rotation rate increases, the MRT results for the blade configurations become almost identical. At higher rotation rates, the rotational forces in the shaft overcome the influence of the blade configuration. This means that the convective mechanism governs mixing and the recirculation mechanism created by the alternating blade configurations no longer has a significant effect on the RTD. In previous work by Vanarase and Muzzio [8], comparison of two blade configurations showed opposite results. Their findings described that the MRT was similar at lower rotation rates and became substantially different at higher rotation rates for blade configurations with forward and alternate configurations. In their case, the MRT was also higher for an alternating blade configuration, which created more recirculation of the powder inside the continuous mixer.

Nevertheless, the blade configurations studied as well as the L:D of the mixer were very different. The summary of the ANOVA for MRT for the effect of blade configuration is shown in Table 6.

5.2.3. Effect of blade configuration on blend uniformity

The effect of blade configuration on the blend uniformity in the continuous mixer was also examined (Figure 11). In this case, a blend with 30% semi-fine acetaminophen in a common excipient (Avicel PH200) was used. The blend uniformity (indicated by the RSD) was very similar for all blade configurations for the flow rates and impeller rotational speeds used. Therefore only the results for 15 kg/hr and 112 RPM are included. All RSD results were below 3% indicating good mixing. These differences and lack of trend could potentially be caused by statistical scatter of the data represented by the error bars. These RSD results are dominated by the NIR error, the root mean square error of prediction (RMSEP), with a value of 0.361. Therefore the minimum RSD that could be obtained using this NIR calibration model would be 1.2% ($100\% \times 0.36 \div 30$). Nevertheless, it can be concluded that for 30% APAP, all the experimental parameters generated desired mixing levels of much less than 6% RSD. In another study, Marikh *et al.* investigated the effect of two agitators in continuous mixing of APIs, similar in particle size and nominal concentration (~23% w/w) [9]. The RSD values obtained in their investigations were higher than those from the current study. Although it is hard to compare different continuous mixers with different geometries, impellers, and materials, it can be said that the continuous mixer characterized in this study, specifically designed for pharmaceutical formulations, is efficient when mixing high concentration (~30% w/w) of cohesive APIs.

To elucidate the effect of blade configuration on the blend uniformity for a low concentration of API (5% w/w), blade configuration #3 was tested for more flow rates and rotational speeds

and compared to blade configuration #2 (as described in subsection 5.1) using Prosolv HD90 as the bulk excipient. Even at low concentration of API, the RSDs were not different for the blade configurations tested. In fact, the effect of blade configuration was not statistically significant (p -value = 0.922). Graphs and ANOVA for these results were omitted for sake of brevity. Overall, the determination of which blade configuration is “better” or “worse” has to be determined from the hold-up and mean residence time. Therefore the effect of hold-up and mean residence time on other final blend properties such as degree of lubrication and flow properties plays an important role. The mixer characterized in this study yielded blends with consistent blend uniformity regardless of the process parameters and blade configurations used.

6. Conclusions

A new continuous powder mixer designed specifically for pharmaceutical blending was studied in detail. The effect of process parameters (flow rate and rotational speed) on hold-up, residence time distribution and blend uniformity (RSD) was investigated. Overall, the hold-up and the mean residence time decreased with increasing impeller rotational speed. The mean centered variance and the number of blade passes increased with increasing impeller rotational speed. The hold-up increased with increasing flow rate. The mean residence time and the number of blade passes decreased with increasing flow rate.

The effect of the blade configuration on the mixing dynamics was also studied. This effect diminished as the rotation rate increased. The hold-up and the mean residence time were sensitive enough to demonstrate the effects of the blade configuration on the mixing behavior in the continuous blender. The convective and the recirculation mechanisms were explained by the blade configuration studies. Overall, mixing performance (blend uniformity) was found to be

robust with respect to processing parameters and blade configurations. The RSD was found to be less than 3% for 30% w/w API (acetaminophen) concentration, and between 5% and 10% RSD for 5% w/w API concentration. These results showed improvements in the mixing performance obtained from studies of other continuous blenders using similar materials and the same analytical method.

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Figure 1 – Equipment: (A) continuous mixer and (B) feeder-mixer setup

Figure 2 – (A) Blades and (B) blade configuration #4

Figure 3 – Hold-up as a function of rotation rate and flow rate. Blade configuration #2: Angled+Flat, All-forward.

Figure 4 – Residence time distribution ($E(t)$) as a function of rotation rate for flow rate of 30 kg/hr. Blade configuration #2: Angled+Flat, all forward.

Figure 5 – Effect of rotation rate and flow rate on (A) mean residence time (τ) and (B) mean centered variance (σ_τ^2). Blade configuration #2: Angled+Flat, all forward.

Figure 6 – Effect of flow rate on residence time distribution ($E(t)$) at 286 RPM. Blade configuration #2: Angled+Flat, all forward.

Figure 7 – Effect of rotation rate and flow rate on number of blade passes (N_p). Blade configuration #2: Angled+Flat, all forward.

Figure 8 – Effect of rotation rate and flow rate on blend uniformity (RSD). Target concentration: 5% w/w acetaminophen. Blade configuration #2: Angled+Flat, all forward.

Figure 9 – Effect of blade configuration (x-axis) on hold-up at (A) 15 kg/hr and 112 RPM, (B) 15 kg/hr and 495 RPM, (C) 45 kg/hr and 112 RPM, and (D) 45 kg/hr and 495 RPM.

Figure 10 – Effect of blade configuration on mean residence time (τ) at (A) 15 kg/hr and 112 RPM, (B) 15 kg/hr and 495 RPM, (C) 45 kg/hr and 112 RPM, and (D) 45 kg/hr and 495 RPM.

Figure 11 – Effect of blade configuration on blend uniformity (RSD) at 15 kg/hr and 112 RPM. Semi-fine acetaminophen target concentration: 30% w/w.

Figure 1A

Figure 1B

Figure 2A

Angled

Flat

Small

Figure 2B

Figure 3

Figure 4

Figure 5A

Figure 5B

Figure 6

Figure 7

Figure 8

Figure 9A

Figure 9B

Figure 9C

Figure 9D

Figure 10A

Figure 10B

Figure 10C

Figure 10D

Figure 11

Material	Type / Name	Vendor	Mean particle Size (µm)
Silicified Microcrystalline Cellulose	Prosolv HD 90	JRS Pharma	110
Microcrystalline Cellulose	Avicel PH 200	FMC Biopolymers	220
Magnesium Stearate	Magnesium Stearate	Mallinckrodt	10
Acetaminophen	Semi-fine	Mallinckrodt	45

Table 1 – Description of materials used.

Material Fed	Flow Rate (kg/hr)	Nozzle Size (mm)	Screw Type
Acetaminophen	0.75 - 5.00	22	Helix
Acetaminophen	4.50 - 13.50	36	Auger
Avicel PH200	10.50 - 31.50	36	Auger
Prosolv HD90	14.25 - 42.75	36	Auger

Table 2 – Feeder configurations for each material depending on their concentration (individual flow rate).

Material of Interest	Excipient	Target Concentration (%)	R ²	RMSEC	RMSEP	Concentration Range (%)	Filter	Points
MgSt	Avicel PH 200	0 - 7	0.9939	0.218	0.215	0-7	SG	9,3
APAP	Avicel PH 200	30	0.9672	0.293	0.361	27-33	SG	7,3
MgSt	Prosolv HD90	0 - 8	0.9964	0.207	0.203	0-8	SG	7,3
APAP	Prosolv HD90	5	0.9808	0.238	0.297	0-7	SG	11,5

Table 3 – NIR calibration model description. Root mean squared error of calibration (RMSEC) and prediction (RMSEP) are used as measures of the accuracy of each calibration model. A second-order polynomial Savitzky-Golay (SG) filtering was used as indicated.

(A)

Blade Type	Diameter	Length (cm)	Angled Tip Length (cm)
Angled	2.6	4	1.5
Flat	2.6	4	-
Small	2.6	1.7	-

(B)

Blade Configuration #	Blades	Blade configuration
1	Angled	all forward
2	Angled + Flat	all forward
3	Angled + Flat	1/3 All-forward + 1/3 alternate + 1/3 all forward
4	Angled + Small	all forward
5	Angled + Small	1/2 all forward + 1/2 alternate

Table 4 – (A) Blade specifications and (B) blade configurations.

	<i>F-values</i>				
	Hold-up	MRT	MCV	N_p	RSD ²
Rotation Rate	50.11	55.49	107.17	390.85	1.44
Flow Rate	11.15	226.71	1.16	302.85	3.05
Rotation Rate*Flow Rate	N/A	2.65	6.19	26.37	N/A
	<i>p-values</i>				
	0.001	0.000	0.000	0.000	0.273
Rotation Rate	0.001	0.000	0.000	0.000	0.273
Flow Rate	0.023	0.000	0.357	0.000	0.082
Rotation Rate*Flow Rate	N/A	0.104	0.011	0.000	N/A
	R^2 , R^2_{adj}				
	96.84%, 93.68%	98.46%, 97.09%	96.41%, 93.21%	99.40%, 98.87%	40.85%, 22.66%

Table 5 – Summary of analysis of variance (ANOVA) for hold-up, MRT, MCV, N_p , and normalized variance (RSD²) for mixing characterization study. *F-values*: Fisher statistic values, and *p-values*: statistical significance. Confidence levels for all intervals: 95%.

	<i>F-values</i>		
	Hold-up	MRT	RSD ²
Blade Configuration	7.33	10.24	4.65
Flow Rate	18.63	38.4	10.79
Rotation Rate	57.49	41.53	2.98
Blade Configuration*Flow Rate	0.59	4.64	3.5
Blade configuration*Rotation Rate	0.22	0.35	0.26
Flow Rate*Rotation Rate	8.51	0.84	2.04
	<i>p-values</i>		
Blade Configuration	0.040	0.022	0.083
Flow Rate	0.012	0.003	0.030
Rotation Rate	0.002	0.003	0.159
Blade Configuration*Flow Rate	0.688	0.083	0.013
Blade configuration*Rotation Rate	0.914	0.832	0.889
Flow Rate*Rotation Rate	0.043	0.410	0.226
	<i>R², R²_{adj}</i>		
	96.70%, 84.32%	97.25%, 86.96%	92.52%, 64.47%

Table 6 – Summary of analysis of variance (ANOVA) for hold-up, MRT, and normalized variance (RSD²) for blade configuration study. *F-values*: Fisher statistic values, and *p-values*: statistical significance. Confidence levels for all intervals: 95%.