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Research Article

Semicontinuous Blending of Pharmaceutical Ingredients and the Impact of Process Parameters on the Blending Performance of an Integrated Feeder Blender Operating Semicontinuously

Sumit Kumar,[1] **Yan-Shu Huang**,[1] **Zoltan Nagy**,[1] **Gintaras V. Reklaitis**,[1] **Marcial Gonzalez**,[2] **and Paul Mort**[3]

[1]*Davidson School of Chemical Engineering, Purdue University, West Lafayette, Indiana 47907, USA*
[2]*School of Mechanical Engineering, Purdue University, West Lafayette, Indiana 47907, USA*
[3]*School of Materials Engineering, Purdue University, West Lafayette, Indiana 47907, USA*

Correspondence should be addressed to Sumit Kumar; kumar344@purdue.edu

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The pharmaceutical industry is looking for new and innovative ways of manufacturing to improve product quality and reduce process complexity. In manufacturing oral solid dosage products, blending is a crucial step in ensuring the homogeneity of active pharmaceutical ingredients (APIs) in the final product. Currently, batch and continuous blending are the two commonly used modes for blending in the industry. However, these methods have limitations in terms of blending time, manual intervention, and flexibility in handling multiple ingredients. To address these limitations, this study aims to explore the feasibility and benefits of using a semicontinuous blending mode in the pharmaceutical industry. A case study is conducted using a binary blend of microcrystalline cellulose and acetaminophen to compare the performance of the semicontinuous mode of blending with the batch and continuous blending modes. The results show that the semicontinuous blending setup can produce blends with good blend uniformity and homogeneity and that the output can be used for both batch and continuous downstream operations. The effect of variation in the three most important process parameters, impeller rotation per minute, blending time, and fill level on the blend uniformity, is also investigated. The semicontinuous blending mode had a higher line rate of 12.5 kg/hour than a similarly sized batch blender at 3.6 kg/hour and less than that of a continuous blender. The benefits of the new blending mode include reduced blending time, minimal manual intervention, flexibility in blending multiple ingredients, easier scale-up, and a smaller footprint. Overall, this study highlights the relative advantages of using this new semicontinuous blending mode in pharmaceutical manufacturing and its potential as a good alternative to the existing blending modes. The semicontinuous mode is well placed between the batch blending and continuous blending mode, with many benefits over the former mode and performance comparable to the latter continuous mode.

1. Introduction

The pharmaceutical industry has predominantly operated on batch manufacturing. Only a handful of Food and Drug Administration (FDA) approved products have utilized continuous manufacturing. This is because most companies already have all the necessary equipment needed for the batch manufacturing and have ample regulatory experience in filing products with agencies. Equipment mapping, cleaning, and accommodating multiple products are also more straightforward in batch manufacturing. However, the industry is undergoing many changes to improve product quality and reduce product development time [1, 2]. Advancements in computing and modelling, Process Analytical Technology (PAT) [3], Industry 4.0 implementation, Quality by Design (QbD), Quality by Control (QbC), and digital twin technologies have all driven the adoption of continuous manufacturing in the pharmaceutical field [4–7]. The significant benefits of adopting continuous manufacturing include a better

understanding of the processes, the possibility of real-time process measurement and control, a smaller equipment footprint, lesser risk of contamination and human exposure, and higher processing rates [6]. The FDA has recognized these benefits and has been encouraging the adoption of continuous manufacturing [8, 9].

Oral solid dosage (OSD) is the most common pharmaceutical product form [10]. The manufacturing of OSD employs various unit operations such as feeding, blending, granulation, compaction, and coating [11]. Blending is one of the essential unit operations as it ensures the homogeneous distribution of the active pharmaceutical ingredient (API), which has therapeutic value, in the blend of API and excipients [12]. The blended material must have a homogeneous distribution of API (one of the critical quality attributes) and good flow properties to aid the manufacturability in downstream processes. Almost all OSD manufacturing processes involve at least one blending step.

Ingredients can be blended to an acceptable level of homogeneity by utilizing either batch blending [13] or continuous blending [14]. The batch blenders, though easy to operate, suffer from limitations such as longer blending time, batch-to-batch variability, larger equipment, and fixed batch sizes [15]. Batch blending also has significant scale-up challenges. For example, the material at the bottom of a large batch blender can get compacted and exhibit different bulk density and flow properties [14]. Consequently, batch blending is not well suited for blending pharmaceutical excipients with high segregation potential [16]. The continuous mode of blending can solve most of these issues as less material is processed at a time and holding times which can lead to segregation are much reduced. Also, there is a higher flexibility concerning batch size and output, and it is not limited by the size of the blender [17–19]. Many benefits of continuous blending have been reported in recent publications, such as more efficient processes with lower manufacturing costs and footprints, easier scale-up, and improved product quality [4–6, 20]. However, continuous blending also suffers from some limitations. The residence time the material spends in the blender is short and depends on the RPM of the impeller and on the length of the blender, which acts as a design constraint. The residence time may not be sufficient when blending many excipients and APIs in such a short time. Continuous blenders require feeders to feed all the necessary ingredients at a constant flow rate [16]. Since the overall inlet mass flow rate equals the outlet mass flow rate, any variation in the flow rate of any ingredients can affect the blending performance of the continuous blenders [21]. Materials with poor flow properties and feeders operating at low mass flow rates typically have higher variations [20]. This is shown later in the results section. Formulations with low API drug concentration products and poor flow properties can be especially challenging [22]. Continuous blending also demands frequent refilling of the feeders, which is also known to cause flow rate variations as the feeders do not operate in loss in weight mode during the refill operation [16]. Lastly, it is crucial to identify whether or not the process has reached a steady state and whether it has a mechanism to discard the material not meeting the content uniformity specifications until a steady state is reached.

Up to now, most of the research work on blending in pharmaceutical manufacturing has focused on batch blending and continuous blending. A lot of work has been performed on the batch blending aspects [23–25]. The amount of work on continuous blending has also increased in the last decade [26, 27]. These studies have focused on important process parameters to optimize blending unit operations and comparison of blending performance between two blending modes. However, not much has been performed on the semicontinuous mode of blending pharmaceutical ingredients and on directly comparing the semicontinuous mode with the two other modes. Even though continuous manufacturing has gained growing interest, the blending of pharmaceutical ingredients is still dominated by batch processes [28]. Challenges such as feeding variability from the feeders, knowledge-intensive process development, and complexity involved in achieving a state of control have limited the wide implementation of continuous blending.

The current study aims to overcome the limitations realized with batch blending and continuous blending of powders [20]. The downside of both modes can be addressed by adopting a novel approach of semicontinuous blending of powders [29]. A series of small batches can be produced semicontinuously using an integrated feeder blender system. Previous studies have reported the implementation of batch blending [23–25, 30, 31] and continuous blending [15]. The implementation of continuous manufacturing has been slower than expected [32]. Semicontinuous blending provides a promising alternative to batch blending and continuous blending, combining the advantages of both the existing blending modes. The authors understand that this is the first work describing the case study on semicontinuous blending mode and its proposed benefits. In this study, we conceptualize the relative advantages of implementing this new semicontinuous mode of powder blending, show a case study that describes the blending performance of a semicontinuous setup, and investigate the impact of different process parameters on the blending performance of an integrated feeder blender operating semicontinuously. The blend properties, performance, and line rate results from semicontinuous blending are compared with batch blending and continuous blending results. This work will help in the implementation of this new approach to blending. The semicontinuous blending mode could be particularly advantageous over batch blending, providing robust blending, easier operations and scale-up, lesser manual intervention, and faster blending times. Overall, the scope of this study includes the use of a binary blend system consisting of microcrystalline cellulose and acetaminophen to investigate the blend uniformity at the end of semicontinuous blending, compare the blend properties and blend homogeneity with the batch and continuous blending modes, and highlight the relative advantages of this new blending mode over the existing modes in pharmaceutical manufacturing.

2. Materials and Methods

2.1. Materials. The materials used are acetaminophen (APAP) as the API and microcrystalline cellulose (MCC) as the excipient to investigate the binary blend system. APAP grade 0048 is purchased from Mallinckrodt, North Carolina, USA. Acetaminophen is sieved before usage to remove any agglomerates. Avicel microcrystalline cellulose (PH 102) is purchased from FMC Biopolymer, Pennsylvania, USA. The blending uniformity of API is studied with the target API concentration set as 10% (w/w).

2.2. Semicontinuous Blending. The Xelum, integrated wet granulation line by Syntegon, is repurposed and used as a semicontinuous setup (Figure 1). The integrated feeder blender setup of Xelum consists of K-Tron feeders, a conical blender, and an automated pneumatic valve. The system can accommodate up to five feeders at the top of the conical blender. The equipment user interface has the provision for defining a set recipe to carry out multiple steps in sequence and can also be used to input the required process parameters and execute a design of experiments (DOE) with minimum manual intervention. The current setup uses two QT20 K-Tron feeders, as the case study only employs two ingredients. Feeders charge a set weight of powder into the conical blender as required by the recipe by using as a target the difference between the initial and final weight as measured by the load cell on which they are kept. Since the amount of material delivered by the feeder for blending is not dependent on maintaining a set constant feeding rate via the built-in control strategy, the blend composition uniformity is not dependent on each input feeder maintaining its set rate. The helix impeller inside the 10-litre conical blender is set to rotate slowly during the feeding stage. Once the feeding operation is completed, the blending phase begins, and the impeller rotation per minute is increased to the set point of each experiment. The pneumatic valve at the bottom opens up upon blending completion, and the material is unloaded into a bag or transferred pneumatically to the next operation. The next batch of materials then starts to be dispensed into the conical blender by using the same steps. The impact of different process parameters on the blending performance is studied. The critical process variables in semicontinuous blending are impeller rotation, blending time, and blender fill levels. The impeller rotation is varied from 80 rotations per minute (RPM) to 160 RPM. Based on the screening experiments, the blending time is varied from 1 minute to 5 minutes and the blender fill level is varied from 30% to 70% of the blender operating volume. A full factorial design of experiment (DOE) is created to understand the impact of these variables on the blend uniformity. Important process parameters to optimize are blending time, impeller rotation per minute, and blender fill level.

2.3. Batch Blending and Continuous Blending. The batch blending is performed by using a 10-litre bin blender from Tote Systems. 250 g of APAP and 2250 g of MCC are charged into the bin blenders. The APAP is passed through the sieve so that there are no agglomerates. The APAP layer is sandwiched between the MCC layers. The blender is rotated for 25 minutes at 20 rotations per minute. After 25 minutes of rotation, the material is unloaded from the bottom of the blender. Continuous powder blending is a relatively recent phenomenon in which the material enters from one end of the continuous tubular blender and exits from the other end of the blender. The mixing happens in both radial and axial directions. Important process parameters are material flow rate and impeller speed. Design parameters include the mixer design, impeller design weir angle, and mixer inclination. For continuous blending, a Gericke continuous blender is used. The blender inlet is attached to two K-Tron feeders. One K-Tron feeder is used to add APAP at 1 kg/hr, and the other K-Tron feeder is used to charge the MCC at 9 kg/hr. The total powder flow is 10 kg/hr, and the impeller rotation speed is 150 rotations per minute. The impellers are oriented in the forward direction, and the weir is kept at an angle of 90°. The output from the continuous blender is collected in a bag. Samples weighing 1 g each are drawn from batch and continuous blenders to characterize the output blend. After completion of blending, the blend is spread on a rectangular tray and eight samples are collected from different locations using an appropriate scoop. The batch and continuous blender process parameters were previously optimized as shown in the work by Yan-shu, Qinglin et al., and Kumar et al. at the Purdue pilot plant [3, 33, 34] for the same formulation. The optimized parameters were then directly used here.

2.4. Sampling and Characterization. The bulk powder is characterized by using the GranuPack instrument, an automated and high-resolution tapped density measurement method. It precisely characterizes the densities and flow properties [35]. The height of the powder bed is measured automatically after every tap. The tap number for our analysis is fixed at 500 taps. Bulk density, tap density, Hausner's ratio (HR), and Carr index (CI) are measured to understand the bulk properties [36]. CI and HR values can explain the bulk flow properties, and the ingredients and the blended powder after every experiment are characterized.

$$\text{Hausner's ratio} = \frac{\text{tap density}}{\text{bulk density}}, \tag{1}$$

$$\text{Carr index} = \frac{(\text{tap density} - \text{bulk density})}{\text{bulk density}} * 100. \tag{2}$$

For blend uniformity analysis, eight samples, 1 g each, are drawn from every batch. After unloading from the blender, the blend is spread uniformly on a rectangular tray, and eight samples are randomly drawn from different locations in the tray. This ensured that the sampling was random and that every material had an equal chance of getting picked. After sampling, API concentration was measured in every sample by using an Ultraviolet-Visible (UV-Vis) spectrometer. A calibration curve is generated using different APAP concentrations. After sample

Figure 1: Syntegon wet granulation line.

preparation, UV absorbance is measured at a wavelength of 243 nm using the UV-visible spectrometer, and the APAP concentration in each sample is calculated. One gram of the sample is accurately weighed using a Mettler–Toledo precision balance with a sensitivity of four decimal places. The sample is then dissolved in a 100 ml solution consisting of a 1 : 3 ratio of methanol to water. To ensure adequate dissolution of APAP, the sample is agitated within a 250 ml volumetric flask for 10 minutes at 250 revolutions per minute (RPM). Subsequently, 10 ml of the solution is extracted via pipette, filtered, and further diluted in a 200 ml methanol-water solution. From this diluted solution, 4 ml is carefully transferred to a cuvette. The baseline absorbance of the methanol-water solution is subtracted, and the absorbance at 243 nm is measured by using a UV spectrometer to determine the concentration of APAP in various samples. This absorbance measurement is repeated three times, and the average is used. The absorbance value is converted to APAP concentration by using the UV calibration curve shown in Figure 2. Relative standard deviation (RSD) is then calculated by using the individual APAP concentration values.

$$\text{Relative standard deviation} = \frac{\text{standard deviation of the samples}}{\text{sample mean}} * 100. \tag{3}$$

RSD values describe the blend uniformity of API in the final blends. Different experiments are then compared for blend uniformity and flow properties. Acceptance criteria for blend uniformity are set at RSD values of less than 5% and the individual API concentration values within ± 10% of the target concentration.

3. Results

Acetaminophen (APAP) is charged to the K-Tron feeder, and the feeder is operated at different flow rates. The flow rate variations at the feeder are shown in Figure 3. First, the mass flow rate set point was kept at 1 kg/hour, and then the set point was changed to 4 kg/hour. Variations in the feed rate are considered acceptable if the actual values are in the range of ± 10% of the set point. At a 4 kg/hour flow rate, the process is within limits but at 1 kg/hr, the same blender shows higher variations. The results of the flow rate show that the same feeder, when operating at different output rates, can exhibit more variation at flow rates close to lower limits. This variation can affect the blending performance in continuous blending mode [20].

The characterization results of APAP and MCC are shown in Table 1. APAP, in particular, has very poor flow properties and is comparatively more challenging to handle. The Carr index for APAP is 37.30, and for MCC is 20.47. The CI range categorization is shown in Table 2 [36]. The APAP hence falls in the very poor to no flow category, and MCC falls in the passable flow category.

Then, the impact of different process parameters on the blending performance is studied. The critical process variables in semicontinuous blending are impeller rotation, blending time, and blender fill levels. The impeller rotation is varied from 80 rotations per minute (RPM) to 160 RPM. Based on the screening experiments, the blending time is varied from 1 minute to 5 minutes, and the blender fill level is varied from 30% to 70% of the blender operating volume. A full factorial design of experiment (DOE) is created to understand the impact of these variables on the blend uniformity. The experimental design is shown in Figure 4. Three center points are also added. The API concentration of each sample after every run is measured, and the RSD value for each run is calculated to understand the level of homogeneity. The RSD

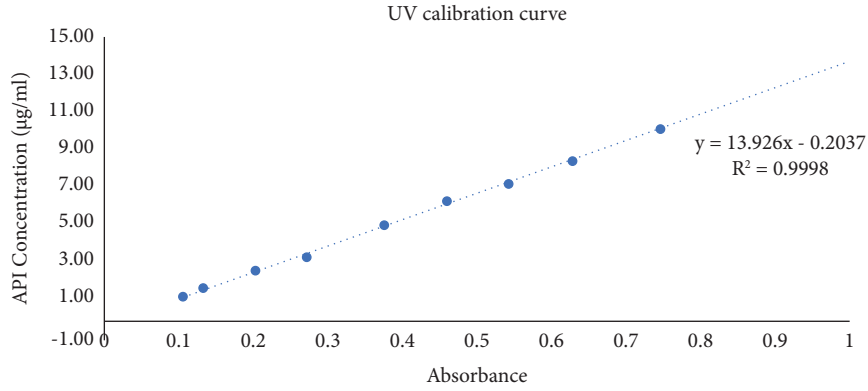

Figure 2: UV calibration curve for APAP concentration (μg/ml) measurement from absorbance values.

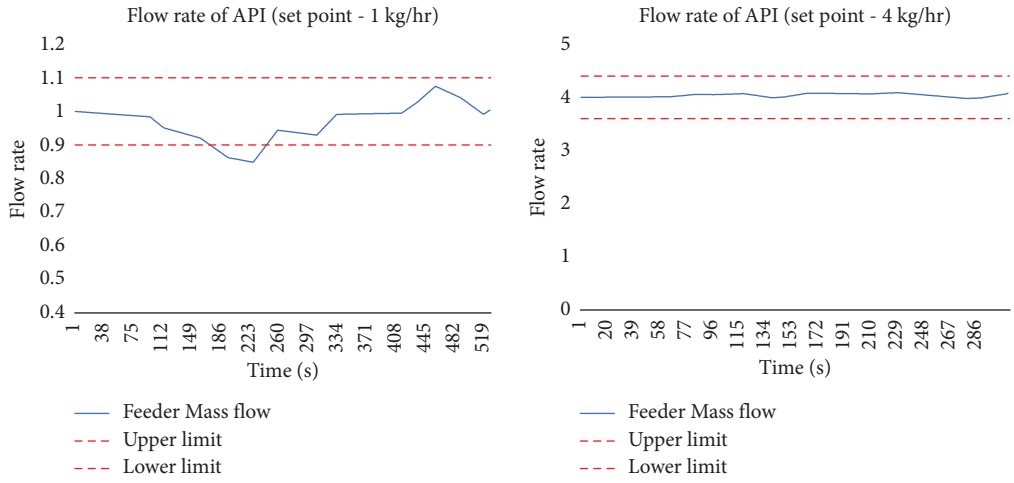

Figure 3: Variation in K-Tron KT20 feeder performance at two different set points.

Table 1: Physical characterization of raw material.

Material	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Carr index
MCC	0.354	0.445	1.257	20.467
APAP	0.318	0.508	1.594	37.299

Table 2: Flowability categorization based on HR and CI values [36].

Nature of flow	Carr index	Hausner's ratio
Excellent flow	<10	1.00–1.11
Good flow	11–15	1.12–1.18
Fair flow	16–20	1.19–1.25
Passable	21–25	1.26–1.34
Poor	26–31	1.35–1.45
Very poor	32–37	1.46–1.59
No flow	>38	>1.60

results of each experiment are shown in Table 3. The model fit is significant, with a R^2 value of 0.99. The analysis of the DOE shows that out of the three process parameters, the rotation speed of the impeller is the most significant factor affecting the blending performance (Pareto chart in Figure 5). The other significant factors are blending time and blender fill level, of which the blender fill level had the least impact on blend uniformity. Higher rotation speed and blending time resulted in better blending performance.

The feasible region where the RSD values are less than 5% (acceptance criteria) is shown in the contour plot (Figure 6). RSD results are plotted against the two most significant factors, impeller rotation speed and blending time. The blue region in the top right corner of the contour plot shows the region where the RSD values are the least. The fill level had the least effect on the blending performance, and the RSD plane at the lowest and highest fill levels is shown in Figure 7. At the highest fill level (70% of blender volume), the RSD values vary from 2.9 to 21.3. At the lowest fill level (30% of blender volume), the RSD values vary from 2.9 to 19.2.

Process variables from the feasible region are chosen (impeller RPM: 160, blending time: 5 mins, and fill level: 50%), and validation experiments are performed. The results

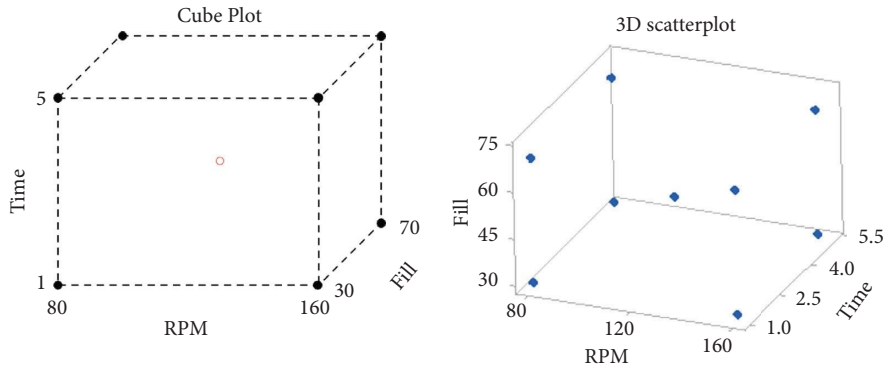

Figure 4: DOE experiment design (center point and factorial points) with process parameters, impeller RPM, blending time, and fill level.

Table 3: DOE experiment parameters, RSD results, and CI results.

S. no.	Impeller rotation per minute	Blending time (min)	Fill levels (%)	Relative standard deviation	Carr index
1	160	1	30	5.34	19.77
2	160	5	30	2.9	20.33
3	160	5	70	2.99	21.41
4	120	3	50	3.82	19.68
5	80	5	70	18.5	18.89
6	120	3	50	4.12	19.78
7	120	3	50	4.44	19.51
8	80	5	30	16.8	18.83
9	160	1	70	5.88	20.12
10	80	1	70	21.3	18.89
11	80	1	30	19.23	18.62

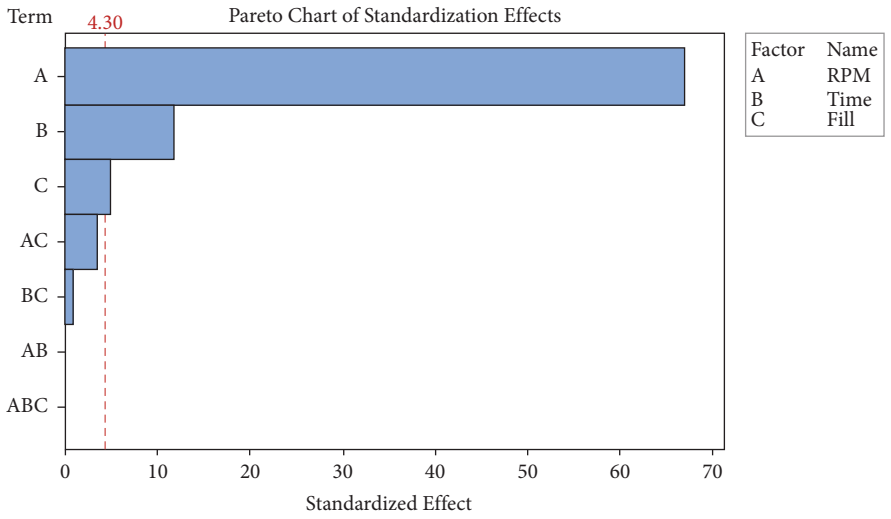

Figure 5: Pareto chart of significant process parameters affecting the blending performance.

from the validation experiments are shown in Figure 8. The RSD values in all three validation experiments at 2.34%, 1.51%, and 1.99%, respectively, are good. The individual values are also in the ± 10% range of target API concentration. The validation runs have shown good repeatability in terms of blending performance.

Now, we compare blending output from batch, continuous, and semicontinuous modes of blending. Results from the batch and continuous blending have been reported previously. The work of Jaspers et al. [15] shows that they achieved RSD values close to 4% by using the batch blender after 30 minutes of blending and 2% using the continuous blenders. Our research group has also worked with the batch blender from Tote Systems and the continuous blender from Gericke Systems. We performed the blending operations by using the optimized parameters in batch and continuous

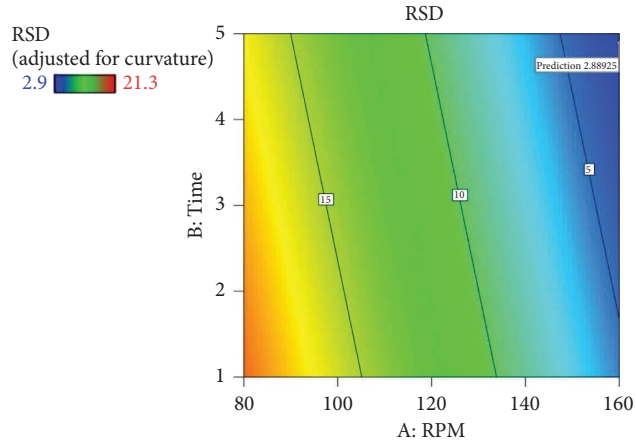

Figure 6: Contour plot of variation in RSD in design space.

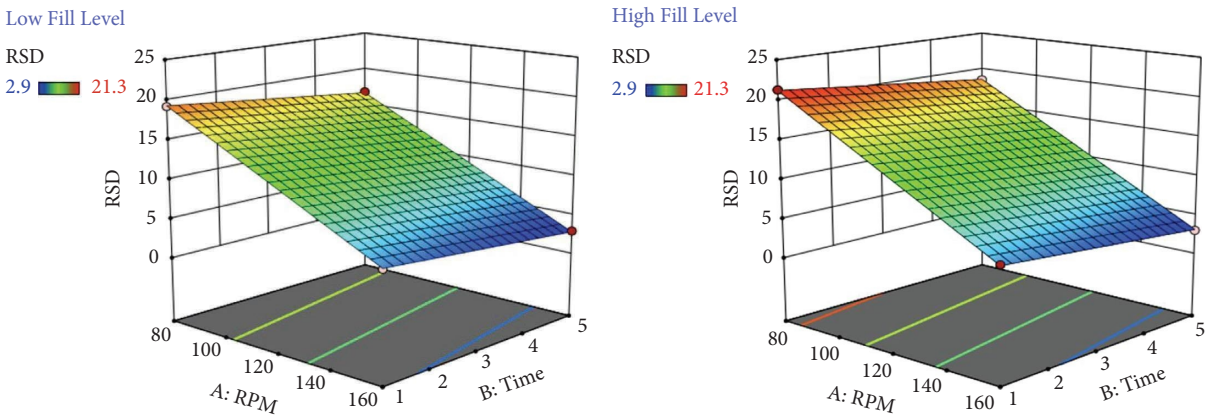

Figure 7: RSD plane at low fill level (30%) and high fill level (70%).

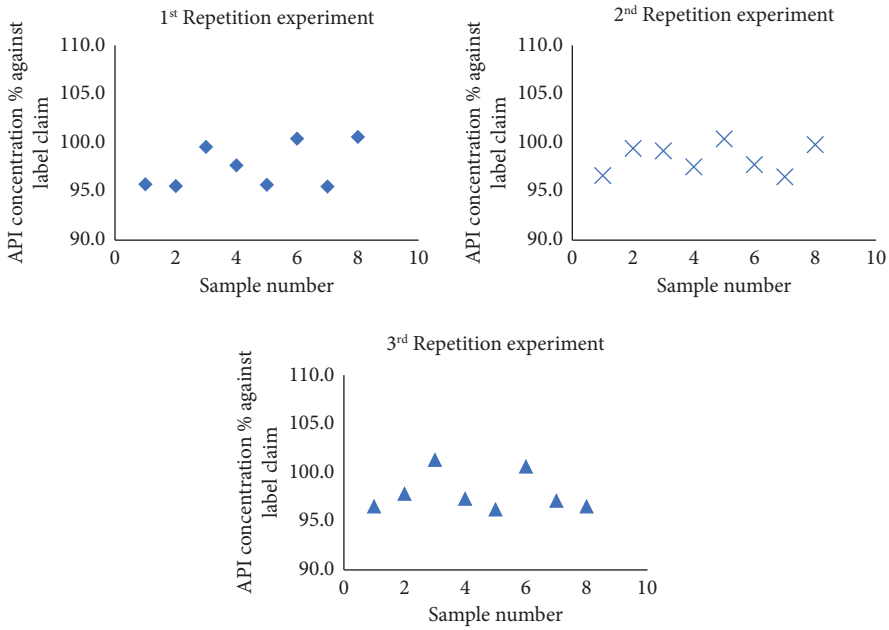

Figure 8: API concentration against label claim in DOE validation experiments.

modes. The samples are collected and analyzed as performed for semicontinuous mode. The RSD values are calculated in these two modes and are compared against the semicontinuous mode. One of the semicontinuous batches taken as part of verification experiments is used for the comparison. The individual values of each of the eight samples for all three modes are shown in Figure 9. The RSD values calculated for these modes are shown in Figure 9. The RSD obtained for the batch blender is 4.01% and for the continuous blender is 1.94%. This is similar to what was obtained in previous studies [15, 28]. The blend uniformity from the new semicontinuous mode at RSD 2.34% is better than that of the batch blender and comparable to the blend uniformity of the continuous blender.

The bulk density, tap density, Carr index, and Hausner's ratio of blend generated via batch blending, continuous blending, and semicontinuous blending are compared in Table 4. The bulk density of the output blend is least in the continuous blending mode, perhaps because the processing time inside the blender is the least in the continuous blender, and the material is not compacted by the weight of the rest of the material on top of the blender. However, the difference in results is not much and all three blending modes produced the output with similar bulk properties. The bulk and flow properties are similar in all three cases; hence, either strategy can be adopted for blending materials without impacting the physical properties.

Samples from all experimental runs are characterized to understand the impact of change in the process parameters on the physical characteristics of the blend. The CI values are shown in Table 3. The DOE analysis shows that the model developed for CI values from the process parameters is significant, with R^2 values of 0.95. The variation in CI values by varying the process variables is shown in the contour plot (Figure 10). The blends with low RPM, low blending time, and low occupancy had better flow properties. This could be because the low RPM and blending time used in the study are sufficient to ensure that the ingredients are well distributed throughout the mixture for this formulation. Blending for a longer period at times can cause overmixing and lead to the formation of new agglomerates. Longer blending time and shear imparted by higher impeller speeds can also lead to particle size reduction due to attrition, impacting the final blend's characteristics. Such analysis could be important during optimization in scenarios where it is critical to have better flow properties.

The material outputs from all three modes, batch blending, continuous blending, and semicontinuous blending, are compared next. Similar-sized blenders, available at the Purdue pilot plant, are used to perform the experiment and calculate the output from each blender system in kg/hour. The important operations in all three modes are shown in Figure 11. In batch and semicontinuous modes, 2.5 kg of the material could be processed at a time. The batch blending required 15 minutes for the following steps: (i) initial dispensing of material manually in the exact amount needed, (ii) passing the APAP through a mesh to remove any agglomerates, (iii) charging the excipient and API in layers inside the blender, and (iv) manually closing the blender and setting up the process parameters. The blending time is 25 minutes, which was established in earlier studies [3, 33]. The time needed to open the blender and unload the blend is 2 minutes. It took 42 minutes for the complete cycle, which corresponds to 3.57 kg/hr. In semicontinuous blending, the dispensing step only required filling up the feeders as the dispensing is automated by loss in weight feeders. The blending time, as studied in the abovementioned case study, was 5 minutes. The time to unload is 2 minutes. The cycle time is 12 minutes for an output of 2.5 kg. We were able to perform five such cycles in an hour, resulting in an overall line rate of 12.5 kg/hr. In the continuous blender, the Gericke continuous blender GCM 250 could deliver between 1 and 25 kg/hr output depending upon the input feed rate of the material and blender RPM. The continuous blender is typically operated at a line rate of 10–12.5 kg/hr. Batch blending required the maximum human intervention. In this case, the output of the semicontinuous mode is better than that of the batch blender and is less than the maximum output of the continuous blender.

4. Discussion

The results from the case study show that the integrated feeder blender setup used in a semicontinuous manner can produce blends with good homogeneity. The material blended using the semicontinuous setup had a good homogeneity, and the validation experiments had a good repeatability.

Mixing phenomena in blenders can be categorized into three major mechanisms, convection, diffusion, and shear. Most blenders involve some level of all the abovementioned mechanisms, but the dominant mechanism varies with the type of blender used [16]. The conical blender in the semicontinuous setup introduces convection by the action of impellers that move the powder inside the conical vessel, which helps achieve the desired homogeneity. The blender offers a stainless-steel conical bowl and a stirrer. The material in this blender spends less time under shear when compared to a batch blender due to the short blending time requirement. Such vertical blenders have a smaller footprint and can provide adequate blending even with excipients having bulk property variations. The vertical blender offers some additional advantages as well. First, they could be operated at wide fill levels from 10% to 100% of operating volume. Second, the powder inside the blender is less susceptible to contamination and abrasion as the seal around the shaft is mounted on top of the blender. Lastly, the conical vessel and the seal are designed in such a way that they can withstand pressure and vacuum conditions [14]. This helps in smooth unloading operations and downstream powder transfer.

The significant benefits that can be realized/theorized by incorporating semicontinuous blending over batch blending are as follows:

(1) The blending time needed in semicontinuous blending, in general, is less than that required for batch blending. For example, in this case study, the

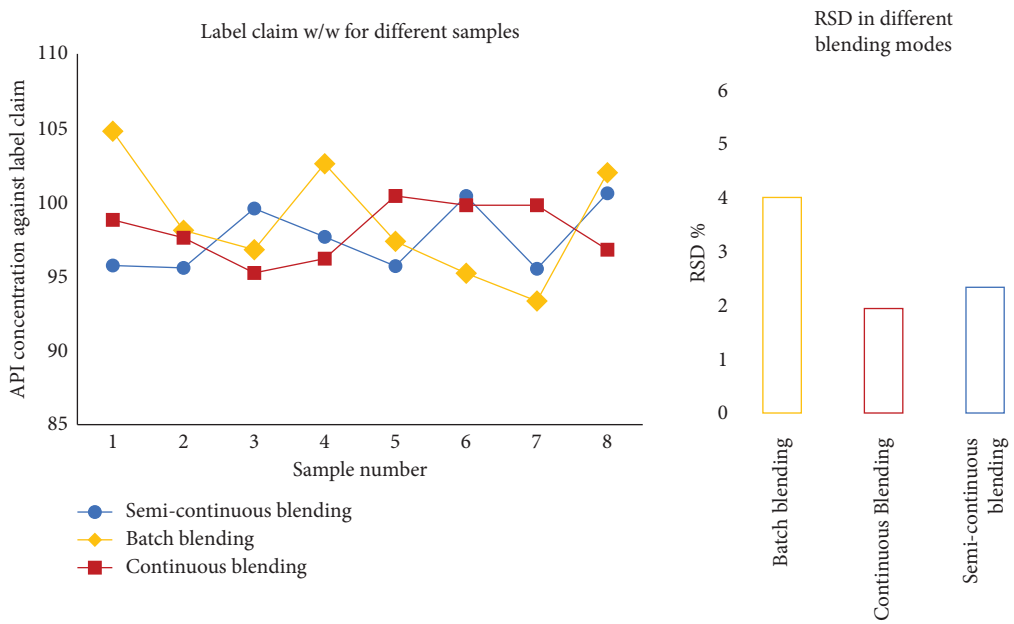

Figure 9: API concentration variations and RSD variation comparison in batch blending, continuous blending, and semicontinuous blending.

Table 4: Comparison of output blend from batch blending, continuous blending, and semicontinuous blending.

	Batch blending	Continuous blending	Semicontinuous blending
Bulk density (g/ml)	0.367 (SD 0.017)	0.358 (SD 0.022)	0.373 (SD 0.016)
Tap density (g/ml)	0.462 (SD 0.012)	0.451 (SD 0.013)	0.470 (SD 0.012)
Carr index	20.515	20.622	20.582
Hausner'S ratio	1.258	1.260	1.259

Standard deviation (SD) is mentioned in parenthesis.

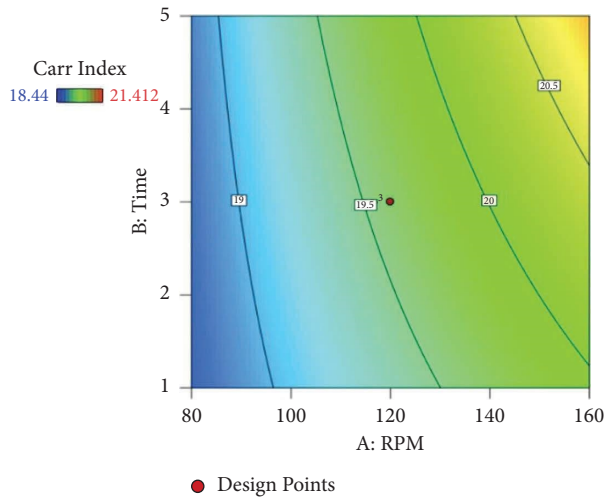

Figure 10: Variation in CI values by changing the RPM (A) and blending time (B) in the design space.

blending time in batch blending was 25 minutes and in semicontinuous blending was 5 minutes. However, different formulations can have different blending times based on the ingredients and material properties.

(2) Batch blending requires extensive manual intervention, and there is a higher possibility of manual error as frequent material dispensing of the exact weight is needed per batch. Manual intervention is also needed during blender opening, material

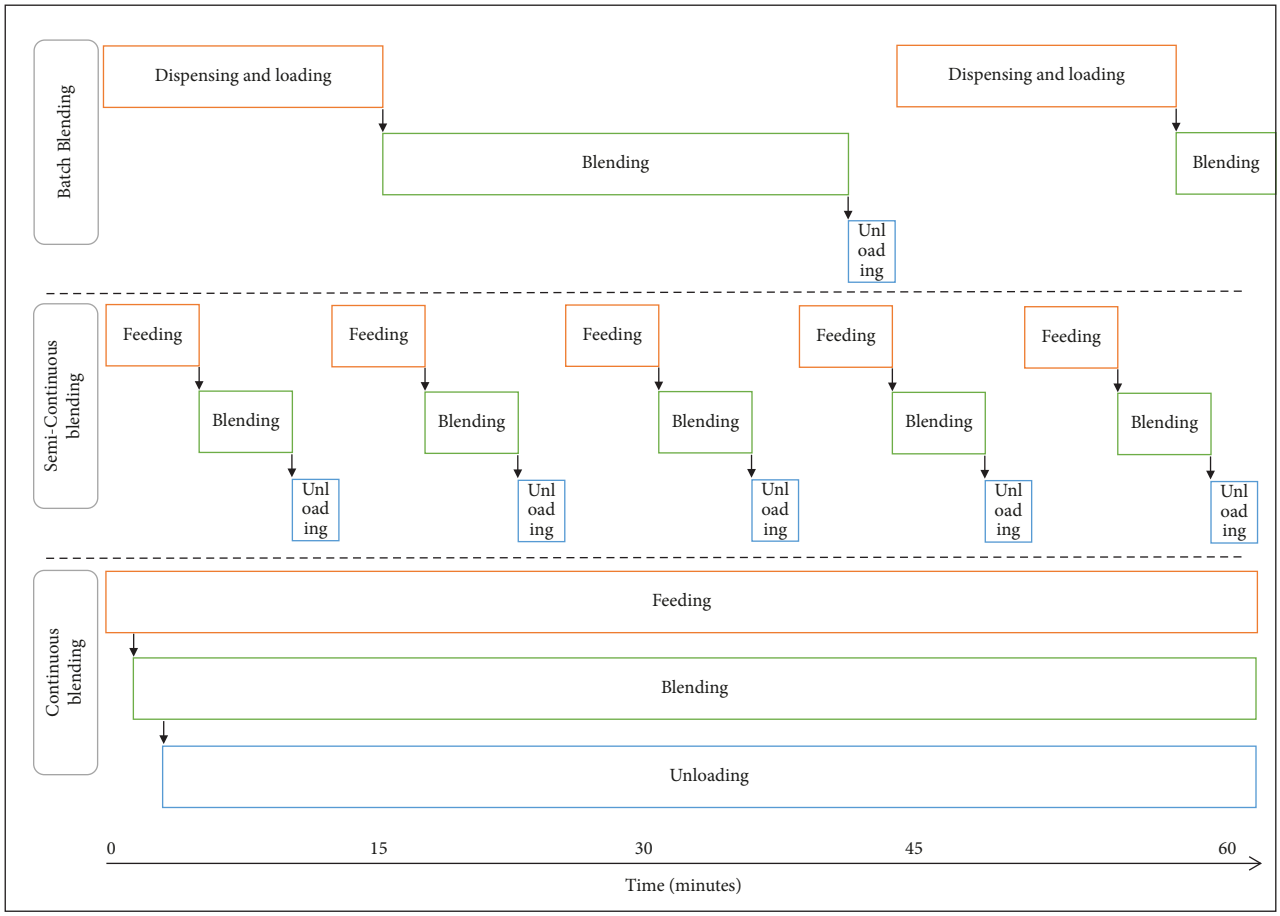

Figure 11: Overview of operations in batch, semicontinuous, and continuous blending modes.

charging, and following the process parameters accurately. In semicontinuous mode, the feeders can dispense the required quantity directly into the blender with little to no manual intervention. There is no risk of human error or potential material loss during dispensing and loading into the batch blender or following the process parameters. All the ingredients can be added simultaneously by different feeders.

(3) Unlike batch blending, the output of the semicontinuous blender can be used to feed either batch or continuous downstream operations. The material can be unloaded for downstream batch operations and charged back to the next unit operation. For continuous downstream operations, the output can be planned so that it can regularly fill the hopper of the following continuous unit operation.

(4) Mixing via a moving impeller during the addition of materials prevents stratification.

(5) The batch size can be varied in semicontinuous blending by varying the number of small batches combined for one batch. As shown in the case study, the blender fill level had the most negligible impact on the blending performance. Hence, the output of each small batch produced semicontinuously can also be varied by testing and changing the fill level inside the blender.

(6) The scale-up would be relatively easier in semicontinuous blending as it is not needed to go to a very large scale. Instead, the semicontinuous setup can be run for longer hours.

(7) The closed operation in semicontinuous mode reduces the chances of contamination and exposure to operators.

(8) Lastly, the semicontinuous blender would require a smaller footprint.

The benefits of semicontinuous blending over continuous blending are as follows:

(1) The blending time in semicontinuous blending can be easily varied for the given set of ingredients. In continuous blending, the amount of time the material stays in the blender is constrained by the length of the continuous blender. The short blender length, however, can be compensated by the use of a weir at the end of the blender which can increase the residence time. The change in impeller design that allows for back mixing can also increase the residence time for blending. In scenarios where many excipients and APIs must be blended in one go, longer blending

residence times may be needed. As there are no such physical constraints in the semicontinuous blender, blending time can be chosen as per the process's need without varying the blender configuration.

(2) In continuous blending, the flow rate of each of the input materials should be as constant as possible. Otherwise, the variation in the flow rate of any ingredients can affect the blending performance. Materials with poor flow properties can show more significant variations in flow rate. Loss in weight feeders operating at flow rates close to the upper or lower equipment operating limit can also show higher variation in mass flow rate. In semicontinuous blending, the feeders operate only as dosing devices and any fluctuation in the input flow rate does not affect the overall blending performance as feeding is terminated when the required mass has been delivered.

(3) In continuous blending, it is crucial to have a more in-depth process understanding to identify the onset of the steady state and have a mechanism to evaluate the beginning of the steady state in real time and throw/divert the material produced before the steady state is reached. In semicontinuous blending, steady-state evaluation is not needed. However, semicontinuous blending will also benefit from real-time monitoring and analysis. PAT tools such as NIR and Raman spectrometers can be used to assess critical quality attributes in line for each small batch that is produced and divert only a small amount of material when a particular batch does not meet the specifications without affecting adjacent small batches.

(4) The semicontinuous blender provides good flexibility regarding the number of ingredients to be added and blending time and hence would be more suitable for products with many ingredients and different material properties. The setup would also be able to accommodate multiple products. Continuous blender also provides good flexibility and the possibility of using multiple feeders. However, while using these blenders in practice at the Purdue pilot plant, cleaning and product changeover operations for the semicontinuous blender were easier in our experience. These benefits over the existing blending modes make a compelling case to test the semicontinuous blending mode.

The possible disadvantage of semicontinuous blending over continuous blending is that the former needs more human intervention while refilling the feeders and unloading the small batches. Automated refilling of feeders could overcome this disadvantage in installations on the production floor. The semicontinuous blending would also utilize the real-time monitoring of API concentration, such as continuous blending, to ensure the blending performance in real time over several batches. The case study with acetaminophen and microcrystalline cellulose provided promising results concerning the uniformity of API distribution and other process improvements. Many pharmaceutical processes have many ingredients that need to be blended in one step, and hence such a case study can be tested out next. An investigation of blend uniformity of API along with three to four excipients with different powder flow properties can be carried out to understand the methodology in such a scenario.

5. Conclusion

The results from semicontinuous blending by using an integrated feeding blending process show good consistency. As conceptualized above, the possible benefits of incorporating semicontinuous blending make it a good alternative for blending in pharmaceutical manufacturing of oral solids alongside the current batch and continuous blending modes. The important process parameters studied here are impeller RPM, blending time, and fill level inside the blender. The impeller RPM has the most significant effect on blending performance. During semicontinuous blending at a 2.34% level, the observed RSD is considerably lower than the acceptable variation limit of 5%. The final blend's bulk properties are similar to those achieved with the other two blending methods. The blending performance could be further improved for this binary blend system. However, the scope of this work was to show the feasibility of the semicontinuous system and conceptualize its potential benefits. Semicontinuous blending mode has several advantages over batch blending mode, such as shorter blending time, smaller footprint, and others, as mentioned in the discussion section. It can produce homogeneous blends with good blend uniformity and requires lesser manual intervention. This study highlights the relative advantages of semicontinuous blending and would lead to more work in the direction of semicontinuous mode as the pharmaceutical industry is actively looking for better processes and alternatives to batch manufacturing. The semicontinuous mode of blending provides one such alternative to the existing blending modes.

Data Availability

The data used to support the findings of this study are included within the article and any additional data are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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