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Research Article

Real-Time Particle Size Analysis Using Focused Beam Reflectance Measurement as a Process Analytical Technology Tool for a Continuous Granulation–Drying–Milling Process

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Abstract. Focused beam reflectance measurement (FBRM) was used as a process analytical technology tool to perform inline real-time particle size analysis of a proprietary granulation manufactured using a continuous twin-screw granulation–drying–milling process. A significant relationship between D20, D50, and D80 length-weighted chord length and sieve particle size was observed with a p value of <0.0001 and R^2 of 0.886. A central composite response surface statistical design was used to evaluate the effect of granulator screw speed and Comil® impeller speed on the length-weighted chord length distribution (CLD) and particle size distribution (PSD) determined by FBRM and nested sieve analysis, respectively. The effect of granulator speed and mill speed on bulk density, tapped density, Compressibility Index, and Flowability Index were also investigated. An inline FBRM probe placed below the Comil-generated chord lengths and CLD data at designated times. The collection of the milled samples for sieve analysis and PSD evaluation were coordinated with the timing of the FBRM determinations. Both FBRM and sieve analysis resulted in similar bimodal distributions for all ten manufactured batches studied. Within the experimental space studied, the granulator screw speed (650–850 rpm) and Comil® impeller speed (1,000–2,000 rpm) did not have a significant effect on CLD, PSD, bulk density, tapped density, Compressibility Index, and Flowability Index (p value>0.05).

KEY WORDS: continuous granulation-drying-milling; focused beam reflectance measurement (FBRM); process analytical technology (PAT); real-time particle size measurement.

INTRODUCTION

Granulation is a common unit operation for manufacturing solid dosage forms, such as tablets, capsules, and sachets. Granule particle size and particle size distribution are important parameters that can impact granule friability (1), granule flowability (1), tablet weight variation (1), tabletability (2), granule bulk density (3), tablet porosity (3), and tablet dissolution rate (4). The ability to assure the manufacture of reproducible product requires that the granule particle size and distribution can be produced within given specified limits. Laser diffraction and sieve analysis are commonly used techniques to measure granule particle size post-milling. Sieve analysis equipment is relatively inexpensive, and it is still widely used atline and for quality control purposes. Although sieve analysis is the most common method for granule particle size analysis in the pharmaceutical industry, the analysis is time consuming and difficult to perform for oily or cohesive powders or granules with particle sizes of less than 25 μm. If the particles retained on any sieve are found to be aggregates rather than single particles, the method is not easily reproducible. The particle diameter information obtained using analytical sieving represents the second largest particle dimension and is influenced by particle shape (5). Laser diffraction methods provide results relatively quickly, but the measurement technique assumes that the subject particle is a sphere which is not necessarily valid especially for aggregates and more irregular-shaped granules. Laser diffraction instrumentation is also relatively expensive compared with an analytical sieve apparatus. An optimum method of granule size analysis would involve inline real-time particle size measurement and feedback control which can reduce human error, decrease analytical time and cost, decrease production cycle time, increase material throughput, and provide enhanced granule size control. As more companies move to continuous processes, process analytical technologies (PAT) that provide inline real-time granule size feedback control become even more critical for manufacturing high-quality cost-effective products.

According to the Food and Drug Administration, "PAT is a system for design, analysis, and control of manufacturing processes, based on continuous monitoring of quality and

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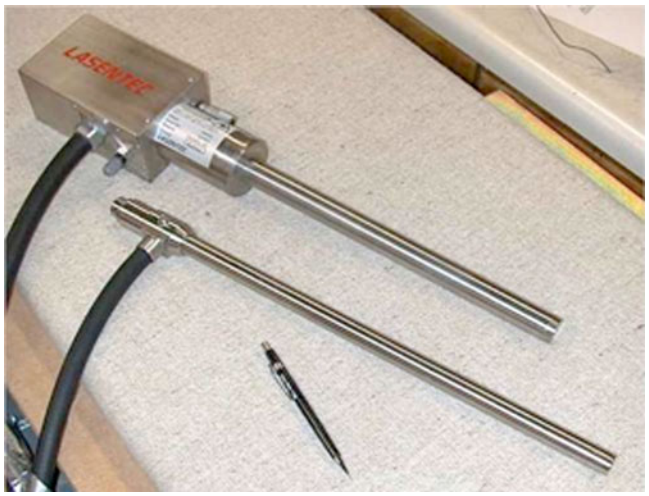

Fig. 1. FBRM probe

performance attributes of raw material, intermediates and products" (6). Focused beam reflectance measurement (FBRM) has been widely employed for monitoring and controlling the crystallization process (7–9). A flocculation study (10) used inline FBRM to report real-time mean particle size and particle size distribution of suspended aggregates. Although the example cited is from the paper industry, it can be applied to pharmaceutical suspensions as well. Heath and coworkers (11) have reported the use of FBRM to provide *in situ* particle size measurements for suspensions over a wide range of suspension concentrations. The factors affecting FBRM particle size determinations for emulsion droplets have also been investigated (12). An atline FBRM technique was developed to monitor the granule growth during fluid-bed granulation. The FBRM chord length data were comparable to particle sizes measured by laser diffraction and sieve analysis (13). Focused beam reflectance has also been used inline to follow particle size enlargement during high-shear wet granulation (14). To the authors' knowledge, this is the first reported study to employ FBRM to size milled granule particles inline in real time during a continuous granulation–drying–milling process.

The FBRM instrument is composed of three parts: a measurement probe (Fig. 1), an electronic measurement unit, and a computer for data acquisition and analysis. The probe is typically immersed in a flowing suspension of particles. FBRM is easy to use and has minimal maintenance and calibration requirements. On the other hand, the major drawback of the technology is potential fouling of the probe window by the dispersed material. If material sticks to the probe window, the same particles tend to be counted multiple times. This problem was encountered in the present study. The newer Mettler Toledo FBRM® C35 probe and icFBRM software have addressed the fouling issue by including a scraper unit (patent pending) that keeps the probe window clean and software that corrects for multiple counting of any adhered particles. Briefly, the FBRM system uses a rotating laser optics design that can determine particle chord lengths by detecting reflected light from the particle. A laser beam is projected through a sapphire window (Fig. 2a) and when the focused rotating laser beam contacts the particle, light is reflected and propagated back through the probe sapphire window. The particle continues to reflect light until the rotating focused beam reaches the opposite edge of the particle. Particle size is measured in terms of a "chord length" (Fig. 2b), which is defined as the distance between the two edges of a particle. The software calculates the chord length by multiplying the optical rotating laser scan speed by the reflected signal time. The scan speed can be adjusted from 2 to 8 m/s to accommodate different sample particle size distributions, dispersion concentrations, and dispersion flow rates. Thousands of chord lengths are acquired per second and are organized in channels (size intervals). The chord length is expressed as a frequency distribution (Fig. 2c). The influence of particle shape, particle refractive index, dispersion media refractive index, focal length, suspension concentration, amount of fines, and particle size on chord length distributions has been investigated to relate chord length distributions to the "real or actual" particle size distributions (15,16). The Lasentec M600P® has been qualified by the Pacific Northwest National Laboratory and Oak Ridge National Laboratory (17). This study evaluated the effect of air bubbles, solids coating, dispersion medium color,

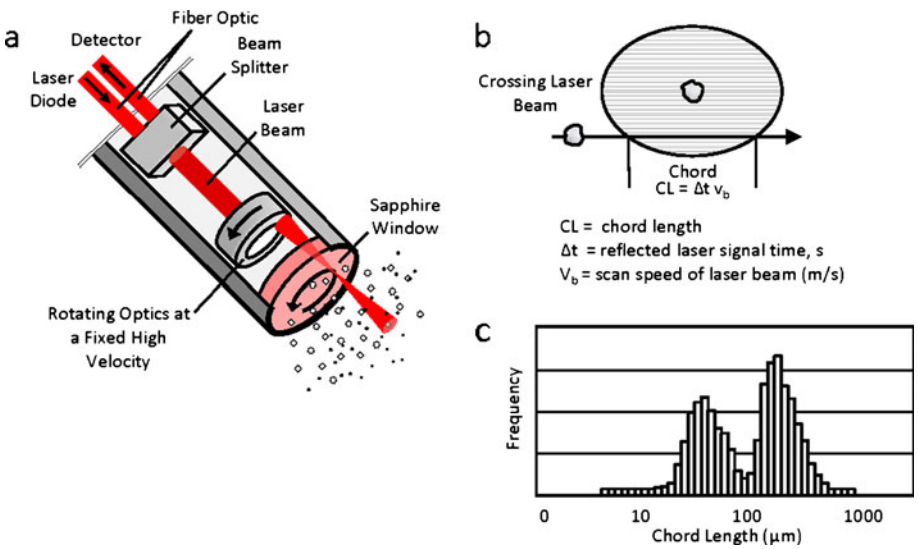

Fig. 2. FBRM measurement: **a** FBRM probe, **b** chord length measurement, and **c** chord length frequency distribution (adapted with permission from Mettler Toledo)

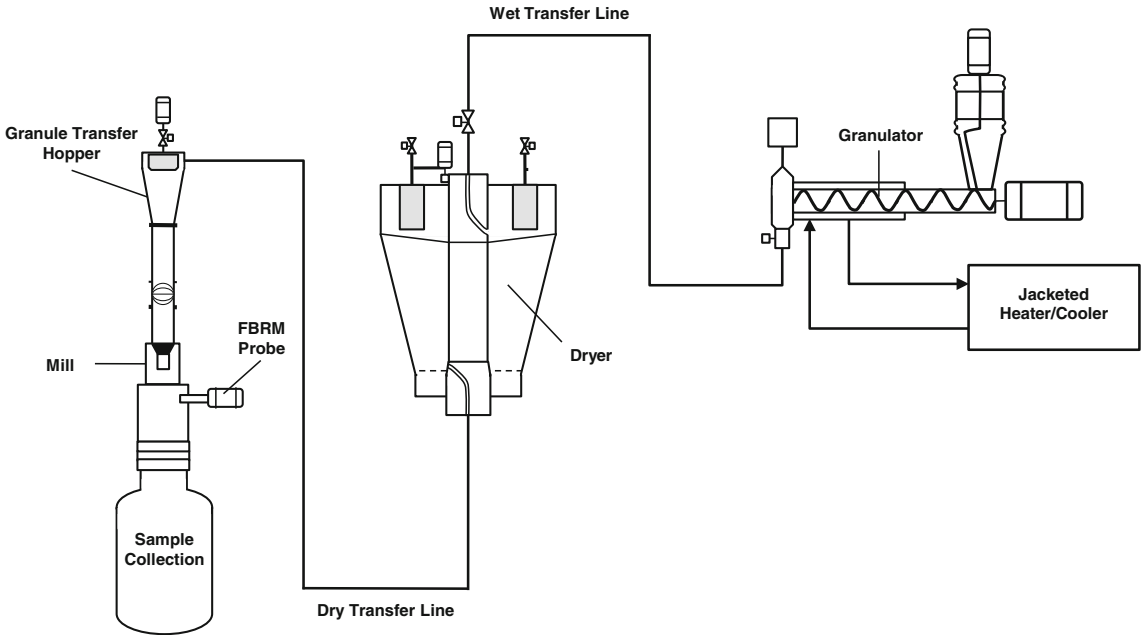

Fig. 3. Flow diagram of ConsiGma™ continuous granulator–dryer–milling kit (Courtesy GSK Zebulon, NC)

dispersion flow rate, solids concentration, scan time, and comparison of inline and offline data analysis. FBRM measurements can be used to qualitatively represent material particle size without converting it into the actual particle size or particle size distribution. For most applications, the relevant inprocess and product attributes may be correlated directly with chord lengths and chord length distribution.

For this study, there was specific interest in correlating the FBRM chord lengths to sieve particle size data because there was significant product history using sieve data. Therefore, the primary aim of this study was to use FBRM as an inline real-time PAT tool to analyze milled granule particle size manufactured by a continuous granulation–drying–milling process and develop a correlation between FBRM chord length and particle sizes determined from sieve data. A secondary aim was to determine the effect of the twin-screw granulator speed and Comil® impeller speed on FBRM chord length distribution, sieve particle size distribution, bulk density, tapped density, Compressibility Index, and Flowability Index measurements.

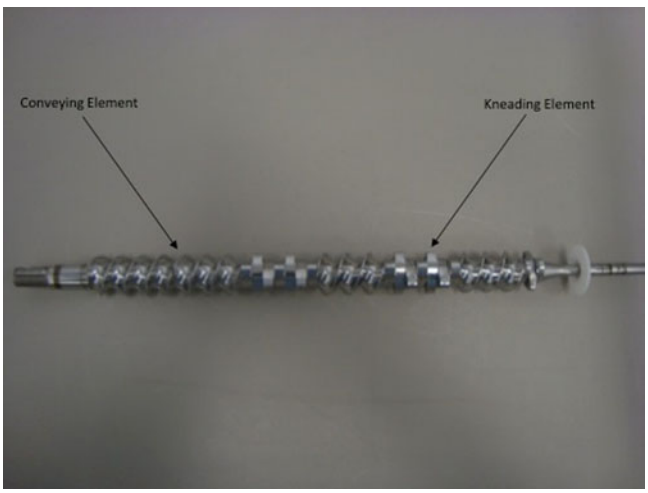

Fig. 4. Representative continuous screw arrangement

MATERIALS AND METHODS

Materials and Equipment

GlaxoSmithKline (GSK), Zebulon, NC, USA supplied the bulk active pharmaceutical ingredient (API), povidone, hypromellose, and US Pharmacopeia (USP) water.

A production scale continuous granulation fluid-bed drying–milling process utilized the ConsiGma™ system (by GEA Pharma Systems nv-Collette™). The ConsiGma system links a continuous corotating, nonintermeshing twin-screw granulator, a semi-continuous six-cell fluid-bed dryer, and a Quadro® Comil® through vacuum transfer connections (Fig. 3). A drug preblend was metered to the rotating screw element that conveys material at a controlled screw speed into the continuous screw work zone. Immediately prior to entering the twin screw work zone, granulating solution was introduced to the moving powder mass at a controlled rate. Kneader elements were added to the core screw that provides work input into the wetted mass. The wet granulation consistency was controlled by amount and

Table I. Granulation–Drying–Milling Parameters Held Constant During Each Experimental Run

Powder feed rate	25 kg/h
Granulation liquid feed rate	21 g/min
Filling time	180 s
Residence time	650 s
Inlet air temperature	35°C
Inlet air dew point	15.5°C
Air flow rate	200 cu ft/min
Sample size	1.25 kg/run
Screen size	850 μm

Table II. Central Composite Response Surface Design

Experimental runs	Screw speed (rpm)	Mill speed (rpm)
1	750	2,000
2 center point	750	1,500
3	650	1,000
4	650	2,000
5	750	1,000
6	650	1,500
7	850	2,000
8	850	1,500
9 center point	750	1,500
10	850	1,000

JMP 8 Statistical Package (21)

rate of powder addition, amount and rate of granulating solution addition, screw speed and kneader configuration. Work input to the granulation process can also be modulated by adding kneading elements at varying angles to the continuous core screw configuration. This body of work utilized two kneaders at 60° (Fig. 4). A predetermined amount of wet granulation was vacuum transferred and loaded into a cell of the semi-continuous fluid-bed dryer by an inlet control valve. Once the wet granulation was loaded, the valve moved to the next drying cell while the granulation in the first cell was undergoing drying. The remainder of the cells were loaded and dried in the same manner. When the drying process was completed for the first cell, a discharge valve rotated to allow the dried granulation to be vacuum transferred to the mill for particle sizing. Milled samples could be automatically diverted for collection as desired.

A Mettler Toledo FBRM® M680 probe and Retsch sieve shaker with calibrated sieves were used to determine granule particle size. The FBRM system was calibrated with polyvinylchloride reference beads (18). The milled granule tapped density was measured with the Vankel tapped density tester (19). A Flodex (20) apparatus (Model 21-101-050) was used to determine the Flowability Index of the granulations.

Methods

Experimental Design

The API was granulated, dried, and milled using the continuous granulation–drying–milling ConsiGma™ system (Fig. 3). The FBRM probe was located just below the mill screen and was placed at a 45° angle to the exiting granulation. A central composite response surface statistical design was used to evaluate the effect of granulator screw speed and Comil® impeller speed on granule chord length and particle size determined by FBRM and nested sieve analysis, respectively. JMP 8 (21) was used to analyze the FBRM chord length and sieve particle size correlation and its significance. The effect of the twin-screw corotating granulator screw speed and Comil impeller speed on granule particle size, bulk density, tapped density, Compressibility Index, and Flowability Index were also evaluated (21). A number of other processing parameters such as powder feed rate, granulation liquid feed rate, filling time, residence time, inlet air temperature, inlet air dew point, air flow rate, sample size, and mill screen size and configuration were held constant (Table I). The randomized experimental run design is shown in Table II. The twin-screw speed and Comil impeller speed were studied at 650, 750, and 850 rpm and 1,000, 1,500, and 2,000 rpm, respectively. The center points of the experimental space were replicated and are represented by experimental runs 2 and 9.

Sampling

Once manufacturing steady state was reached, approximated 1.25 kg of milled granulation was sampled from each experimental run for sieve, bulk density, tapped density, and Flodex analyses. The free flowing milled material was collected in a waste container and at designated times the granulation was diverted into a prelabeled time stamped sample container. Once the free flowing sample was taken, the milled material was diverted back to the waste container. The data from these time stamped samples were matched with corresponding FBRM data that were collected simultaneously while the free flowing milled granule sample was being collected.

FBRM

The FBRM probe was placed below the mill and granule chord lengths were collected using 90 log-channels over the range of 1–1,000 μm. The FBRM software (22) allows the user to select from five different chord length weightings. The weighting choices are 1/length-weighted, unweighted, length-weighted, square-weighted, and cube-weighted distributions which provide amplification or deamplification of the larger chord lengths depending on the selected weighting. In this study, the FBRM length-weighted chord length ("CL" or "chord length") is reported which amplifies the larger chord lengths. This is somewhat analogous to sieve analysis which

Table III. FBRM Chord Length Distribution

	Experimental runs									
Microns	1	2	3	4	5	6	7	8	9	10
45–52.9	9.05[a]	5.41	6.83	7.30	5.95	5.00	5.94	4.36	3.87	5.29
53–74.9	22.26	10.61	12.07	14.21	10.89	12.19	9.90	8.93	10.48	14.90
75–149.9	29.75	22.94	23.75	22.54	22.89	26.15	23.87	25.64	23.50	22.17
150–179.9	4.91	8.85	7.72	4.73	7.29	6.69	6.14	4.98	5.03	6.95
180–249.9	28.24	31.96	37.09	36.80	33.24	36.05	37.04	34.48	33.98	36.53
250–449.9	2.46	15.54	9.88	13.14	15.88	13.11	15.07	19.67	19.64	10.99
450–850	3.30	4.67	2.62	1.24	3.84	0.79	2.02	1.93	3.48	3.17

FBRM focused beam reflectance measurement
[a] Percent chord length in size interval

emphasizes the second largest particle dimension by allowing this dimension to pass through the screen while preventing the largest aspect size from passing through the screen. The length-weighted chord lengths were used to generate the FBRM length-weighted chord length distributions ("CLD"). For the remainder of this manuscript, the terms CL or chord length and CLD or chord length distribution refer to length-weighted size data. The focal point was set to 0 μm (external face of the window) and measurement duration of 10 s was used. A spinning disc assembly was used to avoid probe fouling. The granules exiting the Comil fell directly onto the center of a spinning disc and they were propelled off in a circular pattern by centrifugal force. The FBRM probe was placed such that the propelled granules that contacted the probe window provided probe self-cleaning. A CLD table was constructed by determining the percent CL for each size interval that was equivalent to sieve size intervals. The D20, D50, and D80 CL were determined from a cumulative percent distribution that was generated from the chord length distribution. For example, D20 is the cumulated percent CL size that accounts for 20% or less of the CL which is the 20th percentile. D50 and D80 sizes were determined in the same way.

Sieve Analysis

One hundred and fifty grams of granules were subjected to sieve analysis. The sample amount was calculated considering the density of the granulation (0.8 g/mL) and standard error of 5%. Eight nested sieves were used for sieve analysis. The sieve sizes were 20 (850 μm), 40 (425 μm), 60 (250 μm), 80 (180 μm), 100 (150 μm), 200 (75 μm), 270 (53 μm), and 325 meshes (45 μm). The weighed sample was placed on the top sieve (20 mesh); a lid was placed on that sieve and the assembly was tightly screwed on the Retsch sieve shaker assembly. The amplitude dial was set to 50 where the particles are lifted off the screen surface and set back down 50 times per second at 50 Hz current. Each analysis was carried out for 5 min. After shaking, the assembly was unscrewed and each sieve was removed without disturbing the granulation inside. The amount of granulation retained on each sieve was weighed on a calibrated balance and weight retained on each sieve was recorded. Each run was analyzed in triplicate. A particle size distribution (PSD) table was constructed by determining the percent granule weight for each particle size (PS) interval. Interval sizes were based on the size of the nested screens. The PSD was converted to a cumulative weight percent size plot and the D20, D50, and D80 sizes were determined from this graph. D20, D50, and D80 are the particle sizes associated with the 20th, 50th, and 80th percentile which is the particle size where 20%, 50%, and 80% or less of the granule weight resides. For the remainder of this discussion, PS and PSD represent the particle size and particle size distribution obtained from sieve analysis.

Bulk and Tapped Density

Bulk density and tapped density measurements were made using a modified USP method (23) that evolved through the characterization of this product. A 100-mL graduated cylinder was tared on a calibrated balance and filled up to 50 mL with granules. This volume was considered the unset-

Table IV. Sieve Particle Size Distribution

Microns	Experimental runs									
	1	2	3	4	5	6	7	8	9	10
45–52.9	5.04[a]±2.02	3.16±1.93	4.67±0.10	2.67±0.95	3.09±0.31	1.39±0.49	2.80±1.34	1.03±0.59	1.74±0.20	1.26±0.38
53–74.9	13.61±0.18	12.00±0.10	12.57±1.96	11.97±0.67	10.09±0.44	7.85±1.11	9.78±1.20	6.94±0.80	7.89±0.41	7.54±0.26
75–149.9	24.09±2.14	27.00±1.64	28.69±1.05	25.24±0.65	24.65±1.06	24.69±1.03	27.63±3.76	18.48±1.18	17.97±0.78	19.12±0.09
150–179.9	10.00±1.44	13.19±1.49	10.17±0.96	11.24±1.67	10.59±1.14	12.96±0.96	14.39±3.30	16.64±0.44	20.18±1.61	19.46±1.12
180–249.9	16.29±0.56	21.40±1.53	20.35±0.59	20.42±0.40	18.27±0.39	25.55±2.16	23.94±2.83	26.28±1.19	26.05±0.76	29.07±0.07
250–449.9	21.01±1.77	20.03±0.44	21.54±2.22	25.58±1.23	29.83±1.03	24.69±1.53	19.85±0.42	26.83±1.19	24.14±0.40	21.52±0.35
450–850	9.96±0.70	2.13±0.20	1.94±0.22	2.80±0.49	3.31±0.27	2.88±0.12	1.53±0.11	3.67±0.28	2.00±0.19	2.02±0.01

[a] Mean and standard deviation (n=3) percent in size interval

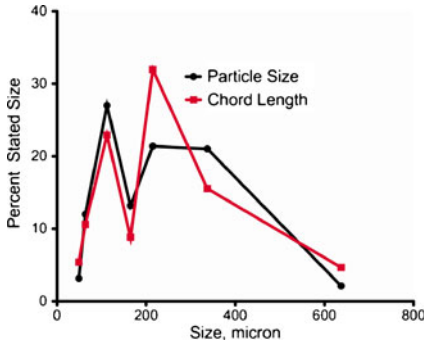

Fig. 5. Chord length and particle size distribution for experimental run 2

tled apparent volume (V_0). The granules were carefully introduced into the cylinder to avoid compacting the powder. Granule bulk density (ρ_{bulk}) was calculated by dividing the granule weight by V_0. The bulk density determinations were performed in triplicate for all ten runs. Following the bulk density determination, the cylinder and granule material used for the bulk density determination were then loaded on the tap density tester. The unit was set to tap for 50 times. At the end of the test, the final volume of granules (V_f) was recorded. The tapped density (ρ_{tapped}) was calculated by dividing the granule weight by V_f. Triplicate tapped density measurements were made for each of the experimental runs.

Compressibility Index

The Compressibility Index was calculated per the USP (24) to characterize the granule powder flow properties. The bulk and tapped density were obtained from the modified USP procedures described above and the Compressibility Index for the ten experimental runs were determined in triplicate using Eq. 1.

$$\text{Compressibility Index} = \left[\left(\rho_{tapped} - \rho_{bulk}\right) \Big/ \rho_{tapped}\right] \times 100 \quad (1)$$

Flowability Index

Several methods for measuring powder flow through an orifice are discussed in USP chapter <1174> Powder Flow (24). These methods measure powder flow under the influence of gravity. In the present study, the Flodex apparatus (25) was

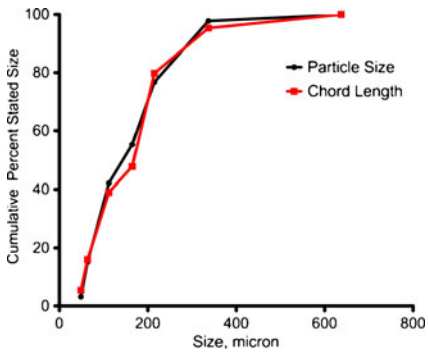

Fig. 6. Cumulative percent plot of chord length and particle size for experimental run 2

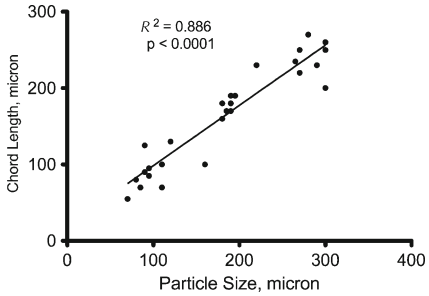

Fig. 7. Bivariant fit between chord length and particle size at D20, D50, and D80 cumulative percent

used to measure the granulation flow properties and Flowability Index. The Flodex Operation Manual (26) procedure was used as the experimental method. The Flodex apparatus was set up with the funnel 2 cm above the cylinder assembly. Each set of flow experiments used the 16-mm flow measurement disk as the starting point. Fifty grams of granules were carefully loaded into the cylindrical container to prevent packing. Thirty seconds after all the granulation had been added to the cylinder the release lever was slowly actuated allowing the closure plate to open. If the material flowed through the 16-mm disk, smaller and smaller diameter flow measurement disks were used until a negative result was obtained. The test was considered to be negative if a hole at the bottom of the disk was not visible from the top of the cylinder. If the material did not flow through the 16-mm disk, larger and larger diameter flow measurement disks were used until a positive result was obtained and a visible hole was observed from the top of the cylinder. The Flowability Index (26) is the diameter of the smallest opening through which the granules form a visible hole on three consecutive tests. The Flodex apparatus was carefully cleaned and dried before each test.

RESULTS AND DISCUSSION

One of the major disadvantages of the FBRM probe system is the tendency of the probe to become fouled with small particles. In this study, a self-cleaning spinning disc assembly was designed to minimize small particles adhering to the probe window. The intent of the design was to allow the milled granulation to fall directly onto the spinning disc. The placement of the disc and the centrifugal force caused the granulation to contact the FBRM probe window to remove

Table V. Compressibility Index and Flowability Index

Experimental run	Compressibility index	Flowability index (mm diameter opening)
1	16.00±1.00[a]	14
2	14.00±0.00	14
3	14.33±1.57	7
4	14.66±1.15	14
5	15.00±1.00	9
6	12.00±2.64	4
7	18.00±2.00	8
8	11.66±0.57	7
9	14.00±2.00	4
10	12.66±1.15	4

[a] Mean and standard deviation (n=3)

adhered material. Unfortunately, data analysis showed that the assembly was not completely self-cleaning which led to small particles less than 45 μm being counted multiple times. The newer Mettler Toledo FBRM® C35 system has addressed the fouling issue by including a patent-pending scraper that keeps the probe window clean. In addition, the new icFBRM™ software program corrects for multiple counting of any adhered particles. In order to compare the FBRM data to the sieve data, particles less than 45 μm were discarded from the present analysis. From the sieve analysis for all 10 experimental runs, particles smaller than 45 μm accounted for only a mean of 1.23% and a range of 0.2% to 3.81% of the total sample weight. This represents only a very small fraction of the entire measured particle size distribution. Typical particle size sieve characterizations for granulated products include particles size ranges from 45 μm to 850 μm as these represent distributions that will provide reasonable flow properties for downstream unit operations such as compression and encapsulation. The FBRM CLD and sieve PSD are given in Tables III and IV. The CLD and PSD for run 2 are shown in Fig. 5. All ten experimental runs exhibited a bimodal CLD and PSD. A cumulative percent plot for experimental center point run 2 is provided in Fig. 6 which shows that CL and PS closely track each other. Similar CL and PS overlays of the cumulative plots were obtained for all ten experimental runs. Figure 7 shows the bivariate fit between D20, D50, and D80 chord length and particle size data. The data show a significant relationship between D20, D50, and D80 chord length and particle size with a p value of less than 0.0001 and R^2 of 0.886. Since there was significant product history using sieve analysis, this relationship can be used to tie real-time CLD to the historical sieve data. Such a correlation can enable the use of real-time feedback control loops within the continuous process to adjust critical parameter inputs such as powder feed rates, amount and rate of granulation solution, inlet moisture dew point, inlet air temperature, inlet air flow rate, dryer residence time, and milling conditions to modulate the granule particle size in real time to match an optimized historical sieve particle size distribution. This PAT control loop would help ensure the generation of uniform, optimized granulation during every manufacturing run regardless of variability introduced by changes in input raw material and other factors.

The Compressibility Index and Flowability Index values are listed for each experimental run in Table V. The Compressibility Index for all samples ranged from 12 to 18 which according to the USP (23) represents granules that have good to fair flow. The Flowability Index ranged from 4 to 14 mm diameter opening where the 4-mm value indicates a better flowing material. A correlation could not be established between the Compressibility Index and the Flowability Index. According to the USP (23), there is no general scale available for flow through orifice methods and comparison between published results has been problematic.

Within the experimental space studied, the granulator screw speed (650–850 rpm) and Comil impeller speed (1,000–2,000 rpm) did not have a significant effect on the CLD, PSD, bulk density, tapped density, Compressibility Index, and Flowability Index (p value greater than 0.05). This suggests that over this relatively wide operating range the manufacturing process provides robust granulations that do not significantly affect the granulation factors studied. It is possible that a different screw configuration with more kneaders at different angles may provide a different result.

CONCLUSIONS

A statistically significant relationship between D20, D50, and D80 chord lengths and particle size ($p<0.0001$, $R^2=0.886$) was achieved when multiple counting of particles below 45 μm was accounted for. Particles smaller than 45 μm accounted for only 0.2% to 3.81% of the total sample weight which is a small fraction of the entire measured particle size distribution. This study demonstrates the feasibility of utilizing inline real-time FBRM measurements to measure chord length in a continuous granulation–drying–milling process. By establishing a meaningful relationship with historical sieve data, real-time feedback control loops within the continuous process can be created based on the knowledge and predictability of the sieve data.

Within the experimental space studied, the granulator screw speed (650–850 rpm) and Comil® impeller speed (1,000–2,000 rpm) did not have a significant effect on CLD, PSD, bulk density, tapped density, Compressibility Index, and Flowability Index (p value>0.05). Response surface analysis showed the continuous process had a wide acceptable operation range that provided robust particle size and granule flow properties.

Newer probes with wipers and software that account for multiple counting are key improvements that should allow FBRM to be used inline in real time to determine the granule chord length and CLD during continuous granulation-drying-milling processes. Using the new FBRM probes and software in additional studies that evaluate broader process ranges and a larger number of process variables will help strengthen the relationship between chord length and particle size.

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