A PAT Approach to Improve Process Understanding of High Shear Wet Granulation Through In-Line Particle Measurement Using FBRM C35

JUN HUANG,[1] GOLDI KAUL,[1] JULIA UTZ,[2] PEDRO HERNANDEZ,[1] VICTOR WONG,[1] DARAGH BRADLEY,[1] ARWINDER NAGI,[1] DES O'GRADY[3]

[1]Pharmaceutical Development Center, Wyeth Pharmaceuticals, 401 N Middletown Road, Pearl River, New York 10965

[2]Excella GmbH, 90537 Feucht, Nürnberger Strasse 12, Germany

[3]Mettler-Toledo, 14883 NE 87th St, Redmond, Washington 98052

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ABSTRACT: This article summarizes the investigation of in-line particle characterization during high shear wet granulation (HSWG) using focused beam reflectance measurement (FBRM) for enhanced process understanding, which is part of an effort to develop this drug product within the framework of quality by design (QbD) and process analytical technology (PAT). Traditionally, the effectiveness of in-line monitoring of HSWG processes is hindered by wet and sticky material fouling the probe resulting in inconsistent and erroneous data collection. For this study, a FBRM C35 probe was used which incorporates a scraping mechanism to maintain a clean probe window ensuring consistent measurements throughout each batch. The evaluations were conducted on nine scale-up DOE development batches and eight clinical sub-lots. In the DOE campaign, the purpose of FBRM was used to study the impact of varying water amount and wet massing time on granule dimension and count during granulation, while batch-to-batch variation or batch reproducibility was evaluated under the same process conditions for the clinical batches. In addition, a preliminary investigation of the most optimal probe position was conducted. The results indicate that FBRM is capable of monitoring the rate and degree of change to granule dimension/count during HSWG, and could be a potential technique for granulation endpoint determination. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: FBRM C35; focused beam reflectance measurement (FBRM); high shear wet granulation; particle size; particle size distribution (PSD); design of experiments (DOE); critical process parameter (CPP); critical quality attribute (CQA); quality by design (QbD); process analytical technology (PAT)

INTRODUCTION

It is well known that granule particle size and particle size distribution are important granule properties, or in many cases intermediate critical quality attributes, in characterizing high shear wet granulation (HSWG) process and its endpoint. In addition, properties such as granule density, porosity, morphology, rheology, and content uniformity are also important quality attributes in HSWG. These intermediate quality attributes may impact downstream product manufacturability such as blend flow, compressibility, and final product quality such as tablet content uniformity, disintegration and dissolution. Therefore, it is crucial to monitor and control granule particle growth and particle size distribution, and thus ensure batch-to-batch consistency during HSWG.

High shear wet granulation presents a complex and challenging condition for in-line granulation monitoring and proper endpoint determination. Few techniques are commercially available for in-line monitoring of HSWG. Existing techniques include the use of torque measurement, power consumption, near infra red (NIR) spectroscopy & acoustics etc.[1–3] NIR spectroscopy has been shown to be promising in measuring particle size due to its cross-sensitivity, not only capturing chemical but also physical information about the samples. However, extraction

Correspondence to: Jun Huang (Telephone: +1-845-602-1075; Fax: +1-845-602-4324; E-mail: huangj38@wyeth.com)

of particle size information often requires chemometric model development and method validation.[4] Other techniques reported in the literature include the use of an *in situ* image processing system and passive acoustic emission techniques to monitor particle size during HSWG.[5–8] All these techniques have shown promising use to a certain extent, but each has its limitations that hamper accurate endpoint determination. For instance, torque/power consumption is scale dependent, and not always sensitive enough to characterize the granulation process. The technique could potentially give inaccurate results in cases where sticky materials build up along the granulator wall instead of staying in the bowl during the measurement. Acoustic approaches depend very much on scale, cleanliness and usage of equipment, and require frequent re-calibration of models. In addition, most of these techniques are insensitive to the variation in the fines population, a common cause of downstream process and product issues.

Both focused beam reflectance measurement (FBRM) and Parsum (Spatial Filtering Technique) are designed to directly track real-time change of particle size and distribution in the process. Both techniques are being recognized in the pharmaceutical industry as effective in-line particle characterization tools, but the reported applications to HSWG are few.[9–11] It may be largely due to the fact that HSWG poses harsh conditions for in-line particle size measurement. Materials may be sticky and adhesive to begin with or get sticky during granulation, causing probe fouling. The newly developed FBRM C35 probe utilizes a mechanical scraper on the sapphire window to prevent probe fouling, whereas pressurized air is used to dilute/disperse particles in the Parsum probe and minimize fouling. Particle size analyses with Parsum are always based on statistical evaluation of a specified quantity of individual particles, while FBRM performs calculations based on particles collected within a specified amount of measurement time. A detailed comparison study of each measurement technique is beyond the scope of this article. The FBRM C35 analyzer has just been commercialized recently. The reported applications of the FBRM C35 analyzer for monitoring HSWG at manufacturing scale have not yet been seen in publication.

Since this article will focus entirely on the use of FBRM to monitor HSWG, it is important to note that FBRM should not be considered as a particle size analyzer in the traditional analytical sense. It is really an *in situ* processing monitoring tool that tracks the rate and degree of change to particle count and size as the particles naturally exist in process. It reports a chord length distribution (CLD), sensitive to particle number and size—not a particle size distribution. Correlations between FBRM and other size analyzers such as laser diffraction and sieving have been reported in granulation processes.[10] However the correlation will depend on (a) particle shape—laser diffraction assumes a sphere; FBRM does not, and (b) fine particles in the presence of coarse particles—FBRM is sensitive to fines; laser diffraction and sieving are not. A review of correlations between FBRM and numerous off-line techniques for a variety of processes has also been published.[12]

Based on quality risk assessment, performed in accordance with ICH Q9 guidance, granule particle size distribution was identified as a potential critical quality attribute, along with other granule properties such as granule morphology and density, as the powder blend of API and excipients proceeds through sequential pre-mixing, binder addition, and wet massing phases to a finished wet granulation. Previous experimental runs suggested that wet granulation of this particular drug product is sticky, and tends to build up along granulator walls during HSWG. It was therefore decided to evaluate FBRM C35 for in-line particle characterization at a commercial-scale high shear wet granulator. This article presents a new process analytical technology (PAT) approach to monitor batch evolution (process trajectory) with regard to in-process particle characterization during granulation. The following studies were conducted: (1) study impact of process parameters on granule counts and dimension; (2) evaluate batch-to-batch variation and batch reproducibility; (3) correlate chord length data with downstream quality attributes. The ultimate goal is to determine granulation endpoint using FBRM, possibly in combination with other approaches, such as multivariate process modeling of process parameters like water and wet massing times simultaneously.

EXPERIMENTAL AND METHODS

Material and Experimental

Materials

API, croscarmellose sodium (Ac-di-sol), microcrystalline cellulose (Avicel PH 101 and Avicel PH 102), povidone K25, poloxamer 188 (Lutrol F68), and magnesium stearate. The API in the formulation was a typical BCS-class II compound, with pH dependent solubility and adequate permeability. The API comprises of >50% by weight of the tablet formulation.

DoE Development Batches

A 125 L bottom impeller driven, vertical Lodige granulator was used for dry blending and HSWG.

The primary aim of this exercise was to identify the elements of the scale-up that required process/product understanding. All of the batches per the scale-up DoE design, shown in Table 1, were manufactured at the 25 kg scale for both wet granulation and blending purposes. Percent water was kept constant during scale-up at 27.12% (w/w) of intragranular for the center point runs. The water amounts for the other DoE batches were varied ±10% from the target of 7.675 L. This equated to water between 25.4% and 29% (w/w) in the runs. The pre-blend time for all the DoE batches was fixed at 4 min. Binder/poloxamer solution was added at different rates depending on water amounts in the wet granulation of the DoE batches so as to complete addition in 8 min. The granulator bowl was opened and scraped after the entire binder solution had been added to remove adherent mass on the walls. Wet massing was done for different times per the DoE design outlined in Table 1. Post-wet massing, samples were collected for particle size distribution and visual assessment.

Clinical Batches

Based on experience with the scale-up DoE batches, process parameters were fixed for the clinical batches. Eight granulation batches were carried out in the same Lodige 125 L. The pre-blend time was fixed at 4 min, which was followed by binder solution addition for 8 min and 5 min wet massing time.

FBRM Method of Measurement

FBRM operates by shining a monochromatic laser beam, of wavelength 790 nm, generated by a class I laser source, via a fibre optic conduit, to an optical assembly housed within a probe shaft. This optical assembly (Fig. 1) consists of a lens mounted eccentrically, and this entire assembly rotates in a circular motion at high speeds. The laser is focused to a tight beam spot fixed at the probe window. As the beam crosses the surface of a particle, light from the beam is backscattered into the probe. The duration of each reflection is multiplied by the velocity of the scanning beam (4 m/s), resulting in a chord length measurement. Typically many thousands of chord lengths are measured per second and these individual measurements can be combined to produce a CLD. The CLD is a robust fingerprint of the particulate system and is sensitive to changes in the size, number, and shape of particles in the system. Importantly it is sensitive not only to the degree of change but also the rate of change making the FBRM technique extremely powerful for studying process trajectory during dynamic particulate processes. The FBRM probe requires no sample dilution and its rapid in-line data collection allows for the possibility of real-time process control, thereby enabling an immediate response to any process change. FBRM has been used to characterize a variety of particulate systems and its use in industry and academia is widespread, for example, crystallization,[13] polymerization,[14] wastewater treatment,[15] flocculation,[16] and plant cell suspensions.[17]

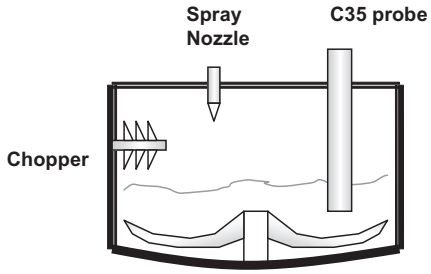

Figure 1. FBRM C35 probe mounted on a Lodige high shear wet granulator.

The FBRM Model C35 system is equipped with a mechanical scraper, which can clear the optical window at a pre-defined time interval. This new feature allows the probe to be used in wet and sticky environments, without having to stop the process and clean the probe. This is one of main reasons that FBRM C35 was selected for monitoring HSWG of this particular product. The system consists of a probe, an air supply, a C35 field unit and a computer running the data acquisition/analysis software iC FBRM®.

The FBRM measurement is calibrated against a known sample of spherical PVC particles to ensure the measurement is within specification. Like any particle characterization technique, results can be validated against other methods once the limitations and differences between each method are known. In this article, FBRM is being used as a process monitoring tool and the absolute particle size is less important than the differences or similarities between the measured trends and distributions. FBRM helps ensure that a process is consistent, robust and repeatable because it is a sensitive and precise relative measurement. It can also be used to

Table 1. Scale-Up/QBD DoE Developmental Batches

Run No.	Wet Massing Time (min)	Water for Wet Granulation (kg)
1	5.0	7.010
2	4.0 (center point)	7.675
3	3.0	8.340
4	4.0(center point)	7.675
5	5.0	8.340
6	4.0(center point)	7.675
7	6.0	7.675
8	4.0(center point)	7.675
9	2.0	7.675
10	3.0	7.010

Figure 2. Probe window before (left) and after granulation (right).

target a repeatable granule size distribution that meets specification.

Installation of the FBRM Probe

Probe position is critical to ensure a representative measurement of the particle system. For particles to be measured they must come in contact with the sapphire probe window where the laser beam is focused. It is critical that the FBRM probe be installed at a proper position in the high shear wet granulator-Lodige 125 L granulator to take representative measurement of the granules. As illustrated in Figure 1, the FBRM probe was vertically inserted into the granulator bowl with a fitting through an existing port on the lid to minimize any equipment modification. As observed, the probe window was still clean due to the scraper after the entire wet granulation process, Figure 2. The probe tip was positioned about 30–50 mm above the impeller blade to ensure that the probe window is immersed into powder bed and stay always in contact with granules during measurement.

Data Acquisition and Analysis

Data acquisition and analysis was performed using iC FBRM. The software displays the particle distribution as well as statistics from this distribution trended over time (i.e., mean, median, #counts/s 0–50 μm, #counts/s 300–1500 μm). The data acquisition /analysis parameters are shown in Table 2.

Selection of appropriate parameters is important to obtain high-quality data representative of the granulation process.

A weighting function can be applied to the CLD in iC FBRM, including no weight, inverse weight, length weight, square weight, and cubic weight. Weighting places more or less emphasis on a particular aspect of the distribution. For this reason, it can be used to significantly enhance the resolution to change occurring in the particle system. For example, the unweighted distribution is more sensitive to change on the fine side of the distribution where as the square weighted distribution is more sensitive to the coarse end of the distribution. CLD profiles and trends can also be smoothed by applying smoothing filters, for example, moving average. All these data treatments or parameters were optimized in the trial runs.

RESULTS AND DISCUSSION

Understand Granulation Behavior by Particle Size Data Trending

Figure 3 displays the trace of chord length X50 (Median, Length-weighted, Moving-average smoothed) during the evolution of Batch 8 (one of the center-point developmental DoE batches). It can be seen that the overall trend of X50 increases as the granulation goes through three phases: pre-blend, water addition, and wet massing. During pre-blending, there is little change in particle size as expected. Clear growth, after an initial small decrease in particle size (X50), can be observed as water addition starts, and granules grow rapidly due to wetting and coalescence. This initial fall in PSD (X50) on addition of water may be attributed to fine mist that is a combination of water droplets and the API/excipient mix produced at the beginning of water addition. Once the initial dry pre-blend starts to get wet, a steady increase is observed in particle size of the blend within the granulator. A downswing in the curve at the 10 min time point may be explained by some variability in chord length measurement as well as variation in sampling within the granulator. Also, as the material wets, it tends to become sticky and adhere to the walls, this stuck material then falls back into the granulator with time. After water addition, granulation process was paused for scrape-down. It was visually observed that the material was sticky and that some build-up occurred along the granulator walls. In the beginning of the wet massing phase, X50 continues to grow rapidly, partially attributed to larger agglomerates scraped down to the bowl. As wet massing continued, it appeared that granules started experiencing a greater extent of breakage and attrition, resulting in decreasing particle size. This is usually observed in granulations at or near the granulation endpoints and is consistent with the principles of HSWG, where granule formation is

Table 2. Data Acquisition and Analysis Parameters

Settings	Scan Speed	Measurement Interval	Scraper Speed	No. of Bins	Weight Type	Smoothing
	4 m/s	5 s	Every 2 s (left and right)	200	Length weight	15 point moving average

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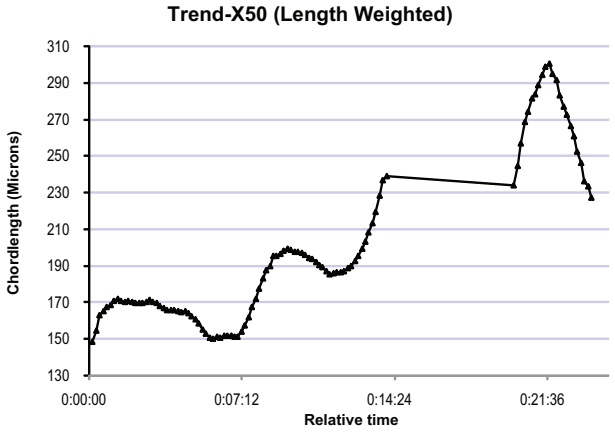

Figure 3. X50 (median chord-length, length weighted) during the granulation developmental DOE Batch 8.

followed by coalescence, agglomeration, and finally breakdown by attrition.

Figure 4 shows CLD selected from pre-blend, water addition and wet massing. Clearly the CLD shifts from left to right over time, indicating increasing particle size during granulation. It is also observed that #counts/s (number of particles per second) on y-axis between size fraction of approximately 70–400μm decrease clearly over the course of granulation, suggesting decreasing number of finer particles and increasing coarser particles as granulation proceeds.

Figure 5 shows more clearly the trend of #counts/s in size fraction <200 μm and >200 μm changing over time. Counts/s for size fraction of >200 μm gradually increase over time, correlated with X50. It should be noted that the distribution profile from wet massing phase appears to be bi-modal, with a peak formed below 100 μm, Figure 4. The exact reason is still unknown. It is unlikely that a fine fraction below 100 μm emerges during wet massing, whereas the phenomenon is not as obvious in the first two phases (pre-blend and binder addition). One hypothesis could be that water droplets form on the probe window as wet granulation process squeezes water between the granules. These water droplets could be measured or mistaken as granule particles by FBRM C35. However, this hypothesis has not yet been verified. Another reason hypothesized could be the fact that during wet massing, the granulation tended to land on the walls. This granulation could also potentially fall back into the granulator. There are size related differences with material in the bowl versus the material on the walls. The granulation on the walls tended to be finer than the one in the bowl. Nevertheless, clear differentiations in CLD profile during granulation indicate that FBRM is capable of characterizing in-process particle size change and potentially determining granulation endpoint based on a target CLD. A target CLD however needs to be specified or defined by studying its impact on the quality attributes of the downstream unit operations. By measuring CLD and number of particles (counts/s) in particular size fractions, FBRM provides useful information to better understand granulation behavior Figure 6.

Impact of Process Parameters on Granule Count and Dimension

In this DoE study, granulation water amount and wet massing time were varied during granulation to study their effect on quality attributes (e.g., particle size

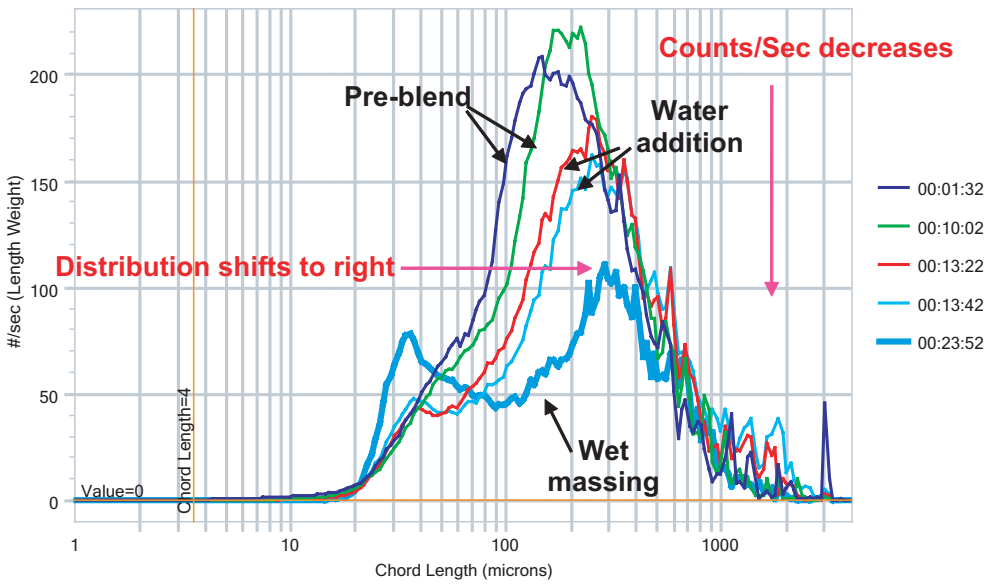

Figure 4. Particle size distribution profiles (length weighted) at the different phases of granulation (Batch 8).

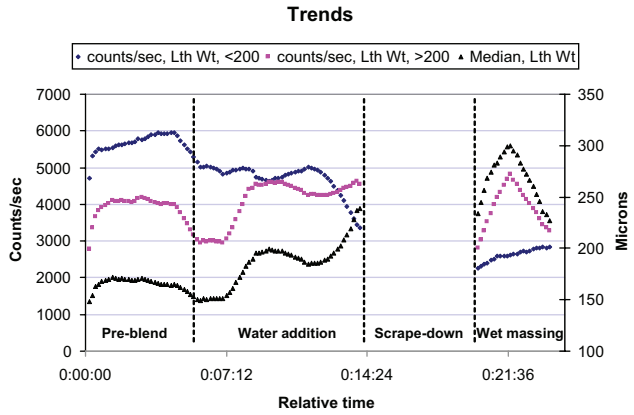

Figure 5. Counts/s of size fraction of <200 μm and >200 μm during granulation Batch 8.

distribution, density) from HSWG, and downstream quality attributes. X50's (Median, length-weighted) for selected DoE batches during wet massing phase are shown in Figure 6.

Batch 3 notably started with higher median size due to the highest amount of water applied to this batch, and continued to grow in the next 3 min. The high amount of water resulted in high addition rate, which could have impacted the overall median size of the granulation. No down-trend in particle size occurred before wet massing ended, due likely to shorter wet massing time. Batch 7 used a mid-level water amount and the longest wet massing time, 6 min. X50 increased in the first 3 min or so, and then decreased continuously till end of granulation. It appeared that breakage and attrition took place to a larger degree than agglomeration in the second half of the wet massing phase. This is consistent with the granulation process, where build-up in size by coalescence is eventually followed by attrition and break-up of particles. For Batch 7, the median dimension decreased the most as it was granulated the longest. The least amount of water was used in Batch 1, leading to relatively smaller and flatter X50 during the entire wet massing phase. Batch 4 is a center-point batch, and its process trajectory appears to evolve somewhere in between all batches. In summary, both water amounts and wet massing times appeared to play in the granulation process trajectory and final granule dimension.

Batch-to-Batch Variation and Batch Reproducibility

Eight granulation batches were manufactured under selected water and wet massing times of 8.34 L and 5 min, respectively in the clinical campaign in May 2009. The water and wet massing time were the same as Batch 5 from the developmental DoE batches. These eight clinical sub-lots were identical w.r.t. water amounts, binder addition rates and wet massing times. The FBRM probe was used to study batch-to-batch variation and batch reproducibility. Due to probe malfunction in two of the batches, data could only be collected for six batches. The impact of probe position on measurement was also investigated. As shown in Figure 7, all batches show similar trends with some degree of variations, mostly attributable to probe positions.

Batches 1a and 2a were measured at the same probe location, and showed excellent reproducibility, evidenced by almost overlapped process trajectories. The same holds true for Batches 3a, 5a, and 6a, which were measured at a higher probe location. Batch 4a also evolved in a similar trend, but showed much smaller size overall, due most likely to the highest probe location used. Batches 1a and 2a used the lowest probe location, and thus showed an overall larger granule dimension. The reason could be that larger particles tend to be distributed more at the lower part of granulator bowl because the centrifugal force within the granulator probably tended to

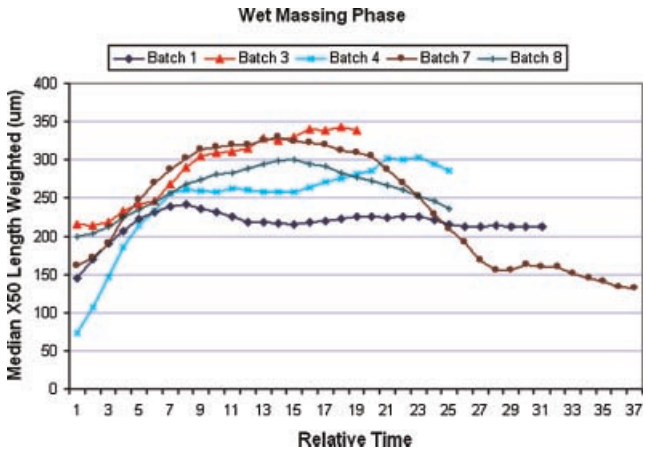

Figure 6. X50 (length weighted) trends during wet massing phase.

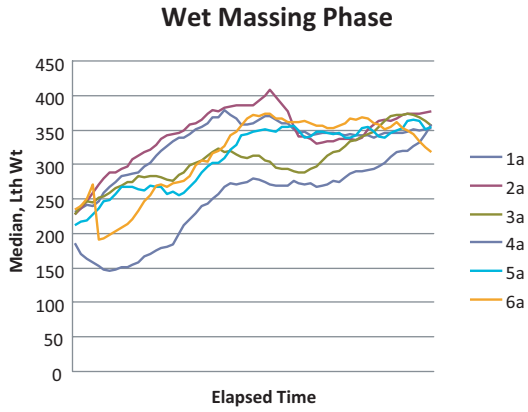

Figure 7. Medians (length weight) of select batches during wet massing phase.

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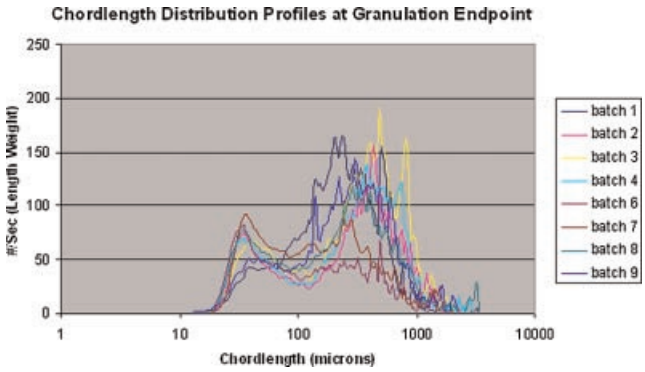

Figure 8. Chordlength distribution (CLD) profiles (length weighted) of the DOE batches at granulation endpoint.

segregate the heavier particles from the lighter/ less dense particles. This probably resulted in the lighter particles rising above the heavier ones. The mid-level probe position produced the trends that evolved somewhere in between those measured at the high and low probe location. It is clear that probe location has a significant impact on the measurement. It is however noteworthy that all batches appeared to converge to the same narrow region towards endpoint, indicating that granulations became more homogeneous as a whole towards endpoint for all these batches.

It should be mentioned that entire CLD profiles can be utilized by multivariate/batch statistical process control (MSPC/BSPC) methodology to study batch-to-batch variation and evaluate overall batch performance. A separate study using MSPC will be reported in a sequel article.

Correlation of Chord Length Data With Downstream Quality Attributes

There are few reports in the literature studying the impact of granule particle size during HSWG on downstream quality attributes. In this study, based on data collected from the scale-up DOE batches, an attempt was made to correlate entire CLD profiles (Fig. 8) at granulation endpoint with downstream quality attributes, such as dried unmilled granule hardness and FFC values for milled dried granules. PLS regression was used to model the relationship. Only 6 or 7 reference values were available. No correlation was found based on limited amount of data, which may also indicate that information other than particle size data is needed to predict downstream attributes. It is also possible that the process parameters varied were not sufficient to cause enough differences in the batches, so as to change the downstream quality attributes. It is known that particle size distribution is not the only quality attribute to determine endpoint. Other attributes, such as density, particle morphology, and content uniformity may also play an important role in influencing downstream quality attributes. Further investigation on this will be conducted in future work as we plan separate experiments to vary these attributes systematically.

CONCLUSIONS

Some issues and limitations were also encountered during the evaluation of the FBRM probe. Measurement did not seem ideal during water addition where wetting/nucleation of particles caused the measurement to be noisy. There thus exists the opportunity to improve the placement of the probe, which in this case could not be explored due to equipment limitations. In the scale-up DoE campaign, it was suspected that not sufficient granules flowed past the probe due to the build up along granulator wall in some batches, evidenced by significant decrease in particle counts. Hence, the probe position was subsequently lowered during the clinical campaign to assure sufficient materials in front of probe. It was also observed that the measurement was noisy at the beginning of wet massing phase. A possible reason for this is that large agglomerates recently scraped down from the granulator wall were outside the FBRM measurement range (3–3000 μm). However, the noisy distribution usually becomes smoother shortly after wet massing starts, as large agglomerates break down due to shear applied by the impeller.

The study has demonstrated that FBRM is a useful PAT tool for in-line particle characterization, and tracking particle growth during HSWG for this drug product. All data generated by the FBRM probe during production can be utilized by multivariate methods to study batch-to-batch variation, diagnose process upsets and evaluate overall batch performance. It should be mentioned that the technique may be useful in scale-up granulation process as particle size distribution is a scale-independent parameter, unlike other scale-dependent process parameters. Therefore, FBRM could be a potential technique, in combination with other tools, for determining granulation endpoint when representative sampling and optimal acquisition parameters are achieved.

Overall, through the limited number of trials at manufacturing scale, FBRM C35 provided a good amount of information for improved process understanding, though some issues and limitations are yet to be resolved. Sampling, data acquisition/analysis settings, for example, probe positioning, focusing, weight type shall be further investigated in the future work.

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