



High Shear Wet Granulation Processes with *In Situ* Particle Characterization

Zane Arp, PD-MOST-PUC, **GSK**
Eric Dycus and Benjamin Smith, **METTLER TOLEDO**

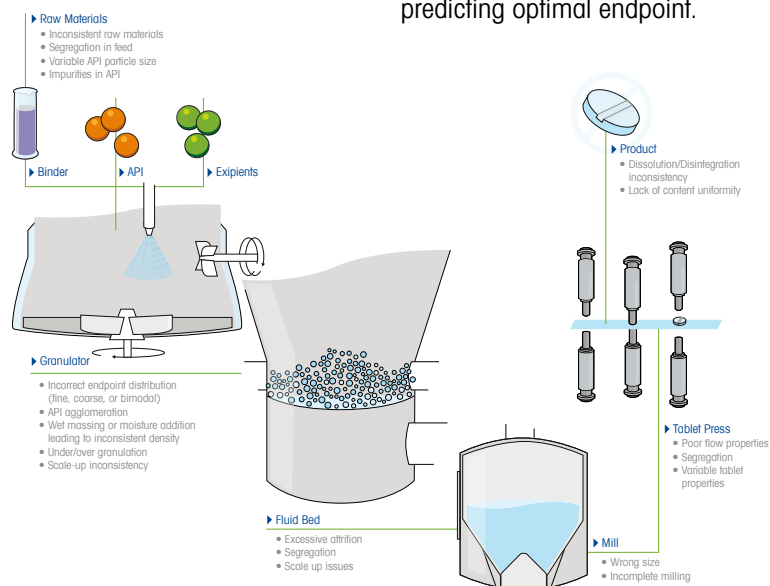
Abstract

One goal of high shear granulation is to yield repeatable endpoint granule size, shape, and density distributions. This is necessary for consistent downstream flow properties, tablet consistency, and content uniformity. Quality by Design (QbD) is a concept applied to gain true process understanding through tools such as Design of Experiment (DOE), risk management, and Process Analytical Technology (PAT). The application of QbD and *in situ* particle characterization techniques, Focused Beam Reflectance Measurement (FBRM[®]) and Particle Video Microscopy (PVM[®]) is demonstrated to track a series of high shear wet granulation batches while varying liquid addition, agitation rate, spray rate, and wet massing time. Ultimately process control may be applied to achieve a specific target endpoint distribution with optimized wet massing time conditions. Promising results lead to the possibility that *in situ* measurements may enable formulators or engineers to minimize batch failures, improve yield, and troubleshoot scale-up to manufacturing. This will allow faster understanding and optimization of a formulation with no sampling required.

Introduction

High shear wet granulation is one of the more complex steps in drug product manufacturing. This step improves the processability of the drug substance largely due to the densification and particle growth during the granulation process which subsequently improves the flow of the drug product in downstream processing. See the flow diagram below outlining where particles play a roll in drug product formulation. Until recently there have been no means by which to measure either the particle dimension or density in real time during granulation. To address this critical need, Focused Beam Reflectance

Measurement (FBRM[®]) fitted with a patented scraper mechanism was utilized to monitor high shear wet granulation. In this study a 12 batch acetaminophen granulation DOE was used to determine optimal endpoint conditions. Optimal granulation endpoint was decided by formulator based empirical examination. This 12 batch training set was then subsequently used to predict the endpoint of batches manufactured with water addition rates that were purposefully varied to conditions outside of those tested in the DOE. FBRM[®] results clearly show similarities and differences between the different DOE batches and was successful in predicting optimal endpoint.



Optimization of High Shear Wet Granulation Processes

Using FBRM® and PVM® *In Situ* Particle Characterization

Methods

A METTLER TOLEDO FBRM® was inserted into a 6L Fluid Air granulator bowl with a modified lid. The probe was inserted directly into the flow of the material above the impellor blades. A 12 batch granulation DOE using the acetaminophen formulation shown in Table 1 was used to test and train the probe to changes in the physical properties of the granulate during the granulation process. The factors changed during this DOE included impellor speed, water addition amount, and wet massing times.

Impellor speed was varied between 271 and 542 rpm, the water concentration was varied between

20, 25, and 30% by weight, and the wet massing time was varied between 1, 2.5, and 4 min.

Optimal processing conditions were determined to be reached with an impellor speed of 542 RPM, water concentration of 25%, and wet massing time of 2.5 min. The chord length distribution corresponding to these ideal conditions was targeted and the FBRM® was used to control the wet massing endpoint in situations in which the water addition rate was purposefully varied to both half and double the rate utilized during the DOE. For all granulation batches the endpoint granule images were acquired with the METTLER TOLEDO PVM® system.

Results

Figure 2 inlay shows the granule growth trends for 2 batches under similar conditions. Figure 2 also shows the corresponding granulation endpoint distributions compared with the distribution measured 1 min into wet massing for the longer batch. As can clearly be seen in this figure, the process could have been stopped at a much earlier time point that would have created a particle distribution very similar to the earlier batch had the FBRM® been utilized to control the process.

Compound	Weight
Acetaminophen	625 g
PVP	20 g
AC-Di-Sol	20 g
Lactose Monohydrate	165 g
Avicel PH-101	135 g

Table 1 Formulation



Figure 1 Picture of the FBRM® inserted into the granulator bowl

Color	DOE#	Actual water addition amount (%)	Wet massing time (min)	Impeller speed (RPM)
Light Blue	6	30	1	542
Green	10	30	1	542
Red	10	30	~4	542

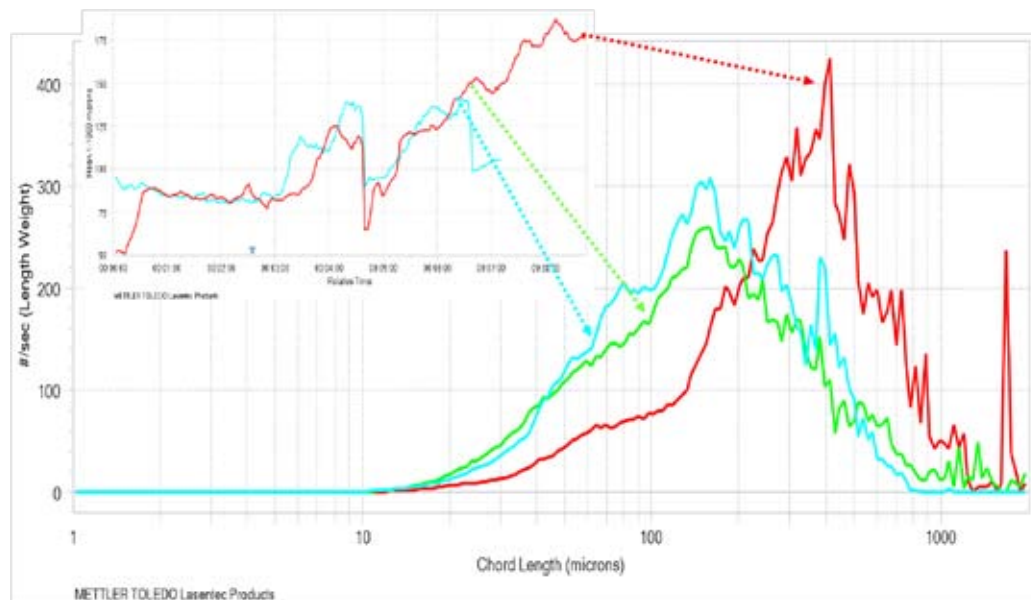


Figure 2

Chord Length trend (inlay) and distributions for two batches demonstrating capability to achieve similar endpoints using the FBRM® distribution for control

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Figure 3 shows endpoint differences observed during the granulation DOE after different water addition conditions. In these batches the FBRM® clearly differentiates over-granulated and under-granulated batches based on the chord length observed at the end of the granulation. This data shows that the use of *in situ* particle characterization during this granulation process can be utilized to quantitatively determine the differences in real time between under, ideally, and over granulated batches. The particle distributions observed are further verified by PVM® images which also show the images of granulates from the different endpoints of this granulation.

Figures 4 and 5 show the results from two controlled batches with widely varying moisture addition rates. DOE 14 spray rate was 125 mg/min; DOE 15 spray rate was 25mg/min. Overgranulation was avoided by stopping the batch before a rapid granule growth phase was reached. Process deviations such as particles sticking to the vessel wall were observed and mitigated using a bowl scrape down implemented after 1 min of growth and the process was then run to the ideal endpoint as determined by the FBRM®. The distribution results of these batches are compared in Figure 5. As can clearly be seen the particle distribution endpoint in the two controlled batches are very similar.

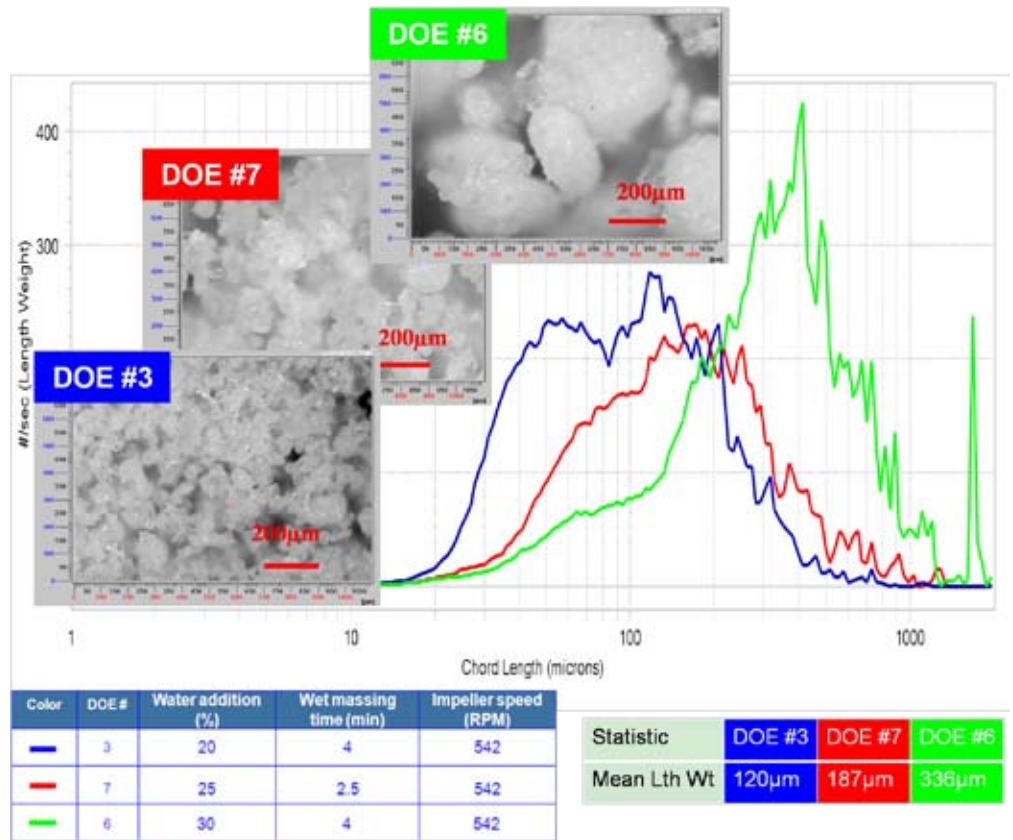


Figure 3 Particle chord length distributions demonstrated in different batches manufactured under different conditions



Figure 4 Mean chord length trend for a controlled batch using varying addition rate processing parameters

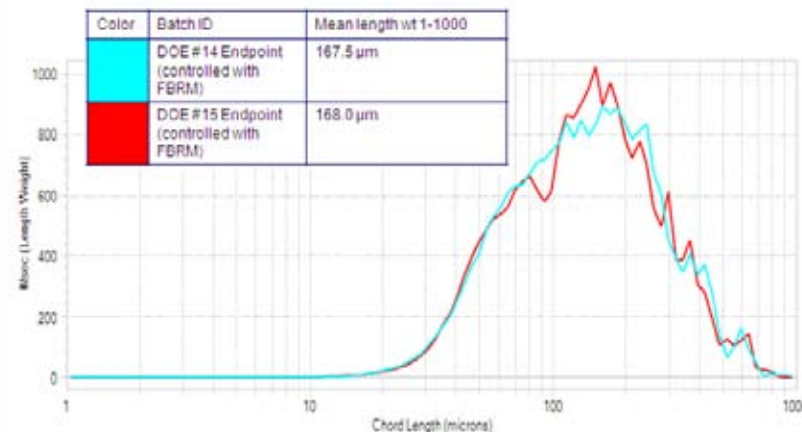


Figure 5 Targeted endpoint chord length distributions for two batches manufactured under varying process conditions

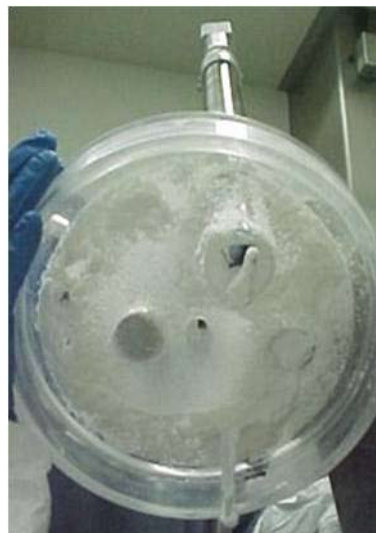
Optimization of High Shear Wet Granulation Processes

Using FBRM® and PVM® *In Situ* Particle Characterization

Conclusion

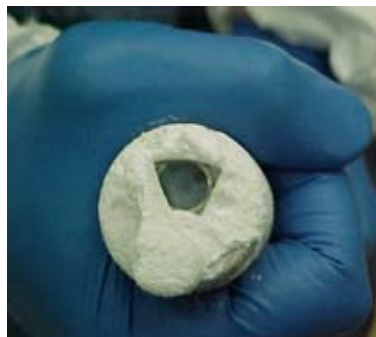
The new FBRM® C35 was highly successful in determining quantitative differences between granulation batches under varying conditions. It has been shown that the FBRM® has the capability to clearly differentiate on a quantitative basis the differences between under, over, and ideal granulation batches. FBRM® can be used to minimize atypical batches and improve batch to batch repeatability. By controlling granulation

processing conditions, FBRM® distributions can help achieve a targeted endpoint distribution, ensuring consistent downstream particle flow, tablet properties, and dissolution rates. Overall the FBRM® C35 window remained clean ensuring consistent data collection and demonstrated the capability to provide real-time optimization of a high shear wet granulation process based on the particle size growth during processing.



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