High Shear Wet Granulation Monitoring: DFF Sensor vs. Focused Beam Reflectance Measurement (FBRM)

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High Shear Wet Granulation

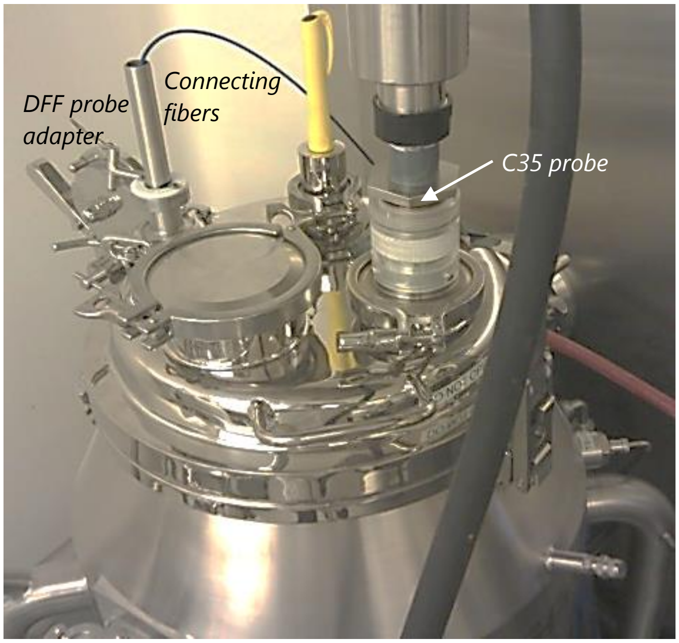
High shear wet granulation (HSWG) process is a complex, high energy, rapid unit operation where the primary powder particles are made to adhere to form large, multiparticle entities called granules. HSWG utilizes granulating fluid (typically water) and a cohesive substance (commonly known as a binder) to effect the adhesion. Characterization of wet mass during the process forms the basis of process analytical technology (PAT) tools, that assist robust and reproducible manufacture by enabling process monitoring, trending, and control (Narang et al. 2017). In addition, PATs can be used to guide development, scale-up, and equipment interchangeability. As a PAT tool, DFF sensor can be applied for monitoring granule densification (Narang et al. 2015), which is one of the key attributes of HSWG (Badawy et. al., 2012, 2016)

By comparing with another in-line PAT, focus beam reflectance measurement (FBRM), this note demonstrates higher sensitivity of DFF sensor in detecting changes in granulation process and resolving formulations with different binder content.

DFF and FBRM probe installation

An FBRM C35 probe by Mettler-Toledo and a DFF sensor model P-4000-40 by Lenterra, Inc. were vertically inserted into the granulator bowl through existing ports in the lid and positioned inside the moving powder mass as seen in the figure.

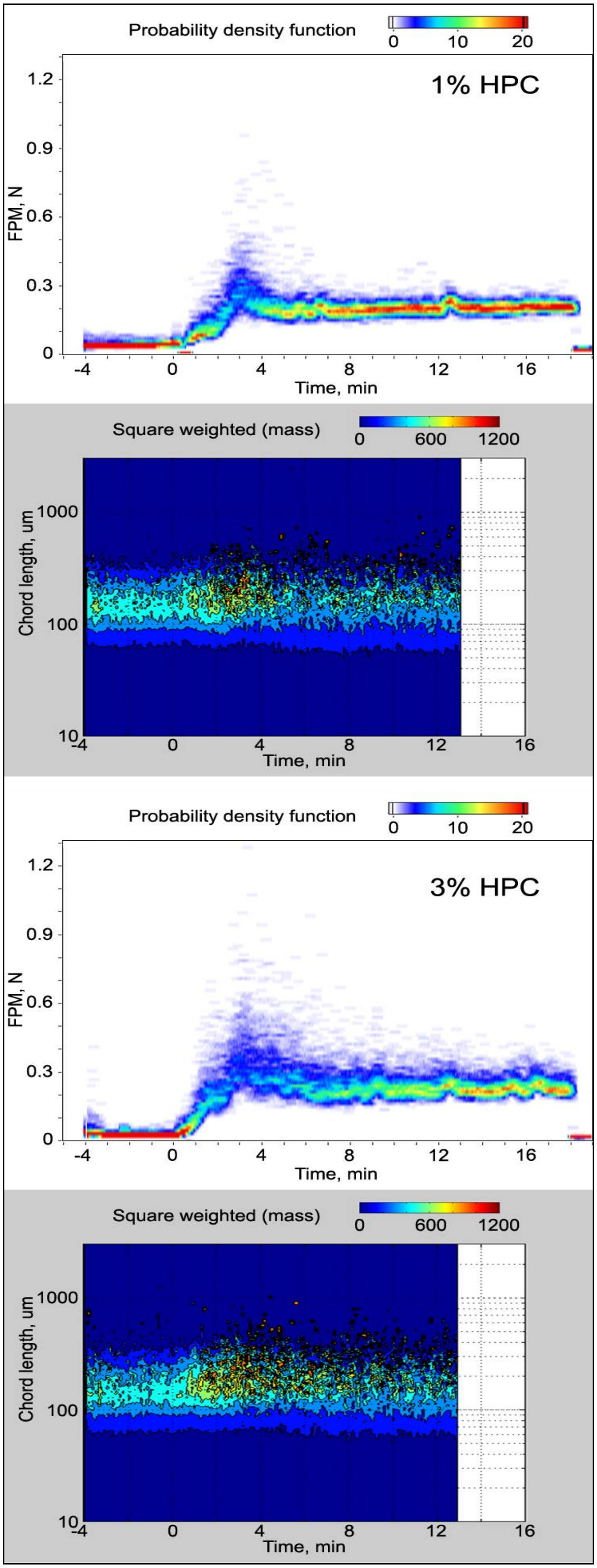
A placebo formulation consisting of 57% w/w microcrystalline cellulose, 37.5% anhydrous lactose, 1% w/w croscarmellose sodium, and different concentrations (1%, 3%, and 5% w/w) of hydroxypropyl cellulose (HPC) was granulated with 40% w/w water in a Aeromatic-Fielder PharmaConnect® 30-liter granulator at impeller rotation speed of 210 rpm and chopper speed of 1000 rpm. In each test, water was added for 3 minutes continuously.

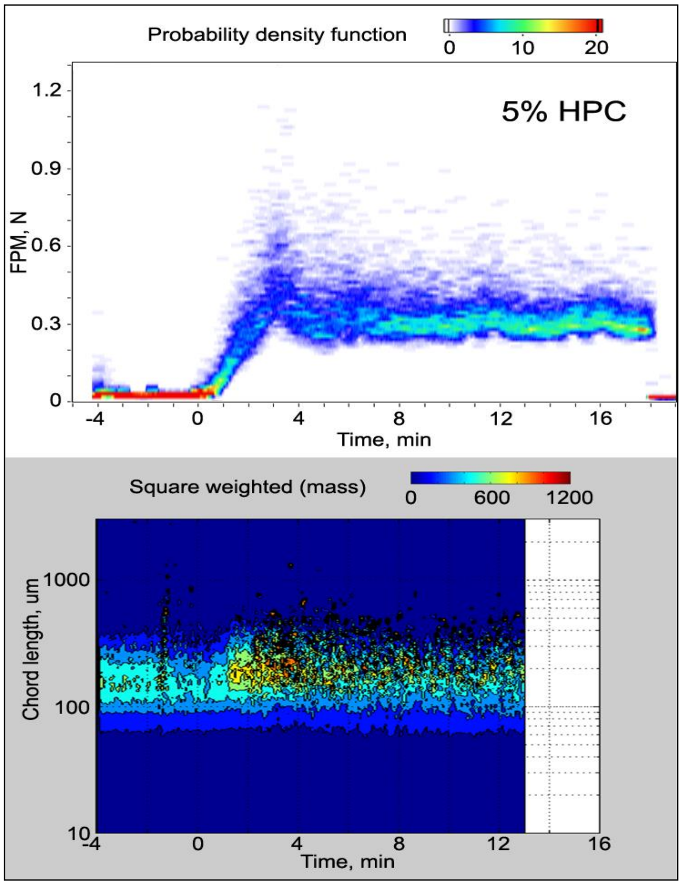


Particle Size and Force Pulse Magnitude Distributions

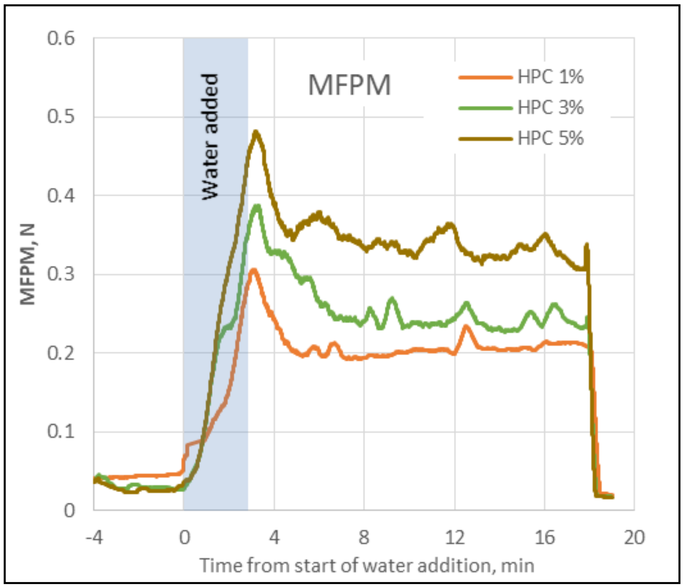
FBRM works by focusing a laser beam on the wet mass particles flowing under the probe through a rotating optical assembly within the probe shaft. Changes in the intensity of the reflected light are recorded as a function of time. Multiplying the time duration for each change in backscatter with the speed of rotation of the laser beam provides a measurement of the size (chord length) of the passing particle or agglomerate. Distribution of chord length data over a small time increment generates a chord length distribution (CLD), which is a dynamic fingerprint of particle size for the wet mass in a high shear granulator. By using the FBRM probe in real-time, changes in particle size during high shear granulation are assessed. The CLD profiles for the three different formulations were generated as color-coded 3-dimensional plots showing chord length as a function of time with the frequency function being represented on the z-axis.

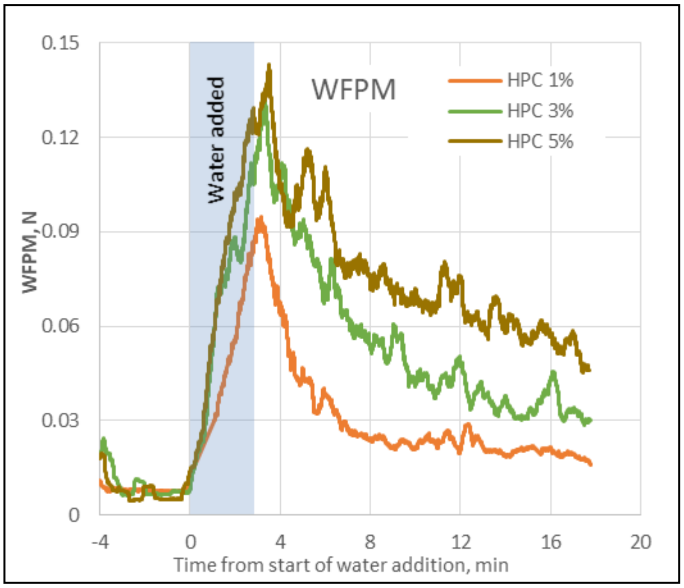
DFF measurements yielded a distribution of force pulse magnitude (FPM) calculated for the frequency of the blades in the tests (10.5 per second). The FPM time course histograms are calculated in a manner similar to that for the CLD profiles measured by the C35 FBRM probe (see Application Note 3). Both evolutions are compared here, synchronized in time.





Two-dimensional charts show how the FPM mean values (MFPM) and the width of FPM distribution (WFPM) change in time, separately for the three formulations.





Conclusion

No significant differences were observed in CLD measurements for the three formulations, especially between formulations with 3 and 5% w/w concentration of HPC respectively. Contrary, both the average value and the width for FPM distribution are significantly different for each of the formulation as seen from the MFPM and WFPM plots. .

Wet granulation process is associated with the formation and growth of granules. Presence of shear in the HSWG process can lead to densification of the granules with reduction in the size and volume of intra-granular pores. Physically, binding or shear forces lead to further increase of the effective mass of a granule as it collides with another granule or an obstacle such as DFF probe. This increase in effective mass manifests itself as increased force measured by the DFF sensor.

In these tests, DFF sensor seems to both reflect the state of the wet granulation and is able to reliably differentiate between batches manufactured with different HPC concentrations, especially between the 3% w/w and 5% w/w HPC formulations. The dynamics of MFPM indicate that the average mass of the granules increases during water addition reaching its maximum soon after the water addition stops, then decreases and flattens out into a plateau. WFPM characterizes the width of the granule size distribution and demonstrate similar behavior, peaking approximately at the same time as MFPM does. One difference between MFPM and WFPM behaviors is that WFPM continues to decrease over the total duration of measurement and does not flat out, especially at 3% and 5% HPC concentrations.

The DFF sensor response is an outcome of particle collision with the sensor, which is measured as a composite force output of all the collisions experienced by the sensor. Thus, the DFF sensor response represents a composite output of granule size and a set of characteristics (such as density and stickiness) that is defined as *wet mass consistency* (Narang et al. 2015). The absence of change in granule size between formulations with 3 and 5% HPC (as measured by the C35 probe) indicates that the DFF sensor response primarily identified wet mass consistency in these formulations, and that this attribute was more sensitive to changes in the granulation conditions than particle size distribution, as measured by the C35 probe.

References

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