In-Line DFF Sensor vs. At-Line FT4 Powder Rheometer® as a PAT tool for High Shear Wet Granulation

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This paper compares the real-time in-line response of DFF sensor with at-line response of FT4 Powder Rheometer® (analyzing wet granules collected at different time points) during the processing of a placebo formulation. This correlation allows better understanding of the DFF sensor response as representing a fundamental powder property of the granules, which is indicative of the resistance of a powder to flow that can be quantitatively measured using an FT4 Powder Rheometer®.

The results reported here are based on the earlier measurements,[1] re-processed and presented in the FPM moving average 300 format.

Methods

Microcrystalline cellulose (MCC, Avicel PH 102®, FMC Biopolymer, Philadelphia, PA; 61% w/w), lactose anhydrous (Sheffield Bioscience, Norwich, NY; 37% w/w), croscarmellose sodium (AcDiSol®, FMC Biopolymer, Philadelphia, PA; 1% w/w) , and hydroxypropyl cellulose (HPC, Klucel EXF®, Ashland Specialty Inredients, Wilminton, DE; binder) were wet granulated with 40% w/w water in a 10-liter PharmaConnect® granulator (GEA, Dusseldorf, Germany) at HPC concentrations of 1% w/w, 3% w/w, and 5% w/w, respectively. MCC concentration was adjusted to accommodate changes in HPC concentrations. Two kilograms of dry powder was granulated with 800 g water, which was continuously added over 180 seconds. The impeller and chopper were turned ON during the dry mixing phase, and they stayed ON through the rest of the granulation cycle. Impeller tip speed was kept at 4.8 m/s for all tests (302 rpm, blade frequency 15 Hz). Chopper speed was 1000 rpm.

All granulation processes were monitored using a DFF sensor with measurement range of ±3N. The probe was installed from the granulator lid using an available ISO KF flange in such a way that the tip of the probe was 2.5 cm above the top of the agitator blade and 8.2 cm off the blade rotation axis.[1] DFF sensor recorded the axial component of the flow force exerted on the cylindrical probe with the measurement rate of 500 data points per second (or one data point every two milliseconds). Along with the flow force measurement, the granulation product temperature was also recorded by the sensor.

The FT4 Powder Rheometer® by Freeman Technology Ltd. measured basic flowability energy (BFE) of the powder samples. All tests in the FT4 were done using the 50 mm bore diameter cylinder that uses a blade of diameter 48 mm. The powder sample was subject to a standard conditioning cycle, to ensure that the state of each powder sample is reproducible before every test.[2] BFE is measured by rotating a precision blade down a helical path through a fixed volume of conditioned powder. During this downward traverse, the torque and axial force acting on the blade are measured. The resistance to flow is calculated and expressed as a flow energy. Both DFF sensor and FT4 Powder Rheometer®, therefore, characterize powder mechanical resistance property that is expected to be influenced by the same complex set of material attributes and process parameters.

For each formulation, granulation process was continued for a predetermined time, after which the granulator was stopped. No sampling was carried out for FT4. The whole granulation mass was retrieved from the granulator and three representative samples withdrawn. The samples were tested in the FT4 Powder Rheometer® immediately after collection. A new batch of the same formulation was then used for the next end-time point. Each granulation process was continuously monitored by the DFF sensor until it was stopped for at-line analysis. A total of six granulation batches with different end time points (1, 2, 3, 4, 6, and 8 minutes from start of water addition) plus one dry powder measurement (0 minutes)were tested, for each formulation separately. Batches with different end-times are indicated on the plots below with their respective colors.

Results

Evolution of the force pulse magnitude (FPM) calculated at FPM frequency of 15 Hz, which is the blade frequency of granulation, is plotted for seven separate batches for each formulation, indicated by different colors. The three values of basic flowability energy (BFE) measured by the FT4 Powder Rheometer® after granulation of each particular batch are shown as circles at the respective time instants. The color of the BFE values match that of the FPM values for the same batch.

The last plot shows BFE overlapped with FPM measurements for the three formulations together. The longest FPM measurement (480 s) is taken from the three previous plots, to compare with values of BFE (that are the means of measurements obtained from three samples that were collected after each run, with the error bars being the standard deviations of mean over the three measurements).

The force pulse magnitude (FPM) is the principal metric provided by the DFF sensor for powder mixing applications such as HSWG monitoring. As discussed in reference[1] and White Paper 3, FPM is the difference between the force at the maximum and the preceding minimum. Each FPM, therefore, characterizes a passing of one blade under the probe pin. In the following plots, FPM evolution is smoothened with moving average value of 300. The moving average order is selected for adequate representation of the trend and typically is between 300 and 600 for HSWG.

For either formulation, immediately after the agitator is turned on, FPM values vary for different batches suggesting different degrees of uniformity in the initial loads. The uniformity significantly improves to the end of the dry mixing stage (time zero) - when FPM measurements appear to stabilize and show similar values near 0.03N for all batches, and for all formulations. Similarly, BFE values for zero-time batches (dry powder) are close to each other for the three formulations.

There is a sharp rise in FPM during water addition as measured by the DFF sensor. The FT4 does not show a rise in BFE during water addition for the HPC 1% formulation. It measures relatively small increase in BFE during water addition in the 3% and 5% HPC formulation. In addition, for 5% HPC, the rise is not monotonic.

All FPM curves peak shortly after water addition is complete. The FT4 measurements for 3% and 5% HPC batches appear to peak during water addition but do not start declining until after the end of water addition, during the wet massing stage. This indicates that the initiation of decline of FPM signal could be used as a PAT parameter for process control. There is no obvious maximum is observed for FT4 measurements in the HPC 1% formulation. The two measurement techniques showed similarities in the profiles for the granulation stage (after water addition ends), where both DFF and FT4 demonstrated decreasing signal.

In general, differences of granule wet mass consistency between formulations manufactured with different HPC concentrations were evident with both DFF and FT4 measurements. Sensitivity of resolving different HPC concentrations is higher for the DFF sensor, which is evident when comparing FPM and BFE evolutions between 1% and 3% HPC. The difference in corresponding BFE values just exceeds the standard deviation, while the difference in peak FPM values for 1% and 3% HPC exceeds the noise level by a factor of ten.

The high sensitivity of the DFF sensor is due to its ability to take 500 measurements in one second - thus allowing for a highly reliable statistical analysis that results in consistent values of FPM for batches with identical formulations.

Conclusion

The FPM metric of the DFF sensor, reflecting wet mass consistency, is an indicator of powder rheology, as confirmed by BFE measured at different processing times for three different formulations using the FT4 Powder Rheometer®. In addition, the FPM measurements have higher sensitivity than BFE measured by FT4, detecting changes in granule attributes as a function of formulation variables.

The DFF sensor provides data rich process fingerprinting in-line and in real-time with significantly higher sensitivity and data density (500 data points/second) to enable process design, scale-up, monitoring, and control applications. These studies indicate that DFF sensor can be a valuable tool for wet granulation formulation and process development and scale-up; as well as for routine monitoring and control during manufacturing.

Bibliography

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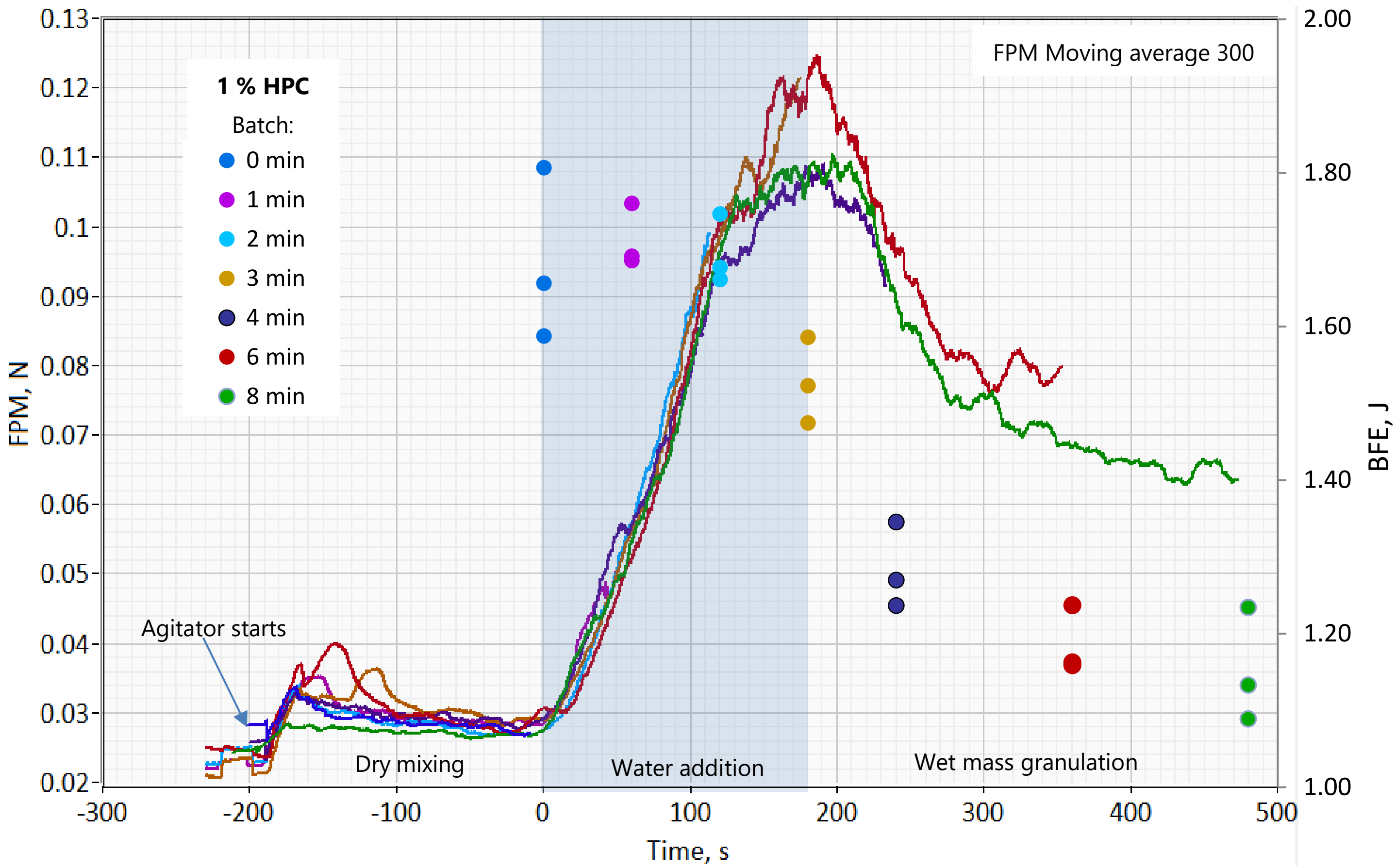
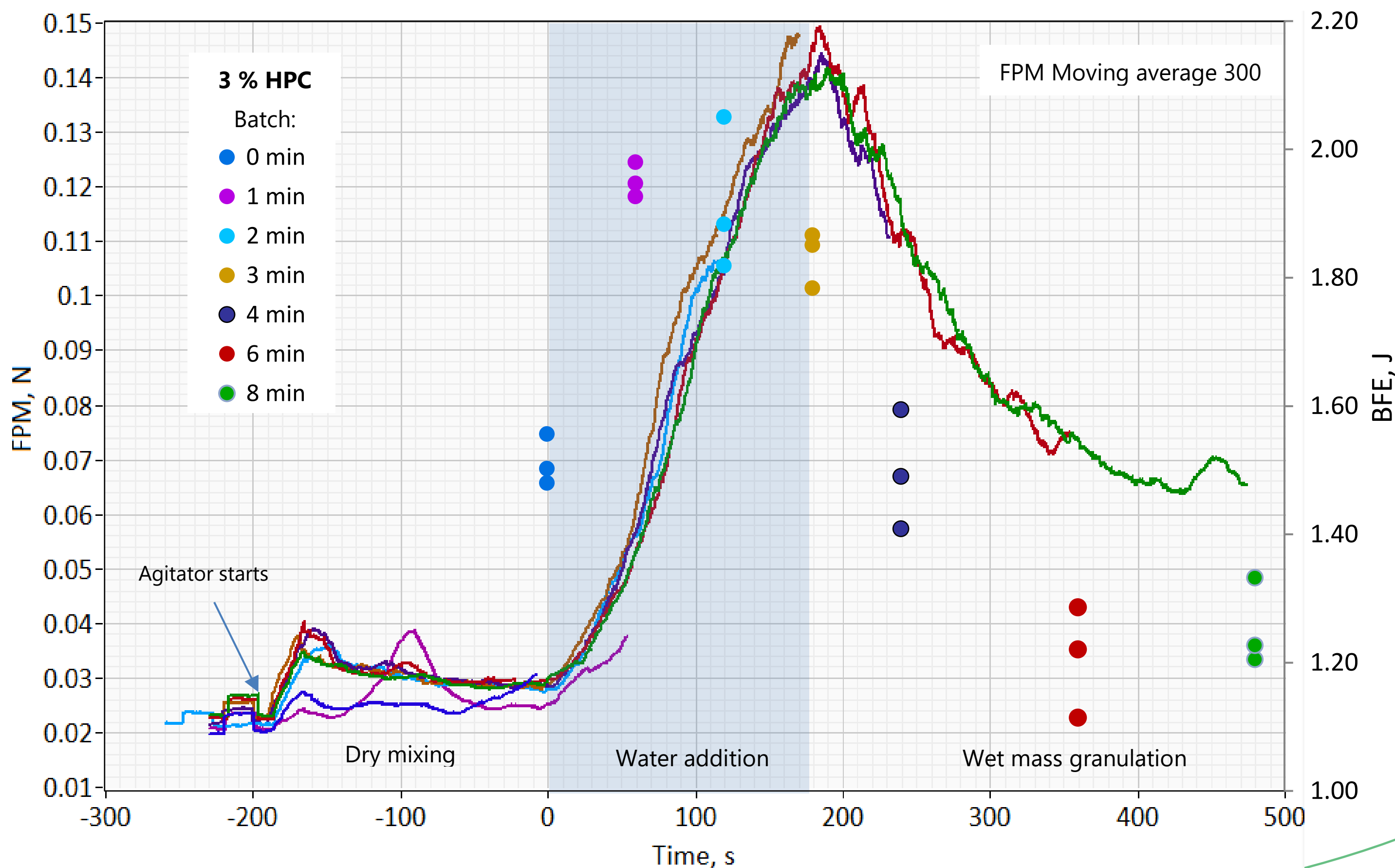
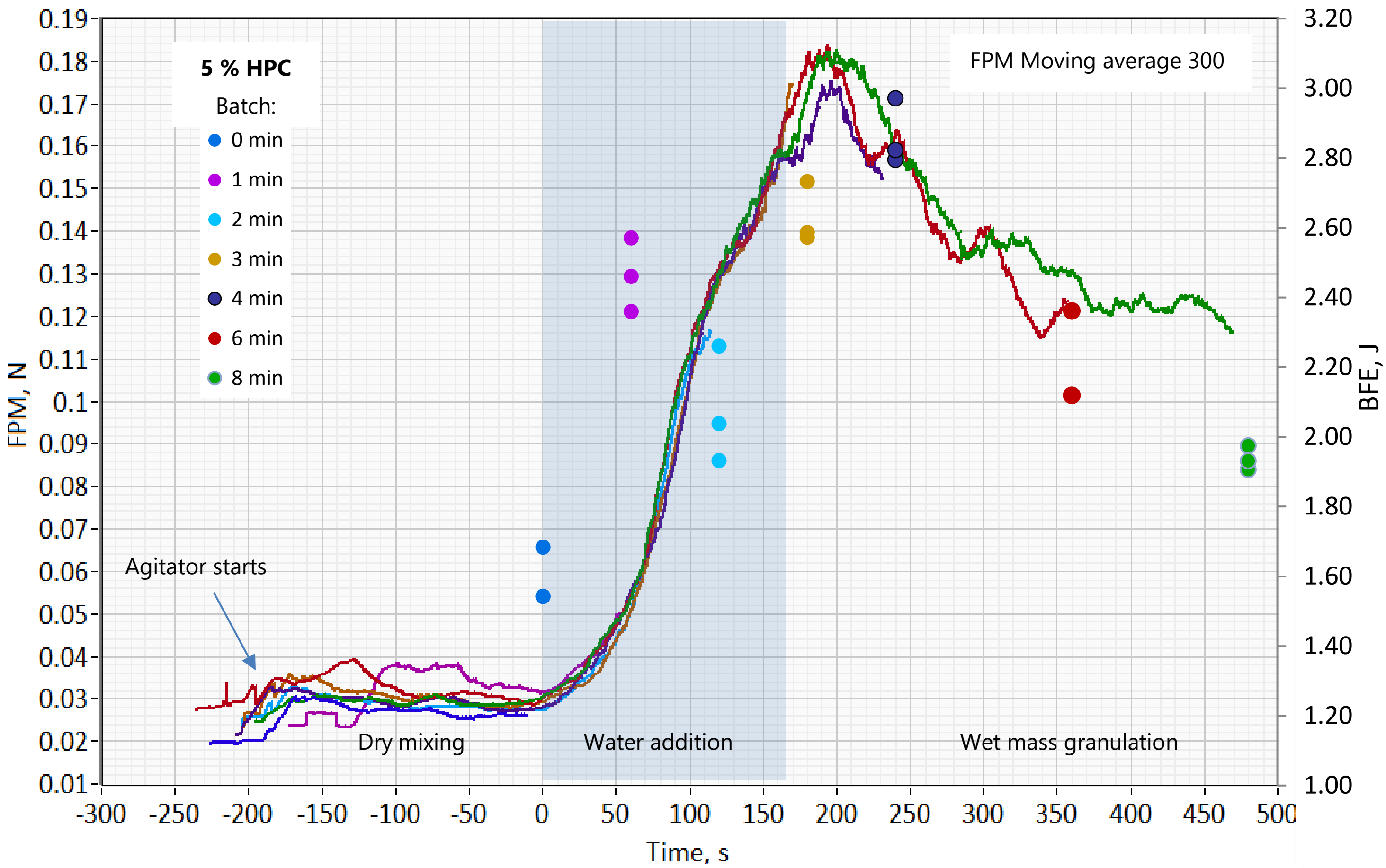
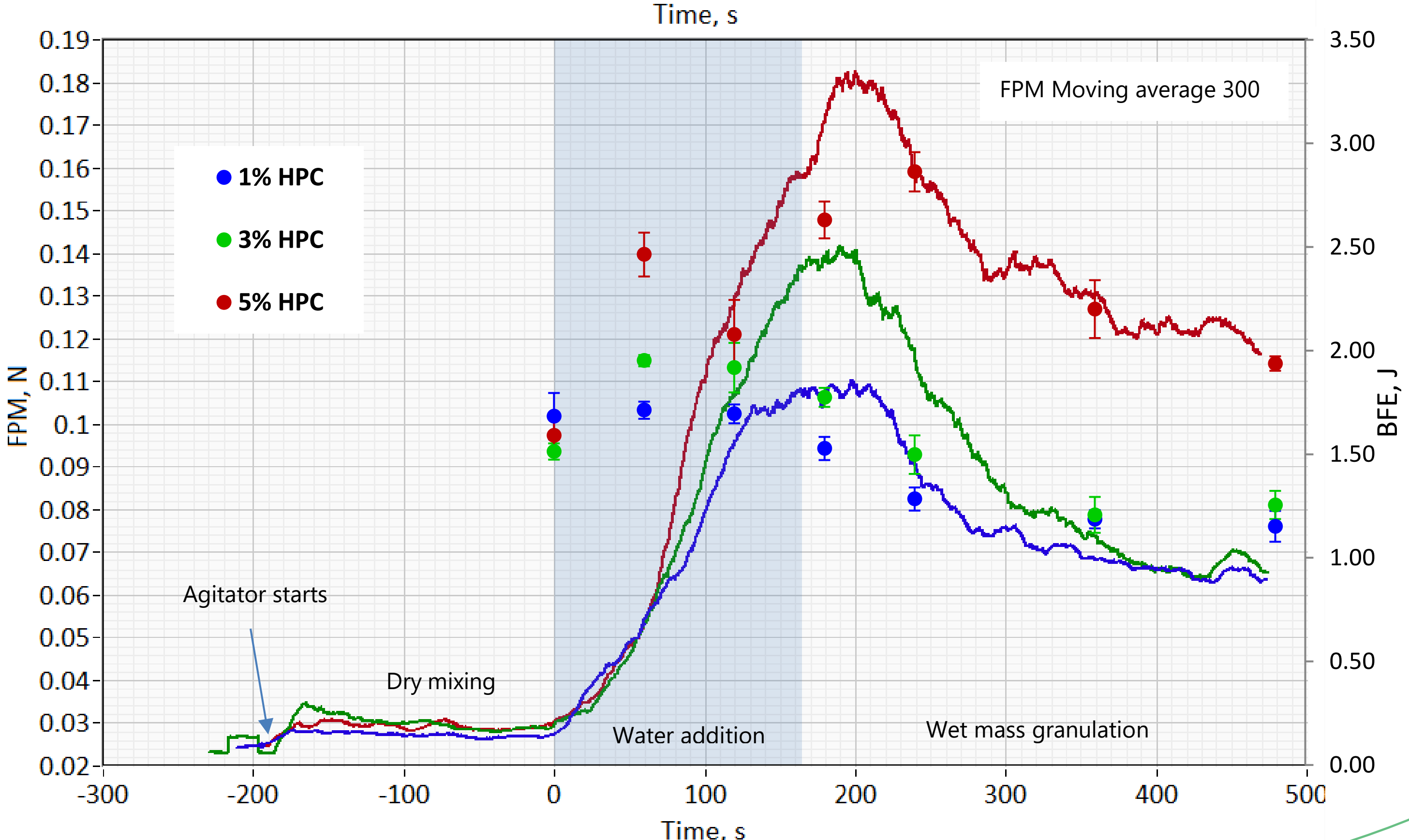
2. Freeman, T., Birkmire, A., & Armstrong, B. (2015). A QbD Approach to Continuous Tablet Manufacture. *Procedia Engineering, 102*, 443-449.


1 % HPC
Batch:
0 min
1 min
2 min
3 min
4 min
6 min
8 min
FPM Moving average 300
Agitator starts
Dry mixing
Water addition
Wet mass granulation
FPM, N
BFE, J
Time, s


3 % HPC
Batch:
0 min
1 min
2 min
3 min
4 min
6 min
8 min
FPM Moving average 300
Agitator starts
Dry mixing
Water addition
Wet mass granulation
FPM, N
BFE, J
Time, s


5 % HPC
Batch:
0 min
1 min
2 min
3 min
4 min
6 min
8 min
FPM Moving average 300
Agitator starts
Dry mixing
Water addition
Wet mass granulation
FPM, N
BFE, J
Time, s


1% HPC
3% HPC
5% HPC
FPM Moving average 300
Agitator starts
Dry mixing
Water addition
Wet mass granulation
FPM, N
BFE, J
Time, s