DFF Sensor as a PAT Tool in High Shear Wet Granulation: Placebo Batch Reproducibility Study

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Lenterra's drag force flow (DFF) sensor is a process analytical technology (PAT) tool that provides real-time in-line measurement of local flow force at a predetermined location within the high shear granulator. DFF sensor response was found to correlate well with granule densification and tablet dissolution.[1, 2] The sensor was shown to be sensitive to changes in formulation composition and process parameters using both a placebo and a brivanib alaninate formulation.[2]

In this paper, we compare the output of DFF sensor in several granulation cycles for identical formulations. The raw data was obtained in a course of a study where the correlation of the in-line response of DFF sensor with at-line response of FT4 Powder Rheometer® analysis was investigated.[1]

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]

Four batches for each formulation stopped at different time points during processing (at the end of water addition, one, three and five minutes of wet mass processing time, respectively) are indicated on the plots with a respective color.

Results

1% HPC

The force measurements for all batches with the 1% HPC formulation demonstrate very similar temporal evolution that is typical for a granulation using an agitator. As seen in the insert to the raw data plot, the force to the probe changes from a minimum to a maximum synchronously with blades passing below the probe. Each maximum corresponds to time instant when the blade is directly under the probe and minimum occurs when the probe is between two blades. Changes in the blade-to-blade peak force variations are indicative of random nature of granule impacts on the DFF probe. Massive granules produce extremely high peaks that are observable for each batch.

A metric for HSWG monitoring is the force pulse magnitude (FPM). FPM is the difference between the maximum and minimum force measured over time with one blade passing under the probe (see White Paper 3 or reference [1] for more detail). Each FPM, therefore, characterizes action of one blade. FPM evolution is calculated from raw data if the frequency of the blades is known. Applying fast Fourier transformation (FFT) to the raw data for one of the batches, post-processing software finds a blade frequency of 15.09 Hz, which is the expected frequency for a 3-blade agitator rotated at 300 RPM. This frequency did not change in any of batches of this study, and it was used for FPM calculations throughout.

FPM plots presented here are those smoothened with a moving average over 600 blades. These plots are identical to mean-FPM (MFPM) plots, which, along with the distribution width (WFPM) plots, are obtained from FPM distributions with sample size of 600 (see White Paper 3 for more details). Analysis of WFPM plots indicated strong correlations between WFPM and MFPM (or smoothened FPM plots), therefore we restrict our attention here to mean force magnitudes.

Since the FPM plots are averaged over 600 points, the curves end 300 points before the end of a particular measurement. For example, for the "yellow" batch, the force/temperature measurements were continued until the 180th second, as does the temperature curve. The FPM moving average of the order 600 end at the 160th second.

Uniformity of dry mixture

At early stages of dry mixing the observed FPM batch-to-batch variations are due to the known non-uniformity in the powder. The uniformity improves after approximately two minutes of dry mixing, FPM signal becomes steadier and at the end of 3 min of mixing (just before the water addition starts). The FPM signal becomes roughly same for all batches at a level of 0.03N.

Water addition

FPM increases at a steady rate for all batches indicating similarity in wetting and early granulation. After two minutes of water addition, FPM for "green" and "yellow" batches continue rising with the same pace while FPM for two other batches ("blue" and "red") begin to saturate. This correlates with differences in powder temperature for the two pairs of batches. Due to a particular sequence of batch manufacturing, temperature was consistently higher in "blue" and "red" batches.

Progress of temperature

Dry mixing started at approximately same temperature for three of four batches. The temperature was expectedly rising with a relatively slow rate of 0.3 to 1.5 degrees per minute during dry mixing phase, which is attributed to friction. For the first minute of water addition, abrupt increase in temperature rate to 3 degrees per minute is observed, similar for each batch. This is likely due to the formation of irregular shaped granules, leading to a higher friction in the powder. After one minute of water addition, the trend reverses and temperature falls, with a rate of 0.5 degrees per minute, also typical for all batches. The decrease is believed to be due to the saturation in chemical activity of the powder, intensive evaporation, and thermal conduction from cooler water. The increasing trends resumes after the end of water addition, with the rate of 0.5 degrees per minute, again typical for all batches.

3% and 5% HPC

As in the case of 1% HPC formulation, the force, FPM, and temperature dependencies for 3% HPC and 5% HPC formulations show little differences between the four monitored batches. After reaching uniformity at about half of a minute before water addition started, the four batches, for each formulation separately, show remarkably similar values of FPM during dry mixing and the first two minutes of water addition. Three of them also peak at the same time (one of four does not continue beyond the end of water addition). Excellent synchronization in peak timing indicates similar granulation dynamics that is sensitively characterized by the DFF sensor.

The absolute value of the FPM maximum varies between the three batches of each formulation. The difference reaches 12%, 4%, and 7% for the 1%, 3%, and 5% HPC formulation, respectively. These variations reflect statistically rare very large magnitude pulses observable on the raw data plots at the end of water addition.

The high sensitivity of FPM sensor monitoring can be observed in FPM signals for 5% HPC formulations. All four batches (with 5% HPC) feature an *inflection* point at about 100 seconds. This inflection point is evident in both FPM and temperature plots. The feature is not present in any of the batches for 1% or 3% HPC. It is evidently characteristic for higher binder content.

Comparing the three formulations

Similarities of four batches for each respective formulation are emphasized by apparent differences between DFF sensor signals for different formulations. Page 6 presents raw data, FPM, and temperature plots for the batch with longest processing time in each formulation (indicated with blue color on pages 3 to 5). The differences in the three formulations can be summarizes as flows:

1) Higher HPC concentration formulations lead to lower minimal force observed when the probe is between two blades, especially during the latter stages of granulation (see the insert in the force versus time plot on pages 3-5). This could be due to increased tackiness of the wet mass at greater binder concentrations.
2) FPM values are similar during dry powder mixing stage, which is expected since densities of HPC and MCC differ insignificantly. The FPM plots split dramatically during the water addition phase reaching a difference of 30% between 1% and 3% HPC, and 75% between 1% and 5% HPC respectively, for peak levels.
3) The time delay for FPM peak is longer for 5% HPC as compared to 1% or 3% HPC. This information may be used for identification of granulation end-point.
4) The temperature change during water addition is stronger for 1% HPC as compared to that for 3% HPC and further to 5%.HPC

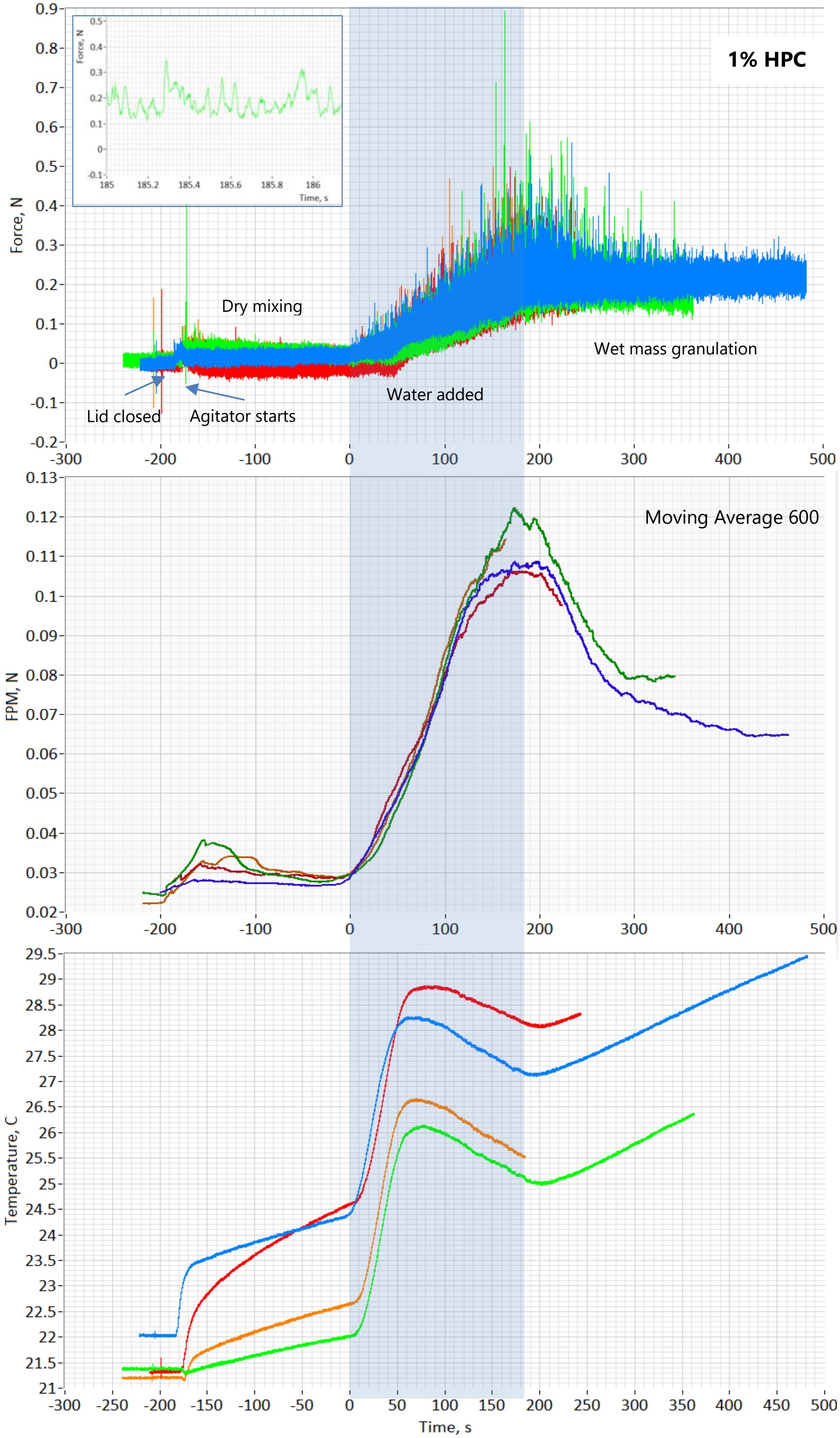
Conclusion

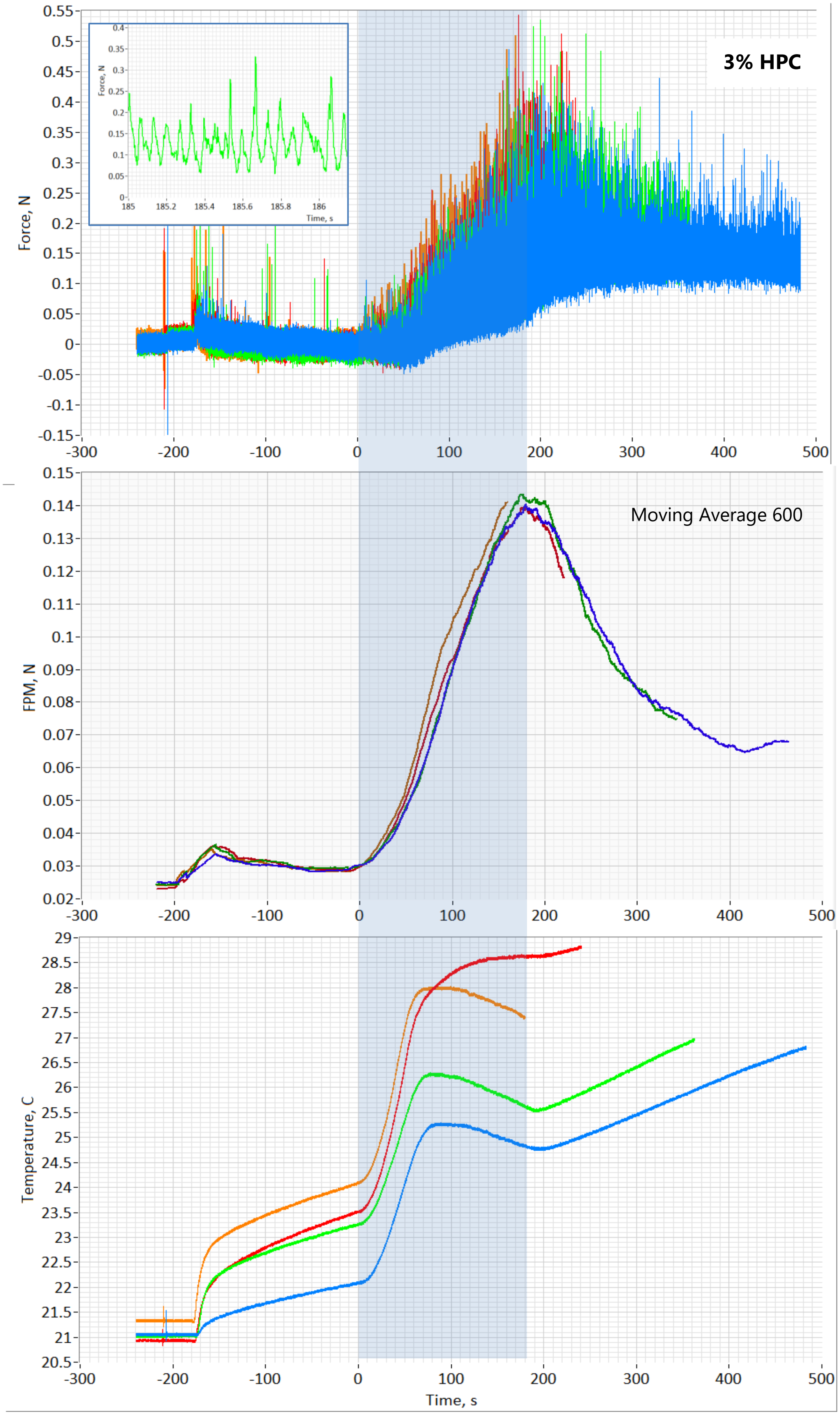
DFF sensor force and temperature measurements were shown to be reliably reproducible in monitoring HSWG of placebo formulations with different concentrations of the binder component (hydroxypropyl cellulose, HPC). At the same time, formulations with 1, 3, and 5% of HPC produced substantially different responses. DFF sensor, therefore, is demonstrated as a dependable PAT tool for HSWG monitoring. The results can be used for identifying differences between formulations, pinpointing granulation end-point, and enabling scale-up. It is also worth to note that DFF sensor gives two, not one, independent outputs, force and temperature. While being indirect characteristics of fundamental material changes that happen during granulation (densification and size change), having two indirect parameters that depend on the same underlying material properties and process parameters and provide a reliable and mutually coherent "fingerprint readout" of the process is extremely valuable and unique for a process analytical technology (PAT) tool..

Bibliography

[1]Narang, A.S., Sheverev, V.A., Freeman T., Both D., Stepaniuk, Delancy M., Millington-Smith D., Macias, K., Subranmanian G., 2016. Process Analytical Technology for High Shear Wet Granulation: Wet Mass Consistency Reported by In-Line Drag Force Flow Sensor Is Consistent With Powder Rheology Measured by At-Line FT4 Powder Rheometer. Journal of pharmaceutical sciences 105, 182-187.

[2]Narang, A.S., Sheverev, V.A., Stepaniuk, V.P., Badawy, S., Stevens, T., Macias, K., Wolf, A., Pandey, P., Bindra, D., & Varia, S. (2015). Real-time assessment of granule densification in high shear wet granulation and application to scale-up of a placebo and a brivanib alaninate formulation. Journal of Pharmaceutical Sciences, 104, 1019-1034


1% HPC
Force, N
Time, s
Dry mixing
Wet mass granulation
Water added
Lid closed
Agitator starts
Moving Average 600
FPM, N
Temperature, C
Time, s



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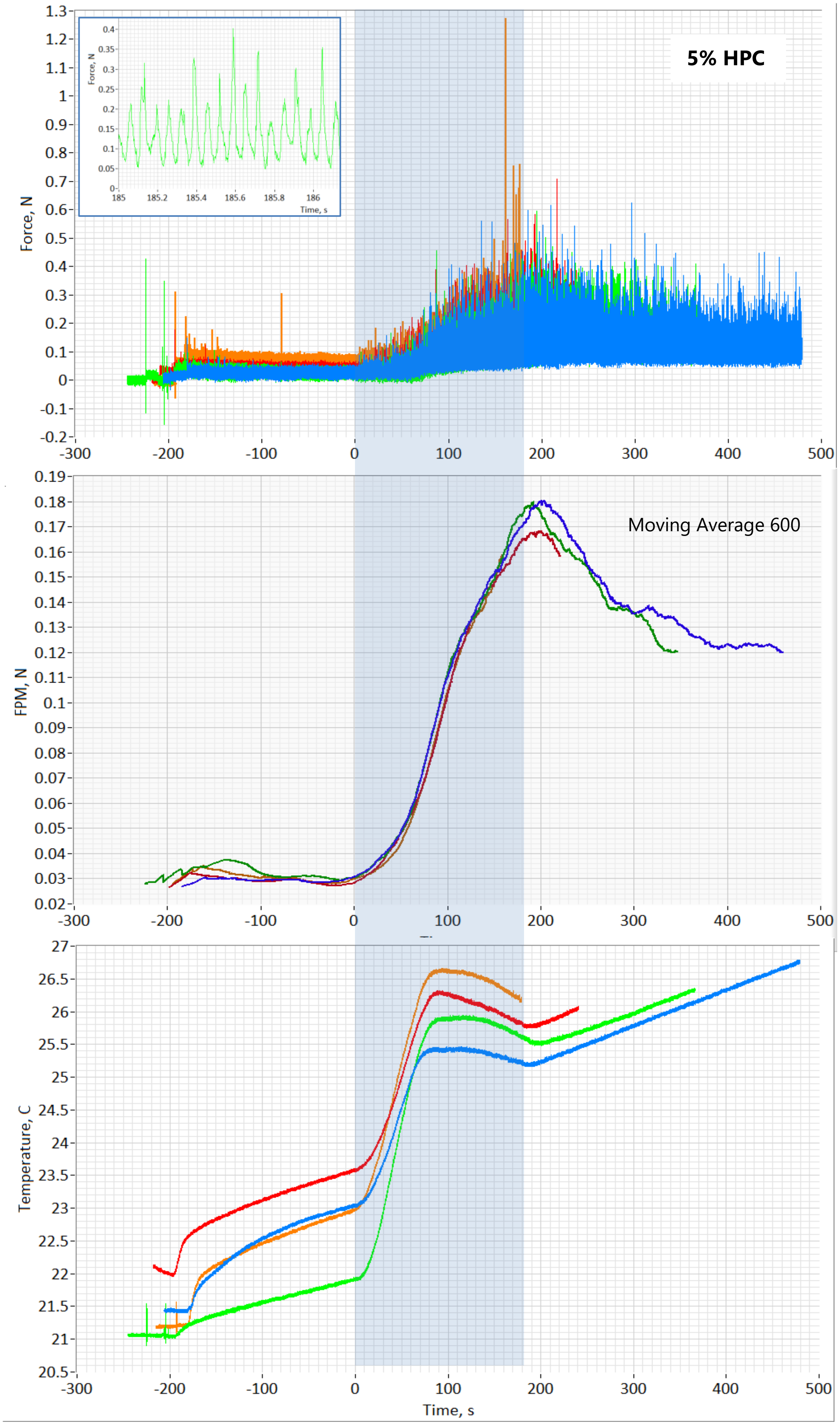
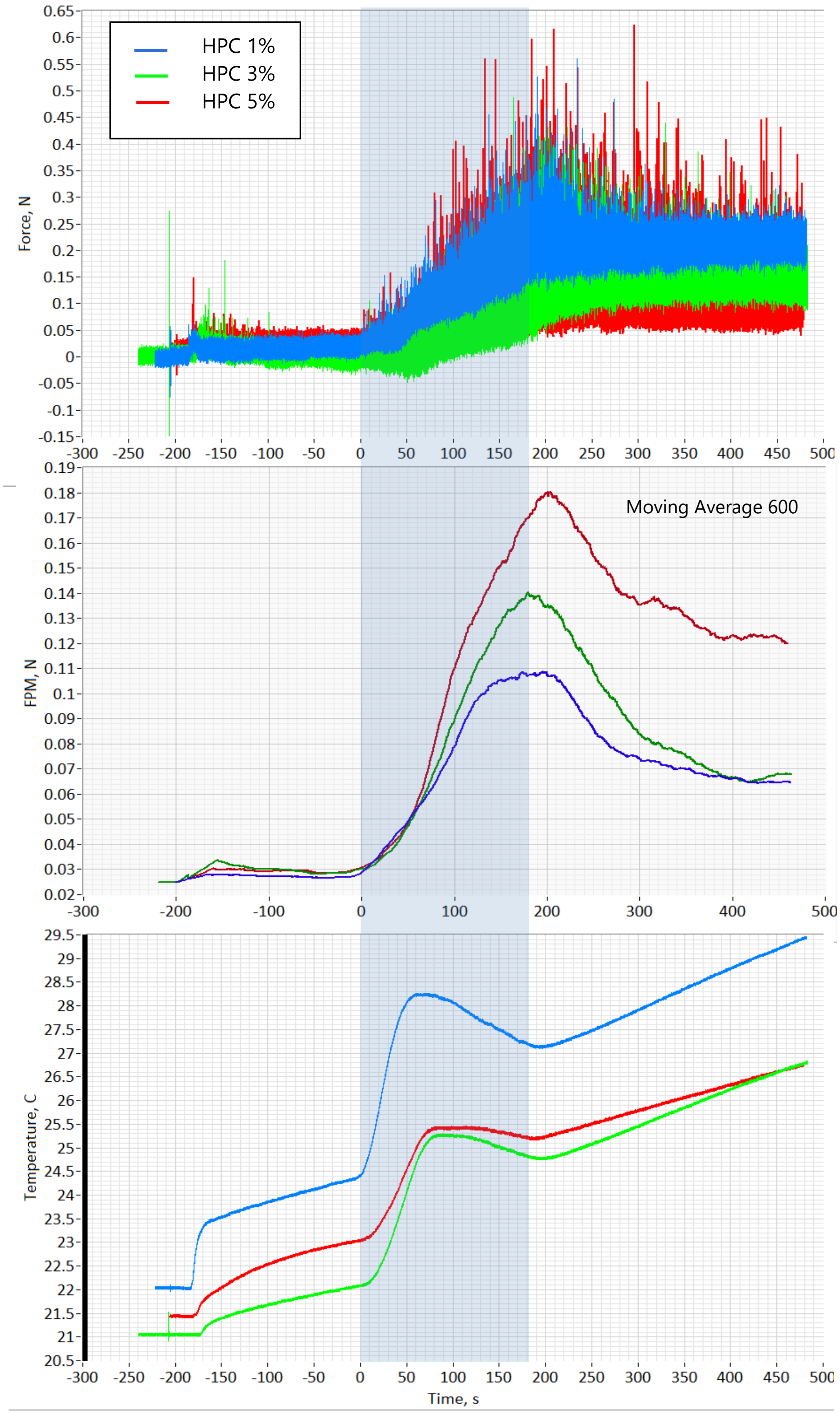

5% HPC
Force, N
Time, s
Moving Average 600
FPM, N
Temperature, C
Time, s


HPC 1%
HPC 3%
HPC 5%
Force, N
Moving Average 600
FPM, N
Temperature, C
Time, s