APPLICATION NOTE 3

Process Monitoring with Drag Force Flow (DFF) Sensor. Raw Data Signal, Force Pulse Magnitude (FPM), FPM Distribution, Mean FPM (MFPM), FPM Distribution Width (WFPM)

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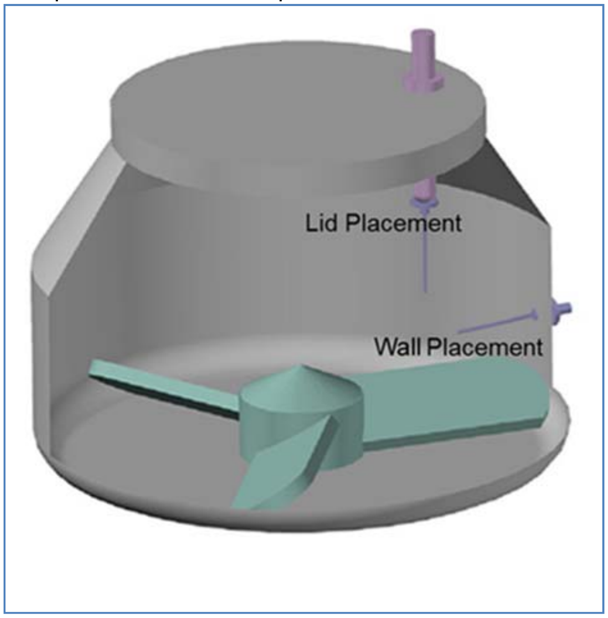
Introduction

This note describes algorithms for **data interpretation** of and introduces two main parameters for the time-dependent measurement of the flow forces by Lenterra's Drag Force flow (DFF) sensor, specifically for applications to agitator-based systems such as mixers or granulators, or other processing devices that characterize with a specific mechanical frequency in operation, such as pumps. As an example, application of the DFF sensor for monitoring of high shear wet granulation (HSWG) is discussed.

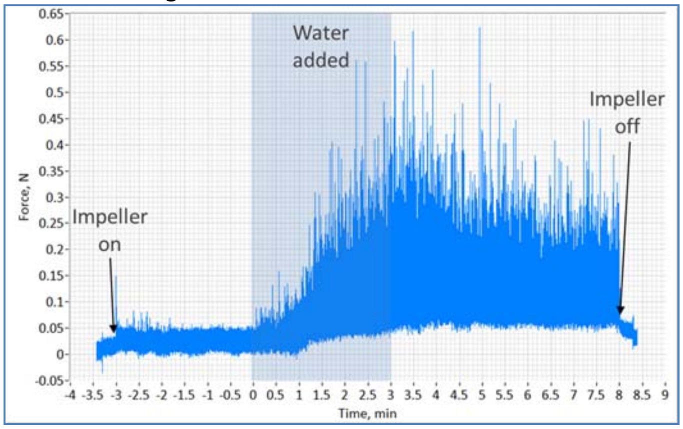
Raw Data

To work as a process analytical technology (PAT) tool, a DFF probe needs to be positioned within the flow. For mixers and granulators the probe is typically introduced into the material through a port on the granulator lid or using a side port, if available. Lid placement allows for flexible positioning using an adjustable shaft to survey the granulator volume.



Placement of the drag flow force (DFF) sensor in the granulator from the lid or side port. Consistent placement in the granulator across the batches that are being compared with respect to the height from the impeller and the radial distance ratio from the shaft are important parameters for consistent data generation and scale-up, since particle flow patterns vary in different regions of the granulator. In addition, the probe should be placed away from the port of granulating fluid addition and the chopper.

The chart below presents a data taken via a DFF sensor during a typical measurement cycle of high shear wet granulation (HSWG) in a GEA PharmaConnect 10 L granulator. These data were generated using a placebo formulation consisting of microcrystalline cellulose and lactose monohydrate as diluents, croscarmellose sodium as a disintegrant, and hydroxypropyl cellulose as a binder (Narang, 2015).



Raw data taken during a granulation cycle in a 10-liter GEA PharmaConnect high shear granulator showing pulses of particle impacts on the DFF probe. Force was measured every 2 milliseconds or 500 times per second.

The HSWG unit operation included a dry mixing phase ['impeller on' to 'water added'], water addition phase [shaded area labeled 'water added'] started at time zero and continued for three minutes, and wet massing phase ['water added' to 'impeller off'] while the contents were mixed at the impeller tip speed of 5 m/s.

This plot contains 360,000 force measurement points taken over approximately 12 minutes and the bottom plot includes 600 measurement points taken over 1.2

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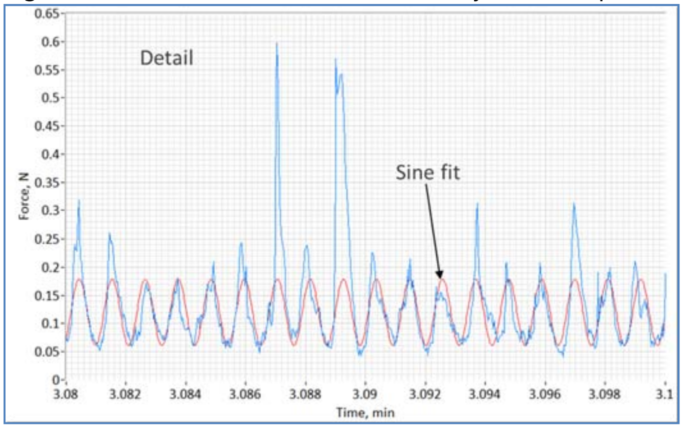
seconds. The signal consists of separate peaks, and the peak occurrence frequency matches the frequency of the blades passing below the sensor. When the blade is directly below the probe the velocity of the wet mass is greatest, and the force measured by the probe is highest. Minima occur when flow velocity near the probe



High temporal resolution portion of the above plot (blue) and its model fit to a sine function (red) indicating the periodicity and the pulses of particle impacts on the drag flow force (DFF) sensor in a high shear granulator.

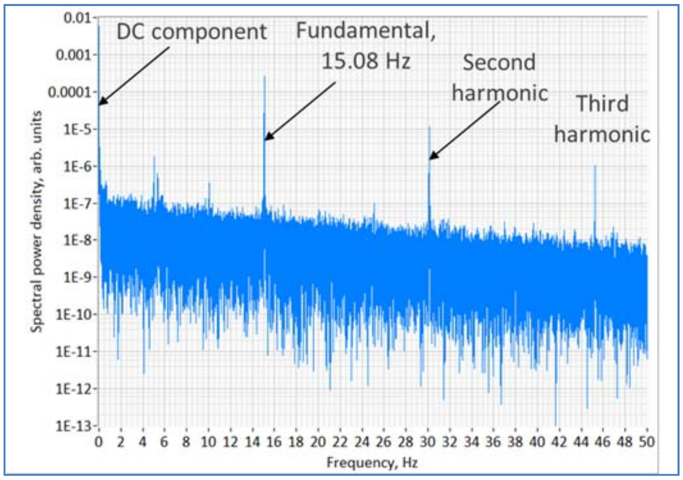
is lowest, which happens when the probe is between the blades. One may also observe a fine structure in each peak that includes a number of narrow pulses with various magnitudes. These are due to elementary impacts of granules of various sizes measured consecutively. Some of them overlap in time and some other have fairly large magnitudes. Overall, the raw signal can be represented with a continuous sinusoidal force vs. time superposed with random narrow pulses. The width of these elementary pulses characterize the time of contact between the granule and the probe, which is related to the granule size and density, and the magnitude of the pulse characterizes the mass of the granule.

Peak forces exerted by dry powder (first three minutes in the plot) are noticeably lower (about two orders of magnitude) than those observed during or after water addition, which is indicative of granulation dynamics. The greatest force is observed sometime after the water addition was stopped, with gradual decrease afterwards that is due to the gradual decrease in granule size and density. This information may be used for identification of the granulation endpoint.

Force pulse magnitude (FPM)

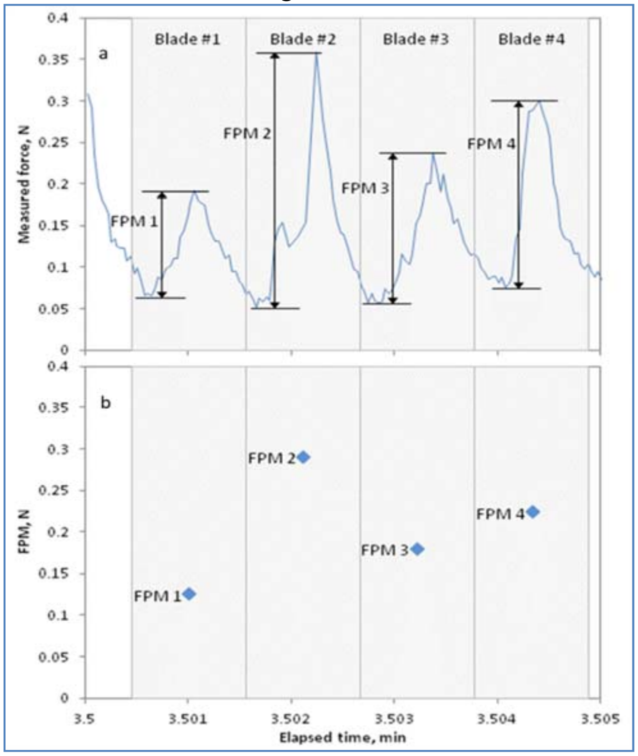
A useful information can be obtained from analyzing magnitudes of peaks observed in a force vs. time dependence. Fourier transformation (FFT) of the raw signal gives a value of the blade frequency.

The blade frequency of 15.08 Hz gives the time interval between two blades passing the probe (period) of 0.066 seconds.



Power spectrum of the raw signal obtained using Fast Fourier transformation (FFT)

Force Pulse magnitude (FPM) is introduced as a difference between the greatest and smallest values of

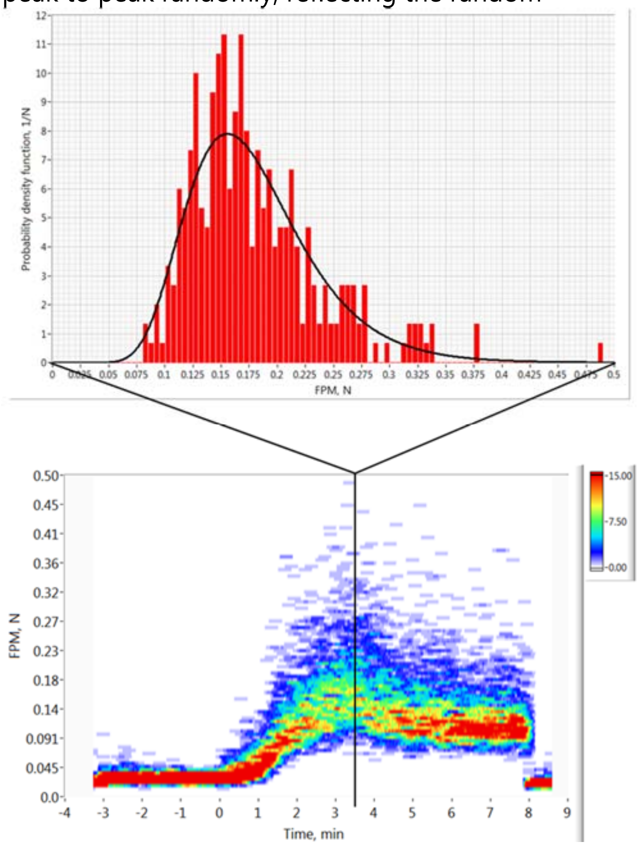


An illustration of calculation of force pulse magnitude (FPM) for each of the waves of particle impacts on the drag flow force (DFF) sensor as a blade passes below the sensor. The FPM reflects maximum measured force of impact during each blade pass force measured over one period. Each FPM, therefore, characterizes a passing of one blade in vicinity of the probe pin.

Being a differential measurement, FPM provides a reliable characteristic of the wet mass consistency and densification since it is independent from possible zero drift in the raw signal.

FPM Histograms

In addition to the measurement of force at each point in time, the signal could be resolved for the frequency of force measurement, which provides time course histograms of FPM. The force magnitudes vary from peak to peak randomly, reflecting the random



(top) *A histogram of 300 force pulse magnitudes (FPMs) measured between 3.33 and 3.67 minutes of the test, solid line represents a log-normal distribution restored from the subarray of FPM values; The vertical scale, probability density finction is the fraction of FPMs in a channel divided by the channel width in Newtons.*

(bottom) Three dimensional plot of 300-FPM moving histograms. The moving increment is the inverse FPM frequency which is here 0.0011 min. For example, histogram shown above is included in this color plot along vertical line at time t=3.5 s. The color scale shows probability distribution function (PDF) that is the horizontal scale on the upper plot.

distribution of granule size in the wet mass. Such a distribution could be observed by selecting a certain number of consecutive FPMs and constructing a histogram. Figure below represents such an "instantaneous" histogram of FPMs calculated for the raw data presented above, for the time interval between 3.33 min and 3.67 min. This histogram contains 300 FPM values.

Evolution of such "instantaneous" histograms carries information about wet mass densification during the granulation process. A reasonable approach in observing FPM distribution dynamics is to construct consecutive histograms for a fixed size array of FPMs shifted by one blade in time. Such, the first histogram is built for an array of N blades counted from blade number 1 to blade number N. The second histogram is built for blades from number 2 to number N+1, and so on. This way we obtain three-dimensional plot (moving histogram) which is presented here as a color map.

The larger is array size N, the more statistically significant FPM distribution is. But when N, measured in time units, significantly exceeds the characteristic time of physical and chemical processes occurring in the course of granulation, rapid changes of wet mass parameters may not be detected. Because of that, consecutive histograms move with a small time increment of one blade. For example, an array of 300 blades (20 s) may seem to exceed the time when the physical and chemical state of the material does not change, but the fact that the following 300-blade-histogram is calculated with an increment of one blade (0.066 s) effectively increases the temporal resolution.

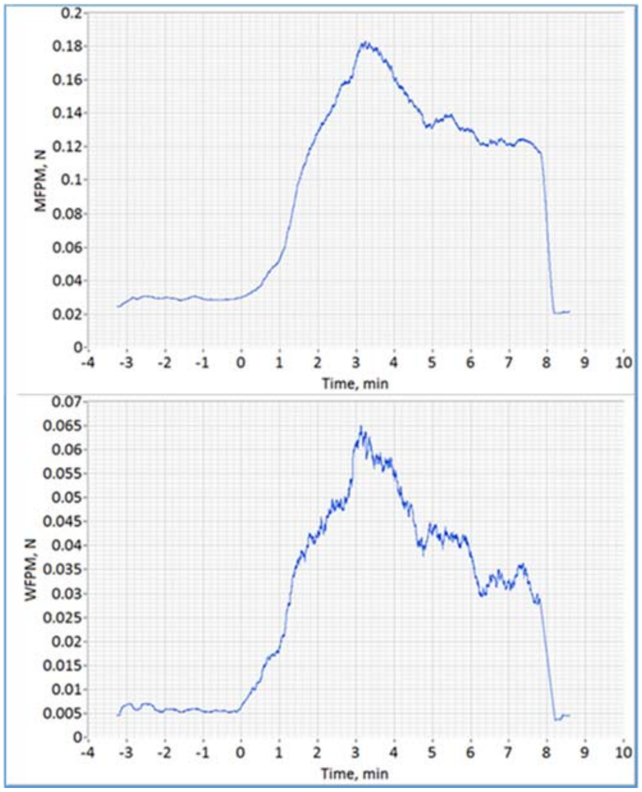
The lognormal distribution is a typical distribution characterizing particle sizes of granulated powders (Masuda, 2006). Fitting with a lognormal distribution is shown in figure (a) with a line. The "instantaneous" state of the FPM distribution thus may be represented with two parameters of a lognormal distribution: the mean that is introduced here as "mean FPM" or MFPM and calculated as:

$$MFPM = e^{\left(\mu+\frac{\sigma^2}{2}\right)} \qquad \text{Eq. 1}$$

and a parameter characterizing the width of the lognormal distribution such as a square root of variance which we call here "width of FPM distribution" or WFPM and calculate as:

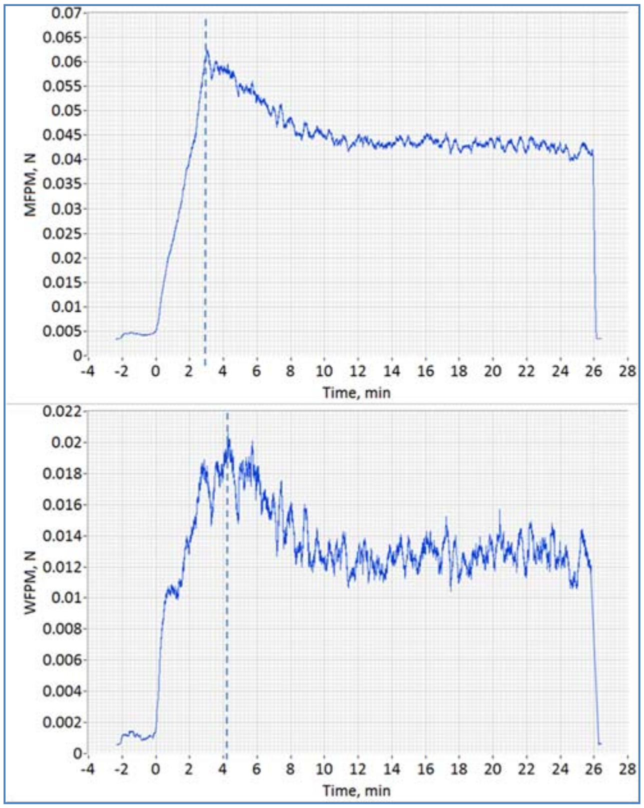
$$WFPM = \sqrt{\left(e^{\sigma^2} - 1\right)e^{(2\mu+\sigma^2)}} \qquad \text{Eq. 2}$$

where μ and σ are, respectively, the standard mean and standard deviation of the FPM's natural logarithm. The MFPM and WFPM values are referred to the time instant that is selected as mid-range for the array. For example, time instant assigned to the distribution given in figure (a) above is (3.33+3.67)/2=3.5 min.



Plots of mean (MFPM) and width (WFPM) of the lognormal distribution restored from consecutive arrays of 300 force pulse magnitudes (FPMs) measured for raw data shown above. Both the distribution mean and width change over the granulation cycle significantly, reaching maximum approximately concurrently with each other. Dynamics of MFPM and WFPM provides convenient means for determination of granulation endpoint and differentiation between formulations.

MFPM and WFPM represent evolution of FPM distribution over the granulation cycle. In the considered example of a placebo formulation, the MFPM and WFPM evolutions are similar to each other peaking at the same instant of approximately 20 seconds after water addition stops (see Fig. 10). The maximum of MFPM evolution corresponds to the highest average mass interacting with the probe and the peak of WFPM indicates the time when the distribution of masses is widest. These peaks can be used for determination of granulation end point.



Plots of moving mean (MFPM - a) and width (WFPM - b) of the lognormal distribution restored from consecutive arrays of 300 force pulse magnitudes (FPMs) measured by DFF sensor in a 4L Bohle mini granulator using same formulation as that of the measurement in a 10L GEA PharmaConnectTM granulator. Contrary to the PharmaConnect results, WFPM reaches its maximum approximately a minute after MFPM does.

Generally, the mean value and the width are independent from each other. In the example of high shear wet granulation, one would expect however the distribution of particle masses being widest at the time of highest tackiness in the wet mass, when most massive agglomerates are formed. For the same reason, the mean value of the granule masses is also highest at the same time. However, depending on the formulation and the granulator type, MFPM and WFPM distributions may depart from each other. An example of such situation shown here is MFPM and WFPM evolutions measured by a DFF sensor in a 4L Bohle-Mini-Granulator, for the same placebo formulation that was used in the above test with GEA PharmaConnect™ 10L granulator. MFPM has a sharp peak at 3 min, immediately after the end of water addition, while the WFPM continues to rise for approximately 1 minute after water addition stops. In this situation one may consider to select the granulation end point between these two maxima.

Conclusion

The DFF sensor detects the drag flow force of the particle mass with tunable and very high sensitivity and temporal resolution. This sensor detects not only the bulk flow properties but also individual force impacts on the sensor that can provide information about particle mass, size, density, and momentum. The high measurement rate of 500 Hz allows to monitor the magnitude of the force pulses created by particle impacts. Temporal distributions of these force pulse magnitudes (FPMs) provide a convenient means to monitor the process dynamics. The DFF sensor has been used to fingerprint HSWG processes to aid in process monitoring, processing endpoint determination, and scale-up.

Bibliography

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