Process fingerprint: combination of mean force pulse magnitude (MFPM) and powder consistency factor (PCF)

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DFF sensor measurement

Lenterra's Drag Force Flow sensor (DFF sensor) measures deviation of a narrow cylindrical pin immersed into a flow and experiencing acceleration as illustrated in Figure 1. The deviation is related to the force exerted on the pin by the material of the flow. The model for calculating the force for exemplary powder impacts is found in references [1, 2].

A standard measurement rate of 500 cycles per second ensures essentially continuous measurement of the force. The sensor therefore depicts instantaneous changes in flow and material conditions such as velocity, particle density and size and/or viscosity.

For monitoring *non-periodic* continuous processes, such as hopper release, extrusion or continuous granulation, the "raw" signal of force versus time***, F(t),*** is the main source of information (see White Papers 6 and 7 for examples of such signals). Changes in the force level reflect process evolution.

Processes characterized by a frequency

A variety of industrial processes involve periodic action. Batch granulation, blending and mixing employ agitators rotating with a particular frequency, and vibrating fluidized beds, tumblers or dryers oscillate with a particular frequency. DFF sensor probe immersed into the material in such a device will return a periodic signal. For example, Figure 2 shows a detail of DFF sensor measurement taken during a granulation cycle in a high shear granulator.

The plot includes 750 force measurement points taken over 1.5 seconds. It contains a series of equidistant peaks. Each pulse corresponds to an event of agitator blade passing in a vicinity of the DFF probe.

Figure 2 highlights the importance of high measurement rate for in-line process monitoring. A signal that is integrated in space and/or time (e.g., agitator shaft torque), does not bear information related to a specific period of oscillation (for vibrating devices) or specific blade action (for agitator-based devices). For example, a moving average over 500 force measurement points or 1 second of time, which is given in Figure 2 with a dark blue line, does not bear information about blade impact forces.

A number of useful metrics can be obtained from analyzing details of the force pulses. These are peak magnitude, pulse width, or a number of elementary impacts observed over one period. Each such a metric may reflect different properties of the powder or wet mass.

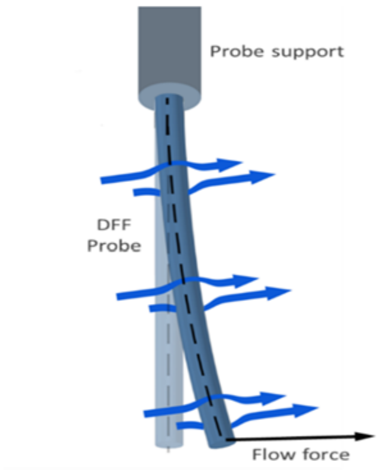

Figure 1. DFF sensor in the flow

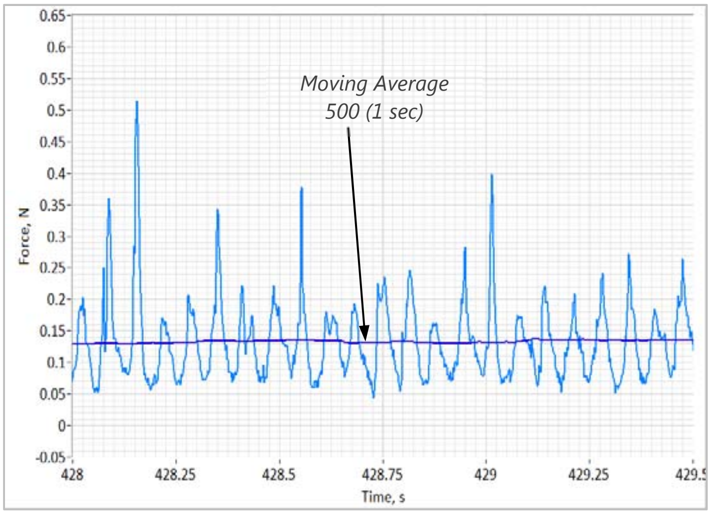

Figure 2. Raw data taken during a granulation cycle in a 10-liter GEA PharmaConnect high shear granulator showing pulses of granule impacts on the DFF probe. Force was measured every 2 milliseconds.

Force Pulse Magnitude (FPM), MFPM and WFPM

Force pulse magnitude (**FPM**) is a difference between the greatest and smallest values of force measured over one period. By analyzing the raw force signal, Lenterra's processing software calculates the period (see more details in [1, 3] and finds an FPM value for every period according to the algorithm illustrated in Figure 3. The FPM

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value is associated with a time instant that is central for each period.

The resulting plot of FPM vs. time may look like that in Figure 4. This figure presents evolution of FPM through a high shear wet granulation (HSWG) cycle. FPMs vary from peak to peak randomly, reflecting random distribution of net forces on the DFF probe over time. Useful information is carried by both the FPM values themselves and the variation of FPM values. To quantify these characteristics, the following statistical approach is used. First, an array size of consecutive FPM values is selected, e.g. 300 values. Such an array is characterized by a histogram, as shown in Figure 5 for the time period between 420 and 440 seconds of the total measurement given in Figure 4.

A lognormal distribution fit is applied to the histogram that returns two standard characteristics: the mean value, which we call **MFPM**, and the width of the distribution, which we call **WFPM** (see [1, 3] for formulas)**.**

MFPM and WFPM are two independent statistical parameters that correlate with generally independent properties of the powder: MFPM reflects the average particle size/density, and WFPM is related to uniformity or cohesiveness of the powder. Moving averages of MFPM and WFPM are given in Figure 6. Both plots look similar peaking at the same time, soon after water addition ends, but WFPM seem to drop faster than MFPM, suggesting improved uniformity of the flow at the end of the granulation cycle.

WFPM is typically higher for larger MFPMs, but the powder is not necessarily less uniform at higher WFPM. Material uniformity is better characterized by ratio of MFPM and WFPM, which is analogues to a concept of fractional uncertainty $\frac{\Delta x}{x}$, or its inversed value $\frac{x}{\Delta x}$ that has a meaning of resolution. Here we introduce Powder Consistency Factor, the ratio of MFPM to WFPM, a metric that replaces WFPM in statistically describing FPM distribution.

Powder Consistency Factor

Powder Consistency Factor is the ratio of MFPM to WFPM, $\mathbf{PCF} = \frac{MFPM}{WFPM}$. The factor quantifies uniformity of the flow or consistency of the powder. If the material contains large agglomerates interacting with the probe intermittently, the WFPM is wide and PCF is small.

PCF is a unitless parameter, and it is better suited to characterize the FPM distribution, as compared to WFPM, since it is normalized with MFPM. The relationship between MFPM, WFPM and PCF could be understood from the illustration in figure 7. The narrower distribution has a higher value of PCF. PCF is a characteristic of the flow/material state that is complimentary to FPM.

Therefore, for a process that can be characterized with a specific frequency, DFF sensor yields two independent metrics: mean force pulse magnitude (MFPM) and powder consistency factor (PCF).

Time evolution of these two parameters represent a process fingerprint. The following example illustrates the correlation between these parameters and granule densification and consistency in an HSWG study [4].

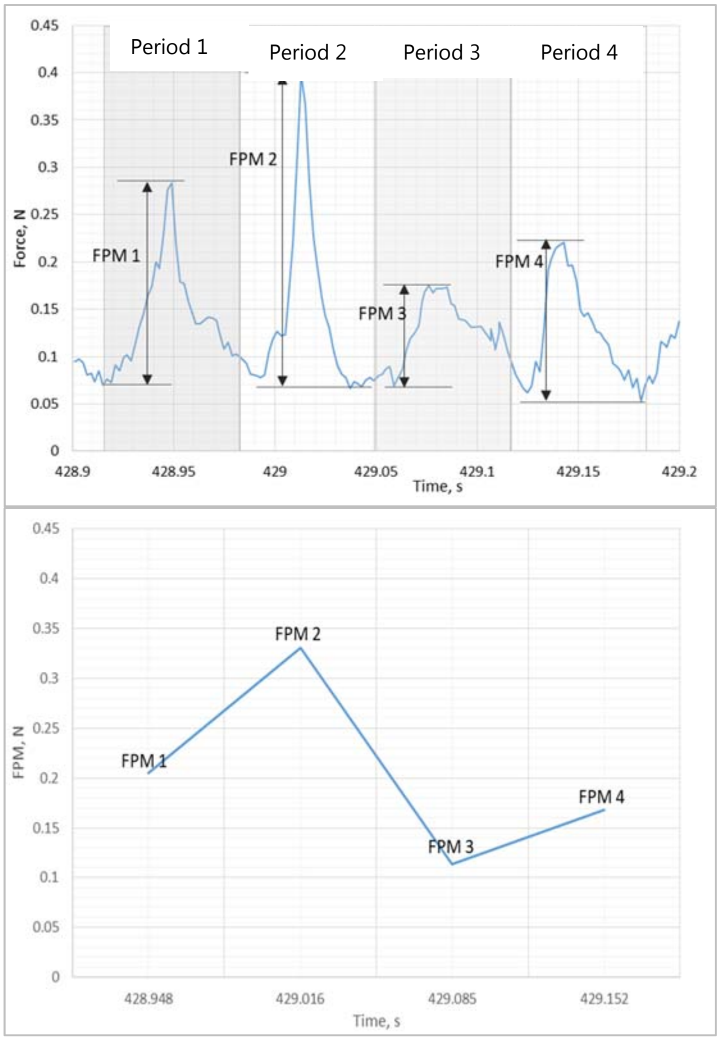


Figure 3. Calculation of force pulse magnitudes (FPM). Upper plot - raw fprce data, lower plot - returned FPM values.

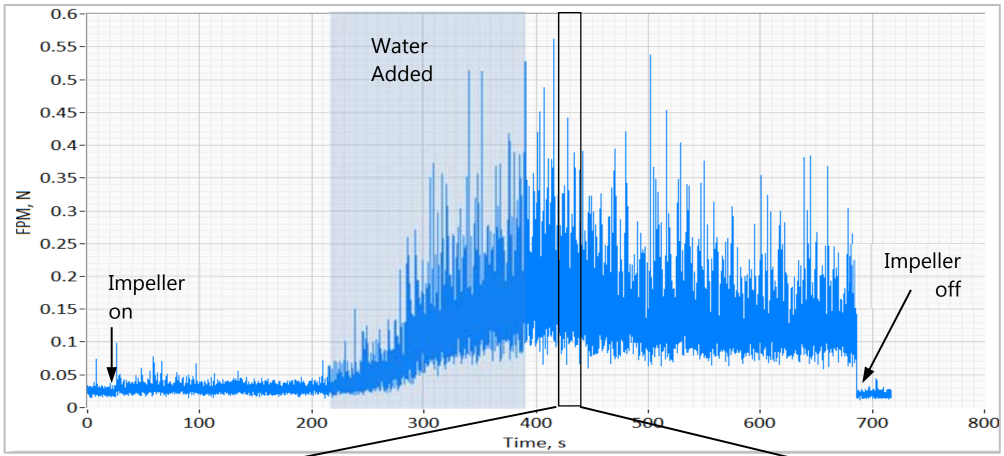


Figure 4. Plot of FPM vs time describing a 12-minute high shear wet granulation (HSWG) cycle of a placebo formulation in a GEA PharmaConnect 10 L granulator. The HSWG unit operation included a dry mixing phase ['impeller on' to 'water added'], water addition phase [shaded area labeled 'water added'] that continued for three minutes, followed by wet massing phase ['water added' to 'impeller off'] while the content was mixed at the impeller blade frequency of 15 Hz, thus providing 15 FPM values per second.

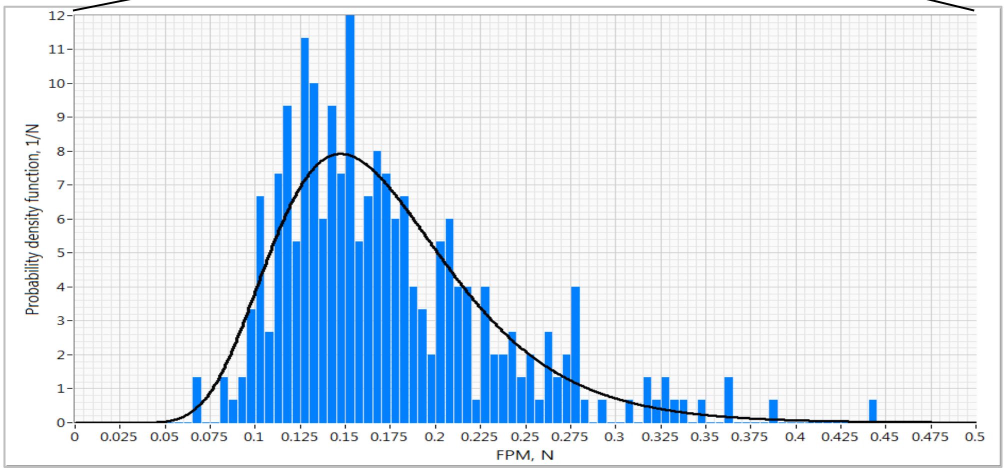


Figure 5. A histogram of FPMs constructed for FPM values in the time interval between 420 and 440 seconds (300 FPM values). The black curve represents a lognormal distribution fit with the mean value (MFPM) of 0.172 N and a characteristic width (WFPM) of 0.057N

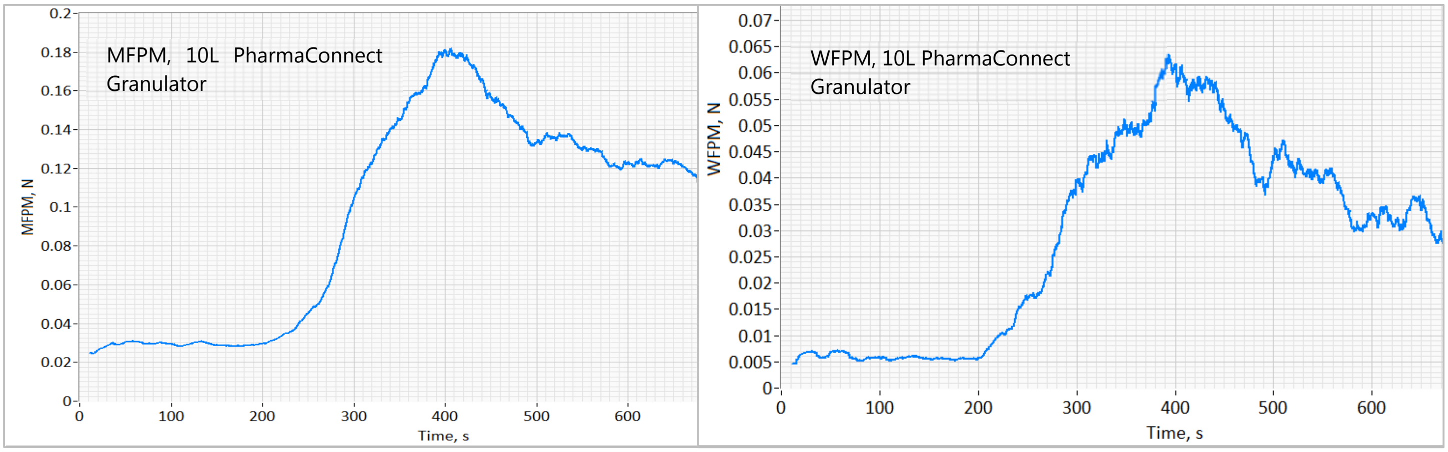
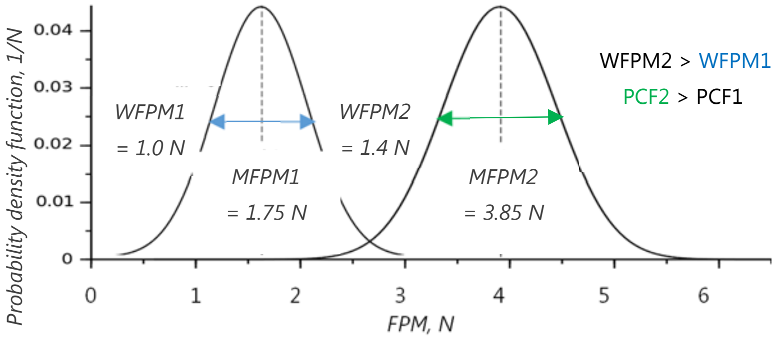


Figure 6. Moving average plots of MFPM (left) and WFPM (right) calculated for FPM evolution given by Figure 4. FPM array size is 300.



$$PCF1 = \frac{1.75\ N}{1.0\ N} = 1.75 \qquad PCF2 = \frac{3.85\ N}{1.4\ N} = 2.75$$

Figure 7. Two distributions characterized by an MFPM and PCF. While WFPM2 is larger, suggesting that the distribution width for the second distribution is larger, the PCF2 is also larger suggesting that the second powder is more inform than the first.

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DFF fingerprint of an HSWG process

DFF process fingerprint is represented by evolution of both MFPM and PCF. Figure 8 shows such a fingerprint for a high shear wet granulation cycle of an API formulation (Brivanib alaninate, more details in [4, 5]).

After two minutes of dry powder mixing (negative time), 58% w/w water was added during initial three minutes of the cycle. The following observations can describe the process:

[-2 to 0 minutes] Dry powder mixing. The powder consistency factor is high, indicating good uniformity of the powder. MFPM is small since no large and heavy granules interact with the DFF probes.

[0 to 2 min] Water is added to the powder at a constant rate. Extensive wetting and nucleation occurs leading to formation of wet granules and agglomerates [6]. The FPM values gradually increase from that of dry powder to larger values, since the impacts of wet granules on the probe are much stronger than that of dry powder. PFC factor decreases since FPM distribution widens – some FPMs are of the level of dry powder, and some others, due to wet agglomerate impacts, are of much higher value.

[2 to 3.5 min] At 2 minutes, all powder is wet, and the granule consolidation continues. Wet mass becomes more uniform since no more dry powder is present. It is now a mixture of wet granules. Their average mass (reflected by MFPM) continues to grow with water added and for 30 seconds after water addition stops.

[3.5 to 4.5 min] Breakage-dominating phase. The large granules and agglomerates break up into various sizes. Both the average force (MFPM) and the uniformity factor decrease.

[4.5 to 6 min] Second stage of granulation. Consolidation of granules leads to a secondary rise of MFPM. This secondary granulation stage is an indication of a center of formulation design space, since it was not observed when one of the design parameters is altered (the amount of water, see details in [4, 5]). The uniformity is decreasing during this stage (PCF drops) suggesting formation of large granules that widen the FPM distribution width (increase WFPM).

[6 to 26 min] Attrition stage. Granules slowly break up decreasing the average force (MFPM). Their size distribution become narrower and PFC increases until reaching a plateau after approximately 16 minutes of granulation, at a level of four. This value noticeably exceeds the minimum value of 2.5 observed during granulation, but smaller than the uniformity factor measured for the dry powder (~6).

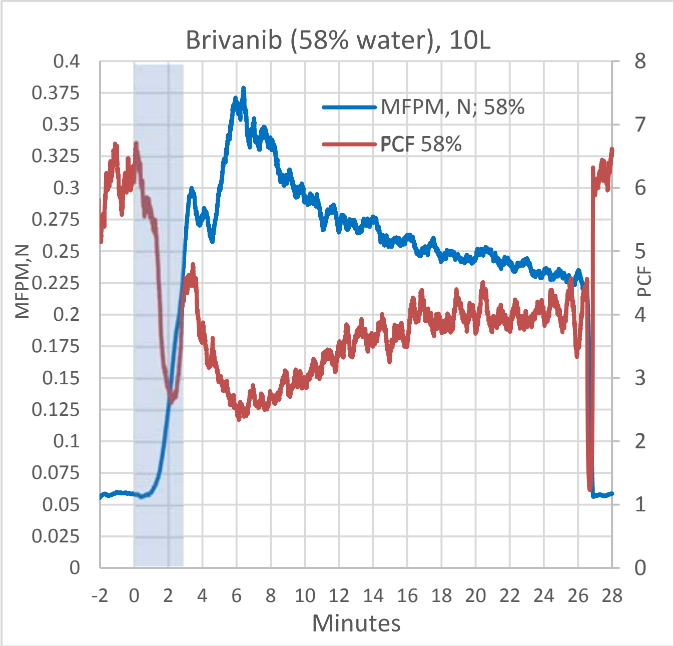

Figure 8. DFF fingerprint (time dependence of MFPM and PCF) for an HSWG process monitored in a 10L GEA PharmaConnect granulator. API formulation is in the center of design space (see [4] for more details). Water added between 0 and 3 minutes. Agitator stops at 26.5 minutes.

Conclusion

DFF sensor fingerprints can help in process optimization and monitoring. Salient features such as MFPM maxima (at 3.5 and 6.5 minutes) and PCF minimum (at 6 minutes) in Figure 8 may help with selecting the granulation end-point and/or scaling, and the absolute value of the powder consistency factor at critical time instants can be a convenient tool for defining the process design space.

References

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