On-line measurement of granule size distribution by dynamic image analysis in a continuous manufacturing line

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Introduction

The granule size distribution (GSD) is a critical quality attribute in the process of granulation. Within the context of continuous manufacturing it is therefore desired to monitor the current granule size during manufacturing. Dynamic image analysis is a well-established process to determine GSD and beneficial for material that was produced using roll compaction/dry granulation (RCDG) as it not only measures the granule size but also parameters such as shape factors. Furthermore, it is a non-destructive analytical tool and it is therefore to measure the size of granules and then join them with the non-measured fraction to maximize material output.

Materials and Methods

The outlet of a roll compactor (BRC 25, L.B. Bohle GmbH, D) was linked to a rotating tube sample divider (manufactured by the Heinrich Heine Universities fine mechanics, Figures 1 and 2). The rotating tube rotated at 49 rpm. Passing by the sample opening, material is sampled from full product stream at every rotation. About 10% of the material was sampled. The material that was not sampled was collected in a vessel underneath the outlet of the compactor. This mass was tracked every 5 seconds using a balance (Sartorius AG, D) and corresponding software (SartoConnect, Sartorius AG, D).

Image analysis was conducted using Haver CPA 2-1 (Haver&Boecker, D). It scans particles using a line scan camera with a frequency of 50 million pixel-scans per second. The moving average of the size parameters D50, D75 and D90 were written into a .csv file every 30 seconds.

Figure 1. the rotating tube sample divider

Dibasic calcium phosphate anhydrate (DiCaFos® A 150, Budenheim, D) was chosen as excipient.

RCDG using 6 kN/cm specific compaction force, a 2 mm gap width and a 1.5 mm rasp sieve was performed. A rotating tube sample divider was used to split 18% of produced material as a sample. Through a funnel, this material was directly entered into Haver CPA and measured. Every 60 seconds, the average of measured particle sizes was tracked. For one minute, a sample of the main fraction was collected and measured.

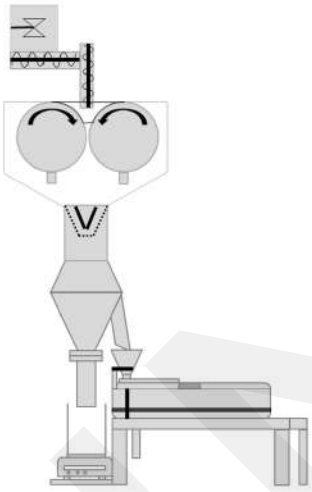

Figure 2. experimental set-up

Results

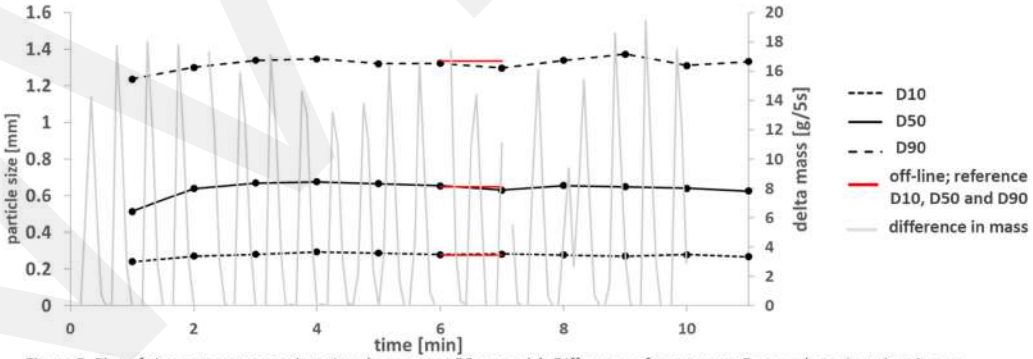

Figure 3. Plot of size parameters against time (mean over 30 seconds). Difference of mass every 5 seconds against time in grey. n=1; on-line data. Red = off-line data of sample taken between minutes 6 and 7, n=3; mean.

Figure 3 shows on-line results of the GSD parameters D10, D50 and D90 against time. The values are nearly constant for the shown 10 minute run. The off-line samples align well with on-line data. The difference in mass recorded highlights the systems fluctuating throughput. At low roll speeds, a ribbon is manufactured and only breaks upon entering the milling unit. A Fast Fourier Transform (FFT) shows a peak at 0.035 Hz (Figure 4) which equals to a surge in material about every 28 seconds. These fluctuations are not seen in on-line results as they are displayed as the mean of all individual scans over a period of 30 seconds. After stopping the process at minute 10, there was still product in the measurement system for analysis. Hence, a data point was registered after stopping the process (Figure 3, minute 12).

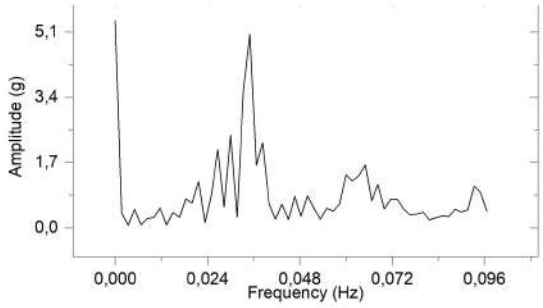

Figure 4. Fast Fourier Transformation (FFT) data: amplitude against frequency plot of the mass variation, n=1.

Conclusion

The used set-up was able to determine the GSD of resulting granules in accordance to off-line measurements. Values did not fluctuate strongly during the measurement. The speed of measurement has to be optimized in order to analyze all material in real-time and avoid accumulation of granules in the analyzer. The fluctuation of throughput has to be kept in mind for further experiments.

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