On-line measurement of granule size distribution by laser diffraction in a continuous manufacturing line

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Introduction

With growing interest in continuous manufacturing of pharmaceuticals, it is of importance to develop valid methods to monitor critical quality attributes. In case of granulation, the granule size distribution (GSD) is a critical quality attribute. Laser diffraction is a well-established technique to determine the GSD. For the first time, a bypass laser diffraction system was set-up in a continuous, dry granulation manufacturing line and compared to an in-line solution. The bypass should enable larger throughputs while also measuring consistently.

Materials and Methods

Microcrystalline cellulose (Vivapur 102, JRS Pharma, D) was granulated on a QbCon® dry (Figure 1) continuous manufacturing line using a BRC 25 (L.B.Bohle GmbH, D) at varying specific compaction forces (SCF) and 2 mm gap width. It was equipped with a 1.0 mm conical sieve (BTS 100, L.B. Bohle GmbH, D). An Insitec® T laser diffractometer (Malvern Panalytical, UK), was set-up in a bypass to measure the GSD on-line (Figure 2).

Figure 1. QbCon® dry. With courtesy of L.B. Bohle GmbH

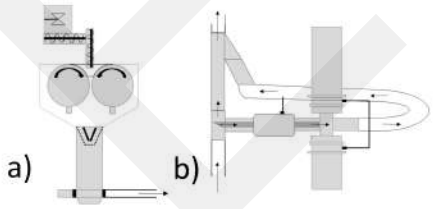

Figure 2. Scheme of a) BRC 25 and b) bypass

Results

GSD determination at varying SCF

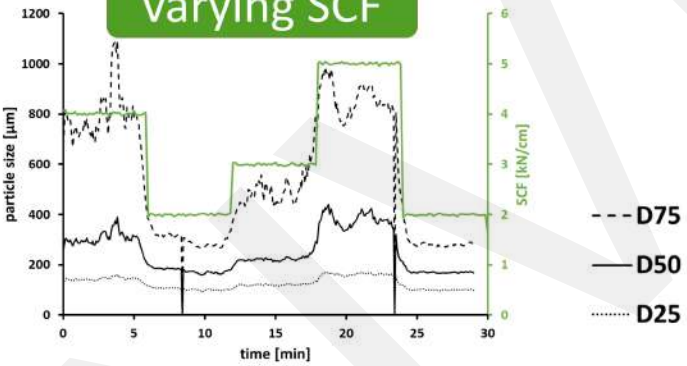

Figure 3. Plot of size parameters and SCF

The size parameters D25, D50 and D75 react to changes in SCF (Figure 3). A SCF of 2 kN/cm was applied twice (minutes 6 – 12 and 24 – 30) and lead to the same size parameters after all process parameters were in equilibrium (F- and t-test, $\alpha = 0.05$). Comparing in- to on- line data showed no differences at low SCF (Figure 4a)). At 5 kN/cm, the bypass could predominantly sample larger granules, as the size distribution is shifted to larger granule sizes and (Figure 4b)).

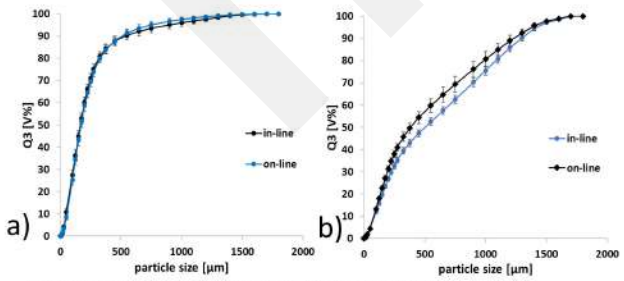

Figure 4. granule size distribution a) 2 kN/cm b) 5 kN/cm

GSD determination at increasing roll speed

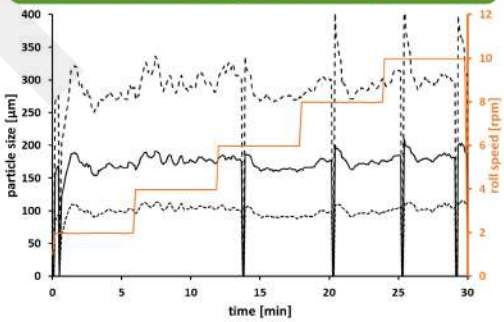

Figure 5. Plot of size parameters and roll speed. SCF = 2 kN/cm, gap width = 2 mm

Measuring the granule size at increasing roll speeds, the size parameters fluctuate around constant values (Figure 5). At high roll speeds (= high throughput) the collection vessel had to be emptied more frequently, leading to an interruption in material transport and abrupt stop of recorded measurements (e.g. minute 14). This inhibited long-term measurement but will not be critical for actual manufacturing processes.

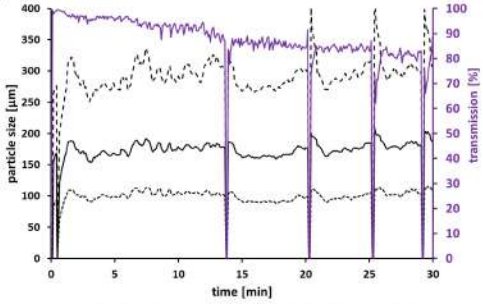

Figure 6. Plot of size parameters and transmission

At increasing roll speed the laser diffraction transmission decreases (Figure 6). 80% transmission still allows for reliable results (optimal measurement range 95 – 60 %).

Conclusion

The on-line bypass method of measuring GSD leads to similar results as the in-line set-up and enables higher throughputs. These are often required and a PAT tool for roll compaction/dry granulation should take this into account. Therefore, it is a promising approach to use this set-up in a continuous dry granulation manufacturing line.

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