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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 Metho[illegible]

Microcrystalline cellulose (Vivapur 102, JRS Pharma, D) w[illegible]anulated on a QbCon® dry (Figure 1) continuous manufacturing line using a BRC [illegible].Bohle GmbH, D) at varying specific compaction forces (SCF) and 2 mm gap wi[illegible]t was equipped with a 1.0 mm conical sieve (BTS 100, L.B. Bohle GmbH, D). An[illegible]ec® T laser diffra[illegible]ter (Malvern Panalytical, UK), was set-up in a bypass to me[illegible] the GSD on-line ([illegible]e 2).

Figure 1. QbCon® dry. Wi[illegible]esy of L.B. Boh[illegible]

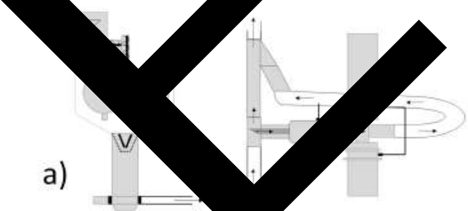
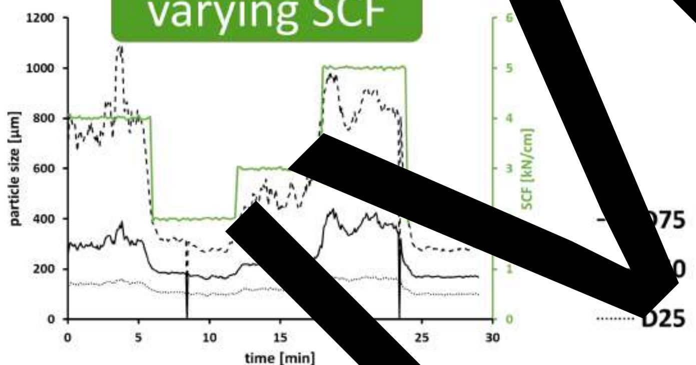


Figure 2. Scheme of a) BRC 25 a[illegible] bypass

Results

GSD dete[illegible]ination at

varying SCF



Figu[illegible]ot of size parameters and SCF

The size par[illegible] D75 react[illegible]anges in SCF (Figure 3). A SC[illegible] kN/cm wa[illegible] 6 – 12 and 24 – 30) and lead[illegible]he same size parame[illegible] all process pa[illegible]ers were in e[illegible]ium (F- and t-test, α = 0.05). Comparing in- to[illegible]e data show[illegible] differences at low SCF (Figure 4a)). At 5 kN/c[illegible]ypass could p[illegible]minantly sample larger granules, as the size dis[illegible]n is shifted t[illegible]r granule sizes and (Figure 4b)).

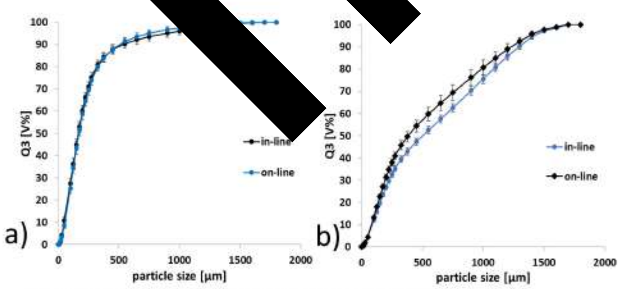


Figure 4. granule size distribution a) 2 kN/cm b) 5 kN/cm

increasing roll speed

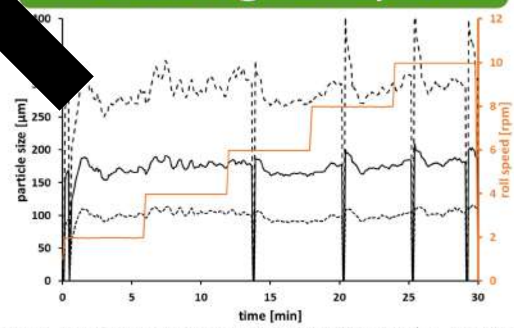


Figure 5. Plot of size parameters and roll speed. SCF = 2 kN/cm, gap width = 2 mm

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.

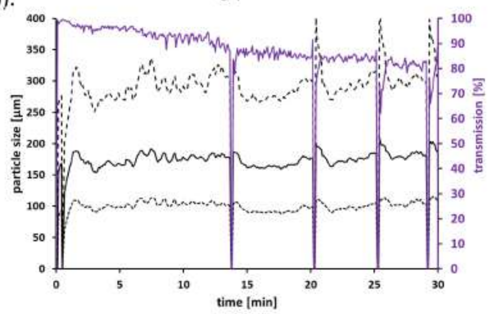


Figure 6. Plot of size parameters and transmission

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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