In-line determination of granule size distribution during continuous roll compaction/dry granulation by laser diffraction

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Introduction

Roll compaction/dry granulation (RCDG) is a granulation technique used in pharmaceutical manufacturing. It is a valuable method to granulate hydrolysis-susceptible APIs and avoid usage of organic solvents [1]. By nature of the process, it is capable of being used in continuous manufacturing as product is continuously fed, processed and discharged [2].

This work concentrates on applying process analytical technologies (PAT) to monitor the critical quality attribute (CQA) granule size distribution (GSD) of RCDG. Instant display of the current GSD and notable differences in GSD parameters when using different process settings are key aspects. Subsequently, the process could be controlled using these PAT-tools.

Materials and Methods

RCDG was performed using a Gerteis Minipactor (Gerteis, CH). Microcrystalline Cellulose (MCC, Vivapur 102, JRS Pharma, D) and dibasic calcium phosphate anhydrate (DCPA, Budenheim, D) were chosen as excipients. A Malvern Insitec T laser diffractometer (Malvern Instruments, UK) was used to monitor the GSD. The complete granule flow (mass flow up to 4 kg/h) was directed through the measuring unit vertically using a funnel. The lens focal length is 500 mm allowing for particle measurements between 0.3 µm and 2000 µm. The lenses were kept clean by a constant flow of pressurized air. This air was aspirated at the end of the measuring cell using a vacuum cleaner. As reference, samples were taken during the process and analyzed off-line via laser diffraction (Mastersizer 3000, Malvern Instruments, UK). The in-line results are displayed as the mean of individual measurements (2000/s) over the sampling period.

Results and Discussion

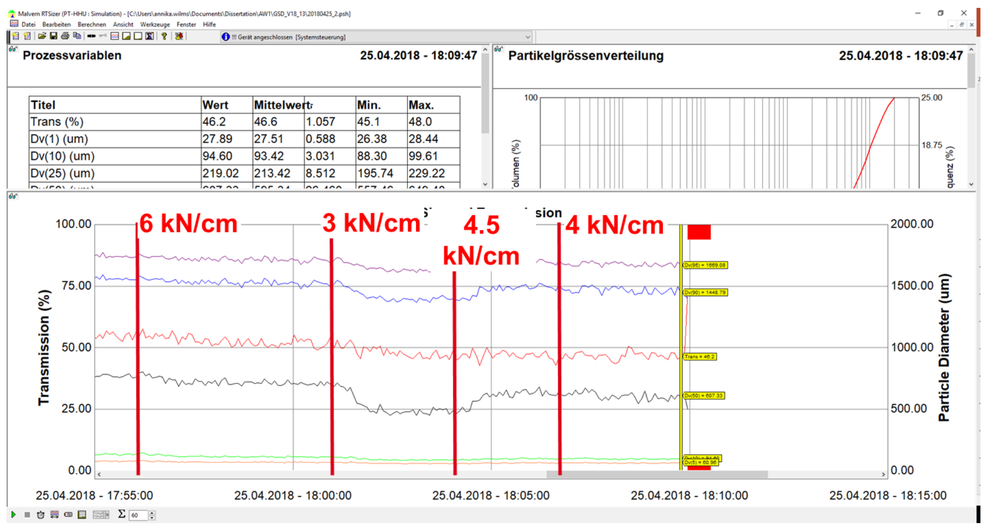

Fig 1: RT Sizer® Software interface.

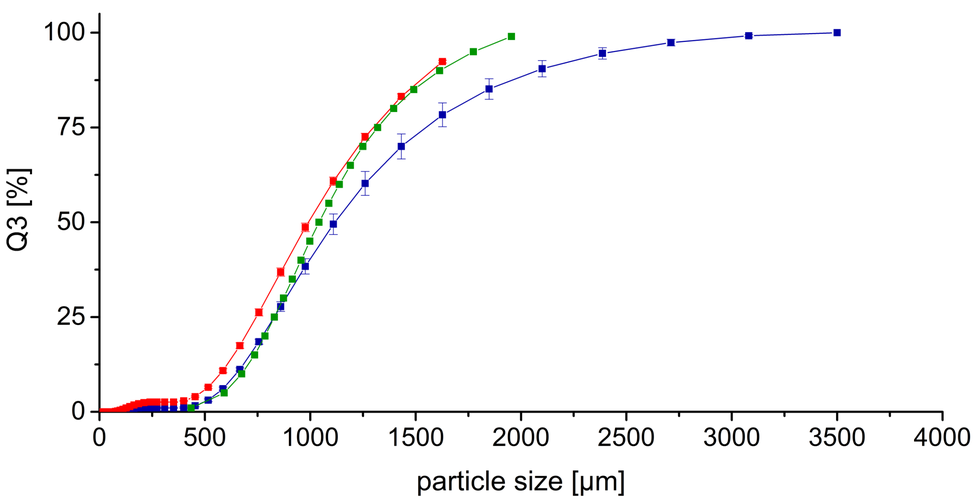

Fig 2:GSD measured off-line using Insitec T (green) vs. Mastersizer 3000 (blue and red) n=3; mean ± sd

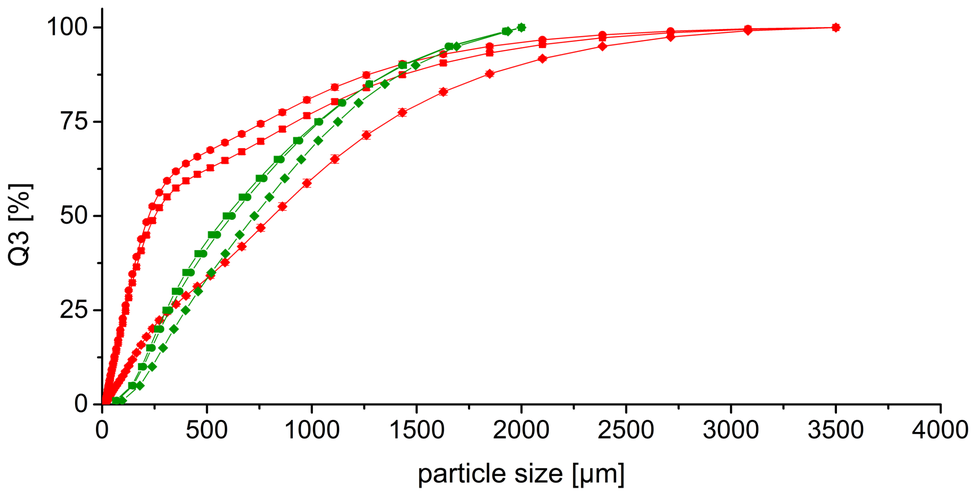

Fig 3:GSD measured in-line (Insitec T, green) vs. off-line analytics (Mastersizer 3000, red). Circle = 2 kN/cm SCF at beginning of process. Square = 6 kN/cm SCF. Diamond = 2 kN/cm at end of process. In-line data, no sd.

RT Sizer ® software was used for in-line analytics. Figure 1 shows the software interface. Results are presented every 5s in form of a table and a current GSD distribution curve (top left and right). The transmission [%] and key GSD parameters (D5, D10, D50, D90, D95) are also displayed in a time-line (bottom).

Results comparing off-line measurements with Insitec T and Mastersizer 3000 can be seen in Figure 2. Granules that were previously produced using RCDG were analyzed for their GSD. The green curve indicates the result obtained using Insitec T. The blue curve are the initial Mastersizer 3000 results. While Insitec® T is limited to particle sizes below 2000 µm the Mastersizer generates data up to 3500 µm. Approximately 10% of the granules were measured with a particle size larger than 2000 µm. A difference between the Insitec and Mastersizer results is therefore inevitable. However, both curves are aligned at the larger particles (above 1000 µm) if only Mastersizer data are evaluated that record particles below 2000 µm (red curve). After matching the curves for large particles, there is a difference in the measurement of the fine fraction. As fines are only a small fraction of the granules, the difference is not profound in this experiment.

Figure 3 shows the GSD observed in-line (green curves) versus off-line (red curves) by laser diffraction. The process was started at a specific compaction force (SCF) of 2 kN/cm, adjusted to 6 kN/cm and readjusted to 2 kN/cm. Samples were taken over the time of 1 minute. It is observed that fines and particles exceeding the upper limit of 2000 µm are not represented accurately. However, the real-time display of the quantiles and transmission (correlating to the current mass flow) are sensitive to changes in SCF. The measured particle sizes depend on the specific compaction force, but the changes are much smaller than those of the off-line measurements.

CONCLUSION

In-line laser diffraction is a promising approach as a control tool for particle size distribution during RCDG-processes. It combines fast measurements and a real-time display of results, and thereby can enable the set-up of ad-hoc control loops to keep the CQA GSD in desired range. Further research has to be done in order to increase the accuracy of in-line results compared to off-line measurements, to optimize the sensitivity of the method and to test it in long-time studies.

Acknowledgement

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