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In-line monitoring of particle size in a fluid bed granulator: Investigations concerning positioning and configuration of the sensor

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ABSTRACT

According to the ICH Q8 guideline, analytic technologies (PAT) are important tools for characterization and optimization of pharmaceutical manufacturing processes. Particle size as a critical quality attribute for granules is therefore an important parameter that should be monitored during the fluid bed granulation process. This work focusses on optimizing position and configuration of an SFT-sensor for the in-line measurement of particle size distribution in a Glatt GPCG 3 fluid bed granulator. As model-substances, different grades of microcrystalline cellulose were used. The in-line measured particle size and particle rate in the sensor were evaluated. A sensor position in the deceleration zone of the granulator was found to be promising for in-line particle size measurement. Most reliable data were generated in this position when the probe was placed in a distance of 11 cm from the chamber wall to avoid bias by the inlet air stream. No major influence of rotation angle of the probe was found in this position. Furthermore, an entire fluid bed granulation process was successfully monitored with the sensor installed in the optimized setting.

1. Introduction

The implementation of process analytic technology (PAT) is recommended by the ICH Q8 guideline and the PAT-approach by the FDA to establish understanding of the critical process parameters (CPP) of a pharmaceutical manufacturing process. Suitable technologies should be used to monitor critical quality attributes (CQA) for rational process design and process control (FDA, 2004; ICH, 2009).

Granulation is a key manufacturing step in the production of tablets. The resulting granule particle size critically influences powder flow rate, blend uniformity and tablet properties such as crushing strength, average mass and friability (Abberger, 2001; Kristl et al., 1993; Faure et al., 2001; Kleinebudde, 2001). For these reasons and to optimize energy consumption and process time, the implementation of PAT to monitor particle size during granulation processes is desirable. In the last few years several new in-line technologies have been developed to monitor the particle size as a CQA during the granulation process. In-line particle size measurement became possible by implementation of near infra-red spectroscopy (NIRS) as early as 1996 (List and Steffens, 1996) but in the past few years some follow-up studies have been published that reveal two major problems of the method (Frake et al., 1997; Rantanen et al., 2000). Firstly, a large amount of data is needed to calibrate the sensor and secondly, reflections on particles or granules that adhere to the measuring window may cause measurement failure (Buschmüller et al., 2009).

Recently, the spatial filtering technology (SFT) was described as a new in-line particle size analysis method that can be used in the fluid bed granulation process (Lipsanen et al., 2008; Närvänen et al., 2008, 2009; Schmidt-Lehr et al., 2007). The advantage of this method is that no calibration of the sensor with the actual product is necessary. The sensor which analyses particle velocity and impulse in a fiber optic array to calculate particle cord length allows for a direct in-line and real time determination of the particle size distribution (Fig. 1A). The manufacturer (Parsum, Chemnitz, Germany) specifies the measurement range from 50 μm to 6000 μm.

In order to validate particle size analysis by SFT, Petrak compared measurement outcomes with off-line results of laser diffraction (Petrak, 2002). He demonstrated that the SFT-sensor

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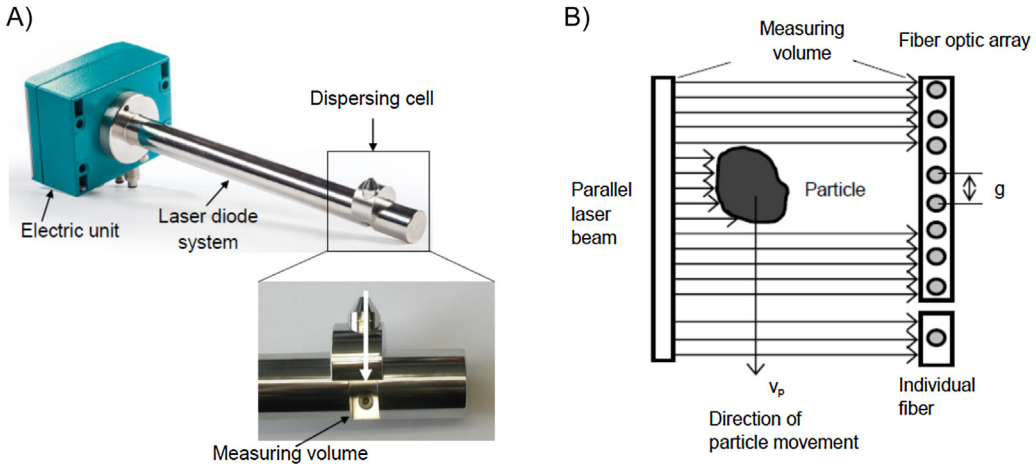

Fig. 1. SFT-sensor (Parsum). (A) Overview of the sensor assembly. (B) Schematic illustration of the measurement principle of the modified spatial filter technology.

provided reasonable particle size data for spherical glass beds with x_{50} = 100 μm, but revealed that typically the SFT sensor provided smaller particle size than laser diffraction and coulter counter. In spite of these differences in absolute particle size, the sensor can be used as a tool to reflect relative changes in particle size and hence monitor particle size development during a granulation process (Huang et al., 2010; Schmidt-Lehr et al., 2007).

Several studies already discussed the use of an SFT-sensor for in-line monitoring of particle size during a fluid bed granulation process (Burggraeve et al., 2010, 2011a; Huang et al., 2010). None of these studies, however, described the effects of sensor position and configuration on the measurement outcome. Schmidt-Lehr mentioned tests for optimization of the sensor position and configuration but no details concerning the instrumental set-up have yet been provided (Schmidt-Lehr et al., 2007). Burggraeve, however, mentioned that the position of the sensor in the granulator has to be considered due to influences of segregation effects on the measurement results (Burggraeve et al., 2013).

In this study we investigated the influence of sensor position in the fluid bed granulator on particle count rate and average particle size. To this end, we generated two different probe positions in the granulator, one in the conical product container and one in the deceleration zone below the spraying nozzle. We tested different probe configurations (insertion depth and degree of rotation) in either position (Fig. 2).

In general, installation of the sensor in the deceleration zone involves the risk of overweighing small particle sizes due to possible segregation processes in the fluid bed (Burggraeve et al., 2011b; Närvänen et al., 2009). On the other hand, measurement in the product container might be influenced by clogging effects of the sensor. To distinguish between these effects, we determined count rates as a measure for particle interactions besides the particles size distributions that were compared to data from laser diffraction. Particle size distributions of two microcrystalline celluloses were investigated; Vivapur 101 with a declared particle size (x_{50}) of 65 μm and Avicel PH 102 with an x_{50} of 100 μm. Especially, Vivapur 101 is an excipient of interest as it is increasingly considered as an alternative for lactose in formulations.

In order to verify the results of the configuration experiments, a granulation process of a model-placebo-formulation was

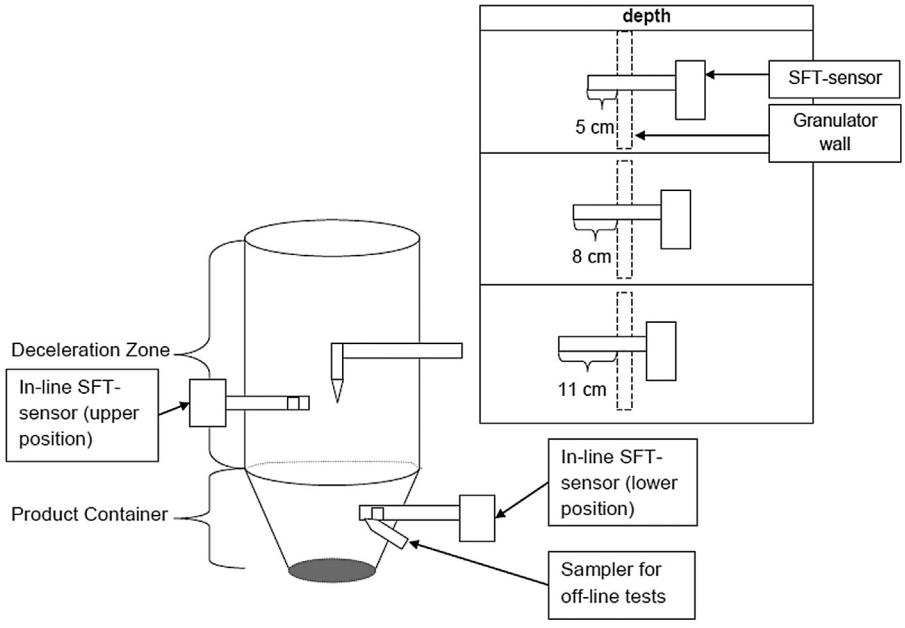

Fig. 2. Scheme of the GPCG 3.1 granulator, the sensor position and insertion depth during in-line measurement.