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Evaluation of an in-line particle imaging tool for monitoring twin-screw granulation performance

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ABSTRACT

Twin-screw granulation is an emerging continuous wet granulation technique in the pharmaceutical industry due to several advantages over batch granulation. However, for the implementation of a fully continuous line in an industrial environment, in-process measurement tools are required to monitor critical process parameters and (intermediate) product quality attributes, and trigger control actions based on such measurements. This study aimed at evaluating the feasibility of implementing an in-line particle imaging technique (Eyecon™) after continuous twin-screw granulation and before the drying system. Off-line sieving was used as reference particle size analysis method. A twin-screw granulator which is part of the Consigma system was used to granulate a placebo formulation composed of lactose and polyvinylpyrrolidone (PVP; 97.5:2.5% w/w). PVP was dissolved in water, which was used as granulation liquid at liquid-to-solid ratios ranging between 8 and 9%. The performance of the in-line measurement method at heterogeneous process conditions was tested by changing the liquid to solid ratio (8–9%), the material throughput (10–25 kg/h) and the screw configuration (16 and 26 kneading discs). The volumetric size distribution obtained from the in-line measurements of the granules leaving the twin-screw granulator using the Eyecon™ camera was compared with the off-line measurements obtained by sieving of the granule samples collected before and after the drying unit operation. For the intermediate size range (diameter 250–1000 μm), the Eyecon™ measurements showed to be promising as they were in agreement with off-line measurement results obtained before the drying unit. However, the image analysis algorithm and data post-processing of the Eyecon™ images for the fines and oversized ranges require modification for improvement in measurement results. In conclusion, the Eyecon™ provides very good in-line images despite a dense moving flow of granules. However, proper analysis of these images is crucial before application as standard in-line particle size monitoring tool and application for control purposes can be realized.

1. Introduction

Granulation in many cases is a key product design step in the pharmaceutical solid-dosage manufacturing process. By using a combination of formulation properties and granulation conditions, granule quality attributes can be modified [1]. Although continuous processing is still in its infancy in the pharmaceutical industry, it holds a great potential due to several process and economic benefits. A 24/7 production capacity eliminates the scale-up requirement and intermediate storage typical for batch manufacturing [2], and the process operation at steady-state results in more uniform granule properties [3]. Therefore, continuous twin-screw granulation has received increased attention since such a TSG can be connected to a continuous drying system, followed by a dry mill and tabletting device, thus making a continuous from powder to tablet manufacturing line possible.

In the implementation of continuous granulation into the pharmaceutical industry, the QbD approach will play an important role [4], and relies on enhancing the product knowledge and process understanding [5]. The needs and opportunities for in-line measurements of various CQA and CPA to realize the switch towards continuous manufacturing have been presented in a recent review [6].

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Several researchers have investigated the effect of key variables involved in continuous twin-screw granulation, including formulation variables [7–12] and process parameters [13–17]. Most of these studies relied on off-line granule characterization tools. However, applications based on high-speed imaging [18,19], near infrared and Raman spectroscopy [20] for the in-process monitoring and control of pharmaceutical production processes are becoming increasingly popular. In case of TSG, Fonteyne et al. used an in-line SFV probe (Parsum, Chemnitz, Germany) to continuously monitor the particle size of the granules in TSG [21]. Although the technique was found to hold potential, the main challenge was to avoid fouling of the optical surfaces in the interfacing system. Other researchers applied the photometric stereo imaging technique (Flashsizer FS3D, Intelligent Pharmaceutics Ltd., Finland) for at-line measurement of granule size in a continuous wet granulation process and reported irregularities caused by shading on the one hand, and dusting of the measurement window by fines on the other hand [22]. A detailed comparison of in-process with off-line GSD measurement methods has been reported by Silva et al. [22]. El Hagrasy et al. performed a feasibility study towards the implementation of Eyecon™, a 3D high-speed imaging camera, for the in-line monitoring of continuous wet granulation using TSG to analyse its capability for real-time process control [19]. This study demonstrated the sensitivity of the Eyecon™ to variation in process parameters, but a strong leverage towards larger particles was observed due to the conversion of the initial measurements as number distributions into volume distributions. The study demonstrated that the D10 of the GSD showed less deviation from the sieving results compared to the D50 and D90 measurements. However, the study only focussed on the effect of variation in L/S while keeping other important TSG operating parameters such as material throughput and screw configuration constant.

The present study critically evaluates the feasibility of implementing an in-line particle imaging technique (Eyecon™) for determination of GSD after the continuous twin-screw granulation and before the drying system. The effect of several changes in key TSG process variables i.e. L/S (8–9%), material throughput (10–25 kg/h) and screw configuration (16 and 26 kneading discs) on the in-line measurement of the GSD immediately after the granulator (using the Eyecon™ camera) was examined. A comparison with off-line sieving measurements of the granule samples before and after the drying unit operation was performed in order to understand the influence of the transfer line from a granulator to a dryer and the drying process on GSD. Finally, recommendations for further improvement of the image analysis algorithm and data post-processing, and the interfacing system of the Eyecon™ camera are made.

2. Materials and methods

2.1. Pharmaceutical formulation

α-Lactose monohydrate (Pharmatose 200 M, DFE-Pharma, Hemiksem, Belgium) was used as model excipient and PVP (Kollidon30, BASF, Ludwigshafen, Germany) as a binder (Lactose:PVP; 97.5:2.5 w/w). The binder dissolved in distilled water was used as granulation liquid.

2.2. Continuous twin-screw granulation and drying

Granulation experiments were performed using a 25 mm diameter co-rotating twin screw granulator, which is the granulation module of the ConsiGma-25 unit (GEA Pharma Systems, Collette, Wommelgem, Belgium). The granulator screws have a length-to-diameter ratio of 20:1. The TSG barrel consists of a feed segment, where the powder enters the barrel and is transported through the conveying zone to the work segment, where the granulation liquid is added to the powder which is further intensively mixed by a combination of kneading discs and transport screws. The barrel jacket was preheated to 25 °C. During processing, pure α-lactose monohydrate was gravimetrically fed into the granulator by using a twin screw feeder (KT20, K-Tron Soder, Niederlenz, Switzerland). The granulation liquid was pumped into the screw chamber by means of a peristaltic pump (Watson & Marlow, Cornwall, UK) and silicon tubings connected to 1.6 mm nozzles. The granulation liquid was added (8–9%, w/w based on wet mass) before the first kneading element (Fig. 1) by dripping through two liquid feed ports, where each port is located on the central top of each screw in the barrel. The TSG has a built-in torque gauge and the steady state criteria were decided based on the equilibration of the measured torque of the granulator. The wet granules from the TSG were discharged into a vacuum wet transfer line and transported to the six-segmented fluid-bed dryer. The granules were dried by hot air, for which temperature and flow rates were controlled. The dryer is semi-continuous meaning that the granules were dried in six "mini-batches", and were sequentially discharged into the dry transfer line towards the mill. In this study the granules were collected after wet transfer and drying, before milling.

2.3. Granulation and drying experiments

Experiments were performed at four different granulation conditions (GC) for the TSG (Table 1). Identical drying conditions were used during all granulation experiments. The inlet air temperature was set at 60. The air flow of the dryer was set at a velocity of 420 m/s and the filling time of each drying cell was 270 s for a throughput of 10 kg/h and 180 s for a throughput of 25 kg/h. The drying time was 380 s.

GC 1 induced less mechanical shear due to the application of only one kneading block and a low screw speed, but was also characterized by a high fill ratio due to high throughput together with a low screw speed. GC 2 resulted in less mechanical shear due to the low number of kneading discs but high mixing intensity and low fill ratio due to low throughput combined with high screw speed. GC 3 had both high mechanical and mixing shear due to the presence of 2 kneading blocks and a high screw speed but the fill ratio was low as the throughput was low and a high screw speed was applied. GC 4 had a high mechanical and mixing shear due to the presence of 2 kneading blocks and high screw speed and the fill ratio was high due to the high throughput.

2.4. Measurement of granule size distribution

2.4.1. In-line granule characterization

During the twin-screw granulation process, the Eyecon™ 3D Particle Characterizer (Innopharma Labs, Dublin, Ireland) was used for the in-

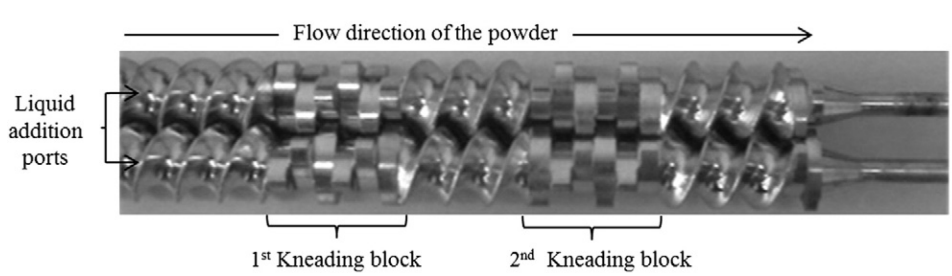

Fig. 1. Screw configuration with 12 kneading discs (2 blocks).