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

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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 to 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 (1×6 and 2×6 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.
Keywords: twin-screw granulation, granule size distribution, in-line measurement, high-speed imaging

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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 twin-screw granulator (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 Quality by Design (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 critical quality attributes (CQA) and critical process attributes (CPA) to realize the switch towards continuous manufacturing have been presented in a recent review [6].

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 spatial filter velocimetry (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 granule size distribution (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 D_{10} of the GSD showed less deviation from the sieving results compared to the D_{50} and D_{90} measurements. However, the study only focussed on the effect of variation in liquid-to-solid ratio (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 (1×6 and 2×6 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 granulator to 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 200M, DFE-Pharma, Hemiksem, Belgium) was used as model excipient and Polyvinylpyrrolidone (PVP) (Kollidon®30, 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.

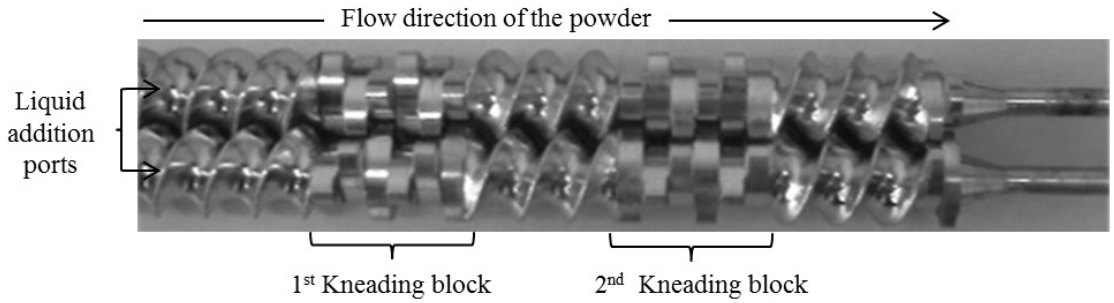


Figure 1: Screw configuration with 12 kneading discs (2 blocks).

Table 1: Granulation conditions (GC) for the granulation experiments

	GC 1	GC 2	GC 3	GC 4
Throughput (kg/h)	25	10	10	25
Liquid addition (%)	9	9	8	9
Screw	1×6	1×6	2×6	2×6
Screw Speed (RPM)	500	900	900	900

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

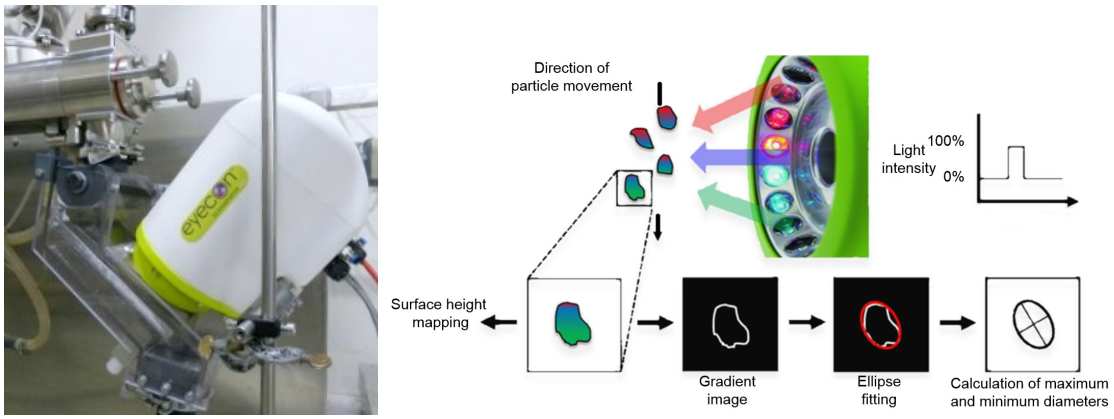
to the presence of 2 kneading blocks and a high screw speed but the fill ratio was low as the throughput was low and a high screw speed was applied. GC 4 had a high mechanical and mixing shear due to the presence of 2 kneading blocks and high screw speed and the fill ratio was high due to the high throughput.

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-line measurement of granule sizes. The camera was installed between the granulation barrel and the wet transfer line. The granules were photographed every second by the Eyecon™ using an in-house developed slide which made the granule flow focused into a narrow stream at the focal point of the camera (Fig. 2i). The distance between the camera and the sample was 30 mm. The 3D-imaging system captures sharp images of the granules moving up to 10 m/s using 1 µs illumination pulses (Fig. 3.a). This illumination method allows deriving three dimensional information from two dimensional images, which is used for improved edge detection, especially of the overlapping particles. The size of the 3D-projected image is subsequently used to obtain the equivalent diameter of the best fit ellipse. The shape of the particles is also estimated by calculating the ratio of maximum and minimum diameter of the fitted ellipse on the particle edges as shown in Fig. 2ii (for details regarding the working principle of the Eyecon™ camera, see El Hagrasy et al. [19]). For practical purposes, this measurement system can be used for pharmaceutical granulation producing granules with a size range between 50 and 3,000 µm.

Being an image analysis based size measurement tool, the Eyecon™ camera results are interpreted as number distribution of granules in the image taken. To convert this number-based distribution into mass distribution, the cube of the mean diameter of each size class is multiplied with the number of granules observed in the corresponding size class. Because of



(i) (ii)

Figure 2: (i) An in-house made interfacing device mounted after the twin-screw granulator and before the wet transfer line to the drying unit for the in-line measurement of the wet granules. (ii) Working principle of the Eyecon™ equipment [22].

the transformation from number based to volume based values, the larger particles have a relatively big influence on the complete distribution [19]. Using the raw data collected by the Eyecon™, it is possible to look at all the granules measured by the device. For a high number of size fractions, the number of granules observed in that fraction is displayed, allowing building of virtual sieves and comparison of these results with data from experimental sieve analysis.

2.4.2. Offline particle size analysis

The GSD of the granule samples, collected at the outlet of the TSG and after the dryer unit, was determined off-line using the sieve analysis method (Retsch VE 1000 sieve shaker (Haan, Germany)). However, sieve based measurements require drying of the granules before fractionation by sieving. The wet granules collected at the outlet of the TSG were oven dried (40 °C, 24 h) before sieve analysis. Granule samples (100 g) were placed on a shaker for 5 min at an amplitude of 2 mm using a series of sieves (150, 250, 500, 710, 1000, 1400 and 2000 µm). The amount of granules retained on each sieve was determined. All granule batches were measured in triplicate. Moreover, utmost care was taken during sample preparation prior to sieving, such as spreading the sample in an as thin as possible layer in large, shallow trays,

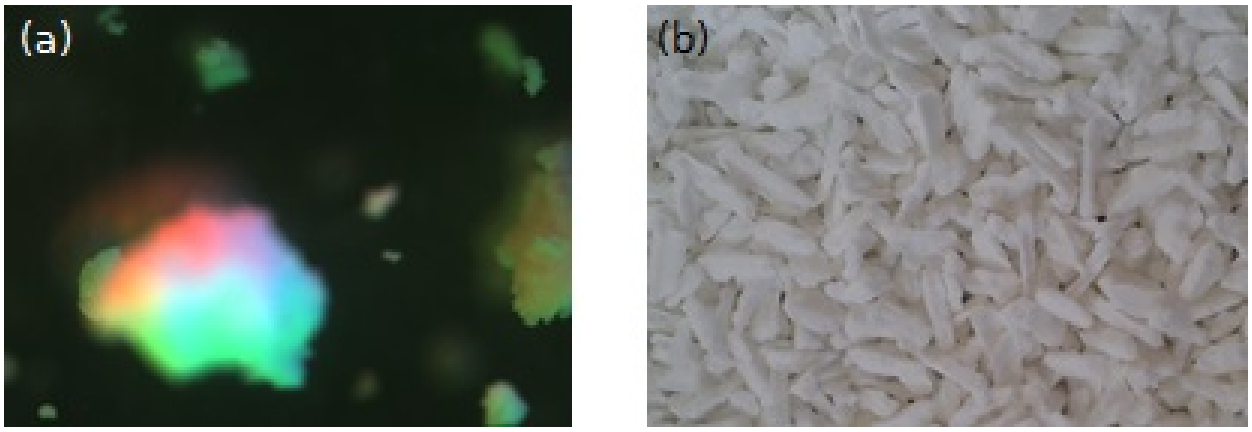


Figure 3: Granules produced by the twin-screw granulator as (a) imaged using the Eyecon™ camera and (b) after oven drying of wet granules for off-line GSD measurement.

and selecting the sieving time and amplitude during sieving such that negligible attrition during sieving occurred. However, the influence of sieving shear on different size fractions cannot be excluded completely.

3. Results and discussion

Fig. 4 shows the change in GSD when in-line and off-line measurements were performed for granules sampled immediately after the granulator and for off-line measurements on samples taken after the drier. A clear difference in trend was observed between the three GSDs especially in case of the off-line measurements after the dryer. The number of granules belonging to each size fraction of the samples collected before the dryer were found to be relatively similar for off-line and in-line measurement tools. The size fractions which showed most difference were located at the extremes i.e. the fines and the oversized fraction. This difference can originate both from physical phenomena of shear in the vacuum transfer line and drying of the wet granules or from the lack of the capability of the analyser to measure samples containing granules with a broad size range. Moreover, a difference in the sensitivity of the measurement technique to certain fractions of granules caused variation in the GSD measured, based on the quantity of that fraction of the granules produced at four different

process conditions (GC 1 to GC 4 in Table 1). Based on the results from sieving which has been used as reference particle size analysis method, a higher amount of larger granules (>2000 µm) were observed in GC 1 after the granulator (SBD) compared to the other granulation conditions (Fig. 4). This was due to less mechanical shear when having only one kneading block and a higher fill ratio at this condition. When the fill ratio was reduced by reducing the material throughput and increasing the screw speed at GC 2, the amount of granules in the size ranges 1000-1400 µm and 1400-2000 µm increased. Since the fill ratio was low and the material was getting exposed to shear-induced mixing at high screw speed further mechanical shear by the second kneading block did not lead to any change in GSD at GC 3, due to which only minor changes were observed between SBD at GC 3 compared to GC 2. However, when the fill ratio was increased by increasing the material throughput and because additional restriction to the flow occurred by the second kneading block, the larger granule fraction (>2000 µm) increased again. This suggests that granules obtained at different granulation conditions had different size and physical characteristics. Therefore a scenario based analysis was performed as presented in the next section.

3.1. Scenario based analysis of GSD measurement approaches

In order to interpret the performance of the in-line analyser and to make a reasonable comparison between both measurement approaches (in-line measurement using Eyecon™ and off-line measurement using sieving), three scenarios were considered (Table 2): (1) in-line measurement before dryer vs. off-line measurement after dryer, (2) off-line measurements before and after the dryer and (3) both in-line and off-line measurement before the dryer. Differences between the two measurements within each scenario suggest an overestimation by the first technique and/or an underestimation by the second technique when a positive value is obtained and vice versa if a negative value was obtained.

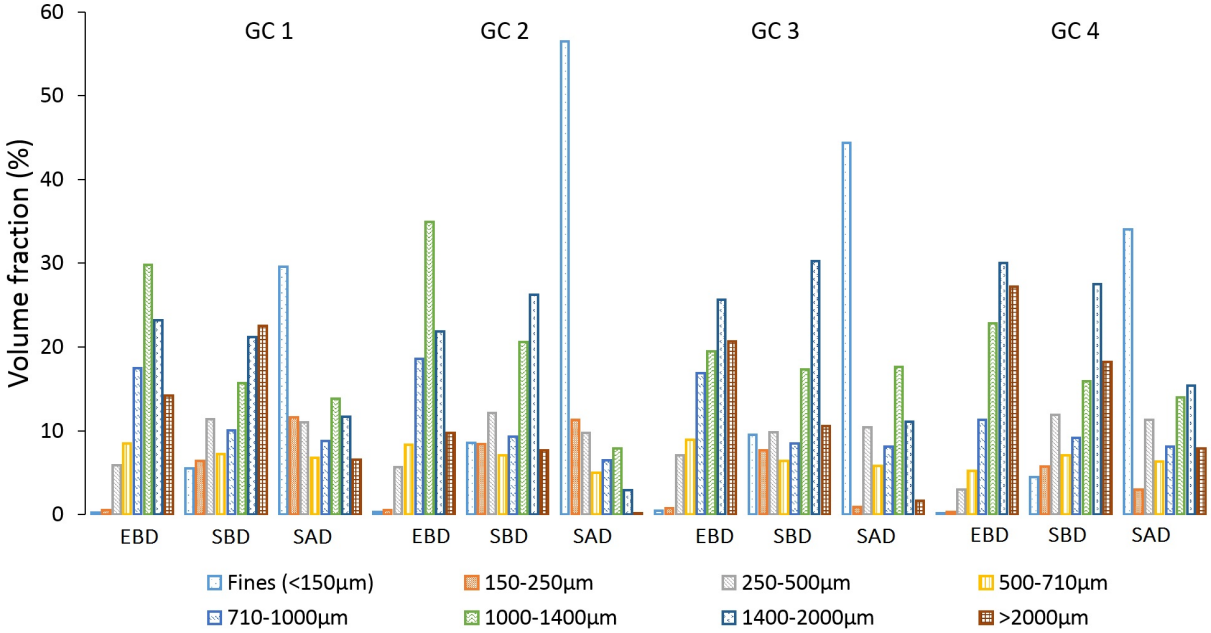


Figure 4: Absolute measurement of granules for each size fraction when measured using the Eyecon™ camera before the dryer, and determined via sieve measurements both before and after the dryer for four process conditions (GC 1, GC 2, GC 3 and GC 4) [EBD: Eyecon™ before dryer, SBD: Sieve before dryer, SAD: Sieve after dryer].

Table 2: Three scenarios for the comparison of the two measurement approaches when applied to the same process

Scenario 1:	TSG	⇒	Eyecon™	⇒	Fluidised-bed dryer	⇒	Sieve test
Scenario 2:	TSG	⇒	Sieve test	⇒	Fluidised-bed dryer	⇒	Sieve test
Scenario 3:	TSG	⇒	Eyecon™				
		⇒	Sieve test				

3.1.1. Scenario 1: In-line measurement before dryer vs off-line measurement after dryer

In the continuous manufacturing line, the in-line analyser was placed immediately after the granulator and before the wet-transfer line to the dryer as PAT tool for direct GSD assessment (Fig. 2i). Hence, a comparison between the in-line granule measurements before the dryer and the off-line measurement after the dryer was attempted to understand the impact of vacuum transfer to the dryer and the drying operation itself on the size of the granules. The difference between the GSDs derived from the two methods for each size fraction was significant (Fig. 5). The plot indicates a switch in size distribution around 500 µm meaning that more smaller granules were observed by the off-line measurement after the dryer compared to the in-line measurement before the dryer, and vice-versa for the oversize fraction. Also, the granules produced by GC 2 showed most variation due to the fragile nature of granules produced at conditions of reduced mechanical shear which were generated by applying a low number of kneading discs as well as a low fill ratio due to the low throughput combined with high screw speed.

The observations of this scenario suggest 3 possibilities: (i) the in-line measurement tool underestimates the number of granules smaller than 500 µm and overestimates others, (ii) the wet transfer and drying process itself create a lot of smaller granules by breakage of granules larger than 500 µm and (iii) that both the first and the second possibility co-exist. Therefore, to confirm the role of the wet transfer and drying process in changing the GSD, another scenario was studied where conventional sieve based measurements of granules sampled before and after the drying unit were performed.

3.1.2. Scenario 2: Offline GSD measurements before and after the dryer

Despite applying the same GSD measurement method (sieve analysis), a large difference was observed in fractions <150 µm and >1400 µm when comparing sieve measurements before and after the dryer for all the granulation conditions (Fig. 6). This indicates that a

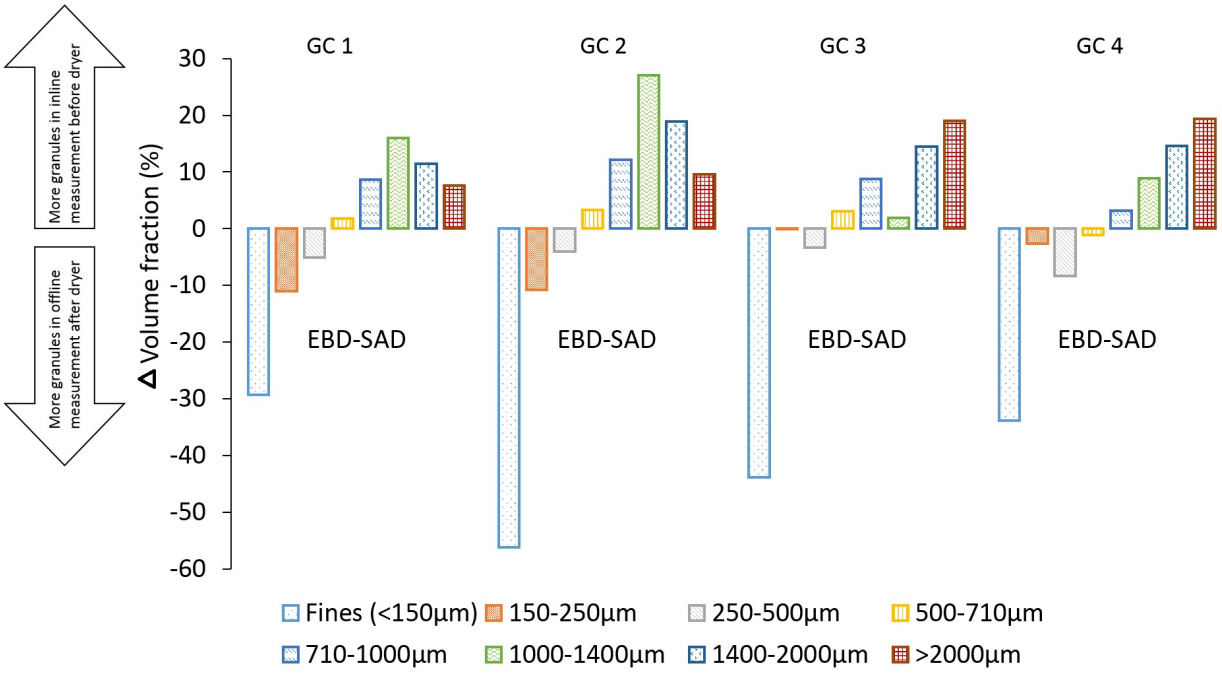


Figure 5: Differential measurement of granules for each size fraction when measured using the Eyecon™ camera before the dryer on the one hand, and using sieve measurement after the dryer for four granulation conditions (GC 1, GC 2, GC 3 and GC 4). A positive value for the size fraction indicated an overestimation by the Eyecon™ camera, and a negative value indicated an underestimation of that particular size fraction by the Eyecon™ camera [EBD: Eyecon™ before dryer, SAD: Sieve after dryer].

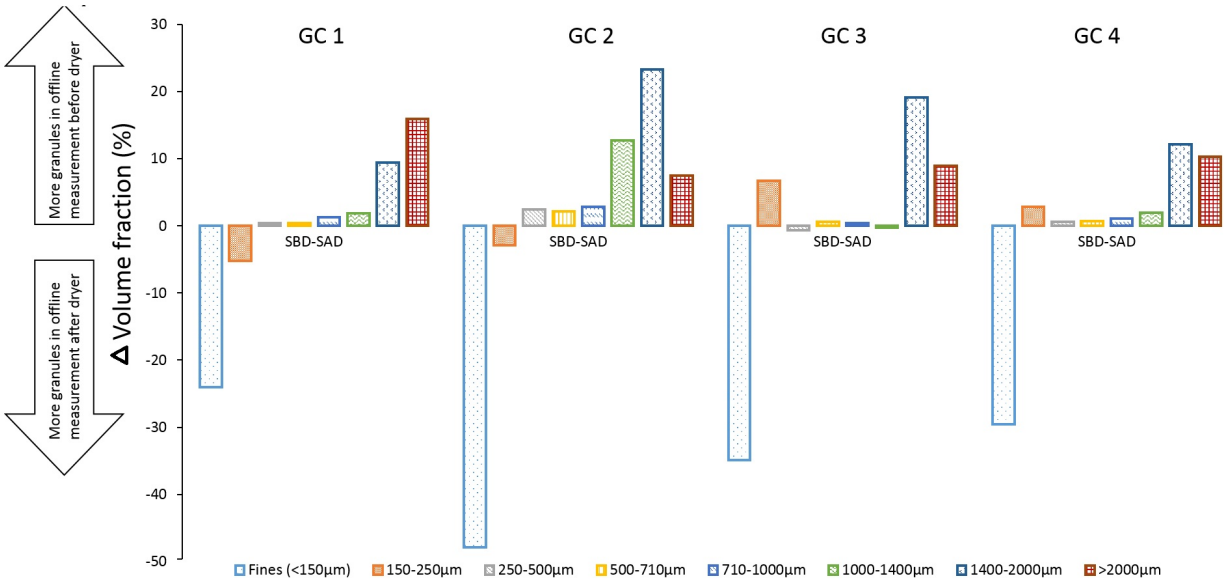


Figure 6: Differential measurement of granules for each size fraction when measured using the off-line measurement tool both before and after the dryer for four granulation conditions (GC 1, GC 2, GC 3 and GC 4). A positive value for the size fraction indicated an overestimation by the sieving before the dryer, and a negative value indicated the opposite [SBD: Sieve before dryer, SAD: Sieve after dryer].

lot of fines (<150 µm) were created in the wet transfer line and/or in the dryer unit and that most of these fines emerged by attrition and breakage of oversize granules which were more abundant in the samples before the wet transfer line. This suggests that an increased level of deviation in scenario 1 was primarily caused by the size reduction sub-processes (attrition, breakage, shrinkage etc.) in the transfer line and the drying unit. Also, the granules produced by GC 2 once again showed most variation due to the fragile nature of granules for the reason discussed in scenario 1. However, granules ranging from 150-1400 µm were less affected by the drying operation which was reflected in less variation in this range. This suggests that the observed difference in this range in scenario 1 was a result of the under- and over-predictions by the in-line particle size analyser.

This led us to a third scenario, comparing both in-line and off-line measurement of granules before the wet transfer line and drying unit.

3.1.3. Scenario 3: Both in-line and off-line measurements before dryer

Both in-line and off-line measurements were performed after the TSG in order to eliminate the effect of wet transfer and drying process on the measurements. Comparison between in-line and off-line measurements showed that the differences between the two measurement approaches were much smaller compared to scenario 1 (Fig. 7). However, measurements still pivoted at 500 µm for all the granulation conditions indicating that more small-sized granules were observed by the off-line technique compared to the in-line method. The opposite observation was made for the oversized fraction.

This observation suggests the need for future improvement in the GSD analysis method by the in-line particle size analyser for achieving improved agreement between in-line and off-line measurements. Additionally, this scenario together with scenario 1 also indicated a high level of attrition/breakage of granules in the wet transfer line and the fluidised-bed drying unit and the risk for attrition when using the sieving based method leading to a lower amount of granules in the oversized fraction. An over-prediction of more than 10 % for the 1000-1400 µm size fraction by Eyecon™ at GC 1 and GC 2 suggests that the granulation conditions also play a critical role, such that some samples are more sensitive to sample preparation methods for GSD measurements than others.

3.2. Recommendations for future development

The Eyecon™ demonstrated to be a potential tool for in-line GSD analysis of twin-screw granulation by providing particle size data and direct images of the particles in real time. The ability of the Eyecon™ as an in-line measurement tool to visualise the granules despite the dense flow of particles from the granulator itself, was observed to be promising. Additionally, the sample presentation by the in house developed interfacing device offered an excellent basis for the commercial-scale integration of the Eyecon™ camera in a continuous manufacturing line. However, changes in the interfacing device to reduce intermittent or potential window fouling issues and improvements in the interpretation of the collected data

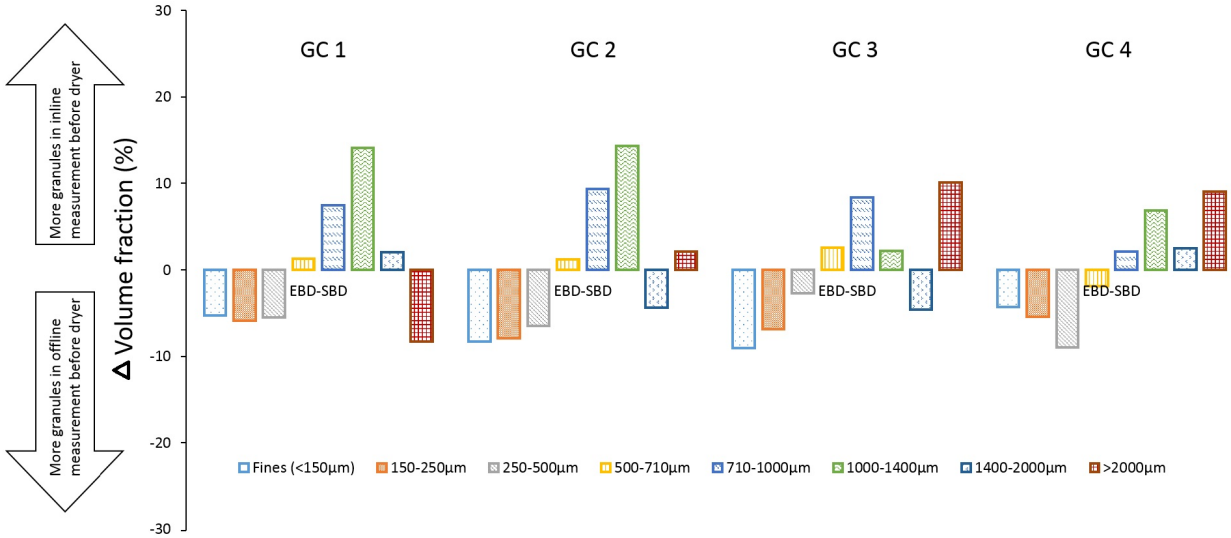


Figure 7: Differential measurement of granules for each size fraction when measured using both Eyecon™ camera and off-line measurement before dryer for four granulation conditions (GC 1, GC 2, GC 3 and GC 4). A positive value for the size fraction indicated overestimation and a negative value indicated an underestimation of that particular size fraction by the Eyecon™ camera [EBD: Eyecon™ before dryer, SBD: Sieve before dryer].

to further reduce the differences between the in-line and off-line standard methods, are required. Therefore, the following recommendations are made to improve the robustness and accuracy of the overall measurement system.

Improvement in image analysis

The Eyecon™ image has a pixel size of 6 µm. However, in this study, we found that all particle size fractions <250 µm were poorly estimated, which led to a left-skewed frequency distribution favouring larger granules in the result (Fig. 8). Therefore, we believe that an improvement in the image analysis algorithm of the device, without any further improvement in the camera hardware itself, will certainly improve the analysis capacity of the Eyecon™ towards more realistic estimation of the GSD.

Changes in data post-processing

For post-processing of the image analysis results, the traditional binning method was used. Thus, the complete size measurement range of the Eyecon™ was divided into 52

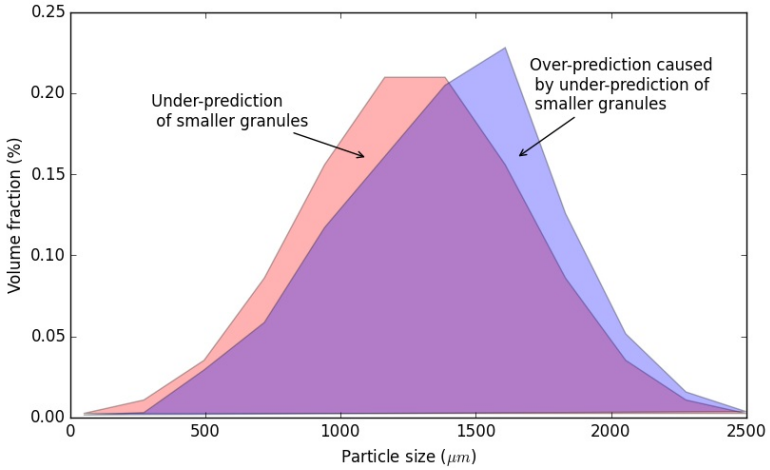


Figure 8: The over-prediction of larger granules caused by under-prediction of smaller granules.

'bins' or size ranges. After measurement of their diameter, granules were assigned to these bins based on the corresponding range. This led to lumping of the measurement for each granule size before further transformation of number distribution to volume distribution. The mean of each size class was then used to transform the number distribution into a mass distribution. Since the size of the granules was already lumped by the bins, using its mean to calculate the volume of all the granules caused further deviation from the real values. This was visually demonstrated in Fig. 9, where binning of the continuous number density data in Fig. 9a yielded binned data represented by the bar chart in Fig. 9a. This binned data sometimes over-predicted and sometimes under-predicted the unbinned data. In Fig. 9b complete number density data was converted into volume data by calculating D^3 of all the size measurements (area plot in Fig. 9a). The bar plot in Fig. 9b was based on the principle used by the Eyecon™ i.e. binned data from number density in Fig. 9a was used directly to calculate the volume of particles in each bin. This was also observed by El Hagrasy et al.[19]. Therefore, it is recommended that the original size of the granules should be used for obtaining the mass distribution and to lump the classes afterwards.

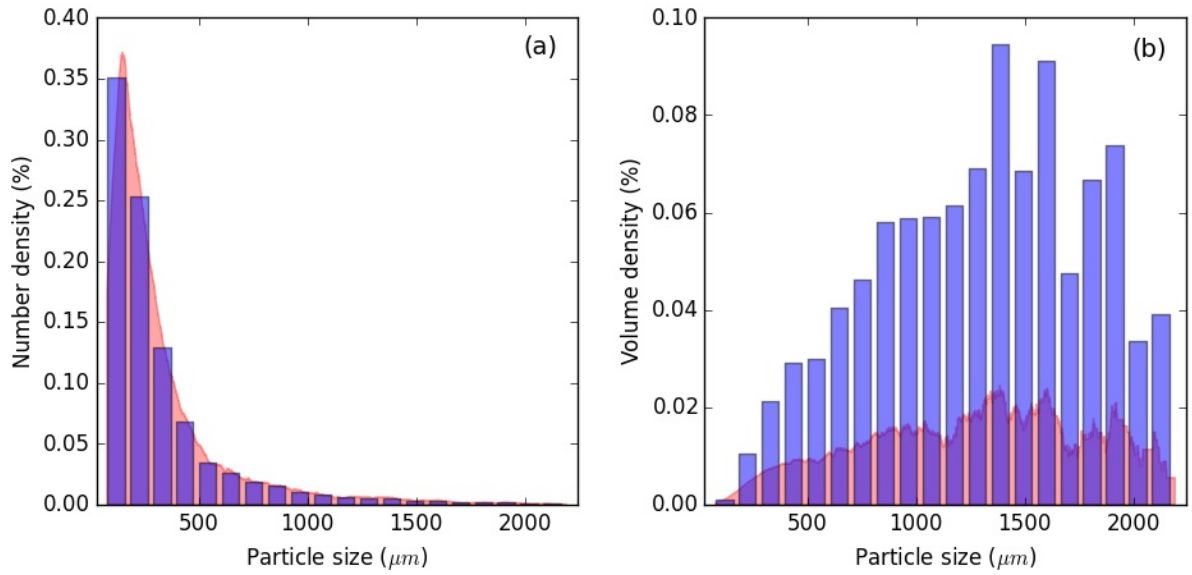


Figure 9: The (a) number density and (b) volume density of granules before and after dividing size range into size classes has been show by the filled area plot and the barplot respectively. The transformation of number density plot to volume density plot causes a large deviation if done after dividing size range into size classes.

Data presentation and preparation

The particle size information by the Eyecon™ was presented in form of percentiles (D_{10}, D_{25}, D_{50}, D_{75}, D_{90}). This information is good for comparison between standard runs, however, some of the important characteristics such as presence of bimodality in the GSD is not available in the percentile data (Fig. 10). This is mainly because a wide-spread distribution (from 50 to 3000 µm) is divided into a small number of bins (i.e. five percentile values), thus reducing any noise due to skewness of the distribution. However, such 'coarse' information may lead to an incorrect monitoring and control action. Therefore, particle size information should be presented in the form of a distribution along with percentile measurements hence allowing to estimate other desired parameters such as skewness and bi-modality index.

Changes in equipment and interfacing system

In the new continuous manufacturing line the vacuum driven transfer line for wet granules is eliminated. However, since this vacuum supports cleaning and dispersion of wet granules

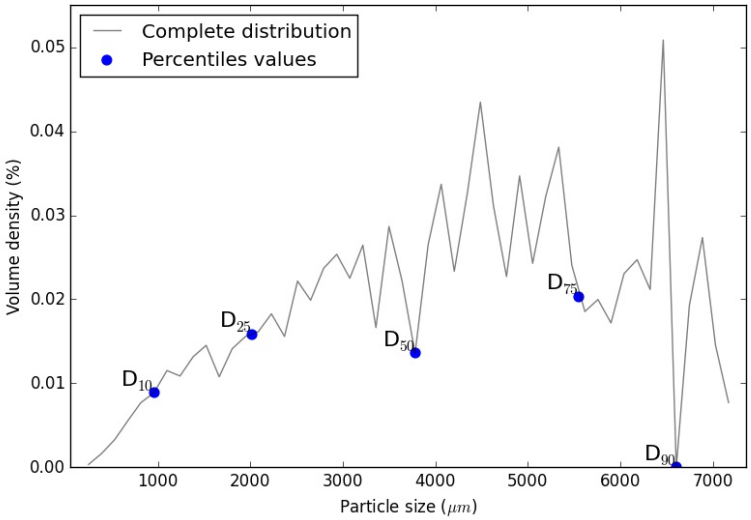


Figure 10: The representation of a complete distribution with five percentile values (D_{10}, D_{25}, D_{50}, D_{75}, D_{90}) is not accurate.

on the observation window, changes in the Eyecon™ interfacing system are desired to allow free flow of granules and cleaning of the observation window without using vacuum. Window fouling in the interfacing system has already been considered in other imaging-based devices such as focused beam reflectance measurement [23], and can be referred for further development.

Shape information

The Eyecon™ camera reconstructs the granules for particle characterisation and thus very detailed shape information about the shape of each granule can be extracted using this method. However, currently, an average of the aspect ratios (shape analysis result) of all the granules during a complete run is calculated for reporting. Therefore, a complete shape distribution profile is usually not available for the detailed diagnosis of the process. A complete display of how granule shape is influenced by increasing size of granules can be made available (Fig. 11). This information is very useful in pharmaceutical applications as granule shape influences the packing density of the granules for quality control during

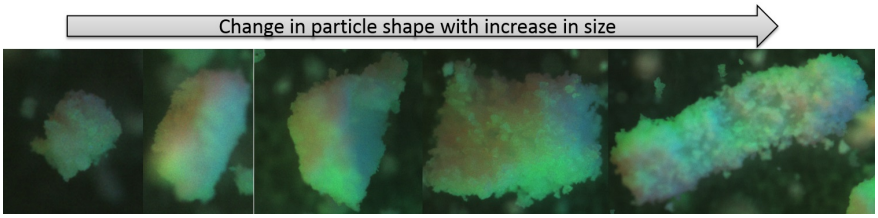


Figure 11: Particle shape may be strongly coupled with the particle size. Incorporating shape information can improve our understanding of the granule size distribution.

compression in the tablet press. Elongated granules not only lead to misinterpretation of the size but also create problems in the tablet press.

4. Conclusions

In this study, the performance of the Eyecon™ camera as a tool for in-line measurement of the granule size distribution in a continuous production line was critically evaluated after continuous twin-screw granulation and before the drying system and suggestions were made for improvement. The measurements were performed at steady state conditions in order to allow the comparison between the samples measured by three different scenarios. The variations in granule size distributions at different granulation conditions are also suitably measured by the in-line measurement approach, suggesting the suitability of the Eyecon™ camera for further use in in-line measurement of particle size in a continuous pharmaceutical manufacturing line. However, an improvement in image analysis and size calculation techniques is required for the fines and oversized fractions before practical application. Also, the GSD of samples obtained after the fluidised-bed drying unit should not be correlated with the Eyecon™ data immediately obtained after the granulator, as the wet transfer and drying process causes a lot of size change in granules, mainly breakage of oversized granules generating fines. Finally, the study demonstrated a great potential of this technique for continuous monitoring of the granulation processes; however further optimisation is desired for improvement in the sensitivity of the high-speed camera for a

wider range of granule size distributions.

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