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Communication

Real-time Particle Size Distribution Evaluation during Fluid Bed Granulation

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Abstract: In this study, a particle size analyser (Spatial Filter Velocimetry, SFV) was implemented into a laboratory scale top-spray fluid bed granulator to continuously monitor the granule size distribution (GSD) during granulation. A 2-level full factorial design (19 granulation experiments) was performed to study the influence of several process *(inlet air temperature during spraying and drying)* and formulation variables *(HPMC and Tween 20 concentration)* upon the end product GSD, measured in-line with SFV. Furthermore, the in-line measured GSD of the end products was compared to off-line laser diffraction reference measurements. Finally, the continuously in-line collected granule size data were related to the off-line-determined end granule tapped density using univariate, multivariate PLS and multiway N-PLS models, hence allowing prediction of this end product quality attribute based on the collected in-line GSDs.
The results of this study demonstrate the beneficial use of a particle size analyser during granulation. The tool was sensitive to any particle size changes during granulation and aided to better understand the impact of the studied process and formulation variables upon granulation. The establishment of a model able to estimate in real-time an end product quality attribute (tapped density) from the acquired process data may improve batch release time.

Keywords: spatial filter velocimetry (SFV); fluid bed granulation; particle size (distribution); in-line measurements; process understanding.

1. Introduction

Fluid bed granulation has extensively been used for several decades within the pharmaceutical industry to improve powder properties (i.e., flowability, compressibility, etc.) for downstream processing. During this 2-phased process (spraying and drying), primary particles aggregate by the addition of a binder liquid which results into the formation of granules [1]. The granule size distribution (GSD) is of major importance to the final quality of the granulated product as an inappropriate GSD influences density, flowability and dustiness of the end product. Hence, the understanding and control of granule growth during manufacturing are of major importance to the delivery of a high quality end product.

Sieve analysis, image analysis and laser diffraction are frequently used off-line particle size determination techniques. These methods are usually time-consuming and labour intensive due to the required sample preparation. During recent years, the interest in the area of real-time process analysis has increased, driven by FDA's Process Analytical Technology (PAT) initiative. Several studies have reported on the use of at-line, on-line and in-line particle size analysers. The application of image analysis [2-8], near-infrared spectroscopy [9-15], acoustic emission spectroscopy [15-19], focused beam reflectance spectroscopy [15, 20, 21] and spatial filter velocimetry [22-24] for real-time granulation monitoring has been investigated.

In this study, spatial filter velocimetry (SFV) was applied in-line during top-spray fluid bed granulation to continuously obtain GSD information. During SFV measurements, particles pass through a laser beam and the corresponding shadow generated onto the detector is used to determine the chord length distribution of the measured particles. The measurement zone at the probe tip is equipped with sapphire windows that are kept clean via an internal compressed air supply system, preventing fouling of the windows. A 2-level full factorial design was performed to examine the influence of different process and formulation variables upon the end product GSD, measured in-line with SFV and compared to off-line LD results. The continuously in-line obtained granule size data were analysed in detail to improve our understanding of the influence of the examined process and formulation variables on the granule growth mechanism. Furthermore, the in-line quantified GSD was related to the off-line-measured tapped density using univariate, multivariate and multiway models, allowing early estimation of this end product property during granulation.

2. Experimental Section

2.1. Materials

The dry powder mass consisted of dextrose monohydrate *(700 g, Roquette Frères, Lestrem, France)* and unmodified maize starch *(Cargill Benelux, Sas van Gent, The Netherlands).* This was granulated with an aqueous binder solution of HPMC *(type 2910 15 mPa s, Dow Chemical Company, Plaquemine-LA, USA)* and Tween 20 *(Croda Chemicals Europe, Wilton).* The amount of HPMC and Tween 20 was varied according to the DoE (table 1). The HPMC binder was always sprayed as a 4% solution, and by variation of the amount of maize starch, the total amount of solids was kept constant at 1 kg.

Table 1. Lower and upper levels of the examined DoE variables.

Variable	*Unit*	*Lower level*	*Upper level*
HPMC	%w/w	1	3
Tween 20	%w/w	0.2	0.3
Inlet air T during spraying	°C	40	50
Inlet air T during drying	°C	50	70

2.2. Fluid bed granulation set-up

Granulations were performed in a laboratory-scale fluid bed granulator (GPCG 1, Glatt, Binzen, Germany). A nozzle with a diameter of 1.2 mm was installed at a height of 26 cm from the distributor plate, and an atomization pressure of 1 bar was used. The liquid addition rate was set at 16 g/min and shaking of the filter bags was necessary every 45 s for a period of 7 s to prevent the entrapment of small particles in the bags. The inlet air temperature during spraying and drying was varied according to the DoE (table 1). Granules were dried until an outlet air temperature of 37°C and a product temperature of 45°C was obtained (granulation endpoint).

An SFV probe *(Parsum IPP 70; Gesellschaft für Partikel-, Strömungs- und Umweltmesstechnik, Chemnitz, Gemany)* was installed in the fluid bed granulator at a height of 20 cm from the distributor plate and at approximately 5 cm from the sidewall of the granulator. Granules passed through a 4 mm diameter aperture and an internal and external air connection prevented fouling of the measurement zone and ensured the dispersion of the powder mass. SFV data were collected every second during the entire granulation processes, but an average granule size distribution was saved every 10 s.

2.3. Design of Experiments (DoE)

A 2-level full factorial design was applied to study the effects of 4 variables (*HPMC concentration, Tween 20 concentration, inlet air temperature during spraying and inlet air temperature during drying*, table 1) upon the end product GSD. Three design center point repetitions were performed (19 experiments in total).

2.4. Off-line characterization of granules

For all granulations, the end product particle size distribution was determined with laser diffraction (LD) (Mastersizer S long bench, Malvern Instruments, Malvern, UK). A 20 g sample was poured into the dry powder dispersing unit where a jet pressure of 0.2 bar and a measurement time of 20 s were selected. The low dispersing pressure was necessary to prevent breaking up of the granules. Average *D*10, *D*50 and *D*90 values were determined based on 3 measurements of each batch.

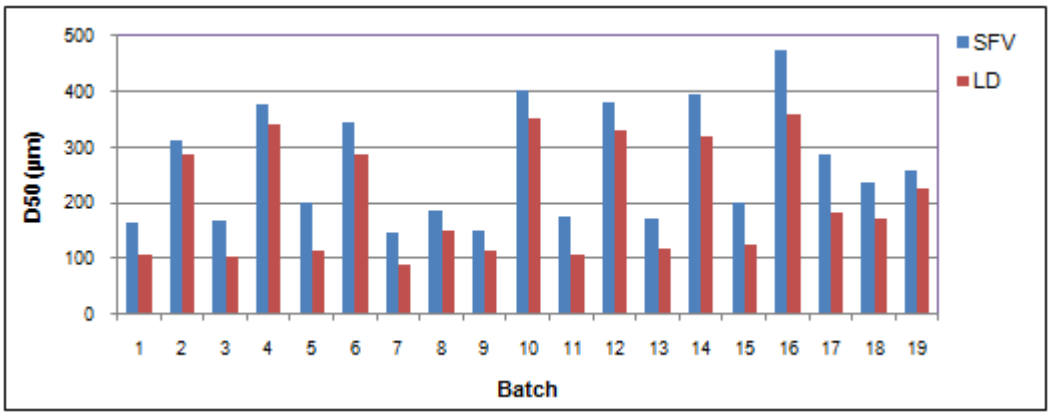
A 30 g sample was poured into a 100 mL graduated cylinder. The tapped volume (1250 taps, J. Englesmann AG, Ludwigshafen am Rhein, Germany) and corresponding weight were used to calculate the end product tapped density. All density measurements were performed in triplicate and the average tapped density was used.

3. Results and Discussion

3.1. Comparison of in-line SFV and off-line LD particle size measurements

The GSD of the end product measured in-line with SFV was in first instance compared to the off-line determined LD granule sizes for all DoE batches. Although SFV and LD are based on a different measurement principle (LD assumes spherical particles whereas SFV does not), similar GSDs are expected. Figure 1 displays the average *D*50 values measured with SFV *(average of the last granulation minute, i.e., 6 data points)* and LD for the end granules of all 19 DoE batches. An identical trend in *D*50 values was obtained by the 2 particle sizing techniques. However, *D*50 sizes measured with LD were always lower than those obtained by SFV (same observations were made based on *D*10 and *D*90 values; data not shown). In first instance, we believe that this GSD difference was caused by the LD measurement technique. The quantified particles experienced rapid accelerations as the air stream passed through a venturi. Due to the high shear applied during this process and the subsequent collisions with the wall of the apparatus, granules may break or crumble. Pressurized air was also used for dispersion of the granules during the SFV measurements, but the particles passed directly through the measurement zone. No collisions occurred as no high shear was applied. This hypothesis was confirmed by the GSD measurement of low friable spherical granules (i.e., Cellets® 100, 200 and 350, Pharmatrans Sanaq Pharmaceuticals, Basel, Switzerland) using SFV and LD under identical software and experimental settings as for the DoE granules. The LD measurements did not systematically underestimate the GSD due to attrition, in contrast to observations obtained for the breakable DoE granules. An additional explanation for the discrepancy between SFV and LD values might be found in the assumption of a spherical shape during LD measurements.

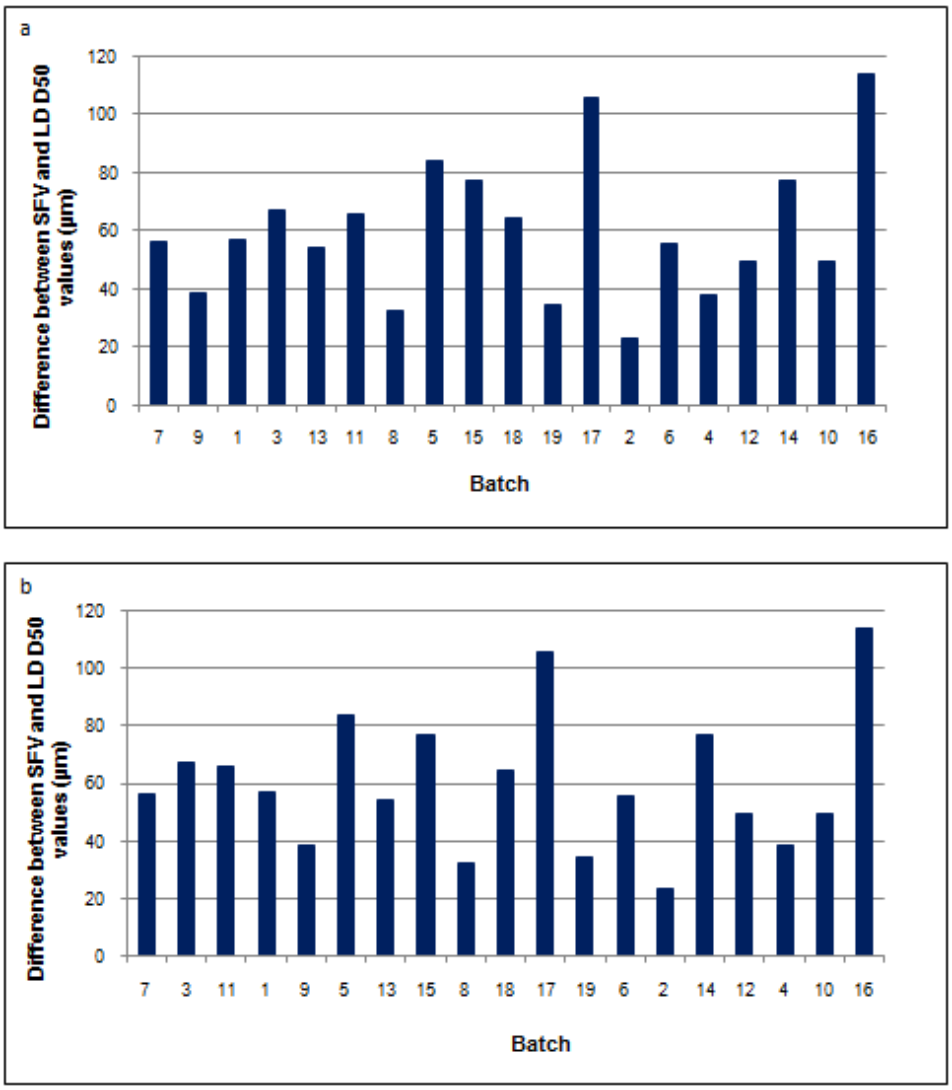
Figure 1. Average *D*50 results obtained with SFV and LD for all DoE batches.



The incidence of size segregation during fluidization should also be addressed as this influences in-line SFV measurements [23]. Due to inappropriate fluidization, a high amount of larger granules can be present in the lower part of the chamber, and a high amount of smaller granules in the upper part of the chamber. The SFV probe was placed in the upper part of the chamber, which cannot be reached by the largest particles when using low inlet air flow rates and would result into an underestimation of granule size. Figures 2a and 2b display the difference between SFV and LD *D*50 results for the 19 DoE batches, arranged according to increasing SFV end granule size (figure 2a) and LD end granule

size (figure 2b) in the x-axes, respectively. As these differences did not increase in function of increasing end granule size, no size segregation occurred.

Figure 2. Differences between average *D*50 values measured with SFV and LD arranged according to increasing SFV particle size **(a)** and increasing LD particle size **(b)**.



These primary results suggest that although a systematic difference between LD and SFV data was observed, the SFV technique is able to successfully describe the actual particle size distribution during granulation.

3.2. Improved process understanding through continuous gathered GSD information

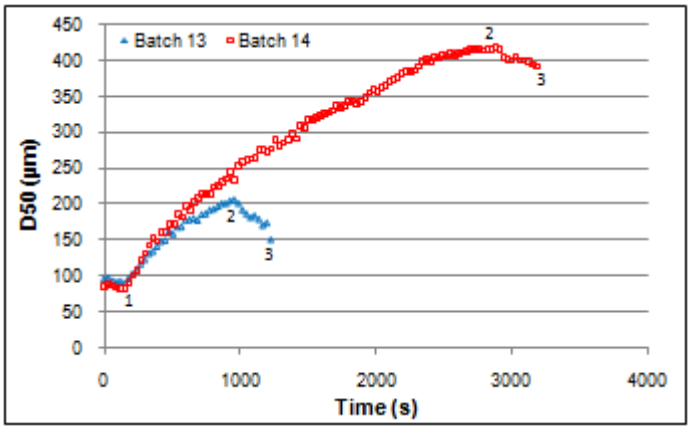
The average *D*50 values, obtained from the in-line SFV measurements during the last granulation minute, were used as DoE responses. The experimental results revealed the following significant DoE variables: HPMC concentration *(positive effect upon particle size)*, inlet air temperature during drying *(positive effect upon particle size)* and the interaction between these factors *(positive effect upon particle size)*. As GSD information was obtained every 10 s via in-line SFV measurements, a closer look is taken to the individual GS profiles of several DoE batches, to better understand the (in)significance of the studied DoE factors.

3.2.1. Influence of the HPMC concentration

The distinctive particle size trajectory during fluid bed granulation consisting of 3 different granulation phases can clearly be distinguished in figure 3. Between the first captured GS data and time point 1 the PS remains constant, which corresponds to the mixing phase. Between time points 2 and 3 the GS increases due to the agglomeration of powder particles. After time point 3 the drying period is depicted. The graph reveals that the positive effect of the HPMC concentration on the GS was caused by two effects:

- Larger HPMC amounts resulted in larger sized particles throughout the spraying period. At time point 2 in figure 3, batch 13 (1% HPMC) had an average GS of 200 µm, while batch 14 (3% HPMC) displayed a GS of 415 µm.
- Larger HPMC amounts created less friable granules, which led to less fines during the drying period. Between time point 2 and 3 in figure 3, batch 13 (1% HPMC) showed approximately a 60 µm average GS decrease, while the GS of batch 14 (3% HPMC) decreased only 25 µm.

Figure 3. Average GS profile of batches 13/14 (***1%/3% HPMC***, 0,2% Tween 20, 50°C spraying T, 70°C drying T). (1) beginning of the spraying phase, (2) end of the spraying phase and (3) end of the drying period.

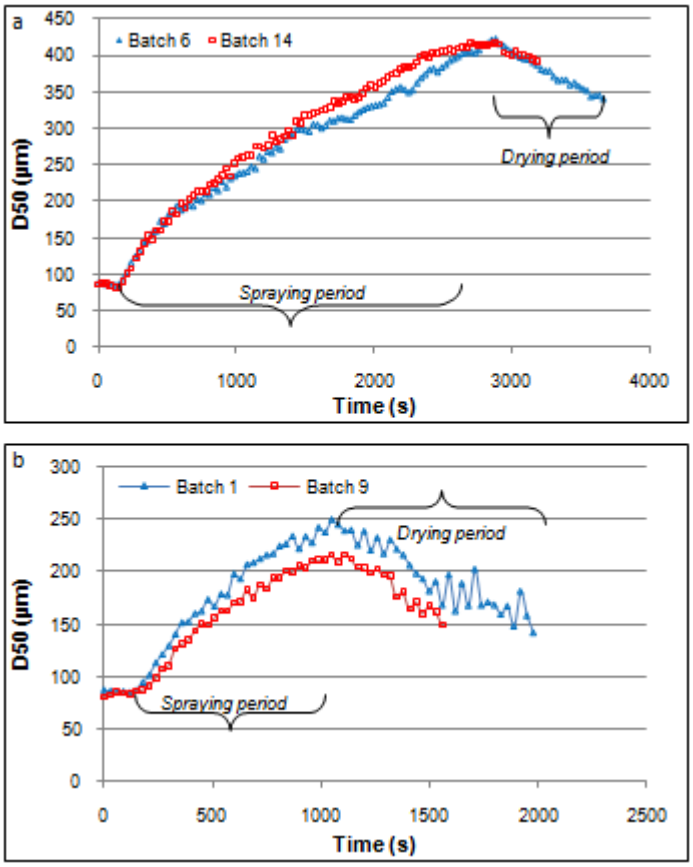


3.2.2. Influence of the inlet air temperature during the drying period

DoE analysis showed that the drying inlet air temperature was of less importance ($p > 0.01$) to the GSD compared to the HPMC concentration ($p < 0.001$). An explanation can be found in figures 4a and 4b. Figure 4a displays the in-line measured *D*50 profiles of batches 6 (50°C drying temperature) and 14 (70°C drying temperature). The other settings were the same for both batches. These batches showed a similar GS trajectory throughout the spraying phase. During the subsequent drying period, batch 6 yielded smaller end sized granules due to higher levels of attrition during a longer drying period. Figure 4b displays the GS data of 2 other batches with different drying conditions (batch 1 dried at 50°C and batch 9 at 70°C). Both batches had identical initial process conditions, but a different granule growth profile occurred during the spraying period. Although, the difference in drying temperature between the 2 batches caused a clear difference in particle size evolution during the drying period (larger decrease in particle size at the lower temperature level of batch 1) the end granule sizes, used to perform a DoE analysis, were similar. Hence, for these batches a similar response value

was used in the analysis of the DoE, despite the fact that the batches showed a different granulation progress. This might explain why the drying temperature was of limited significance according to the DoE. Only through the continuously in-line obtained information from the SFV probe we were able to gather this in-depth understanding.

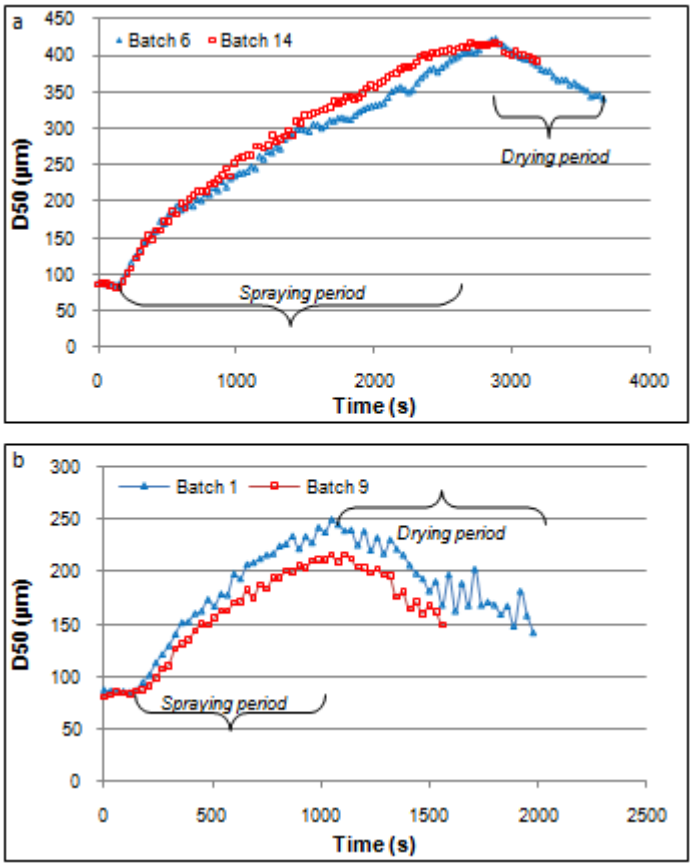
Figure 4. Average GS profile of batches with a different drying temperature. **(a)** batches 6/14 (3% HPMC, 0.2% Tween 20, 50°C spraying T, ***50°C/70°C drying T***), **(b)** batches 1/ 9 (1% HPMC, 0.2% Tween 20, 40°C spraying T, ***50°C/70°C drying T***)



3.2.3. Influence of the inlet air temperature during the spraying period

Figure 5 exemplifies the in-line obtained *D*50 data during the spraying period of 2 batches manufactured at different spraying temperatures. Throughout the agglomeration phase of batch 5 (spraying temperature of 50°C), a higher fluctuation on the GS compared to batch 1 (spraying temperature of 40°C) was observed. This was caused by the continuous entrapment of small particles in and subsequent discharge from the filter bags. At the upper temperature level, small particles were present for a longer period of time than in batch 1 as the agglomeration was slower due to a faster evaporation of binder liquid. However, at the end of the spraying period, a similar particle size was observed at both temperature levels. Hence although, the detailed profile of granule growth via in-line GS monitoring showed a difference in agglomeration kinetics, the different spraying temperature did not create a difference in GS at the end of the spraying period.

Figure 5. Average GS profile during the spraying period of batches 1/5 (1% HPMC, 0.2% Tween 20, ***40°C/50°C spraying T***, 50°C drying T)



3.3. Estimation of granule tapped density from in-line SFV measurements

The tapped density of the end product is, next to granule size distribution, also important to further processing. Univariate, multivariate and multiway approaches were considered to relate the in-line determined GSD to the tapped density of the 19 DoE batches (tapped density as dependent variable: 19 x 1 Y-vector). A univariate linear model was built using the *D*50 SFV values of the end granules of the 19 DoE batches as independent variables (19 x 1 X-vector). A multivariate partial least squares (PLS) model was built using the *D*01, *D*10, *D*25, *D*50, *D*63, *D*75, *D*90 and *D*99 SFV values of the end granules of the 19 DoE experiments as independent variables (19 x 8 X-matrix). A multiway N-way partial least squares (N-PLS) model was built using the *D*01, *D*10, *D*25, *D*50, *D*63, *D*75, *D*90 and *D*99 SFV values of the 19 DoE experiments in function of complete batch process time as independent variables (3-way X-matrix).

In table 2, the explained variances (R^2) and root mean square errors of estimation (RMSEE) of the different models are compared. The multivariate PLS tapped density model had the highest R^2 value in combination with the lowest RMSEE value. The small error of the model suggests the ability of the in-line SFV data to predict the off-line measured tapped density. Nevertheless, the model performance should be tested on an independent test set as the RMSEE value relates to the error within the calibration set and may overestimate the actual model performance.

Table 2. RMSEE and R^2 values of univariate, multivariate and multiway tapped density models with the mean and standard deviation of acutually measured properties.

	Univariate		*Multivariate (PLS)*		*Multiway (N-PLS)*			
	RMSEE	R^2 *(%)*	*RMSEE*	R^2 *(%)*	*RMSEE*	R^2 *(%)*	*Mean*	*St.Dev.*
Tapped density	0.0339	69	***0.0279***	***82***	0.0360	70	0.53	0.059
Hausner ratio	0.0307	46	0.0281	47	***0.0268***	***52***	1.21	0.037

4. Conclusions

The results of this study showed the feasibility of SFV for the real-time GSD monitoring during fluid bed granulation. The GS was not underestimated due to size segregation and probe fouling did not occur during the performed granulations. Due to the continuously obtained GS information, a better understanding of the (in)significance of the studied DoE factors upon granulation was established. This was not possible based on the off-line LD data of the end product. Finally, a multivariate PLS model was built to estimate end product tapped density based on continuously obtained GSD during granulation which may improve batch release time.

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