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In-line particle size measurement based on image analysis in a fully continuous granule manufacturing line for rapid process understanding and development

Lajos Madarász[a], Ákos Köte[b], Bence Hambalkó[b], Kristóf Csorba[b], Viktor Kovács[b], László Lengyel[b], György Marosi[a], Attila Farkas[a], Zsombor Kristóf Nagy[a*], András Domokos[a]

[a] Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, H-1111 Budapest, Műegyetem rakpart 3, Hungary

[b] Department of Automation and Applied Informatics, Budapest University of Technology and Economics, H-1117, Budapest Magyar Tudósok körútja 2 QB-207, Hungary

*Corresponding author: Zsombor K. Nagy; Phone: +36-1-463-4129; Fax: +36-1-463-3648; E-mail: zsknagy@oct.bme.hu

Abstract

The present paper serves as a demonstration how an in-line PAT tool can be used for rapid and efficient process development in a fully continuous powder to granule line consisting of an interconnected twin-screw wet granulator, vibrational fluid bed dryer, and a regranulating mill. A new method was investigated for the periodic in-line particle size measurement of high mass flow materials to obtain real-time particle size data of the regranulated product. The system utilises a vibratory feeder with periodically altered feeding intensity in order to temporarily reduce the mass flow of the material passing in front of the camera. This results in the drastic reduction of particle overlapping in the images, making image analysis a viable tool for the in-line particle size measurement of high mass-flow materials. To evaluate the performance of the imaging system, the effect of several milling settings and the liquid-to-solid ratio was investigated on the product's particle size in the span of a few hours. The particle sizes measured with the in-line system were in accordance with the expected trends as well as with the results of the off-line reference particle size measurements. Based on the results, the in-line imaging system can serve as a PAT tool to obtain valuable real-time information for rapid process development or quality assurance.

Keywords:

Process Analytical Technology (PAT), Dynamic Image Analysis (DIA), Continuous Pharmaceutical Manufacturing, Twin-Screw Wet Granulation (TSWG), Vibrational Fluid Bed Drying

1. Introduction

Continuous manufacturing (CM) in the pharmaceutical industry represents a significant paradigm shift from the traditional batch manufacturing mindset, including both drug manufacturing and development. The benefits of CM are widely recognised by the academic sector, the industry, and the regulators as well (Badman et al., 2019; FDA, 2019; Lee et al.,

2015). A significant advancement of CM is that due to short process settling times, design spaces can be investigated substantially faster compared to batchwise processes. This promotes design of experiment (DoE)-based process development, which contributes to deeper process understanding. Furthermore, it may also accelerate drug development as well as reduce technical transfer activities (FDA, 2019). The fast response of a continuous process to changes in critical process parameters (CPP) allows to gather experimental data with lower time and raw material costs (Lee et al., 2015). Due to steady-state operation, CM also offers great opportunity to develop and utilize predictive models for process understanding and control (Barrasso et al., 2013; Gyürkés et al., 2020). By applying suitable process analytical technology (PAT) tools, critical quality attributes (CQA) and CPPs can be continuously monitored in real-time (Su et al., 2019).

With the incorporation of PAT tools, immense amount of data can be collected during process development for process modelling. These data can also be used to obtain high-resolution residence time distribution (RTD) models. Combined with RTD models, PAT sensors can aid in the identification of out-of-specification (OOS) material. However, if all necessary CQAs are within the limitations, they can also facilitate real-time release of the product (Engisch and Muzzio, 2016; Rantanen and Khinast, 2015).

Several critical material attributes (CMA) such as flowability and compactability can be improved with granulation. As CM process development has gained momentum in recent years, significant focus has been given to continuous direct compression, but less focus on wet granulation processes, mainly because of their additional complexity (Dahlgren et al., 2019). Several approaches have been developed to continuous wet granulation such as continuous high shear wet granulation (Michaels et al., 2009; Mort et al., 2001) or continuous fluid bed granulation (Vervaet and Remon, 2005). However, mainly because of its modularity, twin-screw wet granulation (TSWG) is the most versatile approach. Hence, numerous studies have

been published focusing on the effect of different process parameters of TSWG, as well as the material attributes of the starting materials: liquid-to-solid (L/S) ratio (Liu et al., 2017; Meier et al., 2016) screw configuration (Kumar et al., 2016; Sayin et al., 2015), barrel fill (screw speed) (Portier et al., 2020) (Lute et al., 2018a), powder properties (Lute et al., 2018b), and the interaction between these parameters (Liu et al., 2017).

For further processing, wet granules must be dried. A common method is to incorporate a fluid bed dryer (FBD) at the end of the TSWG. In their work, Leersnyder et al. presented a six-segmented FBD operated at 20 kg/h throughput in semi-continuous operation (De Leersnyder et al., 2018). They found that the unit could dry granules with highly repeatable moisture content, although particle breakage is more prominent compared to vibratory fluid-bed dryers. In these devices, particles are kept in a pseudo-fluidised status and brought into movement by a vibrated mesh. They provide truly continuous operation, ensuring narrow RTD without back-mixing or recirculation due to their first-in-first-out nature. In their work, Domokos et al. investigated the performance of a FBD operated in a continuous granule manufacturing line (Domokos et al., 2021). By building a partial least squares (PLS) model using near-infrared (NIR) spectroscopy, they successfully implemented real-time moisture content monitoring of the dried product. They found that by applying sufficiently high drying air flow rates, low moisture content can be achieved even at low drying air temperatures, making it suitable for drying heat-sensitive materials. Despite being frequently used in the food industry, research on the pharmaceutical application of vibratory fluid-bed dryers is vastly limited.

Particle size is one of the most important CQAs of the regranulated product manufactured on a powder to granule line, as it directly influences powder compactability and porosity. Consequently, it also influences the tablet's mechanical- and tensile strength, as well as the dissolution profile (Mészáros et al., 2020; Wünsch et al., 2021). Therefore, obtaining real-time particle size data is invaluable both for process development and manufacturing. In-line particle

size analysis of granulation processes (TSWG or fluid bed) has been carried out via laser diffraction (Wilms et al., 2020a; Wilms et al., 2020b), spatial filtering velocimetry (SFV) (Huang et al., 2010), and dynamic image analysis (DIA) (Fonteyne et al., 2012; Madarász et al., 2018). A fundamental advantage of DIA is that it provides information about the particle shape as well, which is indispensable when dealing with oddly-shaped particles or objects (Podrekar et al., 2018; Wu et al., 2015). The main challenge of in-line DIA is to prevent the overlapping of particles in the images, which would otherwise falsify the measurement results (Wilms et al., 2019).

Our previous work demonstrated an in-line image analysis-based investigation of a TSWG (Madarász et al., 2018). However, it did not involve the inspection of the subsequent steps (drying and regranulation), which also determine the properties of the final product (most importantly particle size distribution (PSD) and flowability). By investigating consecutive steps of an end-to-end line, the effect of transient production errors (e.g., feeding deviations or temperature control errors) could be followed throughout the manufacturing line. This knowledge then can be used to identify and remove out of specification material from the line where it has the least impact on the process.

Hence, this study serves as an extension of (Madarász et al., 2018) and (Fülöp et al., 2021), aiming for a more detailed investigation of a continuous granule manufacturing line to demonstrate how modern in-line PAT tools can speed up process development. To achieve this, an image analysis-based particle size analysis system was investigated by the authors. After the evaluation of the system's performance, it was fitted into a continuous powder-to-granule production line to obtain real-time particle size data of the product, which was compared to off-line measured reference PSD results. The tool was used to rapidly map the relation between different CPPs (L/S ratio, milling tool type, screen hole diameter and milling intensity) and the

PSD of the product, a key CQA, highlighting the advantages of modern, PAT-based process development compared to its conventional batchwise counterpart.

2. Materials and methods

2.1 Materials

The continuous granulation experiments were conducted using the placebo blend of α-lactose-monohydrate (Granulac® 70, Meggle Pharma, Wasserburg, Germany) and corn starch with a particle size between 15 and 100 µm (Roquette Pharma, Lestrem, France). The resulting premix had a bimodal distribution with a particle size of 121.5 µm (Dv50). The 27 w/w% solution of Polyvinylpyrrolidone (PVP) K30 (BASF, Ludwigshafen, Germany) in purified water was used as granulation liquid.

The comparison of the various particle sizing equipment was carried out using microcrystalline cellulose (MCC) pellets, which were produced in-house. The pellets were sifted using 300 and 500 µm mesh sieves (Retsch GmbH, Haan, Germany).

2.2 Granule production experiments

The experiments were carried out on a continuous granule production line, consisting of an interconnected twin-screw granulator, a fluid-bed dryer and a regranulator. A concept drawing of the manufacturing line can be seen in Fig. 1.

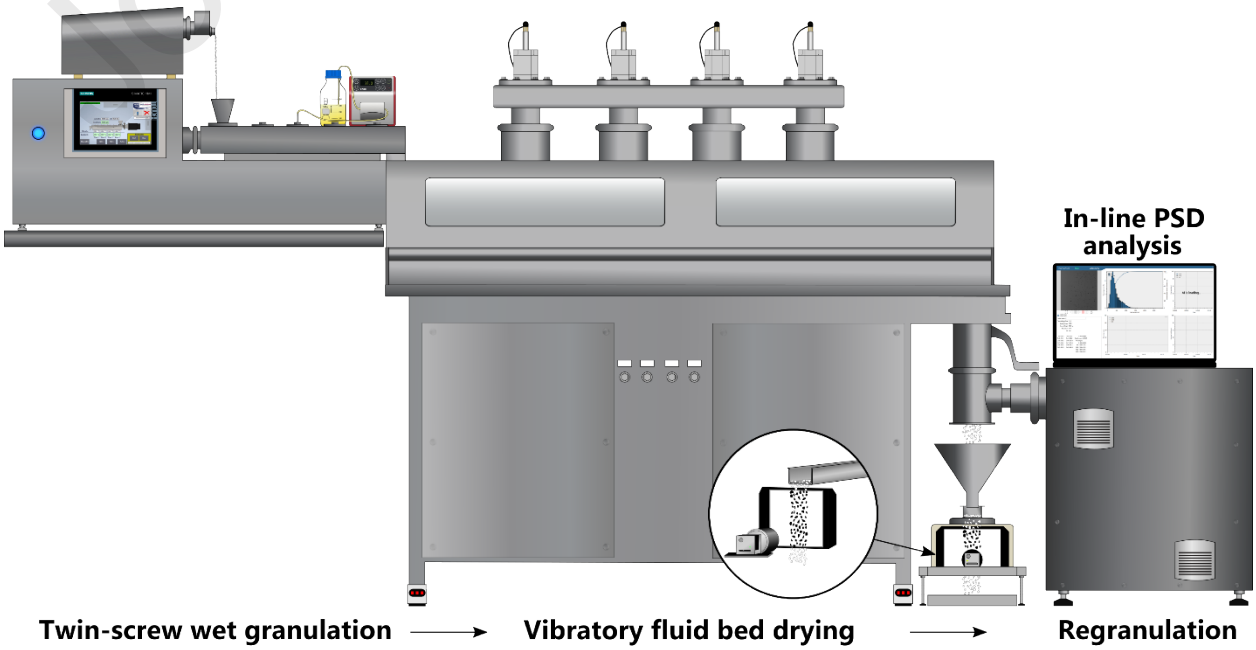


Fig. 1. Physical arrangement of the Continuous Granule Manufacturing line

By installing our in-line camera-based particle size analysis system after the mill, particle size data could be acquired instantaneously during the experiments. The field of view of the process camera covered most of the material stream, which paired with the high frame rate meant that the majority of the produced particles was measured with the in-line system. This allowed for the easy and efficient investigation of the effect of various CPPs on the product's particle size. The experiments involved the investigation of the mill (investigated CPPs: milling tool type, sieve hole diameter and milling intensity (1/min)), as well as the granulator (investigated CPP: L/S ratio). Multiple parallel in-line measurements were carried out at each process setting. During that time, all of the material leaving the production line was collected for off-line analysis.

Granulation was carried out using a multifunctional continuous TSG (Quick 2000 Ltd., Hungary) in wet granulation mode, operating at 100 RPM (revolutions per minute), with a screw diameter of 16 mm (25 length-to-diameter ratio), and a configuration shown in Fig. 2 (CE: conveying elements, KZ: kneading zone). The TSG was operated at room temperature, without any additional heating.

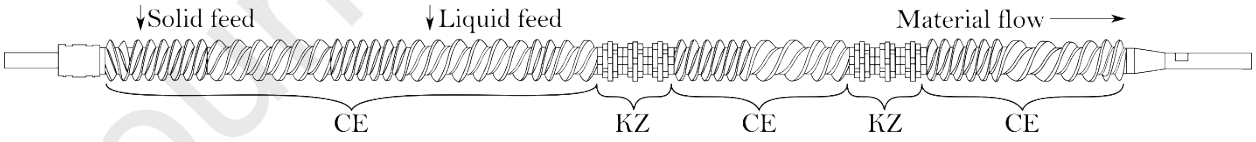


Fig. 2. Screw Configuration of the TSG (CE: conveying element, KZ: kneading zone)

The mixture of α-lactose and corn starch was manually pre-mixed for 5 minutes. A gravimetric feeder (DDW-MD0-MT HYD ISC plus, Brabender Technologie, Duisburg, Germany) was used to feed the solid pre-blend into the TSG, with a constant feeding rate of 0.8 kg/h. The granulating liquid was fed into the second zone of the equipment using a peristaltic pump (Watson-Marlow 120U, Wilmington, MA, USA). The relation between the RPM of the

peristaltic pump and the mass flow of the transferred liquid was previously determined with the granulating liquid. During the milling experiments, the pump was operated at a constant 2.8 RPM (1.47 g/min feed rate, 0.11 L/S). During the granulation experiments with varying liquid feeding rates, the pump speed was modified between 1.8 and 3.1 RPM (which corresponds to 0.93 g/min and 1.63 g/min feed rate, or 0.07 and 0.122 L/S).

After leaving the granulator, the wet granules were dried in a continuous fluid bed dryer (Quick 2000 Ltd., Hungary). In the dyer, the particles fall onto a vibrated perforated metal mesh (10 µm mesh size), which translates the particles through the apparatus. Additionally, the vibration spreads out the particles evenly on the surface of the mesh facilitating even drying. Tempered air is passed through the mesh, which can effectively dry the spread-out particles. It is important to note that no real fluidization occurs in the dryer. However, the mechanical vibration allows pseudo-fluidisation of the bed with relatively low air flow rates. The drying unit is divided into 4 zones, each with its corresponding drying air temperature and air flow. These parameters can be modified independently in each zone. The zones also have separate air filter bags, which can be automatically de-dusted at set intervals, preventing the clogging of the filters, which would otherwise restrict the airflow. The same dryer settings were applied during all of the experiments: 50 Hz vibration, 27 °C air temperature, 60 l/min air flow, and 60 s de-dusting intervals.

The dried granules leaving the dryer directly fell into a continuous mill (Quick 2000 Ltd., Hungary), in which they were regranulated. The mill can be operated with either a conical or an oscillatory milling tool. Screens with different hole diameters were applied for both tools: 0.8, 1.5 and 2.0 mm diameter in case of the conical, and 0.8, 1.0, 1.5 and 2.0 mm diameter in case of the oscillatory milling tool. The milling intensity (1/min) of the regranulator can also be modified. During the milling experiments, the mill was operated at 1000, 1500 and 2000 RPM

in case of the conical, and 100, 150 and 200 oscillations/min in case of the oscillatory milling tool.

Table 1. Summary of the applied CPPs during the experiments

Focus process of experiment	**Milling**							**Milling**	**Granulation**
Milling tool	Conical			Oscillatory				Oscillatory	Oscillatory
L/S Ratio	0.11							0.11	0.07 – 0.12
Screen hole diameter (mm)	0.8	1.5	2	0.8	1	1.5	2	1	1
Milling intensity (1/min)	1000	1000	1000	100	100	100	100	200	200
	1500	1500	1500	150	150	150	150	↓	
	2000	2000	2000	200	200	200	200	100	

In order to acquire real-time particle size information about the regranulated product, the camera-based system was installed after the mill. The mass flow of the regranulated material leaving the mill was ~0.8 kg/h, which would result in immense overlapping of the free-falling particles in the captured images. When particle overlapping occurs, two particles are detected as one, which in high quantities can falsify the measurement results. To increase measurement accuracy, particle overlapping had to be reduced to a minimum in the images. Hence, the regranulated material leaving the mill fell onto a vibratory feeder equipped with a U-shaped chute (Retsch GmbH, Naan, Germany), normally operated at maximum intensity. Due to the intensive vibration, the material was evenly distributed along the width of the chute (30 mm). Additionally, during particle size measurement, the vibratory feeder was set to a lower intensity in order to significantly reduce the mass flow of the regranulated material passing in front of the camera. The combination of these techniques led to the drastic reduction of particle overlapping in the images. Following each measurement, the intensity of the vibratory feeder was set back to the maximum, causing the materal build-up to quickly leave the chute. The measurements lasted ~10-30 seconds, typically recording one to five hundred thousand particles. The in-line camera-based measurements involved three parallel measurements at each

setting. The produced material was collected for off-line granule size distribution (GSD) and flowability measurements.

The alternation of the vibratory feeder's intensity allowed for the in-line monitoring of particle size for an extended time period as well. Hence, a longer milling experiment (~10 minutes) was also carried out to investigate the effect of changing the milling intensity on the fly. The mill was equipped with an oscillatory tool and with a 1 mm diameter hole sieve. Milling intensity was initially set to 200 1/min, which was later modified to 100 1/min. The vibratory feeder's intensity was cycled between low intensity (particle size measurement) for ~30 seconds and high intensity (material build-up discharge) for ~10 seconds. During the experiment, the particle size was calculated from a rolling window (particle buffer). This meant that the particle size values were calculated from the particles measured in the last 10 seconds, rather than cumulating them throughout the whole experiment. This allowed for the better examination of the dynamic response of the system.

Off-line sample collection and the in-line measurements were only started when sufficient time had elapsed after modifying a process setting, in order to ensure that the measurement is carried out when the process is in a steady-state. In case of milling intensity, this time was ~1 minute, as residence time in the mill and the vibratory feeder is short (~10 seconds). After changing the milling screen or tool, a longer time period was allowed before sampling (~2 minutes), as the mill had to be properly filled with granules. The granulation (L/S ratio) experiments required the longest settling times (~5 minutes), as the extruder and the dryer also had to reach steady-state operation, which are slower processes compared to milling.

2.3 Imaging setup & image analysis software

A process camera (acA1920-155um, Basler AG, Germany) was used for the in-line measurements, which was controlled from a computer via a custom software, using the

application programming interface provided by the camera manufacturer (pylon SDK). During the experiments, the camera was operated at a shutter speed of 150 µs with a 700x700 resolution at 200 frames per second (FPS). Particles were illuminated by a custom panel light (Apokormat Ltd., Hungary), providing bright, but homogenious illumination.

Images of the granule stream were analysed using a custom image analysis software written in C++ by the authors, using the OpenCV application programming interface (Bradski, 2000). The images go through the following analysis sequence: Gaussian blur → Binarization → Edge detection. At 200 FPS, each particle is recorded multiple times, which due to the rotation of the freefalling particles, allows for more representative sampling.

2.4 Validation of the camera-based system

The particle size measurement capability of the camera-based system was validated by comparing the PSD obtained via measuring MCC pellet samples with conventional particle sizing methods. The MCC pellets were produced in-house and were sifted using 300 and 500 µm mesh sieves, resulting in a relatively narrow particle size distribution.

The applied reference measurement methods were spatial filtering velocimetry (SFV), using a Parsum IPP-70 probe (Parsum GmbH, Germany), and laser diffraction, using a Malvern Mastersizer 2000 (Malvern Instruments, Worcestershire, UK).

The Malvern Mastersizer calculates particle size via equivalent spherical diameter, the Parsum determines particle chord length, while our imaging system determines the mean of the maximum and minimum Feret diameters. An advantage of the MCC pellets were that they are highly spherical, so the size difference from how different equipment treat particle shape can be reduced to a minimum. The pellets were also quite robust, so no particle breakage could occur even after multiple measurements.

The samples could be fully retrieved from the SFV and the camera-based measurements, but not from the Mastersizer. Accordingly, the measurement order for each sample was: Camera → Parsum → Malvern, with sample recollection between the measurements. This way, the same material could be measured with each method. During the imaging measurements, a vibratory feeder equipped with a U-shaped chute was operated at 60% intensity to feed the samples into the measuring equipment. During the Parsum measurements, the vibratory feeder was equipped with a V-shaped chute and was operated at 10% intensity in order to avoid overlapping of the particles.

2.5 Offline measurements

Reference GSD measurements

The GSD of the samples collected from the granule production line were analysed offline with a Parsum IPP-70 probe. The samples were fed into the measurement probe via a vibratory feeder equipped with a V-shaped chute. The feeder was set to 10% feeding rate in order to avoid the overlapping of particles (the detector load was kept under a few percentages at all times).

Flowability measurements

The impact of varied milling settings and L/S ratios on the flowability of the particles was tested by flow time measurements. The flowability of the regranulated samples were measured with a funnel described in ASTM D 1895 and ISO R60. A process camera operated at 100 FPS was used to record the powder stream exiting the funnel. The images were then analysed with a custom software in order to precisely determine the flow times.

3. Results and discussion

Firstly, the validation of the camera-based system was carried out by measuring MCC pellet samples with the developed imaging system, as well as two reference methods, namely, with a Parsum IPP70-S and a Malvern Mastersizer 2000. The imaging system was then installed in

our continuous granule manufacturing line to obtain real-time particle size data of the regranulated material. First, the effect of milling settings were investigated (milling intensity, screen size and tool type) via shorter in-line measurements. Samples from these experiments were analysed off-line with a Parsum IPP70-S for off-line reference PSD data, which was then compared to the in-line obtained data. Next, a longer experiment was carried out in order to demonstrate the applicability of the tool for prolonged process monitoring. Lastly, the effect of the applied L/S ratio was investigated with sorter in-line measurements which were also compared with off-line obtained reference PSD data.

3.1 Validation of the camera-based system

The sifted, 300-500 µm diameter MCC pellets were divided into three, approximately 5 g samples. The samples were fully recollected after the measurements, so the exact same material could be measured consequently with each measurement method. The measured Dv50 values are presented in Table 2., the cumulative distributions are shown in Fig. 3.

Table 2. MCC Pellet particle sizes obtained via image analysis and the reference measurements

	Sample No.	1	2	3
Dv50 (µm) (Diff. vs. camera)	Camera	434.8	439.8	463.3
	Parsum	416.3 (-4.3%)	423.9 (-3.6%)	443.7 (-4.2%)
	Malvern	442.4 (1.7%)	450.9 (2.5%)	466.8 (0.8%)

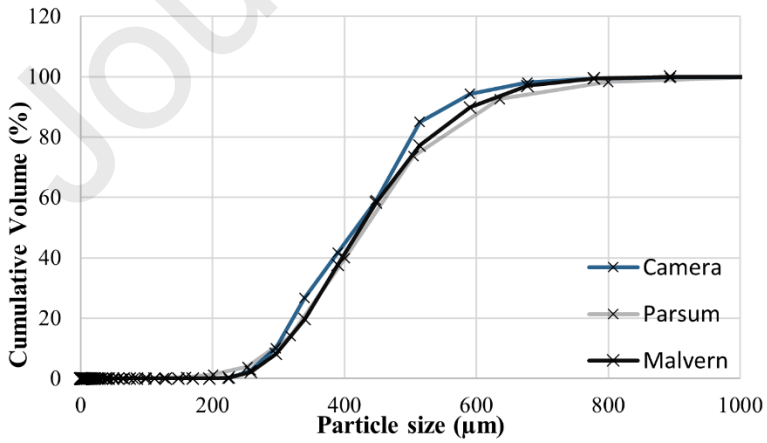
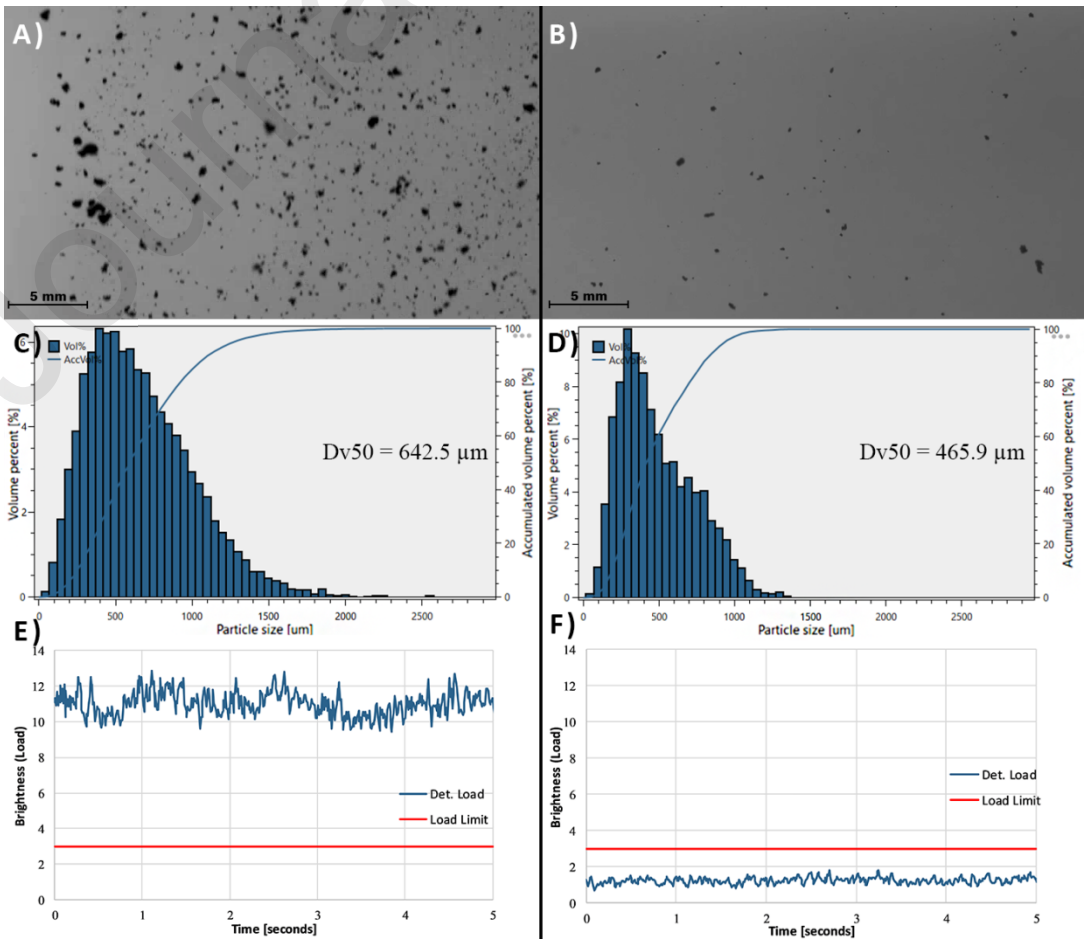


Fig. 3. Measured cumulative PSD of the MCC pellets (each curve represents the average of the three samples)

Table 2. demonstrates that the Dv50 values measured by our imaging system show <5% difference compared to both reference measurement methods in all samples. Fig. 3. also demonstrates adequate correlation between the cumulative PSD measured with the different particle sizing systems. These results showed promising applicability of the camera-based system, so the next step was to apply it in our continuous granule production line.

3.2 In-line application of the camera-based system

The imaging system was installed in our continuous granule production line in order to obtain real-time particle size data about the produced granules. One of the most important challenges of particle size analysis methods is to prevent particle overlapping, otherwise the overlaying silhouette of multiple particles are detected as one, which results in false particle size data. Hence, a vibratory feeder was used to distribute the particles along the width of the feeder's chute (30 mm). Additionally, the feeding intensity of the equipment can also be regulated. This allowed us to reduce the mass flow exiting the feeder until the particle build-up reached the end of the feeder's chute, which typically took ~40 seconds. As a result, the possibility of particle overlapping could be kept to a minimum during the span of the ~10-30 s measurements. Fig. 4.



demonstrates the effect of lowering the feeding intensity during particle size measurement. In Fig. 4. A) and C), we can observe de effect of particle overlapping, which caused significant increase in the measured Dv50 value.

Fig. 4. Image captured at high vibratory feeder intensity (100%) and the resulting PSD and detector load diagram (A), C) and E)), and at low feeder intensity (60%) (B), D) and F))

This technique allowed us to obtain in-line particle size data from a process which would otherwise be impossible with conventional image analysis algorithms. In the following experiments, the system was tested in a real-world application as a tool to efficiently map the relations between a CQA (particle size) and different CPPs (milling tool type, screen hole diameter, milling intensity, L/S ratio).

Investigation of the regranulator

The regranulator's characteristics were determined via the experiments detailed under the "Milling" section of Table 1. As a result, the effect of the applied milling tool, -screen and -intensity could be investigated on the granule properties. Additionally, off-line Parsum measurements were carried out for comparison with the in-line camera-based system.

Fig. 5. presents the Dv50 values obtained with the Conical milling tool, using a 1.5 mm hole diameter screen, measured in-line with the image analysis system, as well as off-line with the Parsum probe.

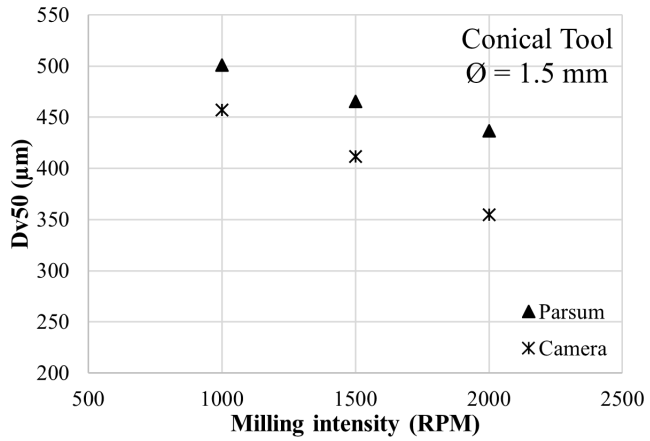


Fig. 5. In-line (Camera) and off-line (Parsum) measured Dv50 values with the Conical mill attachment, using the 1.5 mm hole diameter screen

Both measurement methods reflect the same trend, specifically, that increased milling intensity results in a lower particle size. However, there is noticeable difference in the Dv50 values measured with the different particle sizing equipment compared to the MCC pellets. This mainly arises from how the different measurement methods treat particle shape, as well as the measurement principle itself: the Parsum calculates chord length frequency distribution, while the DIA-based system calculates the mean of the minimum and maximum Feret's diameter. In case of oddly-shaped particles like granules, this can cause significant deviation between the results obtained with the different instruments. This phenomenon has been recorded in several papers comparing DIA-, SFV-, and laser diffraction-based measurements (Folttmann et al., 2014; Kelly et al., 2017).

Fig. 6. summarizes the Dv50 values measured with the in-line imaging system using the oscillatory as well as the conical milling tool. For the sake of perspicuity, values obtained with the Parsum device are not shown in the figure.

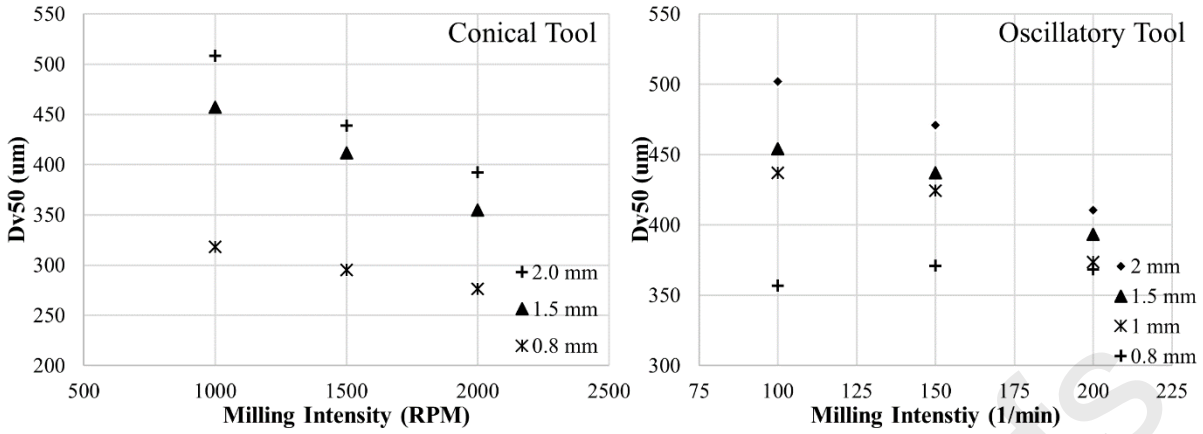


Fig. 6. Camera-based Dv50 values obtained with the conical and the oscillatory milling tool using different hole diameter screens

It is expected that by increasing the milling intensity, and by lowering the screen hole diameter, the product particle size is reduced. Fig. 6. shows that the image analysis-based tool was able to verify these presumptions. Although these relations are trivial, their simplicity can help investigate the feasibility of the in-line application of the developed system. In addition, obtaining real-time numerical data can also help with process understanding and control. The Parsum-based off-line measurements yielded identical trends in the change of particle size in case of all milling settings.

The sole exception was the oscillatory tool equipped with the 0.8 mm hole diameter screen. As passing the 0.8mm sieve requires intense milling, these settings produced the most intensive milling effect, yielding nearly the same PSD regardless of the milling intensity. As the relative standard deviation (RSD) of the DIA-based method exceeds the particle size difference between the settings, the developed system was unable to reflect such small differences in the Dv50 values. This can be enhanced by using higher magnification optics, or even multiple cameras, equipped with different lenses (Sebastian Beil, 2014). This way, both larger and smaller particles can be measured more accurately. Nevertheless, for the purposes of this experiment, the setup provided sufficient resolution.

The flowability of each sample was also characterised via flow time measurement. Flow times were measured using a custom camera-based system, which allowed for highly accurate time measurement (typically <0.2% RSD). The obtained results are shown in Fig. 7.

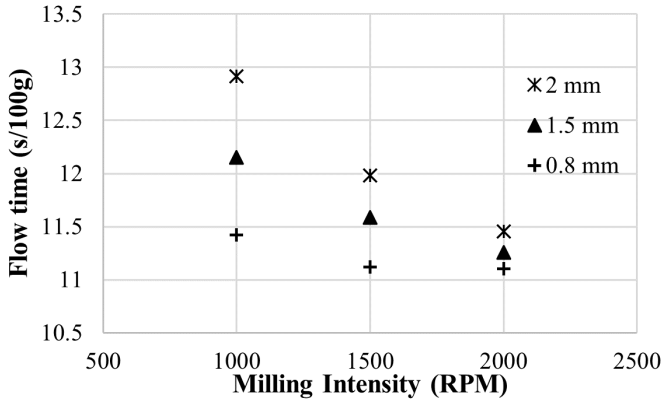


Fig. 7. Flow times of the samples obtained with the conical milling tool

Fig. 7. also implies a monotonous particle size, as well as bulk density change similar to the trends shown in Fig. 6. As these samples had excellent flow characteristics, the particle mass flow was mainly dependent on bulk density, which is in close correlation with particle size.

A longer experiment was also carried out to demonstrate the applicability of the tool for prolonged process monitoring and to investigate the dynamic characteristic of the process. Using the oscillatory milling tool equipped with a 1 mm hole diameter sieve, the milling intensity was initially set to 200 1/min which was modified to 100 1/min after ~4 minutes. Due to the alternation of the intensity of the vibratory feeder, the in-line camera-based PSD monitoring could be applied throughout the whole experiment. The 'detector load limit' function of the image analysis software automatically omitted the frames on which more than 3% of the pixels were occupied by particles (Fig. 4.). This meant that the software automatically halted analysis whenever the feeder was set to high intensity and continued when the feeder was set back to low intensity for PSD measurement. The Dv50 values were calculated from a rolling window (particle buffer) containing the particles measured within the last 10 seconds.

This means that after setting the feeder to low intensity, the buffer was empty, so Dv50 values were only calculated after sufficient number of particles were added to the buffer (~2 s, ~10 000 particles). The results are shown in Fig. 8.

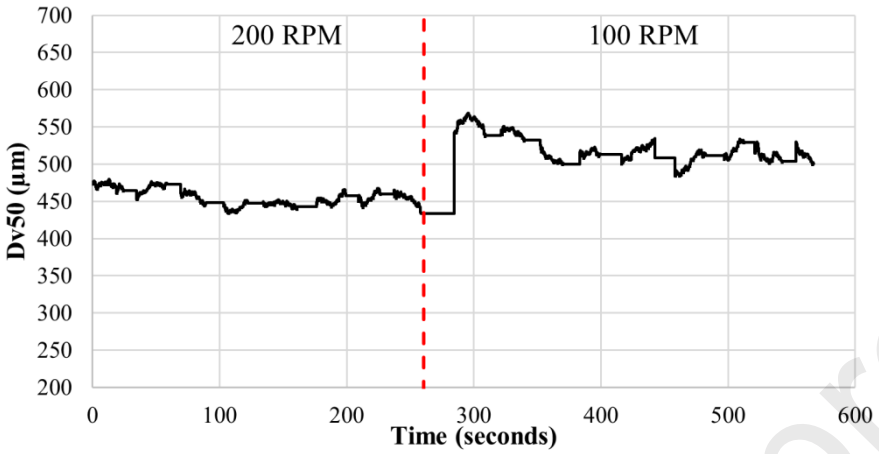


Fig. 8. Measured particle size change as a result of the modified milling intensity (Oscillatory tool, 1 mm screen size, 0.11 L/S)

The horizontal lines indicate that the feeder was set to high intensity, causing the PSD measurement to halt. Based on Fig. 8., the developed system was successfully applied for the in-line monitoring of the regranulated material produced at 0.8 kg/h.

Investigation of modified L/S ratios

The effect of different L/S ratios were also investigated with in-line measurements on the PSD of the regranulated product. The order of the applied L/S ratios was randomised to balance the effect of extraneous disturbances.

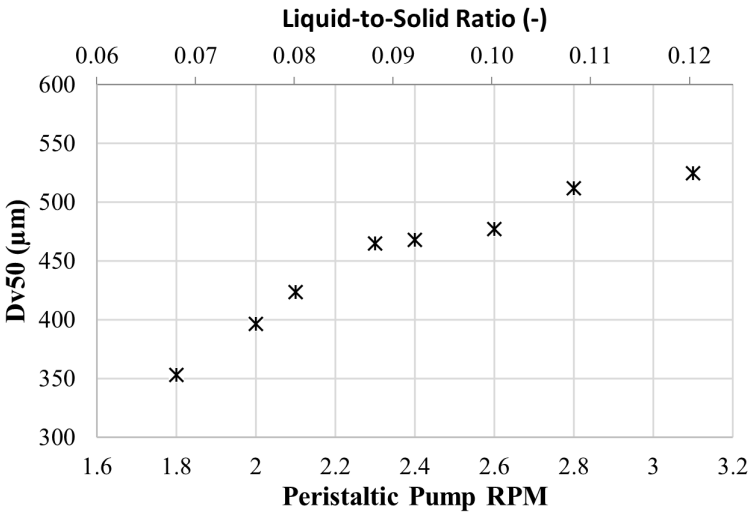


Fig. 9. Particle size of the samples obtained during the experiments with varied L/S ratios, measured with the developed in-line imaging system

By increasing the L/S ratio, the developed system was able to detect an increase in the particle size of the regranulated product. Between the lowest and the highest L/S ratios (0.07 and 0.12), nearly 50% particle size increase was observed (352.9 and 524.3 µm Dv50). Hence, it can be stated that the applied L/S ratio has significant impact on the regranulated material's PSD. This is important for both quality control and process control aspects. With the in-line monitoring of particle size, deviations in the granulation step can be detected (pump malfunction, clogging, etc.). If the granulating liquid contains active pharmaceutical ingredient (API), the impact of this is even higher: in-line particle size analysis might also be used for indirect API content measurement as well (Ficzere et al., 2021).

4. Conclusions

In this work, a custom image analysis-based particle size analyser was developed for in-line application in a fully continuous granule production line. First, its performance was evaluated off-line via comparing the PSD obtained by measuring the same MCC pellet samples with the developed imaging system as well as two reference measurement methods (Parsum and Malvern Mastersizer). The results obtained with the imaging system showed excellent similarity with the reference methods. Next, the developed system was installed in a continuous

granule manufacturing line consisting of an interconnected twin-screw wet granulator, fluid bed dryer and a regranulating mill. The DIA-based system was used to investigate the effect of four CPPs (milling tool type, screen hole diameter, milling intensity (RPM) and L/S ratio during granulation) on the product's PSD. By integrating a vibratory feeder after the mill, the mass flow of the regranulated product could be regulated. This allowed for the temporary reduction of material passing in front of the camera, which drastically reduced particle overlapping. This made the acquisition of real-time particle size data possible, which can aid in rapid process understanding and optimization. The camera-based system was successfully applied to determine how a CQA (particle size) is affected by varying a CPP in real time. Via DIA-based measurements it was found that increased milling intensity and smaller screen hole diameters result in a decreased particle size. The developed system was also able to expose the increase in particle size of the regranulated material which was a result of higher L/S ratios applied during granulation. Off-line granule samples were also collected at each setting for reference Parsum- and flowability measurements, which supported all of the aforementioned findings as well. By applying the most up-to-date algorithms, image analysis carries a lot of potential for further pharmaceutical applications, e.g. deep learning-based image segmentation.

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Lajos Madarász: Conceptualization, Methodology, Validation, Writing – Original Draft, Writing – Review & Editing, Visualization **Ákos Köte:** Conceptualization, Methodology, Software, Investigation **Bence Hambalkó:** Software **Kristóf Csorba:** Conceptualization, Supervision **Viktor Kovács:** Software **László Lengyel:** Conceptualization **György Marosi:** Conceptualization **Attila Farkas:** Conceptualization **Zsombor Kristóf Nagy**: Conceptualization, Methodology, Resources, Writing – Review & Editing, Supervision, Project administration **András Domokos:** Writing – Original Draft, Conceptualization, Methodology

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: