The use of Real-Time At-Line Particle Size Measurement on a Pelletization Process for Accurate End-Point Prediction

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Abstract

The direct pelletization process is a fast and flexible operation with the potential to produce high quality particles appropriate for sophisticated oral solid dose formulations where a narrow Particle Size Distribution (PSD) is required. Particle size is a critical quality attribute for many pharmaceutical applications making control of end-point particle size a fundamental requirement. The Glatt proprietary Complex Perfect Spheres (CPS®) pelletization process is fast and therefore requires a rapid objective PSD measurement method during processing to follow the particle growth curve and accurately determine end-point. Traditional methods are too slow or subjective and therefore may be an unacceptable risk for use as an In-Process Control (IPC) in a control strategy. An at-line direct imaging method with automated high-speed image analysis can be practically used during processing to accurately predict the process end-point with fast objective PSD data, supported by particle images, to significantly improve process optimisation and control. The approach can also be used for other rotor based pelletization processes.

Introduction

Direct pelletizing allows for a variety of drug formulations to be realized in extremely low to very high doses. The technology is particularly suited to oral dosage forms where gastric resistant and modified release is a priority. Furthermore, a relatively narrow PSD is important to achieve a consistent predictable drug release profile in coated pellets. The CPS® technology allows for the manufacture of functionalized pellets/micropellets with perfect roundness and smooth surface. The CPS process is fast and produces uniform product. Process control including prediction of end-point based on particle diameter and size distribution is critical. Traditionally, a microscope-based image capture and analysis system is used to measure in-process samples to predict the end-point. An area within the sample tray is selected and a small number of particles are manually

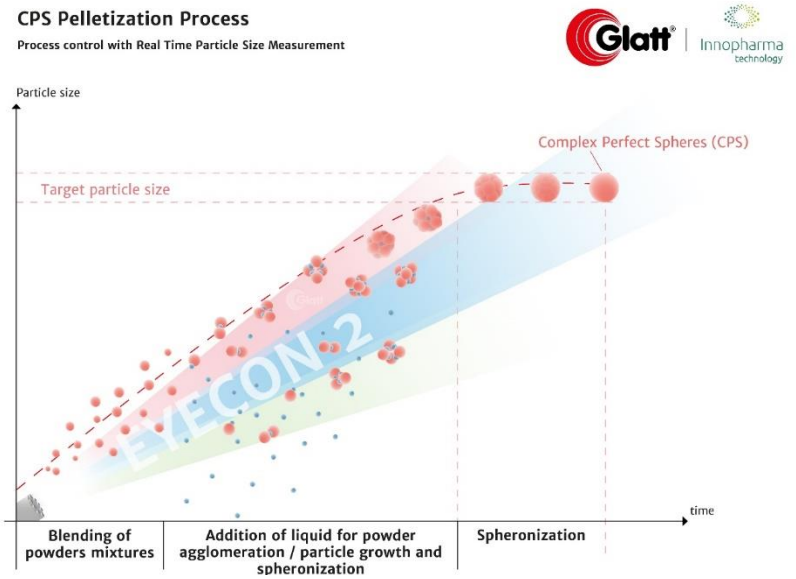


Image 1:Infographic of Pellitization with real time IPC

measured and analysed by the operator using the system's software. Limitations to the use of this in-process test include a reliance on an experienced process operator to select which particles are analysed combined with the small number of particles analysed per process sample. This approach might be assessed as relatively high risk as a process control strategy and could be mitigated by a more objective and rapid in-process test method to more reliably predict process end-point.

The Eyecon$_2$ is a non-product contact Process Analytical Technology (PAT) tool used for monitoring particle size in-line or at-line, in real-time. The Eyecon$_2$ is a direct imaging camera system which provides PSD data and colour images, allowing for a deeper understanding of the key & critical process parameters for a given process/system. The data can be used in conjunction with process parameter optimization and quality control (QC) results to develop a more efficient, robust and reliable process, and deliver a more consistent improved level of process control and therefore product quality.

Objectives & Preparation

The objective of this trial is to monitor and record particle growth during a direct pelletization process run. The process runs over a relatively short time period and particle size is a Critical Quality Attribute (CQA) of the product. The PSD measurement method should:

- Allow systematic and consistent sample preparation.
- Provide short analysis time.
- Be easy to operate.
- Provide PSD data and images of the particles.
- Track the change in particle size during processing.
- Provide fast and accurate PSD data to predict the process end-point.
- Demonstrate that the pellets produced are within the desired PSD range.
- Demonstrate applicability for process development and for process control.

The Eyecon$_2$ is usually configured as an in-line particle analyser, interfaced directly on process equipment to measure particle size through a viewing port. There is potential for such a configuration on the pelletization process in the medium term, however, the short-term focus here is to configure the Eyecon$_2$ for real-time at-line use and prepare samples for analysis on microscope slides as a direct replacement for the microscope method.

Equipment

CPS® technology

The Glatt CPS® technology is an advanced rotor fluidized bed process. It allows for the manufacture of matrix type pellets and micropellets with perfect roundness and surface. Direct pelletizing allows for a variety of drug formulations to be realized in extremely low or very high doses.

Figure 1: Glatt CPS® Technology

Unlike traditional rotor fluid bed systems, the CPS® technology works with a conically tilted rotating disc and additional devices that allows for a directional particle motion. By means of a characteristic rolling particle movement and thereby the application of specific centrifugal forces on the arising pellet cores, a defined densification of the particles can be reached.

No starter pellets are required for direct pelletizing with the Glatt CPS™ technology. The concentrations of the active ingredients in the pellet matrix can vary from less than 0.1 percent up to a drug load of 90 percent. Round, dense and evenly shaped pellets are achieved, with precisely defined pellet sizes between 100 and 1,500 micrometres with an extremely narrow PSD. Microcrystalline cellulose powder is often used as a basic excipient. The pellet formulations can furthermore contain other functional pharmaceutical excipients, such as polymers and disintegrating or solubilizing agents.

CPS® pellets and micropellets are especially suitable to produce carrier cores for subsequent coating applications for controlled drug release or for taste masking applications.

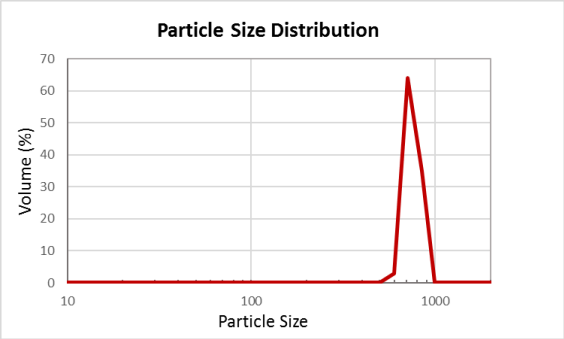


Figure 2:Typical Particle Size Distribution of CPS® pellets

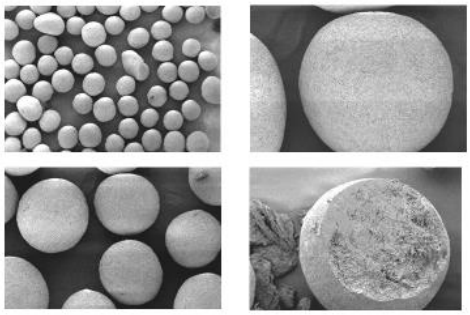


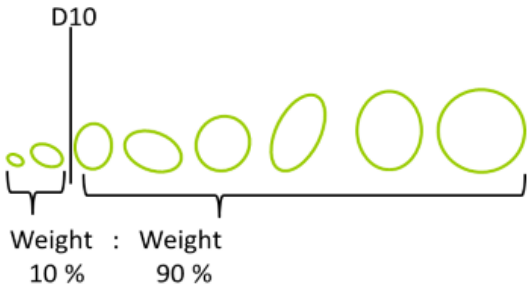
Image 2: Pellets with 75% drug load from a CPS® Process

Eyecon$_2$ Operating Principles and D-Values

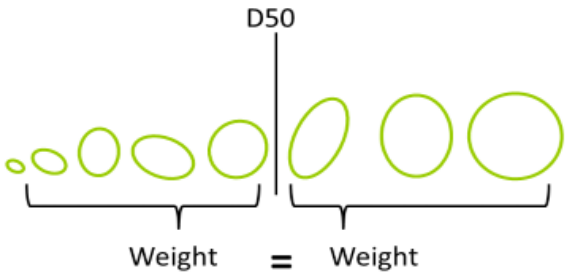
Eyecon$_2$ utilises direct imaging for particle size analysis. In direct imaging particles are illuminated and imaged from the same side. The method can be configured for both bench-top and in-line applications, while allowing the device to remain non-product-contact. This method uses advanced image analysis algorithms to accurately detect particle boundaries, and thereby particle sizes, giving real-time information on the process being analysed.

Eyecon$_2$ provides these real-time results in the format of D-values, histograms, trend graphs and images, and at the end of every analysis a PDF report summarising the measurement is also generated.

A D-value can be thought of as a mass division diameter. It is the diameter which, when all particles in a sample are arranged in order of ascending mass, divides the total sample mass in the given ratio as demonstrated below.



For example, the D10 diameter is the diameter at which 10% of a sample's mass is comprised of smaller particles, and the D50 is the diameter at which 50% of a sample's mass is comprised of smaller particles.



The D50 is also known as the "mass median diameter" as it divides the sample equally by mass.

System Configuration for Real-Time At-Line Use

A removable sample interface for Eyecon$_2$ was designed and configured to allow process samples to be measured in a systematic and rapid manner. Eyecon$_2$ measurement parameters were optimised and a configuration saved for the type of material being produced by the CPS® process.

Image 3: Eyecon$_2$ installation next to a Glatt CPS Processor with Pelletization Sample Interface

Procedure

Batch 1 and Batch 2 Parameter settings and Sample Plan

Batch 1: The CPS processor was loaded with 800 g pre-wetted MCC 105 granules and set to 1000 rpm, 2 Bar, 23.5°C with an initial liquid addition rate of 50 g/min. The liquid addition rate was lowered to 30 g/min after approximately 1000 g of liquid addition. Samples were taken after 600 g of liquid addition and approximately every 50 g liquid addition after that point. Each sample was analysed immediately using the microscope method and then passed for rapid sample preparation and analysis by Eyecon$_2$.

Batch 2: The CPS system was set up as per batch 1. Liquid addition was 50 g/min for the first 15 mins and then reduced to 40 g/min until 2450 g was added. The spray rate was then increased to 50 g/min until the end of the run. Again, once 600 g of liquid had been added samples were taken after approximately every 50 g liquid addition.

Sample Preparation

Samples were taken at intervals based on liquid addition and directly onto commonly available microscope slides (Image 4) which were then positioned on the sample interface for immediate measurement.

Image 4: Samples taken directly to Microscope Slides for immediate measurement

Sample Measurement

The Eyecon$_2$ was set up in the process room beside the CPS process equipment as seen in Image 1 to measure samples at-line in real time. The prepared sample was placed on the sample interface. It was decided to measure samples from batch 1 for approx. 20 seconds and samples from Batch 2 for 10 seconds to compare measurement time and number of particles measured to optimise time for measurement with quality of data. The image capture time can be further optimised on implementation to reduce measurement time if required.

Image 5: Real-Time At-Line Configuration of Eyecon$_2$ for CPS Analysis

Processing of Results

Throughout the analysis particle information such as D-values, mean diameter and volumetric histogram can be seen in real time along with updated images of the samples measured. The Eyecon$_2$ system generates a standard PDF report on demand for each sample measurement which provides Particle Size Distribution information as standard including D_{10}, D_{50} and D_{90} and provides a volumetric histogram. In addition, example images are provided. See Appendix 1 for example.

In addition, all sample data can be exported in csv format for more detailed analysis and all images can be viewed in browsers and exported for inclusion in reports as required.

Results

The D-values and mean diameters were plotted vs. mass of liquid added as seen in Figure 3. The particle sizes at each analysis point are represented by the D-values; D10, D50 & D90, and the mean diameter of the particles measured from the sample. Results for Batch 1 are shown in Figure 3 and trends the particle size change against liquid addition and demonstrates how the measurements can be used for end-point prediction.

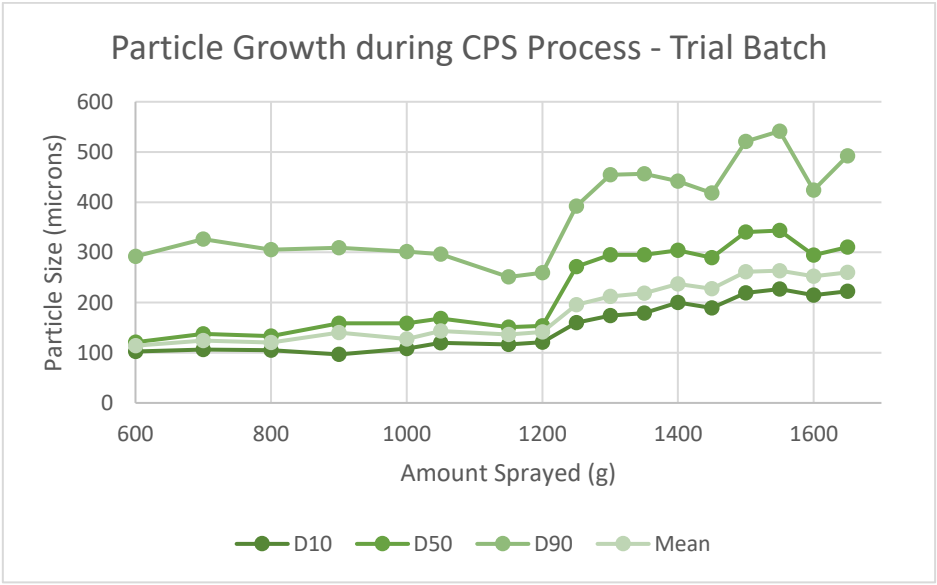
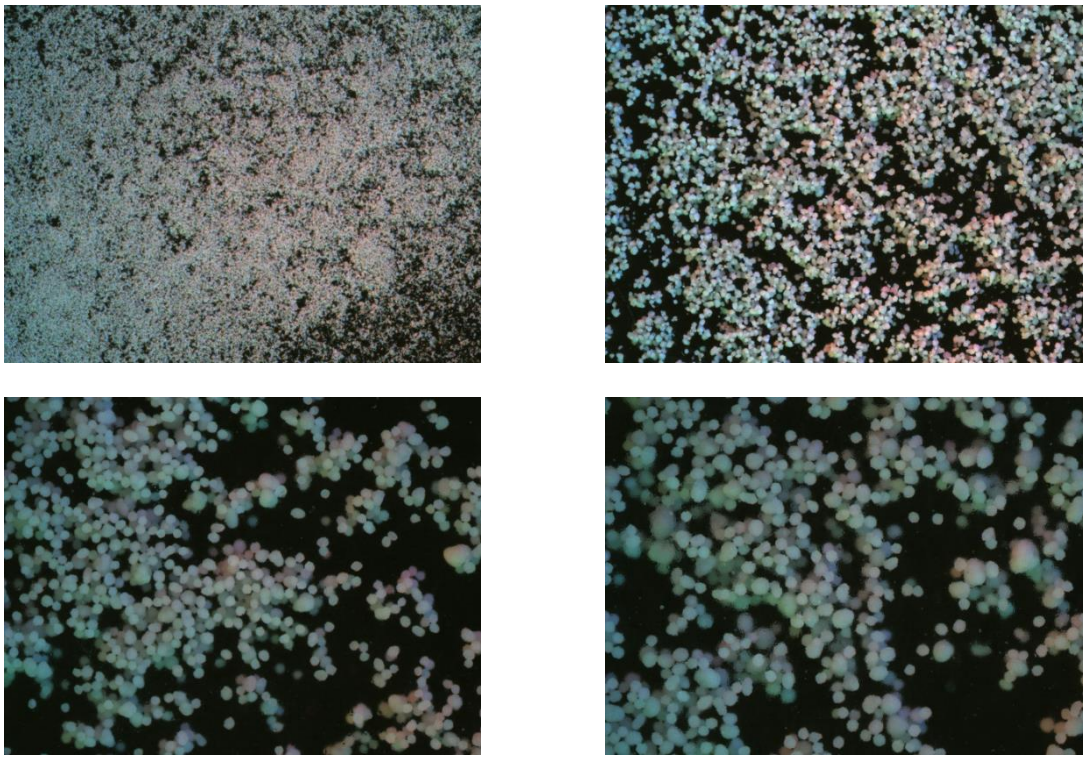


Figure 3: Particle Growth during a Trial Batch represented by D10, D50, D90 & Mean Diameter

Some sample images captured by the Eyecon$_2$ during particle measurement of a Trial Batch can be seen in Table 1. These images are taken from Sample 1, 5, 9, & 15 respectively and demonstrate the presentation of the sample to the Eyecon$_2$, the growth of the particles throughout the process and the issue of particles being out of focus.

Table 1: Sample Images from Trial Batch showing progression of process



20 Seconds vs 10 Seconds Image Capture Periods

Image capture time was compared to balance time to generate a result with the quality of the data. Image capture of 20 seconds was used for batch 1 and 10 seconds for batch 2. A comparison of the output in number of images captured and number of particles counted is presented in Table 2.

Table 2: Comparison of Analysis Times

Amount Sprayed	No. of Images Captured		No. of Particles Measured	
	~ 20 sec	~ 10 sec	~ 20 sec	~ 10 sec
600 g	6	4	6222	2203
1250 g	11	4	2514	2490
1650 g	11	6	1162	724
2150 g	N/A	5	N/A	671
2750 g	N/A	6	N/A	553

Overall, the number of particles analysed even at the shortest analysis time for the largest particles is a significant improvement over the manual method. The manual selection of particles is removed by switching from the manual microscope method to the Eyecon$_2$ method eliminating subjective selection of which particle is measured, as all particles in all images are subjected to image analysis with all particles identified being included in the reported data. Furthermore, the number of particles analysed per sample is significantly increased over the traditional method. A review of the table shows the impact of reducing analysis time on the number of images captured and therefore the number of particles measured. Generally, the more particles

measured the more representative the sample analysis is of the process. The number of particles measured decreases as the amount sprayed increases due to the increase in particle size and therefore fewer particles per unit area on the sample slide.

It would be possible to reduce the analysis time to 5 seconds but as the trend above shows this would lead to fewer images and therefore less particles being measured, particularly towards the end of the process. It is recommended that the procedure is optimised for each process to balance the analysis time with the number of particles counted to achieve the optimal data quality for end-point prediction.

Eyecon$_2$ for IPC of CPS® and Rotor Processes

The CPS® process is rapid and particle size is one of the critical quality attributes. Prediction of end-point is key because it is important to have a uniform particle with relatively narrow PSD but also important in many applications such as taste masking that the particle size remains below a maximum threshold. It is valuable to be able to rapidly predict the end-point for each formulation to ensure the correct PSD is achieved. The traditional IPC relies heavily on operator experience to 'know' when the correct PSD is approaching, with the decision supported by analysis of user selected particles on microscope system. A small number of particles are selected for analysis and recorded as part of the IPC strategy. The selection of particles is largely subjective and can be identified as an unacceptable risk for IPC in a GMP process.

The Eyecon$_2$ coupled with a systematic sample preparation procedure offers a significant improvement to the development of process parameters and a control strategy that is data-driven and science-based, and therefore more acceptable for use in-process development and GMP compliant production. The PSD data is generated during processing and with optimisation can be used to predict the end-point PSD and therefore when to stop the process. The most relevant PSD data (Dv50, Dv10, Dv90, mean etc.) will be used for process decisions with the additional benefit of particle images for each sample point from the process to further aid process understanding during development and investigations and for use in technical reports.

PSD is a critical quality attribute for the CPS® product and process parameters and can be optimised during development using real time data from the Eyecon$_2$ leading to a more robust and efficient process with demonstrably improved IPC strategy. Prediction of process end-point based on PSD will be more data driven and reliable, increasing confidence that later process phases will meet specification. Figure 4 shows a illustrates a batch to batch comparison of PSD change during processing.

The process analytical method can also be applied to other rotor processes for process understanding or as part of process control where Particle Size is a Key or Critical Quality Attribute.

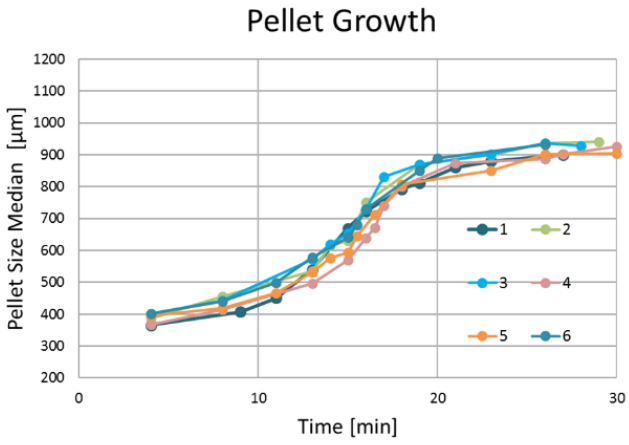


Figure 4: Multiple Batch Comparison of PSD change during processing

Conclusions/Recommendations

From the results of the analysis completed by the Eyecon$_2$ during the evaluation on the CPS® process samples it can be concluded that:

- The Eyecon$_2$ method could be used to rapidly monitor the increase in particle size with liquid addition during CPS® or other rotor fluid bed batch operations. Samples can be taken directly onto commonly used microscope slides and immediately measured to provide a rapid update on size during processing.
- The Eyecon$_2$ system provides real time PSD data to the operator throughout measurement. During and at the end of the session the key PSD data is instantly available allowing an immediate data driven decision for process control based on PSD. A report for each batch can be generated on demand to attach to a batch record or include in an R&D Technical report.
- The Standard Report is designed to present data generated in a format and language common to formulation development scientists, process engineers and quality control/assurance and includes D_{10}, D_{50}, D_{90}, mean and median and provides a volumetric histogram.
- The particle size data and images provide information for a deeper understanding of the impact of process parameter and formulation changes to particle size distribution and therefore product performance. Once implemented, Eyecon$_2$ data can be used in conjunction with critical process parameter data to correlate with critical quality attributes for process development / improvement / monitoring / control purposes.
- Set up and operation of the Eyecon$_2$ was straightforward and could be readily incorporated in day to day process operations without additional specialist personnel to operate and interpret results.

Contact for More Information

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Appendix I

PDF Report example

eyecon2 Innovation by Innopharma Technology

Particle Size Report

eyepass Innovation by Innopharma Technology

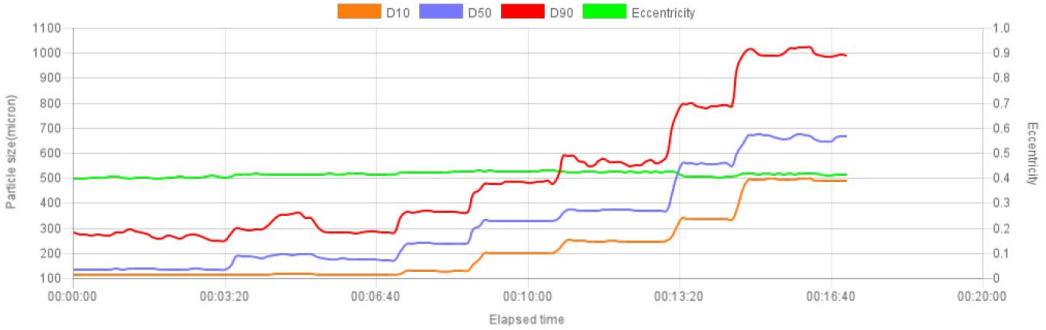
Batch Details

Material	CPS Demo	**Configuration**	CPS Demo	**Start time**	2018-10-03 09:41:42
Batch Number	02	**Started by**	admin	**End time**	2018-10-03 09:58:49
Sublot		**Number of particles**	188749	**Duration**	0:17:07
Instrument details	EYECON2	**Eyecon serial number**	PS2005	**Eyepass version**	2.1.3-beta+002

System & notifications

System events	No

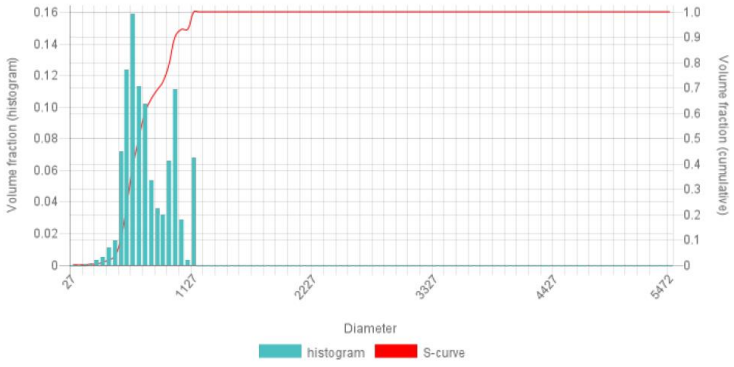
Results: Process Profile



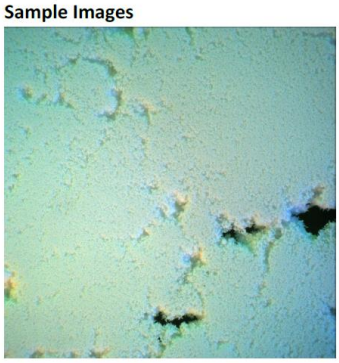
Results: End Point

Data based on final 60 seconds of measurement

Dv10	489
Dv25	557
Dv50	658
Dv75	904
Dv90	989
Dn10	317
Dn25	465
Dn50	539
Dn75	621
Dn90	740
Mean	544
Median	539
Std deviation	180
Eccentricity mean	0.4141
Eccentricity RSD	0.4841



Sample Images



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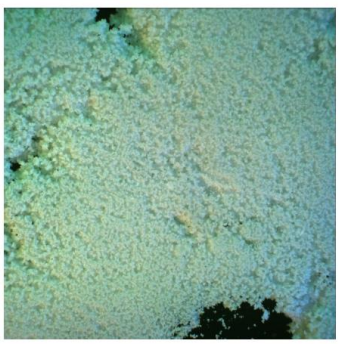

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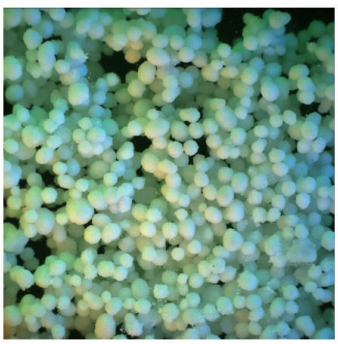

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