Implementation of PAT for In-Line Monitoring of a Milling Process During DoE for Continuous Processing

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Introduction

The study presented here outlines some of the steps involved in developing a component process of a continuous manufacturing system using Design of Experiment (DoE) methodology. A fundamental requirement of continuous processing is continuous monitoring of the process' critical quality attributes (CQAs) to gain a sufficient understanding to devise a data driven control strategy. A suitable in-line Process Analytical Technology (PAT) sensor enables real time measurements of the CQA and provides a real time trend of the stability of the process. The FDA's PAT Framework includes tools such as multivariate analysis, PAT sensors, process control and continuous improvement in a risk-based approach to pharmaceutical development. PAT sensors are used to measure certain quality attributes of product within the manufacturing process, eliminating or substantially minimising the need for sampling for off-line analysis. This approach has several key advantages over traditional off-line analysis methods and includes process measurements in situ with instant access to data which facilitates rapid decision making during both product development and manufacture. This becomes particularly important when developing a process within a continuous manufacturing system. While the time between sampling and off-line results may range from minutes to days depending on the test being performed and the analytical structures in place, many PAT systems are capable of real-time measurement results, enabling control decisions to be made based not just on a process recipe but also on the true CQAs of the material at that point in time. This allows for a more dynamic process control, compensating for variabilities such as raw material variations or mechanical wear in processing components, and supports compliance with newer QA initiatives such as continuous verification. Additionally, the potential to develop an automated control with real time release could minimise operator time when compared to testing samples at-line or off-line and manually adjusting the process within the specification.

Particle size and control of end-product particle size distribution (PSD) is of importance in a wide range of processes where particle size is considered critical. This study investigates the applicability of PAT for measurement of particle size of product material in-line directly after milling. A milling operation involves the reduction in size of material for the benefit of downstream processing, (i.e capsule filling or tableting), in this case extrudate from an extrusion process is being milled to form a fine powder. As this process is being developed as part of a continuous manufacturing line, control of CQAs, in this case PSD, must be obtained and in real time to ensure material of consistent quality is being produced and delivered to downstream processes within the continuous manufacturing system.

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Experimental Plan (Procedural Outline)

The scope of this study is to determine the influence of milling process parameters on the particle size distribution of milled extrudate using a real-time in-line PSD sensor. As part of the DoE the following investigations were conducted:

1) In-line analysis of milled extrudate using an in-line PSD sensor
2) Comparison of in-line data with off-line laser diffraction measurement method

During the DoE, 3 process parameters were studied; mesh size, rotation speed and the feed rate from the dosing hopper delivering the extrudate to the mill. These parameters were varied across 11 experiments to investigate their impact on the particle size of the end-product material. The DoE was created using Nemrod®, France, the parameter settings are laid out in Table 1. Each experiment was conducted on a batch size of 1 kg.

Table 1: Parameters Set for each Experiment

Experiment	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Mesh Size (mm)	0.5	0.5	0.5	1	1	1	0.5	0.5	0.5	0.5	0.5
Rotation Speed (1000 RPM)	10	14	18	10	14	18	10	14	18	14	14
Feed Rate (kg/hr)	2.1	4.7	6.5	4.7	6.5	2.1	6.5	2.1	4.7	2.1	2.1

Materials & Equipment

Materials

The material, composed of API and two functional excipients, is an extrudate produce by hot melt extrusion. Before the milling, the extrudate has an irregular cylindrical shape with a particle size around 2mm.

Process Equipment

The DoE was conducted on Hosokawa Alpine 100 milling process equipment. The Alpine 100 (Figure 1 & 2) is a development scale hammer mill used during the development of this product.

Figure 1: Milling process - Hosokawa alpine 100

Figure 2: Internal milling area

Experiments were conducted under controlled air pressure (5-6 bar), no nitrogen was used. The DoE experiments were carried out in a temperature and humidity-controlled environment.

Analytical Instruments

Eyecon™ – Process Analytical Technology

The Eyecon is a non-product contact, direct-imaging, particle analyser which captures images of flowing or static material, and through advanced image analysis can return data on the particle size distribution and shape of the material. The Eyecon has application in processes including fluid bed coating & granulation, milling, twin-screw granulation and material transfer and can be used to significantly reduce analytical time and increase process knowledge from development to commercial scale manufacturing.

During in-line analysis, sensor-process equipment interfacing is achieved by installing the Eyecon at a view port window in the product container or product transfer system. Images of the in-process material are captured, maximising the number of particles captured per image, and therefore providing accurate, representative measurement of the material particle size distribution. Figure 3 shows the Eyecon installed in-line on a purpose-built interface for the Hosakawa Alpine Mill. Innopharma Technology designed the interface to enable optimal measurement of free-flowing product. The integration flow chute is attached to the outlet of the mill using a tri-clover clamp. Due to the highly static nature of the cellulosic excipient, the view port was manufactured from EUROPLEX® (Evonik, supplied by Experta, France) which was specifically selected for minimisation of fouling from static powders.

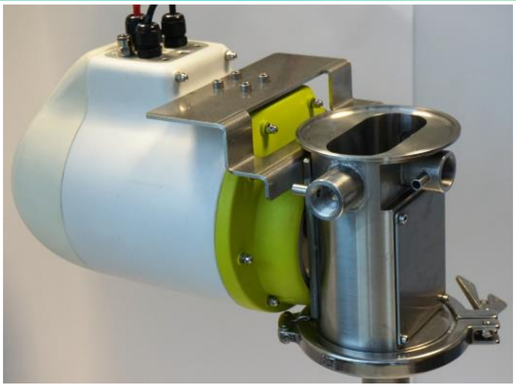

Figure 3: Eyecon mounted on Hosakawa Alpine Mill Integration

Laser Diffraction – Lab Analyser

Laser diffraction is a common offline method for measuring particle size. The light-scattering effect caused by particles passing through a laser beam is measured by an array of detectors. The size distribution of the particles can then be calculated using the principle that the angle of diffraction of the light is inversely proportional to the particle size. The particle size distribution was measured using a Malvern Mastersizer 2000 fitted with a Scirocco 2000 cell, in dry mode. For each measurement the sample size was 1 gram and was repeated once.

While this method has the potential to be extremely accurate, current technologies can be limited by the small sample size used in analysis, the results of this method also become less reliable as the particle shape diverges from spherical. As the analyser is lab based there can be a significant time gap between sampling and acquisition of results.

Results & Discussion

Each of the 11 experiments were analysed in-line with the Eyecon. The Eyecon provides the user with real-time information on milled material along with a report at the end of the process. Figure 4 shows the particle size (D_v50) for each of the process runs in the DoE. The graph also includes the limits for the particle size as set out at the start of the DoE. These limits were defined based on prior knowledge of PSD via laser diffraction measurement of a composite product sample taken at the end of the process. It can be observed that the process in question is robust as all 11 experiments fall within the predefined specification. As the limits were defined based on laser diffraction off-line analysis it is recommended that in-line specifications be defined using Eyecon data rather than off line data.

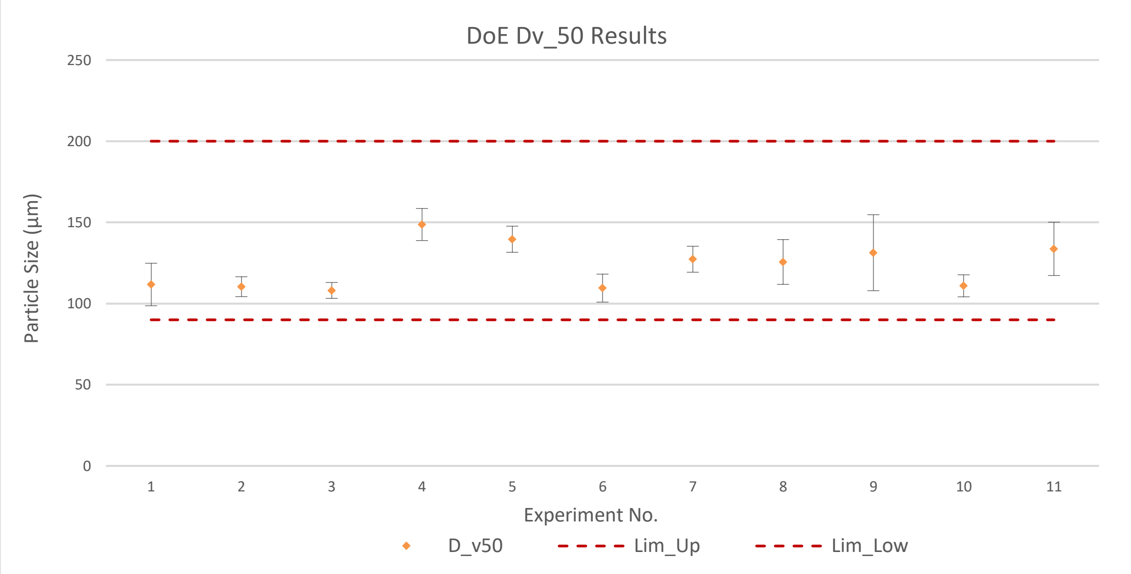

Figure 4: Particle Size (D_v50) for all Experiments, including Limits

Figure 5 shows the process profiles for each of the experiments. There were a small number of spikes in the measured particle size during processing, which were determined to be due to a build-up of fines on the inside of the view port. This occurrence of dust/fines may be significant as it is not seen across all experiment conditions and could be considered a factor of the process parameter settings. These spikes were observed in experiments 6, 8 and 9. However, as this dust is measured as single large particle(s) it was decided to remove these measurements from the rest of the study.

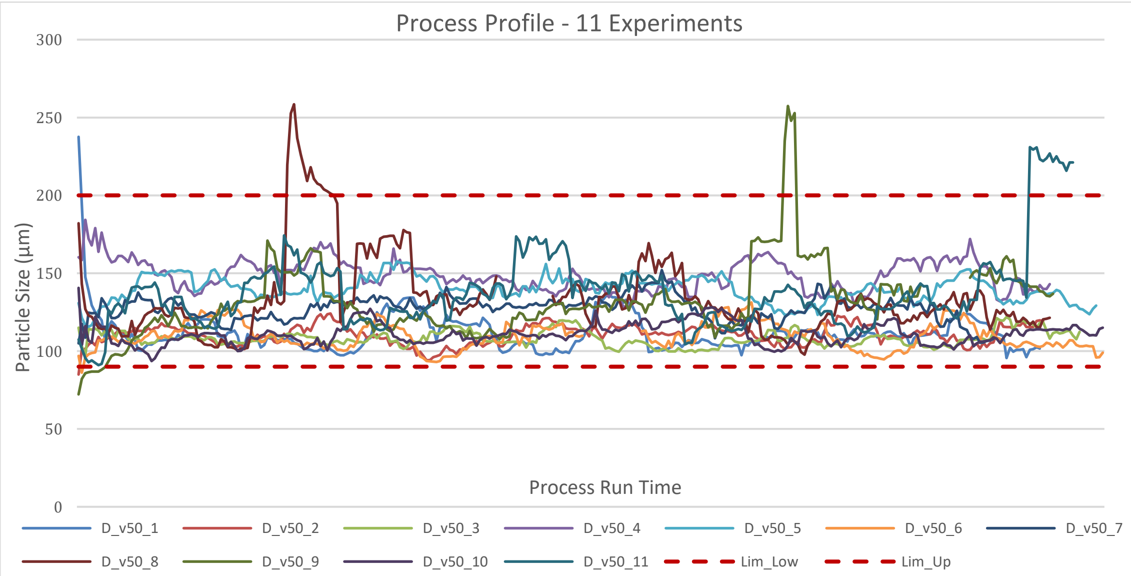

Figure 5: Process Profile for 11 Experiments after Removal of False Detection Measurements Due to Fouling

Reviewing Figure 5 it can be seen that, except for a small number of outliers, all of the data from the 11 experiments remained within the pre-set limits of the DoE.

The results from each of the experiments were investigated to understand the impact of the process parameters on the particle size. It was determined that the mesh size has the most significant impact on particle size with a smaller mesh size resulting in smaller material. Figures 6 & 7 compare the two mesh sizes used, 1 mm and 0.5 mm respectively.

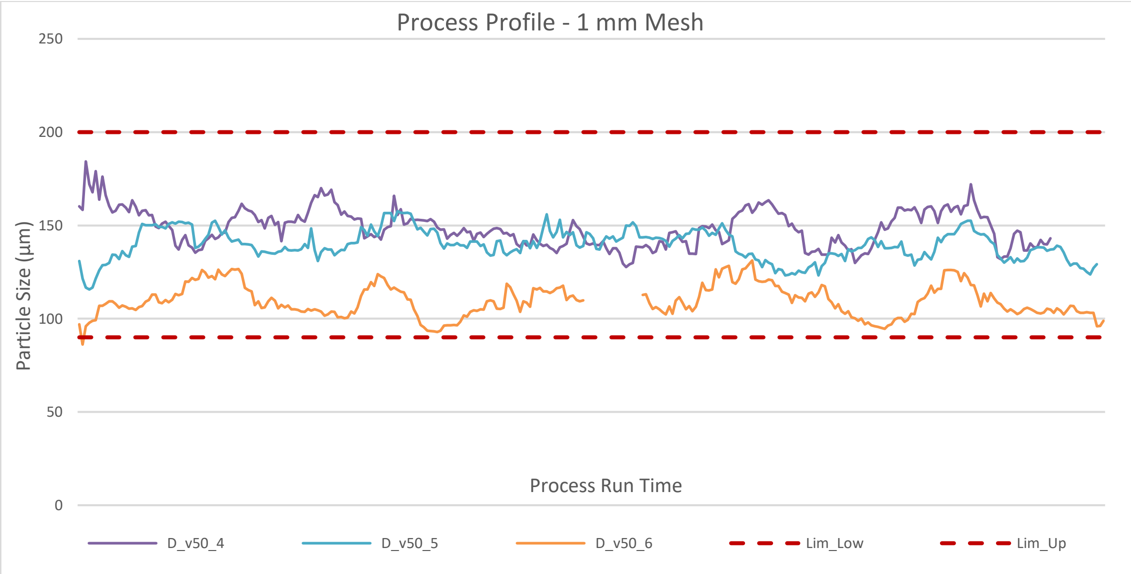

Figure 6: Process Profiles for Experiments with 1 mm Mesh

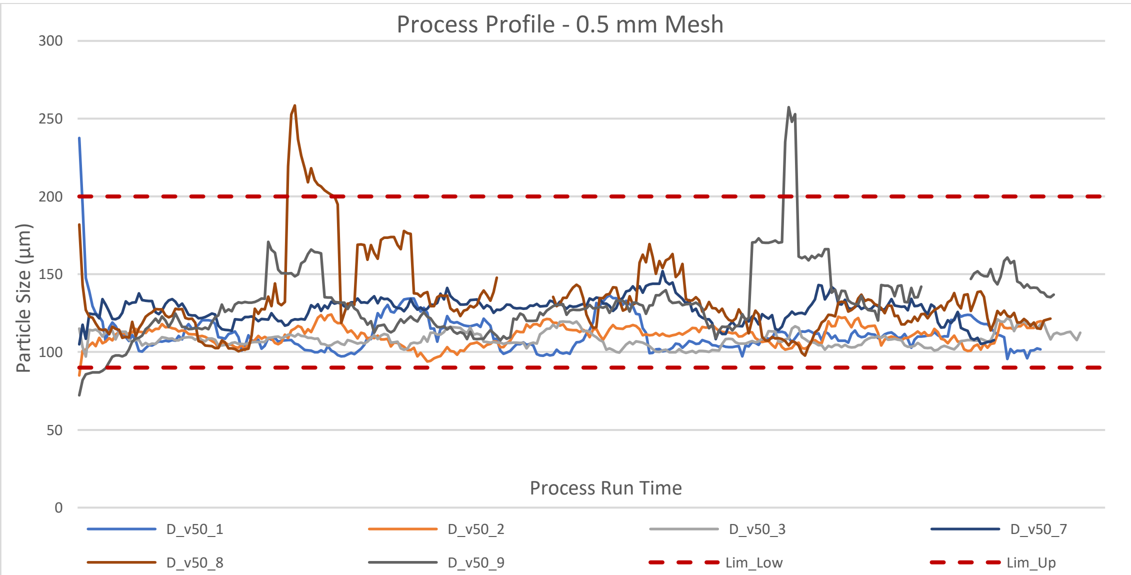

Figure 7: Process Profiles for Experiments with 0.5 mm Mesh

It can be seen in Figure 6 that during experiments 4 and 5 the D_v50 remains close to 150 µm. In Figure 7 it can be seen however, that the experiments run using a 0.5 mm mesh have a D_v50 < 150 µm. The impact of mill speed can also be noticed in Figure 6 where experiment 6, run at 18,000 RPM, has a lower D_v50 than the other two experiments conducted with a 1 mm mesh at 10,000 and 14,000 RPM respectively.

The data from Eyecon was further analysed by calculating the average for each of the D values and comparing across each of the experiments, the standard deviation was also calculated.

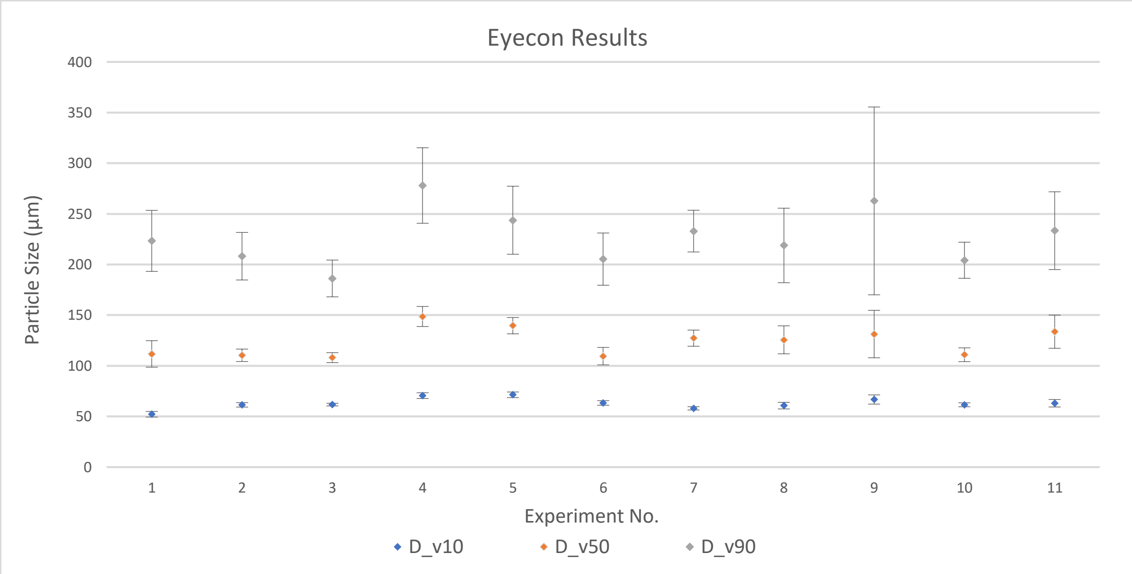

Figure 8: Comparison of Average D_v10, D_v50, D_v90 for each Experiment

It can be seen in Figure 8 that the standard deviation is very low for the D_v10 and increases for the D_v50 and D_v90. This indicates that the level of fines remained quite constant throughout each experiment and it can also be noted that the size of these smaller particles also remained quite constant. As typically seen, the level of deviation increases for the higher D values in each experiment with the greatest amount of deviation in experiment 9. It is noted that prior to experiment 9 the view port was not cleaned, this resulted in an increased presence of fines on the view port causing a larger standard deviation in the D_v90. This indicates the importance of ensuring the view port is kept clear, this could be maintained by scheduled cleaning procedures or through investigation of other view port clearing methods, such as periodic, directional air supply.

Offline sample analysis was carried out by laser diffraction and can be seen in Figure 9. Testing was conducted in duplicate except the sample from experiment 1 which was measured once. Each sample was composed of 1 g of material, taken after each experiment.

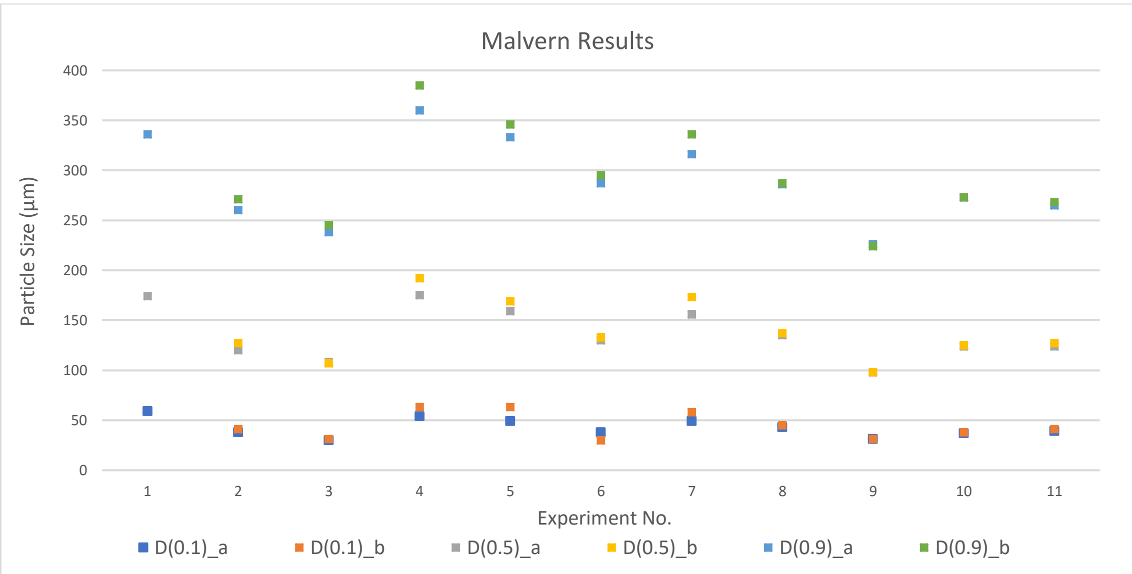

Figure 9: Comparison of 2 x Malvern Sample Analyses (a & b)

The in-line Eyecon results were also compared to the offline laser diffraction results. The average of the duplicate laser diffraction measurements was calculated and compared to Eyecon results, Figure 10.

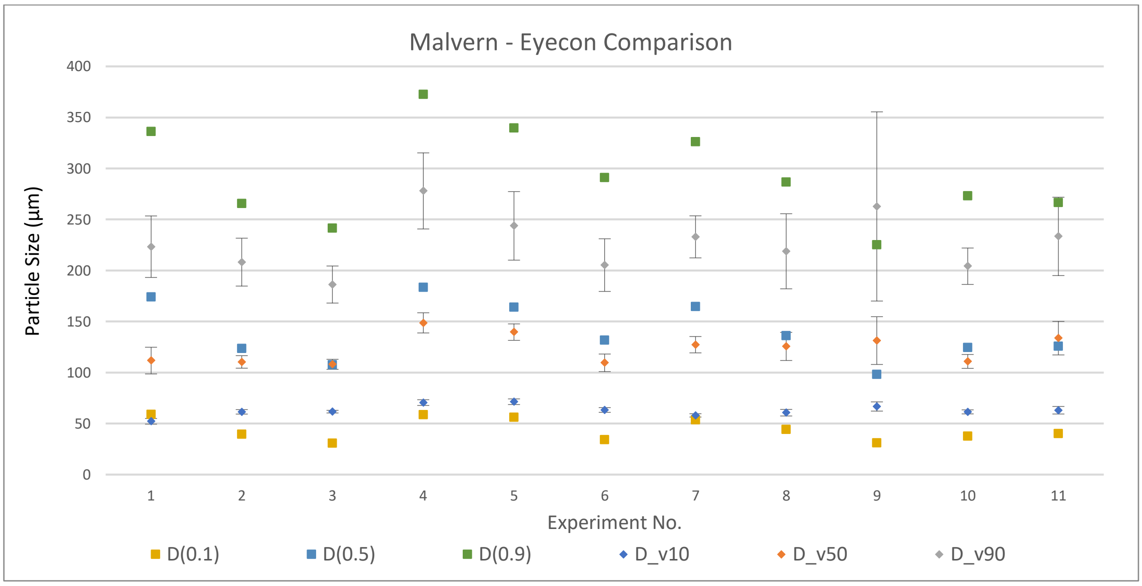

Figure 10: Comparison of Malvern (dashed line) to Eyecon (solid line)

A similar trend can be seen for the D-values across each of the 11 experiments, as measured by the in-line and off-line methods. Laser diffraction measures the D_v90 and D_v50 to be larger than that measured by the Eyecon in-line. Eyecon's measurement of the D_v10 to be larger than the D(0.1) measured by laser diffraction can be attributed to the lower end of the measurement capability of the Eyecon technology, 50 µm, being comparatively larger than the lower end of the measurement capability of the laser diffraction technology, 0.02 µm. The volume of material measured should also be taken into consideration. In-line the Eyecon will measure throughout the entire duration of the process, as all the milled material transitions past the Eyecon. In comparison, the laser diffraction method analyses a sample of 1 g, taken at the end of the process. It is therefore critical that the sample taken for offline analysis is truly representative of the overall process PSD thus enabling reliable comparison and correlation between the in-line and offline methods.

Conclusions

- It was determined that all experiments resulted in acceptable end-product material, within specification limits.
- Implementation of Eyecon in-line allows the influence of process parameters on particle size distribution to be seen in real-time and provides a measure of process stability over time.
- Good correlation was demonstrated between in-line PSD data and the laser diffraction method.
- Eyecon is a highly useful tool for development of processes and for quick acquisition of results and therefore adjustment of milling parameters to obtain the desired end-product material particle size.
- Accumulation of dust on the window was found in some process conditions, resulting in stopping the process to clean the window on occasion.

Future Work

- Implement Eyecon for in-line measurement during scale-up trials and monitoring of pilot scale batches on a full continuous line (blending, melt extrusion, milling, sieving, stick pack).
- Determine in-line particle size measurement specification.
- Use airflow or similar option to clear window periodically to minimise build-up of dust on the view-port, in conjunction with anti-static window material.

Further Information

For More Information on Eyecon™ Technology Please Contact:

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