Unique Advantages of Process Analytical Technology in Twin-Screw Granulation

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Introduction

It is increasingly recognised that the future of pharmaceutical manufacturing will continue towards the development and adoption of continuous manufacturing techniques. This is in part due to lower operating costs, footprint and flexibility that continuous manufacturing offers. Twin-Screw Granulation (TSG) has emerged as a popular continuous manufacturing technology for consistent, repeatable high-quality production of both standard and complex dosage forms.

This technology allows agglomeration of materials in a small footprint with minimal process set-up time and a wide range of throughput rates. However, as the industry moves towards the new mind-set of continuous manufacturing, many of the processes being considered are still currently in the process development stage.

Development of processes on this and other continuous technologies present several challenges. While a great deal of research has been carried out on twin-screw manufacturing, the breadth of knowledge on new continuous equipment and processes in Pharma has not yet reached that of more established processes such as fluid bed or high-shear granulation. This, coupled with the ever-increasing importance of quality by design (QBD), contributes to the challenges faced by the process development engineer. Other new technologies, however, can be used to decrease the process engineer's workload, allowing for overall faster process development than with established batch platforms.

This application note presents parts of a wide-ranging experimental plan involving the building of a data-driven process map for twin-screw granulation using the benchtop Thermo Scientific™ Pharma 11 Twin-screw Extruder and an Eyecon$_2$™ Particle Analyser system (a real-time in-line process analytical technology or PAT instrument) provided by Innopharma Technology. The experiments presented here aim to demonstrate both how PAT can dramatically decrease the time required to define, execute and analyse the data from a DOE, and how it can provide information which is not plausible from traditional off-line analysis methods.

Experimental Plan

The experiments and results covered in this application note involved varying specific input parameters of the twin-screw extruder while running a placebo formulation. The resulting particle sizes were monitored in real time using the Eyecon$_2$ particle analyser, and samples were taken for later offline analysis. As twin-screw granulation is a continuous process with minimal settling time parameters could be changed while the process equipment ran, enabling fast and efficient execution of the DOE. The parameters changed during experimentation were as follows:

- Throughput rate
- Liquid-to-solid ratio (L/S)
- Screw speed
- Screw configuration

A design space was chosen based on prior knowledge of the Pharma 11 extruder and chosen formulation. This consisted of upper and lower practicable values for each of the listed parameters. Two intermediate values for each parameter were also chosen. During experimentation, each of the four parameters was varied while maintaining the other parameters at a mid-range value. Table 1 lists all experimental combinations tested for the data published in this application note.

Experiment	**Throughput Rate**	**L/S**	**Screw Speed**	**Screw Configuration**
1	2.0 kg/h	**18%**	500 RPM	sc2F30
2	2.0 kg/h	**20%**	500 RPM	sc2F30
3	2.0 kg/h	**25%**	500 RPM	sc2F30
4	2.0 kg/h	**28%**	500 RPM	sc2F30
5	1.0 kg/h	20%	**300 RPM**	sc2F30
6	1.0 kg/h	20%	**500 RPM**	sc2F30
7	1.0 kg/h	20%	**700 RPM**	sc2F30
8	1.0 kg/h	20%	**900 RPM**	sc2F30
9	0.5 kg/h	20%	700 RPM	**sc0**
10	0.5 kg/h	20%	700 RPM	**sc1F30**
11	0.5 kg/h	20%	700 RPM	**sc2F30**
12	2.4 kg/h	20%	500 RPM	**sc0**
13	2.4 kg/h	20%	500 RPM	**sc1F30**
14	2.4 kg/h	20%	500 RPM	**sc2F30**
15	2.4 kg/h	20%	500 RPM	**sc3F30**
16	2 kg/h	20 %	500 RPM	**sc1F30**
17	2 kg/h	20 %	500 RPM	**sc1F30**
18	2 kg/h	20 %	500 RPM	**sc1F30**
19	3 kg/h	20 %	500 RPM	**sc1F30**

Table 1 – List of Extruder Parameters for Each Experiment

Materials & Equipment

The formulation used during this experimentation was a common placebo, solid-pre-blend, with the contents detailed in Table 2. The liquid addition consisted of water only since the binder PVP 30 is present in the blend. Figure 1 shows the visible difference between the input material and processed granules.

PVP 30	5 %
Corn Starch	32 %
Lactose	62.8 %
Talcum	0.2 %

Table 2 - Formulation

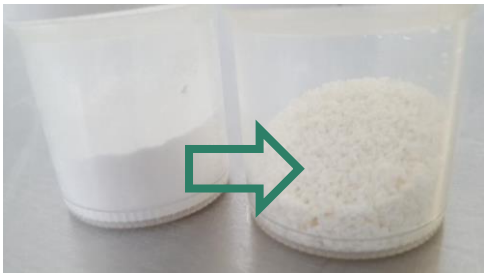

Figure 1 Material Before and After Granulation

The Pharma 11 twin-screw extruder (Thermo Fisher Scientific) is a lab-scale granulator system, which supports both hot melt extrusion and wet granulation. This lab bench extruder uses extremely low throughput rates, reducing the amount of expensive API needed for experimental applications. The screw elements and barrel design scale geometrically across the range of Thermo Scientific twin-screw granulators, supporting easy process scale-up. The Pharma 11 extruder was used in its wet granulation configuration during these experiments and is called granulator in this report.

Figure 2 - Pharma 11 Twin-Screw Extruder

Figure 3 - Pharma 11 Extruder Disassembled for Cleaning

To monitor granule size in real-time on the outlet of the twin-screw the Eyecon$_2$ from Innopharma Technology was used. The Eyecon$_2$ is a direct-imaging particle analyser which captures images of flowing or static material. Through advanced image analysis the Eyecon$_2$ particle analyser can return data on the particle size distribution of the material. The Eyecon$_2$ particle analyser has applications across a wide range of processes including fluid bed coating & granulation, milling and twin-screw

granulation, and can be used to significantly reduce analytical time and increase process knowledge from development to commercial manufacturing.

Figure 4 - Eyecon$_2$ Imaging & Illumination Hardware

Figure 5 - Eyecon$_2$ in At-line Configuration

To measure the material output from the granulator it was necessary to use an "integration device" for the Eyecon$_2$ particle analyser. These devices are custom-designed and manufactured by Innopharma Technology to fit customers' processing equipment, minimising process intrusion while optimising the flow and/or presentation of material to ensure accurate and reliable measurement results. The focus with this integration device was to ensure reliable flow and to avoid fouling; since these experiments were conducted with a placebo formulation in a non-GMP environment the integration device used did not have any containment, and certain parts were made using rapid-prototyping methods. However, an option is available for a fully-GMP, contained design if needed for hazardous APIs.

For optimal measurement, the integration device was designed to channel the flow of particles from the twin-screw into a stream in front of the Eyecon$_2$ imaging area, while keeping them within the focal depth of the camera. As the moisture content from the outlet of the granulator can be high, a key requirement of any integration is to avoid adhesion or fouling of the granulated material on the flow surfaces. This was achieved by a combination of highly polished 316l stainless steel surfaces and active heating elements to prevent any condensation from occurring. The resulting device is pictured in Figure 6 - Figure 8, showing the Eyecon$_2$ particle analyser mounted in place for measurement at the end of the granulator.

Figure 6 - Eyecon$_2$ Particle Analyser with Integration Device in-place on Pharma 11 Extruder in Granulation Mode (View 1)

Figure 7 - Eyecon$_2$ Particle Analyser with Integration Device in-place on Pharma 11 Extruder in Granulation Mode (View 2)

Figure 8 – Eyecon$_2$ Particle Analyser with Integration Device in-place on Pharma 11 Extruder in Granulation Mode (View 3)

Results & Discussion

Effects of parameter changes

For simplicity the results (where a clear trend could be discerned) are presented in the following format that describes the effects of increasing the identified process parameter in each case:

Parameter Change

Particle Size Distribution	$D_{v,50}$	Oversize Particles	Fines	Density of Granules
Distribution width	50 % of mass/volume smaller than this value	> 1500 µm	< 300 µm	+ / -

Table 3 – Explanation of Parameter Change Tables

- Particle size distribution (PSD) describes the basic trend in the distribution width i.e. increasing width, no change or decreasing width resulting from the parameter increase.
- The $D_{v,50}$ column describes whether the mass median diameter of the sample can be expected to increase or decrease with an increase of the parameter identified.
- The oversize particles and fines columns identify whether each size range (defined in header) can be expected to increase or decrease as a proportion of the sample in response to an increase in the process parameter identified.
- The final column describes the effect of the increased parameter on the density of the granules produced. While this could not be ascertained during this study the expected effect based on available literature is given for a completeness of understanding.

Increasing Liquid-to-Solid Ratio

Particle Size Distribution	$D_{v,50}$	Oversize Particles	Fines	Density of Granules
0	+	+	-	+
	[Thompson2010]		[Keleb2004]	[Beer2014]

Table 4 – Effects of Increasing L/S Ratio

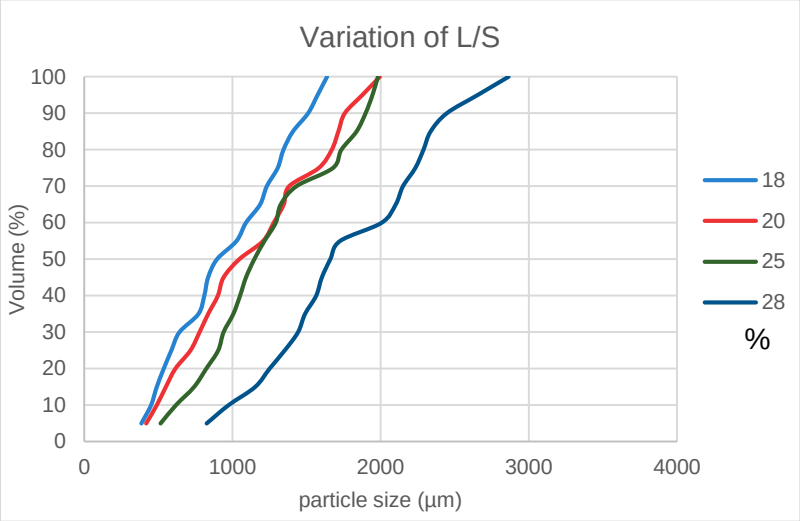

Figure 9 – L/S Ratio's Effect on PSD

Figure 9 illustrates the cumulative particle size curve moving to the right as the liquid-to-solid ratio is increased. This indicates, as would be expected, that the size of granules produced is increasing with the liquid-to-solid ratio. This supports the positive relationships given for $D_{v,50}$ and oversize particles, as well as the negative relationship for fines. We also see little change in the overall slope of this curve, indicating negligible change in the width of the particle size distribution as the L/S ratio is increased.

From [Beer2014] we learn that the density of granules produced at higher L/S can be expected to be higher. From this we can infer that there will be a decrease in the overall dissolution performance of these granules, therefore, while L/S ratio may be used to adjust the size of granules produced by the twin-screw process, its other impacts must also be considered.

Increasing Screw Speed

Particle Size Distribution	$D_{v,50}$	Oversize Particles	Fines	Density of Granules
-	-	-	0	

[Thompson2010]

Table 5 – Effects of Increasing Screw Speed

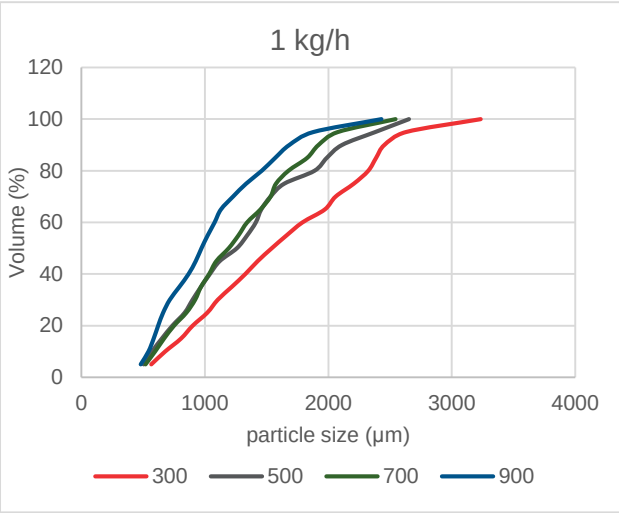

Figure 10 – Screw Speed Effect on PSD

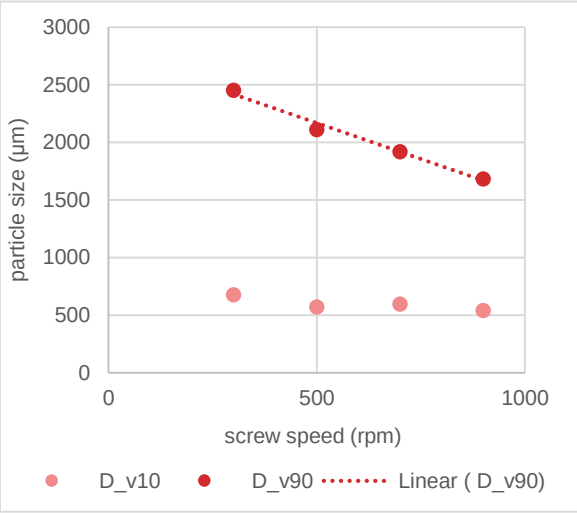

Figure 11 – Correlation of Particle Size with Screw Speed

In varying the screw speed we can also see a significant effect on particle size and distribution. Figure 10 shows the cumulative curve move to the left as the speed increases. This provides the decreases shown above in $D_{v,50}$ and oversize particles, but interestingly almost no change is seen in the starting point (bottom left) of these cumulative distributions, indicating negligible change in the quantity of fines produced. As the slope of the above distributions evidently increases with an increase in screw speed, we can say that the particle size distribution width is decreasing also.

Figure 11 displays the clear correlation between screw speed and other volumetric fractions of the particle size distribution. $D_{v,90}$ decreases linearly with increasing screw speed.

Increasing Number of Kneading Zones

In this section the influence of the number of kneading zones is analysed, using the modified screw configurations shown below. The screw configuration nomenclature denotes the number of mixing zones (e.g., Sc2 indicates 2 kneading zones). Mixing zones with the "F30" suffix indicate a forward mixing angle of 30°.

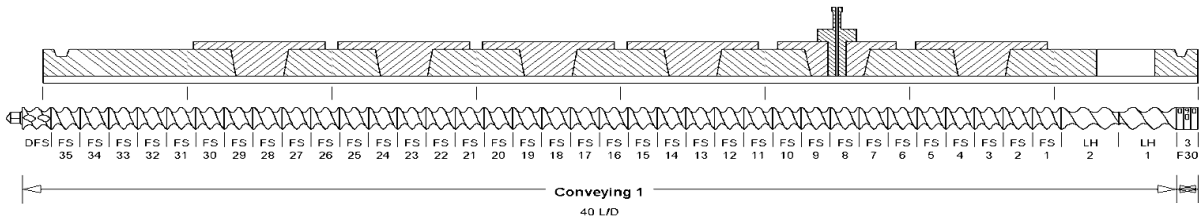

Figure 11 - Sc0

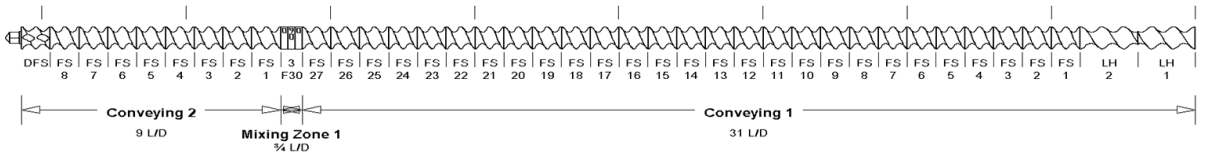

Figure 12 – Sc1F30

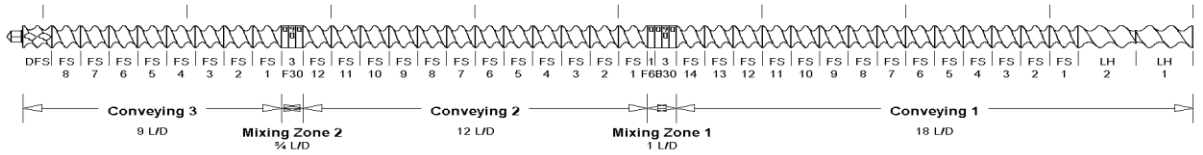

Figure 13 - Sc2F30

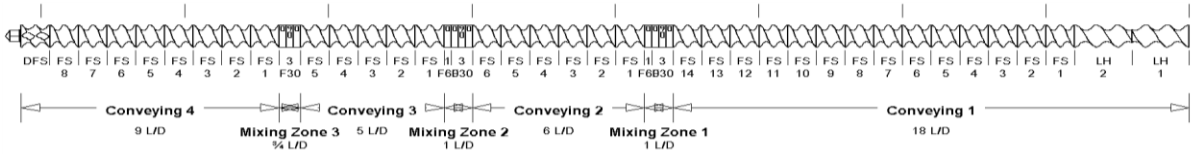

Figure 14 - Sc3F30

Particle Size Distribution	$D_{v,50}$	Oversize Particles	Fines	Density of Granules
	+	+	-	+

Table 6 – Effects of Increasing Number of Kneeding Zones [Djuric2008]

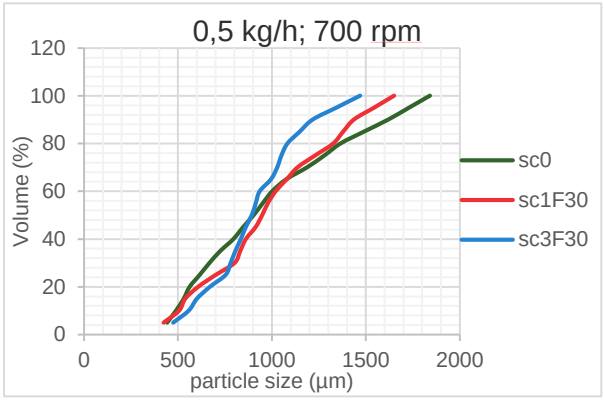

Figure 15 – Kneading Zone's Effect on PSD (low throughput rate)

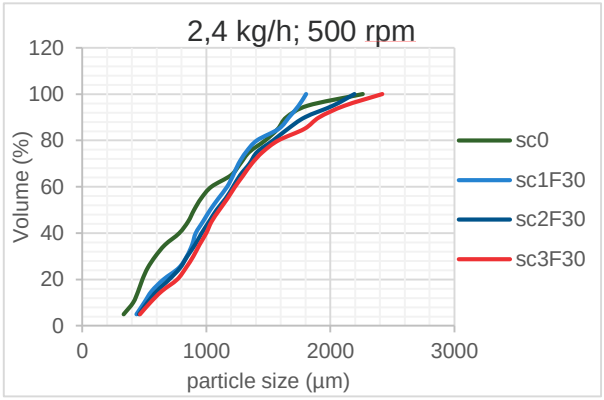

Figure 16 – Kneading Zone's Effect on PSD (high throughput rate)

In Figure 15 and Figure 16 two sets of data for varied screw configurations are presented at relatively high and low throughputs for the granulator.

At the higher throughput rate a trend of overall particle size increase is evident. This can be attributed to the intensity of mixing in a fuller vs more empty screw. With little material present in the screw the mixing element is less effective in creating shear forces in the material, and therefore, has little overall effect on the resulting particle size. With fuller barrels, greater shears are created causing more effective agglomeration of the powders and increasing particle size beyond that produced by the conveying-only screws.

The trends presented in the Table 6 are based only on where a trend can be clearly identified i.e. at higher throughput levels, and therefore, require a minimum throughput to be considered applicable.

Unique Advantages of In-Line Measurement

In conducting the experiments detailed above, several examples emerged demonstrating the unique advantages of inline PAT's measurement. Where the need for testing discreet sample points is removed a much greater understanding of a process fluctuations over time can be achieved. With this added understanding, certain drawbacks to offline measurement methods such as sieve analysis can also be better understood. The graphs and analyses below attempt to summarise these observations.

Figure 17 shows the $D_{v,50}$ of a process over time. Considerable variation in the particle size with respect to time is evident, ranging from ~1000 µm to ~2300 µm. Even after the initial large fluctuation a variability of approximately 500µm can be seen to continue for the length of the measurement. Use of offline sampling-based measurement techniques in this case may lead to incorrect conclusions being drawn about the product, as the time point at which the sample is drawn will significantly affect results – particularly if drawn during the periods highlighted in green.

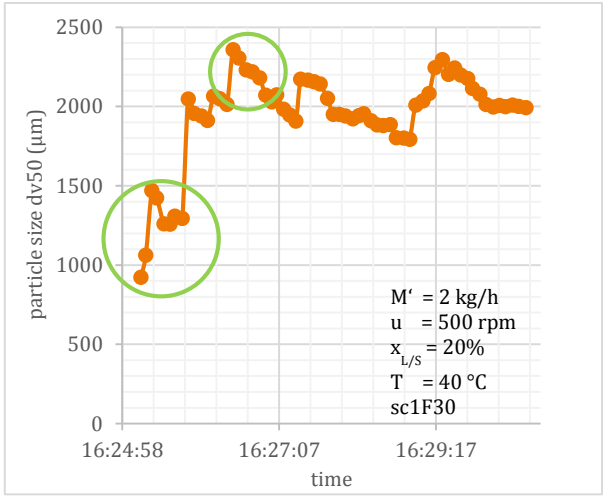

Figure 17 – Example of Output Material Variation

A common strategy to compensate for the above constraint is to take multiple offline samples from the process as a means of determining both the average particle size and process variability. While effective, this does significantly increase the testing overhead.

In Figure 18 we see an example of a process in an unstable state. During this experiment too much water was dosed into the process in the start-up phase, causing over-wetting of the material, leading to a dramatic increase in particle size. This condition was resolved after approximately 7 minutes. Without in-line measurement, however, it is not possible to determine in real time whether the process is in a stable state or not. Further, making any precise measurements on the duration of instabilities during start-up is not possible without in-line measurements.

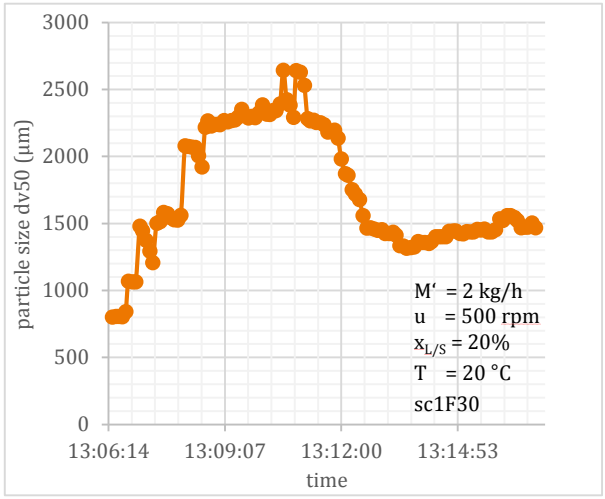

Figure 18 – Example of an Extended Unstable Start-up Condition

In this case in-line measurement provides, firstly, a practical means of process control, secondly, identifies unstable process states, allowing for material diversion and /or corrective measures to be taken, and thirdly, supports the development of optimal start-up procedures by providing accurate characterization of initial process instabilities and their durations.

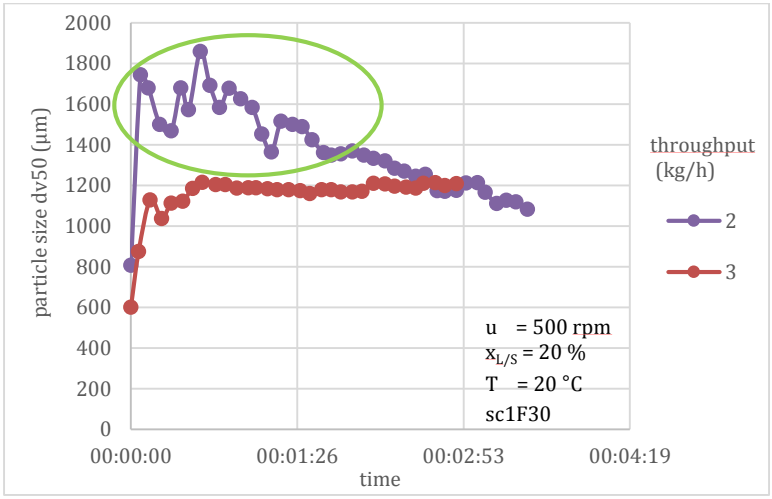

Figure 19 – Comparison of Stable and Unstable Processing Conditions

Figure 19 above gives another example of a process condition from which offline data could potentially be misinterpreted. While exploring the effects of throughput on particle size, the two experiments in the graph were performed. While the data from the 3 kg/h experiment essentially matches the profile of similar experimental runs, the $D_{v,50}$ of the 2 kg/h experiment appears to remain unstable for the full duration, potentially due to a high level of moisture present in the barrel from the previous experiment.

In this case an offline measurement sample taken at 2 or 3 minutes (based on the settling time of other similar runs) would indicate an increased particle size resulting from a decreased throughput. This would be contrary to the anticipated results. However, as the data time component is available to us, we can easily identify the instability in the process, quickly rejecting an incorrect result, which would be far more time-consuming to test and invalidate using offline techniques – i.e. repeating the process for a longer duration with multiple sample measurements to clearly identify and characterise the steady-state condition.

Conclusions

Of the parameters tested in the work published here, the following two were found to be most critical to the twin-screw granulation process:

- Liquid-to-solid ratio
- Filling level of the screws (influenced by screw speed, throughput, screw configuration)

Regarding the equipment used, the following conclusions were made:

- PAT is a valuable tool to analyse, develop and scale-up continuous processes.
- In-line measurement has advantages compared to at-line measurement, particularly relevant to process development. This provides significant insight into process fluctuations and stability which cannot be easily characterised using sampling techniques. Key advantages include:
    - Convenient mechanism for identification of critical process parameters
    - Efficient troubleshooting
    - Defining smart start-up procedures
    - Improved process control
    - Avoiding misinterpretation of data due to time-based sampling effects
    - Greater process insight
    - Improved profiling of the operational space of a process
    - Faster process development
- Twin-screw granulation, as a continuous process, offers the ability to develop and improve the process as it is running. This allows very rapid iterations of process parameters in real time. Since there is geometric scalability among the Thermo Scientific Pharma extruders, parameter optimization time, labour and materials can be reduced when scaling up a manufacturing process with this equipment.

References

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For more information on Eyecon$_2$ Particle Analyser please contact

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