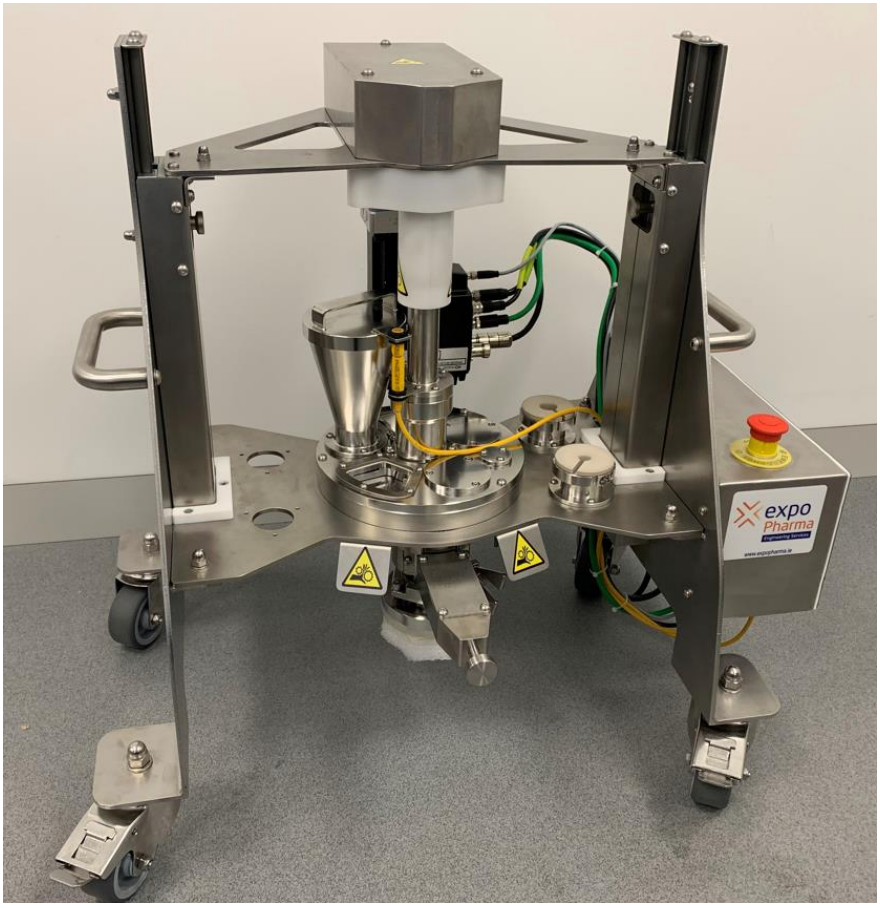
Economic Development of PAT Capability in Pharmaceutical Manufacturing



The solid dose manufacturing simulator

Steve Hammond

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Introduction

Over the last ten years, the path to effective development of PAT has evolved, driven by the advent of continuous manufacturing. The development and deployment of PAT used for pharmaceutical manufacturing has arrived at a point where application development has been miniaturized and streamlined. The availability of fast scanning instruments using fiber optic probes, integrated into processing equipment is now a standard approach for continuous systems, and the same approach can be used for traditional batch manufacturing. The development of devices that can simulate the environment of a fiber optic probe in production equipment, using a small amount of material, in a laboratory environment has enabled the development of working models for the spectrometer using the minimum amount of material, separate from the large-scale manufacturing equipment. This capability has reduced the complexity and cost of developing PAT applications for a production environment.

Industry 4.0 and Continuous Manufacturing

The pharma industry is adopting modern concepts of manufacturing, including real-time integrated measurements and control systems. In addition, the concepts of continuous manufacturing are taking hold. Advances in measurement technology have provided the capability to create an intelligent system capable of real-time adaptive control, even to the level of Artificial Intelligence, all of which encompass the philosophy within Industry 4.0.

Key to the success of this change has been the ability to introduce sensors and computerized systems into manufacturing processes that provide an order of magnitude increase in data density, and in real-time. The ability to turn data quickly into information and knowledge that can be used both to understand how a process behaves, but also impose an immediate course correction on a process step that can affect the overall outcome of manufacture in terms of product attributes.

Both NIR and Raman spectroscopy, particularly in diffuse reflectance mode using fiber optic probes, are the PAT of choice for many of the critical measurements applied to pharmaceutical manufacturing. The ability to analyze moving powder streams, using fast spectrometers is of fundamental importance. These fast instruments, coupled with well-engineered interfaces to control the presentation of the sample to the spectrometer, provide high quality measurements, in real-time to be used to ensure process conformity and product quality in a very dynamic way.

Creating the optimum spectroscopic environment in a plant process stream

Fiber optic probes will rarely function in an optimum way, if simply inserted into moving powder streams. Sampling with fast scanning probe-based instruments requires good control of the interaction of the probe with a moving sample. To create the optimum environment in a process stream requires an interface that is easily inserted into production equipment and will produce tightly controlled characteristics of the powder.

The optimum environment for probe interfaces has been found to be inside the feed-frame of a tablet press, where a spider wheel circulates powder in a very defined state. (See appendix 1 for details of a feedframe.) The speed of the powder movement is well controlled, and thus the density of the powder and the amount of dilation, which are important characteristics in terms of sampling and spectroscopic response. There is a need to be able to create that same environment in any moving powder stream away from a tablet press. Creating such an environment requires good understanding of the way fiber optic probes work in a powder bed. To understand the characteristics of a reflectance probe there is a need to look at the processes taking place at the probe window. Figure 1 shows the diffuse reflectance process used by the probe to obtain a spectrum of a powder. Light is directed into a powder bed. Some of the light interacts with the particles of the powder and is afterwards reflected through a sapphire widow at the front of the probe into the collection optics. For that process to be consistent over time, there must be greater than a minimum thickness of particles for the response from the powder to form good spectra with constant characteristics. This illustrated in figure 1.

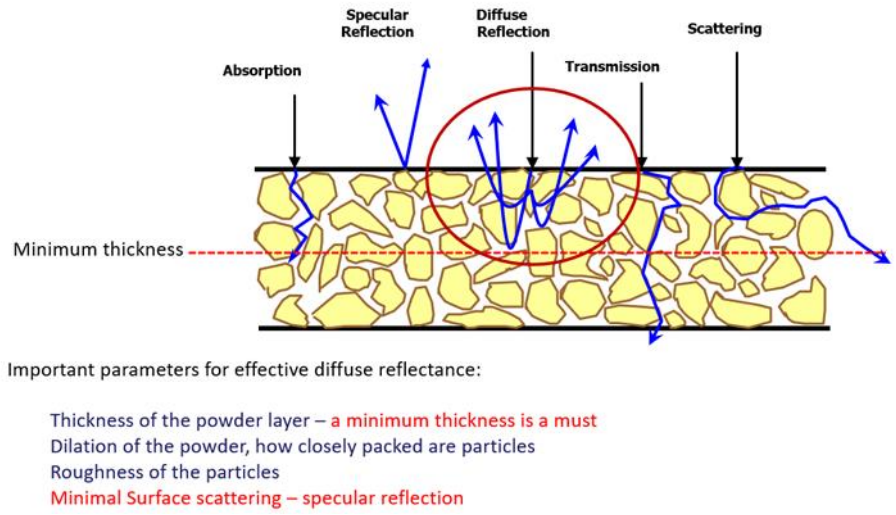


Figure 1. Diffuse reflection process

Figure 2 illustrates the sampling characteristics at the window of the probe. There are many references (Colón et al., 2014) that report the depth of penetration of NIR radiation at the most useful wavelengths around 1660nm to be ~ 0.5mm. Using the illumination area of the probe and density of the powder, we can estimate how much material contributes to a spectrum if the sample is static. That is found to be about 3mg for a typical white powder pharmaceutical blend. Fast scanning spectrometers can collect a single scan in ~20 milli seconds. The instrument software allows for the integration of many scans taken across a time period (integration time) into a single spectrum. If the integration process is taking place while a sample moves in front of the probe window, the contributing mass that is considered in the integrated scans increases with every scan collected. The speed of movement of the powder bed should be matched to the acquisition time for each scan, to ensure fresh sample is at the window for each acquisition.

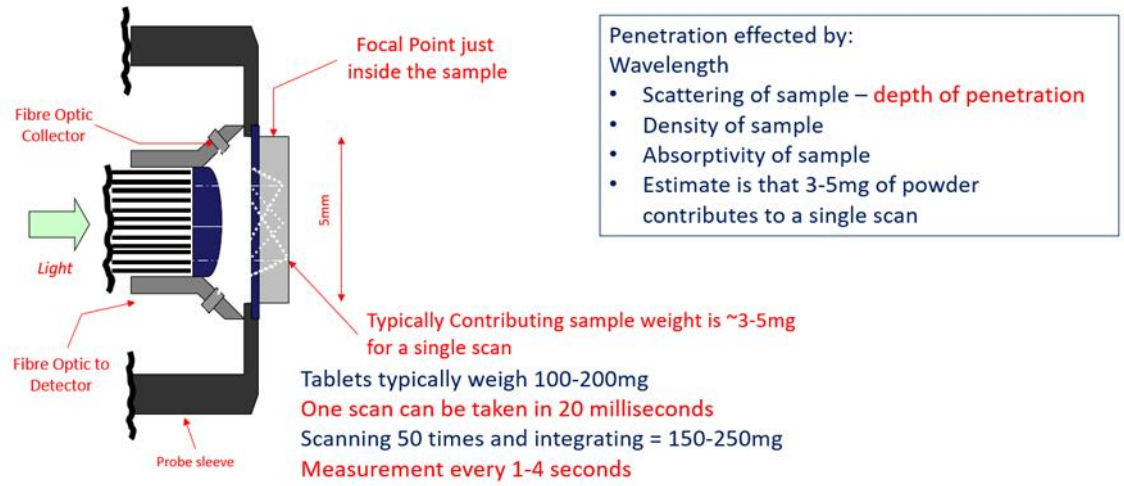


Figure 2. Sampling characteristics of a fiber optic probe

The process of multiple scan integration is illustrated in figure 3. Where 50 scans of a moving powder were integrated to provide a spectrum of 150mg of sample, or a unit dose weight for a tablet weighing 150mg. This is the sampling process that takes place at the window of a fiberoptic probe inserted into the feed-frame of a tablet press where the powder is moving between the fingers of a spider wheel.

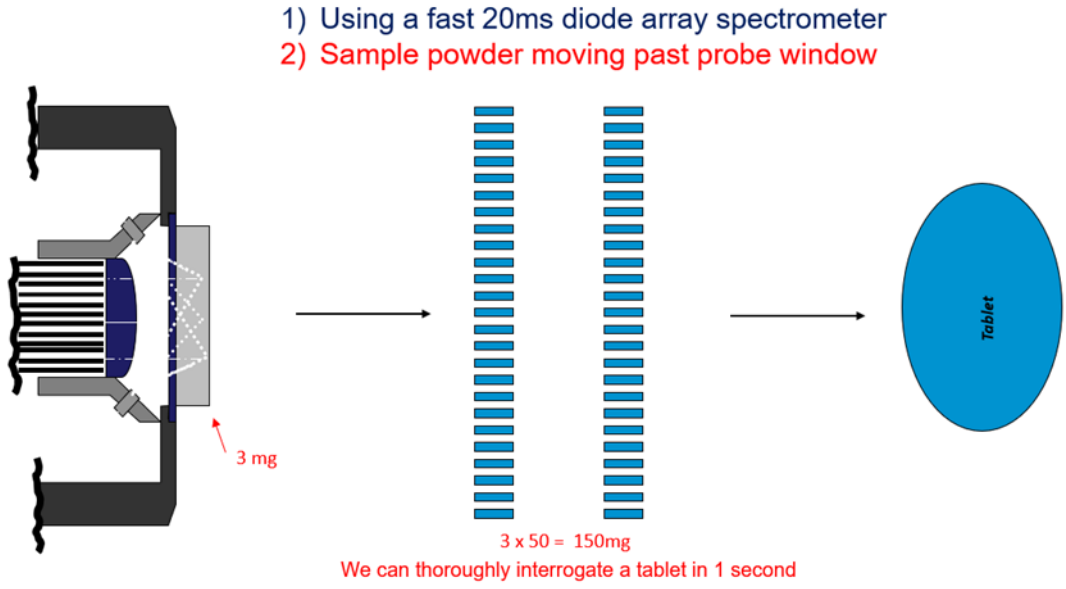


Figure 3. Integration of moving sample scans to achieve unit dose weight sampling.

To provide the same optimum environment of a moving powder, not in a feed-frame, but in any moving sample stream, the spider wheel device in figure 4 has been developed over several years. The spider wheel interface provides the same well controlled sampling of a moving powder for NIR, and Raman probes inserted into a pipe or chute where powder is moving.

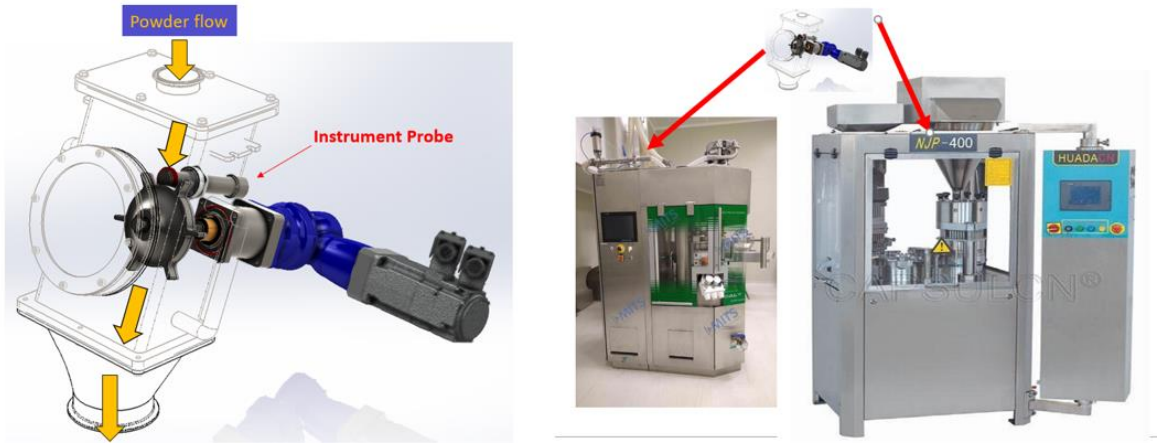


Figure 4. The pharmaceutical application spider wheel. In-let to machines

The spider wheel fingers move the powder over the probe window at a speed that matches the scan time of the spectrometer, ensuring a fresh sample is in front of the probe window every time the spectrometer acquires a new scan. The lined backing of the fingers cleans the window of the probe, ensuring that no blinding of the window occurs.

The use of a feed-frame simulator to streamline application development

There are logistical issues with deploying interfaces that enable probes to function well in moving powder beds. One is getting access to the equipment in a manufacturing environment, and a second the volume of expensive materials that may be needed to develop models. Conventionally, powder mixtures of varying concentrations would be passed through the interfaces, and the data used to develop a model. Such an exercise requires access to manufacturing equipment, often in a GMP environment. It also requires the consumption of a significant amount of expensive raw materials to adequately fill the device while it is sampling a powder stream.

To enable the development of applications using both the spider-wheel and press feed-frame devices, a simulator has been developed following a “science of scale philosophy”. Figure 4.

The simulator can with a minimum amount of material provide the required data to develop PAT applications remotely, outside of a manufacturing environment.

The optimum environment for these instruments and probes can be simulated while thoroughly and safely investigated, using less than 150g of material, and can take place in one piece of equipment, essentially on a bench top. The unit can be considered a simulator of a production environment, fulfilling the role of a pilot plant.

Using the simulator, the optimum probe type and scanning approach can be researched for a specific formulation, using a very small amount of material. This is of value for expensive or hazardous API's. Some examples of the use of the simulator are described briefly below. They have a common theme in that the real production environment is simulated and can be studied safely and with low cost of materials.

Figure 5A shows the simulator with internal mechanical parts, and figure 5B the simulator with a Raman and NIR probe mounted for simultaneous nondestructive data collection on one powder sample with one experiment. Figure 5C the moveable zone rated rig, with dust enclosure.

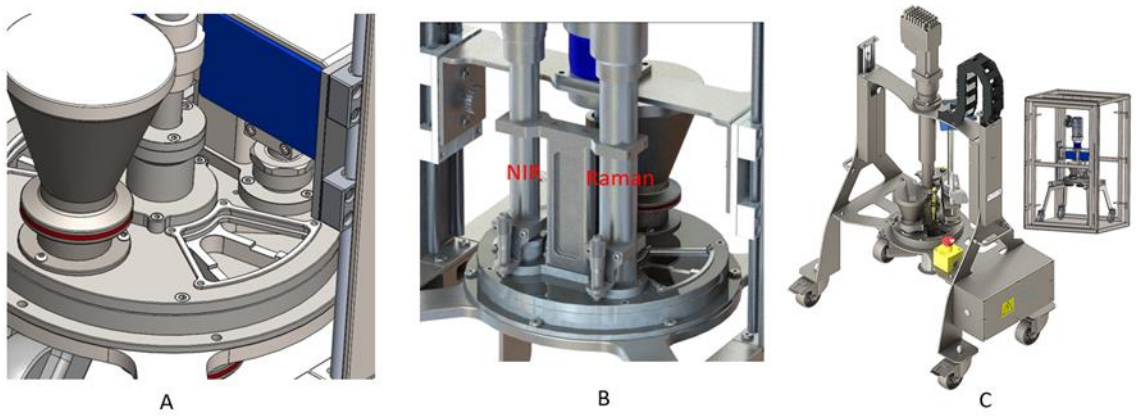


Figure 5A. Simulator internals, 5B. NIR and Raman probes, 5C Rig and enclosure

Figure 6 shows some work that was published by Pfizer, where the optimum interfacing of different Raman probes was investigated using a simulator and a minimum of material.

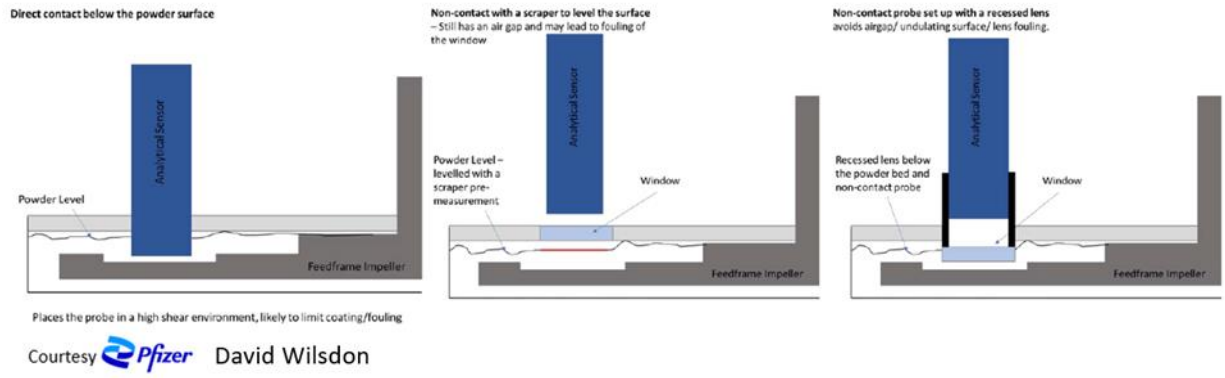


Figure 6. Research into optimum interfacing of a Raman probe

Figure 7 shows the performance of an API calibration developed in the simulator and then run on an instrument inserted into a commercial tablet press feed-frame to predict blend potency and CU.

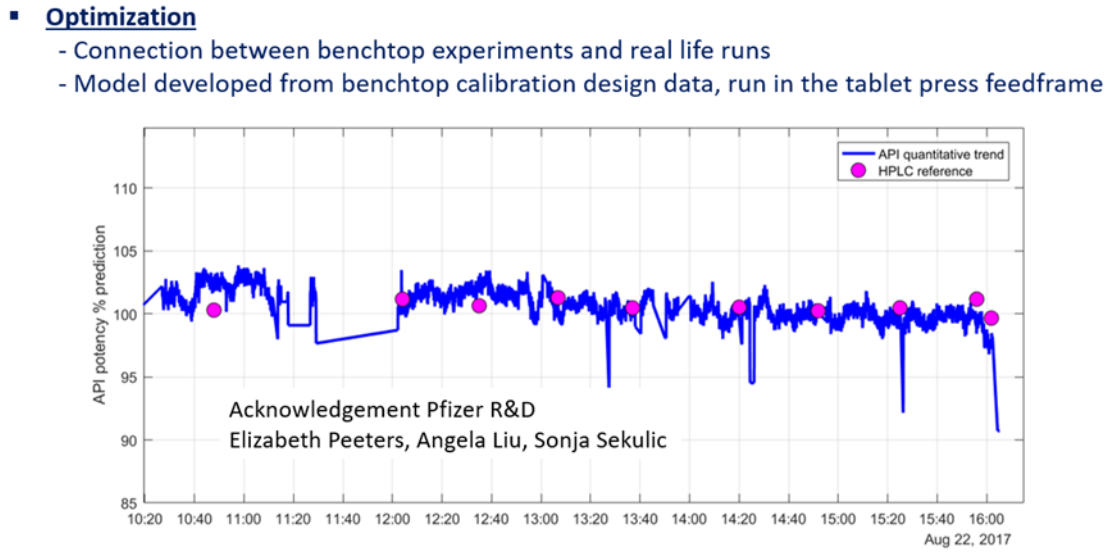


Figure 7. Calibration development in the simulator, run in a commercial press

Figure 8 shows the simulator used to assess the degree of similarity of six identical instruments all the same manufacture, before and after a wavelength calibration algorithm change, which was very successful in making the instruments “match” each other in spectral response.

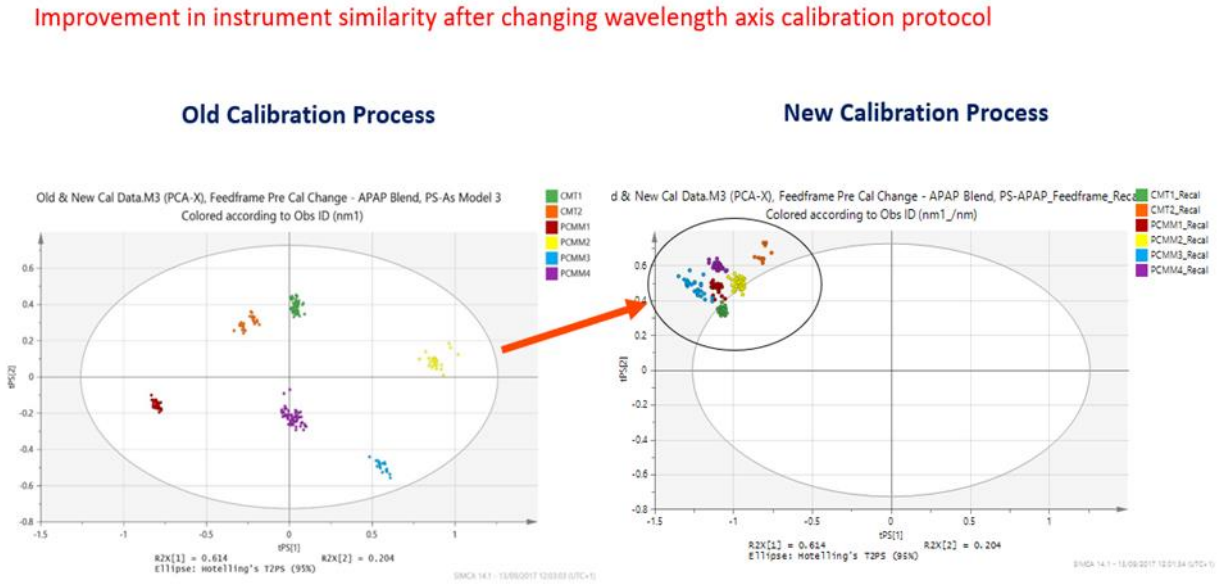


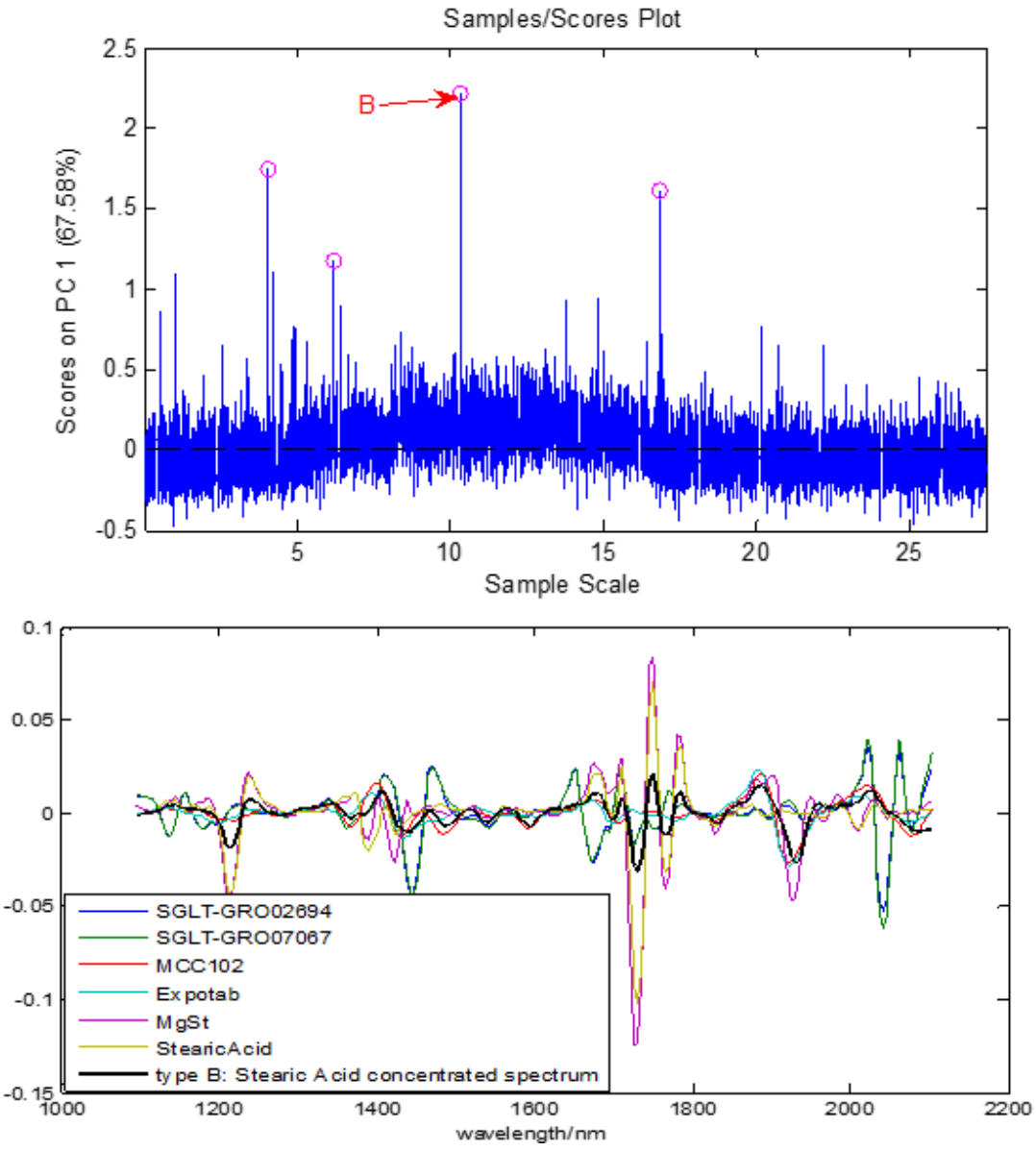
Figure 8. Investigating instrument similarity, with x-axis calibration change

The examples illustrate the versatility and flexibility of the of this material sparing approach to PAT development. For a more detailed example of the use of a feed-frame simulator please see the reference (Alam et al., 2021).

Powder blend Micro-structure information using a single scan acquisition

In general use, multiple scans of from a moving powder are integrated to generate unit dose samples, typically 50-100 scans are integrated together to make a spectrum. However, taking individual single scans of 3mg of a moving powder, at a fast acquisition rate of 10ms and spacing out the acquisitions points at intervals of 100ms can provide good insight into the microstructure of powder mixtures. Figure 9 shows the single scan data for a blend moving through a feedframe. In this figure, the absorbance contributions of the characteristic CH2 absorbances of fatty acids is plotted against time. The absorbance of stearic acid can be seen to be varying significantly in some of sequential single scans resulting from the exposure of each 3mg of powder to the probe. The spikes in the plot identify 3mg powder aliquotes that are enriched with magnesium stearate. The data shows the heterogeneous micro distribution of stearic acid in the powder blend. The effect of the micro sampling at 3mg, is to produce a line

scan across the blend, and pick up the micro distribution of an ingredient. This is very similar to a line scan technique often used in chemical imaging.



Acknowledgement plot provided by Angela Liu of Pfizer

Conclusions

1. The combination of fast scanning spectrometers and fiber optic probes now offer an effective analytical system to provide continuous measurement of powder mixture uniformity.

2. The probes will perform effectively when the sampling of the powder stream is optimized and consistent.

3. Mechanical interfaces that ensure controlled characteristics of the moving powder and reproducible sampling are necessary to provide the optimum environment for the probes.

4. A bench top simulator can be used to investigate optimum probe configurations for a specific product in a moving powder environment.

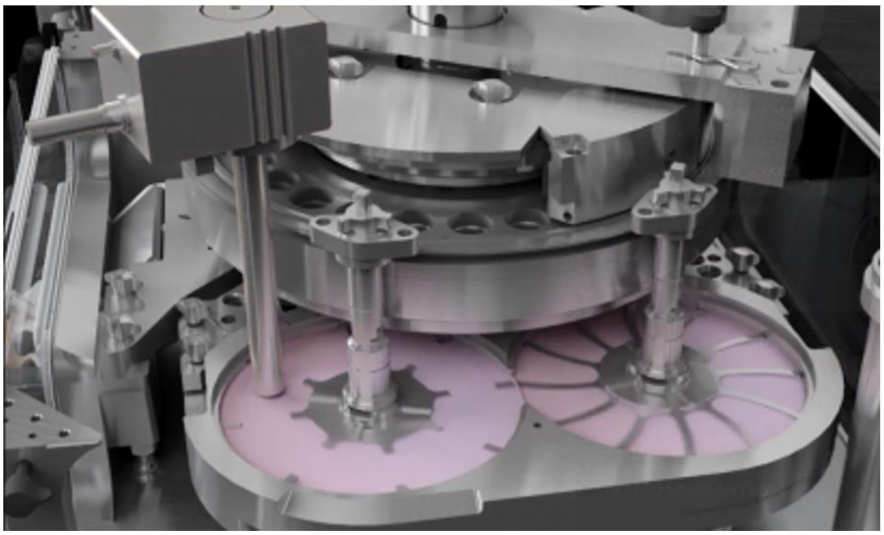
5. The simulator can also be used to develop models for NIR and Raman instruments, using a minimum amount of material.

References

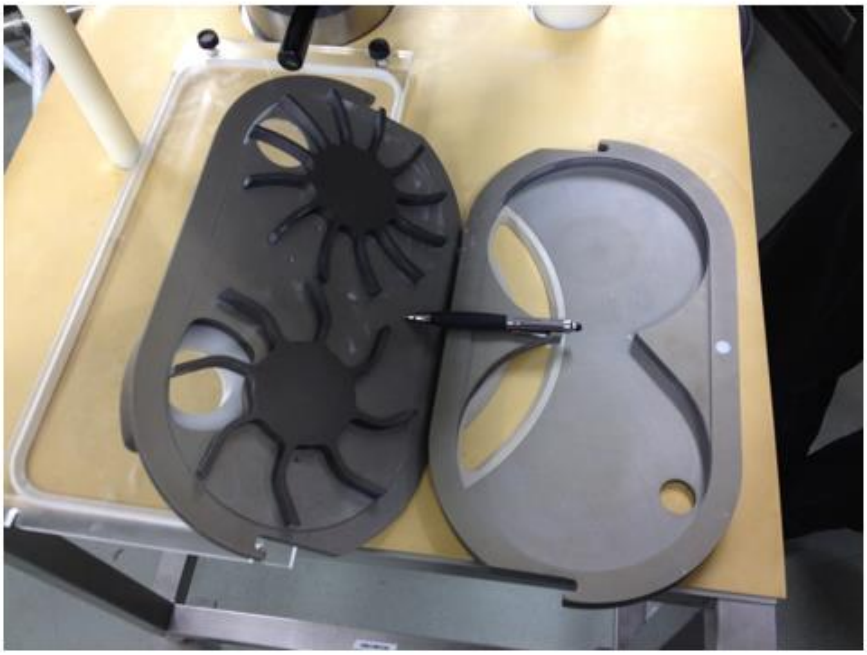
Alam, M.A., Liu, Y.A., Dolph, S., Pawliczek, M., Peeters, E., Palm, A., 2021. Benchtop NIR method development for continuous manufacturing scale to enable efficient PAT application for solid oral dosage form. International Journal of Pharmaceutics 601, 120581.

Colón, Y.M., Florian, M.A., Acevedo, D., Méndez, R., Romañach, R.J., 2014. Near Infrared Method Development for a Continuous Manufacturing Blending Process. Journal of Pharmaceutical Innovation 9(4), 291-301.

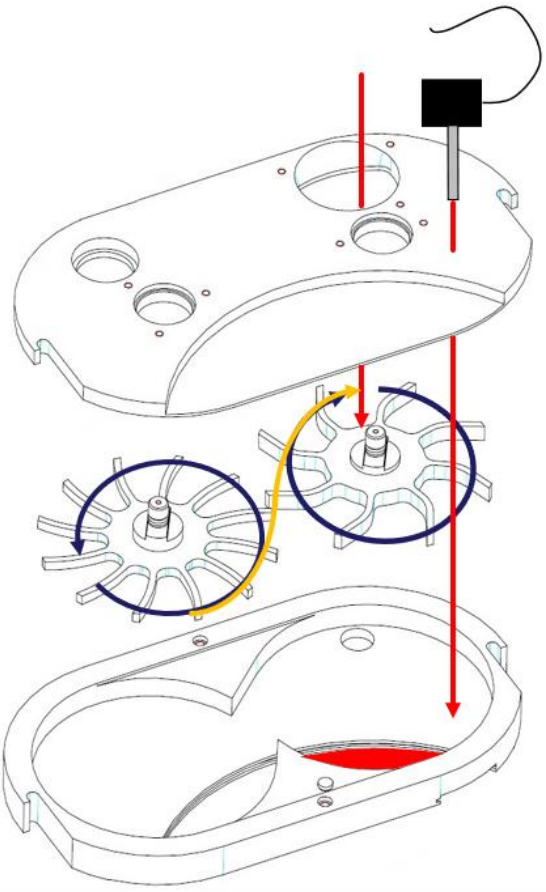
Appendix 1. Tablet press feedframe and fiber optic probes insertion



The insertion of a fiber optic probe into a feedframe



The internal structure of a tablet press feedframe



The direction of powder flow and the position of the probe in the feedframe