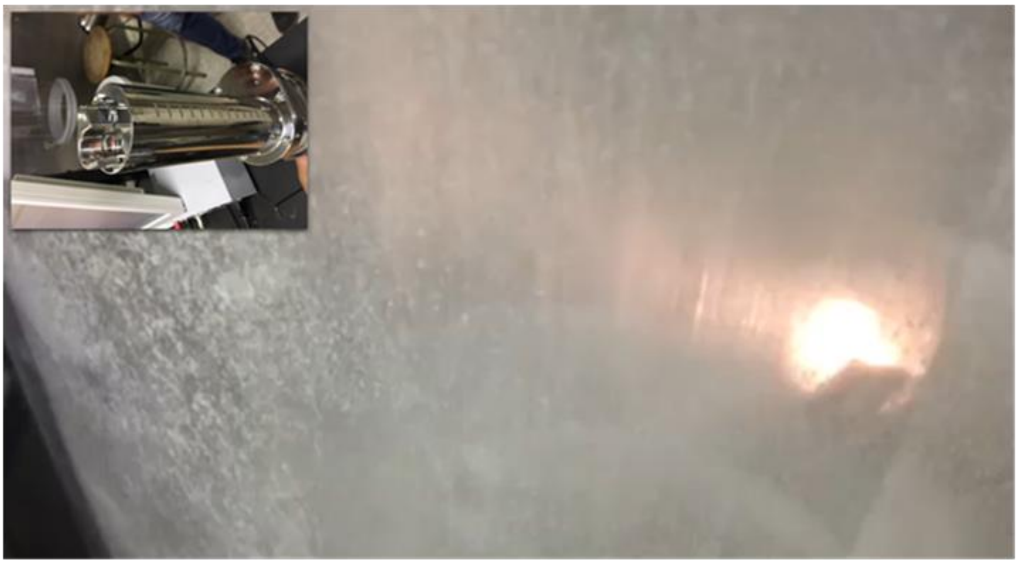
WHITE PAPER

Sampling of dispersed powders for spectroscopic analysis during processing



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1. Introduction

The application of Process Analytical Technology (PAT) in pharmaceutical manufacture has gathered momentum over the last decade. Partly, driven by the advent of continuous manufacturing (CM). In this regard, good signal acquisition is of paramount importance when determining the capability and effectiveness of the PAT. This this is of particular importance when utilizing fiber optic probes for spectral collection. The analytical measurements for solid dosage manufacturing are typically more challenging due to the inhomogeneity associated with the pharmaceutical powder blends.

Different physical and chemical properties of powder such as size, shape, density, compressibility, moisture and API content, can be characterized in continuous mode via spectroscopic techniques using fiber optic probes. Despite the wide applicability of these techniques depends on appropriate design of the probe/sample interface for effective analysis. In the case of very dispersed powders, for example the particulate cloud seen in the picture above at the end of a milling step, or in a fluidized bed during granulation or drying operations, mechanical sampling becomes essential for diffuse reflectance probes to function correctly.

Figure 1 shows the diffuse reflectance process used by the probe to obtain a spectrum of a powder.

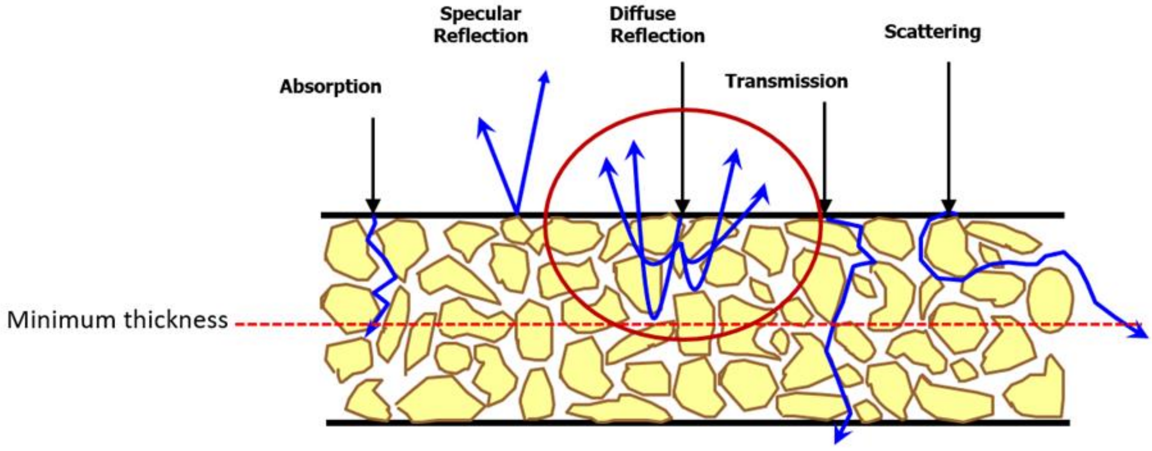


Figure 1. Diffuse reflection and the minimum thickness requirement.

As seen, light is directed into a powder bed. Some of the light interacts with the particles of the powder and is subsequently reflected through a sapphire window at the front of the probe into the collection optics. For that process to be constant over time, there must be a minimum thickness of particles and a consistent density of the powder bed, for the response from the powder to provide good spectra with repeatable characteristics that enables characterization of changes in material properties.

2. A solution for dispersed powder sampling: the TASO Technology

TASO, designed by Expo Pharma Engineering Services is a product for sampling powder in highly dispersed, challenging environments such as those listed above and displayed in the picture at the beginning of this paper.

TASO is a “sleeve holder” designed to integrate most NIR, UV, Raman, or particle size analyzer probes into processing equipment. The insertion and mounting of the holder and thus the probe is adjustable in terms of depth of penetration and angle of insertion into process stream by means of a standard 2” Hygiene Tri Clamp equipment port. Different probe diameters can be accommodated in one holder with the use of liners inside the holder barrel. The device is designed to collect particles from a dispersed product stream into a consistent bed with greater than the minimum required thickness and density to ensure good diffuse reflectance measurements can be made. The Spectrum TASO is designed to periodically invert the spoon, ejecting the captured sample, then resetting to collect refresh samples. Additionally, this actuation wipes the face of the PAT probe clearing away any residual powder caught on the probe face. The TASO is shown in Figure 2.

Figure 2: Photo of TASO designed by Expo Pharma Engineering Services.

The device has been tested and implemented in a fluidized bed drier where the spoon collects granules in a high velocity cloud thus facilitating good data acquisition from the granules using a NIR probe inserted into the TASO holder, which in turn is inserted into the side of the vessel. For this particular installation, the collected data was used to analyze the particle size and moisture content of the powder, which are pervasive properties of the powder. Some TASO models have internal heating which helps in keeping the sapphire window of the probe clean.

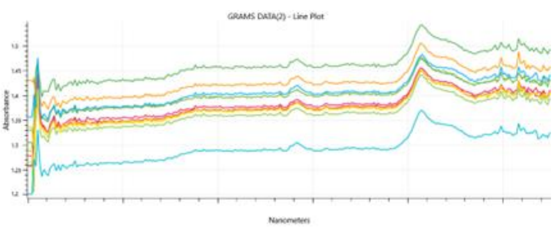
3. Example application

The TASO was mounted into a clear Perspex tube that was installed at the outlet of a mill used to mill dried granules. See Figure 3. The mill was processing granules exiting a continuous twin screw wet granulation and drying process. The TASO was interfaced with a Sentronics instrument and fiber optic probe.

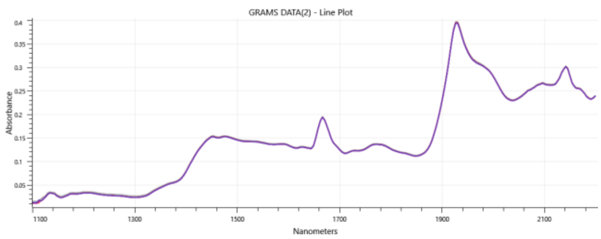
The spoon was set to an automated cycle to collect granules in the spoon for 12 seconds, trigger the spectrometer to scan the granules which takes about 1 second and then flip the spoon up-side-down, emptying the spoon. The spoon then returned to its original position and repeated the cycle.

Figure 3: The TASO mounted into the outlet of a granule mill.

Figure 4 shows data collected by the fiber optic probe with and without the TASO collection spoon, which have been analyzed using the Vektor Direktor package for data analytics.



A: When there is no control of powder bed



B: TASO spoon provides a suitable powder bed
Six spectra overlayed

Figure 4: Representation of collected spectra using TASO.

The plot in Figure 4A is simply raw data, illustrating that the fiber optic probe without the TASO, will collect very poor spectra, composed partially of air, not the powder. The spectra in Fig 4A are badly formed and extremely inconsistent. When the TASO spoon collects the powder into a bed of optimum thickness and density for this type of reflectance probe, the spectra in Fig 4B are the result, with well-formed absorbance characteristics and excellent consistency.

To understand the improvement in the response from the probe when in the TASO holder, the spectrometer was set to a fast scan speed to continuously record spectra as the spoon was filling with powder. Figure 5 shows each spectrum collected during filling of the spoon as a PCA score value plotted against time.

The plot indicates two sections. The first section during the filling of the spoon with the powder and the second which shows the stabilization of the signal from the probe once the spoon is filled. The plot becomes plateau once the spoon is filled, and all the points afterward after filling are the spectra recorded once the minimum required thickness of powder has been achieved and the diffuse reflection process at the probe window is optimum.

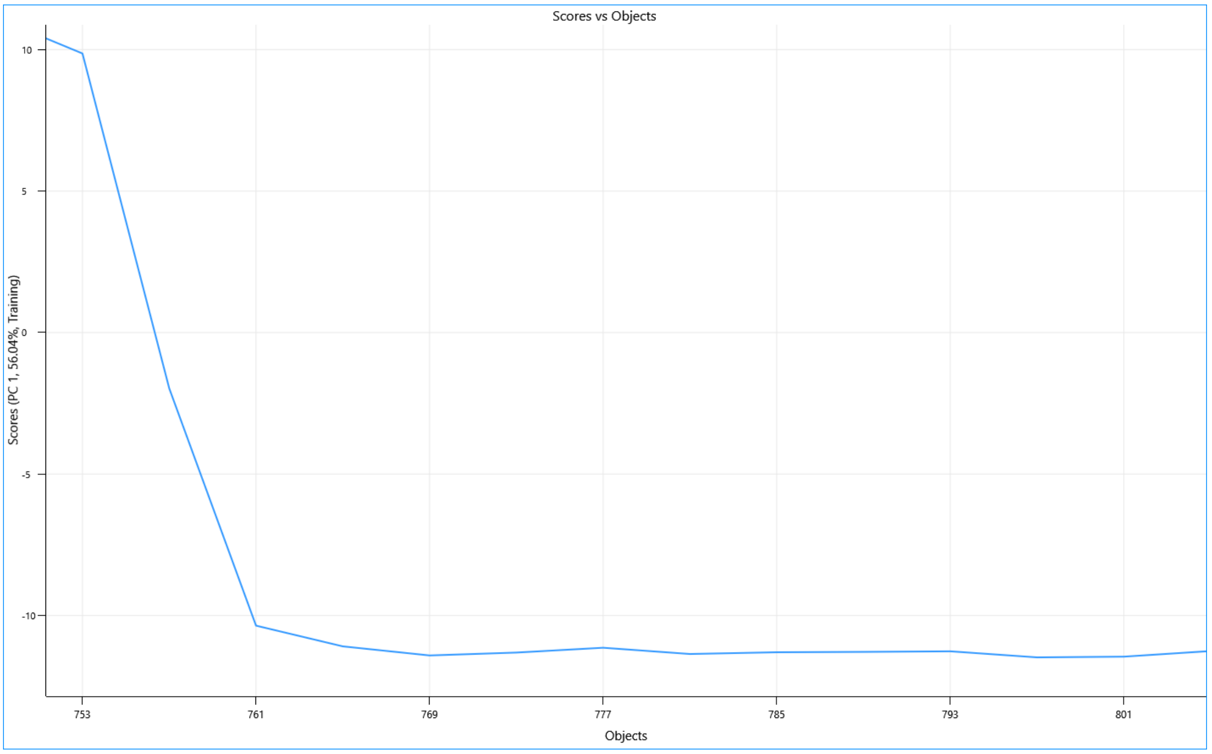


Figure 5: The spectral response from the probe as the spoon is filled.

4. Response to different particle size material.

To assess the performance of the TASO/NIR combination to measure relative particle size, the conditions for the granulation drying and milling were changed. Three different sample types with different particle size were produced in the process including unmilled, milled and finely milled material all of which were passed through the TASO spoon and probe combination.

The data are shown in Figure 6. It is indicated that TASO/probe combination can capture the change in the size of particles, as the baseline offset is shifting down-wards when the particle size is reduced for the mill outputs, i.e. unmilled, milled and finely milled, respectively. It should be noted that the analysis has been performed without any preprocessing to retain the baseline offset effects of the change in particle size.

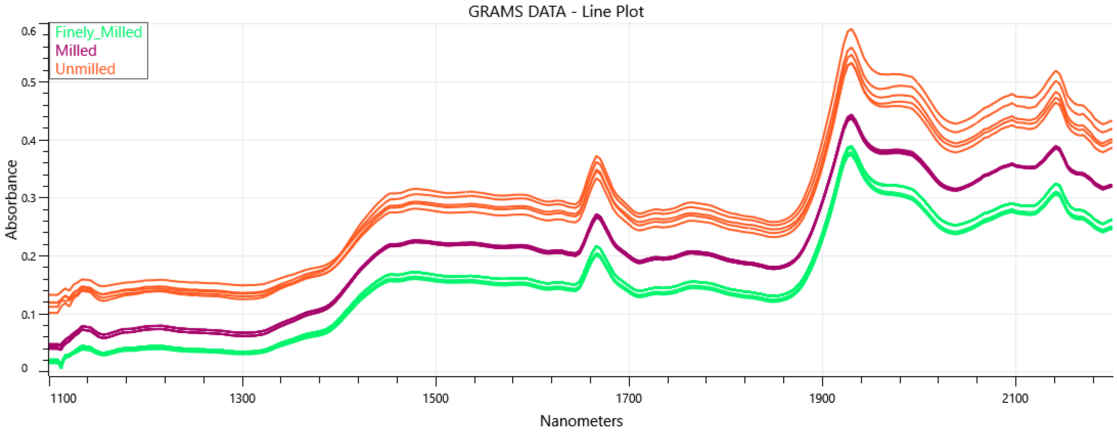


Fig. 6: NIR response for unmilled, milled, and finely milled granules.

5. Sampling considerations for the use of the TASO

The use of the TASO can optimize the performance of diffuse reflectance fiber optic probes inserted into a process producing dispersed powders and ensure high quality spectra are obtained for analysis. The spoon is also a wiper, ensuring window cleaning.

However, it is important for users of the TASO to understand how and for what the spectra obtained can be used, which is related to the sampling that is achieved by the probe.

The TASO was developed to improve spectral collection after the drying and milling steps of a continuous process. The important measurements at that point were water content of the milled granules and the relative particle size of the granules after different milling conditions.

The mass of powder that contributes to a spectrum for this type of reflectance probe is illustrated in Figure 7.

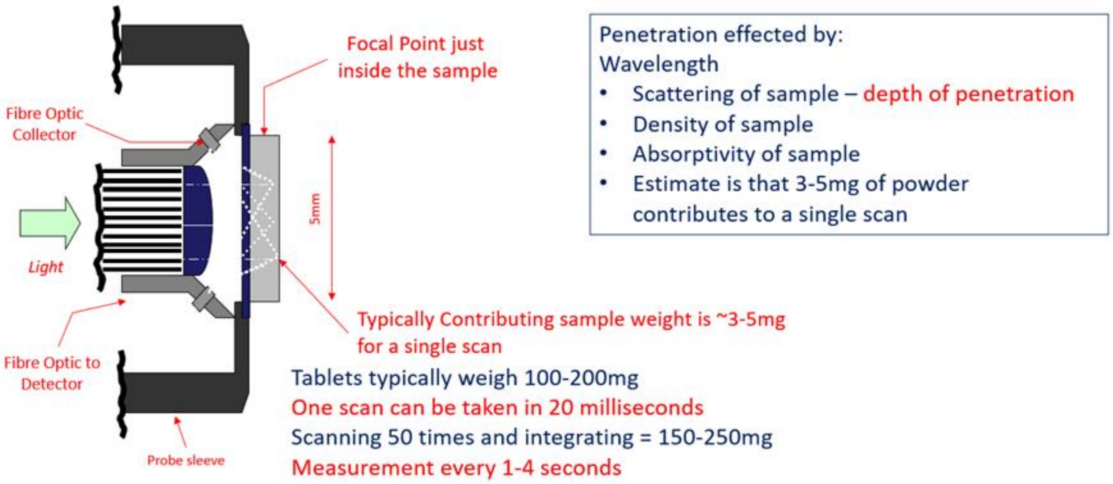


Figure 7: Sampling volume and mass for a diffuse reflectance probe.

Figure 7 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, as it is in the probe TASO combination. For a stationary powder, the contributing mass of sample is found to be about 3-5mg for a typical white powder. Fast scanning spectrometers can collect a single scan in ~20 milli seconds.

Water is pervasive through the granules produced by the drying and milling process. That is the water is uniformly distributed between small (3-5mg) aliquots of powder. Water can be considered a bulk property of a powder. Similarly, the variation in particle size distribution between 3-5mg aliquots of a powder will be small, because particle size is a pervasive property of a powder.

What this means is that the single scans taken of 3-5mg using the probe/TASO combination, will be representative of the powder as a bulk property. However, this in not necessarily so for the individual solid material ingredients within a powder mixture. Figure 8 shows the matrix formed in a powder mixture as a chemical image obtained by NIR Microscopy of a typical pharmaceutical product.

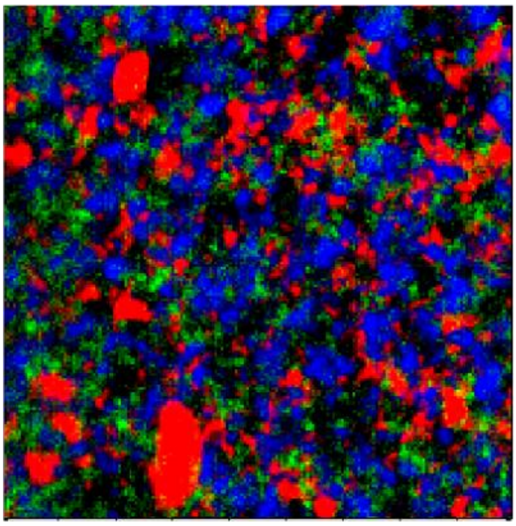


Figure 8: Typical formulation matrix. Red API, Green Lactose, Blue Cellulose.

It can be seen that the different blend ingredients are not homogeneous and tend to form clumps of material in the matrix. In the image about 500mg of material are represented, and so illustrates that, sampling of this formulation will not be representative at the 3-5mg sample size.

The way to gain a representative sample with the TASO, would be to scan 20 spoonful's and integrate the 20 scans into a single spectrum, which then represents about 60mg of sample. The number of repeat scans needed would be formulation specific depending on the API concentration.

To use data collected with a NIR probe/ TASO combination needs a more complex sampling approach for characterization of API in low to medium dose API products. For example, integrating multiple acquisitions, to increase the contributing sample weight that contributes to a spectrum, as the small sample size for individual scans of 3-5mg may not be representative of a unit dose weight. Scanning 20 times and integrating the scans to form a spectrum will provide a contributing weight of between 60 and 100mg, which is much more likely to be representative of a unit dose of a pharmaceutical blend.

References

1. 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.

Acknowledgement

The data analysis referenced in this document was collected and interpreted using the Vektor Direktor platform from KAX Group