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Blending PAT Real-Time Release: Track All Components for Blend Uniformity and Moisture Simultaneously from the Laboratory through Production

Blending is typically a critically-important unit operation in the production of small-molecule pharmaceutical products. Traditional methods of characterizing blending can be difficult and time consuming, leading to delays or even inconsistencies in subsequent process steps.

Proven process analytical technology (PAT) based on near infrared (NIR) spectroscopy is commercially available to determine the process endpoint, quantify the moisture level in the bed, and ensure that all excipients are each homogeneously blended.

These measurements can be done in process and in real-time, and have been successfully filed with the Food and Drug Administration (FDA) in new drug applications (NDA) for use in real-time release of the blend in manufacturing. This work not only ensures that any potential delay following the blending step is minimized, but also eliminates inconsistencies in the blend to ensure batch-to-batch repeatability.

The purpose of this white paper is to describe two of the most common approaches to determining blend uniformity in the pharmaceutical industry, along with practical considerations when implementing PAT for this purpose.

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1. Introduction

In the pharmaceutical industry, blending is a common unit operation used to distribute a consistent mass of active pharmaceutical ingredient (API) powder among other excipient powders present in the final drug product. The dynamics of the blending process can be difficult to predict depending on the species of powders present, and there is a danger of reversibility in a process if it is run for too long. Ensuring a consistent and uniform blend is critically important because the blend ensures consistency of dosage amount and can drive the rate of dissolution in pharmaceutical products.

In addition, monitoring moisture during the blending step can be critically important. Due to changes in weather, ambient conditions such as relative humidity can have a profound effect on an API which is designed to be water soluble. Other excipients in the blend might also suffer adverse effects from excessive moisture exposure during the blend.

Ensuring the uniformity of a blending lubricant might also have a significant effect on the flowability of the resulting powder along with tablet properties such as hardness. If the blend is not performed correctly, any of the subsequent unit operations (such as granulation, tableting, coating, packaging, etc.) will all become an expensive waste of time and resources because there will not be a consistent dosage of API throughout each dose of pharmaceutical product. The product will most-likely not pass quality control dissolution testing and will need to be discarded. As a result, it becomes necessary to ensure uniformity of the blend before doing subsequent production steps.

Offline laboratory techniques, such as high-pressure liquid chromatography (HPLC) and ultraviolet-and-visible-spectrum spectroscopy (UV-Vis), are generally capable of confirming blend uniformity. Unfortunately, there can be delays in getting the results, diminishing manufacturing throughput. Also, offline sampling can sometimes introduce biases in the powder sampled, causing unreliable offline results. In addition, these measurements are destructive, making each sample taken result in some loss of product.

For in-situ measurements, near-infrared (NIR) spectroscopy brings the capability to capture real-time data in a non-destructive manner from a blending process. This data can be used to confidently end the process and send the blended powder to the next processing step with minimal delay.

Not all spectrometers are created equal, as the system is often attached directly to the blender which is typically rotating. In a production environment, vibration is common and various sources of ambient light are present. Some NIR spectrometers are sensitive to these conditions and it can bring noise into the data, attenuating the sensitivity of the system.

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2. Moving Box Standard Deviation

The most common method of determining blend uniformity is also the simplest. The Moving Block Standard Deviation (MBSD) [1] method works on the simple assumption that the NIR spectrum as a whole will vary less from measurement to measurement as the blend becomes more uniform. This is obvious because with less uniformity, each blended component will be seen with a greater or a lesser concentration (compared to a uniform end point) as a function of time. As a result, these fluctuations will be captured by the NIR method and will result in spectra that appear to shift up and down on the absorbance scale over time.

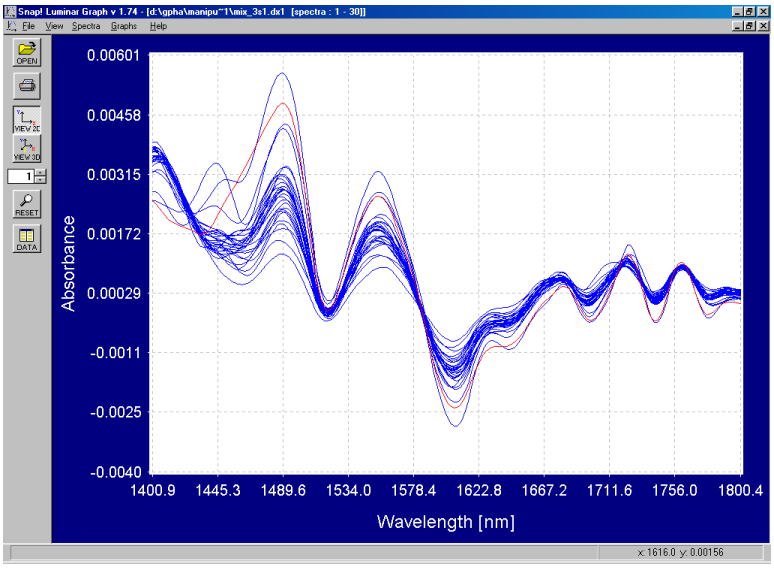

Fig. 1 *- NIR spectra showing more variability with a less-uniform powder blend*

Once the blend has become uniform, the variation in the spectra from measurement to measurement will decrease. This is because the concentration of each component in the blend will be similar throughout the blender over time, therefore the NIR will record a similar spectral fingerprint of the blend from measurement to measurement over time.

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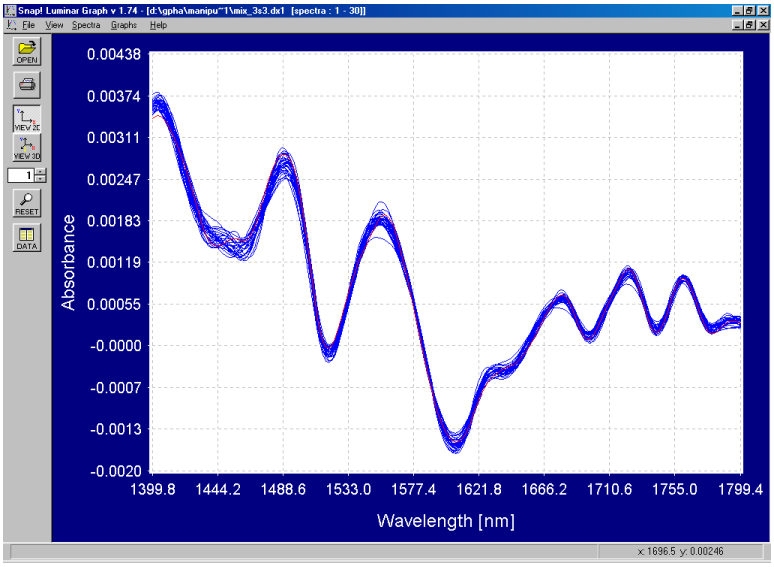

Fig. 2 *- NIR spectra showing less variability from measurement to measurement, indicating greater blend uniformity*

The method to quantify this change is simple. If a spectrum is reported every 5 seconds during the blending, the MBSD uses the current spectrum along with the previous five spectra (for example). This would mean that the standard deviation would be evaluated over a total period of 30 seconds. Next, the standard deviation of absorbance would be calculated at every point in the spectrum for those six total spectra. So, for example, at 1100nm, there would be six different absorbance values. The standard deviation of those six values would be calculated. This would be repeated at every wavenumber in the NIR spectrum, and the total sum of the standard deviations would represent the number of differences seen in the blend.

The number of differences in the blend can be calculated in real-time and used to trend blend uniformity over time. Once understood in the lab and pilot plant, this signal can be sent directly to a programmable logic controller (PLC) or distributed control system (DCS) during a production run to signal the end of the process or make real-time adjustments to the blending process.

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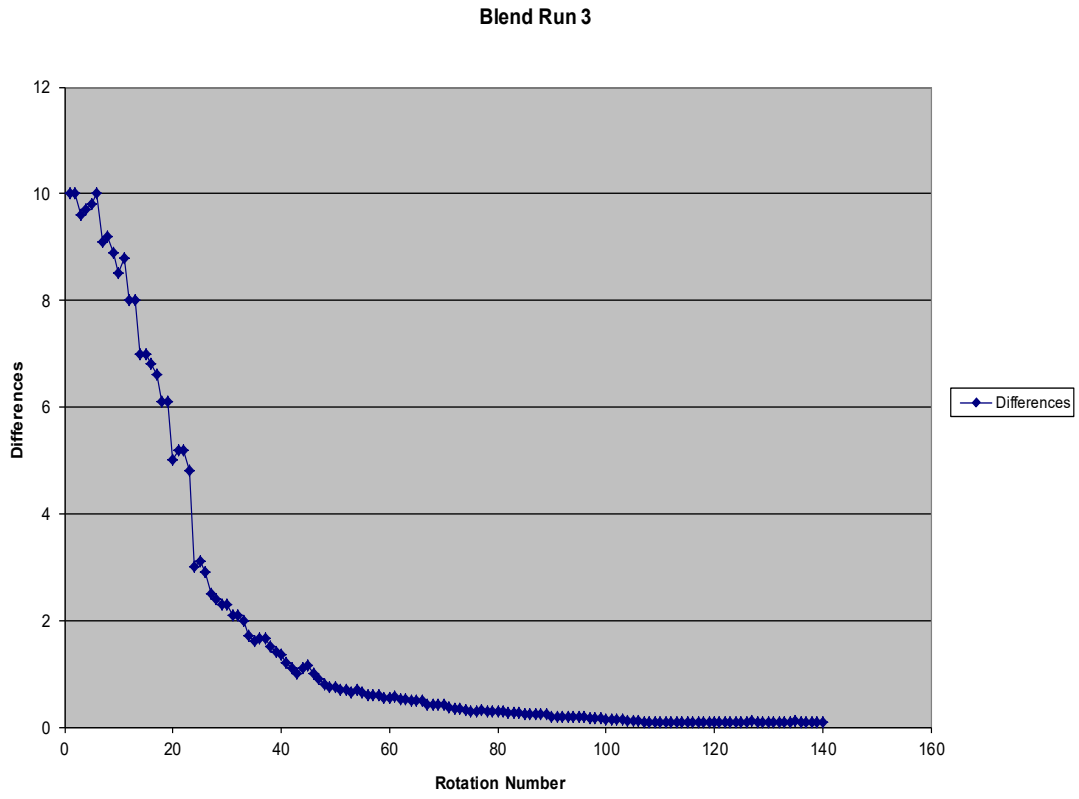

Fig. 3 *- Example MBSD trend showing a decrease over time as blend uniformity increases*

In addition, this information can be (and has been) used with the Food and Drug Administration's (FDA) Process Analytical Technology (PAT) initiative to significantly reduce process cycle time. When the instrument model (verifying that the sensor performs the same from batch to batch) and the process model (verifying that the MBSD signals a uniform blend) are validated for the FDA, the MBSD signal can be used to satisfy the regulatory requirement for blend uniformity verification. This saves hours or even days of delay in performing subsequent unit operations (such as granulation) due to the need to perform the typical offline quality tests.

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3. Chemometrics

Historically, the MBSD approach works sufficiently for most blending applications. However, one example [2] notes that different excipients, lubricants, and the API all might blend at different rates. In addition, excessive moisture from high ambient relative humidity might have an adverse effect on the blend as well.

As a result, a more comprehensive solution may be necessary. While the MBSD might provide a bulk blend end point, chemometrics provides an approach that will allow verification of sufficient blending of each component in the blend along with the moisture content of the blend. Chemometrics is common to multiple types of spectroscopies, and it's also common to multiple types of applications. The approach builds a model to predict a parameter of interest (such as the concentration of API) as a function of the spectrum measured by the sensor.

MBSD can often be preferred to chemometrics because far less effort is needed initially. A threshold of standard deviation has to be established beforehand that's related to a sufficient blend. On the other hand, chemometrics requires known samples to be measured to build the model. If the model will track multiple components, then that might require a large number of "standard" samples to build the model encompassing the full range of concentration expected during the process. MBSD, on the other hand, only really requires one number: the differences threshold under which the blend could be considered uniform.

No in-line spectroscopic tool provides quantitative information in its raw data. However, spectroscopy follows Beer's Law, meaning the absorbance values that it reports have a linear relationship to the concentration of the components measured. As a result, spectra measured by these tools can be correlated to offline techniques which provide quantitative concentration information such as HPLC.

Building a chemometric model with NIR requires measuring the process with the NIR sensor while simultaneously pulling samples to measure with the offline quantitative measurement. It's critical to ensure that a representative sample free of bias is taken. The NIR measurement will only be good as the reference values used to build the chemometric model.

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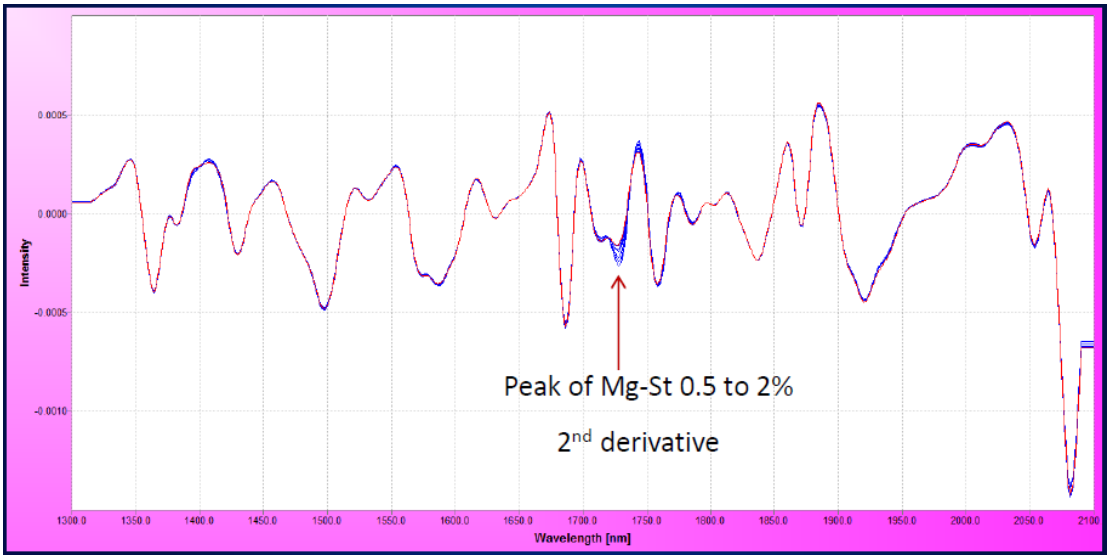

Fig. 4 *- Comparing spectra representing known values of a specific blend component*

A partial least squares (PLS) regression model is calculated between the off line data and the spectra measured by NIR. This data can come from the concentration of every component: excipient, lubricant, and API. In addition, offline moisture data can be incorporated into the PLS model as well.

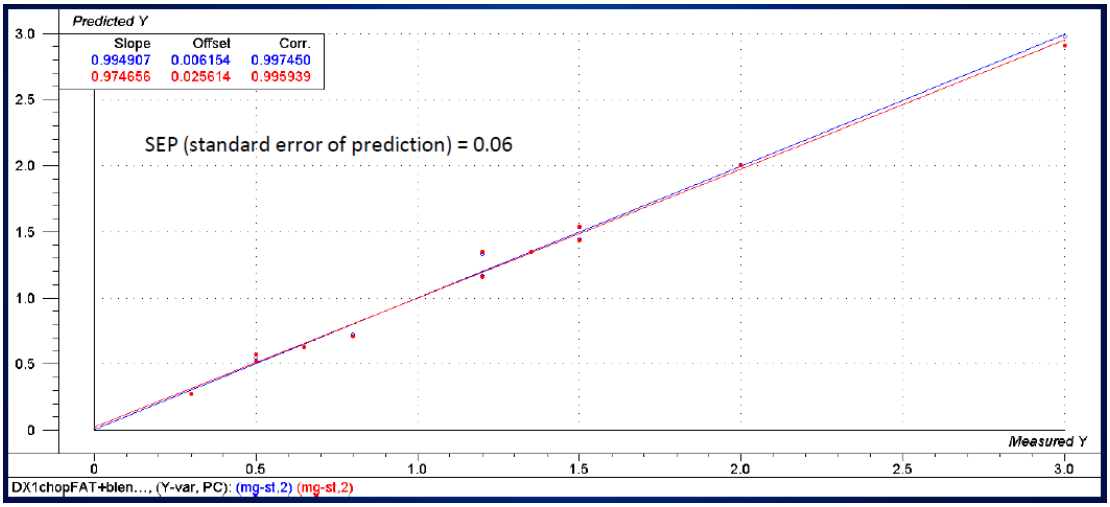

Fig. 5 *- Showing the error between measured and predicted values using the chemometric model. In this case we are comparing the off-line values of Zinc Stearate with the "predicted values" using NIR based on the model.*

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Many different software packages exist to calculate the PLS model. They differ primarily in pricing and ease of use. They range from free (running from a command-line interface) to requiring a significant investment (more intuitive by being tailored for spectroscopic applications).

Once the model is built, all of these parameters can be predicted in real time during the blending process. These predicted values can also be sent to a PLC or DCS system in production to integrate data directly into the process workflow.

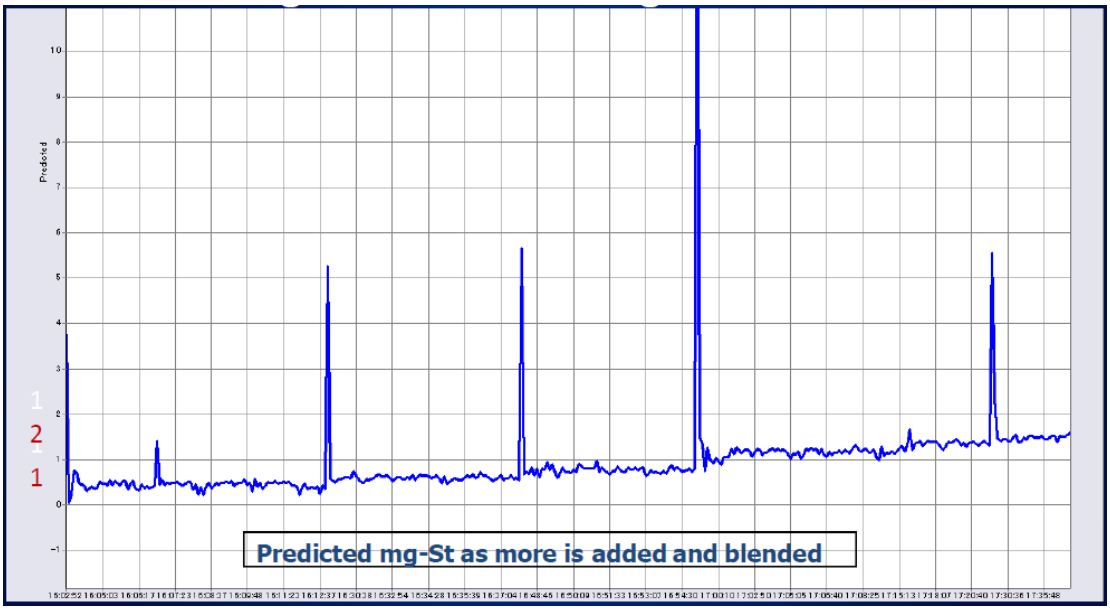

Fig. 6 *- Trends generated in real time from a chemometric model during a blending batch*

This real-time prediction enables corrective action in the event of a disturbance, but more importantly, it enables and has already been used in real-time release of the blended batch when the sensor model is filed with the FDA.

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4. Sensor Selection and Installation

Of course, not all NIR spectrometers are created equally. These measurements must be taken typically from a rotating drum. The sample can only be measured as it falls gravimetrically onto a sight-glass through which the NIR takes the measurement. For the MBSD approach, a lower signal-to-noise ratio in the NIR measurement can be acceptable. For a chemometric approach, on the other hand, it is critical to maximize signal-to-noise in addition to minimizing any unwanted effects from vibration and ambient light which are so common to production environments.

Once the spectrometer is selected, it needs to be mounted to the blender. Certain models can be mounted directly to the blending equipment, whether the spectrometers are a handheld device or not. Spectrometer sizes can vary as well, which can be critical when less space is available. As blender types vary along with their ports and sight-glasses, the vendor will work to provide the proper fittings to mount the system. In most cases the spectrometer vendor cuts a hole in the blender cover and incorporates a sapphire window allowing the NIR spectrometer to "view" the powder per each rotation.

Image 1 *- Handheld NIR system on a rotating drum in the laboratory*

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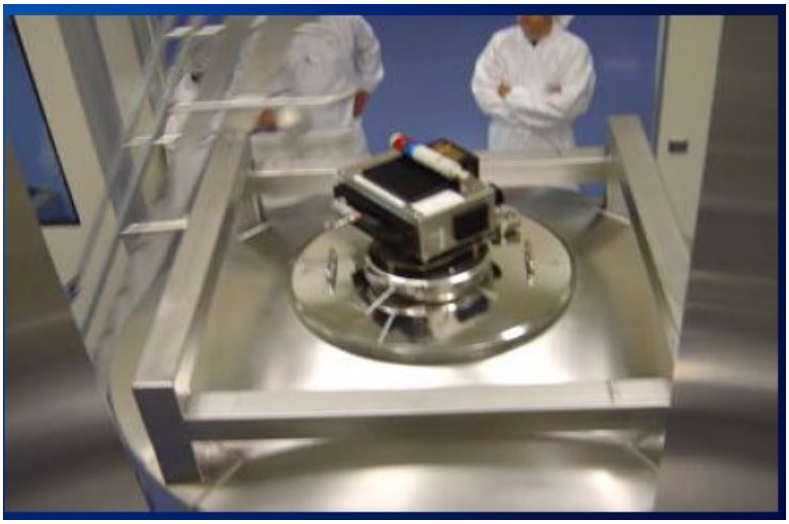

Image 2 *- NIR sensor on a 500-liter blender in a production setting*

Because of the need to measure when powder falls onto the sensor, measurements can only be taken at one point during a blender rotation. If the NIR system measures continuously, most of the data will not be representative of the process. As a result, a prompt is needed for the system to only measure when powder is making contact with the sapphire window that is attached to the sensor. This is done with a gravity trigger or with a proximity switch.

The NIR system settings should maximize the measurement time while the powder is in contact with the sensor. This is done by timing the measurement to begin at a set time after the gravity sensor has been triggered. During that short time, the spectrometer will collect as many spectra as possible to co-add into one spectrum for maximum signal-to-noise.

For stationary blenders stationary [3], a probe-based model can be installed to take readings as paddles push the powder past the probe.

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5. Conclusions

1. NIR technology has two proven routes for determining a uniform blend, and thus can ensure consistency from batch to batch. These approaches can and have been used for real-time release of batches for quality control, saving millions of dollars in delays and plant downtime.
2. While MBSD is easier to set up, chemometrics provides more-detailed information about each component in the blend along with moisture information.
3. The chosen spectrometer will determine which of these approaches is more feasible.
4. Mounting the spectrometer and optimizing measurement signal requires a few easy steps.

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6. Appendices

Appendix A

Acousto-Optic Tunable Filter (AOTF) Technology

Measurement for optimization in real-time – AOTF NIR technology is a precise and sensitive technology that tracks changes to absorbance in the 1100-2300nm range of the electromagnetic spectrum.

Unlike many types of commonly available NIR systems, the AOTF method is solid state. Unlike with Fourier transform, near infrared (FT-NIR) spectroscopy has no moving parts to scan over the NIR wavelength range to characterize absorbance. With no moving parts, the AOTF method enables usage of the MBSD method or a full chemometric model of each component in the blend (along with moisture) to be tracked with no sensitivity to vibration (typical in a production environment) or ambient light. On the other hand, FT-NIR is limited to tracking blending only by the MBSD method due to the lower signal-to-noise ratio. The AOTF method acquires the absorbances of the entire 1200nm range in 0.0625 seconds.

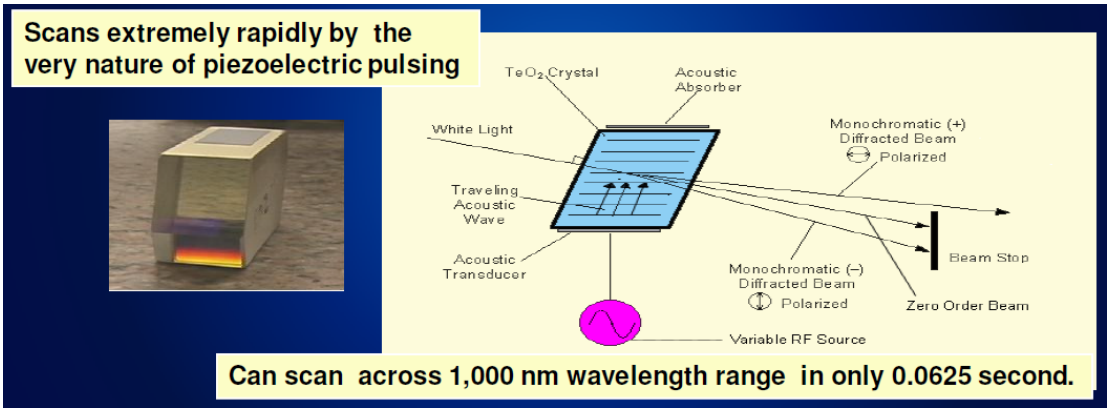

Image 3 - AOTF measurement principle

As a result, the AOTF method captures enough absorbance information, along the entire NIR spectrum at each rotation of the blender, to use the MBSD or chemometric approaches to track blend uniformity. AOTF spectrometers are available in handheld as well as probe-based models. The spectrometer can be directly mounted onto the blender and be run by battery.

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