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Monitoring and Controlling Powder Blending Online at AstraZeneca

An MEMS-based NIR Spectrometer could eliminate the need for thief sampling, potentially reducing the variability of tablet and capsule quality

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Lack of uniform blending is a leading cause of quality variation for tablets and other solid dosage forms. Standards and best practices have been established to ensure blend uniformity, [1-3] but they hinge on post-production testing.

Currently, thief sampling is the accepted technique used to take powder from blenders. However, it is difficult to reproduce exact conditions under which sampling takes place. Often the act of sampling may cause sample inhomogeneity and may lead to result biasing. Thief sampling also is labor intensive for both the operator and the laboratory analyst, and may expose personnel to potentially dangerous compounds that necessitate the operators to be fully gowned in order to grab samples [4].

The development of on-line methods for blend uniformity is a potential solution to satisfy the need for blend sampling, as spelled out in FDA's 2004 Guidance Document on Process Analytical Technologies [5].

AstraZeneca launched a project to evaluate online alternatives to thief sampling for powder blends. We decided to focus on NIR spectroscopy, which can be used to collect high quality reflectance spectra of both the active ingredient and excipients, and is sensitive to chemical as well as physical properties of the powder blend. NIR spectroscopy is non-contact and non-destructive, highly reproducible, rapid and requires no sample preparation.

But on-line blend monitoring places certain demands on NIR instrumentation including wireless communication, battery operation, rapid data collection, appropriate hazard and cleaning rating and software/hardware validation and qualification. It also is important that instruments can be adaptable to lab, pilot and production scale blenders in order to follow the development of a pharmaceutical product. NIR spectroscopy has previously been used for on-line blend monitoring using instruments based on dispersive gratings [6], Fourier transform [7], diode array and acousto-optical tunable filter technologies [8].

MEMS-BASED NIR SPECTROMETER

We decided that a micro electro mechanical systems (MEMS)-based NIR spectrometer could be a potential solution for online blend measurement. MEMS have been used in many industries, are small and light and offer other benefits [9]. They also have been used in pharmaceutical and chemical applications for raw material identification, solvent recovery and dryer control and monitoring [10].

To study the potential for online blending monitoring within its solid dosage form operations, we evaluated the Antaris Target Series Blend Monitor from Thermo Electron

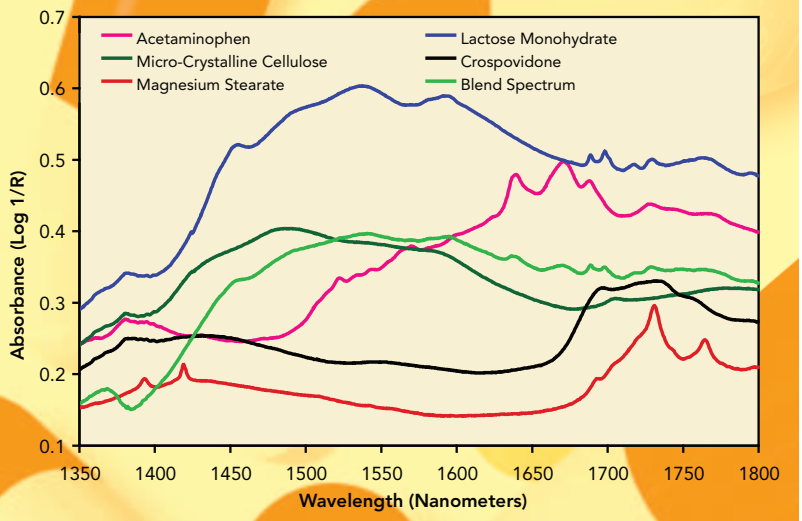

Figure 1. Raw absorbance (log 1/R) spectra of excipients used for model blend.

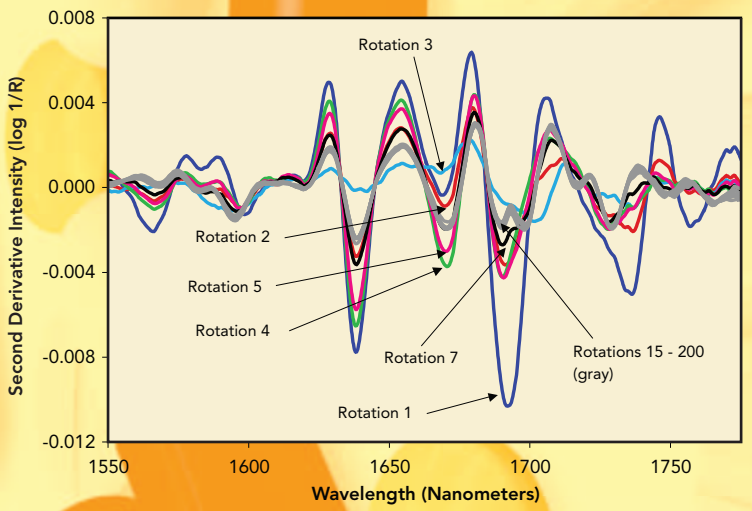

Figure 2. Second derivative spectra of the model blend collected at different times during the blending process.

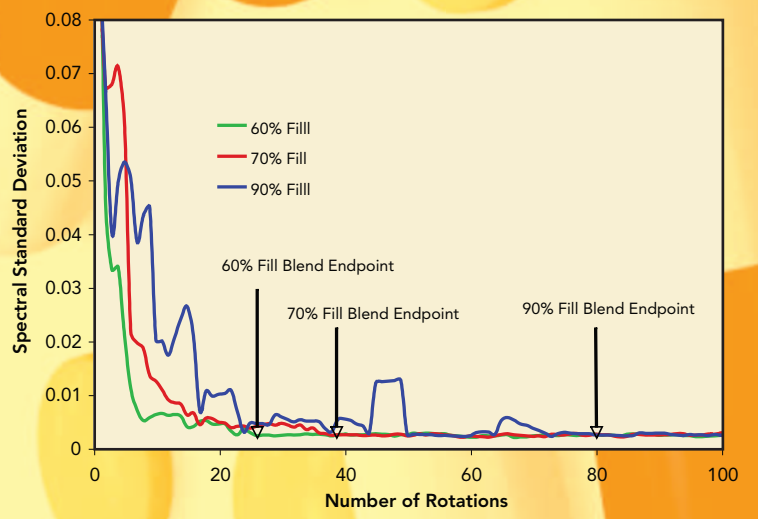

Figure 3. Blend curves of summed spectral deviation plotted vs. the number of rotations for a model blend of acetaminophen and four excipients.

Corporation, an MEMS-based NIR analyzer with a spectral range of 1350–1800 nm. The spectrometer is configured with a semiconductor-based NIR tunable laser source, a high-resolution (4 or 8 cm^{-1}) Fabry-Perot tunable filter for wavelength selection and a single element InGaAs photodiode detector.

The spectrometer "bench" is contained under dry nitrogen within a hermetically sealed compartment. Each spectrum produced from the spectrometer is referenced to an internal standard ensuring optimal wavelength and absorbance reproducibility. The unit is battery-powered and uses a MEMS-based accelerometer board to determine blender position. This instrument is capable of scan speeds of approximately 10 scans per second. The spectrometer has no moving parts and scan performance is insensitive to both blender position and vibration. The spectrometer collects NIR spectra through a sapphire window that can be built into a modified blender lid or directly into the blender vessel. Data are collected when the material in the blender is against the window at the bottom part of the blender's rotation. A spot size of approximately 40mm was used that corresponds to a 600mg dosage form.

RESULTS

We evaluated the spectrometer in a lab-scale Bohle bin blender. The instrument was initially tested using a model formulation of acetaminophen (APAP), micro-crystalline cellulose, spray dried lactose monohydrate, crospovidone and magnesium stearate. The static MEMS collected absorbance spectra of the active (acetaminophen), excipients and a blended sample are shown in Figure 1. The blend spectrum is a composite of the active and excipient spectra.

The model active and excipients were then loaded into a 20-L bin blender with modified lid and the Target blend analyzer was attached to the blender. Data collection was configured so that five scans of the powder blend were collected and averaged during each blender revolution providing a single spectrum for each rotation. Data collection was initiated by the MEMS accelerometer board and programmed to begin when the blender was at approximately a 160° rotation. The spectral data collection was completed in approximately 500 ms. Example spectra (mathematically pretreated via calculation of the second derivative spectrum) collected during the blend have been plotted in Figure 2. Calculation of the second derivative spectrum has the effect of minimizing spectral baseline

differences while enhancing subtle spectral features. A large degree of spectral variation is noticed early on in the blending process and then is reduced greatly after rotation 15.

Since NIR spectra indicate the chemical properties of the powder in the blending vessel, it can be argued that, as variation in the collected spectra is reduced, the components in the blender become more uniform. Thus, when the spectral variation reaches a minimum, the blend endpoint has been reached. There are many potential mathematical algorithms available for the determination of the blend endpoint [11]. One such method is to calculate a moving block standard deviation of the spectra [12]. This is done by first selecting a spectral region of interest. This can be a spectral region where only the active or component of interest has an absorption peak, or a region that is inclusive of all components. Next, a "block" size of rotations to group together is selected (in this case, seven). Following these selections, the variance and standard deviation at each wavelength and for each data block can be calculated. The standard deviations are then summed for each block across all wavelengths providing a single sum total standard deviation for each block. The summed standard deviation can then be plotted versus the number of rotations, thus converting the spectral data into easy to interpret blending plots as shown in Figure 3.

Figure 3 illustrates the results from blending the selected model blend using a 20-liter bin blender and varying the amount of material to produce a 60%, 70% and 90% filled vessel. The importance of blend endpoint determination via NIR is evident when seeing the result of the bin that was 90% filled required approximately three times the number of rotations as the 60% filled bin to reach the same level of homogeneity. Another factor that can influence blend time is the incorporation of new excipient lots that can introduce variability in constituent properties such as bulk density, moisture content and surface area. This plot shows the importance of spectral-based endpoint determination rather than time-based process control.

Other parameters that have been studied with regard to blend endpoint determination and control are active concentration, blender size, blender speed and active/excipient loading methods. The effect of scale-up from pilot scale to manufacturing also will be followed using spectral endpoint determination methods.

We also plan to research algorithms for the determination of blend endpoint. Finally, after assuring the uniformity of the blend, the long-term goal will be to follow the blended material throughout the process, confirming uniformity of the blend at key processing steps including just prior to tablet compression. After compression, the uncoated tablets could be analyzed for content uniformity, thus confirming product quality and potentially eliminating the need for further laboratory blend or tablet uniformity testing.

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