ack of uniform blending is a leading cause of quality varia-
tion 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 ap-
plications 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

Monitoring and Controlling Powder
Blending Online at AstraZeneca

By Peter J. Brush, Ph.D., and Albert W. Alexander, Ph.D., Senior Scientists, AstraZeneca Pharmaceuticals
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
determination methods. Manufacturing also will be followed using spectral endpoint loading methods. The effect of scale-up from pilot scale to concentration, blender size, blender speed and active/excipient to blend endpoint determination and control are active than time-based process control.

The importance of spectral-based endpoint determination rather moisture content and surface area. This plot shows the variability in constituent properties such as bulk density, is the incorporation of new excipient lots that can introduce homogeneity. Another factor that can influence blend time of rotations as the 60% filled bin to reach the same level of 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.

References