Application Note: 51115

The On-Line Monitoring of Powder Blending in a Bin Blender

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Key Words

- Antaris Target
- Blending
- Near IR
- Process

Abstract

A revolutionary miniature near-infrared analyzer, the Antaris™ Target, is used in a case study to predict blend uniformity on a bin blender in a pharmaceutical manufacturing plant. Without the need for precalibrated chemometric methods, as is the norm for most NIR analytics, the Antaris Target blend analyzer uses a moving window standard deviation for prediction. In this application, we show that the Antaris Target can be successfully incorporated into moving pharmaceutical manufacturing processes and give highly accurate, critical in-process data about blend homogeneity.

Introduction

Blending of active pharmaceutical ingredients with various excipients is a common step in the pharmaceutical solid dosage form manufacturing process. The compressed blend is analyzed as finished dosage form for potency and content uniformity. The uniformity of the blend is critical in the establishment of the uniformity of dosage units within a batch of tablets.

In a recent proprietary market study of Innovator and Generic Pharmaceutical solid dosage form manufacturers, 48% of respondents listed blending as a major cause of variability in their manufacturing process. Pharmaceutical scientists recognize that it is unlikely that content uniformity of the dosage form will be achieved unless the blend is mixed to a uniform level.

Additionally, blend uniformity is addressed in the Current Good Manufacturing Practices (cGMP) regulations and drug approval programs. Section 211.110 of cGMP requires manufacturers to establish "control procedures… (that) include adequacy of mixing to assure uniformity and homogeneity." The regulations, however, did not specify the blend testing approach, nor the particulars as to the acceptance criteria, limits, or methods for the testing.

The generic pharmaceutical industry instituted widespread blend testing as a response to Judge Wolin's decision in the United States vs. Barr Laboratories decision in 1993. In 1999, the US FDA announced a draft guidance titled "ANDAs: Blend Uniformity Analysis." Comments by the industry led to the formation of the Blend Uniformity Working Group (BUWG) under the structure of the Product Quality Research Institute (PQRI). Upon their report, the draft guidance was withdrawn and a new draft guidance offered in October 2003. The report and the new draft guidance specified a stratified sampling scheme for dosage units based upon thieving multiple samples from the blender in multiple places and analyzing the samples for blend uniformity by HPLC and measuring content uniformity of stratified dosage form samples.

Figure 1: Antaris Target blend analyzer

Thieving samples proves to be labor-intensive both for the operator and laboratory personnel. The data turn-around time is long, and the sampling technique is difficult to reproduce. Additionally, the act of sampling itself can produce sample non-uniformity. Thieving required sampling personnel to be gowned-up, and could create a safety hazard if the active ingredient is high potency.

In September 2004, the US FDA published the draft guidance, "PAT – A framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Control," which opened the door for manufacturers to explore implementing on-line techniques for real-time blend uniformity analysis. This application note examines the use of the Antaris Target Micro Electromechanical System (MEMS)-based NIR analyzer for the determination of blend endpoint and confirmation of blend uniformity.

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Experimental

The Antaris Target blend analyzer (Figure 1) is a MEMS-based NIR analyzer with a spectral range of 1350-1800 nm. It is powered by a semiconductor-based NIR tunable laser, and uses a high-resolution (1-nm) Fabry-Pérot tunable filter for wavelength selection. The unit is battery powered and uses an accelerometer-based triggering system to initiate data collection. Scan speed is approximately 100 milliseconds per scan. The unit has no moving parts and is totally insensitive to vibration. It attaches to the lid of the bin blender easily, and uses a sapphire window in a modified bin lid for transmission of NIR energy onto the sample. Using the Antaris Target's accelerometer, data collection in this application was triggered without the need for limit switches which have to be constantly adjusted on blenders. The accelerometer triggered the Antaris Target to collect data when the material in the blender was against the window on the bottom part of the blender's rotation. Alternatively, the accelerometer is capable of triggering data collection at any point on the 360° rotation of the bin. Additionally, the accelerometer can sense which direction the bin is spinning. A spot size of 40-mm was used corresponding to the amount of material in a 600-mg dosage form.

The blender used for these studies is a Bohle bin blender making use of Bohle's patented counter-current blending technology. The fill level was between 60-90% with a rotation rate of 15-32 RPM. Both asymmetric and symmetric loading methods were employed.

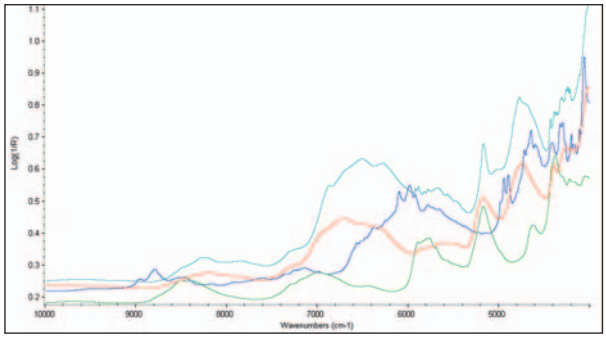

Figure 2: Raw material spectra

Studies were performed blending a formulation of APAP, Lactose, Avicel, and Crospovidone. Figure 2 shows typical FT-NIR spectra of the individual components with Avicel in red, APAP in blue, lactose in light blue and Crospovidone in green. In this case, the APAP (Acetaminophen) is the active pharmaceutical ingredient (API) while the others are common pharmaceutical excipients. Crospovidone is a synthetic homopolymer of cross-linked N-vinyl-2-pyrrolidone that is used as a dissolution aid in direct compression formulations. Lactose and Avicel (Microcrystalline cellulose) act together as a direct compression aid for tabletting. Concentrations of APAP were 2%, 15%, 60% and 70% w/w across different batches. The data in this application note focuses on the analysis of the 70% APAP mixture blended at a rotational rate of 15RPM.

Data Analysis

Typical near-infrared analytics rely on the use of a calibration curve to correlate spectral features to concentration changes. For example, if one application required the ability to predict the concentration of monomer in a polymerization reaction, a series of standards with known concentrations would need to be run to generate a useful calibration curve. For blend homogeneity, or any homogeneity measurement for that matter, the task is much simpler. Instead of needing to generate a calibration curve using lactose, APAP, Crospovidone and Avicel, in the current application all we need to look at is whether or not the spectral output is still changing over time. The theoretical endpoint in this type of measurement is a physical mixture that, at all points, has the exact same concentration of any given component. This does not preclude different concentrations of each component, it merely stipulates that whatever concentration a component has, it is the same throughout the mixture.

Moving window standard deviation is an ideal measurement technique for this application due to its simplicity. Using a function as easy as standard deviation of the area under a curve (or a whole spectrum in this case) one can plot how a spectrum changes over time. Visually, it is easy to see spectra converge to show homogeneity as demonstrated in Figure 3. Here, a second derivative peak corresponding to one of the ingredients in the blend changes from the first rotation to the second and so on. The spectra in Figure 3 show unequivocally that as the blend progresses, the absorbance value of this particular peak, and indeed of the whole spectrum, converges to an average value as the blend becomes more and more homogeneous. The most pronounced peaks in this group of spectra come from three of the first four rotations of the bin lending proof to the theory that the more heterogeneous the blend, the larger the standard spectral deviation. These co-added spectra were saved in a text-based spectral format and transferred to Microsoft® Excel® for the moving window calculation. For the blend of 70% APAP, the rotation speed was 15 RPM and there was one spectrum taken for each rotation in a 251 rotation cycle. Each spectrum consists of 6 co-averaged scans. With a data point every 0.5nm this results in a data matrix that is 901 (data points) rows by 251 columns (rotations). The data in this application was worked up manually in Excel to show the raw data, but the Antaris Target blend analyzer, using RESULT™ software, calculates moving window standard deviations automatically.

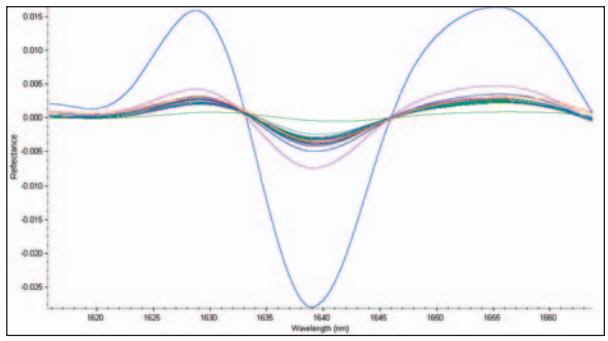

Figure 3: Spectral cluster towards homogeneity

Although measuring the area under a peak or spectrum can be useful, in this case, it is the *relative* area or change in area that is most telling as to the homogeneity of the blend. This can be quickly determined using a moving window standard deviation. In this case, the window width was taken to be 5 rotations. So, in terms of the data workup, the first 5 rotations produced 5 co-averaged spectra each with 901 data points. All 5 of these spectra were averaged, point by point, and the standard deviation for each was calculated. This standard deviation was then summed over all frequencies to make a single measurement of standard deviation over the whole spectrum. The 5-spectrum "window" is moved each time a new spectrum is added to the measurement (every rotation) to give a final plot of total standard deviation versus rotation number (Figure 4). The final 5 measurements in the series (i.e. spectra 247-251) do not have the full complement of 5 spectra in their window.

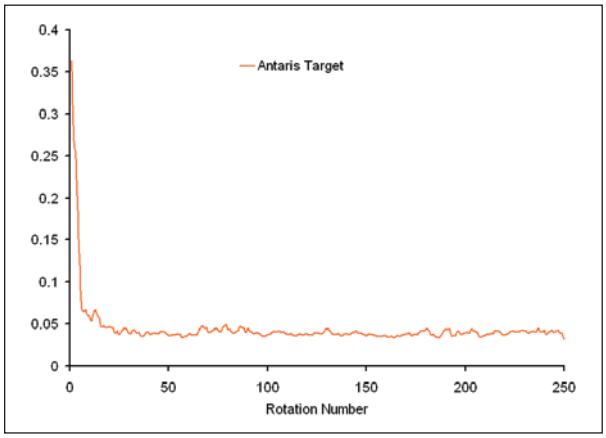

Figure 4: Plot of moving window standard deviation versus rotation

Conclusion

The Antaris Target blend analyzer can be used as an on-line, real-time, blend monitoring tool for the determination of blend end-point and the confirmation of blend uniformity. Blender size, blender speed, and active placement had little effect on blend endpoint. Blender fill level did have an effect on blend end point.

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