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# Mass-balanced blend uniformity analysis of pharmaceutical powders by at-line near-infrared spectroscopy with a fiber-optic probe

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**Abstract**

A near-infrared (NIR) fiber-optic probe was used at-line to study the blending dynamics of pharmaceutical powder blends on a mass-balanced basis. The probe with a flexible fiber-optic cable can be inserted directly into a 10-L bin blender to get quantitative readings. NIR calibration models were developed and validated for the probe based on a designed 50-sample calibration set. A model formulation containing acetaminophen, mannitol, Avicel, magnesium stearate and AcDiSol was used in the study. The blending study was conducted at 18 rpm for 20 min. NIR probe scans were performed at 1 min intervals and five different locations in the bin. Thief samples were collected and later analyzed by a bench-top NIR instrument to confirm the results from the probe. Complete blending profiles were constructed and compared based on the assay results from both instruments.

*Keywords:* Near-infrared spectroscopy; Diffusion reflection; Fiber-optic probe; Blend uniformity; Mass balance; Pharmaceutical

Blending is an important unit operation in the production of pharmaceutical products, especially for direct compression tablets. To satisfy regulatory requirements, the blending process is validated before the product goes into commercial-scale production. The conventional validation is conducted by analyzing manually collected thief samples off-line using HPLC or other suitable methods. The validation usually only involves a few batches and is conducted only for the active pharmaceutical ingredient (API). Validation for excipients is not required and therefore, not conducted. Because of these factors, often times there is the lack of overall understanding and consequently the lack of control of the blending process. To address this issue, the industry and academia have been evaluating more powerful analytical technologies for blend uniformity analysis (Lai et al., 2001; El-Hagrasy et al., 2001; Pan et al., 2003; Hausman et al., 2005). Among them, near-infrared (NIR) spectroscopy is a particularly powerful method for rapid and non-invasive analysis of powder blends.

Early "proof-of-principal" types of NIR applications in blend uniformity were conducted either off-line (Sanchez et al., 1995) or online with small blenders equipped with stationary NIR fiber-optic probes (El-Hagrasy et al., 2001; Sekulic et al., 1996; Hailey et al., 1996). Various chemometrics methods for data treatment and blending end point determination have also been reported (Wargo and Drennen, 1996; Sekulic et al., 1998). Recently, more sophisticated on-line probes have become commercially available (Gupta et al., 2005).

Blend uniformity analysis by NIR can be performed qualitatively or quantitatively. The former approach is characterized by its simplicity. It requires minimum effort in method development. Homogeneity of the blend can be assessed off- or on-line through a series of pre-defined spectral pre-treatment and trend analysis. The latter approach requires extensive method development work including calibration model development and validation. The feasibility of quantitative powder blend analysis on a mass-balanced basis has been demonstrated (Li and Worosila, 2005).

This short communication describes the use of a NIR fiber-optic probe for at-line blend uniformity analysis on a mass-

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Table 1
Blend composition and particle size distribution

| Component | % w/w | Particle size (μm) | | |
|---|---|---|---|---|
| | | $d_{10}$ | $d_{50}$ | $d_{90}$ |
| APAP | 25 | 27 | 93 | 282 |
| Mannitol DC | 60 | 281 | 491 | 789 |
| Avicel | 12 | 25 | 72 | 154 |
| Mg stearate | 1 | 8 | 17 | 24 |
| AcDiSol | 2 | 20 | 45 | 127 |

balanced basis. The NIR probe is connected to the main instrument through a 2-meter long fiber-optic cable. The flexible cable allows the probe to be directly inserted into the powder bed inside the blender to take multiple readings at any desired locations. This study used a simulated formulation contains acetaminophen (APAP) and four excipients (Table 1). Quantitative results for all components can be obtained within minutes. Later on, these results can be used to construct the blending profiles. To verify the NIR probe results, thief samples were collected at the same locations and analyzed off-line using a bench-top NIR. We will demonstrate that the NIR probe can be a very powerful tool in early phase blending studies.

As mentioned above, NIR calibration models have to be developed and validated before quantitative analysis can be performed. A calibration set (Table 2) of 50 samples was prepared using a modification of a scheme published previously (Li and Worosila, 2005). The same set was used for both of the fiber-optic probe and bench-top instrument for calibration model development. The samples were prepared by weighing suitable amount of powders into separate 20-mL scintillation vials using an analytical balance with an accuracy of ±0.01 mg. The total powder weight for each sample was approximately 5 g. Each sample was then mixed manually using a spatula and shaking. The uniformity of the samples was visually inspected and later on confirmed in the validation. Before calibrating the probe, an adapter cap was made by drilling a hole, which should have the same diameter as the probe (a stainless steel tube), through a regular vial cap. During calibration, the probe was inserted, through the adapter cap, about 10 mm into the vial. Then the probe with the sample vial was turned upside down. The powder would cover the tip of the probe to allow reproducible NIR scans. With the bench-top instrument, the samples were scanned directly through bottom of the vials. The following are the NIR conditions:

- Instrument 1: FOSS XDS Smart Probe Analyzer with 2-m fiber length.
- Instrument 2: FOSS XDS near-infrared rapid content analyzer.
- Sampling module 1: XM-1200 XDS Smart Probe module.
- Sampling module 2: rapid module without spot size.
- Detector: reflectance.
- Wavelength range: 1100–2500 nm.
- Data selection: Mahalanobis distance in principal component space.
- Math treatment: 2nd derivative.
- Regression: partial least squares.
- Number of factors: up to 16.

Table 2
Designed calibration sample set (all numbers are in %, w/w)

| APAP | Mannitol DC | Avicel | Mg stearate | AcDiSol |
|---|---|---|---|---|
| 15 | 70 | 6, 9, 12, 15, 18 | 2, 1.5, 1, 0.75, 0.5 | 1, 1.5, 2, 3, 4 |
| | | 6, 9, 12, 15, 18 | 2, 1.5, 1, 0.75, 0.5 | 1, 1.5, 2, 3, 4 |
| 20 | 65 | Same as above | Same as above | Same as above |
| 25 | 60 | Same as above | Same as above | Same as above |
| 30 | 55 | Same as above | Same as above | Same as above |
| 35 | 50 | Same as above | Same as above | Same as above |

The vision software provided by the instrument vendor was used in development of the calibration models. The models were validated by the leave-one-out cross-validation approach. Table 3 compares the number of optimum factors (Li and Worosila, 2005), coefficient of determination and standard error of calibration for NIR models established for the fiber-optic probe and bench-top instrument. The models for the probe use fewer factors and have larger standard error of calibration compared with those for the bench-top instrument, but are adequate for obtaining quantitative results during the blending study.

A Bohle (L.B.Bohle, Warminster, PA, USA) 10-L bin blender was used for the blending study. APAP was charged first, followed by Avicel, AcDiSol, magnesium stearate, and mannitol (direct compression grade). The rotational speed of the blender was set at 18 rpm and the total blending time was 20 min. During the blending study, the blender was stopped at 1-min intervals to allow for fiber-optic probe scanning and thief sampling. There were five sampling positions, one in the center of the bin and the other four at the vertex of a square and about 2 inches away from the wall. About 1 g of sample was collected at each sampling point. A total of four batches were blended in this study, two of them at 60% loading (Batches 1 and 3) and the others at 90% loading (Batches 2 and 4). Results for the batches with the same percentage loading were very reproducible. Therefore, only the results from Batches 1 and 2 will be presented and discussed.

During the blending study, two sets of assay results were obtained for each batch, one set from the at-line probe and another from the off-line bench-top instrument. Each set has 500 data points (5 constituents × 20 time points × 5 sampling locations). For each component (constituent), % relative standard

Table 3
Coefficient of determination and standard error of calibration for NIR models

| Constituent | Optimum factor number | | $R^2$ | | SEC | |
|---|---|---|---|---|---|---|
| | Bench-top | Probe | Bench-top | Probe | Bench-top | Probe |
| APAP | 13 | 9 | 0.995 | 0.990 | 0.58 | 0.79 |
| Mannitol DC | 10 | 6 | 0.983 | 0.963 | 1.09 | 1.49 |
| Avicel | 12 | 5 | 0.993 | 0.951 | 0.38 | 0.95 |
| Mg stearate | 9 | 4 | 0.990 | 0.983 | 0.06 | 0.08 |
| AcDiSol | 9 | 6 | 0.987 | 0.972 | 0.17 | 0.23 |

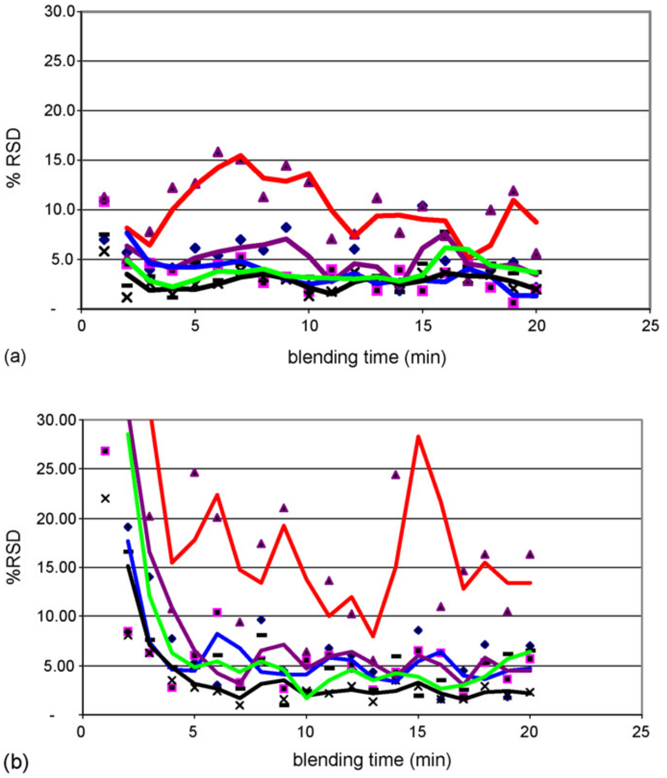

Fig. 1. Blending profiles obtained by the bench-top NIR instrument: (a) Batch 1, (b) Batch 2, (△) AcDiSol, (⧫) APAP, (☐) Avicel, (−) magnesium stearate, and (×) mannitol.

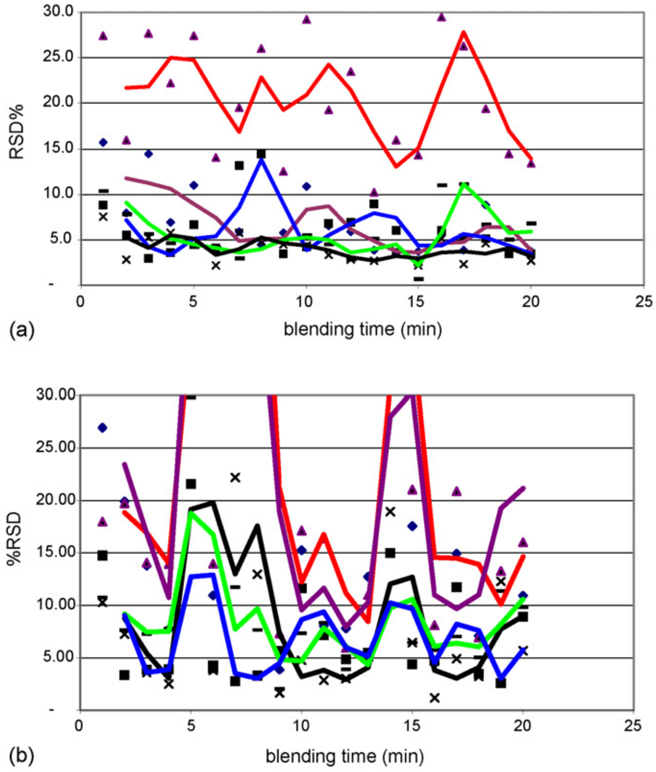

Fig. 2. Blending profiles obtained by the NIR probe (legends: see Fig. 1).

deviation (R.S.D.) is calculated at each time point using data from five sampling locations. Fig. 1 shows the plots of %R.S.D. versus blending time for each component from the thief samples (trending lines = 2-min moving average). Fig. 2 shows the plots of the corresponding data from the fiber-optic probe. In these plots, the %R.S.D. values can be used directly to interpret blend homogeneity for each component. Fig. 1a (Batch 1/bench-top) demonstrates that mannitol became well mixed in a few minutes whereas the API, APAP, did not after 15 min. For the rest of the minor components, AcDiSol showed relatively high %R.S.D. at all time points compared with magnesium stearate and Avicel. Obviously the blending dynamics of these materials are related to their physical and surface properties (Table 1). The related discussions will be out of the scope of this short communication. Similar trends and blending profiles are seen in Fig. 2a (Batch 1/probe), confirming that the fiber-optic probes can be used for blend uniformity analysis.

Fig. 1b (Batch 2/bench-top) shows that it took longer to become well mixed for mannitol at 90% loading, which is expected. Otherwise the blending profiles look similar to those in Fig. 1a. However, Fig. 2b (batch 2/probe) shows dramatically different blending profiles compared with Fig. 1b. To determine the reasons, a two-dimensional map of the assay results versus blending times is presented in Fig. 3, showing all of the 500 data points (Batch 2/probe) along with the corresponding mass balance data (sum of w/w% results for all components at separate sampling locations/time intervals, respectively). The map shows that at 5, 7, 8, 14, and 19 min, the APAP and mannitol assay values were out-of-trend for at least one of five sampling locations. By reviewing the raw NIR spectra, each of the out-of-trend data point corresponded to a uniquely different NIR trace. Fig. 4 shows the five NIR spectra obtained by the probe at minute 5. One spectrum is related to the out-of-trend data point and is distinctively different from the rest. It was easily recognized that the odd NIR trace was similar to that of APAP. Sieving of the Batch 2 blend generated significant number of pea size clumps that contain significantly high amounts of APAP. Due to high loading and relatively slow speed (18 rpm), the blender did not

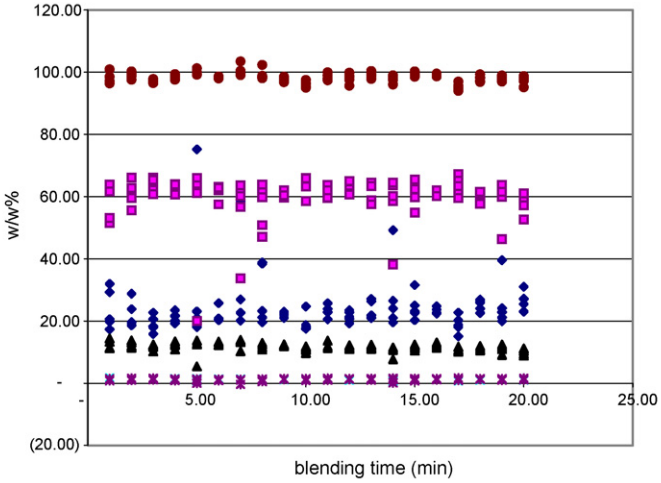

Fig. 3. A map of assay values vs. blending time for Batch 2 by the NIR probe (△) Avicel, (⧫) APAP, (☐) mannitol, (+) magnesium stearate, (×) AcDiSol, and (●) sum of all component.

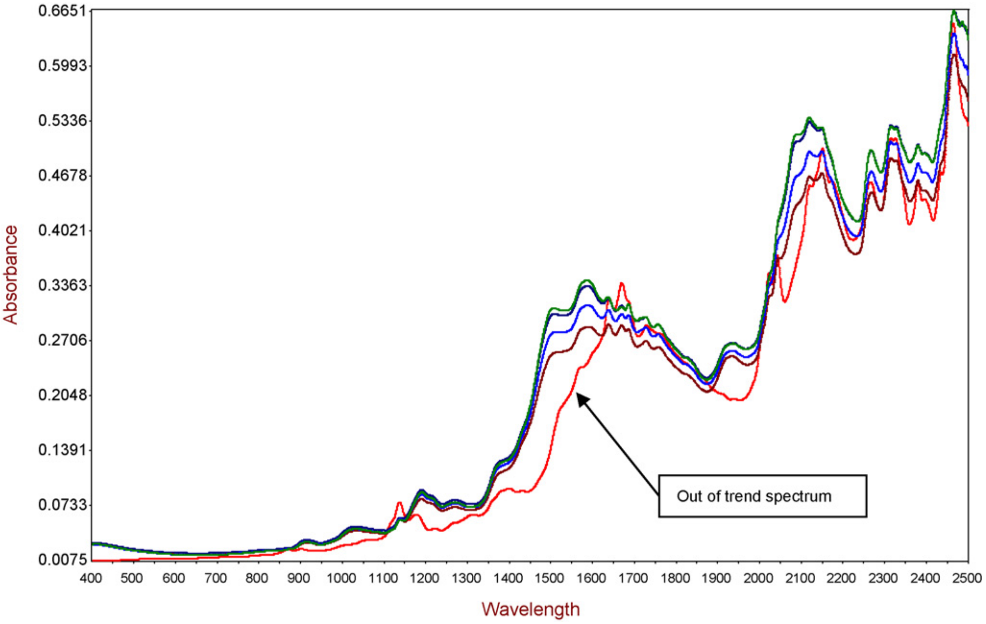

Fig. 4. NIR spectra of Batch 2 blend at minute 5 from five different locations by the NIR probe.

generate enough shear force to break the clumps. It is very likely that the fiber-optic probe caught one of the clumps directly in its light path, which caused the high assay value for APAP. It is interesting to point out that the mass balance was maintained even though when the APAP and mannitol values were out-of-trend (Fig. 3). A few of the thief samples also contained small clumps. However, the assay values of APAP and mannitol were not significantly affected simply because the bench-top instrument has a much larger scanning window.

In conclusion, this study demonstrates that NIR fiber-optic probes can be used for at-line blend uniformity analysis on a mass-balanced basis. Compared with the conventional methods such as HPLC, the NIR method can provide analytical results on site with minimum delay. The NIR method also provides complete blending profiles for all components. Another potential use of the method is for detection and identification of clumps and aggregates in the blending mixture.

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