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# Application of Raman spectroscopy for on-line monitoring of low dose blend uniformity

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**Abstract**

On-line Raman spectroscopy was used to evaluate the effect of blending time on low dose, 1%, blend uniformity of azimilide dihydrochloride. An 8qt blender was used for the experiments and instrumented with a Raman probe through the I-bar port. The blender was slowed to 6.75 rpm to better illustrate the blending process (normal speed is 25 rpm). Uniformity was reached after 20 min of blending at 6.75 rpm (135 revolutions or 5.4 min at 25 rpm). On-line Raman analysis of blend uniformity provided more benefits than traditional thief sampling and off-line analysis. On-line Raman spectroscopy enabled generating data rich blend profiles, due to the ability to collect a large number of samples during the blending process (sampling every 20 s). In addition, the Raman blend profile was rapidly generated, compared to the lengthy time to complete a blend profile with thief sampling and off-line analysis. The on-line Raman blend uniformity results were also significantly correlated ($p$-value < 0.05) to the HPLC uniformity results of thief samples.


*Keywords:* Raman; On-line spectroscopy; Blend uniformity; Low dose; Content uniformity

## 1. Introduction

Blending is a critical process in the manufacture of pharmaceutical dosage forms. Homogeneous distribution of the active pharmaceutical ingredient is necessary to meet expectations of dosage unit uniformity (US Pharmacopeia, 2004). In addition, the homogeneity of functional excipients is necessary for consistent product performance. While the blending or mixing of liquid preparations is well-understood and predictable utilizing tools such as finite element analysis, evaluating the blending of dry powders continues to be a considerable challenge. The importance of a uniform powder blend cannot be minimized, as it affects the final product uniformity and thus the quality, safety, and

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efficacy of the product (Carstensen, 1993). In a formulation optimized for blending, all ingredients would be added in equal amounts, each would be at least 10% of the total amount, and all ingredients would have similar physical properties such as density, particle size, and particle morphology. However, the majority of formulations do not meet all of these criteria. In many cases, one or more of the ingredients is added at less than 5% of the total. Often the active pharmaceutical ingredient is potent and the amount per dosage unit is 1% or less.

The most widely used method for assessing drug content uniformity of a blend involves sampling of the blend followed by off-line analysis, typically using an HPLC method. It has been well documented that the act of sampling, traditionally using a thief while the powder bed is stationary, disturbs the powder bed and can cause sampling that is not representative of blend uniformity (Muzzio et al., 1997; Hwang and Wu, 2004). To address the possibility of sampling methods introducing error into blend uniformity results, the Product Quality Research Institute Blend Uniformity Working Group recommended that if blend sample %R.S.D. results are greater than 5% and/or the individual results are outside the mean $\pm$ 10%, and a mixing problem is not identified, then dosage units (i.e. tablets) should be tested (FDA, 2003). Sampling after compression into discrete units decreases error due to the lack of powder mobility (Chang et al., 2004). However, understanding uniformity in the blender itself is still expected (PQRI, 2002) and sampling for this purpose is performed most accurately when the powder bed is in motion. To avoid error involved in sampling a static powder bed, on-line analytical methods are being evaluated. These methods involve instrumenting a blender with an analytical system, such as near infrared (NIR) or Raman spectroscopy, to allow real-time blend uniformity analysis. These on-line methods allow sampling while the blend is in motion. They also provide a more efficient blend profiling process. When profiling a blend using thief samples, the blender must be stopped at each interval, sampled, and then the samples tested with an off-line method. With on-line methods, generating real-time blend profiles is feasible. The spectral data is analyzed with appropriate software methodologies to create the profile. In addition, the spectral data can be used to create a model that allows for control of the endpoint of blending based on real-time spectral data. Each mixture can be blended until uniformity is reached, adding robustness to the mixing process when raw material properties can vary.

Analytical methodology used on-line is described as Process Analytical Technology (PAT). One definition for PAT is the "systems for continuous analysis and control of manufacturing processes based on real-time measurements, or rapid measurements during processing, of quality and performance attributes of raw and in-process materials and processes to assure acceptable end product quality at the completion of the process" (Hussain, 2002). Pharmaceutical companies and regulatory agencies, such as the FDA, are working to develop faster and more direct analytical techniques to understand, monitor, and control final product quality. Process Analytical Technologies require a synergy of multiple systems including process analytical chemistry tools, information management tools, feedback process control strategies, and strategies for product/process design and optimization.

A number of different technologies have been used to monitor pharmaceutical processes. The most widely used and documented PAT is near infrared reflectance (NIR) spectroscopy. Overtones and combinations of the fundamental mid-IR bending and stretching modes are detected in the NIR region. Absorbances observed in the NIR result mainly from the C–H, O–H, and N–H functional groups. NIR has several characteristics which have enabled its use for diverse applications. NIR has a fast response time, requires no sample preparation, and is non-destructive. NIR technology has been used for blending studies (El-Hagrasy et al., 2001; Wargo and Drennen, 1996).

Raman spectroscopy offers similar advantages to NIR. Raman and NIR probe the vibrational transitions of molecules, providing complimentary information due to different selection rules. In Raman spectroscopy, most incident radiation is either absorbed or elastically scattered (Rayleigh Scatter). A small amount of radiation is modified due to coupling between the photon and the electron cloud of the molecule. Energy can be lost or gained in this process. A "Stokes" shift to longer wavelengths (lower energy) or "Anti-Stokes" shift to shorter wavelengths (higher energy) is detected experimentally. Raman scattering is weak when produced by polar chemical bonds with localized electron clouds. In contrast, non-polar chemical bonds with delocalized electron clouds produce strong Raman scattering.

Significant increases in Raman scattering are associated with aromatic ring systems in highly conjugated molecules. In addition, Raman intensity is generally stronger for crystalline materials as compared to non-crystalline. One key attribute that enables implementation of quantitative measurements by Raman is the relationship between signal intensity and the concentration of material present in the sampled region. The application of Raman for quantitative measurements takes advantage of the proportional relationship between signal intensity and the amount of material that is exhibiting the vibrational shift (Pelletier, 1999). This quantitative relationship is a critical measurement attribute for successful implementation as a process/product control technique. FT-Raman spectroscopy has been used for in-line monitoring of blending of a 50/50 (w/w) mixture of diltiazem pellets and paraffinic wax beads (Vergote et al., 2004).

The objective of this work was to utilize on-line Raman spectroscopy with univariate and multivariate methodology to characterize low dose (1%) blend uniformity, as compared to blend and tablet uniformity based on traditional thief sampling and HPLC analysis. Typical direct compression powder blends were used consisting of azimilide dihydrochloride, spray-dried lactose, crospovidone, and magnesium stearate. Blend homogeneity was determined using on-line Raman spectroscopy due to acceptable azimilide signal-to-noise, whereas 1% azimilide was below the limit of detection of near infrared spectroscopy.

## 2. Experimental

### 2.1. Materials

The formulation in Table 1 was used for these experiments. It consists of azimilide dihydrochloride (Procter & Gamble Pharmaceuticals, Norwich, New York, USA), spray-dried lactose Pharmatose DCL-11 (DMV International, Veghel, The Netherlands), crospovidone (Polyplasdone XL, International Specialty Products, Wayne, New Jersey, USA), and magnesium stearate (Peter Greven, Bad Münstereifel, Germany). The formulation in this study is representative of direct compression formulations often used in commercial pharmaceutical manufacturing, utilizing drug, filler, disintegrant, and lubricant.

Table 1
Drug product formulation

| Component | Unit (g) | Batch (kg) | % |
|---|---|---|---|
| Azimilide dihydrochloride | 0.0025 | 0.058 | 1.0 |
| Spray-dried lactose | 0.2388 | 5.491 | 95.5 |
| Crospovidone | 0.0075 | 0.173 | 3.0 |
| Magnesium stearate | 0.0013 | 0.029 | 0.5 |
| Total | 0.2501 | 5.750 | 100.0 |

An azimilide level of 1% enabled study of low dose blend uniformity using on-line Raman spectroscopy, due to suitable signal-to-noise for quantitation of Raman peaks in the ring breathing spectral region near 1600 $cm^{-1}$. Crospovidone was used as the disintegrant and magnesium stearate as the lubricant. They are routinely used in tablet formulation (Rowe et al., 2003). For this formulation, the amounts of crospovidone and magnesium stearate were below the Raman limit of detection. Spray-dried lactose is a common tablet filler that aids in flow and compression, and its Raman spectrum does not interfere or produce overlapping peaks with azimilide Raman peaks used for quantitation. In contrast, microcrystalline cellulose (another common filler) produces Raman peaks that interfere with azimilide Raman peaks used to monitor blend uniformity. Excipients, which display similar fluorescent properties to microcrystalline cellulose, will also likely interfere with Raman peaks of other blend components. However, there may be multivariate approaches to extract relevant information from highly obscured or overlapping peaks.

The solid-state form of azimilide dihydrochloride is a dihydrochloride hemi-hydrate. The chemical name is (e)-1-[[[5-(4-chlorophenyl)-2-furanyl]methylene]amino]-3-[4-(4-methyl-1-piperazinyl)butyl]-2,4-imidazolidinedione dihydrochloride. The molecular weight is 530.4 and the chemical structure is shown in Fig. 1. Azimilide is white to light yellow in color, crystalline, flat plate-shaped particles. Table 2 summarizes the physical properties of azimilide and spray-dried lactose, which are important to understanding the blending potential of the mixture.

The materials used for HPLC analysis were SuperQ water (Millipore, Billerica, Massachusetts, USA), ammonium acetate ACS grade (JT Baker, Phillipsburg, NJ, USA), acetonitrile HPLC grade (JT Baker, Phillipsburg, NJ, USA), and tetrahydrofuran HPLC

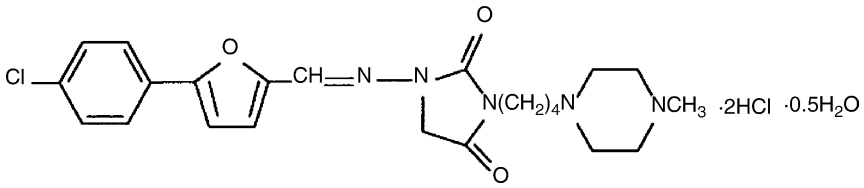


Fig. 1. Azimilide dihydrochloride chemical structure.

grade (EMD Chemicals, Inc., Gibbstown, New Jersey, USA).

### 2.2. Equipment

The manufacturing equipment used was a variable speed 8qt V-blender (Patterson-Kelley, East Stroudsburg, PA, USA), a pocket thief sampler with two 1.0 mL dies, a 10-station Piccola instrumented tablet press (Specialty Measurements Inc., Lebanon, NJ, USA), and modified oval tooling (Natoli, St. Charles, MO, USA).

Analytical instrumentation utilized in these experiments include a Raman Holoprobe with an excitation wavelength at 785 nm and an intensity at sample of approximately 50 mW (Kaiser Optical Systems, Ann Arbor, MI, USA), a custom made immersion probe (Center for Process Analytical Chemistry, University of Washington), Caliper LS Tablet Processing Workstation II v.2.2 (Caliper Life Sciences, Hopkinton, MA, USA), high-performance liquid chromatography (Pump, UV Detector, Column, Column Heater), various balances (PE11, AM50, PE360) (Mettler, Columbus, OH, USA), a Schleuniger hardness tester (Copley Scientific, Nottingham, UK), and digital calipers (Mitutoyo America Corp., Aurora, IL, USA).

### 2.3. Software

Raman spectra were collected using HoloGRAMS version 4.0 (Kaiser Optical Systems, Ann Arbor, MI, USA). Raman peak areas were calculated using Holomap 2.1 rev. 1 (Kaiser Optical Systems) in MatLab R12 (The MathWorks, Inc., Natick, MA, USA). Standard Normal Variant (SNV) pre-processing, multivariate calibration and analysis of Raman spectra were performed using Grams/AI version 7.02 (Thermo Galactic Industries Corp., Salem, NH, USA). HPLC analysis used Turbochrom v.6.1.1 (Perkin-Elmer, Wellesley, MA, USA). Microsoft Excel 2002 was used to create tables, graphs, and for basic calculations.

Table 2
Azimilide and lactose characteristics

| Component | Description | Density (g/mL) | Mean particle size (um) |
|---|---|---|---|
| Azimilide dihydrochloride | Crystalline, flat plates | 0.36 | 70 |
| Spray-dried lactose | Spherical particles | 0.63 | 110 |

### 2.4. Manufacturing process

Azimilide was added to the bottom of the blender, then lactose, crospovidone and magnesium stearate were added to the blender. The components were mixed at 6.75 rpm until the endpoint for the experiment was reached. The normal speed for this size of blender is 25 rpm, however the blender was slowed to 6.75 rpm (27 revolutions in 4 min) for these experiments to aid in the observation of the blending process. Throughout the blending process, the blender content was monitored by Raman spectroscopy. The fiber optic probe head was inserted into the blender through the I-bar port (Fig. 2).

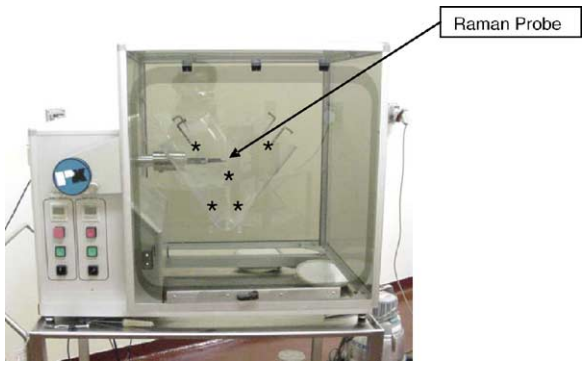


Fig. 2. Blender and Raman set-up with thief sample locations identified with an asterisk.

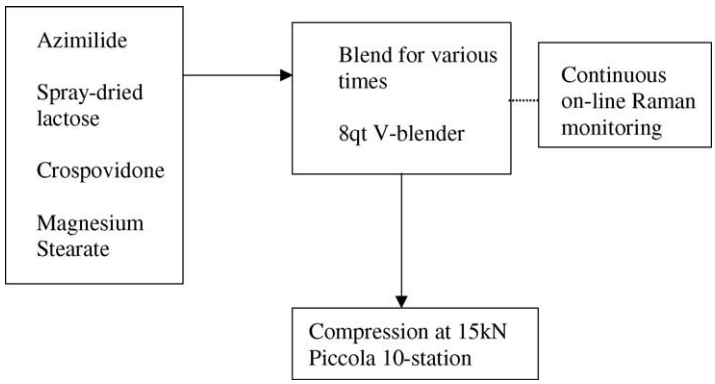


Fig. 3. Manufacturing process flowchart.

This single point probe placement allows for representative sampling during the blending process due to the small size of the blender, combined with frequent Raman acquisitions. During the blending process, Raman spectra were collected every 20 s. The 20 s sampling interval allowed for averaging of two rotations, which is a representative sampling of the entire blend. The sample size probed by Raman spectroscopy during these experiments is calculated at approximately 1 mg based on estimating the number of particles exposed to the laser during the acquisition time. Critical variables for this calculation include particle velocity, average blend density and particle size, and Raman acquisition time. When the blender was stopped, five thief samples of about 500 mg were taken, two down each side of the blender and one in the middle under the Raman probe (Fig. 2). The blend was then compressed into tablets on a rotary tablet press and samples were collected every 4 min, for a total of 20 samples per batch. One tablet from each sample was tested. The manufacturing process is illustrated in Fig. 3.

### 2.5. Experimental design and methods

The blend uniformity was varied by blending to a range of endpoints: 3 min, 4, 5, 6, 7, 8.5, 10, 15, 20, 30, 60, 90, and 120 min. Each blend was then compressed into tablets on a rotary tablet press. For each batch, blend thief samples ($n = 5$) and tablet samples ($n = 20$) were corrected for weight and tested for azimilide content utilizing isocratic reversed phase high-performance liquid chromatography on a C18 column with pH 6.0 acetate buffer:acetronitrile:tetrahydrofuran as the mobile phase at a column temperature of 40 °C with UV detection. Blend profiles were created by plotting the mean percent label and percent relative standard deviation as a function of blend time. Raman spectra were collected every 20 s throughout the blending process.

The spectra produced from analytical methods such as Raman and NIR can be analyzed a number of different ways. An example of a univariate method would be to calculate the change in a peak area or height for a peak that is known to be produced by the compound of interest when undergoing the particular change that is being investigated. However, more sophisticated chemometric data analysis techniques allow additional information to be extracted from the spectrum. There are a number of multivariate techniques that take into account the change of the entire spectrum. Some of the techniques used are partial least squares (PLS), multiple linear regression (MLR) (Blanco et al., 1994), linear discriminant analysis (LDA), quadratic discriminant analysis (QDA), regularized discriminant analysis (RDA) (Wu et al., 1996a), artificial neural networks (Wu et al., 1996b), Conformity Index (CI) (Ritchie et al., 2003), and Mahalanobis Distance (MD) (Ritchie et al., 2003; Whitfield et al., 1987). The MD is similar to the Euclidean distance (ED) except that it additionally takes into account the correlation in the data (De Maesschalck et al., 2000). The Mahalanobis Distance (MD) compares the distance of an observed point to the points that comprise the model space. This model space is set during calibration when a training set is established. The training set is comprised of spectra produced from material exhibiting the desired property.

MD has been described as a multivariate equivalent of a confidence interval (Ritchie et al., 2003). The MD for each object, $x_i$, is computed by the following equation (De Maesschalck et al., 2000)

$$\mathrm{MD}_i = \sqrt{[x_i - \bar{x}]C_x^{-1}(x_i - \bar{x})^T]}$$

where $\bar{x}$ is the mean, $C_x^{-1}$ the inverse of the variance–covariance matrix, and $T$ indicates the transpose of the matrix.

The spectra from these experiments were analyzed by both univariate and multivariate methodology. The univariate methodology required normalizing the spectra in Grams/AI version 7.02 software using standard normal variant (SNV), which centers each spectrum around zero and then scales each data point within a spectrum in variance units. The SNV scaled spectrum was then used to calculate the integrated peak area of the combined azimilide ring breathing bands at 1600 and 1620 $cm^{-1}$ (Fig. 4). Blend profiles were created by plotting this peak area as a function of blend time. Also, a running %R.S.D. of peak area ($n = 3$) was plotted as a function of blend time. The running %R.S.D. was calculated using peak areas from three consecutive spectra acquired with the single probe that was utilized. Variability in peak area and running %R.S.D. will minimize when a uniform blend is reached. The multivariate analysis utilized the Mahalanobis Distance (MD), a conformity index, calculated using Grams/AI version 7.02 software. A calibration set was created from spectra collected in the last 40 min of a 120 min blending process. The 100 spectra collected at the end of this blending process were normalized by SNV and the spectral region between 200 and 3500 $cm^{-1}$ was utilized to develop a multivariate spectral library. Conformity to the calibration spectral library was determined at a MD threshold of ≤4 based on examination of spectral variability within the multivariate calibration set. Therefore, sample spectra with MD of ≤4 indicate a uniform blend has been produced. Spectra recorded in subsequent blending experiments were compared to the calibration library and a MD statistic was calculated for each individual spectrum. Blend profiles were created by plotting the MD values as a function of blend time.

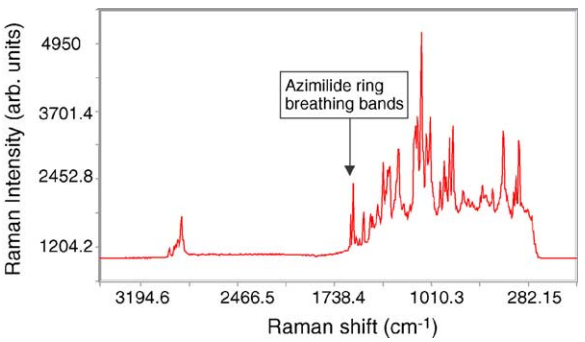


Fig. 4. Raman spectrum of azimilide blend.

## 3. Results and discussion

Azimilide blended with spray-dried lactose at a level of 1% was detected by Raman spectroscopy with suitable signal-to-noise for quantitation. Azimilide displays a strong Raman scattering cross-section that is approximately double the scattering cross-section of naphthalene, which is commonly used for Raman calibration. Azimilide can be detected in this model blend at levels of approximately 0.1% near the detection limit. Low dose azimilide blend uniformity was assessed by on-line Raman spectroscopy, as well as HPLC analysis of blend thief samples and tablets. Variability in the combined area of the azimilide Raman peaks at 1600 and 1620 $cm^{-1}$ minimizes within 20 min of blending at 6.75 rpm (135 rotations). This is equivalent to 5.4 min of blending at 25 rpm. It has been shown that the mixing mechanism, which occurs in tumbler blenders, consistent with this size and range of speed, are essentially unchanged (Brone et al., 1998; Brone and Muzzio, 2000). Azimilide content is homogeneous at this time point, since Raman peak area is proportional to concentration of the material and the time-dependent variability of the azimilide peak area is minimized. These results are shown in Fig. 5. The %R.S.D. of azimilide peak area is shown in Fig. 6. Multivariate analysis also supports blend homogeneity at 20 min of blending at 6.75 rpm (equivalent to 5.4 min at 25 rpm). The Mahalanobis Distances for each blend are shown in Fig. 7. Mahalanobis Distances ≤4 indicate conformity to the calibration set. In these experiments, the calibration set consisted of Raman spectra from a homogeneous blend. After 20 min of blending at 6.75 rpm, the majority of Mahalanobis Distances are less than four in Fig. 7, indicating that the blend is homogeneous. In Figs. 6 and 7, some outliers can be observed

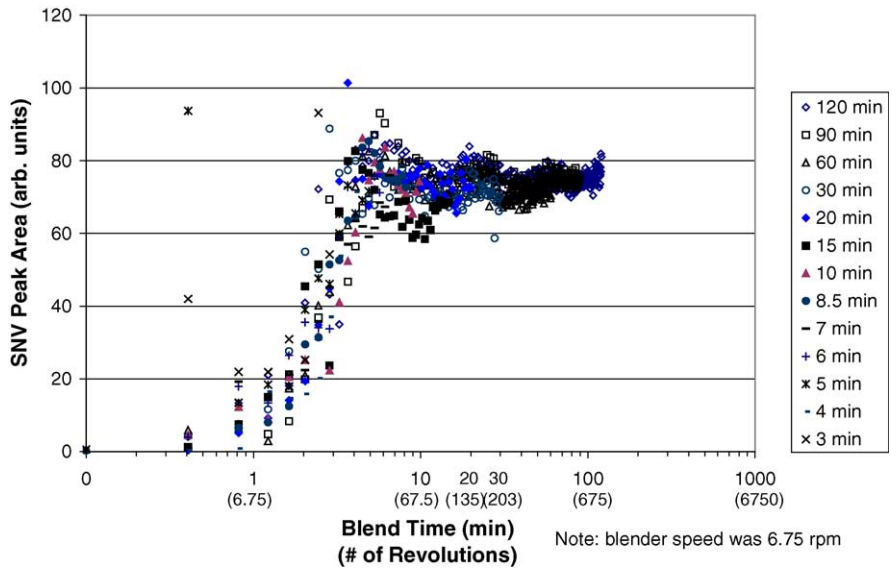


Fig. 5. Effect of blend time on azimilide uniformity of blends measured by azimilide Raman peak area at 1600 and 1620 $cm^{-1}$.

after 20 min of blending. Outliers were classified as values greater than three standard deviations from the mean. There were three outliers in the %R.S.D. data set and five outliers in the MD data set. The spectra corresponding to these data points were reviewed and no gross spectral abnormalities were observed. A possible cause of the MD outliers is the level of variation contained in the calibration set. The calibration set was

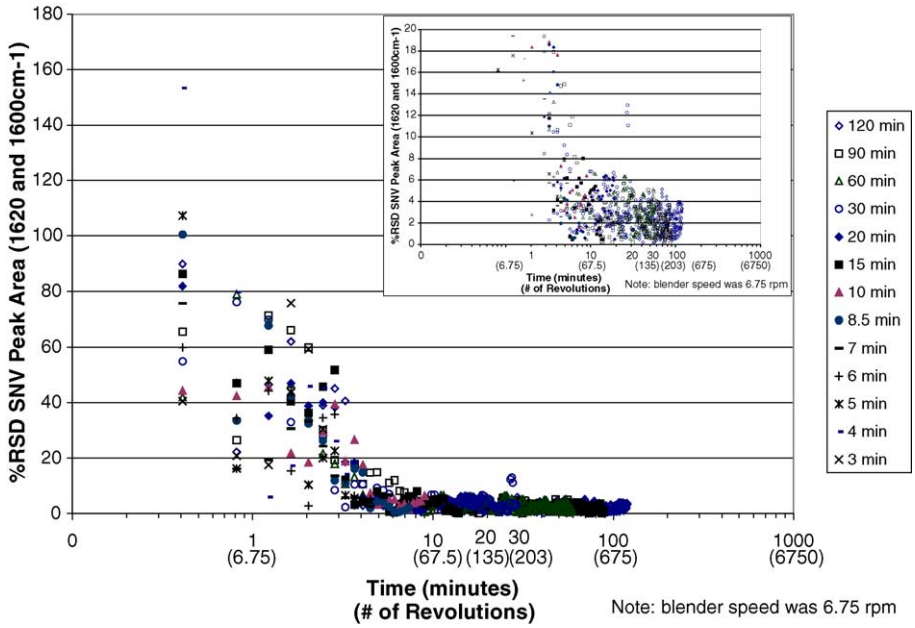


Fig. 6. Effect of blend time on azimilide uniformity of blends measured by %R.S.D. azimilide Raman peak area at 1600 and 1620 $cm^{-1}$.

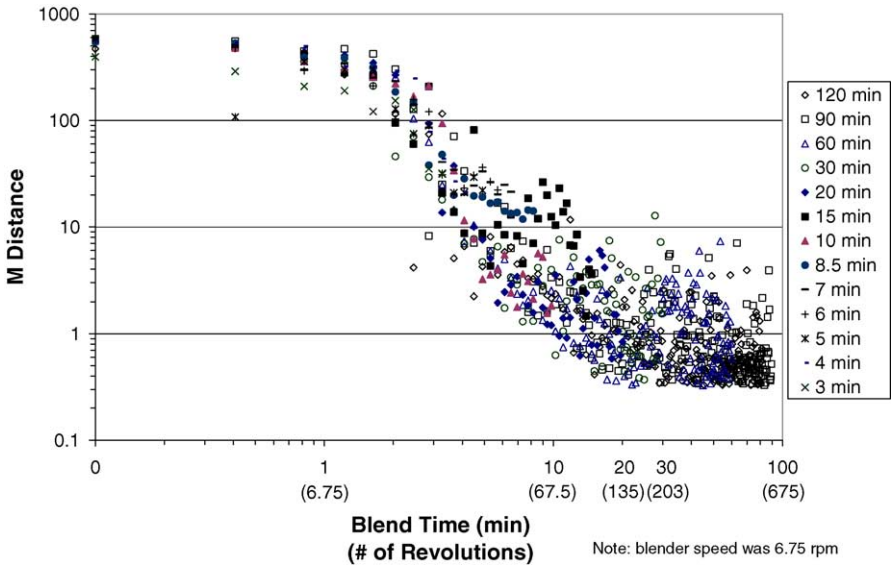


Fig. 7. Effect of blend time on Mahalanobis Distances from Raman spectra.

created from only one blended batch. Outliers are expected within the large data sets produced by on-line monitoring techniques. The topic of outliers is currently under discussion in the PAT community.

One of the advantages of on-line monitoring is realized through inspection of the blending profile that is created. At 20 s of blending at 6.75 rpm (equivalent to 5.4 s at 25 rpm), the blend was not uniform. The %R.S.D. of Raman peak areas ranged from 40 to 160%. The MD ranged from 100 to 550 also indicating a non-uniform blend. After 40 s of blending at 6.75 rpm (equivalent to 10.8 s at 25 rpm), the %R.S.D.

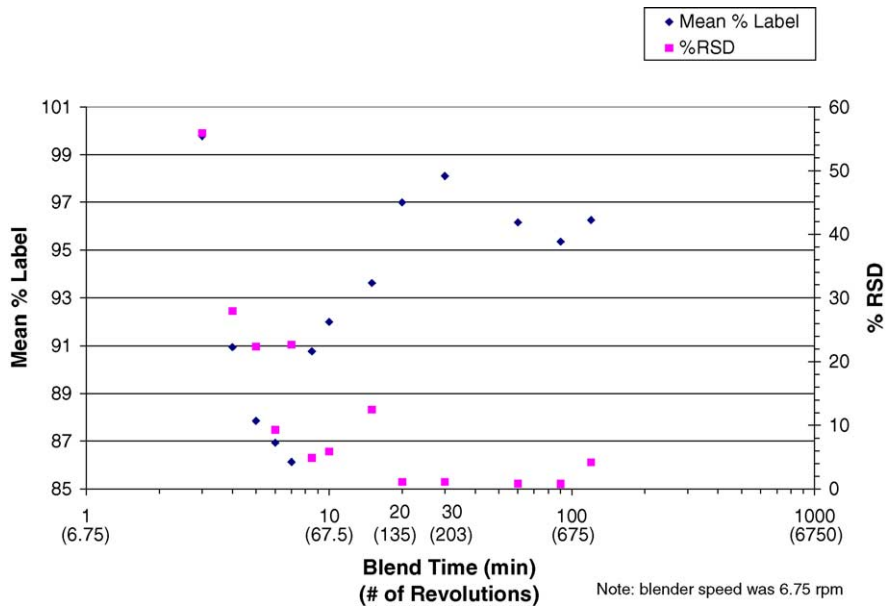


Fig. 8. Effect of blend time on azimilide uniformity of blends measured by HPLC.

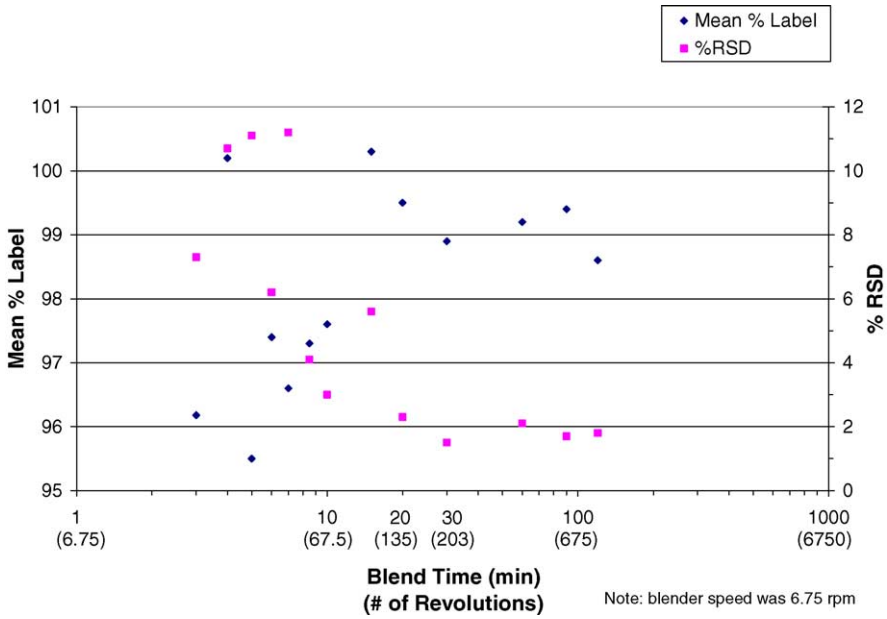


Fig. 9. Effect of blend time on azimilide uniformity of tablets measured by HPLC.

of Raman peak area was 18–80% and the MD was 200–500. These results were improved from the 20 s results indicating that mixing was occurring. At 3.7 min of blending at 6.75 rpm (equivalent to 59.4 s at 25 rpm), the Raman peak area %R.S.D. was 3–26% and MD was 5–70. The %R.S.D. and MD were still very high indicating a non-uniform blend. At 10 min of blending at 6.75 rpm (equivalent to 2.7 min at 25 rpm), the Raman

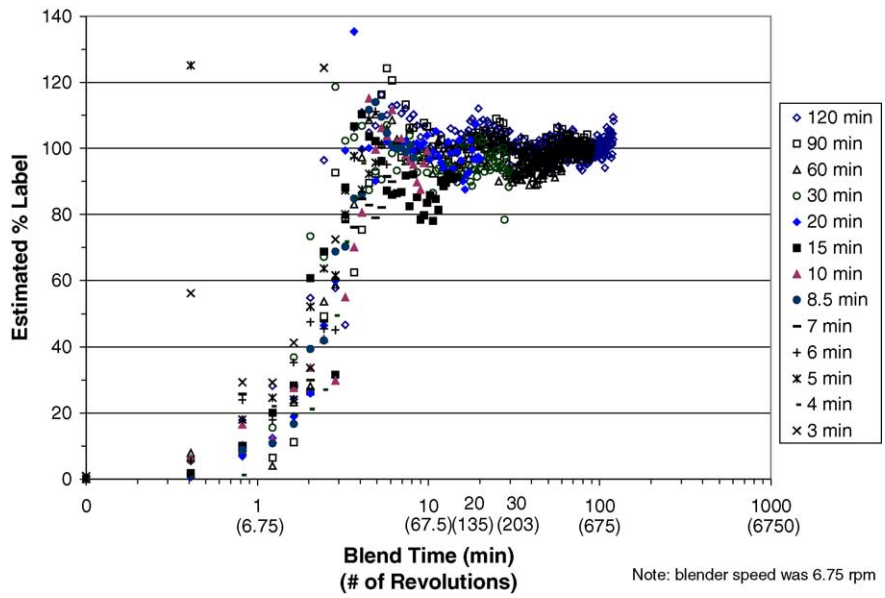


Fig. 10. Estimated blend % label from Raman spectra.

Table 3
Correlations between uniformity determined by Raman and HPLC

| *p*-Values | HPLC tablet S.D. | Raman blend SNV peak area S.D. | Raman blend MD S.D. |
|---|---|---|---|
| HPLC blend S.D. | 0.018 | 0.00006 | 0.012 |
| HPLC tablet S.D. | | 0.026 | 0.03 |
| Raman blend SNV peak area S.D. | | | 0.00004 |

peak area %R.S.D. was 3–7% and MD was 0.6–10. At 20 min of blending at 6.75 rpm (equivalent to 5.4 min at 25 rpm), the Raman peak area %R.S.D. was 2–4% and MD was 0.5–2. At this time the blend is uniform. The %R.S.D. is less than 6% and the MD is less than 4. The results at 30–90 min of blending at 6.75 rpm (equivalent to 8.1–24.3 min at 25 rpm) also showed uniformity and de-mixing was not observed.

Blend thief samples and tablet samples were tested for azimilide content using HPLC. These results are shown in Figs. 8 and 9. The %R.S.D. from the HPLC azimilide blend content uniformity testing was consistently less than 6% after 20 min of blending at 6.75 rpm, indicating blend homogeneity after 20 min (equivalent to 5.4 min at 25 rpm). The %R.S.D. from HPLC azimilide content uniformity testing of tablets was consistently less than 6% after 8.5 min of blending at 6.75 rpm (equivalent to 2.3 min at 25 rpm). These results indicate additional blending occurs in the tablet press feed frame, where the blend is subjected to mixing due to two rotating feeder paddles (Stahl and Langenbucher, 1981). The blend mean % label after 20 min of blending at 6.75 rpm was 97% and the tablet mean % label was 99%.

In addition, the % label of each Raman sample was estimated using the Standard Normal Variant pre-processed azimilide Raman peak area at 1600 and 1620 $cm^{-1}$. To produce an estimate of % label from the Raman spectra, the peak area from each sample was calculated as a percentage of the mean peak area at 1600 and 1620 $cm^{-1}$ from the calibration spectral library. HPLC results indicate the calibration spectral library corresponds to homogenous blend material with a mean assay of approximately 100% label. This approach for estimating % label from Raman spectra assumes spectral variability in the SNV normalized spectra is dominated by variability associated with the concentration dependence of the Raman signal. These results are shown in Fig. 10.

Both Raman and HPLC indicate that blend uniformity was reached by 20 min of blending at 6.75 rpm (equivalent to 5.4 min at 25 rpm). A regression analysis was performed to determine if there was a correlation between uniformity determined by Raman and HPLC methods at each blend time. Variability in the HPLC content uniformity results for blend and tablet samples were regressed against variability in both MD and SNV peak area results from Raman spectra of the corresponding samples. The *p*-values determined from regression are shown in Table 3. There was significant correlation ($p$-value $< 0.05$) between each of the methods of assessing uniformity.

## 4. Conclusions

This study demonstrates feasibility for using Raman spectroscopy as an on-line method to evaluate low dose blend uniformity in a tumbler mixer. Results from univariate Raman analysis were consistent with the multivariate analysis. On-line Raman analysis of blend uniformity provided more benefits compared to traditional thief sampling and off-line analysis. On-line Raman spectroscopy enables generating data rich blend profiles, due to the ability to collect a large number of samples during the blending process. In addition, the Raman blend profile was rapidly generated, compared to the lengthy time it takes to complete a blend profile with thief sampling and off-line analysis. Significant correlation was observed between uniformity measurements from on-line Raman testing and HPLC.

A number of variables that were held constant during this experiment will also affect the ability of on-line Raman spectroscopy to evaluate blend uniformity. These variables include: the chemical structure of the drug and its subsequent Raman scattering cross-section, the drug concentration, the sensitivity and signal-to-noise ratio of the Raman system, the Raman

acquisition time (as it affects the sample size), the spectral properties of blend excipients, and the blend density (as it effects the concentration of particles that the laser impinges on during blending and thus the signal that is measured). With further studies, an automated process control system could be developed to control the endpoint of blending.

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