Characterization of Pharmaceutical Powder Blends by NIR Chemical Imaging

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ABSTRACT: This study demonstrates the capabilities of NIR imaging as an effective tool for characterization of pharmaceutical powder blends. The powder system used in this small-scale powder blending study consists of acetaminophen (APAP, the model API), microcrystalline cellulose (MCC) and lactose monohydrate. Mixtures of these components were blended for different times for a total of ten time points (ten blending trials). Images collected from multiple locations of the blends were used to generate a qualitative description of the components’ blending dynamics and a quantitative determination of both the blending end point and the distribution variability of the components. Multivariate analyses, including pure-component PCA and discriminate PLS, were used to treat the imaging data. A good correlation was observed between imaging results and a UV-Vis monitoring method for determining blend homogeneity. Score images indicated general trends of the distribution of blending constituents for all ten blending trials. The API distribution pattern throughout blending was detected and the API domain size for different blending trials was compared. Blending insights obtained from this study may be transferable to large scale powder blending. Blending process understanding obtained from this study has the potential to facilitate the optimization of blending process control in the future.

INTRODUCTION

Powder blending is a fundamental and important unit operation in the manufacturing of pharmaceutical products. The desired outcome of this operation is a homogeneous mixture of raw materials. Content uniformity of solid oral dosage forms is likely to be compromised without homogeneity at unit-dose scale at the end of the blending stage.

A common blend uniformity practice is to remove samples by thief probe sampling and analyze samples using UV-Visible spectroscopy.1–6 A blend is considered homogenous when the relative standard deviation (RSD) values among multiple samples collected at the same time are within specification. This method of monitoring blend uniformity requires invasive sampling procedures. Significant sampling bias is often introduced with the use of thief probes for removal of samples from powder blenders, as addressed in a number of studies on thief sampling from bulk powder bed.1–3,5,6 An alternate method for blend monitoring is to determine the homogeneity of blend components at a probe location from data collected...
collected by near-infrared spectroscopy (NIR). NIR monitoring is a noninvasive technique with the potential to minimize analysis times and sample preparation while eliminating the sampling errors associated with the disruption of powder beds and removal of non-representative samples from the blender by a sample thief. With the aid of chemometric tools, single point NIR monitoring methods are faster and more reliable alternatives to the traditional monitoring methods.\textsuperscript{7,8} Studies using NIR for blending uniformity assessment have demonstrated qualitative and quantitative approaches for on-line and in-line powder blending process monitoring;\textsuperscript{7–13} explored methods of estimating the effective sample size when using NIR fiber-optic probe for spectral measurement of powder blends;\textsuperscript{14,15} and used design of experiments with varied parameters on critical process variables for a process analytical technology (PAT) approach to assessing powder blending uniformity.\textsuperscript{16–18} It is important to note that most applications of NIR for blend monitoring typically rely upon a single sample point monitored over time as a means of demonstrating homogeneity; this is in contrast to conventional methods which employ several sample locations at a single time point. The typical NIR approach assumes that the sample probed at the single point at different times adequately representative of the contents throughout the blend; thus, it implies that the measurement location is representative of the system as a whole. It is therefore critical that the measurement point is either the most representative or the most variable region (i.e., last to reach homogeneity). Therefore, the choice of probe location is critical for the accurate blending process control by NIR.

Knowledge of the behavior of materials during blending is critical to developing an adequate understanding of the blending process and subsequent process control. Despite the surge of academic interest in industrial applications using single-point NIRS for powder blending evaluation, there is still much to be learned about the dynamic component behaviors during blending. Few models exist for prediction of powder mixing behaviors and fewer empirical studies have been conducted utilizing common pharmaceutical materials to justify these models.\textsuperscript{13,19} Process understanding gained by blend models and accurate process control based on such understanding are critical in the development of process analytical technology (PAT). Therefore, information on spatial distribution of each component during blending is initially the key to gain blending process understanding. To achieve visualization of the spatial distribution of components, and to further delineate behavior of materials during blending, NIR chemical imaging is proposed, since it provides chemical information and spatial distribution of components within a sample simultaneously.\textsuperscript{20,21} While imaging is not expected to be used as a routine powder blend monitoring tool, it is valuable in developing an understanding of the best use of single point NIR systems.

The current surge in interest in NIR chemical imaging has been spurred by the commercial availability of liquid crystal tunable filters (LCTF) and Focal Plane Array (FPA) detectors operating in the NIR spectral region. These are key components for imaging systems capable of collecting high signal to noise images in relatively short times.\textsuperscript{22} These technological advances have enabled NIR chemical imaging to meet the challenging analytical needs of dosage form development laboratories and to serve as a supplement or alternative to conventional, non-imaging NIR spectroscopy.\textsuperscript{23}

The number of applications of NIR chemical imaging in pharmaceutical analyses has increased significantly in the past few years. The versatility of this technique is indicated in many applications including: root cause investigations at drug dosage forms with performance failure back to manufacturing processes,\textsuperscript{24–26} identification of the composition of multiple tablets through blister packaging,\textsuperscript{27} visualization of chemical composition and reaction kinetics,\textsuperscript{28} and, recently, determination of quality for drug products purchased from internet.\textsuperscript{29}

However, among these applications, very little research has been conducted using NIR chemical imaging to understand and characterize pharmaceutical powder blending processes. Lyon et al.\textsuperscript{30} evaluated the blend homogeneity by imaging tablets made from different grades of manually blended powder blends. El-Hagrasy et al.\textsuperscript{31} used imaging as a supplementary tool to confirm the blending end point determination by the single point NIR method. To date, no accounts of NIR imaging to gain critical knowledge of dynamic behavior of components during blending have been reported.

NIR imaging is used in the present study to characterize blending process qualitatively and quantitatively \textit{via} a novel sample preparation and image data collection method. Ten identical
three-component mixtures, consisting of APAP (the model API), MCC, and lactose, were used to represent ten blending trials blended for different periods of time. At each blending trial, after mixing, images of the blend surface were collected; then, the mixture was compressed into a compact and the bottom and cross section of the compacts were imaged. By this means, the distribution of components in a significant fraction of a blend could be assessed. Imaging of multiple locations, especially at internal cross sections of the blends, is crucial for an accurate characterization of blending process. It has been reported previously that mixing patterns at internal cross-sections of mixtures vary significantly from patterns observed from the exposed surfaces (top and bottom), indicating that blending patterns observed at mixture surfaces are not representative of mixing processes inside the powder bed. Multivariate analysis and chemometric tools were applied to the collected images resulting in a qualitative description of the blending dynamics across the blending trials and quantitative determination of the blending pattern. The critical blending areas where the component distribution changes most, or the areas that have the greatest potential to remain non-uniform during blending, were identified. A good correlation between imaging and a traditional UV monitoring method, in terms of end point determination, was established, demonstrating the applicability of the NIR calibration. The API distribution pattern at different locations was detected, and the API domain size distribution variation of different blending trials points was demonstrated.

It is demonstrated from this study that NIR chemical imaging is an effective tool to better understand blending characteristics and mechanisms. Blending process understanding gained through these characterizations by NIR imaging yields valuable knowledge for understanding behavior of blending constituents during blending (i.e., formulation development). Additionally, these data are used to optimize single-point NIR blend monitoring method, and develop blend monitoring applications (i.e., sensors for PAT).

**EXPERIMENTAL SECTION**

**Materials**

A three-component powder mixture consisting of 5% wt/wt Compap® (Acetaminophen USP 90%, Mallinckrodt, Inc., Raleigh, NC) as the active pharmaceutical ingredient (API), 31.7% wt/wt Avicel PH200 (MCC, FMC Biopolymer, Mechanicsburg, PA), and 63.3% wt/wt Fast-Flo lactose (Foremost Farm USA, Rothschild, WI) as the two excipients was used for all time points. Mean particle sizes of Compap®, MCC, and lactose were ~80, 180, and 100 μm, respectively. Methanol (Fisher Scientific, Pittsburgh, PA), which was used in the UV assay, was optima grade.

**Mixing**

A 6 cm (tall) by 4 cm (diameter) cylinder-shaped aluminum mini-blender (made in-house) was used as the blend vessel. A quartz window was designed for sealing the top end and the bottom end was left open for loading blending materials. The blender was charged with lactose, MCC and API through the open bottom end for all ten time points. Once loaded, the mini-blender bottom was sealed by a cork stopper and the vessel was transferred and secured into a lab-scale bin blender (L.B. Bohle, Meschinem +Verfahren GmbH, Enniglohr, Germany) rotated at 25 rpm. A total of ten trials (time-points) were conducted; each used the three-component powder mixture as previously described. The blend time for each trial was: 0.5, 1, 2, 5, 10, 15, 20, 25, 30, and 40 min. At each time point, one mixture was blended and sampled for both UV and imaging data collection. For each blending trial, the total weight of mixture was 30 g (~70% capacity of the blend vessel volume).

**Preparation of Compacts for Imaging**

After surface images were collected, powder blend of each trial was compressed into a compact in the mini-blender using a Carver Press (Fred S. Carver, Inc., Menomonee Falls, WI) at 1000 lbs compression force and a 30 s dwell time. The 1000 lbs compression force was determined by trial and error as the optimal compression force required solidifying the blend, to make the resultant compact solid enough to endure subsequent cutting, but not to disturb the blending pattern of the constituents.

**Imaging and UV Data Collection**

**Near-Infrared Chemical Imaging Data Collection**

The bin blender was stopped at every predetermined time point (according to each blending trial) and the mini-blender was removed.
A MatrixNIR™ (Malvern, Inc., Olney, MD) imaging system was used for image data collection. The field of view (FOV) of the present study, 17.2 × 21.5 mm, was selected based on a prior investigation. The wavelength range was selected from 1400 to 1675 nm with 5 nm increment.

Six images were collected for each blend. The first two images were collected horizontally across the quartz window of the mini-blender to cover a strip view of the blend top, as illustrated in Figure 1a. Mapping of the blend top is achieved via movement along the x-axis of a threedimensional translation sample stage. The x- and y-direction stages control positioning of the sample in the FOV and the z-direction axis is used for optical focusing. Movement along y- and z- axes is controlled by Acudex™ linear stages (Aerotech, Inc., Pittsburgh, PA). Based upon the FOV, the concatenated image of the blend top covered about 60% of the blend top surface area. The next two images were collected from the bottom of the blend after the blend was compacted; the same percent of surface coverage was achieved as images collected from the blend top surface. The blend compact after compression is shown in Figure 1b. The last two images were collected from the cross section of the blend after the compact was cut into halves; these images covered about 70% of the cross section surface area after concatenation, as illustrated in Figure 1c. Light and dark reference images were collected from 99% reflectance standard (Reference_light) (Labsphere®, Cranfield, United Kingdom) and polished stainless steel plate (Reference_dark) for every blending trial, respectively. Pure component images of each of the compacted three blending components after were collected. Although Compa3 was used as the API, which contains 10% w/w starch, the image of this constituent is referred to as a pure component image in this study. Overall, sixty images were collected over the ten blends throughout the blending process; additionally, ten light and ten dark images were collected for the ten blending trials, and three pure components images were collected for reference and model development purposes. Each single image has dimension of 256 × 320 pixels, with the total number of pixels in one image of 81920.

UV Data Collection

Following the image data collection, three UV samples were collected from three locations of each compact. The first UV sample was collected by scraping off powder from the cross section of the compact and was termed as center sample. The second UV sample was collected from one
edge of the compact and was termed as edge sample. The third UV sample was collected from a random section of the blend compact. The mass of each UV sample was ~1 g.

Image Pretreatment

Before image preprocessing tools were applied, all images were converted to log \((1/R)\) absorbance units using the light and dark images collected at the corresponding blending trial (time point) according to the equation below:

\[
\text{Image}_{\text{Final}} = - \log \left( \frac{\text{Image}_{\text{Sample}} - \text{Reference}_{\text{Dark}}}{\text{Reference}_{\text{Light}} - \text{Reference}_{\text{Dark}}} \right)
\]

Here, \(\text{Image}_{\text{Final}}\), \(\text{Image}_{\text{Sample}}\), \(\text{Reference}_{\text{Dark}}\), and \(\text{Reference}_{\text{Light}}\) are the processed sample image, raw data, dark and light reference images, respectively. Standard Normal Variate (SNV) and Savitsky-Golay smoothing (9-point window, no derivative, second order polynomial) were applied in the spectral dimension as to enhance contrast among different constituents in the images. After preprocessing, single images from the same location were concatenated to one continuous image, that is, the two images collected from the blend top were concatenated into one 'top' image. The same concatenation operation was performed on images of other locations (bottom and cross section). All image preprocessing and image analyses were performed using Matlab 7.0.1 software (Mathworks, Inc., Natick, MA) with PLS toolbox (Eigenvector, Inc., Seattle, WA) and custom programs written in-house.

Acetaminophen Assay

At each time point, the UV samples were weighed and dissolved with methanol and diluted to volume with distilled water. Acetaminophen concentrations were detected using a HP 8543 UV-Vis spectrometer (Agilent Technologies, Inc., Wayne, PA) at 280 nm. The calibration curve for acetaminophen (absorbance versus concentration) was linear over the range 0–100 \(\mu g/ml\) \((r^2 > 0.999)\). The precision of the method was examined by preparing the calibration on 5 different days (RSD < 2%). Recovery was calculated to be between 95% and 101%.

RESULTS AND DISCUSSION

Ultraviolet Spectroscopy Analysis

UV spectroscopy is a commonly used method for monitoring of powder blending. Relative standard deviation (RSD) among multiple samples is a common means of determining the end point of a blend. If RSD value is within specification, the blend is considered adequately homogeneous. The RSD profile of each of the ten blend trials, as measured by UV-Vis analyses, is illustrated in Figure 2 (the RSD profile of the imaging data will be discussed in the next section). The RSD is calculated from the assay of the samples from the center, edge and a random part of the compact. The RSD of each trial decreases with increasing blending time with the exception of a spike during trial 5 (at 10 min). The spike indicates that there exists a high variance among the three UV samples collected at this particular time point. However, the cause of this high variance can not be explained from the UV data. The initial RSD value changes are rapid with a local minimum at the trial blended for 15 min.

The same overall blending trend is observed in Figure 3; here, API concentration is plotted for each trial. While the minimum and maximum API samples varied in concert with the RSD of the sample, the mean API content reached the nominal level (C24 5%) with very little blending time. Figures 2 and 3 indicate that the system was relatively well blended at (and after) 15 min. API concentration between center sample and edge sample at each trial is also compared in Figure 3. It is readily observed that all of edge samples...
corresponded to the maximum API%; while most of the center samples were represented by the minimum API%. This indicates an initial tendency for API to be distributed at the periphery of the blend vessel. The data in Figure 3 describe, in a very general way, the pattern of API distribution in the different trials.

The UV monitoring method suggests an appropriate blending time to reach a pseudo-steady state. By segregating samples from the edge and the middle, a general description of the API distribution is developed. However, this method does not provide adequate detail with respect to spatial resolution to begin to understand the behavior of the materials in this system and consequently, the blending process itself. Therefore, a more detailed description of blending tendencies was sought via NIR imaging.

Near-Infrared Chemical Imaging

Near-infrared chemical imaging was used to describe the distribution of the model API and excipients during the blending process. PCA and discriminate PLS in the spectral dimension were used to describe the spatial distribution of the blend components both qualitatively and quantitatively. These visualizations over the ten trials illustrate the general blending behavior of this system.

**PCA Score Images**

Principal component analysis was applied to image data. The components were calculated using a spectral matrix consisting of spectra extracted from the three preprocessed pure component images. A total of 2400 spectra were used to calculate the basis vectors; this matrix was composed of 800 spectra from each pure component image. The first principal component (PC) explained 95.69% of the spectral variance; the second principle component explained an additional 3.97% of the spectral variance. Thus, a PCA model containing these two PCs was developed and used to generate score images for all the preprocessed blend images by projecting the blend image spectra onto the model. The score images on the first PC are used to display the dynamic behavior of the blend components.
The blending trend of the three blending constituents for the ten trials.

The loading spectrum on the first PC is plotted in Figure 4 along with the API spectrum from the mean-centered pure components spectra library and the differential spectrum between API and MCC. It indicates that the loading spectrum on PC1 resembles the mean-centered API spectrum, but is most likely the differential spectrum between API and MCC (spectrum of API—spectrum of MCC), as the correlation coefficient between this loading spectrum and the differential spectrum is 0.999 along the whole wavelength range used. This is because PCA calculates the largest variance in the spectral matrix, and API and MCC spectra are the least similar, it is expected that their spectra difference will be significantly represented in early PCs, especially the first PC. The loading spectrum on PC2, which captured less than 4% of the total variance, resembles the differential spectrum between lactose and MCC (plot not shown), thus this PC can distinguish between the two excipients, but not the API. So, the second PC does not have the discriminating power to differentiate among the three components. Therefore, only score images on PC1 were analyzed in this study.

By projecting the selected PC (PC 1) onto the image data, pixels with high localized API concentration results in higher score values as the mean centered API spectra are similar to the basis vector (PC1), as demonstrated in Fig. 4); whereas pixels with high localized MCC concentration will have the highest negative score values as those spectra possess the greatest similarity to the opposite of the basis vector. The projected score values for pixels with localized high lactose concentration are between the two extremes. As a result, a pseudo-assignment for specific pixels in the score images was established. In all the score images, the white pixels (high positive score value pixels) represent API, dark pixels (high negative score value pixels) represent MCC, and gray pixels (score values in the middle) represent lactose.

Verification of the pseudo-assignment of blend constituents to score ranges was accomplished by comparing the spectra of the selected pixels (high, medium, and low scores) with the pure component spectra, as shown in Figure 5. Spectra of pixels with medium and low score values possess high fidelity to the pure excipients (lactose and MCC). Spectra of pixels with high score values showed high correlation with the API spectra, although spectral contribution from the excipients can be observed in the wavelength region 1450–1550 nm, as demonstrated in Figure 5. The assignment of constituents is thereby justified and will form the basis for subsequent descriptions of blending behavior.

Qualitative delineation of the blending dynamics of each component is illustrated in the resultant score images. Each image in Figure 6a–g consists of three concatenated score images of the three locations of the blend compact (top, cross section, and bottom) at blending time points 0.5, 1, 2, 5, 10, 15, and 40 min, respectively. Score images after 15 and before 40 min have similar distributions of constituents and are not displayed here.

The primary concern of most blend analyses is the distribution of API; here, images of the blend and compact from each trial describe the changes in distribution of API during blending. The initial phase of blending was characterized by convective mixing. The API was charged last into the vessel, and through the first two trials (0.5 and 1 min), Figure 6a and b; it remains primarily on the bottom and top of the blend vessel. Convection distributes the API through the next three trials (2, 5, and 10 min) and the API is distributed along the outer surfaces of the blend parallel. Distribution of API along the outer surfaces of the blend vessel is illustrated in Figure 6c–e. Note that the cross section image in these figures highlights the presence of API at the perimeter of the blend vessel and indicates less API content in the center of the blend. This observation is consistent with the earlier UV-Vis data. The steady state of API
distribution after 15 min is demonstrated in Figure 6f and g, which provides the cause of the stable trend found at the same period of time in Figures 2 and 3.

The PCA images also demonstrate the distribution of excipients for different blending times. In these experiments, MCC is charged after lactose and before API. Isolation of MCC is expected and observed in the cross section from the beginning of blending through 10 min (trials 1 through 5). The volume of the isolated MCC mass is gradually reduced as blending proceeds, and eventually dissipates at 15 min. While API distribution is frequently the only consideration during blending analysis, the appropriate concentration of excipients is important to the manufacturability and performance of the dosage form. As a result, segregation of excipients should be treated with great caution. The API concentration profiles in Figure 3 give no indication of the poor blending of excipients. Thus, insufficient mixing of excipients observed in the images can not be detected from the UV data. This practice is not atypical for blend monitoring in drug products.

Particle properties, such as size, density, shape, friction coefficient and cohesivity play a role in

Figure 5. Spectra of different intensity pixels in a sample score image (a) compared with blending constituents spectra in the powder mixture (b).
Figure 6. Concatenated PCA score images of selected blending trials of three locations (T = blend top surface, C = cross section surface of blend compact, B = bottom surface of blend compact). (a) trial 1 (t = 0.5 min); (b) trial 2 (t = 1 min); (c) trial 3 (t = 2 min); (d) trial 4 (t = 5 min); (e) trial 5 (t = 10 min); (f) trial 6 (t = 15 min); (g) trial 10 (t = 40 min). Pseudo assignments of pixel intensity indicate that white pixels (corresponding to high value in the color scale) represent the API; dark pixels (corresponding to low value on the color scale) represent MCC; and gray pixels (corresponding to medium values on the color scale) represent lactose, or blends of API and MCC. Units of on the x and y axes are number of pixels. Units of the color bar are in arbitrary units.
However, in this system the suggested cause for MCC segregation is the mechanism of radial mixing. It has been reported that radial mixing occurs as the mixture winds around a central point at the interface between the cascading layer and material undergoing solid-body rotation. Since MCC was loaded in the middle, the bulk of MCC powder served as the rotating solid-body due to its location in the blend mixture at early blending times. With increasing rotations, the MCC segregation is reduced due to increased movement-induced diffusion of the MCC particles into the bulk powder body, leading to decreased MCC content stagnant in the center region.

As further example of the utility of NIR imaging, the trial at 5 min demonstrated a high MCC concentration and a small accumulation of API next to it in the cross section (Fig. 6d). In the particular state of blending illustrated by Figure 6d, a sample collected for UV-Vis analysis which included the high concentration of MCC adjacent to a local aggregation of API may contain the correct concentration of API; however, a dosage form resulting from this particular sample would be quite different from a dosage form containing nominal concentrations of all constituents. The UV-Vis analysis for this sample cannot indicate or imply the degree of homogeneity of the API distributed within the sample. This image suggests that a variety of samples should be collected to reflect the overall blending status of the powder bed in order to accurately determine the blending end point when conventional blend monitoring method is used, which supports the sampling protocol in the FDA guidance that extensive sampling of the mixture should be performed when assessing the powder mixture uniformity.

Root causes of abnormal values from the UV analysis can also be sought through imaging. For example, images of the blending trial at 10 min (trial 5, Fig. 6e) demonstrate that more API was distributed at the area near one of the edges in the top and bottom locations, which suggests that one of the UV edge samples (termed ‘sample from the edge’) might have a greater probability of containing excess concentration of API than the other two UV samples. It would be the direct cause of the high variance among the UV samples, thus causing the spike in the RSD profile, at this time point (Fig. 2).

The score images in Figure 6 not only demonstrate the API distribution pattern but also provide interpretations of the cause of the profiles obtained from the UV-Vis data. This qualitative example highlights the importance of utilizing NIR to understand the blending pattern of components. Based upon the PCA score images, a suggested end point for this system is ~15 min. This is the first image in which no visible segregation of any component is apparent. The analysis of images agrees with the local minimum observed in the UV-Vis data.

![Figure 7](image-url)  
**Figure 7.** Predicted APAP concentration (%) from images of top (crosses), cross section(open circles), and bottom(asterisks) of the blend compact at each blend trial, plotted against blending time. Horizontal dark blue solid line indicates the 5% nominal APAP concentration in the mixture.
Figure 8. Predicted APAP concentration variability within locations during blending process for ten blending trials calculated from imaging data.
Quantitative Analyses of PLS Predicted Images

Predicted API Concentration Profiles. A discriminate calibration model using non-linear iterative partial least squares (NIPLS) algorithm was calculated from the same pure component spectral matrix used for PCA. Using this algorithm, spectral information of each pixel is converted into a quantitative measurement of concentration. The coding regimen used in this NIPLS discriminate analysis (DA) is 0 and 1, so that the component concentration in a predicted image is proportional to 1 depending on the spectral information of the pixels.

In this study, quantitative analyses were focused on the predicted API images of the three locations (top, cross section, and bottom) along the blending time. The profile of predicted mean API concentration at the three locations for each trial is illustrated in Figure 7. It is evident that the API concentration was persistently higher in the bottom and top of the vessel, whereas less API was constantly present in the cross section. The profile suggests that higher API concentrations at the two ends of the powder bed were induced by the initial convective mixing, whereas the distribution of API into the cross section can only be achieved through diffusion mixing mechanism.38

In this study, the diffusion of API into the cross-section took about 15 min, as indicated by the time required for the difference of API content of the three locations to reach a minimum (similar to qualitative observations in Fig. 6 and UV-Vis results in Figs. 2 and 3). This quantitative analysis of the data provides further evidence that the blending material loading order is a contributing factor to blending efficiency and a potential rate-limiting factor in achieving blend homogeneity. Further, NIR imaging investigations on the specific effects of the loading order on the material distribution pattern and the blending efficiency are ongoing.

Localized Heterogeneity of Predicted API Concentration. API distribution variability across different blender locations was studied to better understand blending behavior. The API distribution variability within locations was depicted by comparing the predicted API concentrations of four areas within each location (represented by one concatenated image) across the ten trials. For example, the image of the top of the blend was divided along the longest axis into four equal sections (left edge, left-middle, right-middle, right edge). This division allows the comparison of homogeneity at the two edges and the center areas of each blend compact.

The resultant comparison of the four predicted API concentrations and the mean concentration at each location along blending time is demonstrated in Figure 8. The white bar and the bar with upward diagonal pattern represent the two edge areas of the blend (left and right, respectively); the bars with horizontal and downward diagonal patterns represent largely the center areas of the blend. Figure 8 illustrates that API concentration is consistently higher at the edges (left and right) at trials blended less than 15 min. After 15 min, the concentration disparity decreased at each of the three locations. This observation is consistent with phenomena illustrated in Figures 3, 6, and 7, which depict higher API concentration at the edges of the vessel when the mixtures are blended for less than 15 min.

RSD Profiles Based on Predicted API Concentration. The RSD profiles of the predicted API concentration in the three locations (top, center, and bottom) are shown in Figure 9. The RSD values were calculated from the API content of all pixels within a location, and are indicative of the intra-region heterogeneity. The three profiles demonstrated similar trends to UV-Vis analysis over the ten trials, including a spike of high RSD value at 10 min.

Comparison of UV-Vis analysis with image analysis demonstrates the similarity of the techniques when viewed at similar scales. A RSD value for the image data was calculated from all pixels in the top, middle and bottom (N = ~480000). These values were then compared to the RSD values calculated from UV-Vis analysis.
analysis in Figure 2. Similar RSD profiles are observed for both measurements; notably, both profiles reach their respective lowest value at 15 min. The relatively larger magnitude of the RSD profile obtained from the imaging data is due to the large number of data points included in the RSD calculation.

API Domain Distributions. API domain size distribution profiles were calculated from the predicted API images using customized programs written in-house, which incorporated morphological analysis functions from Matlab\textsuperscript{®} Image Processing Toolbox. The term ‘API domain size’ refers to the sizes of the areas containing localized high concentration of API. The API domain size distributions at the top, cross section and bottom of the blend for trials 1 and 6 (blended for 0.5 and 15 min, respectively) are illustrated in Figure 10. As evident for trial 1, the API domain distributions at the three locations are different. Note the API accumulation at the cross section of trial 1 (0.5 min) which results in a single large domain of approximately 1000 μm. In contrast, in trial 6
(15 min), the API domain size distributions at the three locations appear similar. The similar API domain size distributions throughout the blend at 15 min are consistent with other imaging and UV-Vis analyses.

**High Variability Regions Within the Blending Vessel.** Variability at specific locations within the blend vessel was characterized by examining fixed locations through the ten trials. Images were constructed by calculating the standard deviation of each pixel across all ten trials in an effort to visualize the variability in blending homogeneity of regions within the blending vessel. The resulting images are shown in Figure 11. The higher SD value a pixel has, the whiter (or brighter) it appears in the constructed image. Figure 11 indicates that the edges (top, cross-section, and bottom) demonstrated higher variability than other locations in the blend vessel across the trials (different blend times). The center of the cross section highlights an MCC domain as a region of relatively intense change (increased SD) due to the movement of this domain during the blending process. Data in Figure 11 indicate that the two edges and the center of the blend are regions critical to assessing blend homogeneity as a function of time.

**Figure 11.** Images of pixel standard deviation calculated through blending trials for the top (a) cross section (b) and bottom (c) of the blend compact. Units on the x and y axes are number of pixels. Units in the color bar are in arbitrary units.
CONCLUSIONS

In this study, NIR chemical imaging was used to demonstrate distribution of blend components and chemical concentration during trials simulating a small scale blending process. Imaging analyses demonstrate the distribution of blend components and chemical abundance simultaneously, thus providing previously unavailable detail about the blend constituents. The study also suggests that for on-line blend monitoring, a single sensor placed at the edges of the blend vessel would be most appropriate, since high API distribution variability was found in these areas, as demonstrated in Figures 8 and 11. Additionally, the imaging of the cross-section of each trial illustrated distribution of MCC from the center of the blend, highlighting the importance of monitoring non-API constituents during blending. These characterizations of blending are not achieved by traditional blend monitoring methods.

In this study, ten independent powder mixtures were used for both UV and imaging investigation. For the ten individual blends, consistency of certain blending behaviors was observed, which was strongly indicated by the MCC segregation in the cross section and the declined RSD profiles over time from both UV and imaging data. The blending mechanism observed throughout the ten blending trials in the mini-blender is also consistent with what has been reported in the literature using large scale blending. Hence, it suggests that the blending insights obtained from this study may be transferable when studying larger scale blending process using powder systems with similar particle properties (particle size range, shape, flowability, cohesivity, etc.) blended in a device of similar shape as the blender used in this small-scale blending.

The results from this study underscore the valuable role of NIR chemical imaging in achieving a fundamental understanding of pharmaceutical processes and optimization of process monitoring, both of which are critical to process analytical technology (PAT).

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