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Note

Measurement of drug agglomerates in powder blending simulation samples by near infrared chemical imaging

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Abstract

This research note describes a powder blending simulation study conducted using 20-mL scintillation vials and a bench-top rotating mixer on a scale of 2 g for each sample. In order to investigate the impact of mean particle size and size distribution on blending behavior of an active pharmaceutical ingredient (API), the drug substance was separated into sieve fractions using the US standard sieves of 60, 80, 100, 200, and 325 mesh. Each of the fractions was mixed with two excipients (hydroxypropyl methylcellulose and microcrystalline cellulose) for up to 20 min. Then the blending samples were analyzed by a near infrared chemical imaging (NIR-CI) system. The NIR-CI system was able to measure API particles/domains (agglomerates) at 0.001 mm^2 and above within a 11.2 mm × 9.0 mm field of view. It was found that blends prepared with larger API particles (60–200 mesh) contain agglomerated API domains ≥0.1 mm^2. The blends prepared with finer API particles (≤325 mesh) show the characteristics of a randomized mixing. This simple and effective method can be used for evaluation of blending behavior for APIs in formulation development.
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Keywords: Near infrared spectroscopy; Chemical imaging; Blend uniformity; Simulation; Randomized mixing

Infrared (IR), Raman and near infrared (NIR) chemical imaging (CI) techniques are useful analytical tools in pharmaceutical research and development (Bell et al., 2003; Roggo et al., 2005a; Sasic, 2007). Some of the chemical imaging systems rely on automated shifts of the microscope stage and spatial mapping. Sasic et al. used Raman line mapping for analyzing pharmaceutical bead formulations (Sasic et al., 2005). A NIR-CI system equipped with a focal plane array detector can acquire thousands of spectra simultaneously. Roggo et al. reported the use of NIR-CI for characterizing process effects on tablets. The images were used to explain the differences in dissolution properties between samples produced with varied process parameters (Roggo et al., 2005b). In another example, the NIR-CI system was used for high-throughput content uniformity determination of intact tablets. Equipped with a 59.5 mm × 47.5 mm field of view (FOV) lens, up to 20 tablets were analyzed simultaneously. A single-wavelength calibration model was built, which was used to generate CU results that were consistent with those by a UV reference method (Lee et al., 2006). Westenberger et al. discussed the use of an NIR imaging system for detection of API domains within individual tablets (Westenberger et al., 2005). Various chemical image systems are capable of providing spatial information of the API qualitatively or quantitatively in solid dosage forms. This opens a new window for observing and measuring product and process attributes that cannot be easily obtained using the traditional analytical methods.

In this research note, we describe a simple and effective method for studying the effect of API particle size on blending behavior through mini-scale simulation and NIR-CI imaging. The study utilized 20-mL scintillation vials as mixing vessels that were clamped to a bench-top rotating mixer (Glas-Col brand, Terre Haute, IN, USA). During the blending process, the vials moved along the trajectory of a vertically oriented circle of 35-cm diameter with a rotational speed of 30 rpm (Fig. 1). This study involved a proprietary API under development by

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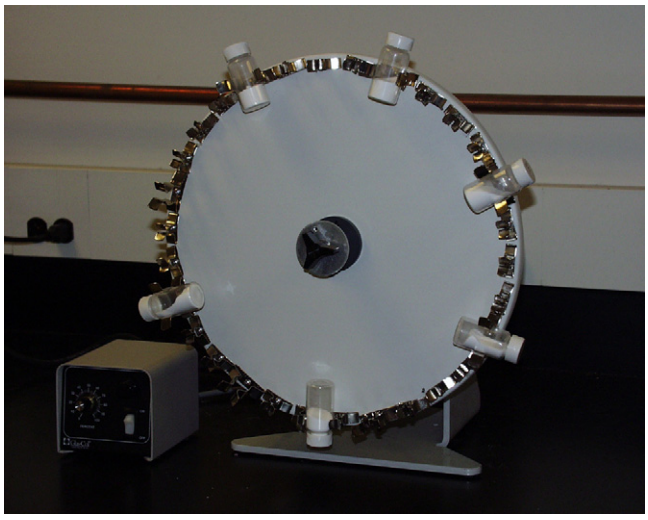

Fig. 1. Rotating mixer and sample vials.

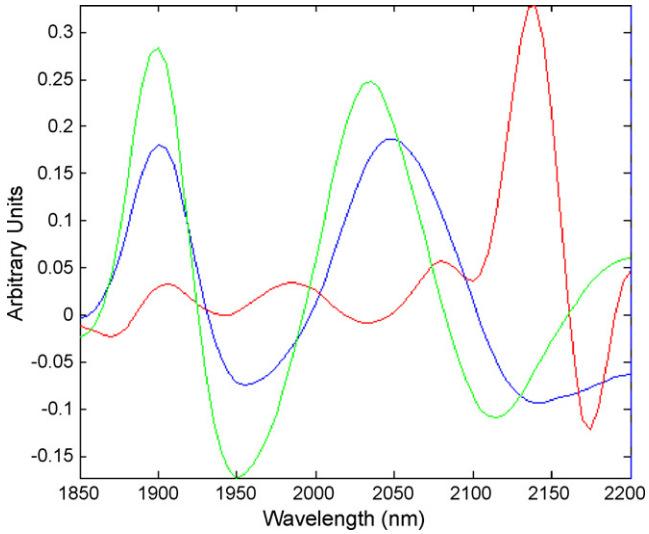

Fig. 2. Mean first derivative spectra of the calibration samples (red = API, green = HPMC, blue = MCC). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Johnson & Johnson Pharmaceutical Research & Development, LLC. In order to study the particle size effect on blend uniformity, sieve fractions (cuts collected between two sieves) of the API were collected using the sieve sizes 60, 80, 100, 200, and 325 mesh. The residues left in the collection pan were also used in the study. Particle size analysis results for the sieved drug substance samples are presented in Table 1. The results were obtained using a Coulter LS 13 320 laser diffraction system and by preparing a suspension of 100 mg API in 10 mL silicon oil. Separate blending samples were prepared according to the ratio specified in Table 2. Duplicate samples were prepared for each sieve fraction of the API with hydroxypropyl methylcellulose (HPMC, Metolose SR 90SH-100000SR from ShinEtsu, Tokyo, Japan) and microcrystalline cellulose (MCC, Avicel PH102, FMC Biopolymer, Philadelphia, USA). The total powder weight for each sample was 2 g, which occupies about one third of the volume in the scintillation vials. In the blending study, one set of the samples (Group 1) was blended non-stop for 20 min. A second set of samples (Group 2) was also blended for 20 min but the process was stopped at 0.17, 0.5, 1, 5, and 10-min time points to allow the samples to be scanned by a NIR-CI system.

A Spectral Dimensions Sapphire/NIRCI-2450 system (Malvern Instruments, Columbia, MD, USA) equipped with a focal plane array detector consisting of 320 × 256 pixels was used in this study. A lens with 35-μm/pixel resolution allowed scan of the blending samples with a FOV of 11.2 mm × 9.0 mm. The samples were scanned from the top of the vials. Spectra were collected from 1850 to 2200 nm in 10-nm increments and 32 co-additions. For each sample scanned, 81,920 spectra were collected to form a so-called data cube, in which the x- and y-axes record physical location of the sample and the z-axis contains the spectral data.

Table 2
Formulation

Ingredient	% (w/w)
API	8
HPMC	14
MCC	78

The NIR-CI data cubes were processed using the chemical imaging software ISys (version 3.1.1) provided by the instrument vendor. The data cubes were background corrected to reflectance (R) and converted to $\log_{10}(1/R)$ or absorbance, followed by multi-step pretreatments including SNV normalization, S. Golay smoothing, and S. Golay first order derivative calculations. At the same time, a spectral library was created by collecting data cubes of a calibration set including an API sample, HPMC and MCC. The size of the data cubes for the calibration set were reduced by truncation using a FOV of 1 mm × 1 mm to simplify chemometrics calculations without causing increased errors in prediction. The same pretreatments were applied to the calibration set, which were then used to create the PLS2 calibration models. Fig. 2 shows the mean first derivative spectra of the calibration set. Based on the PLS2 calibration models, concentrations for each of the three constituents was calculated with respect to each pixel to form a concentra-

Table 1
Particle size analysis results of the API (volume probability[a], μm)

Sample ID	60 mesh	80 mesh	100 mesh	200 mesh	325 mesh	Pan
D50	327	240	205	144	89	68

[a] Particle size expressed in terms of equivalent spherical diameters based on volume of the material.

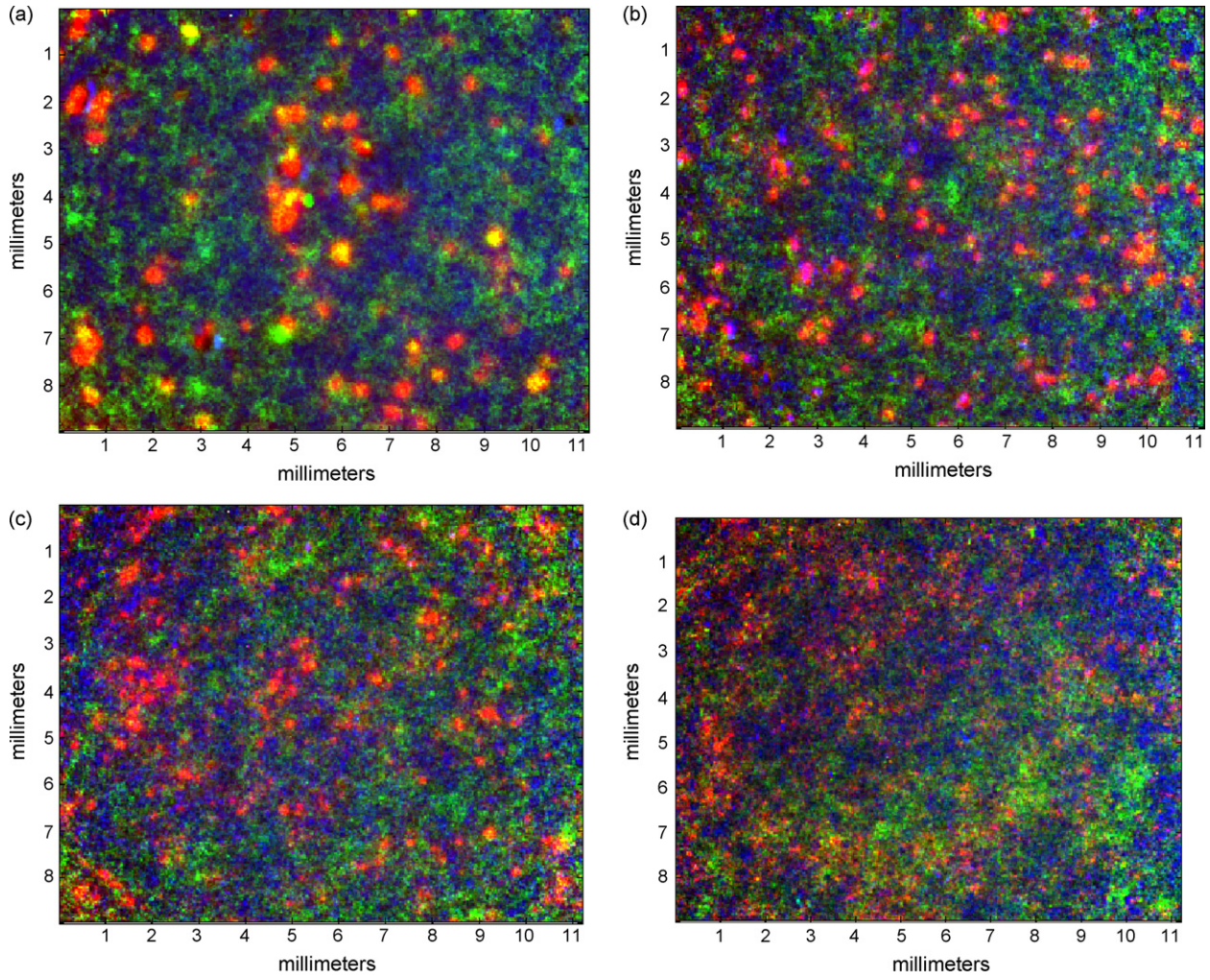

Fig. 3. RGB images of blending samples prepared with different sieve fractions of API (a = 60 mesh, b = 100 mesh, c = 200 mesh, d = 325 mesh) showing the mixing patterns of API (red), HPMC (green) and MCC (blue).

tion cube for each data cube. In a concentration cube, the x- and y-axes record physical location of the sample and the z-axis contains concentration data for each constituent. Three single-channel raw images were created for the constituents from the concentration cube. Finally, the three raw images were used to generate a RBG (red, green and blue) image, which shows the distribution of the API (red), HPMC (green) and MCC (blue) in each blended sample. The concentration cubes were also used to generate binary images, which were used to calculate the number and size of the constituent particles/domains within the images.

In this blending simulation study, the dominant component is MCC, which accounts for 78% (w/w) of the mass. The blending process may be characterized as dispersion of HPMC and API particles into MCC. The RGB images in Fig. 3 confirm this process. These images were obtained for samples that were prepared using 60, 100, 200, and 325-mesh API and blended for 20 min (Group1). The images for the 80-mesh and pan samples are not shown because the former is similar to those of the 60 and 100-mesh samples and the latter to the 325-mesh samples. The presence of numerous API agglomerates (in red) in the 60,

Table 3
API particle/domain statistics in blending simulation samples after 20 min mixing

API size (mesh)	Total particles/domains (≥0.001 mm^2)			API agglomerates (≥0.1 mm^2)		
	Number of domains	Area %	Diameter (mm)	Number of domains	Area %	Diameter (mm)
60	55	4.42	0.28	14	2.78	0.51
80	116	5.02	0.22	11	1.95	0.49
100	139	4.75	0.18	9	1.75	0.48
200	243	4.44	0.13	6	1.12	0.47
325	630	4.11	0.08	0	0	0
Pan	914	4.30	0.06	0	0	0

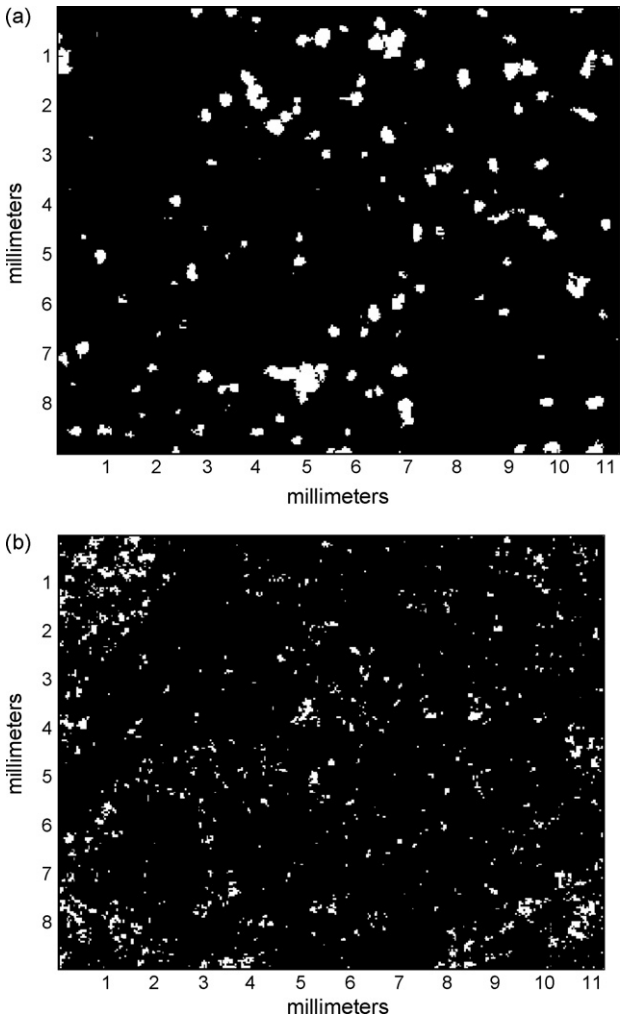

Fig. 4. Binary images of blending samples with 100 (a) and 325 (b) mesh API.

80, 100, and 200-mesh samples were eye catching. On the contrary, large API agglomerates or domains were not observed in the 325-mesh and pan samples.

Based on the concentration cubes, it is feasible to calculate the number and size of the API domains present in the blending samples by using the particle/domain statistics function of the ISys software. This was done by generating binary images of each sample (Fig. 4). The results are presented in Table 3. In this table, each data point represents the mean of six measurements, which were conducted by performing six scans of the same sample. Between the scans, the sample was re-mixed manually by inverting the vial a few times so that a new sample surface could be presented to the NIR-CI system. In Table 3, two sets of statistics are presented, the total API particles/domains and API agglomerates, along with percent area (number of pixels detected as API vs. those detected as excipients) and mean equivalent diameter (assuming the domain is a circle). The statistic results are consistent with those of the images in Fig. 4. API agglomerates were counted in the 60, 80, 100, and 200-mesh samples but were not present in the 325-mesh and pan samples. The percent area values for the samples are between 4.11 and 5.02%, which are lower than the actual 8% of the API. This may be attributed to accuracy of the calibration models, which were built based on pure API drug substance. Another important source of error is the masking step before the binary images were created. However, the low percent area values do not affect the detection and calculation for the number of larger particles/domains. Table 4 presents the particles/domains data from the Group 2 samples. Only the results from the 80-mesh sample are presented. In this case, each data point is the result of one measurement. Results of samples prepared with other API sieve fractions show similar trends and they are not presented in the table. It is interesting to note that there are no significant differences in number and size of API domains/agglomerates amongst samples analyzed at different time points.

This study demonstrates the feasibility of detecting and quantifying agglomerates in powder blends by NIR-CI. The presence of large API agglomerates in powder blends indicates potential content uniformity problems for tablets manufactured using a direct compression process, particularly for those at very low API content/unit dose. This study also shows that the formation of agglomerates is related to API particle size distribution. To characterize a powder blend system thoroughly, factors such as types of excipients, particle size and shape of the excipients, moisture content, blending time and speed may also be important. Usually it is not practical to study all these factors even at the laboratory scales in formulation development. The procedure and method described in this study may be a cost-effective alternative.

In conclusion, the phenomenon of forming API domains or agglomerates in powder blends has been described (Lantz, 1990). However, it is not trivial to measure these domains in solid/solid powder mixtures using the conventional analytical methods. The results presented in this research note show that NIR-CI is a powerful tool for this application. Because the study

Table 4
Particle/domain statistics in blending simulation samples with 80-mesh API

Blending time (min)	Total particles/domains (≥0.001 mm2)			API agglomerates (≥0.1 mm2)		
	Number of domains	Area (%)	Diameter (mm)	Number of domains	Area (%)	Diameter (mm)
0.17	67	4.89	0.28	13	2.36	0.47
0.5	114	6.92	0.25	15	2.93	0.48
1	108	7.50	0.25	18	4.25	0.52
5	106	6.40	0.24	14	2.99	0.50
10	88	4.95	0.23	10	2.33	0.52
20	57	3.28	0.23	10	1.95	0.47

was conducted on a very small scale and uses very limited amounts of drug substance, this approach may be very useful in early formulation development for selection of proper manufacturing process (e.g. blender efficiency) for low-dose solid dosage forms. The remaining important issues of scale up and the impact of API agglomerate on performance of the solid dosage forms are not addressed here because they are out of the scope of this article.

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