middleton research

PHARMACEUTICAL BLEND HOMOGENEITY

Gabor J. Kemeny, PhD - gabor@middletonresearch.com
Gina Stuessy, MS - gina@middletonresearch.com
Natalie Crothers, BS - natalie@middletonresearch.com

Middleton Research - 8505 University Green, Suite 100, Middleton, WI 53562
www.middletonresearch.com

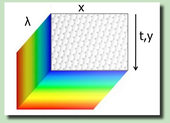
Abstract

Near-infrared chemical imaging (NIR-CI) is an accepted tool for laboratory analysis of the distribution of active pharmaceutical ingredient (API) and excipients in solid dosage forms, such as tablets. Chemical imaging can be used to image tablets, and it can also be used at an earlier stage of production, in blending, to provide information on the evolving patterns of the ingredients' distribution, which is important for successful and repeatable tableting.[4,6] Monitoring of every rotation of blend monitoring was simulated with a lab-scale drum equipped with an optical window and filled with pharmaceutical ingredients. Hyperspectral images of the window area were taken after certain rotations with a SWIR-range (1000-2500 nm) hyperspectral push-broom camera. The images were processed with PLS and SBC methods of composition prediction. Consecutive images showed drastic changes for the first few rotations. The distribution of the ingredients stabilized in the 10-20 rotations range. Hyperspectral imaging (HSI) in the NIR region is a sensitive technique to monitor the blending patterns and homogeneity of ingredients that have a characteristic spectral signature. The wealth of hyperspectral data is beneficial in the formulation development phase, and a simplified blend homogeneity index would be useful for real-time process monitoring.

Background

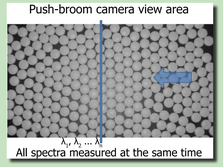
It is important to monitor not only the overall concentration of an API in a pharmaceutical blend, but also the spatial distribution of the ingredients. The authors propose an in-process method of blend monitoring to reduce this risk of improper blending, and the feasibility of the technique discussed and presented here. The use of NIR hyperspectral imaging to characterize the evolution of blending patterns and blend homogeneity of ingredients as a function of the blender rotation is examined.

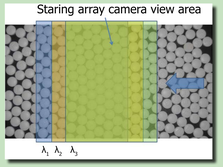
Hyperspectral imaging can improve upon current methods of blend process analysis, including NIR spectroscopy. While conventional NIR spectroscopy can provide the average concentration of an ingredient in the mixture after blending, it is not able to detect the point during the blending process at which all the components are fully integrated/blended. Hyperspectral imaging provides much more information and can provide measures of blendedness throughout the mixing process. HSI can also identify which components become uniformly distributed earlier and which take longer. This information may be helpful during the process development stage.



Left: Spectral hypercube of push-broom imaging; entire spectrum of each spatial point is collected as the sample is scanned line-by-line

Hyperspectral Imaging





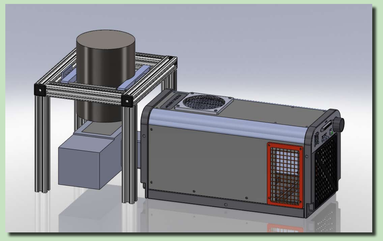
Push-broom imaging

Push-broom imaging is a hyperspectral method in which the area sensor array behind the imaging spectrograph is detecting all spectral information one line at a time, for a whole line, at the same time. Thus, to image a whole sample, either the sample or the camera must be moved. The hypercube is collected by compiling each spatial line of data.

The push-broom method is ideal for imaging large streams of on-line samples typical in many production facilities. The approach of measuring all spectra of the line at the same instance assures that the data is correct even though the sample is moving during the measurement. It also allows line illumination so that the sample would not be under direct heat from the illumination for more than a split-second. With a push-broom system, one can achieve high sample throughput and collect images with less potentially damaging light intensity than with staring array tunable filter systems.

Spectroscopy with hyperspectral cameras

Work with hyperspectral cameras is similar to equivalent off-line NIR or UV-visible spectroscopy. Wavelength calibration, photometric linearity and signal-to-noise must be comparable to achieve performance similar to laboratory calibrations. Spatial resolution and consequent optical energy budget must be optimized for the particular application [1].

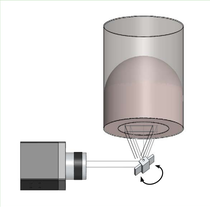


Methods

The experimental setup consisted of a SWIR hyperspectral push-broom camera (Specim Ltd., Oulu, Finland) and lens, a mirror scanner, and a laboratory-scale experimental drum blender. The drum was equipped with a 1.5" borosilicate window and mounted to freely rotate on its central axis above the mirror scanner at a fixed height. Lactose, methyl cellulose, magnesium stearate and talc were weighed in at 35%, 35%, 10%, and 10% respectively, with 10% ketoprofen as the API. Each ingredient was added separately to the drum one at a time. Once the ingredients were sealed in the drum, the first scan was taken with the window side of the drum in place above the scanner window (drum in an upside-down position).

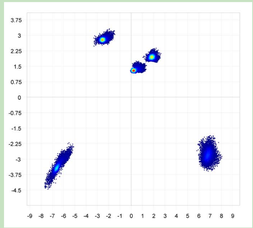
Slowly and consistently, the drum containing the blend was rotated on axis one full rotation (360°) and then stopped in the exact same position with the window in place above the scanner. Another scan was performed. This process was repeated, taking a new scan after every rotation for the first twenty rotations. Maintaining the same slow, consistent rotation, a scan was then repeated every five rotations until turn fifty, followed by every ten rotations until turn one hundred. Finally, a scan was taken at turns two and three hundred to show the effects of long-term blending.

In addition to the blend images, each pure component was imaged separately in the same drum to be used for prediction models in the data analysis phase.



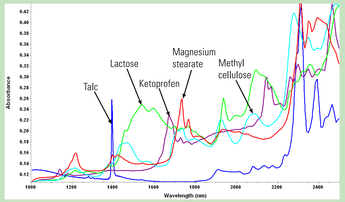
Data Analysis

The hyperspectral images were analyzed in Evince Image analysis software. A PLS model was created from images of the pure components and was used to predict the concentration of each pure component in each of the consecutive blend images. To create the PLS model, our training set included images of the five pure components, and a heterogeneous blend image (taken after 50 turns) to improve the model. An SNV correction was applied to reduce the point-to-point variation due to different particle sizes and orientations. The wavelength range was also narrowed to 1000 - 2450 nm to eliminate the noisier regions. The 2D scatter plot is shown here. This plot shows that there are clear spectral differences between the five pure components, and a PLS model should be able to predict them selectively in a blended image. Their average spectra, shown to the right, are also very different from one another.

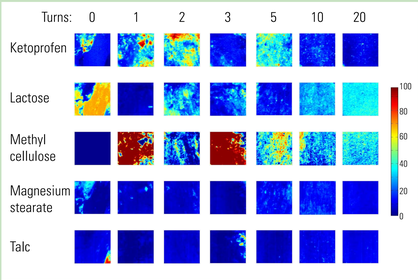


2D scatter plot of the first two loading vectors

In parallel with the PLS, another prediction was performed in Matlab with the Science-Based Calibration (SBC) method [5]. The pure component images were used to obtain estimates of the pure components' response spectra. Estimates of the spectral noise, pure components' noise, and sample presentation noise were included to create a robust model. An operating point correction was applied, which brought the results from the later turns close to the nominal concentrations, thereby correcting for some of the optical nonlinearities.



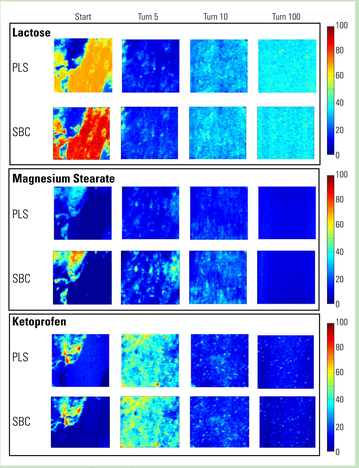
Results



Concentration prediction images from the PLS prediction of the five components. Hyperspectral images were taken prior to blending (turn 0) and after specified rotations. Coloring corresponds to a 0-100% scale of the specified component.

The obtained hypercubes of the images were predicted for each component at each blender rotation using both PLS and SBC methods. The PLS prediction images are shown here to illustrate the evolution of the blending. By visual inspection of these prediction images, we concluded that all the ingredients showed drastic changes for the first few rotations, but were mostly mixed after about 20 rotations, as seen in the figure to the left. The following section contains the prediction images from Turn 100. One can see that from turn 20 to turn 100 there were no significant changes in the homogeneity of either component within the blend. In an actual blend process development, the blend endpoint can be concluded using the hyperspectral chemical images, and it may not be necessary or may even be counterproductive to blend much longer than the optimum. We can also see from the images taken after 100 turns that while there aren't many large aggregates, there are still small regions of higher or lower concentrations. This may indicate that a better blending method is needed, rather than more turns, since increasing the number of turns past 20 did not result in further significant changes.

While it appears that the five components are fairly well blended after 20 turns, all did not appear to become integrated at the same rate. Lactose and methyl cellulose changed drastically in the first few turns, while the other components remained fairly stable after turn three. This tells us that all ingredients are not blended at equal time. There are many factors that may cause differences in blending times, including particle size and moisture content, and these differences may cause transient or permanent residual inhomogeneity. Ketoprofen in this experiment, for example, seems to stay in somewhat larger aggregates than the other ingredients. The remaining specks, although evenly distributed on the image, seem to be around 100 um.



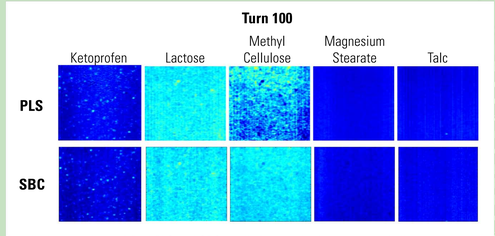
Comparison of SBC and PLS prediction results for lactose, magnesium stearate, and ketoprofen on turns 0, 5, 10, and 100. Coloring corresponds to a 0-100% scale of the specified component.

Comparison of SBC and PLS

After the 100th rotation, the PLS predictions gave concentrations within 2.3% of the nominal, and the SBC was within 1.1%. Overall, both methods predicted the images well. While the images are similar (see figure to the right and below), there are some small differences in the scale. It appears that PLS and SBC handle optical nonlinearities somewhat differently, although the spectral information used by the techniques is the same. The residual lighting non-uniformity due to single sided illumination, for example, is compensated better in SBC, as seen on the turn 100 image of methyl-cellulose.

We are continuing to improve the prediction methods to achieve the most accurate predictions. For the blend monitoring application however, uniformity parameters, such as the degree of mixedness, provide more important information than the absolute concentration, and uniformity is much more difficult to obtain with other techniques.

Using Evince PLS or SPB predictions, one can obtain a fairly good sense of when during the mixing process the blend becomes uniform, which is the most important process information for blend manufacturers.



Detailed comparison of final PLS and SBC prediction results for turn 100 of all components

Conclusion

In comparison to traditional NIR spectroscopy methods, hyperspectral imaging provides more information that can be used to detect poor or uneven blending. One can determine the appropriate amount of mixing time and select materials that will blend together at similar rates, for example by matching their particle sizes and other solid state physical parameters. From the images presented here, one can discern that each component becomes uniformly distributed at different times. With hyperspectral prediction images, one can monitor the evolution of the blend and note the remaining structure at the end of the process, such as whether or not there are still small aggregates of certain components.

We are currently investigating the use of hyperspectral images to provide more quantitative measures of mixedness or homogeneity for use as simplified technological monitoring parameters. Results will be reported at IFPAC in January 2011.

References

1. Kemeny, G. J. (2008). Hyperspectral Imaging: A Practical spectroscopists's perspective. International Diffuse Reflectance Conference, Chambersburg.
2. Vervaet, C. & Remon, J. P. (2005). Continuous granulation in the pharmaceutical industry. *Chemical Engineering Science*, 60(14), 3949-3957.
3. Portilloa, P. M., Ierapetritoua, M. G., & Muzzio, F. J. (2008). Characterization of continuous convective powder mixing processes. *Powder Technology*, 182(3), 368-378.
4. Ma, H. & Anderson, C. A. (2007). Optimisation of magnification levels for near infrared chemical imaging of blending of pharmaceutical powders. *Journal of Near-Infrared Spectroscopy*, 15(3), 137–151.
5. Marbach, R. (2007). Multivariate calibration a science-based method part 1
6. El-Hagrasy et al (2001): Near-Infrared Spectroscopy and Imaging for the Monitoring of Powder Blend Homogeneity, J. Pharm.Sci. 90(9), 1298-1307

© Middleton Research 2010