MICROMIXING ANALYSIS FOR FORMULATION DEVELOPERS

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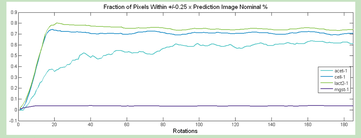
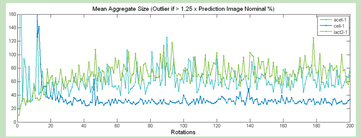
Abstract

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 formulation development, to provide information on the evolving patterns of the blend ingredients' distribution, which is important for successful and repeatable tableting.[4,6]
Monitoring of every rotation of a blend was performed with the imMix system which includes a hyperspectral camera positioned to image a computer-controlled rotating lab-scale blender equipped with an optical window. Hyperspectral images of the window area were taken after specified rotations with the SWIR-range (1000-2500 nm) hyperspectral push-broom camera. The images were processed with the SBC method 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. Image analysis methods – including aggregate sizes statistics, and the fraction of pixels above a given composition threshold – are useful to determine the interactions between ingredients through the rotations. Hyperspectral imaging (HSI) in the NIR region is a fast and sensitive technique to monitor the micromixing and homogeneity of pharmaceutical ingredients that have a characteristic spectral signature. Several image analysis techniques are beneficial in the formulation development phase.



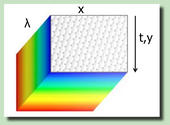
The fraction of pixels within the nominal composition range: APAP was clearly changing up to about 90 turns, while all other ingredients stabilized after about 20 turns.



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 during blending. The authors propose an in-process method of monitoring micromixing to reduce this risk of improper blending, and the feasibility of the technique is discussed and presented here. The use of NIR hyperspectral imaging to characterize the micromixing 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. Hyperspectral imaging provides much more information and composition prediction image analysis can provide metrics 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 formulation development stage.

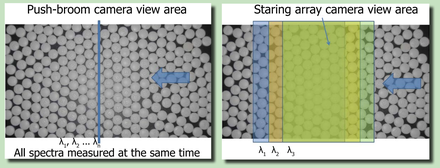


Left: Spectral hypercube of push-broom imaging; entire spectrum of each spatial point is collected as the sample is scanned line-by-line

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 spatial line at a time, in parallel for a whole line. Thus, to image a whole sample, either the sample or the camera must be moving. The hypercube is collected by compiling each spatial line of data.



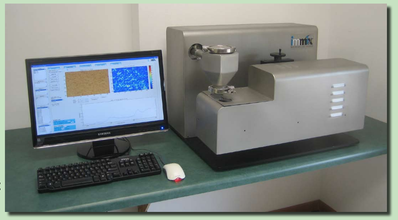
The push-broom method is ideal for imaging large streams of on-line samples typical in many production facilities. The approach of measuring all spectra of the line at the same instance assures that the data is correct even though the sample is moving during the measurement. It also allows line illumination 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.

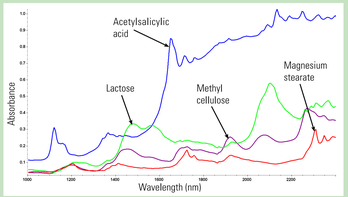
Spectroscopy with hyperspectral cameras

Work with hyperspectral cameras is similar to the 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

A fully-automated imMix system (Middleton Research, Middleton WI, USA) containing a 1 qt (approx. 1 L) IBC blender and a similar size drum blender prototype containing a SWIR-LVDS-100-N25E hyperspectral push-broom camera (Specim Ltd., Oulu, Finland) was used to scan pharmaceutical formulations from 1000-2500 nm, for all, or for selected rotations of the blender. The spatial resolution of the images was approximately 30 µm x 30 µm. The NIR optical window was covered with fresh blend after each rotation. Hypercubes of data for each rotation were saved in ENVI format for the changing blend over two hundred rotations. The 10 gigabytes of data were automatically analyzed by the imMix™ software package using the SBC chemometric method, resulting in a total of 800 composition images of all ingredients for all rotations.





An experiment was performed with the system to study the effect of adding MgSt to a model blend. Methyl cellulose, lactose, and magnesium stearate were weighed in at 24%, 24%, and 2% respectively, with 50% acetylsalicylic acid (all ingredients from Sigma-Aldrich, Milwaukee, WI) as the API. Each ingredient was added separately to the blender one at a time. Once the ingredients were sealed in, the measurement software was initiated to scan specific rotations of the blend. The rotation speed was set to 37 rpm, the scanning speed to 0.17 rpm, and the integrating time was 0.8 ms.

The drum blender rotated continuously, slowing down on each specified rotation to start scanning at a slight angle to the image line and then speeding up again after scanning the optical window. To study the effect of adding MgSt, three blends were performed: one where MgSt was not added at all, one where it was added in the middle at turn 101, and one where it was added at the beginning of the blend.

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

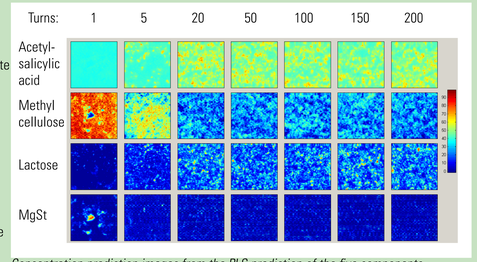
The imMix processing software, with the Science-Based Calibration (SBC) method[5] option was used to predict the composition maps of each component for each rotation measured. The wavelength range was narrowed to 1000 - 2400 nm to eliminate the noisier regions. The pure component images were used to obtain estimates of the pure components' response spectra, shown to the right. 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

The obtained hypercubes of the images were predicted for each component at each measured rotation using the SBC method. Several 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. 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.

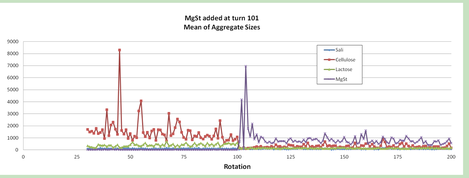
In addition to the visual inspection of prediction images, more quantitative methods of analysis were calculated including:

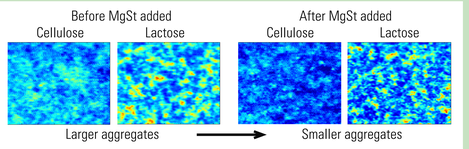
- average composition
- standard deviation of composition
- mean/median/maximum aggregate size
- skew and kurtosis of aggregate size distribution
- fraction of pixels above a specified threshold composition
- fraction of pixels within a specified range of compositions
- ratio of "peaks" (high composition pixels) to "valleys" (low composition pixels)



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.

From the study on the effect of adding MgSt to the blend, we see several interesting and related phenomena. First and most startling is the effect MgSt has on the mean aggregate sizes of methyl cellulose and lactose when it is added in the middle of the blend. One can also see the aggregates diminish in the prediction images corresponding to pre- and post-MgSt addition. Shown here for the blend without MgSt is the fraction of pixels which are above a certain threshold (in this case 125% of the nominal composition). This image processing parameter is indicating the outliers that are not yet well blended. When MgSt is in all rotations, we see a gradual decrease in the mean aggregate size of acetylsalicylic acid and lactose, but an increase for cellulose. This is visible in the plot and in the prediction images below.





Conclusion

Extensive application of hyperspectral imaging for micromixing analysis is a sensitive and fast technique. This approach provides information about blending patterns and homogeneity of the mixture. It also assists ingredient selection, determination of the best blend ratios, blending time, blender type, and speed settings to achieve optimum blending endpoint. At the same time, this approach provides information to avoid residual aggregates or re-aggregation. The wealth of hyperspectral data is beneficial in the formulation development phase to understand the technologically relevant aspects of micromixing. Using the image analysis tools presented here, one can study the effect one ingredient has on the others, and determine the mixing time required to achieve a certain goal as measured by various metrics – aggregate size distribution, fraction of blend within a certain composition range, etc. With hyperspectral prediction images, one can monitor the micromixing of the blend and note the remaining structure at the end of the process, such as whether or not there are still too large aggregates of certain components.

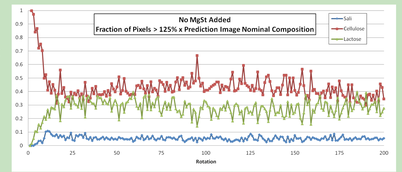
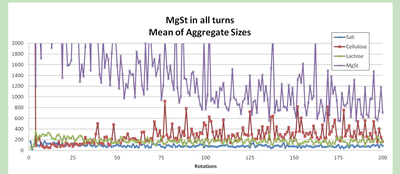
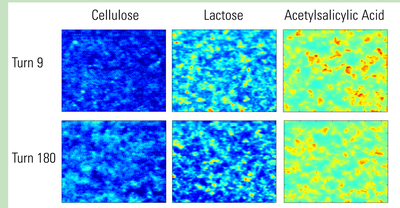


Image processing statistics, including the fraction of the image that is not yet well-blended, are useful development tools.





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