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Determination of the scale of segregation of low dose tablets using hyperspectral imaging

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ABSTRACT

In this work, near infrared (NIR) hyperspectral imaging was used to quantify the spatial distribution of drug in tablets containing tolmetin sodium dihydrate. Hyperspectral data cubes were generated by imaging the same spatial region of a sample while illuminated by a laser at a different wavelength for each image. Images were generated for wavelengths ranging from 1100 to 2200 nm. Ten tablets with concentrations ranging from 0.0 to 10.0% w/w tolmetin were imaged, and the scales of segregation were calculated for the tablets. Lactose anhydrous was used as the diluent, and all mixtures contained 0.5% magnesium stearate as a lubricant. This research has shown hyperspectral imaging to be viable tool for quantifying segregation of low dose drugs in tablets.

1. Introduction

Since particulate materials are used during the manufacturing of 60–80% of products on the market (Ennis, 2006), it comes as no surprise that much research has been dedicated to understanding a variety of powder processes such as powder blending. A critical aspect of both studying blending and assessing blend quality is the ability to monitor component concentrations and spatial distributions of components within mixtures. As a result, significant efforts have been made over the years to develop methods for accurately quantifying the concentration of a powdered substance within another powder matrix.

A number of techniques have been used to do this including near infrared spectroscopy (NIRS) (Ely et al., 2006), Raman spectroscopy (Hausman et al., 2005), thermal effusivity (Léonard et al., 2008), and laser-induced florescence spectroscopy (LIF) (Lai and Cooney, 2004; Lai et al., 2001). NIRS and Raman spectroscopy are used extensively in the pharmaceutical industry due to the range of pharmaceutically relevant materials for which they have unique spectra. Moreover, these techniques are complementary to one another because they are sensitive to a different set of compounds. As an example, NIRS is sensitive to water whereas Raman spectroscopy is insensitive to water. Therefore, NIRS is preferable if the presence of water in a system is critical to distinguishing between components whereas Raman is better if water obfuscates spectral differences.

Additionally, there is a large body of research dedicated to quantifying segregation within powders. A particularly elegant method for quantifying the spatial segregation of powdered mixtures is the linear scale of segregation published by Danckwerts (1952). He based the linear scale of segregation on the correlation between the concentrations of samples a distance r apart. The coefficient of correlation between such samples is given by

$$R = \frac{\langle (a_1 - \bar{a})(a_2 - \bar{a}) \rangle}{\langle (a - \bar{a})^2 \rangle} \quad (1)$$

where a_1 and a_2 are the sample concentrations at two positions a distance, r, apart, $\bar{a}$ is the average of all measured concentrations, a is the concentration of any given sample, and $\langle\,\rangle$ is the expectation value operator. The autocorrelation function, $R(r)$, is generated by calculating R for many r, and the graph of $R(r)$ is called the correlogram. The linear scale of segregation, which is the average diameter of segregated clumps assuming they are spherical, is calculated by integrating $R(r)$:

$$S = \int_0^{\xi} R(r)\ dr \quad (2)$$

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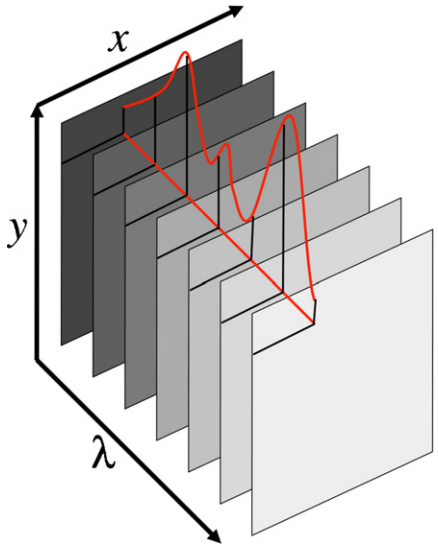

Fig. 1. An illustration of a hyperspectral data cube. Each square represents an image obtained from the same object while illuminated at a different wavelength.

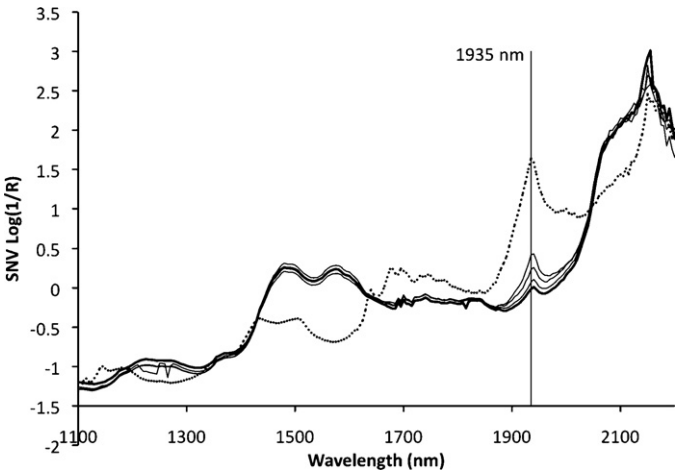

Fig. 2. Average SNV transformed spectra obtained from images of compacts with varying concentrations of tolmetin sodium dihydrate in an anhydrous lactose matrix. The bold spectrum is lactose and the dotted spectrum is tolmetin. Non-bold, solid spectra are mixtures. All samples contain 0.5% magnesium stearate. The 1935 nm peak corresponds to the water of hydration in the tolmetin and was used for discriminating between the anhydrous lactose and tolmetin.

where ξ is a distance r for which $R(r)$ is nearly zero (Danckwerts, 1952).

Although elegant theoretically, this approach has received little attention over the years due to the impracticality of generating correlograms using traditional assaying techniques. However, this concept is particularly well suited for use as an image analysis technique for hyperspectral imaging, which has emerged as a very useful technique for quantifying low component concentrations at the pixel level (Amigo and Ravn, 2009). This is because a single image has many pixels, each of which contain concentration information, located precise distances apart.

The research presented herein demonstrates a novel application of Danckwerts' linear scale of segregation as an image analysis technique for quantifying segregation within low dose mixtures from hyperspectral images of compacted powder blends. Near infrared (NIR) hyperspectroscopy is an imaging technique wherein the same spatial region of a sample is imaged at multiple different wavelengths. Therefore, every (x,y) pixel position for a given image has an entire NIR spectrum associated with it (Fig. 1). The spectra can then be analyzed using univariate or multivariate statistics, and a single image can be rendered showing the spatial distribution of the components. The linear scale of segregation can then be calculated from the rendered image.

2. Materials and methods

2.1. Sample preparation

Tolmetin sodium dihydrate (Noramco Inc, Athens, GA), anhydrous lactose (Quest International, Naarden, The Netherlands), and magnesium stearate (Merck & Co. Inc., West Point, PA) were used as received and blended to form dry powder mixtures. Mixtures were formed in 30 g batches with concentrations of 0.0, 0.1, 0.3, 0.5, 0.7, 0.9, 1.1, 5.0, and 10.0% (w/w) tolmetin with 0.5% magnesium stearate added as a lubricant. Blending was accomplished by placing the tolmetin between two layers of anhydrous lactose in a 4 oz ointment jar used as the mixing vessel and rotating the ointment jar end over end at 36 RPM for 10 min. The mixture was then sieved twice through a #24 Tyler mesh screen and blended for five more minutes with the magnesium stearate added. Environmental conditions were about 20 °C and 20% RH. Approximately 3 g samples of the blends were then transferred to a 1.5 cm × 4 cm die and compressed with flat faced punches on a Carver laboratory press (Fred S. Carver Inc., Summit, NH) controlled by an Auto Series pump unit (Carver Inc., Wabash, IN) at about 10,000 lbs on the ram.

2.2. Instrumentation

NIR hyperspectral imaging of the compacts was conducted by OPOTEK Inc. with a HySPEC™ hyperspectral imager with OPO technology (OPOTEK Inc., Carlsbad, CA). Compacts were imaged at wavelengths spanning 1100–2200 nm in 5 nm increments. Each image consisted of approximately 18.9 μm pixels and was generated by averaging ten frames from the corresponding wavelength.

2.3. Image analysis

Image analyses were performed with Mathematica 7.0 (Wolfram Research Inc., Champaign, Ill). The images from each compact were cropped to 300 × 300 pixels (~5.7 mm × 5.7 mm), and the reflectance from each pixel was calculated in accordance with the ASTM standard E 1655–00 (2000) by dividing the raw signal from each pixel by the average signal from a non-absorbing reference material imaged simultaneously with the compact at the same wavelength. The reflectance values were then compiled as a function of wavelength to form a spectrum for each pixel position. Reflectance values were converted to absorbance as $\log(1/R)$ where R is the reflectance. The absorbance spectra were subsequently transformed using a standard normal variate (SNV) transformation (Fig. 2).

The pixels from the 1935 nm images were selected for subsequent analyses due to the high absorbance in this region from the water of hydration in the tolmetin sodium dihydrate. Anhydrous lactose exhibits a correspondingly low absorbance in this region (See Fig. 2). The 1935 nm images were then binarized according to the following criterion: all pixels which exceed the average pixel value of for the 0.0% tolmetin compact by at least three standard deviations of the average were assigned a value of one. All other pixels were assigned a value of zero. Correlograms were then generated from the resulting binary images, and the linear scale of segregation was calculated from each.

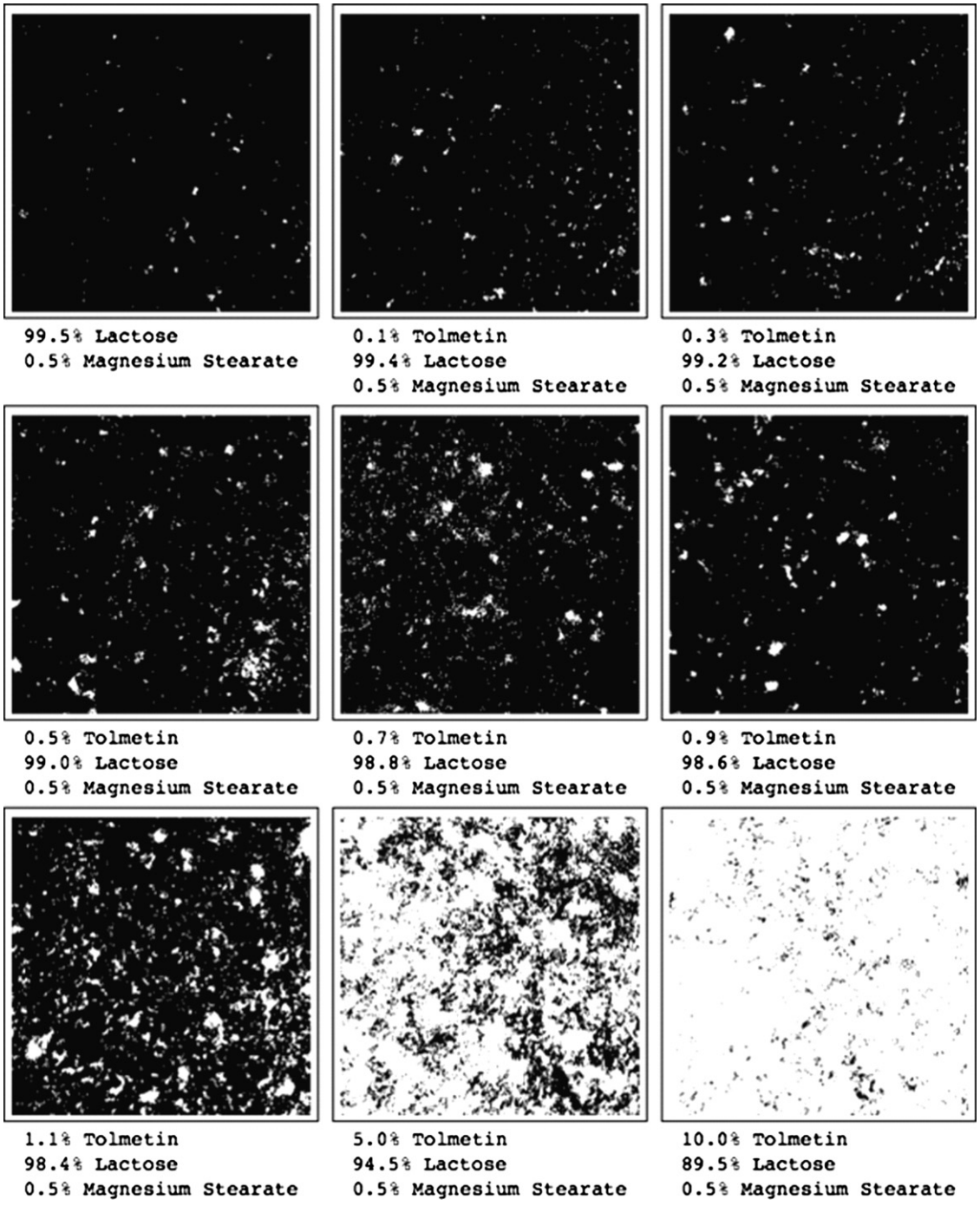

Fig. 3. Binarized, SNV transformed images acquired at 1935 nm. The white pixels indicate the presence of tolmetin.

In order to generate the correlograms, a maximum value of r, r_{max}, for which $R(r)$ approached zero was set. A distance of fifty pixels (~0.945 mm) was chosen for the 0.0–5.0% tolmetin compact images, and a distance of one hundred pixels (~1.89 mm) was chosen for the 10.0% tolmetin compact image. Twenty thousand different pixels were then randomly selected from within the area encompassed by the first $300 - r_{max}$ rows and the first $300 - r_{max}$ columns of each image. The correlograms were then generated based on the values of the randomly selected pixels and all pixels in the line segments formed by the random pixels and the r_{max} pixels to the right and r_{max} pixels down from the random pixels. The linear scales of segregation were then calculated by integrating linear interpolations of the correlograms from 0 to r_{max}.

3. Results and discussion

Similar to other NIR spectroscopic techniques, it was necessary to preprocess the spectra in order to reduce the amount of physical information contained within each spectrum in order to discriminate between different spectra. The SNV transformation proved adequate for elucidating local concentration differences present within a single image of the compacts studied.

The 1935 nm images were binarized after SNV transformation in order to clearly delineate the regions where tolmetin was present (Fig. 3). Fig. 4 shows the correlograms generated from the images. Initially, the scale of segregation, S, computed from each correlogram increased slightly with increasing concentration of tolmetin

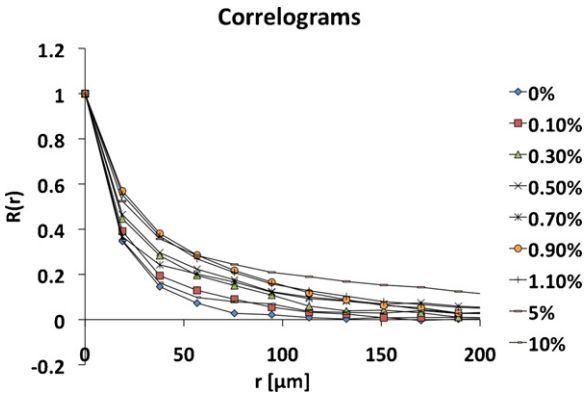

Fig. 4. Correlograms of the binary images shown in Fig. 3.

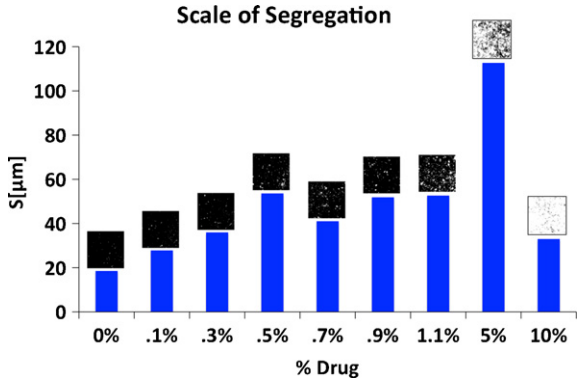

Fig. 5. Scales of segregation obtained from the correlograms shown in Fig. 4.

(Fig. 5). However, it appeared to level off somewhat after 0.5%, but increased substantially from 1.1% to 5%. This was followed by dramatic drop from 5% to 10%. The reason for the drop is that the 10% binary image is mostly white indicating that the pixels containing tolmetin dominate the image. Therefore, *S* is related to the cluster size of the black pixels which correspond to lactose rich regions. Some white pixels were observed in the 0% lactose image, but this has been attributed to noise since the scale of segregation for the image is very nearly the same as the size of a single pixel. Thus, the 0% image had several isolated pixels which varied significantly from the mean.

The initial upward trend of *S* with increasing drug load is consistent with the fact that higher drug load is likely to produce larger "drug pixel agglomerates" because there is more drug present. However, this does not indicate poorer homogeneity with increased drug load. For example, increased *S* does not imply an increased relative standard deviation (RSD) between unit dose samples. In fact, it is well known that increased drug load tends to decrease the RSD (Johnson, 1975). Therefore, *S* cannot be used independently of segregation intensity measurements to draw conclusions about the quality of mixtures with different drug loads. The utility of the scale of segregation is in the ability to compare agglomeration in mixtures of the same drug load such as those produced via different blending operations.

4. Conclusion

In summary, hyperspectral imaging shows promise as a tool for quantifying the scale of segregation of low-dose mixtures. This is made possible by the collection of full spectrum information at a very small scale of scrutiny from well defined spatial locations. Herein, the concept of using the scale of segregation as an image analysis technique was demonstrated. This was accomplished by calculating *S* for binarized images that show the location of pixels containing a detectable level of drug. A next step for this work is to calculate the scale of segregation based on actual pixel concentrations estimated via chemometric techniques such as Classical Least Squares (CLS) or Multivariate Curve Resolution-Alternating Least Squares (MCR-ALS) (Amigo and Ravn, 2009).

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