PHARMACEUTICAL TECHNOLOGY

Drug Product Characterization by Macropixel Analysis of Chemical Images

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ABSTRACT: Traditional monitoring of pharmaceutical manufacturing combines physical sampling and analytical methodologies (e.g. HPLC). Process analytical technology (PAT) can be implemented to collect real-time measurements, although successful monitoring requires that sampling be representative. The maximum spot size for a spectroscopic tool (e.g. near-infrared; Raman) should be equivalent to a single dosage size. A smaller spot size may provide a PAT tool that is sensitive to monitoring process changes, but if too small, produces non-reproducible data. The current study uses chemical imaging to determine appropriate spot size. A chemical image is an array of pixels which maps the chemical composition of the sample. "Macropixel Analysis" is introduced as a measure of image heterogeneity based on clusters of pixels (macropixels) within near-infrared chemical images. Analyses were conducted using non-overlapping tiles of macropixels (Discrete-Level Tiling) and all possible macropixels of the image (Continuous-Level Moving Block). Both methods minimize the variance between macropixel intensities by varying the size of the macropixels. Spot size is then chosen as the minimum macropixel size for which the range of macropixel intensities falls within an acceptable criterion. Both imaging-based algorithms provide useful quantitative information about the heterogeneity of pharmaceutical products. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 96:3390–3401, 2007

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INTRODUCTION

The chemical imager, a combination of digital imaging and optical spectroscopy, produces information-rich, real-time data in a non-contact, non-invasive and non-destructive sampling mode. These traits facilitate the use of chemical imaging as a tool for process analysis in a variety of industries, including pharmaceuticals,[1–3] biotechnology,[4] polymers,[5] and foods,[6] as well as in environmental[7] and medical applications.[8,9] The chemical imager combines the ability of optical spectroscopy to simultaneously identify[10] and quantify[11] several substances along with the spatial mapping capabilities of digital imaging. This combination is very powerful, unique and suitable for the measurement of heterogeneous materials,[12] but may not be a wise choice when measuring homogeneous materials since spectroscopy (without imaging) will yield the same information.

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Given its non-destructive nature and rapid analysis benefits, chemical imaging has potential as a Process Analytical Technology (PAT)[13] tool in the pharmaceutical industry.[14,15] On the pharmaceutical development path from drug substance to drug product, there are a number of instances where heterogeneous materials emerge. Therefore, there are a number of opportunities for chemical imaging to find use in pharmaceutical development and manufacturing.[16] For example, infrared imaging has been used to diagnose a "bad" set of dissolution profiles as being caused by the surface distribution of magnesium stearate[1,17]; and near-infrared imaging has been used for quality assurance purposes, such as monitoring blend homogeneity[15] and assessing tablets to determine blend uniformity.[18] Additionally, chemical imaging has been used for impurity analysis, hydration studies,[14] quantitative determination of API in tablets,[19] polymorph studies, quality assessment of commercial pharmaceutical products,[20] and for imaging the density gradient of tablets containing varying quantities of lubricant (magnesium stearate). As such, chemical imaging continues to be an emerging technology, even as development of more advanced optical components drive chemical imagers to better performance.

The chemical imager produces a cube of data for each sample analyzed. A typical digital image has an array of x and y coordinates occupied by a single value, as in a grayscale image; or occupied by a set of three coordinates, as in an RGB image. In the case of the hyperspectral image, each coordinate pair is occupied by a full spectrum.[21] This leads to extremely large data sets (10–100 megabytes); a reason why the analysis of spectroscopic images can be very time consuming.[22] It is often said that PAT instruments produce real-time data but the more relevant question is whether they can produce real-time results. With adequate calibration, it is possible to produce a concentration image in real-time (or near real-time) but this image may not be the final result of the analysis. The proposed approach of Macropixel Analysis would allow users of chemical imagers to rapidly produce a value that quantitatively represents the level of heterogeneity in a sample.

With the help of chemometrics, fast computers, and modern data analysis software, it has become easier to develop a concentration image for a particular component. Typically, this image is created using principal components regression (PCR) or partial least squares (PLS) regression. After this step, if the user is interested in the sample heterogeneity, the user is left to use the "human mind"—which is subjective—to visually diagnose the image for these characteristics. While this may be useful in some cases, there is a general need to speed up processing time and make the chemical image relevant to the "computer mind".[23] It is understood that heterogeneity is an important property in pharmaceutical processing, as it is related to blend uniformity, and therefore, can affect potency and content uniformity. However, quantitative relations between heterogeneity and critical quality attributes have yet to be examined. With a quantitative and objective metric for heterogeneity, it becomes possible to examine these relationships.

Spectroscopy and chemical imaging for the chemical and physical analysis of pharmaceutical products and processes offer significant advantages over traditional analytical methods. Sensor technologies can rapidly, non-invasively monitor materials during the process, however representative sampling can be challenging. To achieve representative sampling with optical measurements, it is necessary to determine the minimum field of view for an imaging instrument or minimum spot size for a spectroscopic measurement. Our previous study used chemical imaging to compare the homogeneity of multiple samples, an analysis based on the distribution of single-pixel concentrations.[18] That study did not address the scale of scrutiny. The current study extends this approach by introducing methods of analysis for determining a minimum sample size for representative sampling. A chemical image is an array of pixels which maps the chemical composition of the sample. Chemical images were acquired from pharmaceutical products exhibiting different levels of heterogeneity. "Macropixel Analysis" is introduced as a measure of image heterogeneity within near-infrared chemical images based on macropixels. The term macropixel refers to a square cluster of pixels with an intensity value equal to the average value of the included pixels. The Discrete-Level Tiling method used non-overlapping tiles of macropixels while the Continuous-Level Moving Block method used all possible macropixels of the image. Both methods minimize the variance between macropixel intensities by varying the size of the macropixels. Spot size is then chosen as the minimum macropixel size for which the range of macropixel intensities falls within an acceptable criterion. These algorithms

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