analytical chemistry

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Thermal Analysis by Structural Characterization as a Method for Assessing Heterogeneity in Complex Solid Pharmaceutical Dosage Forms

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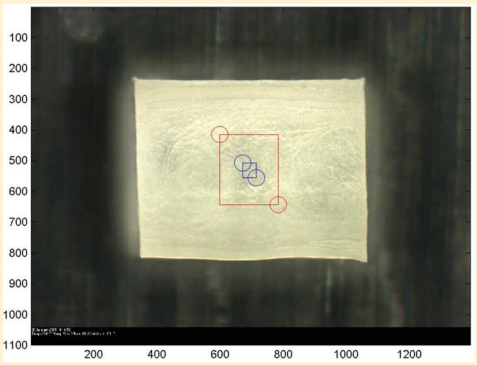
ABSTRACT: Characterizing inter- and intrasample heterogeneity of solid and semisolid pharmaceutical products is important both for rational design of dosage forms and subsequent quality control during manufacture; however, most pharmaceutical products are multicomponent formulations that are challenging in this regard. Thermal analysis, in particular differential scanning calorimetry, is commonly used to obtain structural information, such as degree of crystallinity, or identify the presence of a particular polymorph, but the results are an average over the whole sample; it cannot directly provide information about the spatial distribution of phases. This study demonstrates the use of a new thermo-optical technique, thermal analysis by structural characterization (TASC), that can provide spatially resolved information on thermal transitions by applying a novel algorithm to images acquired by hot stage microscopy. We determined that TASC can be a low cost, relatively rapid method of characterizing heterogeneity and other aspects of structure. In the examples studied, it was found that high heating rates enabled screening times of 3−5 min per sample. In addition, this study demonstrated the higher sensitivity of TASC for detecting the metastable form of polyethylene glycol (PEG) compared to conventional differential scanning calorimetry (DSC). This preliminary work suggests that TASC will be a worthwhile additional tool for characterizing a broad range of materials.



The heterogeneity of material in a complex formulation is often a key parameter that requires monitoring during quality control of pharmaceutical products. In multicomponent formulations, which is the case for most pharmaceutical products, the uniformity of the distribution of excipients and active therapeutic drugs across the dosage form is extremely important for ensuring the quality, such as physical stability over shelf life, and *in vivo* performance, such as drug release rate, which are critically responsible for the overall therapeutic efficiency of the product.[1] However, to characterize and assess heterogeneity within a single formulation often requires the use of multiple off-line localized analytical techniques, which is time-consuming and a costly process. Most analytical techniques with the capacity for characterizing the heterogeneity combine microscopy with either spectroscopic or thermal techniques.[2−6] As an example, micro/nano thermal analysis using a heated probe in a scanning probe microscope is a thermal technique that can provide information on sample heterogeneity using either local thermal analysis or photothermal IR spectroscopy.[7−9] However, it is slow; for example, it can take over an hour for a single high spatial resolution image using transition temperature microscopy.[10] The technique we use in this study, thermal analysis by structural characterization (TASC), is an optical analogue of micro/nano thermal analysis. TASC is a new microscopic analytical method developed recently by Reading et al. for many applications including local thermal analysis (LTA), glass transition kinetics, and thermal dissolution *analysis*.[11]

The method consists of quantifying changes in successive micrographs while at the same time allowing for any movement by the sample. As illustrated in Figure 1a, a region of the sample is selected that is designated the region of interest or ROI (within which lies the structure of interest). Also, a larger area (the target area or TA) over which the ROI is scanned is selected (in this case, the TA is the entire 7 × 7 pixels). Figure 1b shows the extracted ROI that is the template that is raster scanned over the TA. At each point, in the scan, the corresponding pixels are subtracted and the sum of the modulus of all differences is calculated. In this simplified representation, subtracting the same pixel values gives zero and subtracting different pixels gives 1. After the scan is completed, it is the minimum value for the sum of all differences obtained during the course of the scan that is returned by the TASC algorithm. Figure 1c shows the start of the

Received: June 10, 2015
Accepted: October 2, 2015
Published: October 2, 2015

DOI: 10.1021/acs.analchem.5b02192
Anal. Chem. 2015, 87, 10848−10855