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Characterization of pharmaceutical powder blends using *in situ* near-infrared chemical imaging

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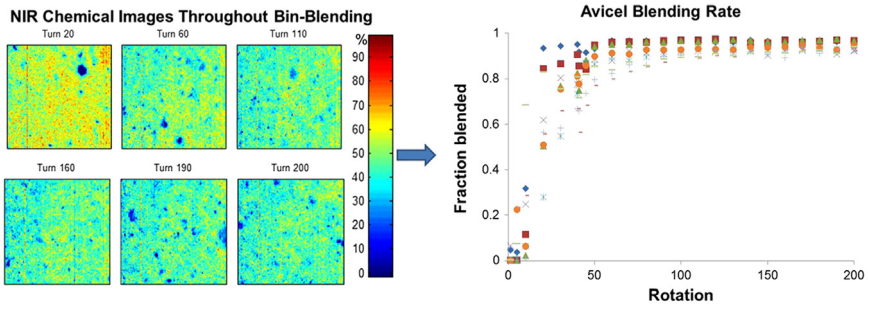
HIGHLIGHTS

- Composition maps of each material in a powder blend measured for selected rotations.
- Automated chemical image analysis parameters were measured to study blending dynamics.
- Large acetaminophen aggregates were observed even after 190 turns in low-shear blending.
- In all blends, Avicel blended significantly more slowly than lactose.
- Increase in acetaminophen concentration slowed the blending of other excipients.

GRAPHICAL ABSTRACT



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ABSTRACT

The present study introduces a new *in situ* near-infrared chemical imaging technique (imMix™) designed to characterize micro-mixing in pharmaceutical powder blends. The technique uses in-line, non-contact monitoring of the blending process, eliminating the bias introduced by commonly used powder sampling techniques. A Science-Based Calibration (SBC) chemometric method, which uses pure component spectral data to create a calibration model, was used to create concentration maps of the blends studied here. The advantage of SBC over the alternative Partial Least Squares (PLS) or Principal Component Analysis (PCA) calibration methods is that it does not require a large number of samples to create a calibration. The imMix system proved to be useful in monitoring the spatial distribution and aggregate sizes of acetaminophen, used as the model drug, and of excipients in the blends. Using a 1-l bin-blender, measurements were able to detect changes in the constituents and other experimental parameters as a function of blending time. Such measurements can be used to determine the mixing time and shear requirements of blends during product and process development.

1. Introduction

Batch powder mixing is one of the most common and important unit operations in a wide range of industries, such as food, cosmetics, pharmaceuticals, chemicals, ceramics, and catalysts. In pharmaceuticals, it has been the focus of intense interest in the past 20 years, and it has been the subject of many studies. Most of the research has focused on characterizing the process for a given

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set of materials and determining the design parameters that will reach the required blend homogeneity. Quantification of mixing efficiency has concentrated on characterizing the bulk homogeneity of the relevant constituents, primarily the active pharmaceutical ingredients (APIs) and, to a lesser extent, other functional ingredients such as lubricants, glidants, and disintegrants in powder blends. Studies have been carried out for several types of blenders, including ribbon blenders (Muzzio et al., 2008), V-blenders (Perrault et al., 2010; Portillo et al., 2006), double-cone blenders (Brone and Muzzio, 2000) and bin-blenders (Mehrotra and Muzzio, 2009). Despite all these efforts, powder mixing remains poorly understood, especially for applications that involve blending small quantities of cohesive APIs in large amounts of excipients with a wide range of flow properties (Muzzio et al., 2002).

In most situations in practice, powder blending involves both macro-mixing as well as micro-mixing processes. Macro-mixing focuses on the quantification of the evolving bulk homogeneity of relevant ingredients. Micro-mixing is the process which describes how particles from different ingredients interact with each other to form a blend with certain properties such as degree of agglomeration, cohesion (Vasilenko et al., 2011), hydrophobicity (Llusa et al., 2010), and electric conductivity (Pingali et al., 2009). Intuitively, while macro-mixing correlates to total process strain, the phenomena governing micro-mixing should be dependent on both strain and shear rate and therefore should be dependent upon the system scale. Nevertheless, despite the importance of micro-mixing, this aspect of the process has been examined much less than the bulk blend behavior. Therefore, there is still a lack of understanding of how the blending of powders at the micro-scale works, how particles interact, and how the final arrangement of particles affects subsequent unit operations and final product performance (Hardy et al., 2007; Pingali et al., 2011). Recent research has shown that the mixing order of materials changes the way particles interact with each other at the micro-scale, affecting final blend and tablet bulk properties such as hydrophobicity and dissolution profiles, respectively (Pingali et al., 2011). These findings highlight the need to further understand the micro-mixing mechanisms of powder blending and how doing so is useful both for new product and process development, and to overcome issues that often arise with existing processes.

While the micro-mixing state of final blends has been characterized in some cases by digital image analysis (Daumann et al., 2009; Realpe and Velazquez, 2003) and magnetic resonance imaging (Hardy et al., 2007; Sommier et al., 2001), these techniques present challenges that have prevented them for becoming a common tool in pharmaceutical blending process design. Their "poor" resolution and the fact that they require color/opaqueness contrast to be detectable or "visible", are limiting factors when studying pharmaceutical powders, since most powders are very similar in color (white). Scanning electron microscopy (SEM) has also been used to examine a single particle or small groups of particles, however this technique is time-consuming, destructive, and not representative of scale (Pingali et al., 2011). Thus, novel techniques capable of fast analysis, suitable resolution, and the ability to examine blends at the particle (or aggregate) scale are needed. Near-infrared chemical imaging (NIR-CI) shares all the benefits of NIR with the additional insights provided by digital imaging processing. Several articles explain in detail the principles of NIR spectroscopy and make specific references to its use in the pharmaceutical industry along with the application of chemometrics to facilitate extraction of relevant information (Beer et al., 2011; Krämer and Ebel, 2000; Porfire et al., 2012; Ravn et al., 2008; Reich, 2005).

NIR-CI has been used to study the micro-mixing distribution of ingredients in tablets (Lyon et al., 2002) and pellets (Sabin et al., 2011) as well as other pharmaceutical dosage forms such as films (Rozo et al., 2011). NIR-CI has also been used to characterize the distribution of API agglomerates in pharmaceutical blends. However, these studies have been carried out using blends obtained in small vials in order to understand the feasibility of NIR-CI for this purpose (Li et al., 2007; Ma and Anderson, 2008). NIR-CI was previously used to monitor mixing in a V-blender (El-Hagrasy et al., 2001). The results for API quantification using NIR-CI were compared with the results of a single point NIR, but the degree of agglomeration of the components was not characterized due to the low resolution of the NIR-CI system at the time. Recently, Šaŝić et al. used NIR-CI to study the effect of milling a powder blend before lubrication and compression (Šaŝić et al., 2013). The results made it possible to examine the degree of agglomeration in blends and tablets.

This paper introduces the use of an *in situ* near-infrared chemical imaging technique able to examine the distribution of the materials while being blended. The non-destructive method used here generates thousands of spectra per second, providing a larger amount of compositional information than other conventional methods. This technique allows monitoring micro-mixing as the blending process progresses while eliminating issues encountered with extractive sampling (Muzzio et al., 2003; Muzzio et al., 1997; Susana et al., 2011; Venables and Wells, 2002), and with long and destructive characterization techniques. A Science-Based Calibration (SBC) method Marcbach, 2010) which uses pure component spectral data and noise estimates to create a calibration model, was used to create the concentration maps of the blends studied here. The advantage of SBC over PLS or PCA calibration methods is that it does not require a large amount of samples to create a calibration. The main objectives of the study reported here were to characterize this NIR-CI analytical technique, to quantify micro-mixing in pharmaceutical blends using statistical analysis of the compositional maps obtained, and to determine the micro-mixing dynamics in a bin-blender as a function of processing parameters. The use of this NIR-CI tool allowed the micro-mixing dynamics studies of various formulations using APAP as the model drug.

2. Materials and methods

2.1. Materials

The materials used in all the experiments reported here were as follows: acetaminophen (semi-fine, USP/paracetamol PhEur, Mallinckrodt, Raleigh, NC, USA), microcrystalline cellulose (Avicel PH101, FMC Biopolymer, Newark, DE, USA), lactose (monohydrate N.F., crystalline, 310, Regular, Foremost Farms, USA, Rothschild, WI, USA), amorphous fumed silica (Cab-O-Sil M-5P, Cabot Corporation, Tuscola, IL, USA), and magnesium stearate N.F. (non-Bovine, Tyco Healthcare/Mallinckrodt, St. Louis, MO, USA). The nominal particle sizes of the materials used are listed in Table 1.

Table 1
Blend constituents and nominal mean particle size.

Material	Mean particle size
Acetaminophen (APAP)	45 μm
Avicel 101	50 μm
Regular lactose	180 μm
Cab-O-Sil (SiO_2)	5–20 nm
Magnesium Stearate	10 μm