Detecting Blending End-Point Using Mean Squares Successive Difference Test and Near-Infrared Spectroscopy

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ABSTRACT: An algorithm based on mean squares successive difference test applied to near-infrared and principal component analysis scores was developed to monitor and determine the blending profile and to assess the end-point in the statistical stabile phase. Model formulations consisting of an active compound (acetylsalicylic acid), together with microcrystalline cellulose and two grades of calcium carbonate with dramatically different particle shapes, were prepared. The formulation comprising angular-shaped calcium carbonate reached blending end-point slower when compared with the formulation comprising equant-shaped calcium carbonate. Utilizing the ring shear test, this distinction in end-point could be related to the difference in flowability of the formulations. On the basis of the two model formulations, a design of experiments was conducted to characterize the blending process by studying the effect of $CaCO_3$ grades and fill level of the bin on blending end-point. Calcium carbonate grades, fill level, and their interaction were shown to have a significant impact on the blending process. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:2541–2549, 2015
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INTRODUCTION

One of the most critical unit operations during manufacturing of solid dosage forms is the blending operation. Achieving a uniform mixture of the active pharmaceutical ingredient (API) and the needed excipients is particularly important. Problems incurred during blending can lead to inadequate final product quality, such as content uniformity, disintegration time, and/or dissolution behavior. All these performance parameters can directly impact the final dosage form efficacy, *in vivo* performance, and ultimately patient safety. For this reason, homogeneity of powder blends and unit dosage forms is especially importance.[1]

A blend, in the classical pharmaceutical sense, is considered to be homogeneous when the API content of the blend samples is within specification, while assuming that all excipients are also evenly distributed.[2] Blending is a reshuffling process involving the random movement of individual groups of particles. Competing process with the powder blending process are segregation and/or demixing.[3,4] Three main mechanisms are responsible for blending, namely, diffusion, convention, and shear. The degrees to which these mechanisms influence a blending process depend on the flow properties of the powders being blended, the specific equipment selected, and the process parameters/settings.[3,5] Several factors such as particle size, shape, density, electrostatic charge, and surface moisture content have a considerable impact on the flow properties of powders.[6,7] As an example, spherical- and cubic-shaped particles often exhibit good flow properties and therefore promote blending. But at the same time, well-flowing material can also be more prone to demixing/segregation. Plate- and needle-shaped particles, for example, have poor flow properties and are more likely to agglomerate, making it more difficult to achieve a uniform blend. However, an advantage of blending these plate and needle-shaped particles is that once they are well blended, they are more likely to stay as uniform blend.[3,4,8]

In industrial practice, the homogeneity of a powder blend is determined by invasive thief sampling followed by a time-consuming off-line chemical analysis of the sampled material.[5] An alternative method to determine the homogeneity is by using near-infrared spectroscopy (NIRS) that is a powerful non-invasive analytical technique and is sensitive to both chemical and physical properties in the measured sample. In addition, NIRS is a fast and easy method to interface with the process for real-time monitoring.[2] Several researchers have used NIRS and different classical statistic, univariate and multivariate approaches, to develop qualitative[2,9–19] and quantitative[13,20–24] methods for studying the blend homogeneity. The qualitative methods are typically simple to use, whereas the quantitative methods are more complex but provide information about the mixture composition. The interested reader is referred to reviews by De Beer et al.,[25] Reich,[26] Roggo et al.,[27] and a book chapter in Drennen and Ciurczak.[28]

One of the most prominent qualitative methods providing reliable results is the use of the multivariate data analysis method, principal component analysis (PCA).[29] A number of authors have used PCA[11,12,15,17,18,30] in order to monitor and estimate the blend homogeneity. One approach is plotting the score values of the first principal component (PC1) against process time and assuming blend homogeneity to be reached when the score level stabilizes around one (arbitrary) point as a function of time.[11,31] Another approach is plotting the first two PCs for replicate target blends (blends that are assumed to be

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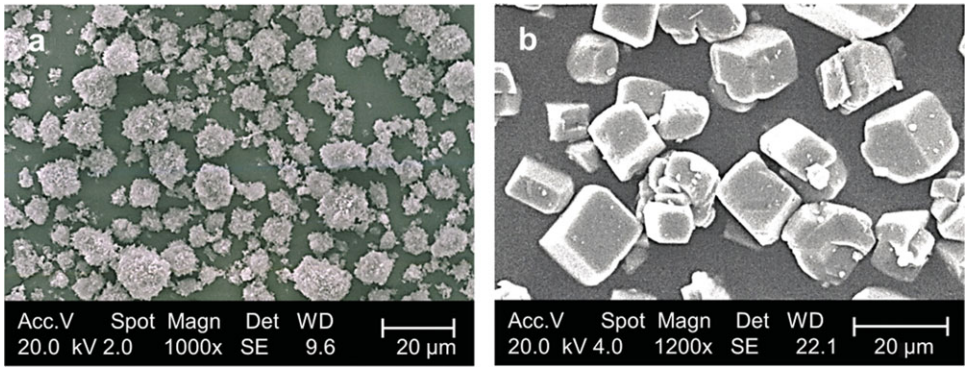

Figure 1. Scanning electron microscope images of (a) $CaCO_3$-A and (b) $CaCO_3$-E.

homogeneous) and test blends in a two-dimensional score plot. If the target blends cluster together in this score plot, then test blends that have reached homogeneity should be close to or overlapping with the target blends cluster.[11,12] However, the establishment of a reliable and coherent end-point detection method with a solid statistical rationale is the keystone where many of the already proposed methods fail, as they do not fully describe what the detection is based on.

In this sense, Puchert et al.[2] proposed a new approach called "principal component score distance analysis." This method establishes a time window where spectral variability in the blend is lower than a preset threshold value and uses Hotelling's T^2 statistics to monitor and report blend homogeneity. However, Puchert et al.[2] did not only consider the process stability to detect the end-point but rather stability compared with a target spectrum. This hampers the method for real-time usage, because the method is strictly depending on knowing beforehand the spectral profile of the final blend. And this is not feasible in many occasions.

In order to have a stable process when working with real-time series data points, it is important to have an understanding of the types of expected variation in the data. Two important classes of variation are the following ones: (1) controlled variation, which is characterized by a stable and constant pattern of (hopefully minor) variation over time. This type of variation comes in a random order and depicts a uniform fluctuation about a constant level; the process is said to be in a state of statistical control. (2) Uncontrolled variation, which is characterized by a pattern of variation that changes over time. This type of variation indicates that the process is not yet in a state of statistical control and further processing (i.e., blending) is required. A process is considered stable if the average process value is constant and the variation is random.[32,33] One approach to evaluate process stability in serial-related data points is the application of the mean square successive difference test (MSSDT) for serial randomness.[34–37]

Using this knowledge, our main aim was, therefore, to develop an algorithm based on MSSDT applied to near-infrared (NIR) and PCA scores to monitor and determine the blending profile and to statistically assess the end-point in the statistical stabile phase. In order to access the ability of the algorithm to determine the correct blending end-point, two powder formulations, composed of different calcium carbonate grades, were investigated. The flow properties of the pure calcium carbonate grades and their powder formulations were determined by a ring shear tester. A design of experiment was conducted to identify how the calcium carbonate grades and fill level of the blender bin affect the blending end-point. For all blending, experiments samples were randomly withdrawn from the surface of each batch in order prevent local segregation because of the thief sampling process. Subsequently, samples were investigated off-line by UV–Vis spectroscopy to determine the API uniformity, thereby validating the ability of the algorithm to detect the blending end-point.

EXPERIMENTAL

Materials and Instrumental Setup for Online NIRS

As a model API, acetylsalicylic acid (ASA) USP grade (Rhodine® 3080; Rhodia, Saint-Fons, France) was used. The excipients used were microcrystalline cellulose (MCC), Comprecel® PH 101 USP grade (MINGTAY Chemical, Taoyan city, Taiwan), and two grades of calcium carbonates ($CaCO_3$) with different shapes, namely, angular $CaCO_3$ Sturcal L® (Specialty Minerals, Lifford, Great Britian) and equant $CaCO_3$ Scoralite D® (Scora S.A., Caffiers, France).

Figure 1 shows scanning electron microscope images of the two $CaCO_3$ grades. Angular-shaped particles are sharp-edged, polyhedral-shaped particles with a rougher (i.e., bumpy, uneven) surface. Equant-shaped particles are cubic or spherical-shaped particles with similar width, length, and thickness and smoother surface.[38] Throughout this study, $CaCO_3$ Sturcal L® and $CaCO_3$ Scoralite D® are noted as $CaCO_3$-A and $CaCO_3$-E, respectively.

After accurate weighing, the ingredients of each formulation batch were transferred to a 10-L bin-blender with baffles (LM 40; L.B.Bohle Maschinen & Verfahren GmbH, Ennigerloh Haan, Germany). A Prozess Analysator spectrometer controlled with the SX-center software (NIR-Online GmbH, Walldorf, Germany) was used for spectral acquisition in diffuse reflectance mode over the wavelength range 1100–1700 nm with a resolution of 5 nm for sample measurements. This enabled acquisition of six scans (integration time: 30 µs) that were averaged into one spectrum for each blender revolution. A schematic drawing of the instrumental setup is shown in Figure 2. The spectrometer was mounted directly onto the Bohle bin blender via a custom-build lid from Bohle. The spectrometer has a built in sensor to determine the orientation and whenever the instrument was located at the bottom position during a bin rotation a triggering device signalled the start of a new spectral recording; a trigger angle of −45° to 45° was