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Modeling strategies for pharmaceutical blend monitoring and end-point determination by near-infrared spectroscopy

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ABSTRACT

The implementation of a blend monitoring and control method based on a process analytical technology such as near infrared spectroscopy requires the selection and optimization of numerous criteria that will affect the monitoring outputs and expected blend end-point. Using a five component formulation, the present article contrasts the modeling strategies and end-point determination of a traditional quantitative method based on the prediction of the blend parameters employing partial least-squares regression with a qualitative strategy based on principal component analysis and Hotelling's T^2 and residual distance to the model, called Prototype. The possibility to monitor and control blend homogeneity with multivariate curve resolution was also assessed. The implementation of the above methods in the presence of designed experiments (with variation of the amount of active ingredient and excipients) and with normal operating condition samples (nominal concentrations of the active ingredient and excipients) was tested. The impact of criteria used to stop the blends (related to precision and/or accuracy) was assessed. Results demonstrated that while all methods showed similarities in their outputs, some approaches were preferred for decision making. The selectivity of regression based methods was also contrasted with the capacity of qualitative methods to determine the homogeneity of the entire formulation.

1. Introduction

Blending is an essential unit operation in the manufacturing process of solid dosage forms. It is critical in ensuring homogeneity of the powder blend before compression. Mixing problems can lead to inadequate tablet performance, possibly affecting patient safety and efficacy (Hickey and Garderton, 2010). Thief sampling followed by quantitative assay has traditionally been the preferred approach to blend homogeneity determination (Muzzio et al., 1997; Venables and Wells, 2002). It is, however, progressively replaced by process analytical technologies (USFDA, 2004) such as near-infrared spectroscopy (NIRS). While thief sampling provides a complete sampling of the blend homogeneity status at discrete time points, NIRS offers the possibility to monitor on-line and in real-time, from one or several locations in the blender, the evolution of a blending unit-operation. Blend monitoring and control (end-point determination) by NIRS has been the subject of numerous publications (Sanchez et al., 1995; Hailey et al., 1996; Sekulic et al., 1996, 1998; Wargo and Drennen, 1996; Maesschalck et al., 1998; Berntsson et al., 2002; Blanco et al., 2002; Duong et al., 2003; El-Hagrasy et al., 2006; Skibsted et al., 2006; Li et al., 2007; Shi et al., 2008; Storme-Paris et al., 2009; Wu and Khan, 2009; Igne et al., 2011, 2013; Koller et al., 2011; Momose et al., 2011; Puchert et al., 2011; Sulub et al., 2011) and the topic of several book chapters (Drennen and Lodder, 1991; Ciurczak and Drennen, 2002).

The continuous sampling provided by NIRS allows the investigation of two blending process characteristics: the process trajectory and the process end-point. Process trajectory refers to the trends observed in the evolution of active pharmaceutical ingredient(s) (API) and excipient(s) homogeneity as a function of time during mixing. Because of variable powder handling and dispensing, blender loading pattern differences, and raw material variability (i.e., lot-to-lot, relative humidity), no two blends will present the exact same mixing kinetics. The consequences will be that until homogeneity is reached, different blends of the same formulation will not

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necessarily have the same composition at a given period of time. Knowledge of this variability will, however, be of great value to pharmaceutical scientists to understand better the natural process variations that can be expected in normal operating conditions. In addition, abnormal process behaviors may be identified and the related trajectories may inform about the root causes of the process anomaly.

Process end-point, on the other side, refers to the time point at which a satisfactory homogeneity level has been reached for a particular product. Due to the various sources of process variability potentially impacting the process trajectory, no two blends will reach homogeneity at precisely the same time. In addition, the conditions for use of a certain algorithm employed to check for homogeneity may lead to different answers related to the end-point detection (even for a same blend) (Igne et al., 2013). Indeed, an end-point will be affected by the number of observations (or predictions) taken into account (period of time considered to estimate homogeneity), the number of components considered (API alone or global formulation), the parameter used for end-point detection (a particular wavelength intensity, API prediction, global formulation predictions, etc.), and the criterion used to stop the unit operation (related to the closeness to a nominal concentration value, to the relative variation among consecutive predictions, predictions within confidence limits, predictions following a particular statistical distribution, etc.).

Statistics used to monitor and control blending are, therefore, of particular interest. Numerous qualitative and quantitative methods have been developed to help determine when a blending operation should be terminated. The end-point is usually specified as when a particular statistic, qualitative or quantitative, fulfills a threshold-related condition or remains constant over a given number of consecutive blending observations.

Qualitative approaches are based on the evolution, or rather the lack of evolution, of spectral shapes or individual absorption values, and hence, chemical composition, over time. First attempts of qualitative on-line blend monitoring methods were based on the calculation of a moving window standard deviation of an optical parameter (reflectance, absorbance) at one or multiple wavelengths of several subsequent spectra, followed by the determination of an overall standard deviation plotted against time (Sekulic et al., 1996). Other approaches were based on the use of dissimilarity indices, principal component analysis, soft independent modeling of class analogies (SIMCA) (Sekulic et al., 1998), Hotelling's T^2 statistic (Maesschalck et al., 1998; Puchert et al., 2011), and principal component modified bootstrap error-adjusted single-sample technique (El-Hagrasy et al., 2006).

In contrast, quantitative approaches rely on developing a regression model to predict the amount(s) of the constituent(s) present in the mixture. These methods ensure specificity to the parameter(s) of interest that can be difficult to assess with qualitative methods. Traditionally, the deviation of concentration (s) over time from nominal/reference values, predicted by multivariate calibration methods and, most often, by partial least-squares (PLS) regression, is evaluated (Berntsson et al., 2002). Quantitative approaches based on control charts have also been proposed (Skibsted et al., 2006).

Basing a blend monitoring and control system on a quantitative approach has the advantage that the changes in homogeneity over a period of time and the deviation of the prediction(s) from target concentration(s) are simultaneously assessed. However, end-point criteria based solely on the evolution of a single compound, usually the active ingredient, may not be sufficient when considering the homogeneity of a global pharmaceutical formulation. When the excipients' distributions are also of interest to obtain a particular drug release profile, it may be more relevant to implement a quantitative approach predicting all the compounds of interest, or a qualitative method assessing the global homogeneity of the powder blend. In cases where wet chemistry methods are not commonly developed for the analytical determination of excipients, or where only limited variability is available to calibrate the end-point determination model (normal operating condition (NOC) samples available), qualitative methods become highly relevant. Mixed strategies, such as developing a regression approach for predicting the API and a qualitative model to monitor the rest of the formulation, can also be applied. The advantages and limitations associated with the information sought and the available modeling methods must be appropriately weighted in order to develop the most suitable control strategy.

The present article contrasts modeling strategies and end-point outputs of a traditional quantitative method based on the prediction of the blend parameters employing partial least-squares regression with a qualitative strategy based on principal component analysis and Hotelling's T^2 and residual distance to the model, called Prototype (Tracy et al., 1992; Kourti and MacGregor, 1995; Preys et al., 2007). In addition, monitoring and control of blend homogeneity with multivariate curve resolution (MCR) will be presented and compared with the previous methodologies (Tauler et al., 1993; De Braekeleer et al., 2000; Jaumot et al., 2013). Multivariate curve resolution has been successfully implemented in numerous industrial applications and offers the possibility to work in a quantitative or qualitative fashion based on the mathematical conditions (constraints) selected (de Juan and Tauler, 2006; de Juan et al., 2009; Tauler et al., 2009). The type of information and the comparison of the end-point detection provided by these methodologies will be presented, taking as example the blending process of a drug formulation monitored by NIR spectroscopy.

2. Materials and methods

2.1. Blending manufacturing and monitoring procedure

The blending process studied was related to a five-component formulation, comprised of acetaminophen (APAP; Rhodapap, Rhodia Organique, Roussillon, France), lactose (monohydrate NF–product 316/Fast-Flo modified spray-dried; Foremost Farms USA, Rothschild, WI, USA), microcrystalline cellulose (MCC; Avicel PH 200, FMC Biopolymer, Mechanicsburg, PA, USA), croscarmellose sodium (Spectrum, Gardena, CA, USA), and magnesium stearate (MgSt; Mallinckrodt, Hazelwood, MO, USA). The active ingredient, APAP, was milled using a Quadro Comil (Model 197S; Quadro Engineering, Waterloo, ON, Canada) to reach a median particle size of 315 μm and avoid potential mixing problems with excipients.

For all blending runs, all ingredients were mixed simultaneously at the rate of 15 rotations per minute in a 3.5 quart, stainless steel, custom made V-blender (60% fill ratio). All ingredients were loaded via the bottom of the blender following the sequence presented above.

Two SpectralProbes Process NIR spectrometers (Thermo Fisher Scientific, Wilmington, MA, USA; serial numbers 1277 (sensor 1) and 1502 (sensor 2)) were used to monitor blending in real-time. However, only the outputs of sensor 1 were considered in the present study to focus on the modeling and not include arm-to-arm variability as well as calibration transfer considerations. Such questions were addressed in a series of articles (Igne et al., 2011, 2013). The instruments collect 100 absorption values between 1600 and 2400 nm in reflectance mode and are triggered by a light intensity sensor (intensity rises when powder falls against the sampling window, enabling collection). The spectrometer uses a single InGaAs detector and employs MEMS technology. Measurements were made through a sapphire window in the top of either arm of the blender. Spectra were sent wirelessly to a computer