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An efficient, maintenance free and approved method for spectroscopic control and monitoring of blend uniformity: The moving *F*-test

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ABSTRACT

Dry powder mixing is a wide spread Unit Operation in the Pharmaceutical industry. With the advent of in-line Near Infrared (NIR) Spectroscopy and Quality by Design principles, application of Process Analytical Technology to monitor Blend Uniformity (BU) is taking a more prominent role. Yet routine use of NIR for monitoring, let alone control of blending processes is not common in the industry, despite the improved process understanding and (cost) efficiency that it may offer. Method maintenance, robustness and translation to regulatory requirements have been important barriers to implement the method. This paper presents a qualitative NIR-BU method offering a convenient and compliant approach to apply BU control for routine operation and process understanding, without extensive calibration and method maintenance requirements. The method employs a moving *F*-test to detect the steady state of measured spectral variances and the endpoint of mixing. The fundamentals and performance characteristics of the method are first presented, followed by a description of the link to regulatory BU criteria, the method sensitivity and practical considerations. Applications in upscaling, tech transfer and commercial production are described, along with evaluation of the method performance by comparison with results from quantitative calibration models. A full application, in which end-point detection via the *F*-test controls the blending process of a low dose product, was successfully filed in Europe and Australia, implemented in commercial production and routinely used for about five years and more than 100 batches.

1. Introduction

The last decade, a paradigm change has been ongoing in pharmaceutical development and manufacturing, largely driven by the introduction of Quality by Design (QbD) concepts [1]. In the QbD approach, quality of intermediate and end products is designed in the manufacturing process by gaining detailed process knowledge and implementing controls, instead of only testing end product quality. Implementation of QbD principles improves cost-efficient approach to delivering high quality medicines. Regulatory bodies (EMA, FDA, PMDA) and the ICH workgroup are placing great emphasis on QbD components as part of regulatory filing and QbD has become crucial in drug development [2].

Within QbD, Process Analytical Technology (PAT) plays an important role to identify and monitor product Critical Quality Attributes (CQA's) in the process, gain process understanding in development and, ultimately, control Critical Process Parameters (CPPs) in process steps entailing a high quality risk [3]. Aside from many more recently emerged in-line methods (e.g., TeraHertz Spectroscopy, LIF, Optical Coherence Tomography and FBRM [4,5]), Near Infrared (NIR) and, to a lesser extent, Raman Spectroscopy still play the most dominant role for PAT in pharmaceutical industry due their ability to monitor both chemical and physical product characteristics.

In development and manufacturing of solid dosage forms, blend uniformity (BU) is among the most important CQA's. For development of dry mixing processes, knowledge on BU and the related

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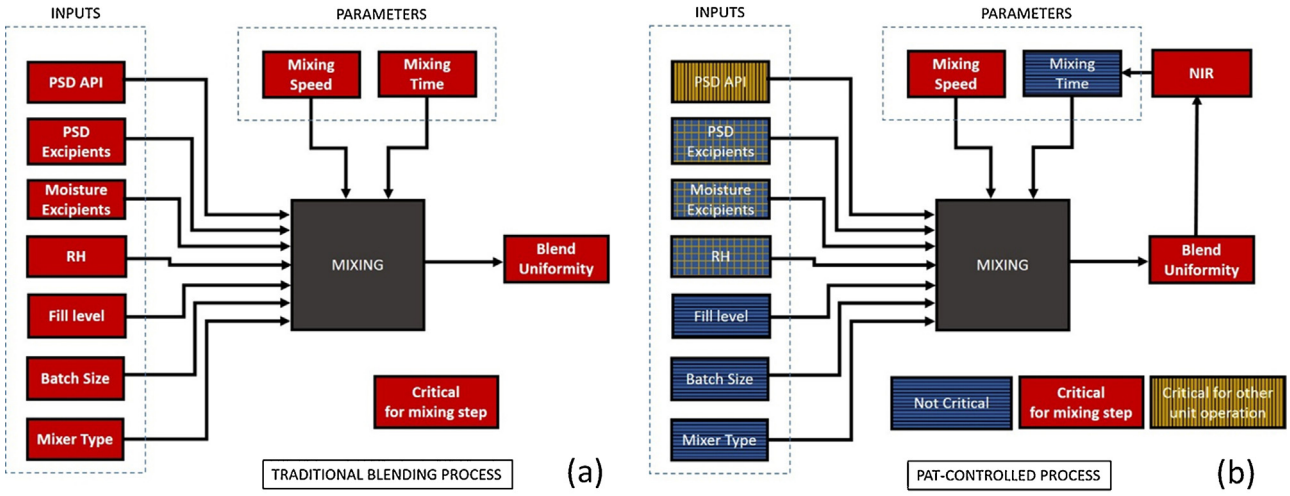

Fig. 1. Criticality of input material variability and process parameters for BU[1] in a traditional blending process is eliminated by applying a robust PAT method to control the process.

process design space (mixing time, fill grade, mixing speed, mixer type etc.) is required at an early stage [6]. NIR methods are well suited to monitor uniformity of the Active Pharmaceutical Ingredient (API) and material or excipient attributes during blending. It is now generally accepted that, with suitable interfacing, robust analysis methods and proper interpretation, in-line NIR offers major advantages in reliability, efficiency and process understanding compared to traditional sampling [7,8]. Availability of PAT data on process performance and variability further offers opportunities to apply continuous process improvement strategies. From a risk perspective, direct BU control (partly) eliminates criticality of raw material properties, process parameters and their interactions for BU, see Fig. 1. This can strongly reduce development efforts and input control requirements in commercial production [3,9].

However, translating in-line NIR data to BU remains challenging. Depending on the methodology, end-point detection methods either lack a sound rational in a regulatory context or the development efforts for a sufficiently robust method can be prohibitive [10,11]. The latter applies to quantitative methods such as Partial Least Squares (PLS) models, which monitor content variation using multivariate calibration. Achieving a robust calibration is the main challenge here [12]. In terms of costs and efficiency, the importance of robustness and transferability of NIR methods cannot be emphasized enough. Quantitative models may also have too large prediction errors for low dose formulations, i.e., those formulations with the most significant BU risk, for which monitoring and control is most needed.

In contrast, qualitative methods typically consider only spectral variance (SV) and either rely on the fact that during blending SV is reduced as components are mixed, or that blend spectra approach an 'ideal' reference spectrum. The Moving Block Standard Deviation (MBSD) [13,14], monitors SV in a block of spectral data progressing with time. As the first method implemented for qualitative BU monitoring it remains popular, despite disadvantages mentioned below. Other qualitative analysis methods without direct use of reference spectra are the 'Mean Square of Difference' [15], Principal Component (PC) Score-plots [16] or PC-Score Distance Analysis [17]. Qualitative methods that explicitely compare blend spectra to a training set (supervised methods) include Conformity Index [18], Dissimilarity [13], PLS-Discriminant Analaysis [19], SIMCA [20] and PC-MBEST [21], see also [8,22]. While analyses such as MBSD do not require historical data as such, qualitative methods commonly require extensive historical/reference data to set a reliable BU criterion [19]. Even with such data available, suitably robust end-point detection (see e.g., [23]) can pose significant challenges: a specific MBSD or 'distance' threshold as stop criterion may depend too much on specific raw material/analyzer/blender variations. Another shortcoming of the qualitative methods above -surprisingly not mentioned in the literature- is that they do not relate non-uniformity risks to regulatory BU criteria for API content *RSD*.

Ideally a BU application for process development and up-scaling should require limited development work. In addition, for technology transfer and routine production, robustness, transferability and limited maintenance are prime considerations. The method should perform well for different batch sizes and blender types. Quantitative methods often require re-calibration in these cases [7]. Selection of adequate calibration samples and measurement may also be challenging since it is very unattractive (from a time and cost perspective) to prepare calibration samples on the actual batch size scale(s).[2] Use of static calibration samples typically fails to adequately incorporate the influence of scale, powder density and rheology, compromising robustness and reliability. Quantitative methods may also suffer from variation in ingredient properties (e.g., particle size or moisture content). While technically possible to incorporate these in a model, the extensive additional work is usually prohibitive. Qualitative methods suffer less from these difficulties and are thus more attractive provided the validity and regulatory compliance is proven [23]. A practical and reliable qualitative method should be applicable at various stages of development and manufacturing without much modeling investment and should readily provide information regarding effects of variation in ingredient properties, process settings and environmental conditions on BU. Finally and foremost, a NIR-BU method eliminates the need for manual blend sampling which, if not properly developed, can be very unreliable [24,25].

This paper describes a qualitative BU method which avoids disadvantages of other qualitative approaches and fulfills the requirements of convenience and reliability: the moving *F*-test. The

[1] Clearly, for end-product CQA's (e.g., disintegration, dissolution), raw material variability may remain critical.

[2] This is less relevant in the area of Continuous Manufacturing/Blending, where no traditional up-scaling occurs. However, 'recalibration' to account for e.g., excipient variations or changes in flow rate may still be required.