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Blend uniformity evaluation during continuous mixing in a twin screw granulator by in-line NIR using a moving F-test

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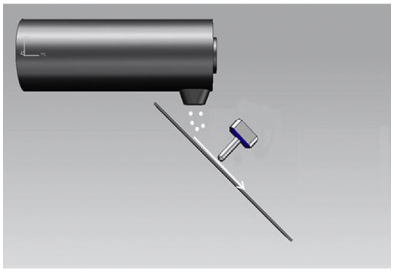
HIGHLIGHTS

- Continuous blending is monitored by NIR spectroscopy.
- The moving F-test is used for this purpose.
- A thorough discussion on the use of the F-test is provided.
- The critical blocksize is calculated.

GRAPHICAL ABSTRACT



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ABSTRACT

This study focuses on the twin screw granulator of a continuous from-powder-to-tablet production line. Whereas powder dosing into the granulation unit is possible from a container of preblended material, a truly continuous process uses several feeders (each one dosing an individual ingredient) and relies on a continuous blending step prior to granulation.

The aim of the current study was to investigate the in-line blending capacity of this twin screw granulator, equipped with conveying elements only. The feasibility of in-line NIR (SentroPAT, Sentronic GmbH, Dresden, Germany) spectroscopy for evaluating the blend uniformity of powders after the granulator was tested.

Anhydrous theophylline was used as a tracer molecule and was blended with lactose monohydrate. Theophylline and lactose were both fed from a different feeder into the twin screw granulator barrel. Both homogeneous mixtures and mixing experiments with induced errors were investigated. The in-line spectroscopic analyses showed that the twin screw granulator is a useful tool for in-line blending in different conditions.

The blend homogeneity was evaluated by means of a novel statistical method being the moving F-test method in which the variance between two blocks of collected NIR spectra is evaluated. The α- and β-error of the moving F-test are controlled by using the appropriate block size of spectra. The moving F-test method showed to be an appropriate calibration and maintenance free method for blend homogeneity evaluation during continuous mixing.

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Abbreviations

CLS	Classical Least Squares
FDA	Food and Drug Administration
MCR	Multivariate Curve Resolution
NAS	Net Analyte Signal
NIR	Near Infrared
PAT	Process Analytical Technology
PCA	Principal Component Analysis
PCR	Principal Component Regression
PLS	Partial Least Squares
rpm	rotations per minute
RSD	Residual Standard Deviation
SIMCA	Soft Independent Modeling of Class Analogies
SNV	Standard Normal Variate
UV–VIS	Ultraviolet–Visible

1. Introduction

By launching its Process Analytical Technology initiative [1], the Food and Drug Administration (FDA) strengthened the need for non-invasive and non-destructive analytical measurement tools for in-line monitoring of critical quality attributes during pharmaceutical manufacturing. Near infrared spectroscopy has clearly proven its usefulness within the pharmaceutical industry [2–8]. For instance, NIR spectroscopy has been researched extensively for the monitoring of pharmaceutical blending. Blending is a common batch unit operation step during the manufacturing of solid dosage forms, i.e. prior to capsule filling, granulation or tableting. Homogeneity of a powder blend is essential to guarantee the correct amounts of drug substances and excipients in every dosage unit. A large number of process input variables such as physical properties of drug substances and excipients, relative humidity, batch size, mixer type and possible interactions between these variables can be considered as critical for a blending process. The use of an in-line NIR blend control application is an alternative approach; since instead of controlling the input parameters the NIR method can control the blend quality itself. Nowadays, it is also possible to blend in a continuous manner [9].

When monitoring a blending process by means of NIR spectroscopy, two different approaches can be used. The first set of methods uses a training set of spectra taken from homogeneous mixture(s). By comparing each new measurement with the reference spectra or training set via dissimilarities or Principal Component Analysis (PCA) [10] it is evaluated whether homogeneity is reached. Partial Least Squares (PLS)-regression is the most applied technique for the development of a quantitative NIR method to monitor pharmaceutical blending [11–44], but also Classical Least Squares (CLS)-regression [45], Multivariate Curve Resolution (MCR) [46], Principal Component Regression (PCR) [29] and the Net Analyte Signal (NAS) [47] have been used for this purpose.

The second approach is based on the evaluation of changes in the consecutively collected NIR spectra during blending: the linear superposition method [29] and a qualitative model based on NAS-values [47] are used for this purpose. Furthermore, the bootstrap error-adjusted single-sample technique (BEST) [48] and Principal Component Modified BEST [49], and another pattern recognition algorithm, Soft Independent Modeling of Class Analogies (SIMCA) [49] have been presented. Additionally, examples of traditional Chi-square analysis [48], SIMPLISMA [50] and additive and iterative mixing models [51] in combination with NIR spectroscopy have been published. In 1998, the group of P. Hailey presented the moving block standard deviation approach applied on NIR spectra collected during blending [52–54]. This is a model-free approach that determines the variability in the NIR spectra as a function of process time, in order to detect the end point of the blending cycle. Their approach has been adopted by several other researchers for NIR in blending [24,28,29,55–58]. For these methods, it is assumed that, once the mixture is homogeneous, the spectra will not change anymore.

Plugge and van der Vlies already demonstrated the usefulness of the F-test for blend homogeneity determination [59] and Flåten et al. combined the moving block strategy with the F-test [60,61]. A pharmaceutical application on *batch* blending has been presented as well [62].

The main aim of this study is to present a new statistical method, based on the moving F-test and without the need for an external calibration model, for the evaluation and control of blend uniformity using NIR spectroscopy during *continuous* mixing via a twin screw granulator (ConsiGma™ 25). The method development differs from conventional batch blending. Furthermore, both the α- and β-error are controlled. The rationale for evaluating the continuous mixing of powders in a twin screw granulator aligns with our future research goals to examine whether continuous powder mixing and continuous wet granulation can be performed simultaneously using the same continuous unit operation equipment.

2. Materials and methods

2.1. Materials

A binary blend was evaluated, using anhydrous theophylline as model Active Pharmaceutical Ingredient (API) (Farma-Quimica sur SL, Malaga, Spain) and lactose monohydrate 200 M (Caldic, Hemiksem, Belgium) as filler.

2.2. Batch blending

To develop the moving F-test method, some theophylline/lactose mixtures had to be blended batch wise (see results section). This was done using a tumbler mixer (20L Bioengineering, Inversina, Wald, Switzerland). Two thirds of the bin were filled (i.e. 6.5 kg) with the envisaged amounts of theophylline and lactose and the powders were mixed during 10 min, at a speed of 25 rpm.

2.3. Continuous mixing using a twin screw granulator

The continuous mixing was performed using the twin screw granulator which is part of the ConsiGma™ 25 system (GEA Pharma Systems nv., Collette™, Wommelgem, Belgium). The screws were equipped with conveying elements only and two feeders were used, each feeding one component in the granulator. Theophylline was added via the first feeder (LWF D5, K-Tron AG, Niederlenz, Switzerland), whereas lactose was added 13.5 cm further in the barrel by a second feeder (K-CL-KT20, K-Tron Soder, K-Tron AG, Niederlenz, Switzerland) (Fig. 1). Under the outlet of the granulator, an aluminium slide was mounted at an angle of 45°. The powder could flow freely on this slide. The flat-faced probe-head of an NIR spectrometer was mounted parallel to the slide with a distance of approx. 5 mm to the slide (Fig. 2).

The feed rate, weight loss and remaining weight of the theophylline feeder were continuously logged, but no logged data could be collected from the stand-alone lactose feeder. Two continuous blending experiments were conducted. Experiment 1