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Development and validation of an in-line NIR spectroscopic method for continuous blend potency determination in the feed frame of a tablet press

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ABSTRACT

A calibration model for in-line API quantification based on near infrared (NIR) spectra collection during tableting in the tablet press feed frame was developed and validated. First, the measurement set-up was optimised and the effect of filling degree of the feed frame on the NIR spectra was investigated. Secondly, a predictive API quantification model was developed and validated by calculating the accuracy profile based on the analysis results of validation experiments. Furthermore, based on the data of the accuracy profile, the measurement uncertainty was determined. Finally, the robustness of the API quantification model was evaluated.

An NIR probe (SentroPAT FO) was implemented into the feed frame of a rotary tablet press (Modul™ P) to monitor physical mixtures of a model API (sodium saccharine) and excipients with two different API target concentrations: 5 and 20% (w/w). Cutting notches into the paddle wheel fingers did avoid disturbances of the NIR signal caused by the rotating paddle wheel fingers and hence allowed better and more complete feed frame monitoring. The effect of the design of the notched paddle wheel fingers was also investigated and elucidated that straight paddle wheel fingers did cause less variation in NIR signal compared to curved paddle wheel fingers. The filling degree of the feed frame was reflected in the raw NIR spectra. Several different calibration models for the prediction of the API content were developed, based on the use of single spectra or averaged spectra, and using partial least squares (PLS) regression or ratio models. These predictive models were then evaluated and validated by processing physical mixtures with different API concentrations not used in the calibration models (validation set). The β-expectation tolerance intervals were calculated for each model and for each of the validated API concentration levels (β was set at 95%). PLS models showed the best predictive performance. For each examined saccharine concentration range (i.e., between 4.5 and 6.5% and between 15 and 25%), at least 95% of future measurements will not deviate more than 15% from the true value.

Abbreviations: 0-0, original paddle wheel without notches; 1-10/2-16, paddle wheel with notches of 1 mm deep and 10 mm wide/2 mm deep and 16 mm wide; 3-30, customized paddle wheel of GEA Pharma systems with a notch of 3 mm deep and 30 mm wide; A%, absorbance ratio; MCC, microcystalline cellulose; MLR, multiple linear regression; MSC, multiplicative scatter correction; NIR(S), near infrared (spectroscopy); PAT, process analytical technology; PCA, principal components analysis; PLS, partial least squares; RMSE(P), root mean square error (of prediction); rpm, rotations per minute; RTR(t), real time release (testing); SFSTP, Société Française des Sciences et Techniques Pharmaceutiques; SNV, standard normal variate; stdev, standard deviation; tpm, tablets per minute.

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1. Introduction

Tablets are worldwide the most important solid drug dosage forms. Tablets are generally produced in rotary tablet presses, enabling continuous tablet production [1]. A key to successful continuous processing is the implementation of real-time release testing (RTRt) and real-time release (RTR). RTRt is based on a firm understanding of the process and the relationship between process parameters, material attributes and product quality attributes [2]. Process analytical technology (PAT) is to be used for the real-time analysis and control of the manufacturing process [3].

The applicability of near infrared spectroscopy (NIRS) as PAT tool for the off-line and at-/on-/in-line, non-destructive and non-invasive, quantitative and qualitative analysis of tablets has been evaluated numerously [4–8]. NIRS provides information about both physical (e.g. particle size, density) and chemical characteristics (e.g. API content) of the observed material (intermediate and end products) [9,10]. In these studies [4–8], tablets were sampled and manually measured off-line or the tablets were transported to a tablet holder [8] or conveyer belt [11] for automatic off-line/at-line NIR spectral acquisition. To allow RTR of tablets, in-line PAT tools are necessary to assure end-quality of the produced tablets (avoiding a lag time between the moment of tablet production and tablet analysis).

Studies were performed on the in-line quantification of drug and excipient concentrations in tablets directly after compression [9,12]. The aim was to measure all individual tablets, therefore the probe was positioned in such a way that it measured the tablets at the ejection area [9] or directly after ejection [12]. Measuring all individual tablets limited the maximum tablet production speed to the maximal acquisition rate of the NIR spectrometer (80 spectra per second corresponding to 4800 tablets per minute).

A few studies were published in which the final blend circulating in the feed frame of the press was monitored by NIRS [1,3,13,14]. Monitoring blend potency in the feed frame enables the ability for feedback (e.g. to the feeders of the tablet press) or feedforward (e.g. gating tablets to the waste) control which is important for RTR in continuous manufacturing. Mateo-Ortiz et al. [1] investigated the die filling process and powder flow in-line inside the feed frame through a sapphire window. This paper focused on the flow behaviour inside the feed frame and only briefly discussed API concentration monitoring of the circulating blend. The performance of the quantification models for API concentration monitoring was evaluated by root mean square error (RMSE) values. No model validation was performed.

Liu et al. observed disturbances in the NIR signal, when directly measured inside the feed frame, caused by the rotating paddle wheel of the feed frame in a tablet press [13]. In contrast to Liu et al., Wahl et al. and Ward et al. performed similar experiments on monitoring of blend potency (inside the powder bed of the feed frame) but did not report disturbances caused by the moving paddle wheels [3,13,14]. This could possibly be attributed to different spectrometer measurement parameters (number of scans, integration time, averaging) that impact the spectral quality.

Spectral pre-processing or (mathematical) averaging is always used in the above mentioned studies to extract the desired information (e.g. blend composition) from interacting effects (e.g. non-specific scatter of the sample surface or variable path length through the sample). However, this can also cause the deletion of important physical information (e.g. particle size and density information [15]) about the powder blend inside the feed frame. Since information about powder density and particle size can be very important to understand and optimise the tableting process, the use of spectral pre-processing techniques should be carefully evaluated.

Table 1
Compositions of formulations used.

Compound	Concentration (% w/w)	
Sodium Saccharine[a]	5.00	20.00
Avicel PH102[b]	30.33	25.33
Lactose[b]	60.67	50.67
Sodium Starch Glycolate	3.00	
Magnesium Stearate	1.00	

[a] The amount of sodium saccharine, MCC and lactose was varied during the experiments for API monitoring.
[b] MCC- lactose ratio: 1:2.

In contrast, in the current study a new approach was used for in-line measurements inside the feed frame of a tablet press. The design of the paddle wheel was adapted, by cutting notches having a well-considered size into the paddle wheel fingers to avoid the spectral disturbances caused by the paddle wheel fingers. Using this set-up, the acquired spectra can be used without pre-processing or filtering. This is essential when physical characteristics (density, particle size) are of interest to be determined in-line, since NIR spectra contain physical information of the material and applying spectral filters on the data will lead to loss of information [1]. Moreover these filters can be complex in cases when the illumination spot of the probe is partly sampling processed material and partly sampling the paddle finger of the rotating paddle wheel. In this study, raw spectra (without pre-processing or averaging) were evaluated to understand the effect of the filling degree of the feed frame upon the collected NIR spectra.

After optimisation of the measurement set-up, an optimisation design was performed to determine the ideal process settings for the development of an API quantification model. Subsequently, a model for continuous API concentration monitoring in the feed frame of the tablet press via NIRS was developed and validated. For the development of a model for concentration quantification, no mathematical filters and a minimum of spectral pre-processing were necessary, due to the optimised measurement set-up. The developed blend potency determination model was evaluated and validated using the approach introduced by the Société Française des Sciences et Techniques Pharmaceutiques (SFSTP) [16–18] based on accuracy profiles.

The effect of process parameters (tableting speed, paddle speed, paddle type) on the predictive performance of the developed model was also shortly evaluated.

2. Material and methods

2.1. Materials

Test formulations (physical mixtures) consisting of sodium saccharine (JMC corporation, Ulsan, South Korea), microcrystalline cellulose (MCC) (Avicel® PH-102, FMC biopolymer, Cork, Ireland) and lactose (Fast Flo 316, Foremost, Wisconsin, USA) were tableted during the in-line NIR monitoring experiments. Sodium starch glycolate (JRS Pharma, Budenheim, Germany) and magnesium stearate (Mallinckrodt, Dublin, Ireland) were added as disintegrant and lubricant, respectively. The quantitative composition of the processed formulations is shown in Table 1.

The mixture was first blended without lubricant in a three-dimensional mixer (Inversina, Bioengineering AG, Wald, Switzerland) during ten minutes at 25 rotations per minute (rpm). Magnesium stearate was then added and blended for an additional five minutes at 12 rpm, hence avoiding overlubrication. Unless stated otherwise, the formulation with 20% (w/w) sodium saccharine was used throughout the study to perform the experiments. The amount of sodium saccharine, MCC and lactose was varied during the experiments for API monitoring (see further, Table 2).