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Detailed analysis of the online near-infrared spectra of pharmaceutical blend in a rotary tablet press feed frame

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ABSTRACT

The present study is an in-depth analysis of the online near-infrared (NIR) spectra acquired with a spectrometer mounted on the rotary tablet press feed frame. A 3.5% active pharmaceutical ingredient (API) formulation is analyzed. An attempt is made to determine the API univariately via the 2nd derivative spectra due to favorable appearance of the API and placebo bands in the formulation. However, the signal at the univariate API peak is ambiguous and principal component analysis is hence applied to understand better the structure of the data. To eliminate effect of the bias along the wavelength axis which is found to dominate the data, the analysis is restricted only to the spectral region that covers the API band of interest. This leads to significantly better results in terms of the univariate profile of the API now heavily overlapping with the first principal component and the elimination of the bias. Having thus proven that the univariate analysis is a viable option, an attempt is made to calibrate the API response by using some previous runs that involved alternation of the placebo and the formulation. This analysis produces mixed results due to baseline differences in the two sets of spectra. The final univariate profile of the API is therefore compared with the assay of the tablets and the two are found to agree very well. It is, therefore, concluded that the NIR probe in the feed frame can rapidly detect moderate changes in API concentration in the blend and be a good predictor of tablet potency at the same time point.

1. Introduction

The widely cited FDA initiative for a more scientific approach to the business of manufacturing pharmaceutical formulations has led to the appearance of a new term, process analytical technology (PAT), which usually stands for using various experimental and theoretical (multivariate) tools for tighter controlling and better understanding of the manufacturing process [1,2]. The goal of the initiative is to facilitate production of high quality products by design. The implementation of the concept led to the widespread use of vibrational-spectroscopy based methods for online monitoring of various manufacturing steps. Near-infrared spectroscopy (NIR) has been particularly popular and NIR spectrometers are, with more or less success, used for monitoring a number of manufacturing steps [3–5]. While NIR spectra feature broad bands with the API responses significantly less distinct in comparison with Raman spectra, NIR spectroscopy is normally the first choice when considering applying PAT.

One of the most common PAT applications is monitoring the API in formulation blends with NIR spectroscopy. There are numerous publications specifically covering the API concentration during the blending operation [6–19]. In addition to the academic laboratories, this is also a technology broadly used in but rarely published from the industrial environment. Although this is an approach with the spectra obtained online and optionally analyzed in real time, the position of the spectrometer during the acquisition (at the bottom of the blender) and shortness of the acquisition suggest that the blend can be considered nearly stationary during the measurement. A more recent activity [20] in this field aims at collecting the spectra at other places in the manufacturing stream which normally implies less well-defined conditions of acquisition (e.g. moving blend). One such place is the feed frame of the tablet press. This is the part of tablet press that introduces the blend to the dies and punches and it is the last opportunity to obtain a PAT feedback before the tablets are produced (Fig. 1). The next target for applying a PAT tool would be analysis of finished tablets.

The goal of work presented here is to thoroughly analyze the online NIR spectra obtained from the blend in the feed frame, to assess the perspective of real-time online reading of the API concentrations, and estimate the complexity of such an approach.

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Of note here is the emphasis on univariate considerations due to the favorable appearance of the API and placebo bands. We believe that the prospects of univariate calibration should be explored first as potential success of monitoring at a single wavelength would substantially simplify the application of NIR spectroscopy in some cases. While no multivariate calibration is carried out in this study, we do use some multivariate analysis to unravel the details of the NIR data. The API loading in the analyzed formulation is 3.5% which, empirically, means that there are decent chances for detecting the API signal without resorting to multivariate analysis (taking again into account the relative lack of interference).

2. Experimental

Three gravimetric feeders (K-tron International, Inc., Pitman, NJ, USA) were used to continuously deliver three separate streams (API, blend of excipients and magnesium stearate stream) into the inlet of an in-line powder mixer (Fig. 1). Here, the material streams were continuously blended together. Material exiting the blender was directed into the inlet of the feed frame of a rotary tablet press (IMA Kilian Gmbh & Co. KG, Köln, Germany). The mass rate of the excipient stream and the magnesium stearate stream was held constant. The settings of the API feeder were altered to force the feeder to "hunt" for its gravimetric setpoint. In this manner, the API mass feed rate entering the in-line blender fluctuated about the target value. The corresponding blend concentration of the material exiting the in-line blender and entering the tablet press feed frame was similarly rapidly and dynamically changing. Most of the NIR spectra analyzed here were obtained from the formulation manufactured in this manner.

A separate series of four experiments were completed using the same active blend (3.5% wt:wt concentration) and a separately prepared placebo blend. The active and placebo blends were prepared by using commonly available pharmaceutical excipients. In this experiment, either 250, 300, 350, or 400 g of the placebo blend was charged into the feed frame of a Kilian T-100 rotary tablet press. The active blend was then carefully layered on top of the placebo blend in the hopper of the tablet press. The compression process was started. Using this technique, as the placebo blend is removed from the feed frame and compressed into tablets, the active blend is drawn into the feed frame and mixed with the remaining placebo blend. Over time, the potency of the blend in the feed frame (and the corresponding potency of the compressed tablets) exponentially increases until the concentration of blend within the feed frame reaches the concentration of the active blend (3.5% wt:wt).

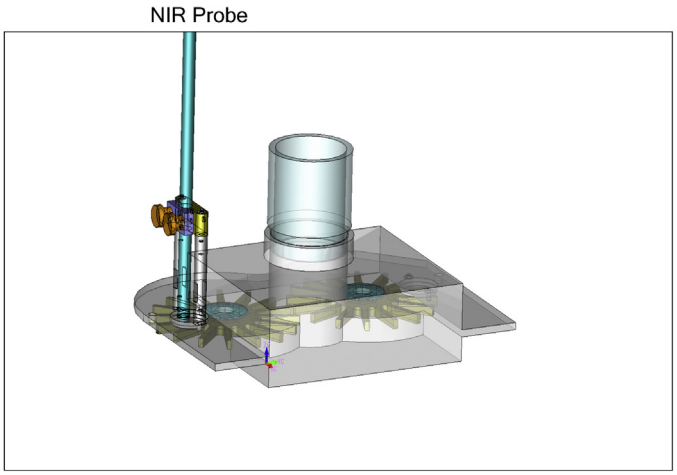

Fig. 1. A scheme depicting the position of the NIR spectrometer on the tablet press feed frame. See Ref. [20] as well.

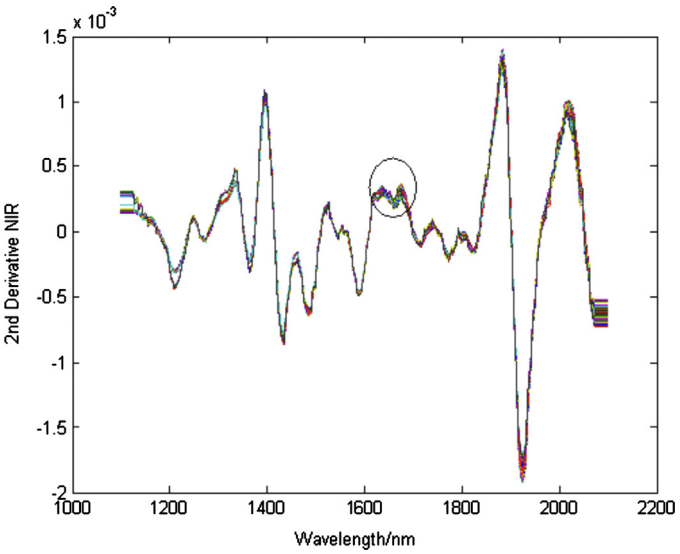

Fig. 2. The 2nd derivative NIR spectra of the formulation obtained from the EPAT611 instrument mounted on the feed frame. Emphasized is the region with the key API band.

The NIR spectra obtained from this setup mostly served for testing the functionality of the NIR methodology and for determining the quantitative reproducibility of the 100% API signal.

For each of these experiments, an ePAT611 NIR spectrometer (Expo Technology, St Louis, MO) was mounted to the feed frame as shown in Fig. 1. The probe was manually positioned into the feed frame so that the probe tip was in contact with the circulating powder blend and slightly above the rotating feed frame paddle wheels. The spectra were continuously acquired for each of the two experimental techniques described above. The total acquisition time of an individual spectrum was 250 ms which included 25 ms acquisition, 10 scans, and the time interval to the next acquisition.

The acquired spectra are analyzed offline by using Matlab (Mathworks, Natick, MA) only. Savgol.m was used for the second derivative pre-treatment with 15 points, 2nd order polynomial selected in all cases. All the figures shown here were also plotted in Matlab. The software on the instrument (NovaMath) could have been used for all the mathematical operations applied in this study (which are rather undemanding) and thus all the results here are obtainable on the computer controlling the spectrometer. Moreover, due to NovaMath being capable of real-time applying and updating the model developed to monitor a selected component, the onscreen curve showing the API concentration could be readily produced. The reason for not exploring it at this time was simply due to this study aiming at comprehensive analysis of the spectra and not necessarily concentrating on building a model as a primary goal.

3. Results and discussion

The raw NIR spectra obtained by the feed frame-mounted NIR spectrometer do not display any indication of artifacts from the manufacturing equipment and are of regular appearance. The data-acquisition software on the employed instrument automatically stops storing the spectra when a certain number of spectra is acquired (~8500 in this case) and automatically creates another file to store the further spectra. In the case studied here, there are two files that are merged to produce the concentration variation of the API during the manufacturing. The spectra in Fig. 2 and the data analysis that deals with the authentication of the NIR signal of the API only addresses the first of these files (ca. 8500 spectra). The quantitative API variation through the whole process is obtained