Talanta 83 (2010) 305–311

Contents lists available at ScienceDirect

Talanta

journal homepage: www.elsevier.com/locate/talanta

Building the quality into pellet manufacturing environment – Feasibility study and validation of an in-line quantitative near infrared (NIR) method

Jérôme Mantanus[a,*,1], Eric Ziémons[a,1], Eric Rozet[a], Bruno Streel[b], Régis Klinkenberg[b], Brigitte Evrard[c], Jukka Rantanen[d,1], Philippe Hubert[a,1]

[a] Analytical Chemistry Laboratory, CIRM, University of Liège, avenue de l'Hôpital 1, 4000 Liège, Belgium
[b] Galéphar Research Center M/F, rue du Parc Industriel 39, 6900 Marche en Famenne, Belgium
[c] Pharmaceutical Technology Laboratory, CIRM, University of Liège, avenue de l'Hôpital 1, 4000 Liège, Belgium
[d] Department of Pharmaceutics and Analytical Chemistry, University of Copenhagen, Universitetsparken 2, 2100 Copenhagen, Denmark

ARTICLE INFO

Article history:
Received 18 June 2010
Received in revised form 1 September 2010
Accepted 8 September 2010
Available online 16 September 2010

Keywords:
Near infrared spectroscopy
Process analytical technology
Chemometrics
Validation
Accuracy profile
Moving particles

ABSTRACT

The present study focuses on the implementation of an in-line quantitative near infrared (NIR) spectroscopic method for determining the active content of pharmaceutical pellets. The first aim was to non-invasively interface a dispersive NIR spectrometer with four realistic particle streams existing in the pellets manufacturing environment. Regardless of the particle stream characteristics investigated, NIR together with Principal Component Analysis (PCA) was able to classify the samples according to their active content. Further, one of these particle stream interfaces was non-invasively investigated with a FT-NIR spectrometer. A predictive model based on Partial Least Squares (PLS) regression was able to determine the active content of pharmaceutical pellets. The NIR method was finally validated with an external validation set for an API concentration range from 80 to 120% of the targeted active content. The prediction error of 0.9% (root mean standard error of prediction, RMSEP) was low, indicating the accuracy of the NIR method. The accuracy profile on the validation results, an innovative approach based on tolerance intervals, demonstrated the actual and future performance of the in-line NIR method. Accordingly, the present approach paves the way for real-time release-based quality system.

1. Introduction

FDA's Process Analytical Technology (PAT) aims at "improving the pharmaceutical development, manufacturing and quality assurance through innovation in product and process development, process analysis and process control" [1]. According to the PAT framework, the process analysis side should include at least the following two steps. First, the critical process steps relating to the final product quality should be identified using appropriate risk assignment approach [2]. Considering the pellet manufacturing process, the processing steps such as blending, granulation, spheronization, drying and coating phases are critical to ensure the final product quality. Second, a proper process measurement system must be chosen to collect at-line, on-line or in-line process information from the identified critical steps of the manufacturing. This information may eventually provide a better understanding of the manufacturing process, giving opportunities for process control strategies to prevent or mitigate the risk of producing out of specification products. Moreover, the data gathered during the production may enable the real-time release of the product, reducing the batch release time which is still dependent on time consuming laboratory tests. The challenge still remains to interface the selected process analytical approach to the real environment and to develop quantitative methods fitted for a real-time release quality-based system.

Near infrared (NIR) spectroscopy is a well-established vibrational spectroscopic technique. In the covered wavelength region (between 800 and 2500 nm), relatively wide bands related to overtones and combination of fundamental vibration of chemical groups with hydrogen, such as C–H, N–H, O–H and S–H, are observed. Such vibrations lead to overlapping bands which contain both physical and chemical information. Consequently, chemometric tools are used to extract the significant information [3,4].

NIR spectroscopy has several advantages, such as fast spectral acquisition, minimization of sample preparation and/or destruction and the use of probes allowing at-line, on-line and in-line analysis. Considering those advantages, NIR spectroscopy matches the process measurement system requirements of the PAT framework. NIR spectroscopy has already been part of PAT applications to monitor critical process attributes such as the blend homogeneity, the coating level, the moisture content, and the active content [5–19].

* Corresponding author.
E-mail address: jmantanus@ulg.ac.be (J. Mantanus).
[1] These authors contributed equally to this work.

0039-9140/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.talanta.2010.09.009

Table 1
API and main excipient percentage (w/w) in the 80, 100 and 120% API formulations.

API formulation	API (%, w/w)	Main excipient (%, w/w)
80%	36	38
100%	45	30
120%	54	22

Validation is a crucial and mandatory step in the lifecycle of an analytical method [20]. Based on β-expectation tolerance intervals, the accuracy profile makes possible a visual and reliable representation of the actual and future performances of the analytical method and thus enables a better risk management. It fully complies with the ICH Q2(R1) regulatory documents as it integrates all the useful required validation criteria such as accuracy, trueness, precision, limits of quantification, range and linearity [21,22,23].

In a previous work [12], a NIR method able to quantify the API in non-coated pharmaceutical pellets was successfully developed and validated. Using the commercially available formulation, coated pharmaceutical pellets as model particles, the feasibility of a quantitative in-line method was evaluated. The first aim was, for qualitative purpose, to interface a dispersive NIR spectrometer with four realistic particle streams found in the pellets manufacturing line. Second, for quantitative purpose, to interface one of the previous particle stream with a FT-NIR spectrometer. Finally, based on the previous interfacing, to develop and to validate a NIR method able to determine the API content of the pellets.

2. Materials and methods

2.1. Materials

2.1.1. Pharmaceutical pellets

For this work, pellets were used as model particles. Eighteen batches of pharmaceutical pellets were manufactured via extrusion spheronization followed by two coating steps. In the standard pellet formulation, which will later on be called 100% Active Pharmaceutical Ingredient (API) formulation, the API is 45% (w/w) of the formulation whereas the formulation main excipient represents 30% (w/w) of the formulation. As shown in Table 1, the ratio of raw materials was modified in order to manufacture batches containing 80 and 120% API formulations (6 batches per API level). Moreover, the coating levels were kept the same to provide the same sustained release behavior for all the batches. All the batches were sieved after the manufacturing, the fractions between 800 and 1600 μm were kept for the experiments.

2.1.2. Qualitative study samples

For the qualitative study, Nine batches of pharmaceutical pellets were analyzed, three batches per API level.

2.1.3. Quantitative study samples

For the quantitative study, eighteen batches of pharmaceutical pellets were analyzed, six batches per API level.

2.2. Methods

2.2.1. NIR analysis

For qualitative purpose, a dispersive NIR spectrometer NIR-256L-2.2T2 (Control Development Inc., South Bend, IN, USA) having a thermoelectrically cooled 256 element InGaAs array detector, a tungsten light source and a fiber optic reflectance probe (six illuminating fibres around one collecting fibre) was used. The spectra were collected between 1090 and 2220 nm with a 10 ms integration time. The spectral range used in the data analysis was 1340–1640 nm.

For quantitative purpose, a Bomen FTLA 2000 series FT-NIR spectrometer (ABB Bomen, Quebec, Canada) was used. Samples were measured in the 1000–2500 nm range with a resolution of 8 cm^{-1}.

The number of scans selected for the off-line and the in-line measurements will be described in the following sections.

2.2.2. Off-line measurements

For the dispersive NIR spectrometer, off-line measurements were performed with the reflectance probe directly through the side of glass vials. For the FT-NIR spectrometer, samples in vials were analyzed on the reflectance sample stage. For both systems, each spectrum was the average of 32 scans.

2.2.3. Process interfaces for the dispersive NIR spectrometer

2.2.3.1. Fluidization interface. 150 g of pellets sample were introduced in a Mini-Glatt (Glatt GMbH, Germany) fluid bed coater. The system was working in drying mode and no heat was applied while fluidizing the particles. The fluidizing air pressure was 1.75 bar. As can be seen from Fig. 1a, the NIR probe was placed outside the coater, directly against the acrylic glass housing of the fluid bed coater. A background of the acrylic glass housing was taken before each measurement. The spectra were collected by averaging 16 scans. One spectrum was acquired every 3 s. Ten spectra per batch were kept for the data analysis.

2.2.3.2. Slow particle flow velocity device. For this interface, pellets slide down through a homemade sample holder. For 100 g of pellets, the average time for the particles to flow through the sample holder was 20 s, leading to a particle mean flow rate of 5 g/s. Fig. 1b shows how the particles flow was interfaced in a non-invasive way with the NIR probe. The spectra were collected by averaging 4 scans. One spectrum was acquired every second. Ten spectra per batch were kept for the data analysis.

2.2.3.3. Fast particle flow velocity device. For the fast particle flow device, pellets were freely flowing through a funnel. In this case, the particle mean flow rate was higher (7 g/s) as the samples were falling in the air. As can be seen from Fig. 1c, the NIR interfacing was done perpendicularly to the particles flow without disturbing the flow. The spectra were collected by averaging 4 scans. One spectrum was acquired every second. Ten spectra per batch were kept for the data analysis.

2.2.3.4. Interface for compacts. Using a hydraulic press, a pressure of 50 MPa was applied to 1.6 g of pellets samples. The obtained tablets were then analyzed with the NIR probe while rotating on a sample stage as displayed in Fig. 1d. The rotating speed was set at 10 rpm. The spectra were collected by averaging 16 scans. One spectrum was acquired every 3 s. Ten spectra per batch were kept for the data analysis.

2.2.4. Process interface for the FT-NIR spectrometer

The particle flow velocity device was the same as the slow particle flow velocity device developed for the dispersive NIR spectrometer. However, as can be seen from Fig. 1e and f, the interfacing with the FT-NIR spectrometer was performed via the reflectance sample stage, through the glass bottom of the sample holder. The spectra were collected while averaging 16 scans.

2.2.5. Multivariate data analysis

Principal Component Analysis (PCA), Partial Least Squares (PLS) regression and Multiplicative Signal Correction (MSC) were carried out with PLS Toolbox 5.0 for Matlab version 7.6. The data were mean-centered before performing PCA or PLS. Cross-validation was performed based on contiguous blocks. Using contiguous blocks,