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Process analytical technology for continuous manufacturing tableting processing: A case study

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ABSTRACT

The use of Near Infrared Spectroscopy (NIRS) as a fast and non-destructive technique was employed for the control and monitoring of the tableting step during a continuous manufacturing process.

Two NIRS methods were optimized in order to in-line control the blend uniformity in the tablet feed frame and the API concentration of freshly pressed tablets prior the ejection. The novelty of this work first lies in the acquisition speed of NIR spectra reaching up to 70,000 tablets/h. Partial Least Square (PLS) regression was used as chemometric tool for the computation that resulted in excellent predictive calibration results. A coefficient of correlation (r) value of 0.99 was obtained for both probes. The root mean square error of calibration (RMSEC) and the root mean square error of prediction (RMSEP) were respectively 1.8% and 1.8% for active content in the tablet feeder and 2.2% and 2.3% for the tablet content. In addition, calibration performance and robustness of the methods were evaluated. Moreover several qualitative methods were proposed to monitor the tableting process in different stages of development (single wavelength, Principal Component Analysis, and Independent Component Analysis). In early phase development, the requirement/quality of the input material is not established yet; hence the use of a qualitative approach allows to confirm the suitability of the PAT methodology for in-process material monitoring & control. Later, the qualitative approach constitutes the foundation for the quantitative approach when input materials are fixed and larger production size occurs. The proposed strategy is a performant PAT tool for continuous manufacturing and a step forward to real time release.

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1. Introduction

Continuous Manufacturing (CM) of pharmaceutical drug products is a new approach within the pharmaceutical industry, opposing traditional batch manufacturing processes based on its potential to increase manufacturing flexibility and efficiency. In CM, all process units are directly connected to each other. Starting material is continuously charged into the first process unit at the beginning of the line, while final product is simultaneously discharged at the end. In combination with suitable process analyzers, this manufacturing approach allows to constantly monitor the processed material and if required, to control critical process parameters and thus critical quality attributes of in process material and final products. In a continuous manufacturing process, and contrary to a traditional batch production process, the tablet press runtime is not limited by the batch size; tableting of granules can be proceeded as long as the upstream unit operations are supplying materials to the press in a controlled process state. A controlled process state can be ensured by implementing suitable in-line and/or at-line PAT-tools (PAT = process analytical technologies) that deliver real-time information about the process state and/or product quality, together with associated control loops to adapt critical process parameters accordingly [1–3].

Near Infrared Spectroscopy (NIRS) has become a popular qualitative and quantitative PAT-tool in the pharmaceutical industry, as it is a safe, fast, and non-destructive method which does not require sample preparation. The integration of NIRS into pharmaceutical manufacturing was initially endorsed by the US Food and Drug Administration (FDA) as part of their PAT initiative in 2004, and further emphasized by the International Conference on Harmonization (ICH), by publishing a guideline on NIRS method validation [2,4]. The guideline was then picked up by the FDA and

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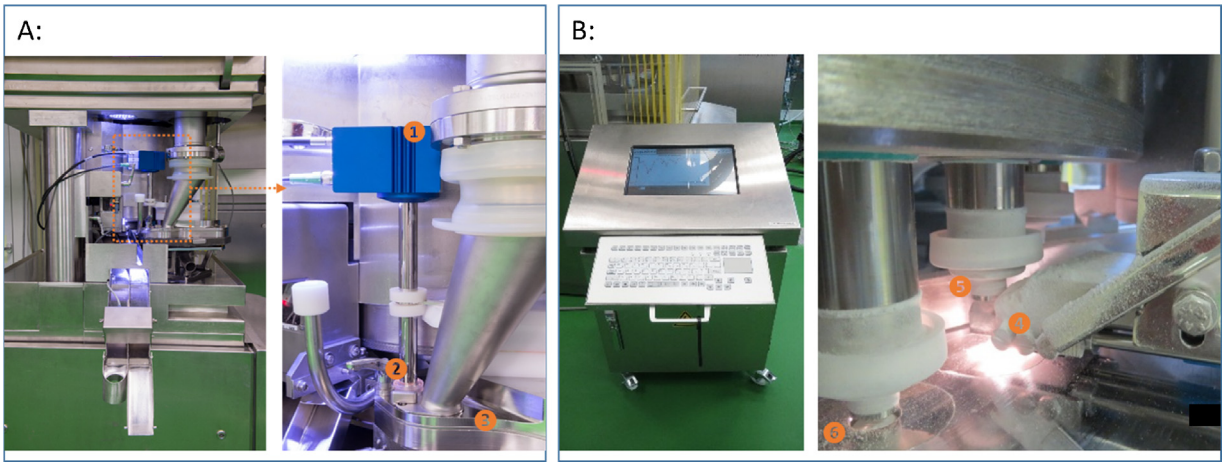

Fig. 1. Installation of the Near Infrared probes in the tablet press. (A) Sentro PAT FO for granules blend uniformity in the tablet press feed frame, with light source (1) and probe head (2) inserted into the tablet press feed frame (3). (B) VisioNIR for content uniformity of tablets after compression with the probe head (4) installed between the upper punch (5) and tablet being ejected by lower punch (6).

the European Medicines Agency (EMA), as well as the United States Pharmacopeia Convention (USP) and the European Pharmacopoeia (Ph. Eur.), who developed their own guidelines based on the initial ICH document [5–10].

Nowadays, NIRS is frequently applied for the identification of raw materials, in-line monitoring of process steps like blending, granulation, and drying by compound quantification, as well as for process troubleshooting [11–16]. Another well described application is the quantification of API content in tablets to demonstrate content uniformity [17–20]. However, most reported methods are merely suitable for offline or at-line sample measurement, as long sample handling times and spectral acquisition times of available spectrometers allow only a limited percentage of produced tablets to be tested [17–20]. This approach can be sufficient for process control, where blending and granulation are done according to a validated range and content uniformity for batch-release is demonstrated via offline analysis of finished goods according to Ph.Eur. Chapter 2.9.40 – Uniformity of Dosage Units [21]. However, when blending and granulation are done continuously, variations in process parameters or starting material characteristics over the course of production may cause fluctuations in granules content uniformity and therefore in the tablets API-content, water content, or tablet hardness. These variations might go undetected with the common approach of sampling and analyzing only a limited number of randomly selected tablets.

Alternatively, calibration-based approaches for 100% tableting-process control through chemometric compression parameter measurements could be implemented [22–24]. These methods however are mainly limited to control the tablet weight variations, while lacking the ability to measure the actual API content of each tablet [22–24]. Thorough quantitative in-line control of solid dosage forms via NIRS at full production speeds is still limited up to this date, due to limitations in measurement speed. One available instrument that can perform 100% quantitative testing of API content in tablets at production speeds of up to 125.000 tablets/hour is the VisioNIR LS (Uhlman, VisioTec GmbH, Laupheim, Germany), as reported by Järvinen at al. in 2013. The authors described 100% control of powder mixtures and tablet drug content during a continuous mixing and direct compression process of a three-ingredient powder blend at varying tableting speed and compaction force in a technical research environment [25].

Based on this paper, further work on establishing NIRS for 100% in-line real-time control of tablet API content was conducted on a GMP-qualified, continuous from powder-to-tablets manufacturing process with a six-ingredient formulation similar to a commercial one. In detail, granules at varying API-contents from a twin-screw wet granulation process were dried in a continuous fluid bed dryer and subsequently transferred to a tablet press for compression while granules and tablets content uniformity was monitored with two independent NIRS instruments. The first instrument was installed in the tablet press feed frame, to ensure the absence of segregation issues that could occur after milling and transfer. The second instrument was installed in the tablet press to measure every tablet right before being ejected from the press. A NIRS validation strategy was proposed in order to create a robust calibration where focus was put on selection of suitable calibration and validation samples, assessment of different preprocessing techniques, and evaluation of different chemometric options for process monitoring. Additionally, uniformity of dosage units using large samples sizes based on NIR predictions from tablets being ejected from the press was demonstrated according to Ph.Eur. 9.5 chapter 2.9.47 [32]. The development of an efficient ejection system and corresponding control loops is currently ongoing and not discussed in this manuscript.

2. Materials and methods

2.1. Materials

Diclofenac Sodium (Acros Organics, Geel, Belgium) was used as Active Pharmaceutical Ingredient (API) in all performed trials. The standard formulation contained 25% Diclofenac Sodium, 5% Sodium Starch-Glycolate, 5% Sodium Stearyl Fumarate, 4% Hypromellose (Cellulose-HP-M 603), 12.2% Calcium Hydrogen-Phosphate Anhydrous and 48.8% Microcrystalline Cellulose PH102 (all excipients supplied by Novartis Pharma AG, Stein, Switzerland). To generate granules at varying API content, formulations containing 70–130 % of the original drug content were prepared, by adapting the amounts of Hypromellose and Calcium Hydrogen-Phosphate Anhydrous accordingly, while keeping their ratio constant at 80:20. Purified water was used as granulation liquid at a Liquid/Solid-ratio of 0.3. The targeted tablet weight was 240 mg with a targeted label claim (LC) of 60 mg API/tablet (LC = 100%).

2.2. Solid dosage forms

2.2.1. Preparation of powder blends

For preparation of powder blends for continuous granulation and tableting, all ingredients were weighted into a drum and blended two times for 10 min at 11 rpm with a Pharma Telescope

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