On-line near infrared spectroscopy as a Process Analytical Technology (PAT) tool to control an industrial seeded API crystallization

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ABSTRACT

The final step of an active pharmaceutical ingredient (API) manufacturing synthesis process consists of a crystallization during which the API and residual solvent contents have to be quantified precisely in order to reach a predefined seeding point. A feasibility study was conducted to demonstrate the suitability of on-line NIR spectroscopy to control this step in line with new version of the European Medicines Agency (EMA) guideline [1]. A quantitative method was developed at laboratory scale using statistical design of experiments (DOE) and multivariate data analysis such as principal component analysis (PCA) and partial least squares (PLS) regression. NIR models were built to quantify the API in the range of 9–12% (w/w) and to quantify the residual methanol in the range of 0–3% (w/w). To improve the predictive ability of the models, the development procedure encompassed: outliers elimination, optimum model rank definition, spectral range and spectral pre-treatment selection. Conventional criteria such as, number of PLS factors, R^2, root mean square errors of calibration, cross-validation and prediction (RMSEC, RMSECV, RMSEP) enabled the selection of three model candidates. These models were tested in the industrial pilot plant during three technical campaigns. Results of the most suitable models were evaluated against to the chromatographic reference methods. Maximum relative bias of 2.88% was obtained about API target content. Absolute bias of 0.01 and 0.02% (w/w) respectively were achieved at methanol content levels of 0.10 and 0.13% (w/w). The repeatability was assessed as sufficient for the on-line monitoring of the 2 analytes. The present feasibility study confirmed the possibility to use on-line NIR spectroscopy as a PAT tool to monitor in real-time both the API and the residual methanol contents, in order to control the seeding of an API crystallization at industrial scale. Furthermore, the successful scale-up of the method proved its capability to be implemented in the manufacturing plant with the launch of the new API process.

1. Introduction

The Process Analytical Technology (PAT) initiative promoted by the Food and Drug Administration (FDA) has encouraged the Pharmaceutical Industry to increase research and use of new analytical technologies to perform timely measurements of the critical quality attributes of raw materials and intermediates allowing process understanding and control [2]. PAT concept is embraced in the Quality-by-Design (QbD) framework, introduced and developed by the ICH Q8(R2), Q9 and Q10 guidelines [3–5], that aims product and process understanding and process control, based on science and quality risk management, with the goal of ensuring a predefined final product quality.

Crystallization is a purification operation resulting in a solid intermediate or API, commonly used in pharmaceutical processes. Understanding and controlling the crystallization process is critical to produce an API with desired and highly reproducible solid state properties [6] such as crystal purity, polymorphism, crystal size distribution (CSD), density and flowability. These properties can have a large impact on the downstream unit operations such as filtration and drying, as well as on the bioavailability of the final drug product. Consequently high accuracy in-process and real-time measurement of solute concentration is required to control the level of supersaturation that drives the nucleation and the crystals growth.

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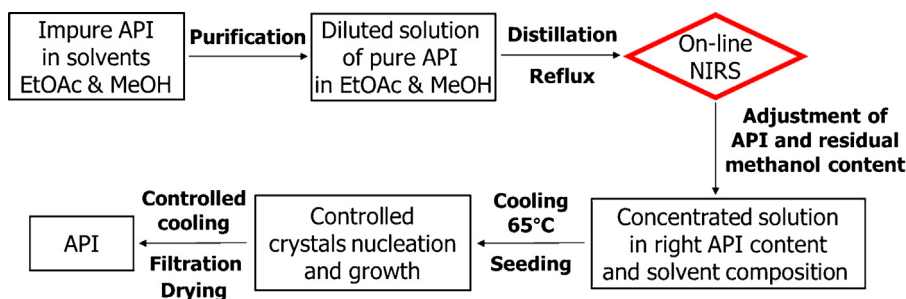E-mail address: cedric.schaefer@ucb.com (C. Schaefer).

Fig. 1. PAT implementation in the API manufacturing process.

This study focuses on a seeded crystallization, forming the last step of a new API organic synthesis process under development phase (Fig. 1). After purification step, the solution is concentrated in API while the residual methanol is eliminated by distillation. The API and the methanol contents should be accurately controlled in order to reach a predefined seeding point set at 10.5% (w/w) in API, not more than 0.50% (w/w) in methanol and temperature of 65 °C. Under these precise experimental conditions the supersaturation is maintained at a low and constant level. As a result, crystal growth is predominant over nucleation leading to a controlled crystallization and formation of API in a predefined polymorphic form without risk of dissolving. The implementation of on-line near infrared (NIR) spectroscopy as a PAT tool during the crystallization step will allow the real-time monitoring of both the API and the residual methanol contents in order to reach accurately the seeding point and to ensure a maximum process efficiency. Furthermore, this approach presents the advantage to avoid a tedious and difficult sampling phase due to the high process temperature and the rapid crystallization of the API.

NIR Spectroscopy has become a widely used analytical technique in pharmaceutical industry due to its high acquisition speed and non-destructive nature, its capacity to measure both physical and chemical properties and, based on the weak absorbance of the overtone and combination bands, it requires little or no sample preparation [7,8]. Moreover the possible use of high dimension optical fibers linked to process probes allows remote measurements and in- or on-line implementation in manufacturing plant. As NIR spectra are characterized by broad and overlapping absorption peaks and may have thousands of wavelength variables, assignment to specific chemical group vibrations may be rather difficult. To overcome these drawbacks, chemometrical tools such as multivariate data analysis are used to extract useful information from NIR spectra and to correlate them with reference values [9].

Several NIR spectroscopy applications in pharmaceutical fields dealing with monitoring of analytes solute concentration were reported. Nevertheless most of them were developed and tested in laboratory scale [10–14], whereas the ones monitoring industrial processes were not used as primary analysis in substitution of classical reference methods [15–20].

The draft of the new version of the European Medicines Agency (EMA) guideline dealing with the use of NIR spectroscopy in the pharmaceutical industry [1] exposed that a complete feasibility study should be carried out before the development and the validation of any qualitative or quantitative NIR method. In-line with this recommendation, the aim of this study is to demonstrate that on-line NIR spectroscopy is suitable for its intended use, *i.e.* as a primary analytical method for the real-time monitoring of both the API and methanol contents during the final crystallization step of a new API manufacturing process. Robust NIR models were developed at laboratory scale using chemometrics methods, then were evaluated in the industrial pilot plant.

2. Materials and methods

2.1. Materials

API batches used for this study were in-house manufactured with a purity not less than 99.1% assessed by high performance liquid chromatography (HPLC). Ethyl acetate, used as the crystallization solvent and methanol, added during previous process steps were purchased from commercial suppliers with a purity not lesser than 99.0%. The impurities generated during previous process steps were synthetized then purchased from commercial suppliers compliant with internal analytical specifications.

2.2. Spectroscopic data

An ABB – Fourrier Transform Laboratory Analyser (ABB-FTLA2000-160) near infrared spectrometer with InAs (indium arsenide) detectors and equipped with an immersion transmission probe 661.137-NIR Hastelloy C-22 (Hellma), optical path light of 5 mm; was used to record in- and on-line data, respectively at laboratory and pilot scale. The probe was connected to the spectrometer by a 20 m optical fiber, core diameter 600 μm. A dedicated computer system was used to collect the spectra with the GRAMS/AI software version 7.0 (Thermo Galactics) and to verify the spectral qualities of the spectrometer with the AIRS software version 3.12 (Thermo Galactics). Each spectrum recorded was obtained by averaging 256 scans with a resolution of 8 cm^{-1} over the range from 4300 to 10,450 cm^{-1}. A high number of scans was chosen to improve the spectral signal and to reduce some interferences caused by harsh experimental conditions in industrial plant [17]. A background spectrum was daily taken in air at laboratory scale and in N_2 at pilot scale.

2.3. Experimental procedure and setup

2.3.1. Laboratory scale

The NIR immersion probe was directly inserted in a 250 mL jacketed glass reactor with temperature controlled through a Hüber CC 240 wl thermo-stated bath. The solution was stirred at 200 and 300 rpm using a blade impeller. A platinum resistance thermometer with a temperature recorder (Fuji Electric) was used to measure the solution temperature. To prevent loss of solvent the condensate was refluxed back into the reactor using a glycol/water mixture cooled with tap water. Fig. 2(1) shows a schematic representation of the laboratory scale experimental setup.

2.3.2. Pilot scale

On-line NIR measurements were performed by inserting the immersion probe in a recirculation loop (Prosys) equipped with a 0.450 L flow cell and a valve sample cell. The loop was linked to a 400 L jacketed Hastelloy reactor with thermostatic tips. The solution was stirred using a two-story pitched blade impeller at the