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Research paper

Moisture and drug solid-state monitoring during a continuous drying process using empirical and mass balance models

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ABSTRACT

Classically, the end point detection during fluid bed drying has been performed using indirect parameters, such as the product temperature or the humidity of the outlet drying air. This paper aims at comparing those classic methods to both in-line moisture and solid-state determination by means of Process Analytical Technology (PAT) tools (Raman and NIR spectroscopy) and a mass balance approach. The six-segmented fluid bed drying system being part of a fully continuous from-powder-to-tablet production line (ConsiGma™-25) was used for this study. A theophylline:lactose:PVP (30:67.5:2.5) blend was chosen as model formulation. For the development of the NIR-based moisture determination model, 15 calibration experiments in the fluid bed dryer were performed. Six test experiments were conducted afterwards, and the product was monitored in-line with NIR and Raman spectroscopy during drying. The results (drying endpoint and residual moisture) obtained via the NIR-based moisture determination model, the classical approach by means of indirect parameters and the mass balance model were then compared. Our conclusion is that the PAT-based method is most suited for use in a production set-up. Secondly, the different size fractions of the dried granules obtained during different experiments (fines, yield and oversized granules) were compared separately, revealing differences in both solid state of theophylline and moisture content between the different granule size fractions.

1. Introduction

About 80% of the currently available pharmaceuticals are formulated as solid dosage forms, the majority of them being tablets. In many cases tabletting requires granulation of the starting materials (powders) prior to compaction. As a consequence industrial tabletting is still a multi-step process nowadays. In case of wet granulation, a drying step follows the granulation step. Afterwards the dry granules may be mixed with an external phase (i.e. lubricant, disintegrant). The final blend is then fed to the tabletting machine for compaction, which might be followed by coating, before the tablets are blistered and packed. *After* each step of this production chain the critical (intermediate) product characteristics of random samples of the batch are generally evaluated by means of off-line analyses in analytical laboratories. Batches will either proceed to the next processing step or will be rejected in case of failure of these analysis tests. Hence, traditional batch production is a time-consuming and expensive production method. Partly due to the increasing competition and decreasing profits in the pharmaceutical industry (i.e. generics, smaller pipelines, expiring patents, etc.), innovative manufacturing models are more and more desired in order to make the production processes faster, cheaper, more efficient and hence more competitive. Therefore, continuous production gains increasing interest in the pharmaceutical industry, also in tabletting applications. Recent manufacturing

Abbreviations: API, Active Pharmaceutical Ingredient; DoE, Design of Experiments; KF, Karl Fischer; NCO, Non-contact optic; NIR, Near Infrared; PAT, Process Analytical Technology; PC, Principal Component; PCA, Principal Component Analysis; PLS, Partial Least Squares; PVP, polyvinylpyrrolidone; RMSEP, Root Mean Square Error of Prediction; rpm, rotations per minute; SNV, Standard Normal Variate.

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technology advances have already shown the advantages of this approach [1–6].

Recently, full continuous from-powder-to-tablet production lines became commercially available [7–11]. The traditionally applied quality assessment approach based on off-line analysis is not applicable in a continuous manufacturing environment, since the process cannot be stopped and immediate and continuous process and product quality information is required. The need for off-line tests would counterbalance the advantages of continuous manufacturing. Therefore, continuous real-time quality control should be ensured by means of in-process analysis methods as it is advised in the Food and Drug Administration's PAT guideline [12].

Conventionally, the end point of a drying process – usually performed in a fluid bed dryer – after wet granulation is determined by means of *indirect* parameters. The humidity and the temperature of the outgoing drying air, the product temperature and the pressure difference over the fluidized bed can be evaluated in order to control the fluidized bed drying of wet granules [13,14]. These methods give an idea about the water evaporation progress. The drying process is considered as finished when water evaporation is no longer detected. However, the in-line monitoring of residual moisture content during drying using Near Infrared (NIR) spectroscopy is beneficial for two reasons: (i) monitoring the moisture content allows end point detection of the drying process and makes real-time decision making possible, hence preventing over-drying; and (ii) information regarding possible structural changes of the Active Pharmaceutical Ingredient (API) or/and excipients can be obtained.

The utility of NIR spectroscopy for the in-line monitoring and moisture assessment during fluid bed and spray drying processes has been demonstrated extensively in the literature [15–23]. Furthermore, NIR spectroscopy has also recently been used for the monitoring of a continuous granulation and drying process [10]. However, in this study the measurements were performed after the drying unit and not during drying. Besides monitoring of the drying process, NIR spectroscopy can also be used for the continuous evaluation of process induced solid-state transformations of both APIs and excipients. Romer et al. [24] monitored the solid-state conversions of erythromycin dehydrate using an in-line NIR spectrometer in a miniaturized fluid bed dryer. Aaltonen et al. [14] used both NIR and Raman spectroscopy to monitor the solid-state changes of theophylline using the same mini-dryer. They linked the in-line obtained spectra to the traditionally monitored fluid bed parameters such as absolute humidity of the outlet air and pressure difference over the fluidized bed. The solid-state changes were quantified in real-time, which is impossible with the traditional indirect parameters. Furthermore, the same micro scale fluid bed dryer was used by Kogermann et al. [25] to quantify the solid-state changes of piroxicam and carbamazepine in-line using Raman spectroscopy.

The presented study aims at evaluating Raman and NIR spectroscopy for the in-line monitoring of the drying process and determination of the end point, the residual moisture content and the product solid state *during* continuous drying *in* a six-segmented continuous fluid bed drying unit, which is part of a fully continuous from-powder-to-tablet manufacturing line (ConsiGma™-25, GEA Pharma Systems nv., Collette™, Wommelgem, Belgium). Furthermore, data derived from the in-line acquired spectroscopic data are compared with the conclusions obtained from the conventional *indirect* approach using the logged univariate parameters such as humidity of the outlet air and product temperature. Additionally, the spectroscopic observations are compared with the residual moisture content conclusions that can be derived from a mass balance model, which was recently developed for the six-segmented continuous fluid bed dryer [26]. This mass balance model is based on the physics governing the continuous drying process, hence forcing fundamental process understanding. Mass balance modeling requires the definition of the composition of the physical in- and outgoing gas (moisture content) and the liquid and solid streams in the process. It is examined whether feeding the continuously logged process parameters (e.g., humidity and temperature of inlet and outlet air, product temperature, etc.) into this mass balance model allows visualizing the drying process progress and calculating the end point of drying and the corresponding residual moisture content. By comparing these results to the spectroscopic results, the necessity of using spectroscopic monitoring during drying is evaluated and discussed.

2. Materials and methods

2.1. Materials

Anhydrous theophylline (Farma-Quimica Sur S.L., Malaga, Spain) (30%, w/w) was used as a model drug and granulated together with lactose monohydrate 200 M (Caldic Belgium NV, Hemiksem, Belgium) as filler. Polyvinylpyrrolidone (Kollidon 30®, BASF, Burgbernheim, Germany) was added as a binder to the dry powder mixture in a concentration of 2.5% (w/w). Distilled water was used as granulation liquid. Sodium lauryl sulfate (Fagron, Waregem, Belgium) was added to the granulation liquid (0.5% w/v) to improve the wettability of the dry powder mixture.

2.2. Continuous twin-screw granulation and fluid bed drying

Continuous granulation and drying was performed using the ConsiGma™-25 unit (GEA Pharma Systems nv., Collette™, Wommelgem, Belgium), which consists of three major units: a continuous twin screw high shear granulator, a six-segmented fluid bed dryer and a discharge system. The system has been extensively described elsewhere [7,11]. After discharging, a lubricant can be added and blended into the dried granules, after which the final blend can be compressed using an in-line tabletting machine. One of the assets that ConsiGma™ offers is the continuous logging and storage of numerous process parameters and outcomes in each unit (i.e., temperature granulator barrel, torque on twin screws, weight powder dosing unit, temperature of product in the dryer, etc.).

2.3. NIR spectroscopy

A Fourier-Transform NIR spectrometer (Thermo Fisher Scientific, Zellik, Belgium, Nicolet Antaris II near-IR analyzer) equipped with an InGaAs detector, a quartz halogen lamp and a fiber optic contact probe was used. The probe was inserted in cell 5 of the six-segmented fluid bed dryer by means of an in-house developed accessory (Fig. 1). Each spectrum was collected in the 10,000–4500 cm^{-1} spectral region with a resolution of 16 cm^{-1} and was averaged over 16 scans. Spectra were recorded continuously during drying and a spectrum was collected approximately each 10 s. The same fiber optic contact probe and spectrometer settings were used for off-line measurements. Spectra were mean centered and Standard Normal Variate (SNV)-corrected prior to multivariate data analysis. Data collection and data transfer were done using Thermo Fisher Scientific's Result Software.

2.4. Raman spectroscopy

A RamanRxn1 spectrometer (Kaiser Optical Systems, Inc., Ann Arbor, Michigan, US) equipped with an air-cooled CCD detector (back-illuminated deep depletion design) was used. For the in-line