Journal of Pharmaceutical and Biomedical Analysis 78–79 (2013) 57–64

Contents lists available at SciVerse ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

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

Development and in-line validation of a Process Analytical Technology to facilitate the scale up of coating processes

M. Wirges[a], A. Funke[b], P. Serno[b], K. Knop[a], P. Kleinebudde[a,*]

[a] Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University Düsseldorf, Universitätsstr. 1, 40225 Düsseldorf, Germany
[b] Global Chemical & Pharmaceutical Development, Bayer Pharma AG, Müllerstr. 178, 13353 Berlin, Germany

ARTICLE INFO

Article history:
Received 5 November 2012
Received in revised form 18 January 2013
Accepted 19 January 2013
Available online xxx

Keywords:
Raman spectroscopy
Multivariate analysis
Active coating
Scale up
Endpoint determination

ABSTRACT

Incorporation of an active pharmaceutical ingredient (API) into the coating layer of film-coated tablets is a method mainly used to formulate fixed-dose combinations. Uniform and precise spray-coating of an API represents a substantial challenge, which could be overcome by applying Raman spectroscopy as process analytical tool. In pharmaceutical industry, Raman spectroscopy is still mainly used as a bench top laboratory analytical method and usually not implemented in the production process. Concerning the application in the production process, a lot of scientific approaches stop at the level of feasibility studies and do not manage the step to production scale and process applications. The present work puts the scale up of an active coating process into focus, which is a step of highest importance during the pharmaceutical development. Active coating experiments were performed at lab and production scale. Using partial least squares (PLS), a multivariate model was constructed by correlating in-line measured Raman spectral data with the coated amount of API. By transferring this model, being implemented for a lab scale process, to a production scale process, the robustness of this analytical method and thus its applicability as a Process Analytical Technology (PAT) tool for the correct endpoint determination in pharmaceutical manufacturing could be shown. Finally, this method was validated according to the European Medicine Agency (EMA) guideline with respect to the special requirements of the applied in-line model development strategy.

1. Introduction

Due to a lack of process understanding, coating operations are far from being readily understood. This concerns critical coating parameters such as pan speed, spray rate or pan loading. In particular the up scaling of a film coating process is demanding [1]. While for continuous processing, up scaling simply means extending the process time, the up scaling of a batch-wise film coating operation is much more complicated. Today, in pharmaceutical manufacturing the optimal coating parameters have to be established separately for each production set up. Changes in equipment and scale may critically influence the product quality. As a consequence, batches might be rejected due to a failure to meet critical quality attributes such as target coating thickness, API content or coating uniformity. For this reason, it is vitally important to establish a method that is capable of reliably probing critical quality attributes upon scale up processes in order to avoid unnecessary expense and delays in time to market.

The paradigm shift in the pharmaceutical industry to process understanding and quality by design led to new approaches such as dimensional analysis [2], design of experiments (DoE) and numerical simulations of particle motion using the discrete elements method (DEM) [3–7]. As a consequence, scale up processes will not have to base on trial and error anymore, but on knowledge instead. To gain a better insight into the scale up of a pharmaceutical unit operation, process analytical technology tools (PAT tools) have been introduced. Chemometric techniques, both DoE to produce reliable data and multivariate data analysis to extract relevant information from highly dimensional data, are needed to enable the implementation of PAT tools such as vibrational spectroscopic techniques [8]. These tools have already been implemented to a vast range of processes and have proven their right for existence [9]. In the case of coating processes, PAT-tools are used to monitor, for instance, the product moisture [10], the increase of coating thickness [11] or the API content.

For an active coating process the quality, safety and performance of the final product largely depend on the amount and uniformity of coating applied. Consequently, the scale up from lab to production scale demands tools that are able to monitor and determine the endpoint of a coating operation.

* Corresponding author. Tel.: +49 211 811422; fax: +49 211 8114251.
E-mail address: kleinebudde@uni-duesseldorf.de (P. Kleinebudde).

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http://dx.doi.org/10.1016/j.jpba.2013.01.037

Table 1
Coating parameters BFC 5 (lab scale).

Step	Pan speed (rpm)	Spray rate (g/min)	Inlet air volume (m^3/h)	Exhaust air temperature (°C)	Inlet air temperature (°C)
Warm up	5	–	160	40	60
Coating I (0–60 min)	16	8	160	45	55
Coating II (60 min–end)	16	12	160	45	55
Drying	16	–	160	45	55
Cooling	5	–	160	30	25

Previous research showed that Raman spectroscopy in combination with multivariate data analysis is capable of providing in-line information about actual product conditions during the process. This means that in contrast to traditional approaches, such as measuring the amount of coating liquid used or weight gain, the coating process does not have to be interrupted when using Raman spectroscopy for process monitoring. Feasibility studies [12] and proof of concept trials with complex solid dosage forms [13] have built a solid base for the transfer of process applications from lab to production scale.

This study focuses on the transferability of Raman spectroscopy as a PAT-tool from lab scale to production scale. To achieve this, first a multivariate calibration model (PLS) was successfully developed for a production scale process. In a second step, a multivariate model, which was developed for a lab scale process, was tested on in-line measured Raman spectra of different production scale validation trials in order to evaluate the predictive ability and the robustness of the lab scale model.

2. Materials and methods

2.1. Materials

2.1.1. OROS tablet cores

The circular and biconvex OROS (osmotic-controlled release oral delivery system) tablet cores (Adalat GITS® (Bayer Pharma AG, Berlin, Germany)) consisted of a nifedipine layer and a layer containing osmotically active excipients together with iron oxide as a pigment. Each layer contributed differently to the resulting spectroscopic signal. The tablet cores were covered with a diffusion membrane made of cellulose acetate. The mantle coating of the dosage forms comprised candesartan cilexetil (Bayer Pharma AG, Berlin, Germany) as a second API and a polyvinyl alcohol based film-forming polymer.

2.1.2. Coating suspension

An aqueous-based coating suspension was prepared out of micronized candesartan cilexetil and a commercially available polyvinyl alcohol based polymer mixture (Opadry® II, Colorcon GmbH, Idstein, Germany).

2.1.3. Equipment

The active coating experiments were performed in a side-vented lab scale pan coater with a batch size of 3 kg (BFC 5, L.B. Bohle, Ennigerloh, Germany) and a production scale pan coater with a batch size of 250 kg (BFC 400, L.B. Bohle, Ennigerloh, Germany). For the Raman measurements a Raman RXN2™ analyzer from Kaiser Optical Systems (Ann Arbor, MI, USA) was used.

2.1.4. Software

For data collection and the calculations including spectral preprocessing, intensity normalization and partial least squares (PLS) regression, the following software packages were used: icRaman® data collection software package (Kaiser Optical Systems, Ann Arbor, MI, USA), SIMCA-P®+ 12.0.1 (Umetrics, Umea, Sweden), the Matlab® software package (version 6.5, The MathWorks, Inc., Natick, MA, USA), and Excel® (version 2010, Microsoft Corporation, Redmond, WA, USA).

2.2. Methods

2.2.1. Coating suspension

An aqueous-based coating suspension was prepared, consisting of 11.8% (w/w) candesartan cilexetil and 17.6% (w/w) ready-to-use film coating mixture. The micronized candesartan cilexetil and the polyvinyl alcohol based polymer mixture were added to the specified amount of purified water and dispersed homogeneously with a dispersion plate for at least 45 min. The prepared suspension was poured through a 0.35 mm sieve and stirred during spraying to prevent settling.

2.2.2. Tablet coating

Batches of 3 kg tablets were coated in a laboratory film coater BFC 5 (L.B. Bohle, Ennigerloh, Germany) with a pan diameter of 316 mm and a length of 356 mm. The production scale batches of 250 kg tablets were coated in a BFC 400 pan coater with a pan diameter of 1500 mm and a length of 1600 mm. The process parameters are illustrated in Tables 1 and 2. During the lab scale coating process 20 tablets at a time were collected at different coating levels. At the end of the coating process an average of (32 ± 1.3) mg API as obtained by HPLC analysis was coated onto each tablet. In the case of the production scale coating process, every 30 min samples were taken for the production scale model calibration and validation sets. At the end of the process an average of (8.55 ± 0.54) mg API or (16.37 ± 0.64) mg API for the second coating run, respectively, was found to be coated onto each tablet.

2.2.3. Raman measurements

The Raman RXN2™ analyzer from Kaiser Optical Systems (Ann Arbor, MI, USA) with a laser wavelength of 785 nm (GaAlAs laser-diode laser) was equipped with a non-contact optic sampling device (PhAT probe, Kaiser Optical Systems, Ann Arbor, MI, USA). The excitation laser was introduced and magnified to form a circular illumination area of 6 mm diameter (6-mm lens: nominal focal length 250 mm, area: 28.3 mm^2, approximate laser power at a 6 mm spot: 200 mW, spectral resolution: 1.85 cm^{-1}/pixel) to cover a large sample area, which improves the reliability and reproducibility of

Table 2
Coating parameters BFC 400 (production scale).

Step	Pan speed (rpm)	Spray rate (g/min)	Inlet air volume (m^3/h)	Exhaust air temperature (°C)	Inlet air temperature (°C)
Warm up	9	–	2900	40	60
Coating	9	180–360	2900	42	52
Cooling	4	–	2900	30	25