Research paper

Evaluation of in–line Raman data for end-point determination of a coating process: Comparison of Science–Based Calibration, PLS-regression and univariate data analysis

Shirin Barimani, Peter Kleinebudde *

Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University, Universitaetsstr. 1, 40225 Duesseldorf, Germany

ABSTRACT

A multivariate analysis method, Science–Based Calibration (SBC), was used for the first time for endpoint determination of a tablet coating process using Raman data. Two types of tablet cores, placebo and caffeine cores, received a coating suspension comprising a polyvinyl alcohol–polyethylene glycol graft–copolymer and titanium dioxide to a maximum coating thickness of 80 μm. Raman spectroscopy was used as in–line PAT tool. The spectra were acquired every minute and correlated to the amount of applied aqueous coating suspension. SBC was compared to another well–known multivariate analysis method, Partial Least Squares-regression (PLS) and a simpler approach, Univariate Data Analysis (UVDA). All developed calibration models had coefficient of determination values (R^2) higher than 0.99. The coating endpoints could be predicted with root mean square errors (RMSEP) less than 3.1% of the applied coating suspensions. Compared to PLS and UVDA, SBC proved to be an alternative multivariate calibration method with high predictive power.

© 2017 Elsevier B.V. All rights reserved.

1. Introduction/purpose

Film coating of solid dosage forms is a common process in pharmaceutical industry and manufacturing. Numerous functions can be achieved by this unit operation such as taste or odor masking, modified release profiles or protective or cosmetic layers [1]. One important parameter for the performance is the coating thickness. In order to monitor the coating thickness during the production process and to be able to determine a correct endpoint of the process, real-time information is needed. Using this information could avoid insufficient product quality and save time and costs.

According to the Food and Drug Administration "quality cannot be tested into products, it should be built–in or should be by design" [2]. Therefore, a regulatory framework was outlined, where the implementation of Process Analytical Technology (PAT) is recommended for the purpose of improving a production process. PAT is defined as "a system for designing, analyzing, and controlling manufacturing".

Using analytical instruments as process analysers in-line offers several advantages: the sample does not need to be prepared, it can be measured without removing it from the process stream and in–process information can be obtained. One highly selective method [3,4], which offers the possibility for fast and non–destructive measurements, is Raman spectroscopy. It was detected in 1928 [5,6]. A substance is irradiated with monochromatic light and the scattered light with a different frequency to the incident beam is detected. The feasibility of Raman spectroscopy as a PAT tool was shown for several pharmaceutical unit operations, such as crystallization, blending, granulation, tableting and coating [7]. Romero–Torres et al. [8] investigated the tablet–to–tablet coating variability by correlating off-line acquired Raman spectra of coated tablets to the coating time. El Hagrasy et al. used Raman spectroscopy off–line for tablet coating uniformity determination [9]. The same workgroup used this method for in–line monitoring of a tablet coating process [10] and developed a quantitative model for coating thickness using titanium dioxide (TiO_2) in the coating suspension which scattered the incident beam strongly, resulting in an intense Raman signal. Müller et al. monitored an active coating process [11]. Cahyadi et al. [12] compared several non–destructive methods to quantify tablet coating thickness. Raman spectroscopy could differentiate tablets which were coated under different conditions.

The data volume generated by Raman spectroscopy can be large and complex. Therefore, it is challenging to extract useful information. One approach is the usage of chemometrics [13–15]. The

* Corresponding author.
    E-mail address: kleinebudde@hhu.de (P. Kleinebudde).

mathematical relationship between Raman band area and analyte concentration is proportional and can be described by analytical models. Quantitative models can be developed univariate or multivariate [16,17]. Univariate models include one single Raman band whereas multivariate models include multiple signals. One multivariate data analysis method, which offers the advantage of direct calibration, was first introduced in 2002 by Marbach [18]. The author published a paper about a statistical multivariate calibration method, which is based on Wiener filter. Using a known signal, this filter is an approach for calculating a statistical estimate of a signal, which is unknown. Noise from the original signal is reduced. In 2005, Marbach introduced "A new method for multivariate calibration" [19], which is based on the theory of the first published article from 2002. It is announced as a new method which combines the best features of classical and inverse calibration where is virtually no need for lab–reference values. The method was demonstrated on a set of data of spectra acquired by near-infrared (NIR) spectroscopy of pharmaceutical tablets. Additionally, the calibration method was used to calibrate the latex concentration at the surface of coated paper [20] which was acquired off-line using attenuated total reflection spectroscopy. In 2006 the method was termed Science–Based Calibration (SBC) for the first time [21]. Here, the spectral signal is divided into signal and noise. All other information, which is not wanted, is called noise. In SBC, only the pure component spectrum of the analyte of interest is used in the calibration step. Performing SBC on data acquired by NIR spectroscopy, the glucose concentration in blood and aqueous solutions could be measured in 2008 [22]. In 2010, Marbach showed the feasibility of SBC to detect the distribution of active pharmaceutical ingredients (APIs) in tablets using offline NIR spectroscopy [23] and for API level detection in tablets [24]. This method was also demonstrated on chromatographic data [25,26]. Möltgen et al. [27] used SBC for coating thickness determination of tablets using real–time NIR spectra. The robustness of calibration and predictability of different multivariate calibration methods (e.g., SBC and PLS), using NIR spectra of aqueous mixtures, was compared by Sharma et al. [28]. One alternative popular multivariate data analysis method is the Partial Least Square Regression (PLS) [29,30]. It has a high predictive accuracy and is even able to predict collinear X–variables. In order to build robust models, the method needs a calibration set which is varying in concentration. Hence, this step is time consuming. A simple mathematical approach for data interpretation is the Univariate Data Analysis (UVDA) [31]. It uses one single Raman band for the model building. As Raman spectra are typically well resolved, UVDA results often in robust models [32]. However, in case of complex mixtures, this analysis method is often not sufficient.

The aim of this work was to investigate for the first time the applicability of SBC on data acquired by Raman spectroscopy. The two multivariate calibration methods SBC and PLS should be compared to univariate calibration for determination of coating endpoint and in–line monitoring of a process, using spectral data acquired by a Raman probe, which was implemented into the process.

2. Materials and methods

2.1. Materials for tablet cores

Lactose (Pharmatose® 200 M, DFE pharma, Goch, Germany), microcrystalline cellulose (Avicel® PH 101; FMC BioPolymer, Philadelphia, USA), povidone (PVP K25; Sigma-Aldrich, St. Louis, USA), croscarmellose sodium (Ac–Di–Sol®, FMC BioPolymer, Philadelphia, USA), saccharin sodium (DKSH GmbH, Hamburg, Germany), hydroxypropyl methyl cellulose (HPMC 5 cP, Colorcon

GmbH, Idstein, Germany) and magnesium stearate (Peter Greven GmbH & Co. KG, Bad Münstereifel, Germany) were used as excipients for placebo cores. Caffeine cores consisted of caffeine (caffeine anhydrous granular 0.2/0.5; BASF, Ludwigshafen, Germany), (Ludipress®, composed of 93% lactose monohydrate, 3.5% povidone, 3.5% crospovidone, BASF, Ludwigshafen, Germany), microcrystalline cellulose (Avicel® PH 101; FMC BioPolymer, Philadelphia, USA), and magnesium stearate (Mallinckrodt, Hazelwood, USA).

2.2. Materials for coating suspension

The aqueous coating suspension contained titanium dioxide (TiO_2; KRONOS® 1171, Kronos Titan, Leverkusen, Germany), polyvinyl alcohol–polyethylene glycol graft-copolymer (Kollicoat® IR, BASF, Ludwigshafen, Germany) and deionised water.

2.3. Tablet cores

Biconvex placebo cores with an average mass of 202 mg, a diameter of 8 mm and a 4 mm height, consisted of 3.2% (w/w) lactose, 21.5% (w/w) microcrystalline cellulose, 6.2% (w/w) povidone 4.2% (w/w) croscarmellose sodium, 3.3% (w/w) saccharin sodium, 1.1% (w/w) hydroxypropyl methyl cellulose and 0.5% magnesium stearate. They were obtained by L.B. Bohle (L.B. Bohle Maschinen + Verfahren GmbH, Ennigerloh, Germany). The caffeine cores were biconvex and had an average mass of 329 mg, a diameter of 9 mm and a height of 5 mm. They were composed of 15.15% (w/w) caffeine, 72.43% (w/w) Ludipress® (w/w), 12.12% (w/w) microcrystalline cellulose and 0.3% (w/w) magnesium stearate. These cores were obtained by BASF.

2.4. Tablet coating

In order to compare non Raman active cores and highly Raman active cores, four tablet batches were coated: 3300 g of placebo cores and 3000 g of caffeine cores, each twice. The tablets were coated in a laboratory film coater (BFC 5, L.B. Bohle Maschinen + Verfahren GmbH). The suspensions were applied using two 1 mm nozzles placed with a distance of 10 cm from the rotating tablet bed. Table 1 shows the process parameters of the coating experiments of both core types. The placebo cores were coated with 1897 g of an aqueous coating suspension containing 5% (w/w) TiO_2, 15% (w/w) Kollicoat® IR and 80% (w/w) deionised water for 169 min until the calculated coating thickness of 80 μm was achieved. The thickness was calculated based on the surface to be coated and the film density. The calculations are described in the supplementary material. The mass of the aqueous coating suspension, containing 2.25% (w/w) TiO_2, 12.75% (w/w) Kollicoat® IR and 85% (w/w) deionised water, which was applied on the caffeine cores, was 1486 g. The coating time was 130 min and the calculated coating thickness 70 μm. In order to ensure that the spray rate and amount of coating mass on the cores were constant, the weight change of the coating suspension was monitored and a linear regression was performed.

2.5. Raman spectroscopy

Raman spectra were collected during the whole coating process using the Raman RXN2™ Analyser (Kaiser Optical Systems, Ann Arbor, USA) and the iC Raman™ 4.1 software package (Kaiser Optical Systems, Ann Arbor, USA). The excitation laser had a wavelength of 785 nm and 400 mW power. The spectrometer was equipped with a PhAT probe, a non-contact optic sampling device. Thereby, the sample area was increased: the laser spot formed a circular illumination area with 6 mm diameter. The probe was fixed in the front door of the coater and the spectra were acquired with a work-