Drug Development and Industrial Pharmacy, 2010; 36(2): 234–243

informa
healthcare

ORIGINAL ARTICLE

Feasibility of Raman spectroscopy as PAT tool in active coating

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Abstract

Background: Active coating is a specific application of film coating where the active ingredient is comprised in the coating layer. This implementation is a challenging operation regarding the achievement of desired amount of coating and coating uniformity. To guarantee the quality of such dosage forms it is desirable to develop a tool that is able to monitor the coating operation and detect the end of the process. *Method*: Coating experiments were performed at which the model drug diprophylline is coated in a pan coater on placebo tablets and tablets containing the active ingredient itself. During the active coating Raman spectra were recorded in-line. The spectral measurements were correlated with the average weight gain and the amount of coated active ingredient at each time point. The developed chemometric model was tested by monitoring further coated batches. Furthermore, the effects of pan rotation speed and working distance on the acquired Raman signal and, hence, resulting effect of the chemometric model were examined. *Results*: Besides coating on placebo cores it was possible to determine the amount of active ingredient in the film when coated onto cores containing the same active ingredient. In addition, the method is even applicable when varying the process parameters and measurement conditions within a restricted range. *Conclusion*: Raman spectroscopy is an appropriate process analytical technology too.

Key words: *Active coating; in-line measurement; multivariate curve resolution; process analytical technology; Raman spectroscopy; tablet coating*

Introduction

In formulation of solid dosage forms, film coating represents an important unit operation that can fulfill different functions like taste masking, product identification, and protective layering. Furthermore, film coating is frequently used to improve the therapeutic effect, for example, enteric or controlled release coatings, which influence location and period of drug release. Active coating is a specific application of film coating where the active ingredient is comprised in the coating layer. This implementation is beneficial for low-dose active ingredients such as strong analgesics[1] or hormones[2] or to achieve an immediate dose with a quickly dissolving coating layered onto a delayed release core[3,4]. Both functional and active coatings are challenging operations regarding the achievement of desired amount of coating and coating uniformity. To guarantee the quality of such dosage forms it is desirable to develop a tool that is able to monitor the coating operation and detect the end of the process.

The aim of this work was the implementation of a noninvasive and rapid process analytical technology (PAT) tool for in-line quantitative monitoring of active coating. Process understanding, optimization of manufacturing efficiency, and reproducibility of product quality are the primary objectives of the PAT guidance issued by the FDA[5]. The ultimate goal is the real-time release whereby batch release is based on data collected throughout the process without off-line testing of manufactured products. Near-infrared spectroscopy is a suitable analytical method for in-line monitoring and was frequently applied for tablet coating processes[6–8].

Alternatively, Raman spectroscopy has recently emerged as a complementary analytical tool to near-infrared spectroscopy. Romero-Torres et al.[9] correlated

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(Received 30 Apr 2009; accepted 23 Jul 2009)

ISSN 0363-9045 print/ISSN 1520-5762 online © Informa UK, Ltd.
DOI: 10.3109/03639040903225109

Raman spectra of coated tablets with coating times using partial least squares (PLS). Furthermore, they demonstrated a novel approach to the measurement of colored tablet coating thickness, which employed Raman spectroscopy with univariate and multivariate data analysis[10].

El Hagrasy et al.[11] developed a quantitative calibration model for the prediction of amount of coating tablets by correlating the measured Raman spectra with the average weight gain of tablets. In addition they used Raman spectroscopy for the determination of coating uniformity by the use of a multivariate quantitative calibration and tested the model by following the progress of coating in independent batches[12].

In our work, we focused on the use of Raman spectroscopy for the determination of the amount and uniformity of active coating with diprophylline as model drug. Therefore, we developed a multivariate quantitative calibration using tablets collected at different stages of coating from a small-scale pan coater. We performed coating experiments at which the diprophylline is coated on placebo tablets and tablets containing the active ingredient itself. The spectral measurements were correlated with the average weight gain and the amount of coated active ingredient at each time point. Afterward the developed model was tested by monitoring the progress of coating. Furthermore, the effects of pan rotation speed and working distance on the acquired Raman signal and, hence, resulting effect of the chemometric model were examined.

Materials

Drug

The water-soluble caffeine derivative diprophylline (dph; BASF, Ludwigshafen, Germany) was used for the active coating as model drug because it could be detected well by Raman and UV spectroscopy.

Tablets

Lactose monohydrate (Tablettose® 80, Flowlac® 100; Meggle, Wasserburg, Germany), microcrystalline cellulose (Avicel® PH 102; FMC International, Little Island Co., Cork, Ireland), copovidon (Kollidon® VA 64; BASF), magnesium stearate (Welding, Hamburg, Germany), and diprophylline (BASF) were used as excipients of the core.

Coating solution

The aqueous coating solution contained hydroxypropyl methylcellulose (HPMC, Walocel® HM5 PA2910; Wolff Cellulosics, Walsrode, Germany), polyethylene glycol 1500 (Clariant GmbH, Frankfurt am Main, Germany), and diprophylline (BASF).

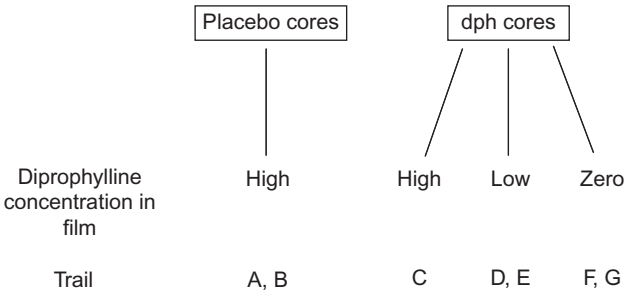

Figure 1. Experimental plan.

Methods

Figure 1 illustrates the performed coating trials that varied in the composition of the core and the coating solution.

Placebo cores

The tablet cores were biconvex (4 mm in height, 7 mm in diameter, and an average weight of 148 mg) and were composed of 49.75% (w/w) lactose monohydrate (Tablettose® 80), 49.75% (w/w) microcrystalline cellulose, and 0.5% (w/w) magnesium stearate.

Diprophylline cores

The biconvex diprophylline cores (4 mm in height, 8 mm in diameter, and an average weight of 200 mg) consisted of 10% (w/w) diprophylline, 84.5% (w/w) lactose monohydrate (Flowlac®), 5% (w/w) copovidon, and 0.5% (w/w) magnesium stearate.

Coating solution

The aqueous coating solutions with high and low diprophylline concentrations contained 20% and 11% of solids, respectively. The composition of the solid fraction of the coating solution with high diprophylline concentration was 30% (w/w) HPMC, 10% (w/w) polyethylene glycol 1500, and 60% (w/w) diprophylline. The coating solution with low diprophylline concentration contained 67.5% (w/w) HPMC, 22.5% (w/w) polyethylene glycol 1500, and 10% (w/w) diprophylline related to the solid fraction. The aqueous coating solution without diprophylline contained 9% of solids and was composed of 75% (w/w) HPMC and 25% (w/w) polyethylene glycol 1500 related to the solid fraction.

Table 1. Process parameters.

Step	Pan speed (rpm)	Spray rate (g/min)	Inlet air volume (nm^3/h)	Exhaust air temperature (°C)	Inlet air temperature (°C)
Warm up	5	—	150	40	60
Coating	16	12	150	40	55
Drying	16	—	150	40	55
Cooling	5	—	150	30	25

Tablet coating

In each case a batch size of 3.5 kg was 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 process parameters are illustrated in Table 1.

Raman equipment

Raman spectra of tablets were collected using a PhAT System (Kaiser Optical Systems, Ann Arbor, MI, USA) equipped with a noncontact optic sampling device. The excitation laser (785 nm diode laser) was introduced and magnified to form a circular illumination area of 6 mm diameter (area: 28.3 mm^2) to cover a large sample area. This wide area illumination scheme improves the reliability of sample representation and the reproducibility of sampling because of less sensitivity of sample placement with regard to the focal plane[13,14]. The scattered radiation was collected by an array of 50 optical fibers and delivered to an air-cooled CCD detector. A holographic transmission grating dispersed the radiation from the optical fibers and integrated a combined signal over the total illuminated area. Data collection and data transfer were automated using the HoloGRAMS^{TM} (Kaiser Optical Systems) data collection software package, the HoloREACT^{TM} (Kaiser Optical Systems) reaction analysis and profiling package, the Matlab® software package (version 6.5; The MathWorks, Inc., Natick, MA, USA), and Excel®.

In either case of the experiment the spectral data were preprocessed by standard normal variate (SNV) and mean centering to facilitate calibration development.

Calibration development

Tablets collected at different stages of coating were used for off-line quantitative calibration development with a scanning time of 15 seconds for each tablet. An extra set of validation samples was collected at each sampling point for model validation. The weight gain of tablets measured by the gravimetric method and the amount of coated diprophylline determined by UV spectroscopy were used as reference analytical methods.

Gravimetric analysis was performed for experiments A, B, F, and G (Figure 1). The individual weights of 30 tablets for each sample coating time (30 minutes intervals) were measured on a Sartorius CPA224S analytical balance (Sartorius AG, Goettingen, Germany). To minimize the effect from individual tablet weight variation and to improve the precision of the calibration model the average weight gain at each sampling point was used. Additionally, 10 tablets for each interval were used for the validation.

For the coating experiments A–E the coated amount of diprophylline of six tablets for each coating time (30-minute intervals) was determined individually by UV spectroscopy (Lambda-2; Perkin-Elmer, Ueberlingen, Germany). An extra set of validation samples of three tablets for each coating time were determined additively. A calibration for the range of diprophylline concentrations 0–15 mg/500 mL (A, B) and 15–32 mg/1000 mL (C, D, and E) was performed with five different concentrations and two repeated measurements on different days in each case. After dissolving the tablet in 500 mL (A, B) or 1000 mL water (C, D) the absorption was measured at 273 nm.

In-line monitoring

A noncontact Raman probe was fixed outside the coating pan to collect spectra during the process with a working distance of about 22 cm. To protect the probe against dust compressed air was blown through an iron pipe [95 mm length, 33 mm diameter], which was attached in front of the probe. The scanning time for every spectrum was 30 seconds followed by cosmic ray filtering that was offset to one single spectrum per minute.

Multivariate analysis

A multivariate model was constructed for trial A by correlating Raman spectral data with weight gain (%) and coated amount of diprophylline (mg) using PLS. The calibration model was based upon a set of 210 tablets (gravimetric method) or rather 42 tablets (UV spectroscopy). A separate set of 70 rather than 18 tablets was used to test the model.

To estimate the applicability of the constructed model, it was tested on an independent batch (trial B). The samples were collected and analyzed as in experiment A. For trial C Raman spectra were correlated with diprophylline increase (%) related to the diprophylline core. The calibration model was based upon a set of 36 tablets. Additionally a separate set of 15 tablets was used to test the model.

The total amount of diprophylline (mg) was correlated with Raman spectra for trial D. A set of 42 tablets was used to construct the multivariate model and a separate set of 18 tablets was used to test the model. The samples of trial E were collected and analyzed in the same way as in experiment D to test the constructed model.

A multivariate model was constructed by correlating Raman spectral data with weight gain (%) for trial F

using PLS. The calibration model was based upon a set of 210 tablets, and a separate set of 70 tablets was used to test the correlation. The constructed model based on the data of trial F was examined by a repeat test (G).

In each case PLS models and data preprocessing (mean centering and SNV) were carried out using the Simca-P+ 11.5 software (Umetrics AB, Umeå, Sweden). Additionally, multivariate curve resolution (MCR) was performed using the HoloREACT^{TM} (Kaiser Optical Systems) reaction analysis software.

Pan rotation speed

The effect of the pan rotation speed on the Raman signal was examined at the end of the coating process at six different rotation speeds: 0, 2, 5, 10, 15, and 18 rpm. Seven repeated measurements were carried out for each rotation speed with a scanning time of 30 seconds per measurement.

Working distance

Depending on the working distance off-line measurements of the same tablet were performed in seven stages: 12.5, 15, 20, 22, 24, 26, and 28 cm with nine repeated measurements and 15 seconds scanning time per measurement. This experiment was performed with a finished coated tablet of trials A and B.

Results and discussion

To the best of the author's knowledge it was the first time that Raman spectroscopy was used for the determination of the amount and uniformity of active coating in a pan coater.

Placebo cores

The sensitivity of the Raman signal to changes in the coating level on tablets can be seen in Figure 2, which demonstrates baseline-corrected Raman spectra of tablets at different stages of coating in the region 1200–1400 cm^{-1}. The intensity of the peaks 1290 and 1330 cm^{-1} increases as function of coating time and can be assigned to diprophylline. The methylated N^3 atom (CN) stretch occurs at 1290 cm^{-1} and the imidazole ring stretch at 1330 cm^{-1}.

Determination of diprophylline amount as reference analytical method

A PLS predictive model was constructed using the SNV spectral data and the tablet sets from 0 to 12.7 mg diprophylline. Most improvement for this model was

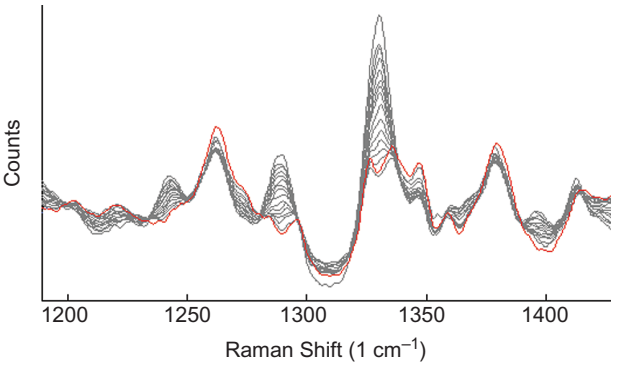

Figure 2. Baseline-corrected spectra of tablets during the coating process.

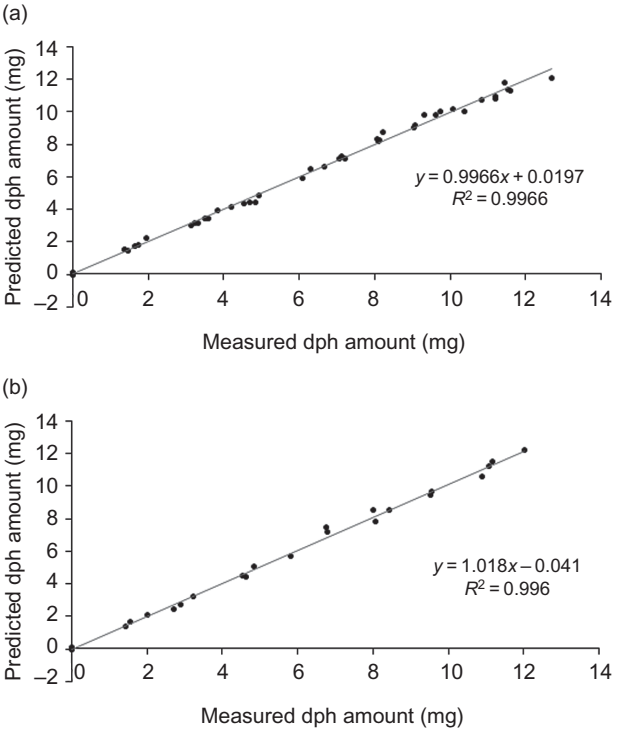

Figure 3. Calibration (A; $n = 48$) and prediction (B; $n = 24$) variance regression model for SNV Raman spectra (trial A).

obtained by using three principal components. The root mean square of errors for calibration and prediction (RMSEC and RMSEP) was 0.2354 and 0.2585 mg (Figure 3). By fitting the measured spectra during the whole coating process in the model the predicted diprophylline amount was consistent with the measured samples that were collected at the according sampling points (Figure 4A). Noticeably, the diprophylline amount increased to a small extent in the drying step after the coating process was finished. This can be explained by two considerations. There was no adequate sample measured at the point in time after coating and a certain

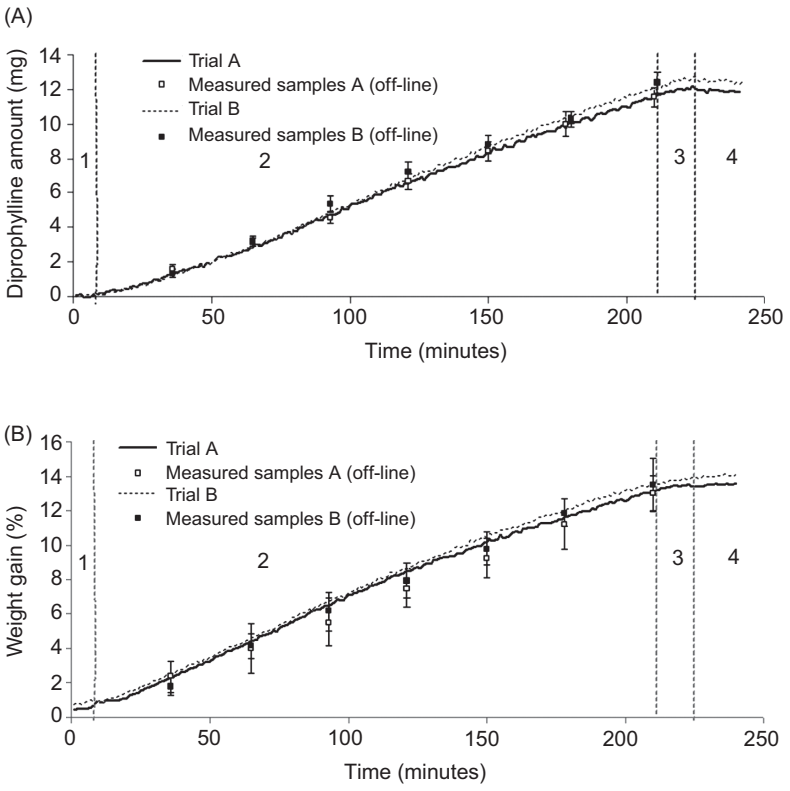

Figure 4. (A) Prediction of diprophylline amount for trials A and B from in-line data ($n = 9$; mean ± SD); process steps: 1, warm up; 2, coating; 3, drying; 4, cooling. (B) Prediction of weight gain for trials A and B from in-line data ($n = 30$; mean ± SD); process steps: 1, warm up; 2, coating; 3, drying; 4, cooling.

period was necessary to achieve a representative sample. Furthermore, the tablets were measured shortly after they had passed the spray jet and therefore, they were moist. During the process they dried, which led to higher diprophylline concentrations in the film.

Finally the model was tested on an independent batch (trial B). The prediction of the test set with 48 tablets (RMSEP = 0.4258 mg) and of the in-line measurements (Figure 4A) yielded good results.

The obtained results demonstrate that Raman spectroscopy is an appropriate PAT tool for active coating. Subject to the application the constructed model can determine the amount of coated active ingredient with sufficient accuracy. In the case of coated active ingredient in high dose like dosage forms with a delayed release core coated with an immediate dose the method is applicable. But for active coating with low-dose active ingredients such as strong analgesics or hormones with a small therapeutic index, the method must be improved.

Reference analytical method weight gain

Alternatively a PLS predictive model was constructed by using the weight gain of tablets measured by the gravimetric method as reference analytical method. In this case two principal components were needed for the model that gave an RMSEC of 0.7008% and an RMSEP of 0.8358%, respectively, for the tablet set of 0–13% weight gain. Figure 4B shows the predicted weight gain resulting from the in-line measured spectra in dependence on the coating time whereby weight gain was also observed in the drying step as discussed before. Compared to the determination of the amount of coated diprophylline the results of predicted weight gain were less precise.

The prediction of the test set with 220 tablets of the independent batch (trial B) gave an RMSEP of 0.6322%. In addition the weight gain resulting from the in-line measurement of the process could be monitored (Figure 4B).

By comparison of the two reference analytical methods it becomes clear that the diprophylline amount determined by UV spectroscopy is more appropriate. Tables 2 and 3 show that the results predicted by the Raman method (constructed PLS model) coincide with the reference method at each sampling interval. The variation of the diprophylline concentration by the Raman method and the UV spectroscopy is similar (Table 2). The variation in the Raman-predicted weight is smaller compared to the variation based on the weight measurements (Table 3). This can be explained

Table 2. Comparison of diprophylline amount (mg) obtained by UV and Raman spectroscopy ($n = 9$; mean ± SD).

	UV spectroscopy		Raman	
Coating time (minutes)	Mean (mg)	Standard deviation (mg)	Mean (mg)	Standard deviation (mg)
30	1.63	0.24	1.75	0.25
60	3.25	0.30	3.26	0.19
90	4.57	0.35	4.38	0.31
120	6.65	0.48	6.74	0.51
150	8.42	0.56	8.76	0.67
180	9.97	0.71	10.03	0.52
214	11.54	0.56	11.42	0.52

Table 3. Comparison of weight gain (%) obtained by gravimetry and Raman spectroscopy ($n = 30$; mean ± SD).

Coating time	Gravimetric method		Raman	
(minutes)	Mean (%)	SD (%)	Mean (%)	SD (%)
30	2.38	0.89	2.07	0.41
60	4.01	1.45	3.75	0.55
90	5.53	1.38	5.83	0.71
120	7.49	1.12	8.05	0.55
150	9.24	1.14	9.50	0.72
180	11.22	1.44	11.06	0.55
214	13.01	1.04	12.38	0.63

by the variation of the tablet weight itself, which was already discussed by El Hagrasy et al.[12] A variation of 2% of the target weight of 148 mg will result in a range of 5.92 mg (145–151 mg) in the weight of the tablets. The amount of coating material applied on a 168 mg tablet at the end of the coating process can thus range between 11.3% and 15.0% for untreated tablets ranging from 145 to 151 mg. As the Raman method only detects the coating material and is not affected by the variation of the tablet weight it is more appropriate to calculate the coating amount.

Diprophylline cores

The relation between core and coating signal during the coating process was described by Kauffman et al.[15] By coating acetaminophen tablets with HPMC and polyethylene glycol he used target factor analysis to correlate Raman spectra with tablet coating thickness based on physical models of the spectral composition.

In active coating the film can be used to combine an immediate dose and a delayed dose in the core containing the same active ingredient. Trials C–G were used to examine the ability of the method to determine the amount of active ingredient in the film when coated onto cores containing the same active ingredient. In trial C the intensity of the peaks arising from the active ingredient diprophylline increased with proceeding coating time (figure not shown). It was postulated that the total analytical signal is a result of the core and the coating material. Furthermore, the core contribution of the analytical signal decreases with increasing coating time and, conversely, the coating contribution to the analytical signal increases with the coating time. Thus, it was expected that the total analytical signal of diprophylline is a result of the diprophylline core and the coating material containing the active ingredient. Because of these assumptions the possibility to determine the amount of coated diprophylline on diprophylline tablets was investigated.

MCR is a very profitable tool for the operator of analytical spectroscopy because all spectra of the collective mixture are fragmented into chemically interpretable basis spectra that reflect the fundamental components of the whole data set. Increment or decrement of a defined component within the data matrix is pointed by the score values. Finally, it is possible to calculate the individual spectra of the single components from the mixture.

In trial C tablets collected at different coating stages ($n = 6$; 30-minute intervals) were analyzed by MCR. The results of the MCR of the baseline-corrected spectra indicated that the resulting data could be described sufficiently with a two-factor model. Figure 5 shows the resultant basis spectra of the two components. The reproduced spectra were similar to the spectra of the diprophylline core and the coating solution. By examining the score values of the components (Figure 6) it was obvious that the contribution of the core to the analytical signal decreased and that the contribution of the coating to the signal increased with the coating time or the coated diprophylline amount as postulated. However, the contribution of the diprophylline core was still the main part of the whole signal at the end of the coating process. This could be related to the PhAT probe, which has a penetration depth of about 2 mm, so that even after the coating process the core could be detected sufficiently.

The Raman spectral changes were correlated with the diprophylline increase (%) relating to the diprophylline core by using PLS. The constructed PLS model using SNV and mean-centered spectral data of tablet sets from 0% to 60.5% diprophylline increase resulted in a root mean square of errors for calibration and prediction (RMSEC and RMSEP) of 1.822% and 3.361%. Subsequently, the in-line measured data were fitted in the model to predict the coated diprophylline amount in dependence on the coating time (Figure 7). The diprophylline increase predicted by the in-line data shows good analogy with the measured samples that were collected at the according sampling points. Like in experiments A and B there was a small diprophylline increase after the coating step.

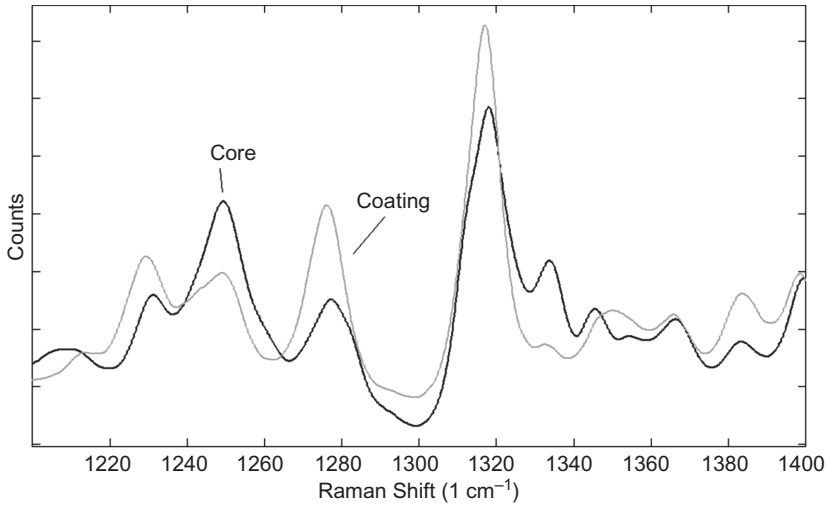

Figure 5. Reproduced spectra by MCR of coating material and diprophylline core (trial C).

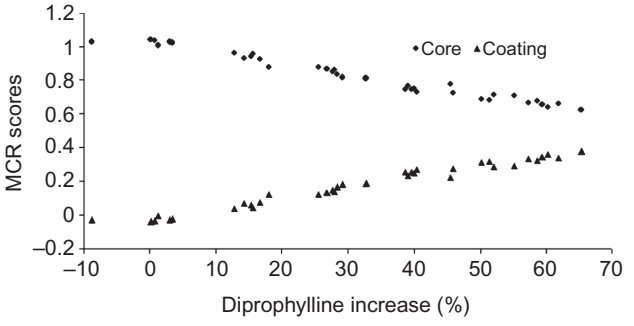

Figure 6. MCR scores (trial C) in dependence on the diprophylline increase (%) ($n = 6$).

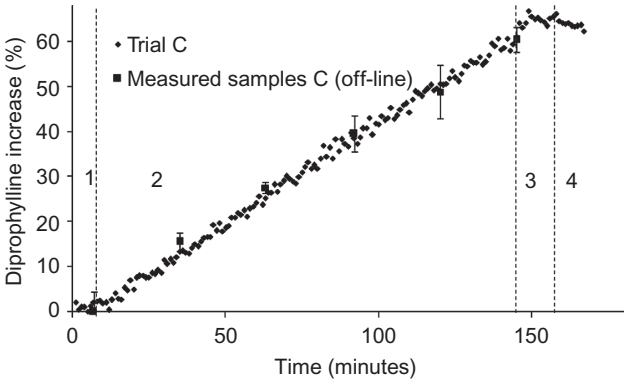

Figure 7. Prediction of diprophylline increase (%) from in-line data (trial C). Process steps (1) warm up, (2) coating, (3) drying, and (4) cooling.

The results show the ability to predict the diprophylline amount in the film even if the active pharmaceutical ingredient (API) is coated onto diprophylline cores. It should be noted that the concentration of diprophylline in the coated film (60%) was much higher than the concentration of diprophylline in the core itself (10%). The attenuated core signal did not affect the prediction significantly because of the difference of the diprophylline concentration between core and coated film. Furthermore, the penetration depth of the laser spot was adequate to detect the tablet core after the finished coating step.

The feasibility of monitoring the coated diprophylline amount on the diprophylline cores was furthermore investigated by another experiment (trial D) with the coating formulation mentioned above, but with a different diprophylline concentration. The concentration was reduced to 10% related to the solid fraction to eliminate the effect of the substantial higher concentration of the coated amount of diprophylline related to the core. As a result of the equal diprophylline concentration in the core and the coating solution it was postulated that the total analytical signal of diprophylline would be nearly constant over the coating process. The attenuation of the diprophylline core by the coated film should be compensated by the contained diprophylline concentration in the coated film.

MCR of the baseline-corrected spectra of tablets from trial D collected at different coating stages ($n = 6$) indicated that the resulting data could be described by a two-factorial model like in trial C. As well the resultant basis spectra of the two components were similar to the spectra of the diprophylline core and the coating material, respectively. The score values of the components (figure not shown) show that the main part of the analytical signal arose from the core. Over the entire coating process the signal decreased only marginally. The coating formulation accounted to only a small portion of the analytical signal and increased only to a small extent. Furthermore, the variation of the characteristic

diprophylline bands between untreated (0 minute) and finished coated (190 minutes) diprophylline tablets was not explicit. This result certifies the assumption of compensation of the attenuate core signal through the adequate diprophylline concentration in the film. Furthermore, this illustrates the difficulties of monitoring the coating process based on the reduced diprophylline concentration in the coating formulation. In addition the coated amount of diprophylline was low compared to the diprophylline amount contained in the core. The diprophylline amount of the untreated diprophylline cores determined by UV spectroscopy was 20.86 ± 0.34 mg (n = 9; mean ± SD). At the end of the process the determined amount of the finished coated tablets was 22.32 ± 0.22 mg (n = 9; mean ± SD), which indicated an average diprophylline gain of 1.5 mg.

The Raman spectral changes were correlated with the diprophylline amount by using PLS. For the constructed PLS model using SNV and mean-centered spectral data of tablet sets from 20.4 to 22.7 mg diprophylline, one principal component was needed for the model that gave an RMSEC of 0.1950 mg and an RMESP of 0.1663 mg. Furthermore, the prediction of the test set of 42 tablets of an independent batch (trial E) gave an RMESP of 0.2195 mg. Finally, the in-line measured data were fitted in the model to predict the diprophylline amount in dependence on the coating time (figure not shown). Although the coated amount of diprophylline was low the coating procedure could be monitored by the in-line measurements but it was not possible to predict the diprophylline amount with adequate accuracy. This can be explained by using the whole area 1200–1400 cm^{-1} for the development of the model. Because of the different composition of the core and coating material there were noticeable differences in the spectra that could be assigned to the other components of the coating solution. The differences in the spectra could be used to correlate the spectra with the coating procedure. To avoid the implementation of noise in the model it must be considered that the differences must be significant and correlate with the coating procedure.

At last the diprophylline cores were coated with the composition mentioned above but without diprophylline (trial F). The intensity of the peaks arising from the diprophylline compared to D and E decreased as a function of the coating time (figure not shown), which attests the assumption of compensating the attenuate core signal through an adequate concentration in the coated film. The intensity of the peaks was attenuated by the coated film but the core was still identifiable. This indicates that the penetration depth of the laser spot is adequate to detect the tablet core after the coating step was finished.

A PLS predictive model was constructed by using the weight gain of tablets measured by the gravimetric method as the reference analytical method. Two principal components were needed for the model that gave an RMSEC of 0.3547% and an RMSEP of 0.380% for the tablet set of 0–5.96% weight gain. The predicted weight gain resulting from the in-line measured spectra gave good results compared to the measured weight gain of the samples that were collected during the process (figure not shown). Finally, the prediction of the test set with 210 tablets of an independent batch (trial G) gave an RMSEP of 0.5118%, which indicated the applicability of the method.

Pan rotation speed

To estimate the effect of the pan rotation speed on the Raman signal, speed trials were performed at the end of the coating processes of experiments A, B, and C. In addition the untreated diprophylline cores were examined. The sensitivity of the acquired Raman signal to changes in the pan rotation speed is shown in Figure 8, which indicates the intensity of the peak 1330 cm^{-1} in dependence on the coating step. It can be seen that the intensity increases as a function of coating time but there is a noticeable step in the warm up and cooling period, which can be attributed to the decrease of the pan rotation speed. The pan speed during the warm up and cooling step was only 5 rpm in comparison with the coating and drying step, which had a pan speed of 16 rpm (Table 1).

By analysis of the six different pan rotation speeds it was observed that the pan rotation speed affected the Raman signal (Figure 9). At low pan rotation speeds like 2 and 5 rpm the Raman signal had a significant higher intensity than at higher pan rotation speeds like 15 and 18 rpm. This is likely due to a different distance between the tablet bed and the Raman probe by different pan speed, which was discussed by El Hagrasy et al.[11,12] Furthermore, the packing density is an important element. By increasing pan speed the packing density decreases and the acquired Raman decreased likewise.

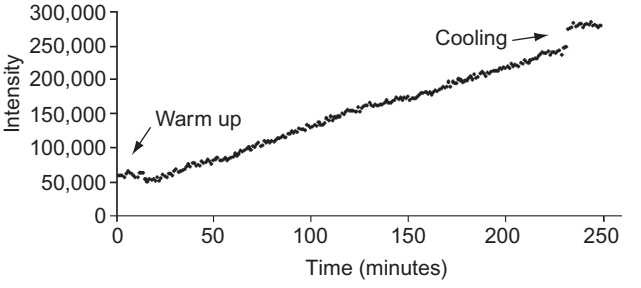

Figure 8. Raman intensity during the coating process with characteristic steps by warm up and cooling.

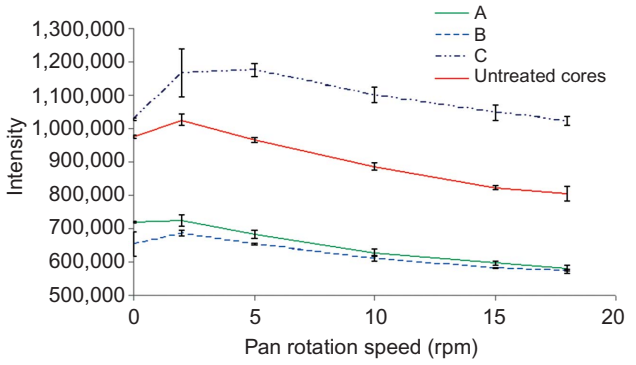

Figure 9. Raman intensity (peak 1330 cm^{-1}; baseline corrected) in dependence on the pan rotation speed ($n = 7$; mean ± SD).

Resulting from principal component analysis of the SNV Raman spectra for the region 1200–1400 cm^{-1} the pan speed with rpm = 0 differs significantly from the other pan rotation speeds. The score plot (Figure 10) demonstrates that the first principal component (PC 1) discriminates between 0 rpm and the others. So the greatest discrimination between samples is observed between stationary and running pan. This can be explained by different considerations. On the one hand the probe detects a signal of a single static sample (0 rpm) and on the other hand the average of moving samples is detected. The second principal component (PC 2) discriminates between 0, 2, 5, and 10 and 15 and 18 rpm. The same result was demonstrated by the chemometric model. The prediction of diprophylline amount or diprophylline increase was not effected decisively by the pan speed, besides 0 rpm which predicted a lower diprophylline amount of about 0.8 mg (A) and 0.6 mg (B) and a higher diprophylline increase of about 9.4% (C).

In the case of the untreated diprophylline cores the prediction of diprophylline increase should be 0% prior to coating, but because of the inhomogeneous cores (20.86 ± 0.34 mg; $n = 9$) the prediction varied between 0.39% and 2.65%. Furthermore, the prediction of diprophylline concentration at rpm = 0 was lower compared to the other pan speeds at the coating experiments with placebo tablets. Contrary the prediction of diprophylline increase was higher at rpm = 0 compared to the other pan speeds at the coating of diprophylline cores. Altogether the variation of the pan speed during the coating process does not effect the prediction of the model decisively.

Working distance

The aim of this experiment was to investigate whether little displacements of the sample related to the probe disturb the chemometric model, because it is not possible to ensure the same working distance during the process. The manufacturer proposes a working distance of 15–25 cm. The experiments were performed between 12.5 and 28 cm with a finished coated tablet of trials A and B. In Figure 11, the Raman intensity (Peak 1330 cm^{-1}) subject to the working distance is illustrated. In evidence, there is a maximum intensity at the working distance 20 and 22 cm. Except the measurements at 12.5 cm which predicted a lower amount of about 0.31 mg diprophylline and 0.48% in weight gain, the predicted weight gain and amount of coated diprophylline of the different working distances is not significantly different. It should be noted that the working distance influences the prediction of the model, but it is possible to assess the weight gain or the amount of diprophylline with adequate accuracy if the working distance varies within a restricted range between 15 and 25 cm.

Conclusion

Raman spectroscopy is an appropriate PAT tool in active coating. The constructed model is applicable to

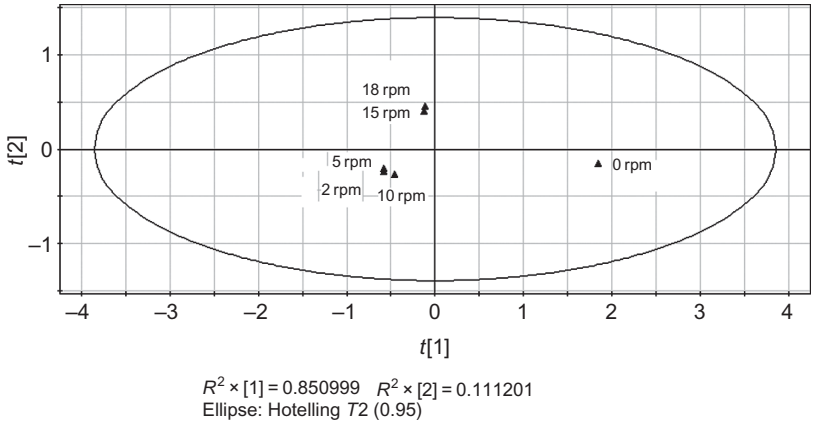

Figure 10. Score plot of the SNV Raman mean spectra ($n = 7$) acquired by different pan speeds.

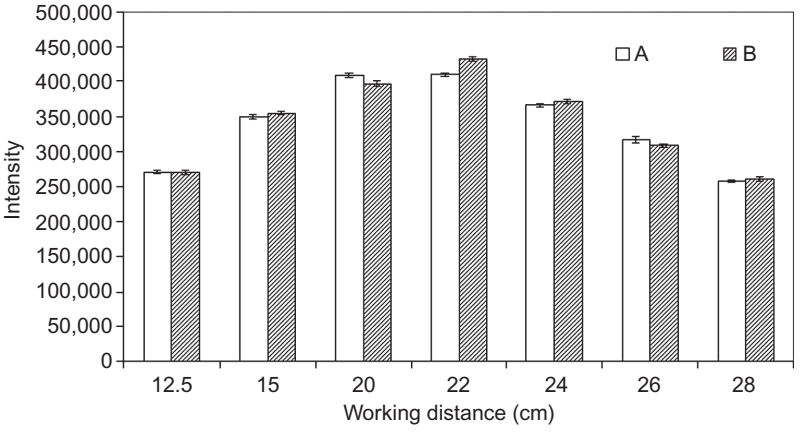

Figure 11. Intensity of peak 1330 cm^{-1} (baseline corrected) in dependence on the working distance ($n = 9$; mean ± SD).

determine the amount of coated active ingredient with sufficient accuracy. It was possible to detect the amount of coated active ingredient on cores with the API itself, which is beneficial and applicable for dosage forms with a delayed release core coated with an immediate dose.

However, for active coating with low-dose active ingredients such as strong analgesics or hormones, which have a small therapeutic index, the method must be improved.

From the procedural point of view it is not possible to ensure the same working distance during the process, but little displacements of the sample related to the probe do not effect the prediction of the model decisively. Furthermore, the variation of the pan speed in dependence on the coating step does not affect the prediction of the model to a high extent. These results indicate that the method is not vigorously disturbed by variation of process parameters or measurement conditions within a restricted range.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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