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Real-time predictions of drug release and end point detection of a coating operation by in-line near infrared measurements

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ABSTRACT

The aim of this work was to carry out real-time near infrared (NIR) predictions of drug release from sustained release coated tablets and to determine end point of coating operation.

In-line measurements were ensured by implementation of a NIR probe inside a pan coater. Tablets were coated using a functional aqueous dispersion of ethylcellulose blended with PVA–PEG graft copolymer to obtain a controlled drug release dosage form over 16 h. Samples were collected at regular intervals and subjected to a standardized curing step. Percentages of released drug at 4 h, 8 h and 12 h were selected to describe the controlled drug release of cured tablets. These dissolution criteria were used as reference values to calibrate NIR spectral information and to develop three partial least squares regressions.

Low predictive errors of 1.7%, 1.9% and 1.5%, respectively, were obtained. The coating operation was stopped while desired dissolution criteria were achieved, corresponding to a coating level around 10%.

The present study demonstrated that real-time NIR measurements could be performed on non-finished drug products to predict dissolution properties of cured coated tablets. This novel and innovative approach fulfils the expectations of ICH Q8 guideline on pharmaceutical development, in terms of process understanding and process analytical technology (PAT) control strategy. This approach should be however adapted to curing operation to allow a real-time release testing.

1. Introduction

Functional polymer coating is frequently applied to solid dosage form to decrease the drug release rate and to obtain a continuous release profile (McGinity and Felton, 2008). In the present study, a polymer combination of ethylcellulose/poly(vinyl-alcohol)–poly(ethylene-glycol) graft copolymer, plasticized with triethylcitrate was used as coating materials. A controlled drug release dosage form was prospected over a 16 h period. Homogeneity and thickness of the coating are well-known to be critical regarding the drug release rate (Porter et al., 2009). In the case of aqueous-based coating, a curing stage at elevated temperature is generally required after the coating operation to enhance the coalescence of polymer particles and to obtain a long term stable dosage form (Muschert et al., 2009). Currently, *in vitro* dissolution test is the most widely used method to establish dissolution properties of cured solid dosage forms and thus to ensure the drug product quality. This method is destructive and time consuming, especially when dealing with controlled drug release dosage forms. In addition, the robustness of the analytical procedure must be demonstrated (Banakar, 1991).

According to the ICH Q8 guideline on pharmaceutical development (ICH Q8 (R2), 2009), real-time control of drug product quality is recommended rather than end-product testing on limited samples of final product. The process analytical technology (PAT) approach can be implemented to perform timely measurements of critical quality attributes allowing both process understanding and process control, including end point detection (FDA, 2004). Near infrared spectroscopy (NIRS) is a widespread used PAT tool for its high speed acquisition, non-destructive nature and little or no need for sample preparation (Reich, 2005), but required appropriate chemometric tools to extract relevant information from NIR multivariate signal, as well as reference values to calibrate NIR spectral information (Roggo et al., 2005). Nevertheless, NIRS appears as a powerful analytical technique to control and monitor, in real-time, various critical process information until the detection of process end points. Several in-line NIR case studies were reported and recently reviewed by De Beer et al. (2011). Real-time monitoring of a coating operation was previously reported by several authors (Andersson et al., 2000; Lee et al., 2011; Perez-Ramos et al., 2005; Römer et al., 2008). Recently, our work demonstrated that coating

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thickness as well as mass of coating materials applied to tablets were monitored and predicted in real-time, throughout coating operation, by in-line NIR measurements (Gendre et al., 2011). However, NIR predictions were not directly related to the dissolution properties of coated tablets. The real-time control and monitoring of dissolution properties, especially in the case of sustained release coated tablets would extensively reduce the end-product testing, ensure product quality and allow accurate detection of coating end point.

The few studies dealing with NIR predictions of drug release were performed by off-line, and not in-line, measurements. These NIR predictions were carried out in order to predict the dissolution properties related to (i) tablet compression force (Blanco et al., 2006a, 2006b; Donosso and Ghaly, 2004; Otsuka et al., 2007), (ii) tablet excipient content (Freitas et al., 2005; Tabasi et al., 2009), (iii) polymer blend ratio in coating formulation (Tabasi et al., 2008a), (iv) amount of coating (Kirsch and Drennen, 1995) and (v) curing conditions (Tabasi et al., 2008b). To our knowledge, no study reported real-time predictions of drug release by in-line NIR measurements, during a pan coating operation.

To establish NIR predictions of the drug release from finished products, dissolution specifications must be selected. In the present study, percentages of dissolved drug at three specific dissolution times were chosen as criteria to describe controlled drug release of cured coated tablets, as recommended by pharmaceutical regulations (EMEA, 1999). An early point was considered to ensure exclusion of dose dumping, *i.e.* percentage of released drug at 4 h. This early point of release was also selected to prevent lag-time in drug release. An intermediate point was selected to ensure compliance with the shape of the dissolution profile, *i.e.* percentage of released drug at 8 h. A third point was used to ensure that the majority of the active substance was released, *i.e.* percentage of released drug at 12 h. These three points were used as reference values to develop NIR monitoring.

The objectives of the present work were thus to predict in real-time, during a pan coating operation, the percentages of drug release at three specific dissolution times by in-line NIR measurements and to determine the end point of the coating operation.

2. Material and methods

2.1. Core tablets and coating materials

Hydrophilic matrix tablets (average mass of 200 mg), made from hypromellose and calcium hydrogenophosphate as main excipients and containing a freely soluble drug substance were supplied by Les Laboratoires Servier Industrie (Gidy, France).

Aqueous ethylcellulose dispersion (Aquacoat ECD 30®, FMC Biopolymer, Philadelphia, USA), poly(vinyl alcohol)–poly(ethylene glycol) graft copolymer (PVA–PEG, Kollicoat IR®, BASF, Ludwigshafen, Germany) and triethylcitrate (TEC, Citroflex 2®, Morflex, Greensboro, USA) were purchased as coating materials. Ethylcellulose powder (EC, Ethocel® Standard 10), used to assign NIR absorption bands, was supplied by The Dow Chemical Company (Midland, USA).

2.2. Coating operation

The preparation of the coating suspension, as well as the coating operation was described in detail by Gendre et al. (2011). Briefly, the composition of the coating suspension is presented in Table 1. Coating suspension was prepared prior each coating operation.

Tablets were coated inside a partially perforated pan coater (Driacoater 500®, Driam, Eriskirch, Germany). Batch size was 4 kg, rotational pan speed was 20 rpm. The process was stopped after spraying 15% of the theoretical polymer blend (w/w expressed as percentage of core tablet mass). Approximately, 20 tablets were collected at regular intervals between 5% and 15% of the theoretical applied polymer blend, *i.e.* 11 samples. Sampling was performed without interrupting the coating operation by removing tablets located in the front of the drum coater. All samples were then subjected to a standardized curing step in an oven (24 h, 60 °C, ambient relative humidity).

Table 1
Composition of the coating suspension: manufacturing formula for 1 kg of core tablets.

Materials	Suspension (g)	Solid (g)	Percent (%)
Aquacoat ECD 30®	450.0	135.0	49.0
Kollicoat IR®	15.0	15.0	1.6
Citroflex 2®	33.8	33.8	3.7
Purified water	420.2	–	45.7
Total	919.0	183.8	100.0

2.3. Dissolution studies

In vitro drug release from coated tablets was evaluated using USP apparatus 2 dissolution system (AT 7 Smart On-line, Sotax, Basel, Switzerland), with a paddle rotational speed of 50 rpm, in 0.05 M phosphate buffer pH 6.8 (1000 mL dissolution medium, 37 °C, $n = 6$ per collected sample). At appropriate time intervals, 10 mL samples were automatically collected over a 16 h period. The drug release was assayed by UV spectrophotometry at 230 nm (Perkin Elmer Lambda 25 Photometer, Shelton, USA).

Three dissolution criteria were selected from dissolution profiles, *i.e.* percentages of released drug at 4 h, 8 h and 12 h. The averaged percentages, obtained from 6 tablets collected per sample, were used as reference data to build the calibration models.

2.4. Near infrared analysis

NIR equipment and set-up parameters were previously reported by Gendre et al. (2011). A photodiode array spectrometer (MCS 611 NIR 1.7H spectrometer, Carl Zeiss, Germany), equipped with an OMK 500-H reflectance measuring head (wavelength range of 950–1690 nm) was used. The reading surface of the probe was approximately 2.5 cm. Integration time was set at 75 ms. Each spectrum was the average of 20 scans. The total spectrum measurement time was 1.5 s. The OMK measuring head was integrated inside the rotating drum without interfering with the coating process, as shown in Fig. 1. The probe was positioned at the front of the drum, parallel to the spray to prevent clogging of the reading surface.

In-line NIR spectra acquisitions were performed every 3 s, without interrupting the coating process, until the required mass of

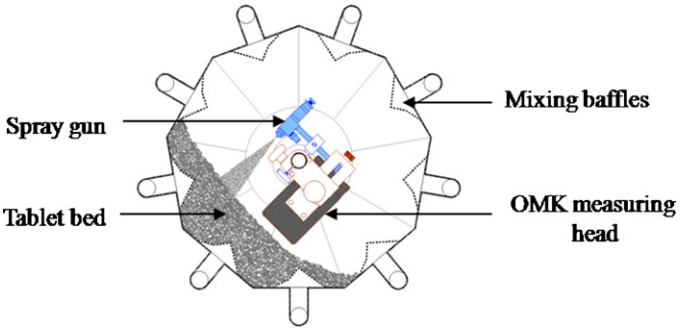

Fig. 1. Schematic integration of the probe inside the pan coater.

coating materials was sprayed. At each sampling time, from 5% to 15% of the theoretical applied polymer blend, 10 NIR spectra (bracketing the corresponding sampling time) were selected to carry out multivariate analysis. This methodology minimized the influence of tablet bed moving on spectral information (due to drum rotation and mixing baffles) and allowed a representative sampling of coated tablets.

ProcessXplorer® software (version 1.2.0.30, Carl Zeiss, Germany) was used to collect NIR spectra. All NIR data were exported from processXplorer® software and analyzed using Matlab® 7.8, R2009a (The MathWorks Inc., Natick, MA, USA) software and PLS Toolbox 5.8.3 (Eigenvector Research Inc., Wenatchee, WA, USA).

2.5. Multivariate data analysis

Multivariate quantitative analyses were carried out using partial least squares (PLS) regression (Wold et al., 2001). Three independent calibration models were created based on in-line NIR spectra and percentages of released drug at 4 h, 8 h and 12 h.

To reduce impacts of physical effects and random noise on spectral information, standard normal variate (SNV) transformation (Barnes et al., 1989), Savitzky–Golay smoothing (filter width of 15 points and a second-order polynomial fitting) (Savitzky and Golay, 1964) and second derivative were applied to NIR data before the PLS calculations.

Models were evaluated by cross-validation, using a random subset method. The optimum latent variable number was selected with respect to the lowest root mean square error of calibration (RMSEC) and the lowest root mean square error of cross-validation (RMSECV). The most appropriate PLS models were selected from their predictive abilities based on the root mean square error of prediction (RMSEP), given by Naes et al. (2002):

$$\mathrm{RMSEP} = \sqrt{\frac{\sum_{i=1}^{N_p}(\hat{y}_i - y_i)^2}{N_p}} \quad (1)$$

where $\hat{y}_i$ and y_i correspond to predicted and measured percentages of released drug, respectively. N_p is the number of samples included to the validation set.

In this study, three different batches, each containing 110 spectra, were used to develop and evaluate PLS models. To take the production variability into account, coating operations were performed during three different days with different batches of raw materials. Within the 330 spectra, 220 samples were randomly chosen to construct the calibration set and the remaining 110 one build the validation set. External batches, independents of the calibration set, were manufactured and monitored by NIR spectroscopy to assess the PLS model abilities for drug release calculations at 4 h, 8 h and 12 h and to determine the coating end point.

3. Results

3.1. Drug release for successive collected samples

The influence of coating level on drug release is shown in Fig. 2. Coated tablets were subjected to identical curing conditions. The increase in mass of applied polymer blend, from 5% to 15%, resulted in a significant decrease in drug release. A lag-time appeared with increasing coating level. Similar dissolution profiles were obtained from samples of three different batches. The averaged percentages of released drug at the three specific dissolution times were then selected from dissolution profile of each collected sample, for the three batches, and used as reference values to create the PLS calibration models.

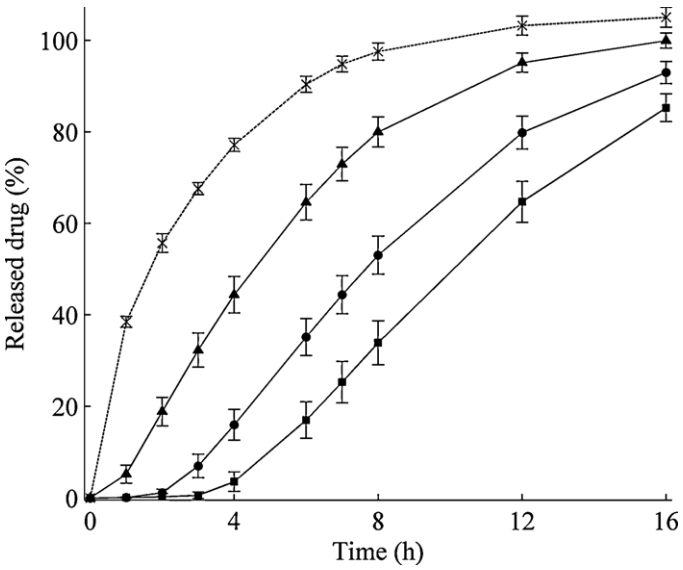

Fig. 2. Dissolution profiles of uncoated tablets (dotted line) and tablets coated with various percentages of polymer blend: 5% (▲), 10% (●) and 15% (■) (curing at 60 °C for 24 h). Error bars correspond to standard deviations of samples from three independent batches.

3.2. NIR band assignment

SNV pre-processed NIR spectra of uncoated and coated tablets for successive collected samples are represented in Fig. 3. Different NIR regions of interest were observed over the whole spectra. An increase in absorbance corresponding to an increase in the mass of coating materials, while the drug release previously observed decreased, was highlighted over the ranges 1150–1210 nm and 1360–1440 nm. These both NIR regions are encircled in Fig. 3, respectively named A and B.

Applying a second derivative pre-processing method to NIR spectra allowed to clearly demonstrate the correlation between the mass of coating materials and the spectral absorbance. Both second derivative pre-processed NIR regions of interest were enlarged and depicted in Fig. 3.

In addition, it can be noticed that the spectral region over the range 1500–1700 nm could be considered as another potential NIR region of interest. A decrease in absorbance related to an increase in the mass of coating materials was indeed observed. However, subsequent development of quantitative models revealed that this NIR region was not relevant in the construction of the models. For this reason, only NIR regions over the ranges 1150–1210 nm and 1360–1440 nm were selected and used to build optimized calibration models.

NIR spectrum of ethylcellulose, the main constituent of the coating suspension, was acquired in static mode, using the OMK measuring head, and was superimposed to in-line NIR spectra of coated tablets to assign both specific NIR regions (Fig. 4).

Absorbance over the 1150–1210 nm region was attributed to the C–H second overtone corresponding to functional groups of ethylcellulose, while absorbance over the 1360–1440 nm region was attributed to their C–H stretching and deformation vibrations and to their O–H first overtone (Osborne et al., 1993). The increase in absorbance observed in both selected NIR regions while the applied amount of polymer increased was mainly linked to the presence of ethylcellulose.

3.3. NIR calibration

Three different PLS calibration models (denoted as models 1–3) were built based on in-line NIR spectra and averaged percentages

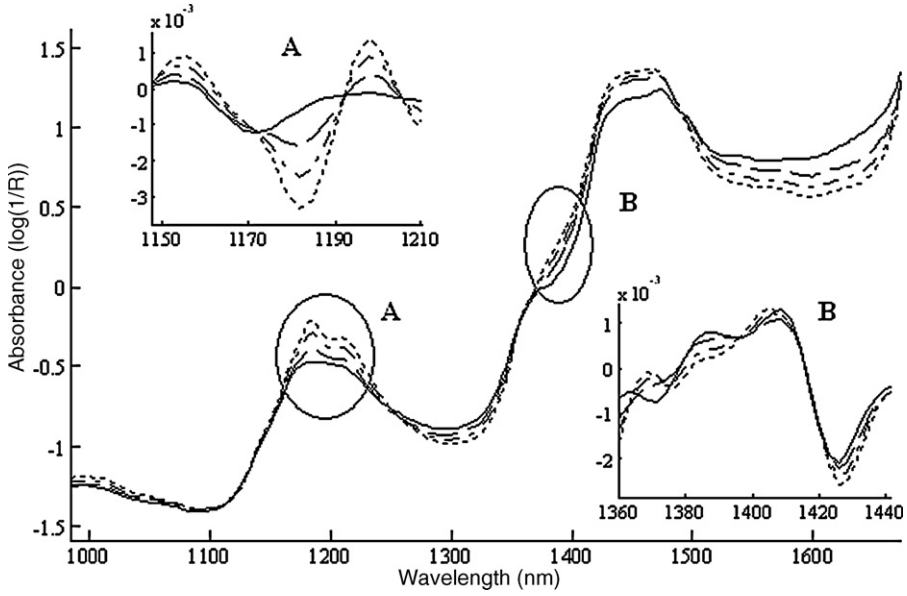

Fig. 3. SNV pre-processed NIR spectra of core tablets (continuous line) and tablets coated with various percentages of polymer blend: 5% (dashed line), 10% (dash-dotted line) and 15% (dotted line). Both encircled areas, A and B, indicate NIR spectral regions of interest. Subparts A and B represent second derivative pre-processed NIR spectra over the range 1150–1210 nm and 1360–1440 nm, respectively.

of released drug at 4 h, 8 h and 12 h. Development of the three PLS models was independently performed using initially an identical combination of pre-processing methods of NIR spectra, spectral range and number of latent variables included in the PLS regression. Although results of the three models were convincing, new models were developed in order to reach the lowest errors of calibration and cross-validation. Different pre-processing methods, as well as the selection of one or two NIR regions of interest and the number of latent variables were then studied to optimize each PLS model.

PLS results are summarized in Table 2. For the three generated calibration models, a linear relationship (high coefficient of determination R^2) between predicted and measured values was observed (Fig. 5A–C). In addition, the quality of the PLS models was confirmed by the low errors of calibration and cross calibration. PLS predictions and experimental measurements of the drug release at 4 h, 8 h and 12 h for the validation set are shown in Fig. 5D–F. The RMSEP values of 1.7%, 1.9% and 1.5%, respectively, confirmed appropriate model development.

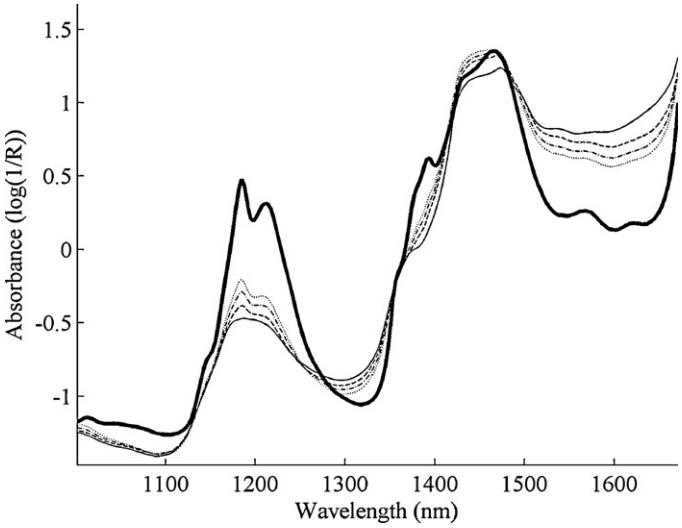

Fig. 4. SNV pre-processed NIR spectra of core tablets (continuous line), tablets coated with various percentages of polymer blend: 5% (dashed line), 10% (dash-dotted line) and 15% (dotted line) and ethylcellulose (bold continuous line).

3.4. Real-time NIR predictions and detection of the coating end point

The accuracy and the reliability of the PLS models were demonstrated by comparing NIR predicted values and experimental measurements of drug release for an independent coating operation. Real-time NIR predicted values were calculated over the entire range of polymer deposit. The ability of in-line NIR measurements to monitor in real-time the percentages of released drug at three different dissolution times was depicted in Fig. 6.

Dissolution tests were performed for three randomly collected samples, corresponding respectively to 7%, 10% and 11% of applied polymer blend. These values were estimated from the mass of coating materials sprayed onto tablets. Averaged experimental values of drug release for the three dissolution criteria were compared to the real-time NIR predictions (Fig. 6 and Table 3). Residuals, *i.e.* the differences between these both calculated and measured values were low whatever the dissolution criteria. The mean value was indeed around 1%, with no individual value above 3%.

The end point of the coating operation should correspond to a specific dissolution profile, in agreement with target specifications. For the studied drug product, these target specifications were defined for the three selected dissolution criteria (Table 4). In accordance with pharmaceutical regulations (EMEA, 1999), the permitted variability in release should not exceed a total numerical difference of ±10% of the labelled content of active substance. However, in the present study, more stringent and non-symmetrical limits were considered in order to avoid a premature stop of the coating operation, corresponding to a dissolution profile at the upper limit of the regulatory specifications (Table 4).

To accurately determine the coating end point at an appropriate time, it was decided to take into account five consecutive in-line NIR spectra, giving the three dissolution criteria in agreement with specifications, before stopping the coating spray. To assess the relevance of the PLS models to detect the coating end point, two different batches were manufactured and monitored by

Table 2
PLS calibration and validation results obtained from in-line NIR spectra and experimental values corresponding to the three dissolution criteria.

Model Reference values	1 Released drug at 4 h	2 Released drug at 8 h	3 Released drug at 12 h
Pre-processing method	SNV and second derivative	SNV and second derivative	Second derivative
Selected spectral range (nm)	1150–1210	1150–1210 and 1360–1440	1150–1210
Latent variables	4	4	3
Calibration	Fig. 5A	Fig. 5B	Fig. 5C
R^2	0.98	0.98	0.98
Slope ± S.D.	0.98 ± 0.01	0.98 ± 0.01	0.98 ± 0.01
Intercept ± S.D. (%)	0.32 ± 0.20	0.94 ± 0.50	1.87 ± 0.83
RMSEC (%)	1.7	1.9	1.5
RMSECV (%)	1.7	2.0	1.5
Validation	Fig. 5D	Fig. 5E	Fig. 5F
R^2	0.98	0.98	0.98
Slope ± S.D.	0.98 ± 0.01	0.98 ± 0.01	0.97 ± 0.01
Intercept ± S.D. (%)	0.47 ± 0.29	1.27 ± 0.72	2.80 ± 1.18
RMSEP (%)	1.7	1.9	1.5

S.D.: standard deviation.

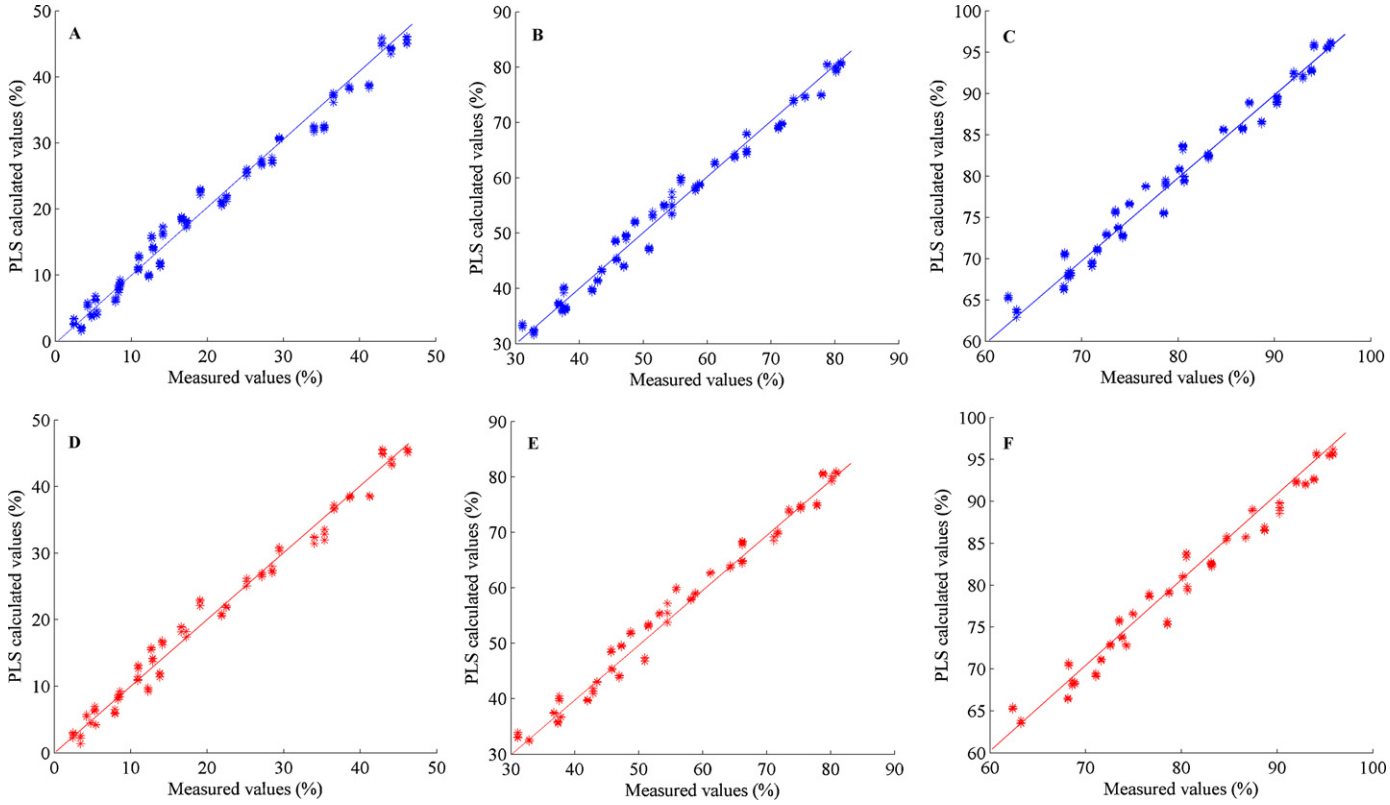

Fig. 5. PLS calibration results for the three dissolution criteria, percentages of released drug at (A) 4 h, (B) 8 h and (C) 12 h. PLS validation results for percentages of released drug at (D) 4 h, (E) 8 h and (F) 12 h.

Table 3
Real-time NIR calculated values and measured percentages of released drug at 4 h (Model 1), 8 h (Model 2) and 12 h (Model 3), for three collected samples, during an independent coating operation.

Samples	Released drug at 4 h (%)		Released drug at 8 h (%)		Released drug at 12 h (%)	
	Calculated value	Measured value[a]	Calculated value	Measured value[a]	Calculated value	Measured value[a]
1	32.3	29.3 ± 0.8	69.6	66.9 ± 1.8	88.8	88.0 ± 2.2
2	15.6	15.4 ± 1.6	52.9	53.0 ± 0.8	78.6	78.8 ± 1.4
3	12.7	11.9 ± 2.1	48.9	49.7 ± 2.2	76.3	76.2 ± 1.3

[a] Mean value ± standard deviation; $n = 6$.

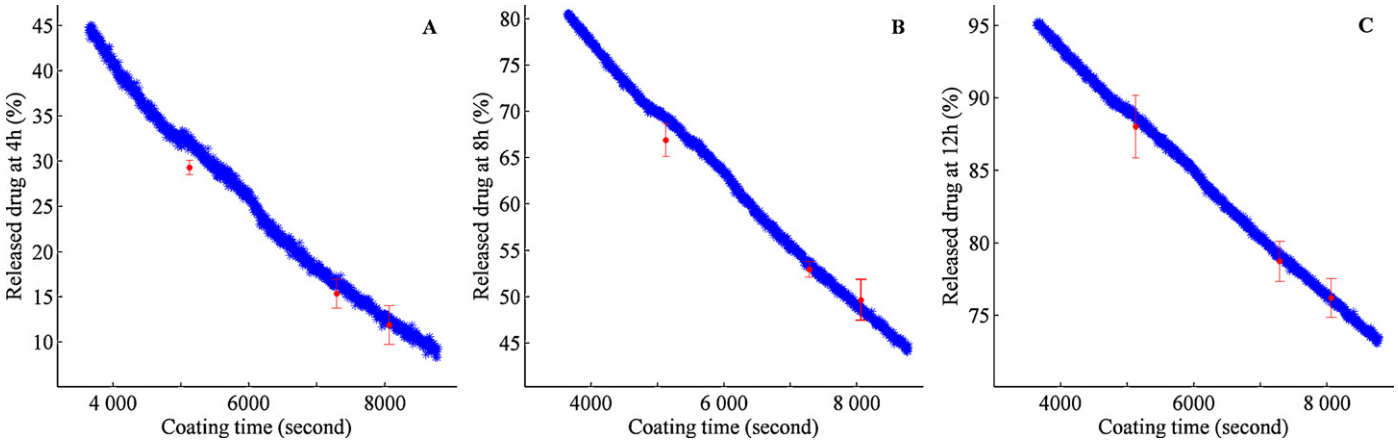

Fig. 6. Real-time NIR predicted values (+) and experimental values of drug release, for three different samples (○), at (A) 4 h, (B) 8 h and (C) 12 h, during an independent batch.

Table 4
Detection of the coating end point: target specifications and acceptable variations for the three dissolution criteria.

Dissolution criteria	End point target	End point lower limit	End point upper limit
Released drug at 4 h (%)	16.0	11.0	18.0
Released drug at 8 h (%)	53.0	48.0	55.0
Released drug at 12 h (%)	80.0	75.0	–

in-line NIR measurements. Samples corresponding to the determined end point were collected and analyzed. NIR predicted values and measured percentages of released drug at the three specific dissolution times are reported in Table 5. In both cases, the desired dissolution criteria were obtained from cured tablets coated with 10% and 9.6% of theoretical applied polymer blend, respectively. All calculated and measured percentages of released drug for the three dissolution criteria were within the selected dissolution specifications. The end point detection was validated regarding low residuals.

4. Discussion

The aim of the present study was to perform real-time NIR predictions of drug release from coated tablets and to detect the coating end point corresponding to achieved dissolution criteria.

To obtain the desired drug release pattern, formulation and processing parameters must be controlled, as the mass of coating materials applied to tablets. In the present work, a functional polymer combination of ethylcellulose/poly(vinyl-alcohol)–poly(ethyleneglycol) graft copolymer, using triethylcitrate as plasticizer, was chosen as coating materials to adjust the drug release rate of matrix tablets. Suitable and stable controlled drug release profiles were previously obtained from pellets coated with the above mentioned polymer combination (Siepmann et al., 2007). A curing step was shown to be crucial (Muschert et al., 2011). Currently, no study reported results about cured tablets coated with this ethylcellulose/PVA–PEG combination. In the present work, the drug release from cured tablets was modulated by varying the coating level to meet the release requirements to obtain a controlled drug release over a 16 h period (Fig. 2). As expected, a lag-time was observed and was dependent on the mass of the coating materials applied to tablets. In parallel, the drug release at 4 h, 8 h and 12 h decreased with the increase in coating level. It was assumed that variations in dissolution rate were only representative of the effect of coating level and not of the curing effect, since all coated tablets were subjected to an identical and standardized curing step. In addition, taking into account that dissolution studies were performed in standardized conditions, percentages of released drug at three specific dissolution times could be used as reference values to carry out the multivariate data analysis.

Kirsch and Drennen (1995) reported pioneer work dealing with off-line NIR measurements and coated tablets without curing, in order to predict dissolution properties. However, their calibration development was based on a single dissolution criterion, *i.e.* the time required for 50% of the API to be released. Accurate determination of dissolution profile was thus limited. In addition, no in-line monitoring was presented.

The ability of NIRS to predict the drug dissolution properties from cured coated tablets containing various blend of Eudragit® copolymers was also studied by Tabasi et al. (2008a). In their study, four PLS calibration models were built using the percentages of released drug at 1, 2, 3 and 4 h and off-line NIR measurements. Dissolution criteria were predicted according to standard errors of prediction around 2.8%. Once again, no real-time information on dissolution properties was available.

Table 5
Real-time NIR calculated values and measured percentages of released drug at 4 h (Model 1), 8 h (Model 2) and 12 h (Model 3), obtained for samples collected at the coating end point, during two coating operations.

	Released drug at 4 h (%)		Released drug at 8 h (%)		Released drug at 12 h (%)	
	Calculated value[a]	Measured value[b]	Calculated value[a]	Measured value[b]	Calculated value[a]	Measured value[b]
Batch 1	17.2	15.0 ± 2.4	53.3	53.7 ± 4.8	79.6	80.7 ± 4.8
Batch 2	17.9	17.8 ± 2.3	54.3	50.0 ± 2.5	79.9	76.5 ± 2.0

[a] Calculated value corresponding to the last in-line NIR acquisition before stopping the coating spray.
[b] Mean value ± standard deviation; $n = 6$.

Furthermore, Tabasi et al. (2008b) reported NIR calibration for curing study using dissolution testing as reference method. In their study, NIR calibration development failed due to a narrow calibration range. In our study, it was verified that samples used in calibration set presented distinct dissolution rates and spanned a large collected sample range. Furthermore, to avoid lack of homogeneity in coat structure and subsequent high variability in drug release rate, the calibration set was built using samples collected from 5% to 15% of theoretical applied polymer blend.

The present work demonstrated a novel and innovative approach. In-line NIR spectra, acquired during a coating operation, were successfully correlated to three selected dissolution criteria (Table 2 and Fig. 5A–F). The predictive abilities of the three developed PLS models were highlighted from different collected samples during an independent coating operation. Percentages of drug release at each selected dissolution time were indeed accurately predicted from real-time NIR spectral acquisitions (Table 3 and Fig. 6). Two experimental values (sample 1, percentages of released drug at 4 h and 8 h) were however slightly overestimated but remained within specifications (EMEA, 1999). The influence of tablet bed moving or low variations in temperature occurring during the coating operation could generate variations in spectral information, especially in the case of in-line acquisitions. This could explain the observed differences.

Systematic time consuming dissolution tests could be reduced by rapid and non-destructive NIR measurements performed directly inside the coating apparatus, and thus allowing an adaptation of the drug product control strategy. The dissolution properties of finished products, after a curing step, could be controlled in real-time throughout coating. In addition, in-line NIR measurements combined with appropriate chemometric analysis allowed to accurately determine the end point of the coating operation, while the real-time NIR predictions of the three dissolution criteria reached predetermined values (Table 5). For the studied drug product, NIR predicted values were in agreement with dissolution specifications corresponding to a theoretical percentage of applied polymer blend around 10%. This work illustrates how the dissolution properties from cured coated tablets can be accurately predicted from in-line NIR measurements performed on non-finished products.

5. Conclusions

The present work demonstrated the powerful ability of NIRS to predict in real-time the drug release from coated tablets at predetermined dissolution times and to detect the end point of the coating operation, by in-line measurements. The determination of dissolution properties from sustained release coated tablet is a major step in pharmaceutical development to ensure the desired quality of the drug product. Real-time control and monitoring of these critical quality attributes therefore represent a real interest in an industrial context in terms of process understanding and process control. This novel and innovative PAT control strategy should be nevertheless adapted to the curing step to ensure a real-time release testing, since curing will still be required to obtain the final product.

Acknowledgements

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