

Monitoring of a film coating process for tablets using near infrared reflectance spectrometry

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Abstract

A process analytical chemical method using near infrared diffuse reflectance spectrometry was developed for the determination of the amount of tablet coating on single tablets. This method is based on calibration of the spectra versus the added mass of coating solution. The tablet core was composed of two halves of different chemical composition and spectra were recorded from both sides of the tablets. The calibration was carried out using the chemometric methods principal component analysis (PCA), partial least squares (PLS), and multiplicative signal correction (MSC). The PLS-model utilised spectra obtained from both sides, pretreated with MSC, and ordered into one object. This method can be used in process analytical chemistry at-line. Additional characterisation of the measurements was obtained by calibrating the spectra versus coating thicknesses obtained from optical microscopy. Using PCA, it was possible to roughly estimate the maximum depth in the coating material that returns chemical information, the 'information depth', which was 0.1–0.2 mm. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

Tablets are often covered with a coating. The reasons may be to protect the tablet core from external effects like photo-induced decomposition or acidic degradation, to mask the taste, or to make the tablet easier to swallow [1]. If the thick-

ness of the coating is incorrect, unwanted effects may occur. A too thin coating will not protect the tablet, whereas if the coating is too thick, the production time and costs will increase and dissolution may be delayed. In many cases, it would therefore be important to monitor the coating process by measuring the coating thickness or some other quantity, e.g. the amount of coating applied, that can be related to the coating thickness.

Some methods, e.g. microscopy, have the potential of providing an accurate and direct deter-

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mination of the coating thickness but require laborious sample preparation and are therefore not suitable for process chemical analysis. Measurement by a tablet thickness tester [2] is indirect and requires a measurement also of the tablet core thickness. Chemical methods such as column liquid chromatography [3] can be used to determine the amount of coating applied on the tablets. However, this involves laborious sample pretreatment. Instead, fast and simple, but often indirect methods have been preferred such as the 'weight gain' method [2], in which the increase in the mass of a number of tablets is determined and related to the mass of the same number of tablets before starting the coating process. Another indirect method is performed by continuously weighing the vessel from which the coating solution is taken, or by calculating the amount of coating solution having been applied at different times, provided that the flowrate of coating solution is known.

The method presented in this paper is based on spectrometric measurements using near infrared (NIR) diffuse reflectance spectrometry. Measurement by NIR spectrometry is rapid and simple [4] and should be useful for in-process or at-line monitoring of film coating. In the near infrared region, 800–2500 nm, the information comes from overtones of molecular vibrations [5,6]. Because molecules differ in their vibrations, and hence in their vibrational overtone spectra, the near infrared region can be very useful in characterising chemical systems.

Only a few examples of using NIR for monitoring the film coating process are known [2,7,8]. These procedures are based on spectral changes occurring when the coating thickness varies and the procedures make use of chemometrics to relate the spectral information to the amount or thickness of the coating.

The aim of the present study was to show how to quantitate the amount of coating applied on a combination tablet, the core of which consisted of two halves. Each of the halves had different chemical composition achieved by compressing two different granulates. Each granulate contains only one of two active ingredients. Thus, a two-layer tablet core was obtained. The use of NIR

reflectance spectrometry takes advantage of the fact that the chemical composition of the coating layer is different from that in the two tablet core matrices. Provided the incident radiation penetrates into the core and is reflected and detected, changes in the coating layer thickness will show up as a change in the reflectance spectra obtained from the two sides.

The NIR-data were analysed with principal components analysis (PCA) and partial least squares (PLS) [9–13]. The PLS-model was used to estimate the amount of coating applied on the tablets and can be used for process analysis at-line. Inhomogeneities between tablets can be detected while inhomogeneities within a tablet cannot.

This study contained additional information, i.e. it was possible to use the data to estimate the maximum depth in the coating material that returns chemical information.

2. Experimental

The tablets contained two different active ingredients, namely compounds A and B. Each tablet was compressed from two different granulates, each containing A and B, respectively. A two-layer tablet core was made from these granulates. The tablets had a diameter of 10 mm and a thickness of 4.1–4.8 mm.

The film coating was performed by spraying inside a rotating drum. A 24 in. Accela Coata (Manesty, Liverpool, UK) laboratory scale equipment was used and each batch was run at different process conditions spanned by a factorial design. The amount of consumed suspension was measured by a balance.

Forty tablets, taken out from the coating process at different times, were investigated. To identify which side of a tablet had the A core, the coating on some of the tablets was removed with a scalpel. The identification was carried out using the fact that the cores of the A and the B side had different colour. An optical microscope was used to estimate the coating thickness on six tablets which had been cut using an in-house constructed rotating saw and a miniature lathe [14].

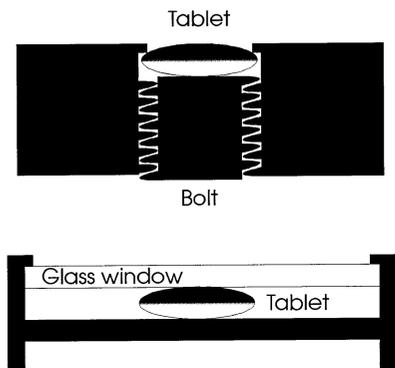


Fig. 1. The two tablet holders, not drawn to scale. The upper is the bolt holder, where the tablet was fixed by a bolt, and the lower is the glass window holder, where the tablet was sandwiched between a glass window and a metal support.

A NIR-systems 6500 spectrophotometer (NIRSystems, MD) was used to collect NIR reflectance spectra. The instrument was equipped with a tablet holder kept in a Spinning Sample Module for standard capsule (NIRSystems 6504) which was stopped in different positions before each acquisition of a scan. A total of 16 scans were collected and the arithmetic average spec-

trum was stored. The spectrometer output beam, centred at the tablet centre, illuminated a larger area than that of the tablet so that the detectors would record reflectance also from the surfaces surrounding the tablet.

Two different tablet holders were used. In one—the bolt holder—the tablet was fixed in an open hole in a black anodised aluminium unit and in the other—the glass window holder—it was fixed behind glass (Fig. 1). In both holders, the tablet centres were positioned in the centre of rotation. In the bolt holder, the hole had a diameter of 8 mm and therefore 1 mm at the edge of the tablet was not exposed to radiation.

PCA, PLS and multiplicative signal correction (MSC) were performed using B. M. Wise's toolbox [12] for Matlab (The Mathworks, Natick, MA) and Unscrambler 5.0 (Camo A/S, Trondheim, Norway). The PLS-models were evaluated with respect to both interpretability of factor loadings and predictive ability. Parallel factor analysis (PARAFAC), was performed using R. Bro's algorithms for Matlab, which can be found at <http://newton.foodsci.kvl.dk>.

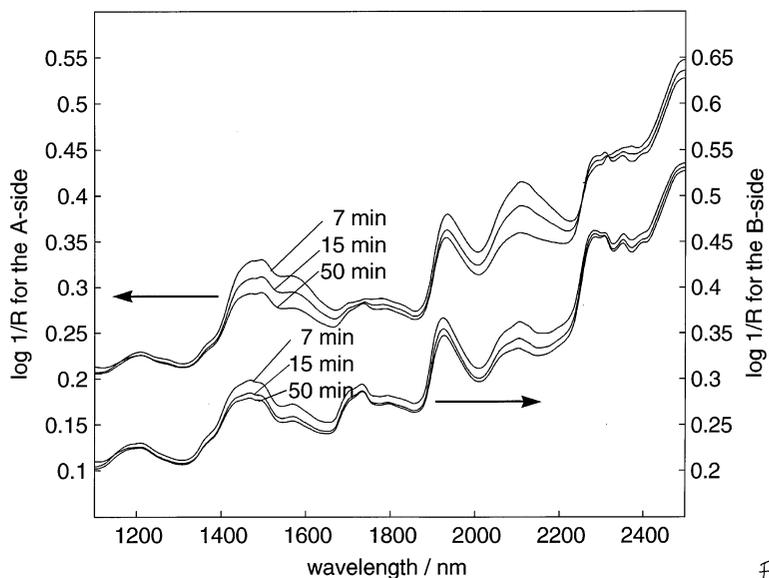


Fig. 2. Log $1/R$ -spectra from the A and B sides of three tablets using the bolt holder. The spectra were recorded from tablets coated for 7, 15 and 50 min, respectively. For most bands, log $1/R$ decreased as the amount of coating increased. The ordinate on the left is for the A side and the ordinate on the right side is for the B side (where the scaling is offset).

3. Results and discussion

Spectra from the two sides of the tablets differed significantly, even when the largest amount of coating was applied (Fig. 2). This is explained by the fact that the core gives different reflectance spectra from the two sides due to the different chemical composition. It was therefore concluded that the incident NIR-radiation had penetrated into the core, which is a prerequisite for this study, so that the reflectance spectrum changed when the amount of coating was varied. However, for a sufficiently thick coating, all reflected and detected radiation will originate from the coating only and the spectra from the two sides would then be identical.

The spectrometer output was presented as $\log 1/R$ versus wavelength [15], where the reflectance, R , is the fraction of the incident light reaching the detectors by diffuse reflection. When the coating thickness was gradually increased, some bands in the NIR-spectra had gradually changed their $\log 1/R$ -values. This is explained by the varying proportions of reflected radiation from the coating and the core and indicates that the spectral information can be coupled to the amount of coating.

The reflectance spectra for the same tablet were different for the two holders. The most obvious difference was found in the offset. The spectra with the higher offset came from the bolt holder where a larger amount of the radiation was absorbed by the black aluminium surface, and the ones with a lower offset came from the glass window holder where a greater amount of specular reflection from the glass was reaching the detectors. The two tablet holders were equally good for calibration which was proved when complete calibration models were performed on spectra from each of the tablet holders. In terms of standard error of prediction (SEP) determined by cross validation, no significant difference could be noted. For future work it is recommended to use the bolt holder since it was easier to fix the tablet by the bolt than by the glass window. The following discussion is based on the results from using the bolt holder.

It turned out that the spectral change was more

sensitive to the amount of film coating on one side as opposed to the other. This was probably due to a larger spectral difference between the coating and the core on this side.

3.1. Qualitative interpretation of the spectra

A NIR-spectrum shows overtone and combination bands that are related to molecular vibrations. Spectra from the two sides of the tablets are shown in Fig. 2. Around 1930 nm, a distinct –OH peak appeared which can come from water or –OH groups in the celluloses. It is difficult to assign the bands specifically to compound A, B, or excipients (typically celluloses). Studies of the extremes, where thin and thick coatings were applied, showed that $\log 1/R$ was very sensitive to the amount of coating at some wavelengths (Fig. 2) especially at 1450–1650 and 1900–2250 nm, whereas at other wavelengths, the sensitivity was much less. In general, the change in $\log 1/R$ due to increased amount of coating, was found to be much more pronounced for the A-side. Differences between the two sides were found in the peak shapes at 1450–1650 and at 1950–2200 nm. Furthermore, at 2270 nm, the shoulder was more enhanced for the B-side spectrum.

3.2. Multivariate interpretation of the spectra

The multivariate methods used were PCA and PLS. Both methods are based on a bilinear approximation of the data [10]:

$$\mathbf{X} = \mathbf{t}_1\mathbf{p}'_1 + \mathbf{t}_2\mathbf{p}'_2 + \dots + \mathbf{E} = \mathbf{TP}' + \mathbf{E}$$

Here, \mathbf{X} is a matrix containing all the spectra used to construct the calibration model. The X -matrix is thus described by a chemical model (\mathbf{TP}'), containing relevant information plus irrelevant information, noise (\mathbf{E}). The interpretation was carried out on the resulting \mathbf{t} - and \mathbf{p} -vectors (and \mathbf{w} -vectors [10] for PLS). In the following multivariate analyses, X -data were centred, but not scaled to unit variance. Scaling to unit variance was not used since all spectral data are using the same scale. The interpretation of the spectral information in the loading vectors is also easier

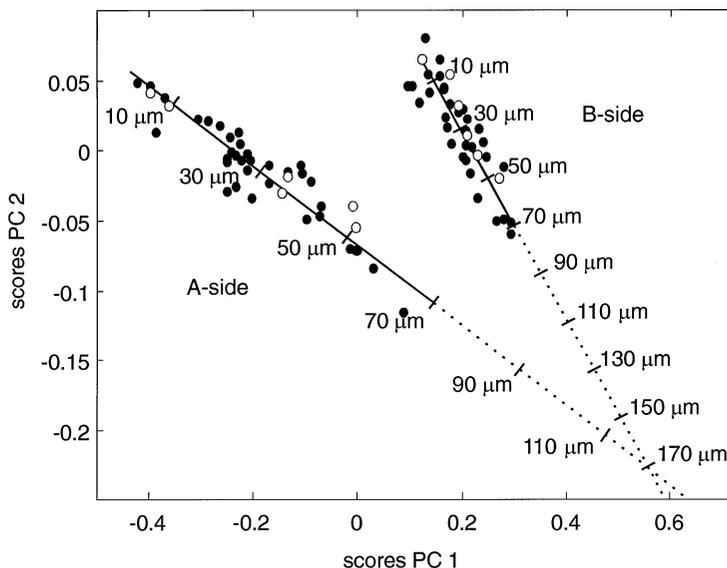


Fig. 3. PCA score plot for the two sides of the tablets. Abscissa: scores for principal component 1, ordinate: scores for principal component 2. The μm -scale is the coating thickness. \circ , objects used for coating thickness measurements by microscopy to obtain the μm -scale.

without scaling since the basic features of the peaks are unchanged.

3.3. Data pretreatment

MSC was used to adjust the spectra [10,16]. In the present case, the model vectors were easier to interpret in the PCA models if MSC was used. When the calibration with PLS was examined, similar interpretative improvements were observed after the use of MSC. This pretreatment did not significantly improve the standard error of prediction (SEP) determined by crossvalidation when the models without MSC were allowed to have an additional principal component. Other pretreatment methods were also tested, but no improvement in standard error of prediction from crossvalidation was observed compared to MSC. The other methods tested were standard normal variate (SNV), de-trending and second derivative [16]. The aim of the study was not to compare different pretreatment methods, hence MSC being chosen as a well-accepted standard method.

3.4. Calibrations of the amount of coating

The X -matrix consisted of $\log 1/R$ measurements and was centered. The Y -matrix consisted of two variables: the total amount of tablet coating suspension consumed by the spraying process at the time of sampling, and the total time that the tablets spent in the process after starting the spraying. Both of these variables can be related to the tablet coating thickness. These Y -variables were scaled to unit variance because they were measured in different scales.

Outlier inspection was performed by plotting the residual variance against the leverage. Objects with a high leverage have a large influence on the model. Therefore, objects with a high leverage and high residual variance may be outliers. Outliers were also searched for using cross-validation [10]. No outliers were detected.

It appeared that the A side made a better calibration model than the B side. This could be explained by looking at the PCA score plot where both sides were examined (Fig. 3). The corre-

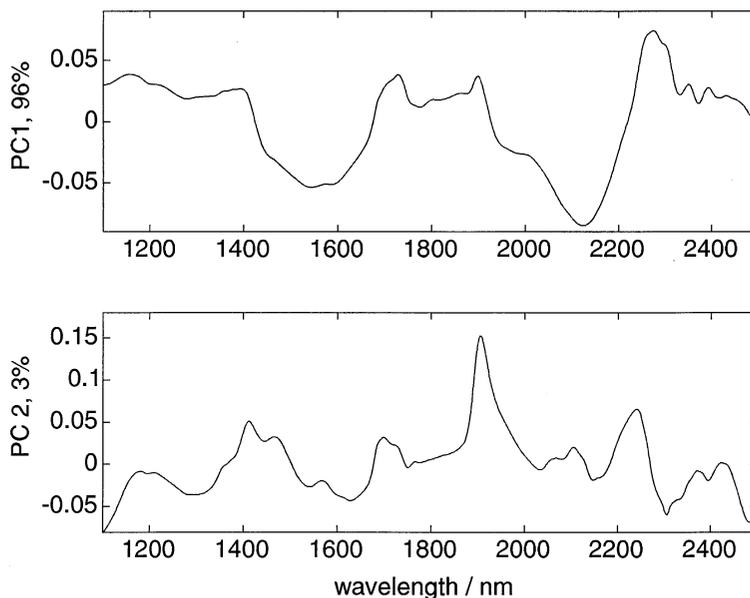


Fig. 4. PCA loadings corresponding to the scores in Fig. 3.

sponding loading vectors are shown in Fig. 4. The A group was more spread out than the B group and therefore described the variation during the coating process with better resolution. Nonlinearities may be seen in score plots, but in this case, no nonlinearities were observed.

After pretreatment with MSC, the best models were a two-component model for the A side and a three-component model for the B side (Table 1). The number of components was determined at the point where an increase in modelled variation in Y levelled off. This would lead to higher order components subsequently describing properties other than the amount of tablet coating.

A model was considered, enabling the estimation of the amount of coating for as large part as possible of the whole tablet. This requires measurements on both sides of the tablet so as to utilise the maximum available information and obtain an estimation of the average coating thickness of a tablet. The spectra from the two tablet sides were put together in a total model to achieve a weighted average of the two sides. This has the added advantage of a doubled amount of X -variables supporting the calculation in the same way as an average over several repeated measure-

ments. If one of the measurements was better, i.e. had a lower noise level than the other, the use of both still reduces noise and improves detection of anomalies. This was obtained by combining the A side spectrum with the B side spectrum. The order is not important, but has to be consistent. Each spectrum consisted of 700 points and therefore the calibration objects consisted of $2 \times 700 = 1400$ points. By doing this, the sides were weighted by the PLS-calibration. The weighting of the sides became apparent when the regression coefficients (often called the b -vector or regression vector) were studied. A satisfactory model was found to be a two-component model. The two-component model for both sides is amongst the best, and no further significant variance was described in the Y -variables with more components. In Table 1, there are many models that can be regarded as equally good, but as discussed above, the one-side models were not to be chosen. Among the two-side models, the model with MSC-pretreatment, separate for the two sides, appeared to be the best. Furthermore, this model provided more easily interpretable loading vectors (Fig. 5). The second component consisted of almost pure $-OH$ spectra.

Table 1
Evaluated calibration models

Data set	Pretreatment	One PLS-projection				Two PLS-projections				Three PLS-projections			
		Slope ^a	Offset ^a	Correlation (<i>r</i>) ^a	Prediction error ^b	Slope	Offset	Correlation (<i>r</i>)	Prediction error	Slope	Offset	Correlation (<i>r</i>)	Prediction error
A-side	None	0.74	342	0.86	0.26	0.89	143	0.94	0.12	0.90	128	0.94	0.12
B-side	None	0.40	803	0.60	0.64	0.71	390	0.82	0.33	0.78	294	0.88	0.24
Both sides in one model	None	0.69	410	0.82	0.32	0.87	179	0.93	0.14	0.90	141	0.94	0.12
A-side	MSC	0.89	148	0.94	0.12	0.90	128	0.95	0.11	0.90	127	0.94	0.12
B-side	MSC	0.68	429	0.81	0.34	0.81	263	0.89	0.22	0.86	184	0.92	0.17
Both sides in one model	Separate MSC for each side	0.89	153	0.94	0.12	0.90^c	130	0.94	0.12	0.91	123	0.94	0.12
Both sides in one model	MSC, both sides simultaneously	0.87	177	0.93	0.14	0.89	151	0.94	0.12	0.90	134	0.94	0.12

^a One Y-variable only = the amount of coating.

^b Both Y-variables, scaled to unit variance, determined by cross validation.

^c The numbers in bold belong to the suggested model.

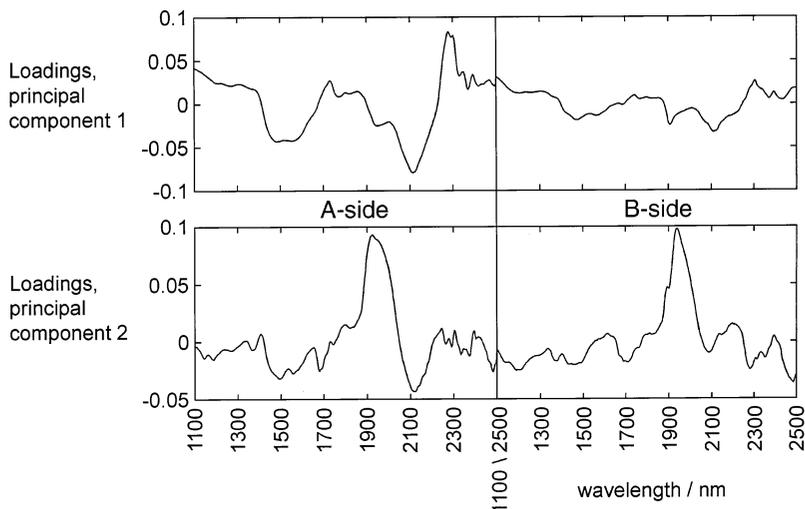


Fig. 5. Loadings for the two-sides PLS-model. Loadings much differing from zero indicate a larger variation. The A side spectrum is varying most during the coating process. The second principal component contains an $-OH$ peak, and is very similar for the two sides.

The way of ordering the spectra, as described above, can be regarded as unfold-PLS [17], because the examination actually resulted in 3-way data, with objects in the first mode, spectra in the second, and the side of the tablet in the third mode. Higher order data can be treated using methods like unfold-PLS [17] (as preferred here), unfold-PCA [17,18], TUCKER [18] and PARAFAC [19], where PARAFAC, constrained for positive solutions, would be interesting in this case because the pure spectra could be achieved. A three-component PARAFAC model, constrained to have positive solutions, was examined. However, the predictive ability of this model was not better than the unfold-PLS-model, while the interpretability was better because of the pure spectra achieved. Due to the main goal for this work being quantitative rather than qualitative, the unfold-PLS approach was chosen, and for simplicity, unfold-PLS will be referred to as PLS only. Higher order methods will not be discussed any further.

The model was tested using cross validation [10], where the responses were total process time and the amount of added tablet coating solution. The cross validation was performed using 'leave one out', because all the calibration objects were from different times of the process. The deviation

from the expected intercept was equal to zero with a slope of $+1$, in the total model, evaluated by cross-validation, and was regarded to be within the experimental error (slope, 0.90; offset, 130 g; r , 0.94; prediction error from cross validation, 0.12). The offset value can be compared with the mean value of the data set equal to 1328 g coating solution and the values of the other models examined (Table 1). The prediction error from cross validation is referred to as the validation variance in the Unscrambler. Due to the autoscaling of the Y -variables, the prediction error from cross validation can be expected to be between 0 and 1, but preferably close to zero.

The process conditions estimated using this model are represented as time and the amount of tablet coating solution added. It is important to understand that these estimates are referring to the original process. By measuring another processes (with the same type of tablet and the same type of coating) with the developed NIR-calibration, the condition of this other system could be related to the condition of the original system, where calibration was performed, which would then act as a reference process. In this study, the Y -data did not contain any thickness measurements, which made the model less easily portable. With thickness measurements in the calibration,

the model would estimate the coating thickness directly. A simpler way of making the model portable would be to convert the predictions to amount of coating per kilogram of uncoated tablets, which requires no additional measurements. The two Y -variables used in this calibration are strongly correlated, and from the preliminary microscopy results, the tablet coating thickness measurements correlate well with each of the Y -variables. The Y -variables support each other and increase the precision of the PLS calibration. A separate calibration with the thickness measured by microscopy was considered, however, the data set became too small for useful calibration as only six tablets were examined. Future work should consider including thickness data from microscopy.

However, it was considered that converting another process, with the same type of tablets and the same type of coating, to the conditions of the reference process would be enough. In this way, an up-scaled process may be studied with the same NIR-calibration. When the predicted values show that the final apparent time is reached for the smaller scale reference process, this also means that the same condition is reached in the upscaled process, but probably after a different period of time.

The complete examination of the tablets is suggested as follows, where the fifth step may be omitted:

1. Measure both sides of the tablet.
2. Perform MSC independently on each of the two sides.
3. Determine which side is A and which side is B with two PCA-classification models, one for each side, and put the spectra in correct order. This can be carried out using SIMCA-classification [13].
4. For a new process, determine the equivalent condition (time, amount of coating solution) of the reference process, where calibration was performed via the PLS-model.
5. Calculate an estimate of the amount of coating per kilogram of tablet (or the tablet coating thickness).

The procedure 1–4 (or 5) should be repeated with replicates to obtain a more accurate estimate.

From a process analytical chemical point of view, it is beneficial to have the reference process in the reference equipment closely compared to the batches produced in another equipment in terms of processing time and homogeneity between tablets. The exhaust air of the coating process can be discharged differently, and this will influence the losses of coating due to spray drying. Furthermore, since some of the coating solution will hit the walls in the coating chamber instead of the tablets, it is obvious that the geometry of the coating chamber will influence the time necessary to reach the appropriate thickness of the tablet coating. A typical case of high interest to the process analytical chemist is where the geometry differs when scale-up is performed. NIR reflectance measurements can therefore be a tool when studying scale-up problems.

If the flow of coating solution is disrupted, the process time cannot be used as a variable for controlling the film coating thickness. If a leak occurs, neither time nor the amount of coating solution added can be used as control variables. Another problem with these measurements is that there is no control of the homogeneity between the tablets. Only the average tablet coating thickness is estimated and no information is given on how individual tablets differ in coating thickness. Such inhomogeneity problems can occur if the spraying equipment in the process does not work appropriately.

3.5. Estimation of the information depth

The method discussed above requires both that the incident radiation penetrates beyond the total thickness of the coating and that the reflected radiation can reach the spectrometer detectors. Hence, it is of interest to know the coating thickness that the tablets had in this study. This may serve to judge the limitations of the method and as a guidance for future work. Estimations of the coating thickness by microscopy showed that it ranged up to $\sim 60 \mu\text{m}$. The upper thickness limit for this method may however be larger than this. To get an estimate of the limit, a method for determining the thickness of the layer that returns chemical information—termed the information

depth—was developed. It can be used on tablets, provided that the tablets are compressed from two chemically different granulates, as described above, and that the two granulates and the coating material all have different NIR diffuse reflectance spectra.

The spectra from both sides of the tablets, already evaluated in the above study of the amount of coating at different times in the process, were used. A PCA score plot (Fig. 3) was found to represent the spectral differences. In the score plot, each point corresponds to a spectrum. The variability between the MSC-pretreated spectra became apparent in the score plot when the principal components 1 and 2 were evaluated. The points are divided into two groups. To identify the two groups, six tablets were examined in order to identify their A and B sides. One of the groups was found to belong exclusively to the A side and the other to the B side.

The distribution of points in each group is elongated in character. This leads to the conclusion that it may be possible to estimate the information depth. Straight lines were fitted to the score coordinates by least squares minimisation of the distances from the points to the line, using the direction of the eigenvectors extracted for each of the groups, by a singular value decomposition [10]. This is equivalent to PCA with two variables. The scores were centered and scaled to unit variance within each of the groups, making equal influence in both directions. The two lines can be thought of as generalised spectral changes as the coating thickness is increased. The scattering of the points in the score plot was probably due to the distribution of coating thickness between tablets. Each point was then projected onto the corresponding line, resulting in secondary scores for each point along the line.

The six tablets were also examined to have coating thicknesses of 1, 1, 3, 3, 5 and 5×10^{-5} m, respectively. A microscope method for similar studies will be described in future work. In the score plot (Fig. 3), these tablets are shown as non-filled circles. The secondary scores were then used together with the thicknesses above to fit a straight line between the secondary scores and the coating thickness, using singular value decomposi-

tion, applying the same strategy as described above.

Assuming that the spectral response to the different species in the tablet coating and the core is linear, in the extrapolated coating thickness interval, the μm -scale would have constant step-lengths and would proceed linearly. Due to reflectance being a rather complex process, it is difficult to know to what extent these assumptions are valid, especially when extrapolation is performed.

The two lines would intersect at the point where the spectra for the two sides were similar, i.e. where the information depth is equal to the coating thickness. When the coating thickness is further increased, and becomes larger than the information depth, the information from the core cannot be comprehended in the spectrum. Thus, the thickness of the tablet layer that supports the two first PCA-components, the information depth, was found to be in the order of 0.1–0.2 mm. The two sides gave different estimates (120 and 170 μm), but the uncertainty in these figures was considered high. If the sensitivity to the amount of coating is decreasing with the amount of coating, the μm -scale would not have a constant step length and then a larger information depth could be expected.

By visual interpretation of the $\log 1/R$ spectra, one would suspect the intervals 1450–1650 and 2050–2200 nm to be the most informative. This was confirmed by studying the spectral loadings (Fig. 5). The principal components 1 and 2 were found to be mainly linear combinations of coating thickness and spectral difference between the two sides. Component 1 was very dominating (96% X -variance explained) over component 2 (3% X -variance explained). The loading in component 2 contains a peak at 1930 nm. This is probably due to a variation of water content but may also be caused by a variation of the $-\text{OH}$ content in the modified cellulose used in the coating.

4. Conclusions

It is possible to estimate the amount of tablet coating from NIR diffuse reflectance spectra using

chemometrics. There may be limitations in precision. Some of the standard error of prediction from cross validation may come from a distribution of the amount of tablet coating between tablets. The method should therefore be useful in studying process parameters that influence coating homogeneity. Another application of high interest is scaling up of the coating process where NIR diffuse reflectance measurements can be a helpful tool in detecting changes in process behaviour.

Due to the two sided structure of the tablet, supplementary knowledge about the NIR measurements was obtained. It turned out that a PCA score plot revealed data that characterise the spectrometric information depth in the coating. This may guide in optimising the spectrometer properties to the thickness of a certain material from which spectral information is sought for, or to judge the upper limit of quantification of coating thickness, equal to the information depth, for a given instrument and coating type. The limit of quantification is ~ 0.1 – 0.2 mm in this study using a two-component PCA model. This value only roughly estimates the limiting conditions and may not be valid for another type of coating material and a different instrument where factors such as sample presentation, detector noise, detector sensitivity, and light source intensity are different.

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