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Application of process analytical technology in tablet process development using NIR spectroscopy: Blend uniformity, content uniformity and coating thickness measurements

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Abstract

Near-infrared (NIR) spectroscopy was employed as a process analytical technique in three steps of tabletting process: to monitor the blend homogeneity, evaluate the content uniformity of tablets and determine the tablets coating thickness.

A diode-array spectrometer mounted on a lab blender (SP15 NIR lab blender) was used to monitor blend uniformity using a calibration-free model with drug concentration ranging from 2.98 to 9.25% (w/w). The method developed accurately depicted the changes in concentration of the drug during blending and the positive effect of a delumping step in the production process. Blend homogeneity was reached within 2 min of the blending step post-delumping, with relative standard deviation (R.S.D.) values varying from 1.0 to 2.5% depending on the drug concentration of the blend.

A Fourier-transform spectrometer (Bruker MPA) was used to analyze content uniformity and coating thickness with calibration based models. Prediction of a validation set with tablets compacted at pressures not present in the calibration set yielded an root mean square error of cross validation (RMSEP) of 1.94%; prediction of tablets compacted at pressures present in the calibration set yielded a RMSEP of 1.48%. Performance of the model was influenced by several physical tablet properties, which could be reduced by spectral pre-processing.

A model based on reflectance spectra predicted coating thickness and its variation more accurately than the model based on transmission spectra. Inter-tablet coating variation was predicted with NIR and compared to reference thickness measurements. Both methods gave comparable results. Initial inter-tablet variation of tablets sampled in-process during coating was high, but stabilized after 30 min into the process.

Keywords: Process analytical technology; Blend uniformity; NIR; Tablet coating; Content uniformity

1. Introduction

The process analytical technology (PAT) initiative, started by the FDA at the beginning of this century, has stimulated the pharmaceutical industry to increase its research into new analytical technologies, which enable in-line measurements of critical product parameters. These technologies can be used to "control and understand the manufacturing process" and ensure improved product quality. Moreover, these technologies can be a valuable tool in the development of new products, since "*quality cannot be tested into products; it should be built-in or should be by design*" (CDER PAT subcommittee, 2005). Near-infrared (NIR) spectroscopy is one of the techniques found to be suitable for a variety of PAT applications, and is subject of many studies in the pharmaceutical and nutritional field. Major advantages of NIR spectroscopy are its non-destructive nature and its immediate (real time) delivery of results; drawbacks are the influence of physical properties on spectra and the need for cal-

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ibration using a reference technique, e.g. HPLC. NIR spectra contain chemical as well as physical information therefore pre-processing the spectra is frequently needed before the actual analysis can take place. Physical information originates from differences in packing densities and particle sizes between powder or tablet samples. As a result differences in path length and scatter properties emerge which show as linear and/or non-linear baseline shifts. Light leakage effects (Sparén et al., 2002), instrumental and random noise are further sources of non-chemical information influencing NIR spectra.

Various methods have been developed to pre-process spectra before actual analysis takes place. Most of these methods such as multiplicative scatter correction (MSC), standard normal variate (SNV) and de-trending are specially designed to remove unwanted physical information from spectra leaving behind only the desired chemical or physical information. Older methods such as spectral derivatives are also frequently used. Multiplicative scatter correction, developed by Martens et al. (1983), separate chemical light absorption from physical light scatter and is based on the difference between wavelength dependency of scatter and chemical absorption in NIR spectra. Every sample spectrum is scatter corrected with respect to the average spectrum (the 'ideal sample') resulting in an even amount of scatter in each spectrum. Standard normal variate (Barnes et al., 1989) is a mathematical transformation designed to reduce linear baseline shifts due to non-specific scatter of radiation at the surface of particles and variable spectra path length through the sample. Derivation is often used in NIR spectroscopy to eliminate baseline shifts. The first derivative removes the baseline off-set difference, the second derivative also removes the slope of the spectra. Furthermore, derivation enhances resolution of overlapping bands. In-depth reviews of NIR pre-processing methods are provided by Heise and Winzen (2002).

This article describes the application of NIR as a PAT tool in three steps of the production process of a new potent drug, NIR was used to monitor the active component during blending, to evaluate the content uniformity of tablet cores and to determine the individual coating thickness of tablets. The main goal of the research was to develop and test a blend monitoring method using NIR and to develop/test models for tablet content uniformity and coating thickness measurements.

2. Materials and methods

2.1. Raw materials and process description for manufacturing the tablets

In the preparation of the direct compression mixtures a so-called blend–delump–blend process was used, which consists of a primary mixing step in the NIR SP15 lab blender (GEA Process Engineering Ltd., UK), a delumping step (used to break up agglomerates of the drug) in a Quadro Comil model U10 rotating impeller mill (Quadro Engineering LP, Canada), and a final mixing step in the NIR lab blender. Duration of each mixing step was 25 min; rotational speed was 15 rpm. The primary mixture contains an active component, a filler, a filler/binder and a disintegrant. A lubricant and a flow enhancer were added after the milling (delumping) step. Tablets were compressed at a Korsch XL100 rotating press (Korsch AG, Germany) at a speed of approximately 600 cores per minute and compaction forces of 100, 200, 300 and 400 MPa.

2.2. NIR instruments

The NIR lab blender consists of a Zeiss MCS 511 NIR 1.7 spectrometer (Carl Zeiss, Ltd., UK) and an OMK measuring head mounted on an adapted IBC lab blender from Buck systems. The OMK measuring head is connected via power and optical cables to the spectrometer inside the steel housing of the bin blender. The MCS 511 NIR 1.7 HR spectrometer is a diffuse reflectance InGaAs diode-array spectrometer, equipped with 256 pixels covering approximately 950–1680 nm with a resolution of ~3.0 nm. The OMK measuring head, shown in Fig. 1, has 15 optical fibers placed at 45° for sample observation. The amount of powder sampled during a NIR measurement is approximately 250 mg, depending on the density of the powder. Measurements can be manually, chrono or gravity triggered. Initial processing of light signals from the OMK measuring head is done by a MCS 511 NIR 1.7 spectrometer. A total of 10 scans are averaged into one raw energy spectrum; the resulting raw energy spectra are transported via a radio frequency signal to a nearby computer with Aspect Plus® (version 1.76 Carl Zeiss, Germany), and Process Explorer® software (version 1.1.0.6; Carl Zeiss, Germany). The Aspect Plus® program was used to collect reflection spectra during blending; these spectra were later converted to simulation files which were loaded into Process Explorer® for off-line analysis. Spectrometer calibration was done in the Aspect Plus software using black and white standards.

The Bruker multi-purpose analyzer (MPA; Bruker Optics, Germany) was used in the content uniformity and coating thickness experiments; it is a Fourier-transform spectrometer equipped with both an indium gallium arsenide (InGaAs) and a lead sulfide (PbS) detector able to record reflection and transmission spectra with various sample techniques.

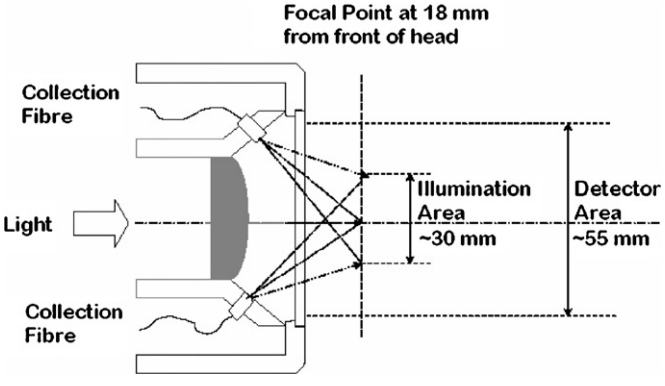

Fig. 1. OMK measuring head of the NIR lab blender (courtesy of Carl Zeiss Inc.).

3. Experimental

3.1.1. Blend uniformity monitoring

The product under development is a new chemical entity with multiple strengths. Therefore, it was important to first determine which tablet strength was at the detection limit of the system. From all individual components and all drug-containing strengths, off-line reflection spectra were recorded by placing enough powder blend on top of the OMK measuring head to cover the sapphire glass window. Measurements were triggered manually within the Aspect Plus® software. Ten spectra, recorded from 942.04 to 1715.1 nm, were averaged into one reflectance spectrum; this reflectance spectrum was converted into a pseudo absorbance (log 1/*R*) spectrum and saved. The collected spectra were used to find drug-specific spectral regions and to estimate the limit of detection. Following the initial experiments formulations with 2.98, 5.23 and 9.25% (w/w) drug were used in the development of a blend monitoring method. Reflection spectra were recorded during the primary and final mixing step of all blends produced. Before the start of in-line measurements a test spectrum was recorded to test instrument and settings. During blending, measurements in the Aspect Plus® software were triggered by gravity switches when the OMK measuring head was between 5 and 7 o'clock positions.

The method development process was divided into three phases: preliminary, model development and test phases. In the preliminary phase duplicate blends of the three drug-containing and one placebo formulations were produced. Each batch was thief-sampled at three time points: end of the primary mixing, after the milling and end of the final mixing steps. In the model development phase duplicate blends with drug concentrations corresponding to 80 and 120% of the nominal value were produced. Thief samples were only collected at the end of the final mixing step. In the test phase three additional blends of each formulation were produced, one of which with an extended final mixing time of 45 min instead of 25 min. Blend uniformity samples were collected at four time points during the standard final mixing step; and at three time points during the extended final mixing step.

Different drug concentrations of blends in the model development phase were produced by replacing drug with lactose, in case of 80% blends, and vice versa in the case of 120% of nominal value. Moving block calculations were performed in Microsoft® Excel (version 2003, Microsoft Cooperation, USA). Plots were generated with Sigmaplot® (version 9.0, Systat software, USA). The spectra collected in Aspect plus® did not contain time stamps; the process time was therefore estimated as follows. Average blend speed was 15 rpm which gives an average time of 4 s between each collected spectrum. The first spectrum was collected at a process time of 0 s, the second spectrum at 4 s, etc.

Evaluation of blend uniformity was done according to procedures laid down in the Draft guidance for industry: powder blends and finished dosage units—stratified in-process dosage unit sampling and assessment (FDA, 2003). Ten locations were selected from three depths along the axis of the blender; only the last time point was sampled three times at ten locations. Sample preparation was performed on a tablet processing workstation. A standard was prepared from an analytical reference standard of the drug in dilution solvent. UV absorbance of samples and standard was measured using dilution solvent as a blank. Recovery of every batch, defined as percentage drug in the final blend relative to the drug's label claim was determined. Duplicate powder samples of approximately 20 tablet weights were taken from all final mixtures. Sample preparation was done on a tablet processing workstation following the procedure described for blend uniformity analysis. Samples and standards were analyzed on a HPLC apparatus (Agilent Technologies Inc., USA) with UV detection. The mean of both independent determinations was reported as percentage relative to the drug's label claim.

3.1.2. Tablet content uniformity model

A total of 720 tablets selected from five batches compacted at 300 MPa, were used as calibration set; drug concentration of the cores corresponded to 80% (320 cores), 100% (280 cores) and 120% (120 cores) of the target value of 2.98% (w/w). The validation set consisted of four sets of 15 cores each compacted at pressures of 100, 200, 300 and 400 MPa and containing 2.98% (w/w) drug. Calibration set tablets were divided into groups of 20 tablets each. Every tablet was scanned separately in transmission mode; reference assay analysis was performed on each group as a whole. Tablet spectra of each group were averaged into a single spectrum and coupled to the weight percentage of drug determined by the group assay. Tablet assay analysis was similar to the powder assay procedure. Validation set tablets were scanned twice in transmission mode after which the weight percentage drug was determined of each individual tablet. The average spectrum of both transmission measurements was used to predict the weight percentage drug. Individual tablet analysis was similar to the blend uniformity procedure.

Transmission spectra were recorded with a Bruker MPA spectrometer by placing a tablet with the inscription facing upward in a dedicated sample-holder which in turn was placed in the transmission sample position. A total of 32 scans were averaged into one spectrum. Each scan was taken over a range of 12,500–5800 cm^{-1} with a resolution of 4 cm^{-1}. A background scan was taken every day before the first sample measurement to correct for possible deviations owing to changes in temperature, humidity, ambient light, etc. An OPUS® software package (version 5.0.53; Bruker Optics, Germany) was used to construct NIR PLS models with varying pre-processing methods and spectral ranges. Model rank was chosen automatically by the software, or by hand, based on the true-difference plot, the loading vectors and the root mean square error of cross validation (RMSECV). The root mean square error of prediction (RMSEP) and the true-difference plot were used to evaluate model performance when predicting individual drug content of the tablet cores of the validation set; the best performing model was selected for further analysis.

3.1.3. Coating thickness determination

During NIR transmission experiments with coated drug-containing tablets differences between spectra of uncoated tablet cores and coated tablets were found; further experiments with pure coating compacts and tablets with varying thickness of the coating were done to confirm the hypothesis that spectral deviations were caused by coating thickness variations. Comparison of transmission and reflection spectra showed that reflection spectra were more susceptible to changes in coating thicknesses; it was therefore decided to develop a model for coating thickness based on reflection spectra. Three batches of tablets which differed in coating thickness were produced by varying the amount of tablet cores loaded in the coater. Batch A had a total core weight of 200 g; batch B had a total core weight of 240 g and batch C had a total core weight of 160 g. Coating was performed in a fluidized-bed coater (Combi-Coata; Aeromatic Fielder, Switzerland), with a 15% (w/w) coating/water suspension of white Opadry II coating. During the coating process the coater was stopped at 10-min intervals to take samples of approximately 40 tablets; coating was continued for a total time of 52 min after which a final sample was taken. The total amount of coating suspension applied on batches A, B and C was respectively 65, 66 and 70 g. This resulted in final average coating thicknesses of 0.0378, 0.0318, and 0.0504 mm for batches A, B and C respectively. From each sample point 24 tablets were selected and scanned in reflection mode, tablet weight and dimensions were also determined.

Reflection spectra were recorded by placing a tablet with the inscription facing upward in the reflectance sample position. A total of 32 scans were averaged into one spectrum; each scan was taken over a range of 12,500–3600 cm^{-1} with a resolution of 4 cm^{-1}. A background scan was taken every day before the first sample measurement. Twenty-four tablets of each sample point were divided into three groups of eight tablets each; tablet spectra of each group were averaged and coupled to coating thickness values. Coating thickness was determined by subtracting the average tablet diameter of 48 uncoated tablets, measured with micrometer guage, from the average tablet diameter of each group of eight coated tablets. The resulting value was divided by two to yield final coating thickness, because only one side of each tablet is exposed to NIR radiation. Model building and evaluation was performed in the OPUS® software package similar to the procedure followed for the content uniformity model. Batches B and C were used as calibration set, batch A was used as validation set. Prediction of the validation batch was evaluated using the RMSEP value and the true-difference plot; the best performing model was selected for further analysis.

4. Results and discussion

4.1. Blend uniformity monitoring

Blending is one of the most critical steps in the production process of solid dosage forms. The process has become even more critical since the discovery of very potent drugs, with a content which is frequently below 1% of the total tablet weight. Blend homogeneity is crucial to ensure content uniformity in the end product, especially in a direct compression process where blending is the only step prior to compression. Research into the application of NIR in blend uniformity analysis has progressed from off-line analysis to in-line real-time measurement. For the interpretation of the spectral information collected during blending several methods have been tested, most based on comparing blend spectra directly or indirectly with spectra of pure compounds (Sekulic et al., 1996, 1998) or an ideal mixture spectrum (Ciurczak, 1991; Cuesta Sánchez et al., 1995; Wargo and Drennen, 1996; Sekulic et al., 1998; De Maesschalck et al., 1998; Blanco et al., 2002). Differences between spectra or values derived from spectra are quantified and used as a function of blend homogeneity with the limitation of defining the ideal spectrum.

The so-called calibration-free methods based on average spectral standard deviation (S.D.) of a moving block of spectra collected at different points in time have been developed to overcome this challenge. Blend homogeneity is assumed to be reached when the S.D. at compound-specific wavelengths approaches zero (Hailey et al., 1996). Other calibration-free approaches have been proposed by Cuesta Sánchez et al. (1995), Blanco et al. (2002), and Sekulic et al. (1996, 1998). The major advantage of these methods is that there is no need for pre-existing data, such as an ideal mixture spectrum, making them ideal for the use within early process development stages. A problem with all calibration-free methods is that only differences between spectra from a single blend are measured, therefore deviations from nominal content will not be detected, thus a content determination will still be necessary afterwards. A solution to this remaining problem is a quantitative model that uses the S.D. method. Berntsson et al. (2002) built a PLS model using a limited number of off-line samples to predict the concentration of the drug during blending.

In our study a combination of the above-mentioned techniques was used. We applied the calibration-free method and calculated a moving block relative standard deviation (R.S.D.) from compound-specific wavelengths. This method offers increased sensitivity by using compound-specific wavelengths instead of total spectra. In addition, calculation of R.S.D. instead of S.D. values makes it easy to compare NIR data from various blends as well as with traditional blend uniformity data. Further research will focus on adding a quantitative model to the procedure enabling the detection of deviation from nominal content. The drug has two principal peaks at locations where other excipients of the tablets exhibit minor absorption. The difference between excipients spectra can be seen more clearly using second derivative spectra (Fig. 2). The lubricant is likely to interfere with drug substance measurements because it has absorbance values which are significantly higher than those of the drug substance. However, the amount of drug in formulations monitored in this study (2.98–9.25%, w/w) is considerably higher than the amount of lubricant; moreover addition of lubricant to the mixture is done after the primary blending step. Both factors will limit the potential interference by lubricant on blend uniformity results obtained by NIR monitoring. Differences within the wavelength range (1050–1650 nm) between

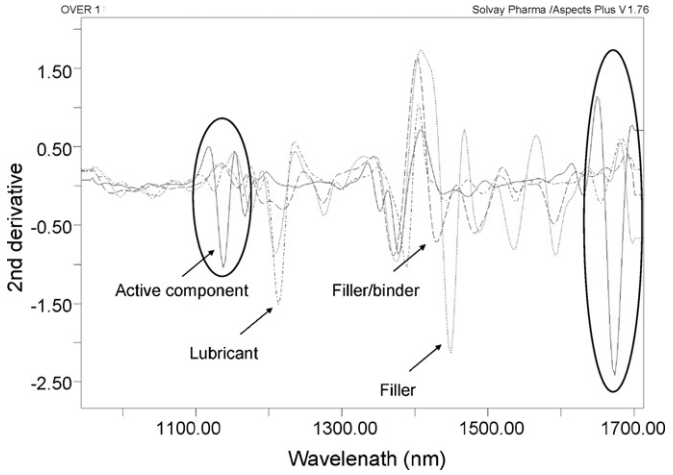

Fig. 2. Second derivative reflectance spectra of drug tablet components: ovals indicate drug spectral regions of interest compared to the excipients, which show minimal absorptions.

placebo and active blends containing the drug appear mainly at 1138 nm and are most visible in second derivative spectra (Fig. 3). An increase in the amount of the drug leads to a more negative absorbance level and a larger peak area. Differences in area and absorbance level are clearer between blends with the drug concentrations above 2.98% (w/w); below concentrations of 0.70% (w/w) differences are minimal. Below is a further description of the stepwise phases we employed to develop and test the blend uniformity model.

4.1.1. Preliminary phase

Monitoring of a blending process in time can be accomplished by several methods; the first steps of such methods involve data reduction and spectral pre-processing. As the goal of the final method is to monitor drug concentration, a wavelength specific to the drug was chosen instead of the whole spectrum. The peak at 1138 nm was selected because at this location a strong correlation between peak height and concentration exists.

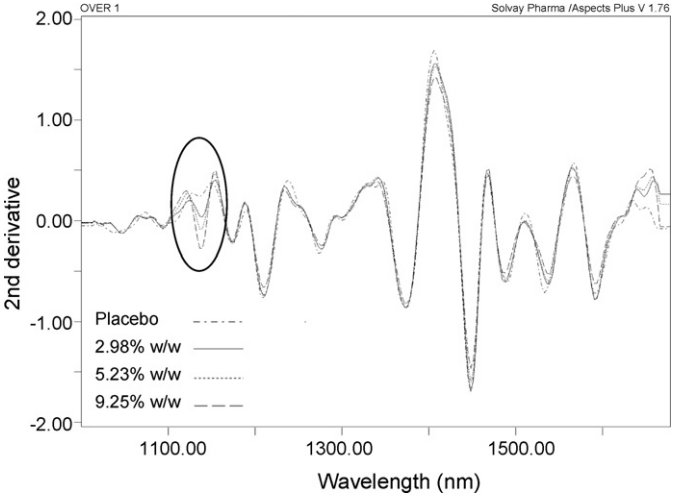

Fig. 3. Second derivative reflectance spectra (off-line) of drug blends containing different amounts of the drug substance: oval indicates that the drug spectral region of interest is concentration-dependent.

A pre-processing step consisting of a second derivative calculation and a SNV transformation precedes the data reduction step. This combination was used to minimize the influence of particle size differences and variations in packing density which may occur during blending. Second derivative was chosen as pre-processing instead of first derivative because locations of peaks remain the same in second derivative spectra. This particular property becomes very important when spectral interpretation and model building is performed without the help of multivariate analysis. Nevertheless, data collected in this study can be used for construction of a semi-quantitative multivariate model. A multivariate method could use the first derivative without any problems and would therefore have the advantage of a smaller amount of noise introduced by spectral derivation. Because the Savitzky–Golay (Savitzky and Golay, 1964) method requires spectra with equidistant wavelength values, spectra were converted to equidistant steps of 3.0 nm. The value of 3.0 nm was the average distance between points in a raw unprocessed spectrum. In between, second derivative calculation and SNV transformation, spectra were truncated to remove spectral information from outside the optimum detector range. Absorbance values at 1138 nm were quantified to allow for further processing, the average peak height was calculated from the distance between the peak top and two baseline points.

The ability to detect differences in active concentration is essential for any method that monitors blend uniformity. A range of 80–120% of nominal drug concentrations was chosen, this range is sufficient to develop a model which could detect 5% differences from nominal concentration (Moffat et al., 2000). Peak height values were calculated for all blend spectra collected in the preliminary and model development phases. All blends were assumed to be homogeneous near the end of the final blending step after examination of the NIR peak height plots and the UV absorbance reference values. An average peak height value was calculated from the last 20 spectra of each blend and plotted against the corresponding label claim (Fig. 4).

Average peak height increased with drug concentration, but there are inexplicable differences in average peak height of blends with equal label claims, for instance 2.98 and 9.25% (w/w) blends. Between 2.38% (w/w) and 5.23% average peak height increases more with drug concentration than between 5.23 and 11.10% (w/w). This non-linearity could present difficulties in building a single quantitative model that will accurately predict all drug tablet strengths.

4.1.2. Model development phase

Standard deviation, average and relative standard deviation of the peak height values at 1138 nm were calculated from a moving block of five spectra. About 10 spectra were collected after each turn of the bin at a blending speed of 15 rpm, therefore a moving block of 5-points corresponds to a total of 50 separate spectra collected at five time points. In summary the blend monitoring method contains 12 steps (Table 1); steps 1–3 is data collection; raw energy spectra were converted to log 1/*R* spectra. Steps 4–7 represent the pre-processing; spectra were pre-treated to remove as much non-relevant data as possible. Step 8 is data selection; a single wavelength strongly related to the drug was selected.

Table 1
NIR blend monitoring method

Stage	Action
Data collection	(1) Recording of raw energy spectra
	(2) Correction of raw energy spectra by reference spectra
	(3) Conversion to pseudo absorbance spectra
Pre-processing	(4) Interpolation: 3.0 nm
	(5) Second derivative calculation: Savitzky–Golay, 7 points
	(6) Clipping: 1050–1650 nm
	(7) SNV transformation
Data selection	(8) Drug peak height calculation: average value of the absolute distance between absorbance values at 1119 and 1137 nm, and the absolute distance between absorbance values at 1137 and 1152 nm
Result generation	(9) Calculation of a 5-point moving block peak height average
	(10) Calculation of a 5-point moving block peak height standard deviation
	(11) Calculation of a 5-point moving block peak height relative standard deviation
Visual presentation	(12) Plot generation: moving block peak height relative standard deviation vs. process time

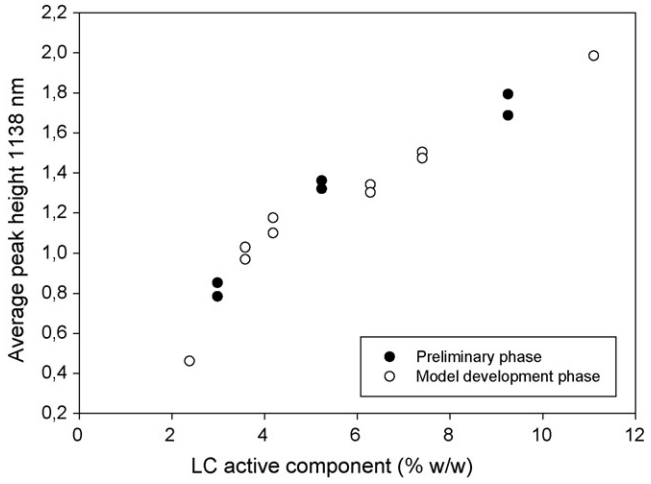

Fig. 4. Concentration dependence of average peak height at 1138 nm ($n = 20$) against LC drug (%, w/w). Average peak height rises with drug concentration, although the relation is not linear over the total concentration range. Between 2.38% (w/w) and 5.23% average peak height increases more with drug concentration than between 5.23 and 11.10% (w/w).

Steps 9–11 are result generation; secondary values are derived from the peak height. Step 12 is visual presentation; the results generated in steps 9–11 were plotted against time. Result generation and visual presentation was performed outside process explorer.

4.1.3. Test phase

The NIR method developed was used to monitor blends from the test phase during both mixing steps, e.g. primary and final mixing. In the first 250 s of the primary mixing step when the majority of mixing takes place, R.S.D. values dropped from values far above 50% to values below 10%. During the remaining part of the primary mixing step, R.S.D. values dropped to a basic level typical for each drug concentration. Blends with 2.98% (w/w) drug expectedly gave higher deviations than the 5.23 and 9.25% (w/w) drug formulations. R.S.D. plots clearly showed major fluctuations in the primary mixing step which do not appear in the final mixing step.

After 1500 s blending was stopped, the mixture was put through the delumper and lubricant was added. When the final mixing started all plots gave relatively high R.S.D. values, but decreased within 100 s to R.S.D. values that remained constant throughout the rest of the final blending step. After 1600 s process time the R.S.D. values of the 2.98% (w/w) drug blends ranged from 1 to 5% with an average of approximately 2.5% (Fig. 5). Around 2200 s batch B had a R.S.D. value that exceeded the 5% limit. This deviation was most probably a result of intermediate reference sampling for which it is necessary to remove probe and bin. If this limit is applied on respective NIR R.S.D. values to assess blend uniformity, batches A and B would both qualify as uniform blends after 1650 s. After initial R.S.D. values of approximately 11 and 5% for both 5.23% (w/w) batches, respectively, R.S.D. values dropped to the range of 0.5–2.5% with an average of approximately 1.5%. There were no differences between the R.S.D. values of the two 5.23% (w/w) drug

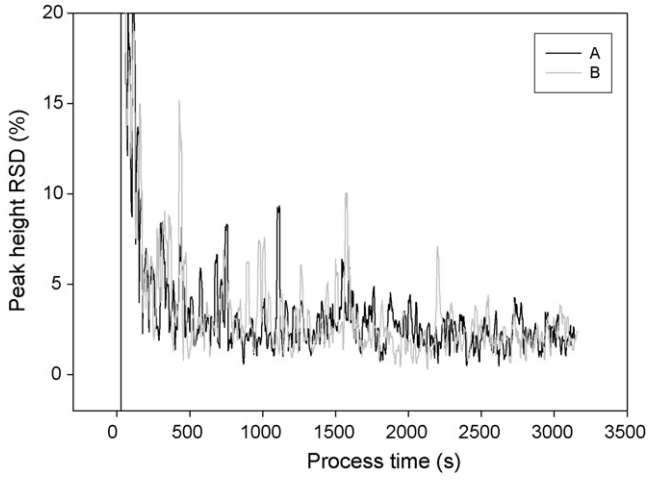

Fig. 5. Relative standard deviation plot of peak height against process time of 2.98% (w/w) drug blend (obtained during the test phase). During the primary mixing phase (till 1500 s) variation in peak height is high and frequently above 5%. After the delumping step the final blending step is started. Variation quickly drops after 1500 s and becomes stable for the remainder of the blending at a level of approximately 2.5%. The spike at 2200 s in the plot of B is caused by disturbances due to intermediate reference sampling.

Table 2
UV and NIR R.S.D. values final blending step (test phase blends)

Drug (%, w/w)	Average UV R.S.D. (%)	Average NIR R.S.D. (%)	*p*-Value
2.98	3.6	2.1	0.12
2.98	2.4	2.3	0.98
5.23	1.6	1.7	0.91
5.23	2.2	1.5	0.30
9.25	0.9	1.3	0.26
9.25	1.4	2.1	0.22

blends (data not shown). The R.S.D. values of both 9.25% (w/w) batches only exceed 2.5% around 1500 s; the remainder of the final blending stage R.S.D. values stay within a range from 0.5 to 2.0% with an average of approximately 1.0%. Both blends appear to have reached the same blend homogeneity based on the R.S.D.-time plot (data not shown).

To further evaluate performance of the NIR method, UV absorbance R.S.D. values were statistically compared with NIR R.S.D. values. The variation in UV absorbance values collected at 25 min were compared with the variation in the last calculated peak height values by using an *F*-test. The resulting *p*-values show that there are no significant differences (alpha 0.05) between UV and NIR values (Table 2). It is noteworthy that the established trend of increased R.S.D. with decreasing drug concentration was recorded with NIR as well.

4.2. Content uniformity model

Most of the research on NIR applications in solid oral dosage forms focuses on content uniformity testing because of significant potential savings. NIR testing requires no chemicals and needs no or only minor sample preparation. Both NIR reflectance and transmittance spectroscopy have been used in content uniformity testing with promising results. Furthermore the non-destructive nature of NIR radiation and the speed of NIR analysis offer the possibility to analyze more samples and/or analyze samples multiple times. Pure drug spectral characteristics are visible at two locations in transmission spectra of tablets; tablet spectra were similar to blend spectra collected with the NIR lab blender. Spectral differences between tablet strengths were caused by a change in concentration of the drug and the main excipients, filler and filler/binder (Fig. 6).

A plot of drug tablet concentration of the validation batch determined by NIR and UV shows no trend in predicted values; predicted points are randomly distributed around a trend line where UV and NIR values are equal. In Fig. 7 the differences between NIR and reference values were plotted against reference values. Differences were calculated by subtracting predicted values from the reference values. Higher predictions were visible as negative values; lower predictions were visible as positive values. Tablets were divided in subgroups according to compaction pressure. Tablets compacted at 100 MPa mainly have negative deviations from reference values, while tablets compacted at 400 MPa mainly have positive deviations from reference values. Tablets compacted at 300 MPa seem to be best predicted

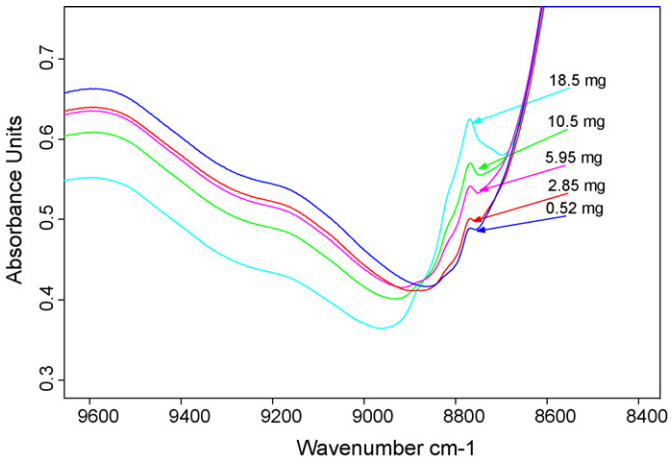

Fig. 6. Transmission spectra of tablets with different amounts of drug. The peak around 8800 cm^{-1} increases as drug concentration rises while the peak around 9600 cm^{-1} decreases.

by the NIR model according to the distribution of predicted values around zero. Visual findings were in compliance with RMSEP values calculated for different subsets of the validation set. RMSEP value was 1.94% when all compaction pressures were included in the validation set. When only the tablets compacted at 300 MPa were used in the validation set the RMSEP value became 1.48% (Table 3).

The regression coefficient of selected CU model along with a pre-processed pure drug spectrum is depicted in Fig. 8. Preprocessing consisted of first derivative (25 smoothing points) and MSC transformation. It can be seen that the regression coefficient is very similar to the pure drug spectrum in the range used by the CU model. Results of the validation set show that it is possible to construct a NIR model which enables accurate determination of the content uniformity of 2.98% (w/w) drug

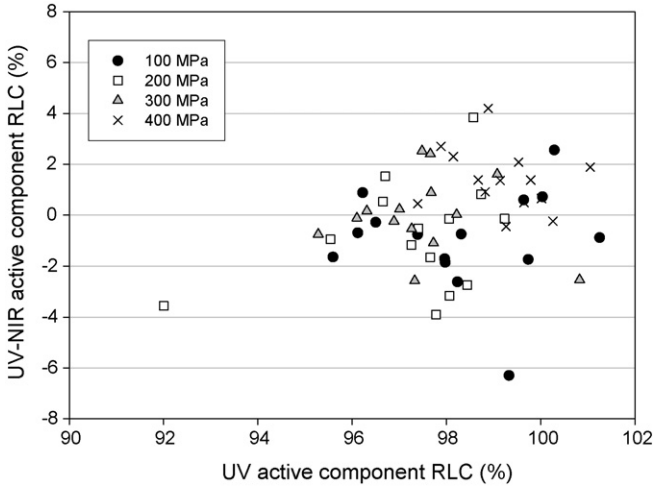

Fig. 7. True-difference plot of the external validation set; subdivision into core compaction pressures. Largest differences between NIR and UV values occur in the 100 MPa subset; smallest differences between NIR and UV can be found in the 300 MPa subset. The latter compaction pressure was also used in the production of calibration set cores. This indicates influence of compaction pressures on model performance, most likely owing to increased tablet thickness at lower compaction pressures.

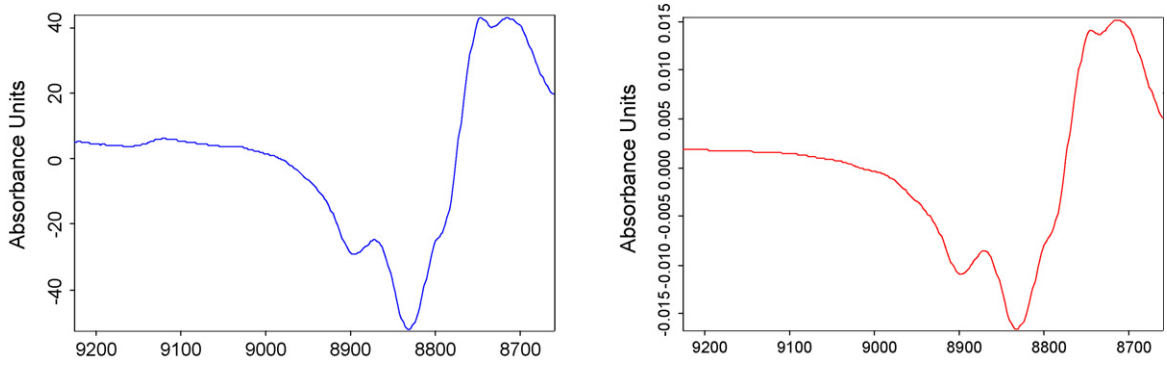

Fig. 8. Model regression coefficient (left) and a pre-processed pure drug spectrum (right). The apparent similarity between both regression coefficient and pure drug proves that model prediction is predominantly based on the drug spectral signature.

tablets. The similarity between the model regression coefficient and a pre-processed pure drug spectrum ensures that model predictions are based on changes in drug concentration (Fig. 8). The fact that the model is able to accurately predict content of tablets produced at compaction pressures not included in the calibration set shows that the chosen pre-processing method is effective. However, a trend can be observed in the accuracy of predictions which can be quantified with the RMSEP (Table 3); predictions outside the model calibration range are less accurate than predictions within the calibration range of the model. Moreover, a relation between compaction pressure and prediction error seems to exist. Apparently pre-processing is not able to remove all spectral information related to physical tablet properties. It should be noted however that compaction pressure variations of production tablets are small compared to the compaction pressure variations within these experiments.

4.3. Coating thickness determination

Coatings are applied to many solid dosage forms produced today for cosmetic, taste properties or to control dissolution rates. Traditionally, coating thickness of tablets is determined by their average weight gain, calculated from samples taken near the end of the expected coating endpoint to determine whether or not the required amount of coating is applied.

An increase in coating thickness is visible in NIR reflectance spectra in two distinctive ways (Figs. 9 and 10), absorbance values of coating components increase, while absorbance values of core components decrease as coating thickness increases (Kirsch and Drennen, 1995). The explanation for this two-folded effect lies in the fact that as coating thickness increases NIR radiation reaching the tablet core decreases and radiation reflected by coating components increases.

Table 3
Validation set results content uniformity model

Validation set (MPa)	RMSEP	NIR R.S.D.	UV R.S.D.	*p*-Value
100	2.15	2.58	1.75	0.15
200	2.21	2.33	1.85	0.40
300	1.48	2.21	1.37	0.10
400	1.81	1.77	0.99	0.05
All pressures	1.94	2.3	1.67	0.02

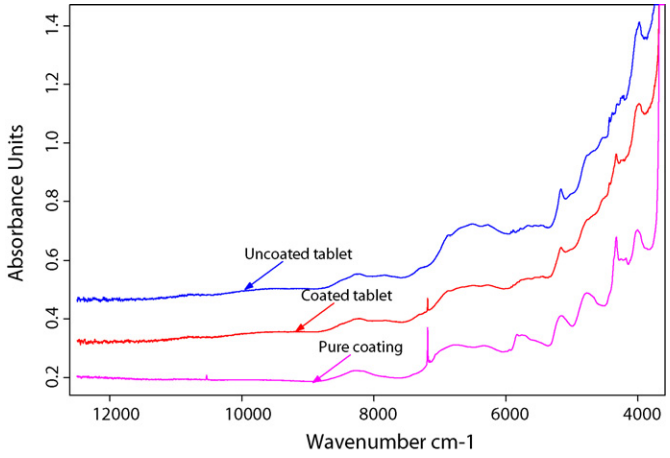

Fig. 9. NIR reflection spectra of a coated tablet and compact of pure coating powder showing a distinguishing peak at ~7200 cm^{-1}, while an uncoated tablet showed no peak.

NIR has been used to determine coating thickness off-line (Kirsch and Drennen, 1995), at-line (Kirsch and Drennen, 1996;

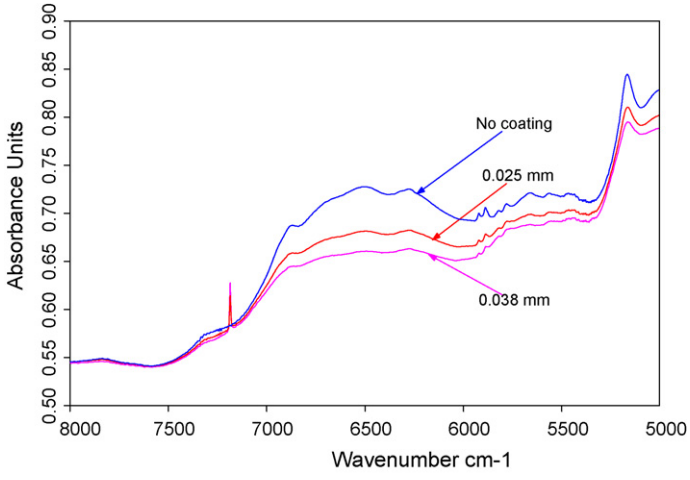

Fig. 10. NIR reflection spectra of three coating thicknesses showing a thickness-dependence of the coating peak at ~7200 cm^{-1} and the core region below ~7000 cm^{-1}.

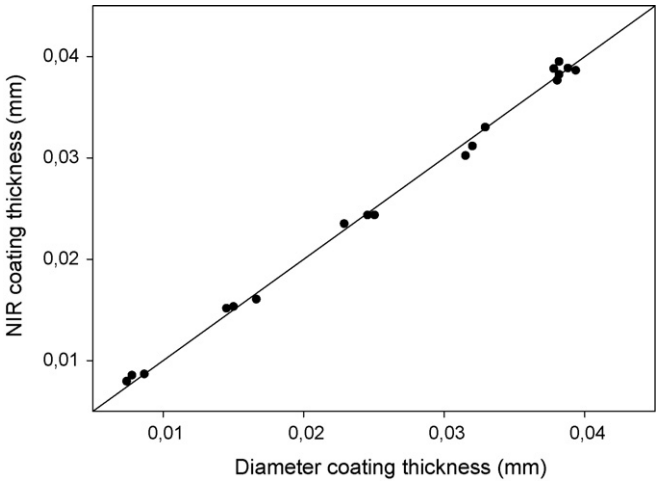

Fig. 11. True vs. predicted coating thickness of validation set with a correlation coefficient of 0.9965, showing that the model built is sufficiently accurate to be used in determining tablet coating thickness.

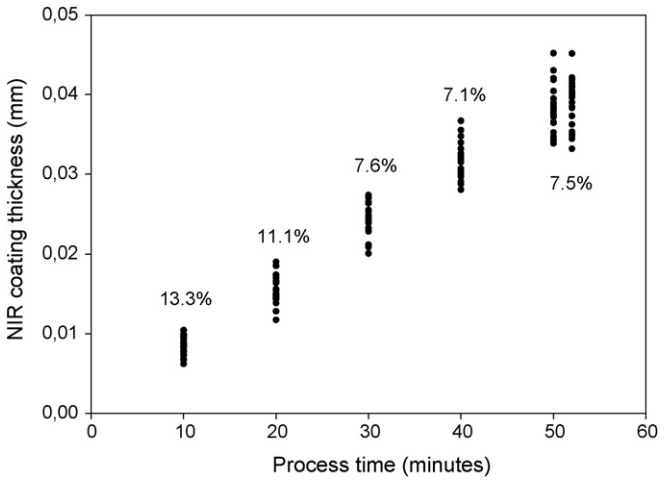

Fig. 12. Individual coating thicknesses and coating R.S.D. predicted by NIR. Coating R.S.D. value decrease as the coating process progresses and becomes stable at a value of approximately 7.5% around 30 min. NIR values comply with values calculated from diameter measurements and values found in literature for fluid-bed processes. This confirms that the model built can predict individual coating thicknesses.

Andersson et al., 1999), and on-line in a fluid-bed apparatus (Andersson et al., 2000a) and most recently in a pan coater (Pérez-Ramos et al., 2005). NIR coating models can predict individual coating thicknesses much faster and cheaper than image analysis and scanning electron microscopy (SEM). Various methods of determining coating thickness have been used as reference for NIR models; tablet dimension measurements (thickness, diameter and weight), amount of coating suspension used, elapsed process time and image analysis. The best reference method is to determine the coating thickness of an individual tablet by methods such as SEM and image analysis (Andersson et al., 2000b). However, these methods require bisection of the coated tablets which can alter the coating thickness at the cutting plane.

Because of the good performance of the NIR coating model (Fig. 11) it was decided to determine coating thickness values of individual tablets; these values can be used to estimate coating thickness variation between tablets. Individual coating thickness of batch A was predicted (Fig. 12) and S.D. and R.S.D. values were calculated. Coating thickness variation was also calculated based on S.D. values of coating thickness reference measurements (Table 4).

Measuring dimensions of coated and uncoated tablets offer a possibility to estimate the variation in coating thickness applied on tablet cores. Two propositions were made: core diameter variance was caused by natural variations in core diameter; tablet diameter variance was caused by natural variation in core diameter and natural variation in coating thickness. Thus the difference between the variance of cores and tablets is the variance of the applied coating. Taking the square root of this variance gives the standard deviation; subsequent division by the coating thickness gives the coating R.S.D.. Values of both methods used to predict coating gave comparable results. Initially variation of coating thickness was high but after coating for approximately 30 min the coating thickness variation stabilized around 7.5%. Similar findings were also reported by Wnukowski (1989) and Andersson et al. (2000a), in the latter study NIR was also used to predict coating thickness variation. This proves that the developed model was capable of predicting inter-tablet coating variation and individual coating thicknesses.

Precise knowledge of the amount of coating applied and its standard deviation will be particularly useful in cases where coatings are used to produce extended release tablets. Application in scale-up processes will also be valuable. Variation in coating thickness is an objective quality parameter that can be used to evaluate and compare the quality of coated tablets during development and production. Coating thickness can be calculated by subtracting tablet dimension values of uncoated tablets from coated tablets, but calculations on single tablets will cause a major error in the value of the coating thickness because of the large variation in tablet thickness. Averaging the values of multiple coated tablets and uncoated tablets improves the accuracy of the coating thickness values. To improve the accuracy even more it was chosen to use the tablet parameter with the lowest relative standard deviation, the tablet diameter. The low R.S.D. of the tablet diameter can be explained by the fact that changes in compression force or tablet weight are reflected in the tablet thickness and weight; and not in the tablet diameter. Because tablets are most of the time inside the dies during the tablet-

Table 4
Coating thickness variation from NIR values and tablet diameter values

Time (min)	Difference calculation*		NIR calculation	
	S.D. (mm)	R.S.D. (%)	S.D. (mm)	R.S.D. (%)
10	0.0017**	10.4	0.0011	13.3
20	0.0045	14.8	0.0017	11.1
30	0.0044	9.1	0.0018	7.6
40	0.0048	7.5	0.0022	7.1
50	0.0054	7.0	0.0029	7.5
52	0.0056	7.3	0.0029	7.5

* *Note*: Difference calculation method used two sided coating thickness values.
** *Note*: Standard deviations do not differ at a 95% confidence level.

ting process so expansion of the tablet diameter is prevented. A low R.S.D. ensures a small distribution of the values around the average value; hence the error caused by subtracting values of coated and uncoated tablet is kept as low as possible. Using tablet diameter instead of tablet thickness seems contradictory as NIR measurements take place at the face of the tablets; therefore, it is important that tablet edge coating growth is comparable to tablet face coating growth. Because tablet diameter values instead of tablet thickness values were used as reference, it was important to verify that coating thickness derived from these values was the same.

The two methods seem to produce the same results over the whole coating range for all three coated batches (figure not shown; correlation coefficient 0.9831). A small upward deviation from the straight line was seen; apparently diameter measurements result in slightly higher coating thickness values than thickness measurements. Furthermore, the variation of the values of the various sample subgroups does not reveal any trend. At some points there is a larger spread in the *X*-direction than in the *Y*, at other points this relation is inverted. Comparison of coating thickness values generated by both methods shows that values are comparable in the coating thickness range used by the coating thickness model. Therefore, tablet shape, coating variables and coating apparatus used in this study do not cause a major difference between face and edge coating thickness values.

5. Conclusion

A method which monitors the drug homogeneity in powder blends was developed using the NIR lab blender. The method accurately measured the changes in drug uniformity during blending; results obtained are in concordance with reference blend uniformity measurements and data from previous studies (data not shown). Blend monitoring is possible in powders with a concentration equal to or higher than 2.98% (w/w) of the drug. The role of the delumping step in improving deagglomeration of drug substance lumps was clearly proven using this equipment. Furthermore, the NIR technique will be a useful tool to support reducing duration of the post-delumping blending time since blend uniformity was reached within 5 min after delumping. The NIR lab blender is a very useful tool for development studies.

Content uniformity testing by NIR can be influenced by tablet shape and compaction force. Careful selection of pre-processing methods and specific wavelengths ranges can reduce the influence of these and other unwanted factors to acceptable levels. A small calibration set which uses accurate reference methods can be used to construct a simple NIR CU model with good performance. The NIR can be modelled to accurately measure individual coating thicknesses and inter-tablet coating variation off-line during processing.

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