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Development, validation and transfer of a Near Infrared method to determine in-line the end point of a fluidised drying process for commercial production batches of an approved oral solid dose pharmaceutical product

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ABSTRACT

Pharmaceutical companies are progressively adopting and introducing the principles of Quality by Design with the main purpose of assurance and built-in quality throughout the whole manufacturing process. Within this framework, a Partial Least Square (PLS) model, based on Near Infrared (NIR) spectra and humidity determinations, was built in order to determine in-line the drying end point of a fluidised bed process. The in-process method was successfully validated following the principles described within The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – ICH Q2 (r1) – Validation of Analytical Procedures: Text and Methodology. However, in some aspects, the cited guidelines were not appropriate to in-process methods developed and validated exclusively with in-line samples and implemented in dynamic systems, such as drying processes. In this work, a customized interpretation of guidelines has been adopted which provided the framework of evidence to support a validated application.

The application has been submitted to the United States Food and Drug Administration (FDA) and The European Medicines Agency (EMA) during applications for grant of licences. Representatives from these Regulatory Authorities have specifically reviewed this novel application during on-site inspections, and have subsequently approved both the product and this application.

Currently, the NIR method is implemented as a primary in-line method to control the drying end point in real-time (to below a control limit of not greater than 1.2% w/w) for commercial production batches of an approved, solid, oral-dose medicine.

The implementation of this in-process method allows real-time control with benefits including a reduction in operation time and labour; sample handling and waste generation; and a reduced risk to product quality in further unit operations due to improved consistency of intermediate output at this stage. To date, this has achieved approximately 10% savings in energy efficiency and operational time for this part of the manufacturing process.

1. Introduction

The Process Analytical Technology (PAT) guidance published by the Food and Drug Administration (FDA) establishes a holistic framework for designing, developing, analysing and controlling both the critical quality attributes of raw materials and intermediates and the critical quality parameters of the manufacturing process, with the goal of ensuring final product quality. In this context, the underlying principle is that "Quality cannot be tested into products; it should be built-in by Design"[1]. Throughout the Drug Product Development cycle, embracing the science-based PAT principles provides understanding to support process control, enables regulatory approval and improve manufacturing flexibility to operate within a design space.

Drying is an important operation in pharmaceutical solid oral-dose processing. Important quality attributes such as stability, flow properties and compressibility are all influenced by residual moisture [2]. Thus, moisture content can potentially be a critical quality attribute. If the granules are over dried then the action of the fluid bed dryer may cause the attrition of granules, thus creating undesirable fines that can damage the formulation due to hydration changes in some actives and excipients. Conversely, if the granules are insufficiently dried then the product may not flow properly, which may cause problems with downstream processing, including product sticking to the faces of the tablet press punches and problems with product stability during storage.

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Traditionally, moisture content throughout fluid bed drying of aqueous granulation has been modelled based on heat and mass balance transfer equations [3]. However, these mechanistic models are based on restrictive assumptions and can fail if the process conditions are not consistent between granulation batches [4].

In the last two decades, Near Infra-Red Spectroscopy (NIRS) has proved to offer many industrial possibilities in pharmaceutical analysis [5] due to its potential to measure both physical and chemical properties. The NIR region of the electromagnetic spectrum comprises the molecular vibrations (overtones and combinations of the fundamental vibrations) of highly an harmonic bonds like C–H, N–H and, especially, O–H [6], which make it particularly suitable for measuring water content in an extensive range of sample matrices. Indeed, the measurement of water was one of the first pharmaceutical applications of NIR [7]. NIR technology is also a fast and non-destructive technique that requires no- or minimal analyst intervention. Furthermore, the possibility of using it in conjunction with fibre optic probes, which allow the non-invasive delocalization of the measurements, render it a tool for in-line implementation.

NIR spectra are characterised by wide and overlapping peaks which are often visually difficult to interpret as they are not bond specific. Thus, the determination of chemical and physical properties by NIRS involves the use of multivariate calibration tools [8] to model the property of interest. Samples that are used to construct such models should encompass every source of variability in the process that potentially influencing the properties to be measured. Frequently, under commercial production, the variability in the process parameter is too limited and is highly correlated to ensure adequate accuracy, robustness and precision. To overcome this drawback, the set of samples used to build the model can be enlarged with both synthetic laboratory samples and pilot-scale (development) samples which expand the natural process variability [9]. Nonetheless, this approach cannot be feasibly implemented for fluid bed drying monitoring, because the way the sample is presented to the probe, in a fluidised bed, cannot be easily reproduced off-line [10]. Despite this inconvenience, NIRS has been used in fluid bed drying monitoring, albeit that most of the applications were not fully validated [11,12,13] or were developed off-line [14,15].

This paper describes the application of the PAT principles to the development and analytical validation of a Near Infrared (NIR) method for the measurement of water content in-line during the fluid bed drying process of a drug product. Thus, this primary method is currently being applied on the commercial scale to control the drying end point, which avoids the burden of sampling and the at-line determination of moisture.

2. Experimental

2.1. Materials

This NIR application is used to monitor the drying stage post-granulation of a Novel Drug Product, formulated as a solid oral-dose medicine—absolute percentages or ratios of amounts within the formulation may not be disclosed. However, the Active Pharmaceutical Ingredient (API) comprises 60–70% of the granule, which also includes micro-crystalline cellulose, sodium starch glycolate, and povidone.

The API is a hydrochloride salt which possesses no chiral centres, acyclic double bonds or hydroxyl groups. This is manufactured within a GlaxoSmithKline Primary Production facility.

All excipients were purchased from commercial suppliers as complying with the current edition of the European Pharmacopoeia (Ph. Eur.).

2.2. Process description

All the data analysed herein were collected from batches manufactured at full commercial scale in a 300 l Glatt fluid bed dryer (FBD). The drying process starts after completion of the high-shear wet granulation process. Once the granule transfer is complete, the inlet air temperature is set to 60 °C and the inlet air volume is maintained within 1400–2300 m^3/h. The drying time is variable, but is approximately 30 min, and is deemed complete when the moisture content of the solid is not greater than 1.5% (w/w) as measured off-line using a weight loss on drying balance (LOD).

Full commercial scale batches were grouped into seven different campaigns during which process operating conditions and raw materials were varied in order to gain process understanding and knowledge.

2.3. Spectroscopic data

An ABB – Fourier Transform Process Analyzer (ABB-FTPA2000-260) Near Infrared spectrometer, with thermo electrically cooled, InGaAs detectors and equipped with a diffuse reflectance probe; was used to record in-line NIR data throughout the drying process. A dedicated computer system monitors and controls the spectrometer during operation and is used to retrieve, analyse and store the generated data. This computer includes the FTSW100 Process Control Software and the SIMCA QP Multivariate Prediction Software.

Spectra were recorded in-line over the range 1178–2075 nm. Each spectrum was the average of 32 scans. A reference spectrum was obtained at the beginning of each batch using a 99% reflectance Spectralon® standard.

An interface/adaptor plate was manufactured to facilitate the insertion of the diffuse reflectance probe into the fluid bed dryer. The plate also includes a sample port and sample thief. The design and location of the adaptor plate allows the recording of NIR spectra throughout the entire drying process and the extraction of thieved samples (<10 g) at a similar position to the NIR probe.

For this system, the height of the probe with respect to the base of the dryer bowl and the angle of insertion of the probe in the dryer are critical to obtain both representative spectra of the drying process and also to avoid deposition on the sapphire window of the NIR probe. The NIR probe was inserted into the product bowl at a height of approximately 50 cm from the bottom plate to the window, pointing downward at an angle of approximately 30° from horizontal, and protruding approximately 20 cm into the bowl.

2.4. Reference data – loss on drying (LOD) determinations

Thieved samples were collected periodically throughout the drying process. The measurement of water content, LOD% (w/w), for each sample was determined by the drying to constant weight method using a Computrac Moisture Analyzer (type Max1000). The method uses approximately 3–5 g of sample evenly distributed on a pre-weighed disposable balance dish. The product was then dried at 90 °C until a change in weight of less than 0.01 g was registered during 24 consecutive seconds. In order to determine the Standard Error of Laboratory (SEL), triplicate determinations were performed on selected samples.

2.5. Model building

Prior to model development, both NIR data and LOD% (w/w) values were trended and visually inspected to exclude gross-outliers and anomalous samples using in-house scripts built in Matlab R2008b (Mathwork).

Commercial Software SIMCA-P+ v.11 (Umetrics) was used to build a Partial Least Square (PLS) model using the LOD% deter-

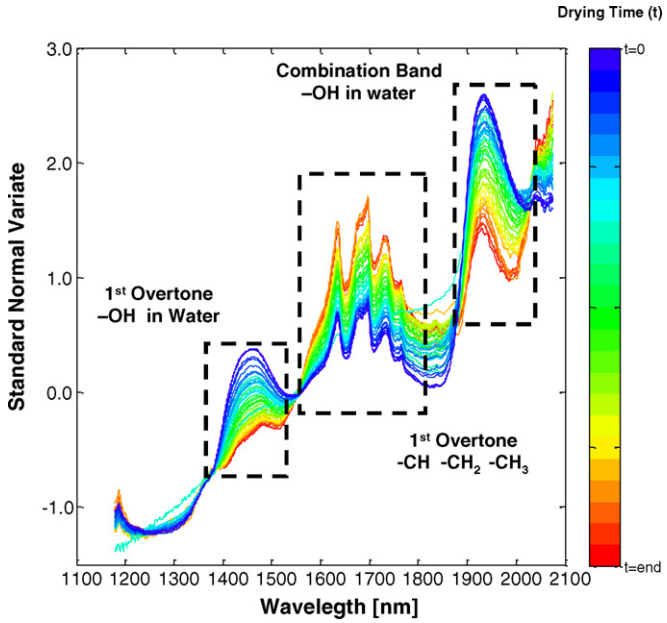

Fig. 1. NIR spectral evolution for a typical batch during the fluid bed drying process.

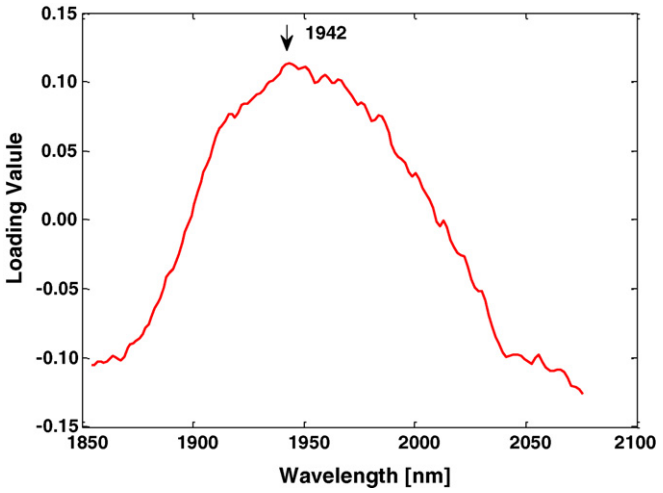

Fig. 2. Loading plot for the 1st PLS component. Maximum observed at approximately 1942 nm.

mination as dependent variable and the NIR spectra ascribed to the moisture measurements as predictive variables. Both types of variables were centred before modelling.

The PLS model was built with 24 samples from 10 different batches. These batches were manufactured according to a design of experiments plan expanding the process variability within the design space. The model was externally and independently validated with 47 samples obtained from 29 additional batches manufactured during 5 clinical campaigns. In-house procedures based on international guidelines [16,17] were followed in order to validate the model.

Since NIR spectra were acquired from a continuously evolving system in the diffuse reflectance mode, significant variations in the spectral baseline were detected. Several combinations of pre-processing filters and wavelength selection were studied in order to minimize the distorting effect of the scattering and to enhance the signal related to the moisture content. Standard Normal Variate (SNV) in the band between 1854 nm and 2075 nm was finally selected as the spectral pre-processing treatment.

Every LOD% (w/w) value predicted by the model also has a DModX [18] value associated. The DModX or Distance to Model is a diagnostic test that provides information on the spectral similarity between the spectrum of the sample under scrutiny and the set of spectra used to build the multivariate model. The smaller the DModX, the greater the similarity of the sample to those included in the calibration set. Conversely, samples with a high DModX may be considered as potential outliers and thus the associated predicted LOD value cannot be relied upon to decide whether the end point has been reached.

3. Results

3.1. NIR spectra

Changes in physical and chemical attributes during drying can be monitored using NIR as illustrated in Fig. 1. The plot shows all the spectra collected during a drying operation under SNV pre-processing. The colorimetric legend is related to the drying time indicating blue to red for the beginning to end of the drying process respectively. The spectral evolution is characterised by the strong absorption around 1940 nm, which corresponds to the combination between the fundamental stretching and deformation vibration of the O–H bond [19]. Around this region, the water signal decreases progressively throughout the drying process.

Another characteristic zone of the spectra is the first overtone region for the CH, CH_2 and CH_3 around 1600–1800 nm. Here, the signal increases as the drying progresses. Finally, the spectral evolution around the band at 1440 nm, which is the 1st overtone of the hydroxylic bond, is similar to that for 1940 nm.

3.2. Model calibration

The PLS model for the prediction of LOD% was built with 24 samples. The optimum number of PLS components, selected by cross-validation, was just one, explaining 97.66% of the LOD-variance.

Fig. 2 shows the loading value associated with the 1st PLS components. Although loadings and coefficient vectors must be cautiously interpreted [20], the shape of the loading plot resembles the absorbance band for water and presents an absolute maximum at 1942 nm, which is concordant with the absorption for the hydroxylic bond for water.

Table 1 (upper) shows the statistics for the relationship between the LOD values predicted by the PLS model and the LOD values determined in the laboratory. The slope and intercept of the regression line are 1 and 0 respectively, matching the desired values; whilst the coefficient of determination (R^2) is 0.98. The Root Mean Square Error of Calibration (RMSEC) is 0.10% (w/w); this value is comparable to the Standard Error of Laboratory which is equal to 0.09% (w/w).

Finally, the residuals of the PLS model shown in a normal probability plot in Fig. 3, follow a trend similar to the normal distribution line (in red). This indicates that the variability not explained by the model is just a random perturbation. The statistics presented shows the suitability and goodness of fit of the PLS to model the water content.

3.3. Method validation

In order to demonstrate the suitability of the NIR model for the quantification of moisture content in terms of LOD% during the drying process of these granules, an independent set of 47 samples was used to validate the model.

Current guidelines [16,17] suggest that the number of samples available should be a split of 2/3 for calibration and 1/3 for valida-

Table 1
Statistics for the relationship between the LOD% (w/w) predicted by the PLS model and the laboratory reference values for the samples in the calibration set (upper table) and for the samples in the external validation set (lower table).

Calibration				
Number of samples 24				
Parameter	Coefficients	Standard error	Confident limit	
			Lower 95%	Upper 95%
Intercept	0.00	0.05	−0.10	0.10
Slope	1.00	0.03	0.93	1.07
R^2 = 0.98		Bias = 0.00% (w/w)	RMSEC = 0.10% (w/w)	
External validation				
Number of samples 47				
Parameter	Coefficients	Standard error	Confident limit	
			Lower 95%	Upper 95%
Intercept	−0.03	0.07	−0.18	0.12
Slope	1.01	0.05	0.91	1.11
R^2 = 0.90		Bias = −0.02% (w/w)	RMSEP = 0.17% (w/w)	

tion. However, for this application a more conservative approach was taken to demonstrate suitable model performance. Therefore, the proportion of samples was reversed here (1/3 calibration and 2/3 validation); allowing 24 samples for calibration and 47 samples for a more thorough independent validation. The following analytical properties were evaluated.

3.3.1. Range

The range of the model was determined by the LOD% (w/w) values of the extreme samples (lower and upper) in the calibration set, which was 0.62% (w/w) and 2.64% (w/w), respectively. The NIR model is only valid within the range of the method. Any use outside of the range is purely extrapolatory. All the samples used to validate the model were within the range of the method.

3.3.2. Specificity

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present.

As stated in Section 1, one of the features of NIRS is the overlapping peaks. Thus, the specificity of any analytical methods based on NIRS can only be achieved with the help of proper multivariate tools. The following three facts support the demonstration of specificity of the NIR model to predict LOD% (w/w):

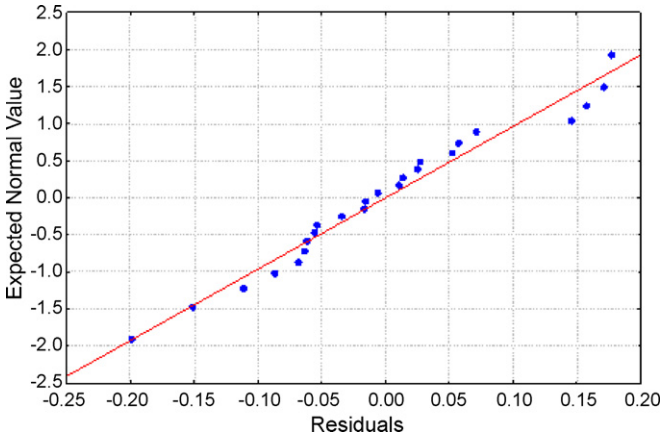

Fig. 3. Normal Probability Plot of residuals. The line represents the normal distribution.

1. Fundamental spectroscopic principles: The wavelength range selected to build the model, from 1854 nm to 2075 nm, includes the combination band for water with a maximum around 1940 nm
2. Spectral difference: The NIR spectra recorded presents a characteristic relative maximum around 1940 nm. Fig. 4 shows the spectra corresponding to the samples with extreme LOD values 0.62% (w/w) (red) and 2.64% (w/w) (blue), which represent the range of the method. The spectrum resulting from the subtraction of these extreme spectra is shown in black. As can be seen, the highest difference between the extreme spectra is found at 1942 nm.
3. Modelling perspective: The loading plot for the 1st (and only) PLS component of the model also present an absolute maximum at 1942 nm. The spectrum of differences and the first loading vector are highly similar, presenting a similarity index, measured as the sin between both vectors, which is equal to 0.9898.

Consequently, it can be stated that the PLS model is based on a NIR region highly related to free water, presenting a loading vector highly related to the hydroxylic band and showing an abso-

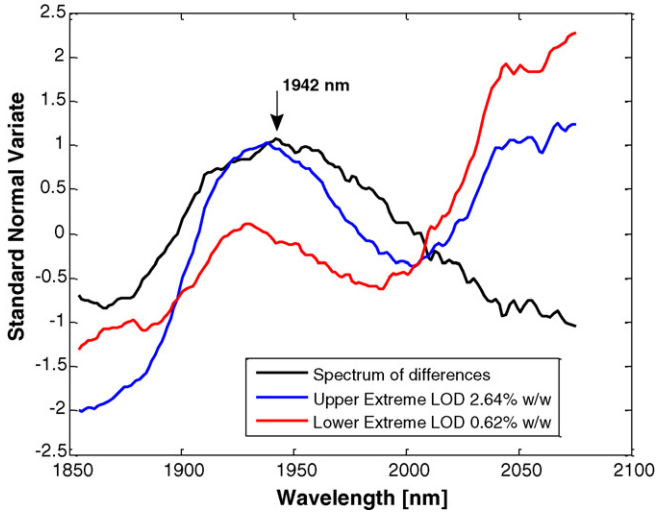

Fig. 4. NIR spectra in the calibration set with extreme values of LOD% (w/w) (red for the lowest content and blue for the highest) along with the spectrum resulting from the subtraction of both (black) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

Table 2
Demonstration of accuracy.

Set	Method	Number of samples	Mean	Variance	*F*-test (0.05)			*t*-test (0.05)		
					Tab.	Exp.	*p*	Tab.	Exp.	*p*
Calibration	NIR-PLS	24	1.38	0.40	2.014	1.024	0.955	2.013	0.000	1.000
	Laboratory	24	1.38	0.41						
Validation	NIR-PLS	47	1.38	0.25	1.632	1.130	0.680	1.986	−0.210	0.834
	Laboratory	47	1.35	0.28						

lute maximum at the wavelength with the highest sensitivity to water.

3.3.3. Linearity of the method

The linearity of the method was demonstrated by establishing the correlation between the LOD values predicted by the model and those determined by the reference method.

Fig. 5 shows the scatter plots of the LOD values determined in the laboratory against the LOD values predicted by the NIR model for both the calibration (blue filled circle) and validation set (black circle). The line of best fit for both sets are also shown but cannot be clearly distinguished as they overlap. The properties of the regression line for the samples in the validation set are shown in the lower part of Table 1. The confidence interval for a significance level of 0.05 for the intercept and the slope include zero and unity, respectively.

3.3.4. Accuracy

To establish the accuracy of the NIR method a paired *t*-test for independent samples by variables was performed between the LOD% (w/w) values predicted by the model and those determined in the laboratory. The analysis was carried out both for samples in the calibration and in the validation set.

Before the paired *t*-test, the variance of both methods was compared using an *F*-test to assess whether they differed significantly. The results obtained are included in Table 2. Considering the *F*-test for a significance level of 0.05, the experimental statistic is lower than the critical, thus it can be concluded that there are no significant differences between the standard deviation of the methods, both for the calibration and validation sets.

Equally, *t*-experimental is also lower than *t*-critical for a signification level of 0.05 for both the calibration and validation sets. Finally the SEL, RMSEC and RMSEP values are respectively 0.09%, 0.10% and 0.17%, which are all of a comparable magnitude. They were considered acceptable from a manufacturing perspective.

Consequently, it was concluded that the differences between the LOD% (w/w) values predicted by the NIR-PLS model and the LOD% (w/w) values determined in the laboratory are not significant or, in other words, that the accuracy of both methods was comparable.

3.3.5. Robustness

A risk assessment for the robustness and ruggedness of the analytical method for granule LOD% was performed by a panel of multidisciplinary experts. Table 3 includes the range for the quality attributes (QA) of the API and the critical Process Parameters (PP) potentially affecting the performance of the NIR model. Ideally, robustness is built-in by selecting samples in the calibration encompassing variability across the range for all the critical PP and QA.

Principal Component Analysis (PCA) based on the values of the critical QA and PP for the samples in the calibration and validation sets were performed to assess robustness. Score and contribution plots were useful to identify clusters of samples and to explain their differences or similarities. As a way of an example, Fig. 6 shows the score plot for the first two principal components using the QA as variables. Each point represents a granulation batch. The labels C and V stand for calibration and validation. The legend is related to the bulk density of the API. Batches manufactured with API of low bulk density are plotted with squares, whilst batches with mid and high bulk density are shown with circles and triangles, respectively. Samples in the calibration set encompass the whole range for bulk density. The RMSEP for the batches with low, mid and high API bulk density were 0.14% (w/w), 0.18% (w/w) and 0.17% (w/w) respectively, which can be considered similar to the global model RMSEP (0.17% (w/w)). Hence robustness against the bulk density of the API was assessed, and similar results were obtained for the critical QA and PP listed in Table 3.

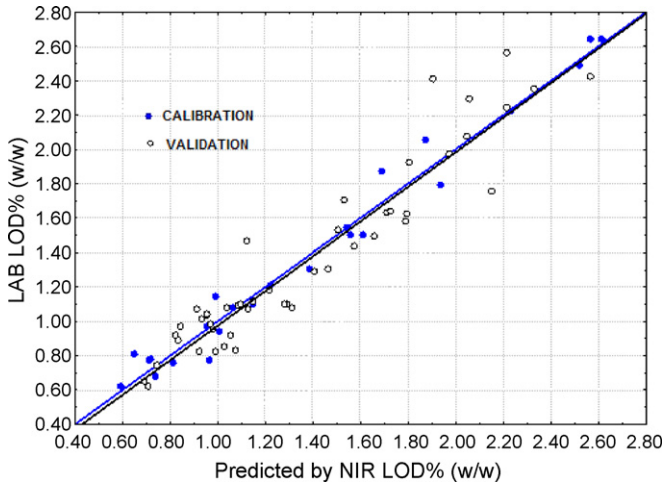

Fig. 5. Regression lines for the samples in the calibration and validation sets.

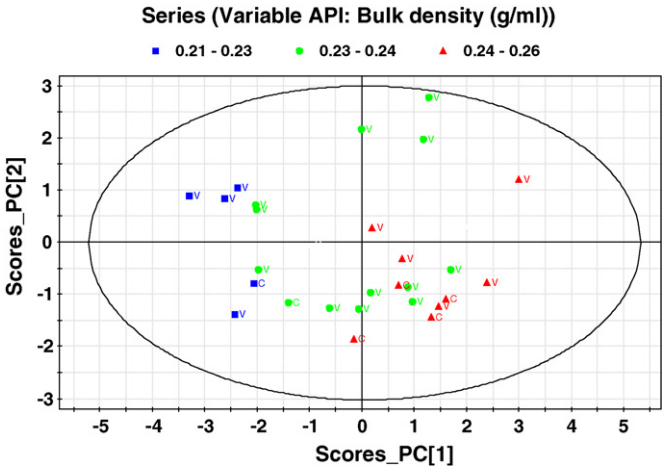

Fig. 6. Score plot for the first 2 Principal Components based on the critical quality attribute values of the batches of API. C and V stand for Calibration and Validation. Legend colour based on Bulk density.

Table 3
Range for the critical quality attributes of the API and the process parameters.

API quality attributes		Range		Drying process parameters	Range	
		Min.	Max.		Min.	Max.
Chemical properties (% (w/w))	Water	0.30	0.68	Inlet air temperature (°C)	59.3	61.0
	Residual solvents	0.03	0.18	Product bed temperature (°C)	27.2	48.0
Particle size distribution (microns)	X10	0.85	1.14	Outlet air temperature (°C)	23.8	45.7
	X50	2.22	2.90	Inlet air humidity (% RH)	3.8	12.2
	X90	4.62	7.38	Inlet air volume (m^3/h)	708	1863
Density (g/mL)	Initial	0.17	0.25	Differential pressure in bowl (kPa)	0.53	1.01
	Tapped	0.28	0.38	Differential pressure in filter (kPa)	0.43	1.51
	Bulk	0.21	0.26	Manufacture site	A	B

3.3.6. Precision

Precision is defined as the closeness of agreement between a series of measurements under the prescribed conditions. Precision may be considered at two main levels: repeatability and reproducibility.

3.3.6.1. Repeatability. Repeatability expresses the precision under the same operating conditions over a short interval of time. This definition is more suitable for off-line/at-line methods where the analysis conditions can be easily controlled and reproduced. However, it is not readily applicable to in-line methods developed for dynamic evolving systems, e.g. a drying process. This is because the process conditions cannot be kept constant between consecutive measurements. Taking samples from the process to perform replicate NIR measurements in, an off-line way, is also not realistic since the sample presentation would be different in a static state versus the spectra of samples from the dynamic process. Therefore, a customized interpretation of repeatability is provided to demonstrate the repeatability of determining the end point, which is more important for this application rather than repeatability of measurement on the same sample.

3.3.6.1.1. Custom developed criteria for assessing end point "repeatability" for a method developed in-line on a dynamic system. The NIR method was developed to monitor the moisture content at the end of a drying operation and ultimately control the end of the process. Once the water predicted by NIR had reached the end point value, the drying process would stop accordingly. Repeatability is of paramount importance at this stage. If the method was not repeatable, the consecutive prediction could randomly fall above or below the end point values and thus the control strategy would fail.

Due to the lack of procedures and guidelines to define how to assess the repeatability for end point methods applied to dynamic evolving systems, a customized interpretation of repeatability was established. Thus, repeatability was interpreted as the precision to estimate the end point in a clear and unambiguous manner. A simulated example is shown in Fig. 7. In the upper-plot this is represented by the predicted values of a non-repeatable method. When the end point (discontinuous line) is reached, the successive predictions fall above and below the specification limit. However, the lower-plot indicates the predictions of a method demonstrating repeatability. This is because when the end point is reached, successive predictions systematically fall within the specification limit and the end point of the batch can be clearly and unambiguously determined.

In evolving systems in which an analytical property of interest is monitored in-line, the variability due to the method of measurement cannot be independently estimated from the intrinsic process variability. The proposed method for assessing repeatability ensured that both sources of variability are under control, or in other words, that the method of measurement is repeatable and that the process evolved homogenously.

To assess the repeatability, the first predicted value below the specification limit was identified as well as the subsequent five predictions which were weighted according to the following criteria:

- A weight of 1 was given if the predicted value was below specification.
- A weight of 0 was given if the predicted value was above specification.

The repeatability around the end point was measured as the ratio "sum of weights divided into five". In that way, for the non-repeatable example of Fig. 7, the repeatability around the end point is 0.4 = 2/5. Whereas for the repeatable example, it is 1.0 = 5/5.

The repeatability of determining the end point was assessed in five randomly selected batches. The repeatability achieved around the end point was 100% in the five cases, which means that the end point could have been determined with precision.

In spite of the demonstration of high repeatability of the method, but due to the lack of guidelines in that respect, a safeguard clause was established for this application to ensure that the batch would be released in compliance with the specification: "The drying pro-

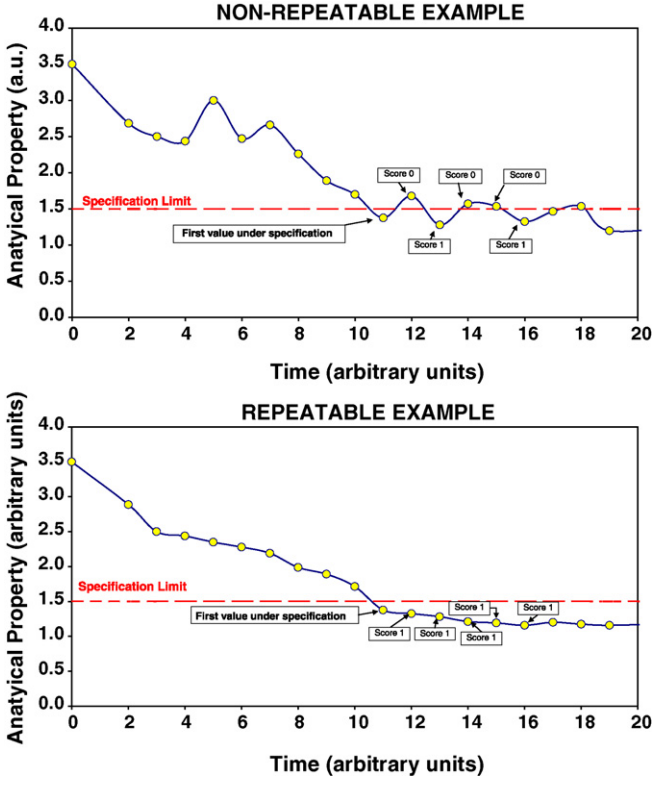

Fig. 7. Theoretical examples of non-repeatable (upper-plot) and repeatable (lower-plot) methods applied to determine the end point of a batch process. Simulated data.

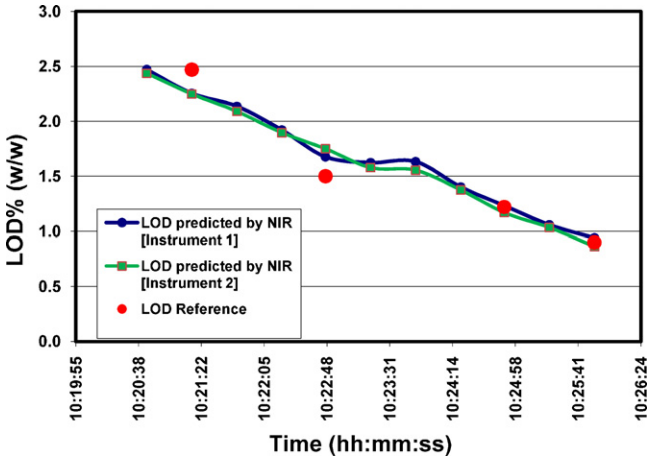

Fig. 8. The dark blue line represents the LOD% (w/w) predicted by the NIR used to developed the NIR model (instrument 1). Green line represents the LOD% (w/w) predicted by the NIR with the transferred model (instrument 2). The reference values are shown in red (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

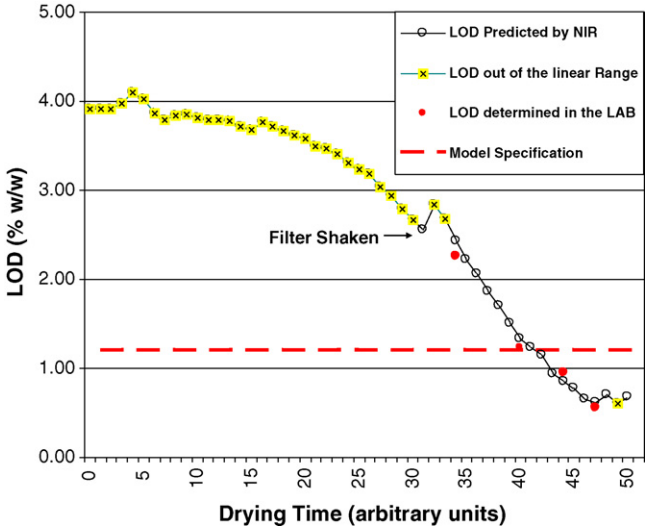

Fig. 9. LOD% (w/w) evolution during drying predicted by the NIR model.

cess will only be deemed completed after three consecutive LOD% (w/w) predicted values had reached the desired end point".

3.3.6.2. Reproducibility. Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology).

After validation and continuous verification of the performance of the method, this application was transferred to a similar spectrometer from the same vendor, although the model type was different (FTPA 2000 Series Type 263). During manufacture of two full-scale commercial batches, NIR data were collected on both spectrometers at the same time. The validated chemometric model was loaded on each NIR system allowing real-time predictions of LOD% (w/w) during each batch. Samples were also taken at regular intervals during the drying process for LOD% (w/w) measurement by the reference method.

Since the sampling rates between the two NIR instruments were not identical, three criteria were defined to assess method equivalence:

- An appropriate initial statistical "visualisation approach" between both instruments' collected data.
- An appropriate statistical "differences from the mean" test between both instruments' predicted data.
- An appropriate statistical "*t*-test for time-aligned and paired data" between both instruments' predicted data.

The performance of the method for each instrument was found to be equivalent and satisfied the three pre-defined criteria mentioned above. Thus, the method was successfully transferred. Additionally, Fig. 8 shows the LOD% (w/w) predicted by the NIR used to build the Model (instrument 1) along with the LOD% (w/w) predicted by the NIR with the transferred model (instrument 2). The reference LOD% (w/w) values are shown as red points. This demonstrates a close agreement between the three determinations.

3.4. Parallel testing

Post-validation, the NIR method was applied in-line to monitor the drying end point of 12 additional batches that were not used either during calibration or validation. However, the manufacturing process was not controlled by the NIR predictions but by the conventional end point based on product temperature within the drying bowl. Fig. 9 shows a typical drying profile of one of those batches. Crosses represent LOD% (w/w) predicted values outside the linear range of the model. The predictions within the linear range are represented by circles, the full circles are the LOD% (w/w) values determined by the reference method. The end point specification is shown by the discontinuous horizontal line. A good agreement between the values predicted by NIR and those predicted by the LOD balance was observed for parallel testing.

It is noteworthy to discuss the local maximum in the LOD% (w/w) predicted value at around the 33rd spectra from the start of drying. This peak in the drying profile is observed in all the batches and it is caused by a pre-programmed filter shake (filter socks at the very top of the drying vessel located in the expansion chamber). When the filter shake is triggered, the product entrapped in the filters dislodges and then falls back down into the product bowl to mix with the major portion of the product. As the drying conditions are milder in the upper part of the bowl, the water content of the product in the filters is higher than the water of the fluidised product within the product bowl. As a result of the mixing, the profile of the LOD% (w/w) predicted by NIR shows a relative maximum. The study of the perturbation introduced by the filter shake event on the LOD% (w/w) values predicted by NIR provides important information to understand the dynamic of the process and the overall drying kinetics unique to this product and process.

If the predictions by NIR had been used to control the end of the process, the batch would have stopped at time 44 (a.u.) – that is when three consecutive values had reached the specification limit. However, with the stop criteria based on product temperature, the batch was stopped at time 50 (a.u.). Clearly for this batch, if the NIR method had been used to control the end of the process, a saving of 12% in drying time would have been achieved.

Fig. 10 shows the end of drying LOD% (w/w) values that would have been achieved if NIR had been used to stop the drying process (left box plot) and the final LOD% (w/w) (right box plot) for the 12 batches in the parallel testing campaign. As can been seen, if NIR had been used to stop the drying process, not only the mean of the 12 batches would have been closer to the drying specification, 1.2% (w/w), but also the end point would have been more consistent than with the conventional control mode, which is based on product temperature.

Finally, if NIR had been used to control the end point, the batches would have been released in real-time for down-stream manufacturing. With the traditional operational mode, the batch is retained until the final sample is extracted and the result from the analy-

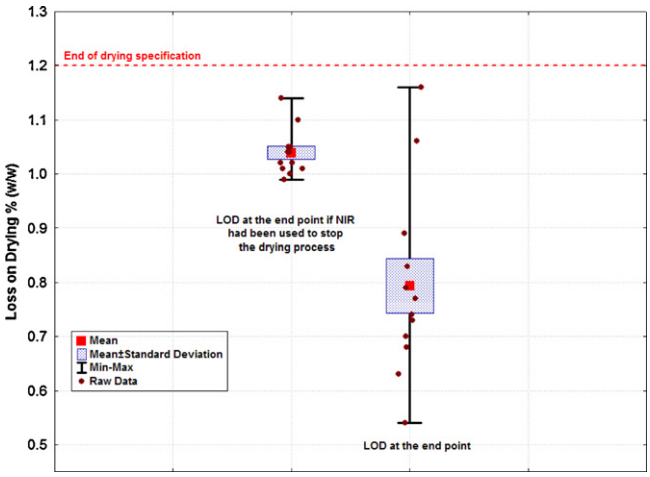

Fig. 10. Box plot with the end of drying LOD% (w/w) values that would have been achieved if NIR had been used to stop the drying process (left plot) and the final end of drying values obtained (right plot).

sis is obtained. The "conventional procedure" implies not only a considerable increment in manufacturing time and labour, but also a potential risk of over-drying the granules retained in the drying bowl, whilst the off-line LOD% (w/w) measurement is taken and determined. However, the validated NIR application is now routinely used to realise these benefits.

4. Conclusions

A Partial Least Square model based on Near Infrared spectra and loss on drying measurements was built in order to determine in-line, the drying end point of a fluidised drying process. The model was developed exclusively with samples taken from batches manufactured at full commercial scale. The predictions of LOD% (w/w) from the NIR model were similar to the reference method.

After development, the method was validated according to the local procedures and external guidelines. However, a customized interpretation of some elements of the guidelines was required to assess the precision around the end point. The goodness of the results obtained upon assessment of the main analytical properties, advanced the model toward in-line implementation in a monitoring mode.

From an analytical perspective, the precision of the determination at the drying end point provided by NIR was also four times greater than the precision of the reference method.

During parallel testing of the model, the advantages of using NIR were undoubtedly revealed. The NIR predictions were closer to the end point specification limit (i.e. not excessively over dried). Therefore, this would have resulted in an average saving in drying time of around 10% if NIR had been used as the primary method for control during parallel testing.

This saving is now realised since the NIR model is implemented in-line to control the drying end point in real-time for commercial production batches of an FDA and EMA approved, solid, oral medicine.

References

[1] American Food Drug Administration (FDA), Guidance for Industry PAT (2004). Available from: http://www.fda.gov/downloads/Drugs/../Guidances/UCM070305.pdf.
[2] M.E. Aulton, Pharmaceutics: The science of Dosage Form Design, Churchill Livingstone, London, 2002.
[3] A.J. Hlinak, A. Saleki-Gerhardt, An evaluation of fluid bed drying of aqueous granulations, Pharm. Dev. Technol. 5 (2000) 11–17.
[4] T. Lipsanen, O. Antikainen, H. Räikkönen, S. Airaksinen, J. Yliruusi, Effect of fluidisation activity on end-point detection of a fluid bed drying process, Int. J. Pharm. 357 (2008) 37–43.
[5] J. Luypaert, D.L. Massart, Y. Vander Heyden, Review. Near-Infrared spectroscopy in pharmaceutical analysis, Talanta 72 (2007) 865–883.
[6] D.A. Burns, E.W. Ciurczak, Handbook of Near Infrared Analysis. Revised and Expanded, Marcel Dekker, New York, 2001.
[7] J.E. Sinsheimer, N.M. Poswalk, Pharmaceutical applications of the near infrared determination of water, J. Pharm. Sci. 57 (1968) 2007–2010.
[8] Y. Roggo, P. Chalus, L. Maurer, C. Lema-Martinez, A. Edmond, N. Jent, A review of near infrared spectroscopy and chemometrics in pharmaceutical technologies, J. Pharm. Biomed. Anal. 44 (2007) 683–700.
[9] M. Blanco, J. Coello, H. Iturriaga, S. Maspoch, N. Pou, Influence of the procedure used to prepare the calibration sample set on the performance of near infrared spectroscopy in quantitative pharmaceutical analyses, Analyst 126 (2001) 1129–1134.
[10] M. Andersson, O. Svenssonb, S. Folestad, M. Josefson, K. Wahlund, NIR spectroscopy on moving solids using a scanning grating spectrometer—impact on multivariate process analysis, Chem. Intell. Lab Syst. 75 (2005) 1–11.
[11] P. Frake, D. Greenhalgh, S.M. Grierson, J.M. Hempenstall, D.R. Rudd, Process control and end-point determination of a fluid bed granulation by application of near infra-red spectroscopy, Int. J. Pharm. 151 (1997) 75–80.
[12] J. Rantanen, O. Antikainen, J. Mannermaa, J. Yliruusi, Use of the near-infrared reflectance method for measurement of moisture content during granulation, Pharm. Dev. Technol 5 (2000) 209–217.
[13] R.L. Green, G. Thurau, N.C. Pixley, A. Mateos, R.A. Reed, J.P. Higgins, In-line monitoring of moisture content in fluid bed dryers using near-IR spectroscopy with consideration of sampling effects on method accuracy, Anal. Chem. 77 (2005) 4515–4522.
[14] A.C. Jorgensen, J. Rantanen, P. Luukkonen, S. Laine, J. Yliruusi, Visualization of a pharmaceutical unit operation: wet granulation, Anal. Chem. 76 (2004) 5331–5338.
[15] J. Mantanus, E. Ziémons, P. Lebrun, E. Rozet, R. Klinkenberg, B. Streel, B. Evrard, Ph. Hubert, Moisture content determination of pharmaceutical pellets by near infrared spectroscopy: method development and validation, Anal. Chim. Acta 642 (2009) 186–192.
[16] ICH Harmonised Tripartite Guideline, Validation of analytical procedures: Text and Methodology, 2005. Available from: http://www.ich.org/LOB/media/MEDIA417.pdf.
[17] European Medicament Agency (EMEA), Note for guidance on the use of NIRS by the pharmaceutical industry and the data requirements for new submissions and variations, 2003. Available from: http://www.ema.europa.eu/pdfs/human/qwp/330901en.pdf.
[18] L. Eriksson, E. Johansson, N. Kettaneh-Wold, J. Trygg, C. Wikstrom, C. Wold, Multi- and megavariate data analysis. Part I. Basic principles and applications, Umetrics AB, Umea, 2006.
[19] P. Williams, K. Norris, Near-Infrared Technology in the Agricultural and Food Industry, American Association of Cereal Chemists, St. Paul, MN, 1987.
[20] K. Faber, B. Kowalski, Propagation of measurement errors for the validation of predictions obtained by principal component regression and partial least squares, J. Chemom. 11 (1997) 181–238.