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Building the quality into pellet manufacturing environment – Feasibility study and validation of an in-line quantitative near infrared (NIR) method

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ABSTRACT

The present study focuses on the implementation of an in-line quantitative near infrared (NIR) spectroscopic method for determining the active content of pharmaceutical pellets. The first aim was to non-invasively interface a dispersive NIR spectrometer with four realistic particle streams existing in the pellets manufacturing environment. Regardless of the particle stream characteristics investigated, NIR together with Principal Component Analysis (PCA) was able to classify the samples according to their active content. Further, one of these particle stream interfaces was non-invasively investigated with a FT-NIR spectrometer. A predictive model based on Partial Least Squares (PLS) regression was able to determine the active content of pharmaceutical pellets. The NIR method was finally validated with an external validation set for an API concentration range from 80 to 120% of the targeted active content. The prediction error of 0.9% (root mean standard error of prediction, RMSEP) was low, indicating the accuracy of the NIR method. The accuracy profile on the validation results, an innovative approach based on tolerance intervals, demonstrated the actual and future performance of the in-line NIR method. Accordingly, the present approach paves the way for real-time release-based quality system.

1. Introduction

FDA's Process Analytical Technology (PAT) aims at "improving the pharmaceutical development, manufacturing and quality assurance through innovation in product and process development, process analysis and process control" [1]. According to the PAT framework, the process analysis side should include at least the following two steps. First, the critical process steps relating to the final product quality should be identified using appropriate risk assignment approach [2]. Considering the pellet manufacturing process, the processing steps such as blending, granulation, spheronization, drying and coating phases are critical to ensure the final product quality. Second, a proper process measurement system must be chosen to collect at-line, on-line or in-line process information from the identified critical steps of the manufacturing. This information may eventually provide a better understanding of the manufacturing process, giving opportunities for process control strategies to prevent or mitigate the risk of producing out of specification products. Moreover, the data gathered during the production may enable the real-time release of the product, reducing the batch release time which is still dependent on time consuming laboratory tests. The challenge still remains to interface the selected process analytical approach to the real environment and to develop quantitative methods fitted for a real-time release quality-based system.

Near infrared (NIR) spectroscopy is a well-established vibrational spectroscopic technique. In the covered wavelength region (between 800 and 2500 nm), relatively wide bands related to overtones and combination of fundamental vibration of chemical groups with hydrogen, such as C–H, N–H, O–H and S–H, are observed. Such vibrations lead to overlapping bands which contain both physical and chemical information. Consequently, chemometric tools are used to extract the significant information [3,4].

NIR spectroscopy has several advantages, such as fast spectral acquisition, minimization of sample preparation and/or destruction and the use of probes allowing at-line, on-line and in-line analysis. Considering those advantages, NIR spectroscopy matches the process measurement system requirements of the PAT framework. NIR spectroscopy has already been part of PAT applications to monitor critical process attributes such as the blend homogeneity, the coating level, the moisture content, and the active content [5–19].

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Table 1
API and main excipient percentage (w/w) in the 80, 100 and 120% API formulations.

API formulation	API (%, w/w)	Main excipient (%, w/w)
80%	36	38
100%	45	30
120%	54	22

Validation is a crucial and mandatory step in the lifecycle of an analytical method [20]. Based on β-expectation tolerance intervals, the accuracy profile makes possible a visual and reliable representation of the actual and future performances of the analytical method and thus enables a better risk management. It fully complies with the ICH Q2(R1) regulatory documents as it integrates all the useful required validation criteria such as accuracy, trueness, precision, limits of quantification, range and linearity [21,22,23].

In a previous work [12], a NIR method able to quantify the API in non-coated pharmaceutical pellets was successfully developed and validated. Using the commercially available formulation, coated pharmaceutical pellets as model particles, the feasibility of a quantitative in-line method was evaluated. The first aim was, for qualitative purpose, to interface a dispersive NIR spectrometer with four realistic particle streams found in the pellets manufacturing line. Second, for quantitative purpose, to interface one of the previous particle stream with a FT-NIR spectrometer. Finally, based on the previous interfacing, to develop and to validate a NIR method able to determine the API content of the pellets.

2. Materials and methods

2.1. Materials

2.1.1. Pharmaceutical pellets

For this work, pellets were used as model particles. Eighteen batches of pharmaceutical pellets were manufactured via extrusion spheronization followed by two coating steps. In the standard pellet formulation, which will later on be called 100% Active Pharmaceutical Ingredient (API) formulation, the API is 45% (w/w) of the formulation whereas the formulation main excipient represents 30% (w/w) of the formulation. As shown in Table 1, the ratio of raw materials was modified in order to manufacture batches containing 80 and 120% API formulations (6 batches per API level). Moreover, the coating levels were kept the same to provide the same sustained release behavior for all the batches. All the batches were sieved after the manufacturing, the fractions between 800 and 1600 μm were kept for the experiments.

2.1.2. Qualitative study samples

For the qualitative study, Nine batches of pharmaceutical pellets were analyzed, three batches per API level.

2.1.3. Quantitative study samples

For the quantitative study, eighteen batches of pharmaceutical pellets were analyzed, six batches per API level.

2.2. Methods

2.2.1. NIR analysis

For qualitative purpose, a dispersive NIR spectrometer NIR-256L-2.2T2 (Control Development Inc., South Bend, IN, USA) having a thermoelectrically cooled 256 element InGaAs array detector, a tungsten light source and a fiber optic reflectance probe (six illuminating fibres around one collecting fibre) was used. The spectra were collected between 1090 and 2220 nm with a 10 ms integration time. The spectral range used in the data analysis was 1340–1640 nm.

For quantitative purpose, a Bomen FTLA 2000 series FT-NIR spectrometer (ABB Bomen, Quebec, Canada) was used. Samples were measured in the 1000–2500 nm range with a resolution of 8 cm^{-1}.

The number of scans selected for the off-line and the in-line measurements will be described in the following sections.

2.2.2. Off-line measurements

For the dispersive NIR spectrometer, off-line measurements were performed with the reflectance probe directly through the side of glass vials. For the FT-NIR spectrometer, samples in vials were analyzed on the reflectance sample stage. For both systems, each spectrum was the average of 32 scans.

2.2.3. Process interfaces for the dispersive NIR spectrometer

2.2.3.1. Fluidization interface. 150 g of pellets sample were introduced in a Mini-Glatt (Glatt GMbH, Germany) fluid bed coater. The system was working in drying mode and no heat was applied while fluidizing the particles. The fluidizing air pressure was 1.75 bar. As can be seen from Fig. 1a, the NIR probe was placed outside the coater, directly against the acrylic glass housing of the fluid bed coater. A background of the acrylic glass housing was taken before each measurement. The spectra were collected by averaging 16 scans. One spectrum was acquired every 3 s. Ten spectra per batch were kept for the data analysis.

2.2.3.2. Slow particle flow velocity device. For this interface, pellets slide down through a homemade sample holder. For 100 g of pellets, the average time for the particles to flow through the sample holder was 20 s, leading to a particle mean flow rate of 5 g/s. Fig. 1b shows how the particles flow was interfaced in a non-invasive way with the NIR probe. The spectra were collected by averaging 4 scans. One spectrum was acquired every second. Ten spectra per batch were kept for the data analysis.

2.2.3.3. Fast particle flow velocity device. For the fast particle flow device, pellets were freely flowing through a funnel. In this case, the particle mean flow rate was higher (7 g/s) as the samples were falling in the air. As can be seen from Fig. 1c, the NIR interfacing was done perpendicularly to the particles flow without disturbing the flow. The spectra were collected by averaging 4 scans. One spectrum was acquired every second. Ten spectra per batch were kept for the data analysis.

2.2.3.4. Interface for compacts. Using a hydraulic press, a pressure of 50 MPa was applied to 1.6 g of pellets samples. The obtained tablets were then analyzed with the NIR probe while rotating on a sample stage as displayed in Fig. 1d. The rotating speed was set at 10 rpm. The spectra were collected by averaging 16 scans. One spectrum was acquired every 3 s. Ten spectra per batch were kept for the data analysis.

2.2.4. Process interface for the FT-NIR spectrometer

The particle flow velocity device was the same as the slow particle flow velocity device developed for the dispersive NIR spectrometer. However, as can be seen from Fig. 1e and f, the interfacing with the FT-NIR spectrometer was performed via the reflectance sample stage, through the glass bottom of the sample holder. The spectra were collected while averaging 16 scans.

2.2.5. Multivariate data analysis

Principal Component Analysis (PCA), Partial Least Squares (PLS) regression and Multiplicative Signal Correction (MSC) were carried out with PLS Toolbox 5.0 for Matlab version 7.6. The data were mean-centered before performing PCA or PLS. Cross-validation was performed based on contiguous blocks. Using contiguous blocks,

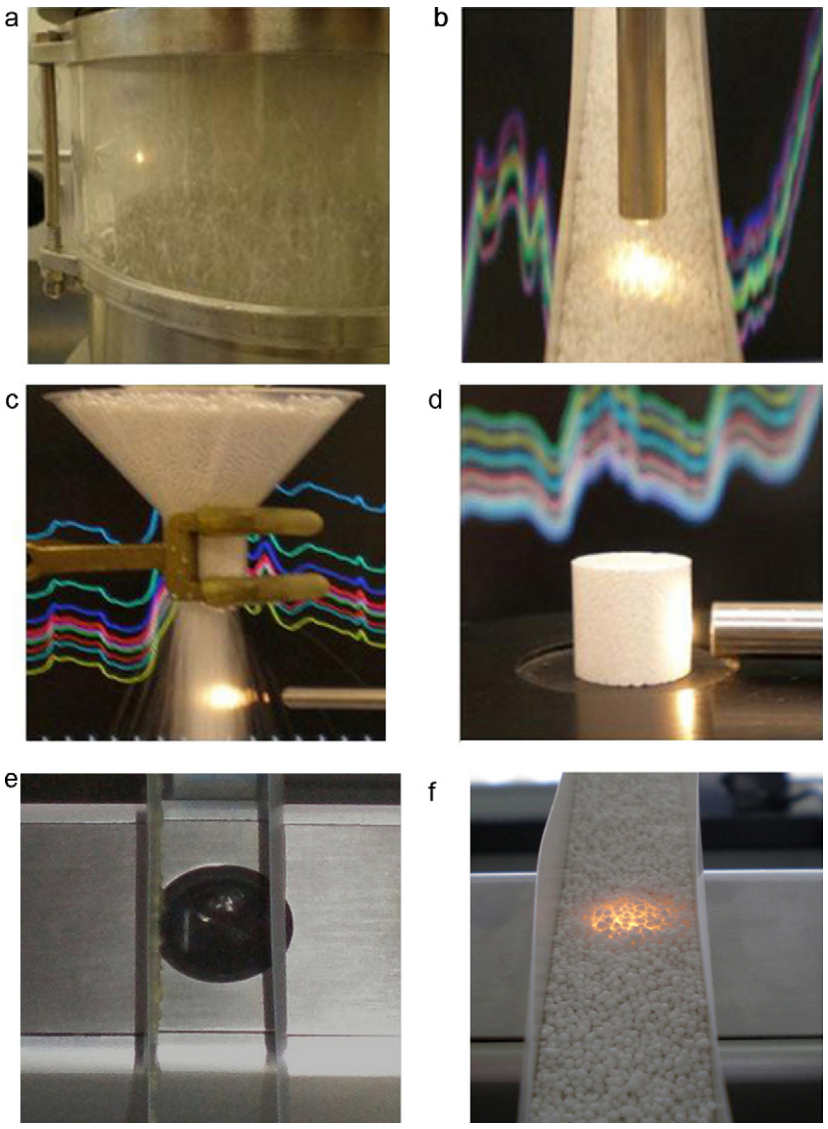

Fig. 1. Process interfaces for the dispersive NIR spectrometer: (a) fluidization interface; (b) slow particle flow velocity device; (c) fast particle flow velocity device and (d) interface for compacts. Process interface for the FT-NIR spectrometer: (e) without particles and (f) with particles.

each test set is determined by selecting contiguous blocks of n/s objects in the data set, starting at object number 1 where n is the total number of objects and s the number of data splits specified in the cross-validation procedure [24].

2.2.6. Near infrared quantitative method: calibration and validation protocols

Sources of variability such as batches, API levels and days were introduced in the calibration and validation sets.

2.2.7. Reference method

A confidential HPLC reference method previously developed and validated by Galéphar Research Center M/F was used to determine the amount of API in the batches of pharmaceutical pellets. Per batch, three HPLC determinations were performed. The average API content was used as the reference value for each batch.

3. Results and discussion

3.1. Qualitative study

The NIR spectra of the 100% API formulation, the API and the main excipient are shown in Fig. 2.

It can be observed that a major part of the pharmaceutical pellets spectrum belongs to the API regarding its amount in the formulation. The main excipient which represents 30% (w/w) of the 100% API formulation seems to influence the spectrum of the final product in the 1415–1555 and in the 2000–2200 nm area.

In the present study, the four process interfaces were developed based on real life pharmaceutical process streams – especially particle streams which can be found in the pellets manufacturing. As fluidization is a critical step in the manufacturing of sustained release formulations, fluidization interfacing can be used to monitor the coating and drying steps. In the production line, feeding lines lead the pharmaceutical product towards the packaging site or inject the raw materials in a blending process for example. The

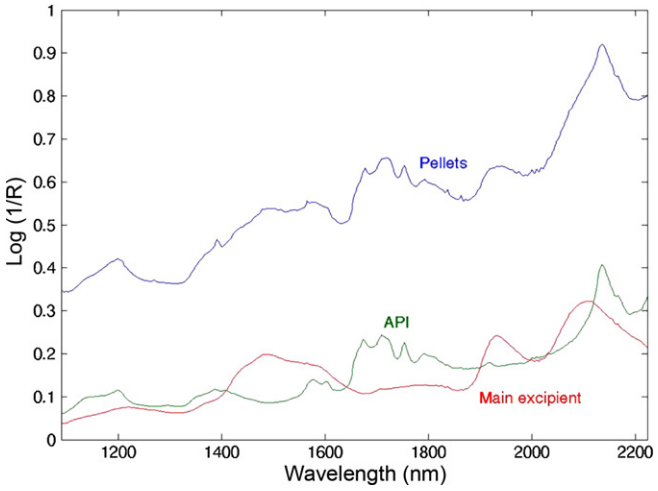

Fig. 2. 100% Active Pharmaceutical Ingredient (API) formulation, API and main excipient off-line NIR spectra (dispersive NIR spectrometer).

slow velocity flow motion device was developed to mimic the typical motion observed in those feeding lines. Moreover, the objective of the high velocity flow motion device was to simulate the capsule filling stage which is also critical to guarantee the final product conformity. Finally, as formulations using compacted pellets are also available on the market, rotating compacted pellets were interfaced, simulating the real-time monitoring of tablets transferred towards the packaging line.

Given the moving particles density and speed, a defined number of scans was chosen for each spectral acquisition interface. The sample density being the lowest for the fluidizing particles, 16 scans were necessary to collect representative NIR spectra of the samples. As the samples density and speed were higher for the low and high velocity devices, 4 scans were selected for those set-ups. Although the compacts density was the highest, 16 scans were selected to collect a general overview of the samples during a low speed rotational movement.

A spectral range containing the API contribution and compatible with the 4 spectral acquisition systems was chosen. As the spectral interferences coming from the polyacrylic glass housing of the fluidbed coater were minimal in the 1340–1640 nm region, this spectral range was selected. Fig. 3 (top) shows the spectra obtained with each set-up after MSC signal pre-processing on the chosen spectral area. Regardless of the acquisition system, it is possible to distinguish the 3 API formulations. The selected spectral range reflects the increase of the API content and the simultaneous relative decrease of the main excipient content. The API and the main excipient have a strong signal and it is the ratio between both ingredients that mainly defines the three different API content formulations. The main spectral feature that differentiates the 4 acquisition interfaces is the noise affecting each type of particle movement. When comparing the high velocity flow device to the slow velocity flow device which both share the same NIR acquisition settings, the slower particle movement resulted in less noise. In the case of the interface for compacts, the dense particulate system had a smoothing effect on the spectra. The spectral noise obtained with the fluidization interface may be caused by the polyacrylic glass housing of the fluid bed coater or a combination between the housing interferences and the interfaced particles movement. Moreover, because of the different speeds, densities, numbers of scans, the effective sampling volume varies between each spectral acquisition interface. All the previous considerations consequently lead to spectral noise variations between the four spectral acquisition interfaces.

Table 2
Quantitative NIR method: variability sources included in the calibration and validation sets.

Variability sources	Amount of variability	
	Calibration set	Validation set
Independent batches	9	9
API levels	3 (80, 100 and 120% API)	3 (80, 100 and 120% API)
Number of batches per API levels	3	3
Series of measurements	3	3

PCA was performed with the spectra collected with each spectral acquisition interface. The data were pre-processed with MSC. Fig. 3 (bottom) shows the PCA plots of the corresponding spectral acquisition interfaces. A clustering given the type of API formulation can be observed for each spectral acquisition interface. Most of the variance is explained by PC1 which discriminates the samples according to their active content. A minor part of the variance is represented by PC2 which may modelize batch-to-batch variations and/or moisture contents. For the fluidization interfacing, PC2 is also affected by the spectral interferences caused by the acrylic glass housing of the fluid bed: it separates the different batch measurements, especially for the 80 and 120% active content levels. The loadings on PC1 and PC2 were checked to confirm the previous observations. As the loadings on PC1 and PC2 look the same for all the spectral acquisition interfaces, Fig. 4 only displays the loadings of the PCA performed with the slow particle flow velocity device. The loadings on PC1 contain information about the API at the 1390 and 1590 nm areas whereas the region between the two previous ones is related to the main excipient. PC1 then discriminates the samples according to their active content as it contains information about the ratio API/main excipient. PCA was performed over a wider spectral range to determine whether PC2 was responding to batch-to-batch moisture or to other batch-to-batch differences. The corresponding loadings highlighted moisture content sensitive spectral regions (1320–1635 and 1850–2030 nm).

The quality of spectral acquisition is suitable for all the different set-ups as they all allowed discriminating the batches of pharmaceutical pellets according to their active content. Therefore, the first part of the study confirmed that qualitative real-time process monitoring with NIR spectroscopy can be achieved in various process streams.

3.2. Quantitative study

As shown in the qualitative study and as demonstrated by Andersson et al. [25], spectral artifacts appear in NIR spectra when conducting measurements on moving solids by a dispersive NIR spectrometer. For quantitative purpose, the slow particle flow velocity was therefore interfaced with a FT-NIR spectrometer. At the sample velocity investigated, artifacts appeared outside the NIR wavelength region. Based on the samples average flow rate and the time necessary for the NIR acquisition (4.5 s), the average effective sampling volume was around 22 g of pharmaceutical pellets. This volume was selected taking into account that in the manufacturing line, it would be interesting to detect small API level changes within kilograms of moving particles. Table 2 displays the variability sources included in the calibration and validation sets. As this study focuses on the feasibility of an in-line NIR method, the expected sample variety that the model will meet in the manufacturing environment was introduced in the calibration set. Nine different pellets batches were manufactured, including 80, 100 and 120% API levels, three batches per API levels. Moreover, three series

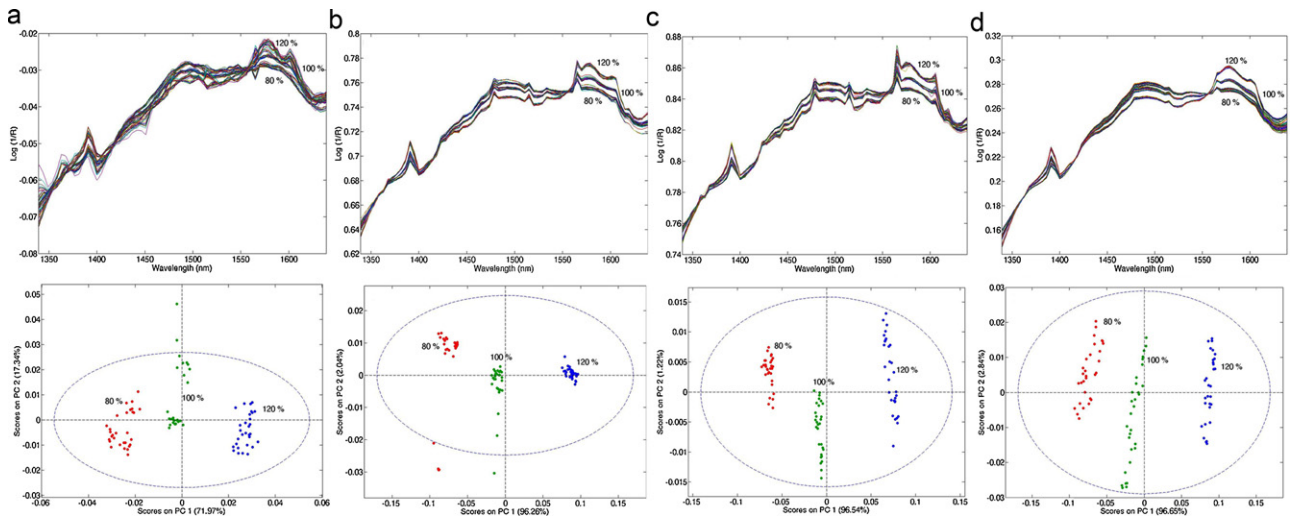

Fig. 3. Top: MSC corrected NIR spectra in the 1340–1640 nm region collected while interfacing (a) the fluidization, (b) the slow particle flow velocity device, (c) the fast particle flow velocity device and (d) the compacts. Bottom: Corresponding PCA score plots.The NIR spectra were pre-processed with MSC.

Table 3
Conventional criteria of the NIR method.

NIR model	Selected parameter
Spectral area (nm)	1320–1040, 2090–2200
Spectral pre-processing	MSC
Number of PLS factors	4
RMSEC (%)	0.7
RMSECV	1.1
RMSEP	0.9

of measurements were integrated in the calibration set, one series of measurements was performed per day. Each sample was analyzed in triplicate by NIR spectroscopy. Per series of measurements, a total number of 27 NIR spectra were recorded. As the calibration is built with three independent series of measurements, the entire calibration set contains a total of 81 NIR spectra. The accuracy and the robustness of the NIR model were further tested with an external validation set containing the same sources of variability as the calibration set. The validation set protocol is the same as the calibration protocol, a total of 81 NIR spectra were recorded.

Table 3 shows the selected parameters for the NIR model. As can be seen from Fig. 5, the selected spectral area is related to the API content of the sample. It was further confirmed by the first loading factor of the PLS model.

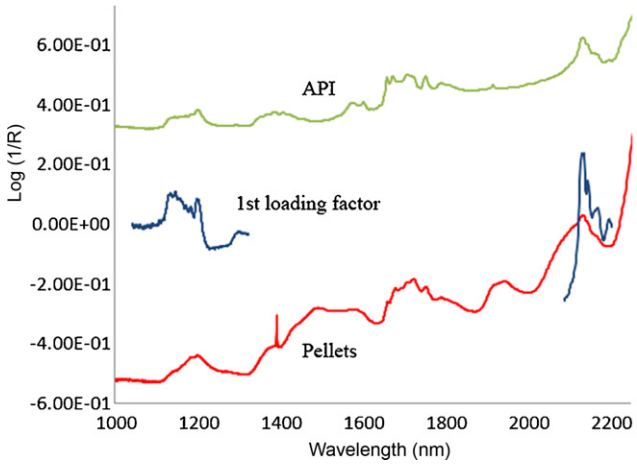

Fig. 5. FT-NIR spectra of the API, the pharmaceutical pellets and the first loading factor.

MSC was selected as signal pre-processing taking into account that this signal pre-processing reduces the effect of scattered light on diffuse reflection NIR spectra.

Contiguous blocks cross-validation was carried out with the calibration set, the number of data splits was 3, defining each calibration series of measurements as a test set.

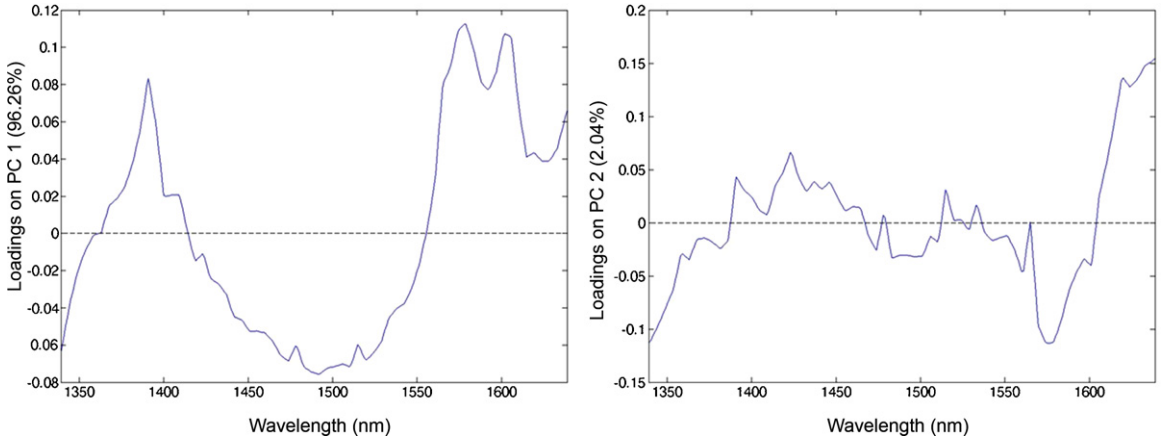

Fig. 4. PCA loadings plot computed with the NIR spectra acquired while interfacing the slow particle flow velocity device.

Table 4
ICH Q2 (R1) validation criteria of the NIR method.

	Concentration level (% API)	Relative bias (%)	
Trueness	77.0	1.1	
	96.7	0.0	
	114.5	0.0	
	Concentration level (%API)	Repeatability (RSD%)	Intermediate precision (RSD%)
Precision	77.0	1.1	1.1
	96.7	0.5	0.6
	114.5	0.7	0.7
	Concentration level (%API)	β-Expectation tolerance limits (%API)	
Accuracy	77.0	[76.0, 79.7]	
	96.7	[95.5, 98.0]	
	114.5	[112.8, 116.3]	
LOQ	Lower LOQ (%API)	Upper LOQ (%API)	
	77.0	114.5	
Linearity of results	Intercept	Slope	R^2
	2.43	0.98	0.997

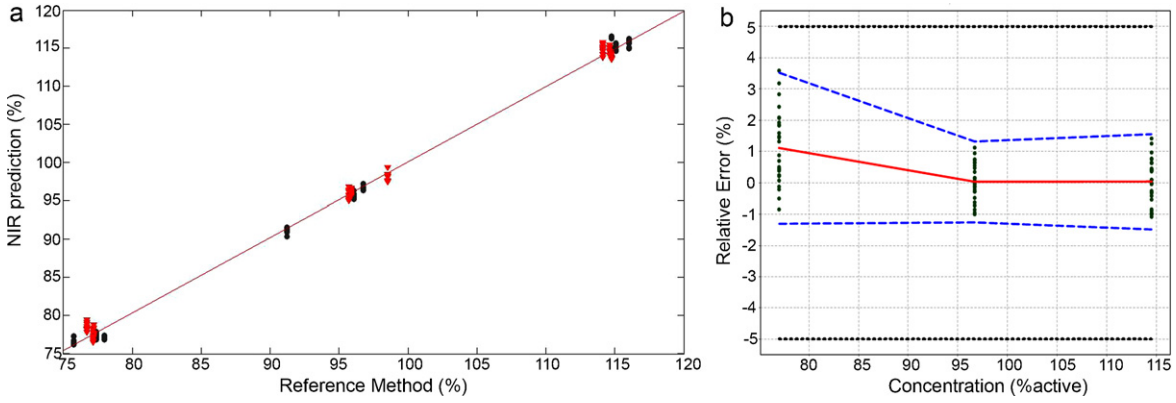

Fig. 6. NIR method: (a) API NIR predictions versus the Reference Method results. The black dots and the red triangles represent the results of the calibration and validation sets respectively; (b) Accuracy profile based on the validation results of the NIR method. The plain line is the relative bias, the dashed lines are the β-expectation tolerance limits (β = 95%) and the dotted lines represent the acceptance limits (±5%).

Four PLS factors were selected for the NIR model as the RMSECV was the lowest from this number of PLS factors (data not shown).

Considering the RMSEC, RMSECV and RMSEP values, the RMSECV and RMSEP are both low and close to the RMSEC indicating the robustness and the global accuracy of the NIR model. Fig. 6a shows the agreement observed between the NIR predictions and the reference method results for both the calibration and external validation sets. However, those criteria do not assess the ability of the NIR method to predict the API content of new samples. Therefore, the model predictive performance was evaluated with accuracy profiles computed on the validation results. This innovative approach uses tolerance intervals as statistical methodology that allows predicting a region of concentration where each future result has a defined probability to fall [21,22,23]. This probability is defined by the analyst. As the focus of the present study is the determination of an API in a pharmaceutical formulation, the acceptance limits were set at ±5% for the validation of the NIR method while the probability to obtain results within the tolerance interval was set at 95%.

The lower and upper limits of quantification (LLOQ and ULOQ) define the range where an analytical method is able to quantify accurately. They are respectively the smallest and highest concentration levels where the β-expectation tolerance intervals are included within the acceptance limits. If the β-expectation tolerance interval never crosses the acceptance limits, then the LLOQ and ULOQ are located at the beginning and at the end of the active content range investigated.

Fig. 6b displays the accuracy profile computed with the external validation set results. It can be seen from this figure that the validation results concentrations are different from the ones displayed in Fig. 6a. Indeed, for the accuracy profile calculation, it was necessary to perform an alignment on the mean concentration obtained

Table 5
NIR method: estimates of measurements uncertainties related to the API content at each concentration level investigated.

Concentration level (%API)	Uncertainty of the bias (%API)	Uncertainty (%API)	Expanded uncertainty (%API)	Relative expanded uncertainty (%API)
77.0	0.2	0.9	1.8	2.3
96.7	0.2	0.6	1.2	1.2
114.5	0.2	0.8	1.7	1.5

by the reference method per API concentration level to compute repeatability and intermediate precision variance estimates. From this figure, it can be observed that the tolerance interval is narrow and fully included within the ±5% acceptance limits. Therefore, each future result has at least 95% probability to fall within the ±5% acceptance limits.

Table 4 shows the ICH Q2(R1) validation criteria of the developed method. As can be seen from the accuracy profile, the bias is 0 for the 100 and 120% API levels whereas it is 1.1% for the 80% API level. The precision of the method was estimated by measuring repeatability and intermediate precision at the three concentration levels investigated. The dispersion of the results observed in the accuracy profile is small for the concentration levels investigated. Consequently, repeatability and intermediate precision are both very satisfactory and never exceed 1.1% as shown in Table 4.

Concerning the linearity of the NIR method, the intercept, and the slope are close to 0 and 1 respectively confirming the absence of proportional and constant systematic error of the model.

The uncertainty characterizes the dispersion of the values that could reasonably be attributed to the measurand [26,27]. Several uncertainty results were generated and are present in Table 5: the uncertainty of bias of the method at each concentration level of the validation standard, the uncertainty which combines the uncertainty of the bias with the uncertainty of the method obtained during the validation step, i.e. the intermediate precision standard deviation, and the expanded uncertainty which equals to the uncertainty multiplied by a coverage factor $k = 2$ representing an interval around the results where the unknown true value can be observed with a confidence level of 95% [28,29]. In addition, the relative expanded uncertainties with the corresponding introduced concentrations are not higher than 2.3%, which means that with a confidence level of 95%, the unknown true value is located at a maximum of ±2.3% around the measured results.

Based on the present feasibility study, accurate quantitative real-time monitoring of a pharmaceutical pellet formulation can be achieved with NIR spectroscopy. The present quantitative method is now being transposed in the real manufacturing environment before the capsule filling stage in order to reduce the post-manufacturing laboratory analysis, paving the way for product real-time release.

4. Conclusions

The present study confirmed that NIR spectroscopy can be interfaced with a great variety of particle streams to provide reliable real-time qualitative data. Regardless of the particle stream investigated, PCA was able to classify the samples according to their active content, indicating the quality of each interfacing.

The developed quantitative NIR method also revealed that accurate quantitative measurements from moving particles could be achieved with NIR spectroscopy. The validation results in terms of RMSEP indicated the good performance of the model. However, such performance indicator is only related to past results while the main issue is to know how accurate the future results will be. Therefore, the accuracy profile based on tolerance intervals was used to generate a complete validation report. It guaranteed that the future results will be included within the acceptance limits with a defined probability chosen by the analyst. Consequently, such NIR method enables the real-time monitoring of products directly from the production line, giving the opportunity to ensure the final product conformity at the end of the manufacturing process itself and thus enabling real-time release (RTR) of the batches.

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