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Tablet potency of Tianeptine in coated tablets by near infrared spectroscopy: Model optimisation, calibration transfer and confidence intervals

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ABSTRACT

A near infrared (NIR) method was developed for determination of tablet potency of active pharmaceutical ingredient (API) in a complex coated tablet matrix. The calibration set contained samples from laboratory and production scale batches. The reference values were obtained by high performance liquid chromatography (HPLC) and partial least squares (PLS) regression was used to establish a model. The model was challenged by calculating tablet potency of two external test sets. Root mean square errors of prediction were respectively equal to 2.0% and 2.7%. To use this model with a second spectrometer from the production field, a calibration transfer method called piecewise direct standardisation (PDS) was used. After the transfer, the root mean square error of prediction of the first test set was 2.4% compared to 4.0% without transferring the spectra. A statistical technique using bootstrap of PLS residuals was used to estimate confidence intervals of tablet potency calculations. This method requires an optimised PLS model, selection of the bootstrap number and determination of the risk. In the case of a chemical analysis, the tablet potency value will be included within the confidence interval calculated by the bootstrap method. An easy to use graphical interface was developed to easily determine if the predictions, surrounded by minimum and maximum values, are within the specifications defined by the regulatory organisation.

1. Introduction

Near infrared spectroscopy has been used for many years in pharmaceutical firms for water content estimations [1], content uniformity controls [2] or counterfeit product investigations [3]. Pharmaceutical firms adopted NIR spectroscopy because of the numerous advantages offered by this technique: high speed, freedom from pollution, no need for reagents or sample preparations, non destructive and capable of providing information about API and other components of a tablet [4–6]. However, although NIR spectra contain a lot of information, this technique requires a good knowledge of chemometric tools for analysis and interpretation of the data. It can be assumed that NIR spectra contain two kinds of information: the first can be defined as a chemical part, which is constituted by tablet components (API and constituents) and the second can be defined as a physical part, which is constituted by uncontrollable factors such as light variation or surface of the tablet [7]. Fourier-transform NIR (FT-NIR) spectroscopy associated with multivariate data analysis were used to build a model for tablet potency of coated tablets from Servier. To ensure uniform potency of low-dose drugs, a content uniformity test based on tablet potency results is required for tablet release to the patients. It ensures the presence of accurate and uniform API content in the dosage unit. The sample preparation for conventional analytical methods of dosage unit determinations typically involves dissolving, extracting, and diluting API into a solution of appropriate concentration that can be accurately detected by chromatography.

PLS regression is one of the best known chemometric tools used to carry out this kind of data analysis. However, using the spectra acquired on a second spectrometer (such as a production spectrometer) with the model previously built on a specific spectrometer is a real problem [8]. A technique called Piecewise Direct Standardization (PDS) performs a spectra transformation by using transfer samples recorded by the two spectrometers [9]. The transfer function established is essential to use the same model with spectra acquired on different spectrometers.

The model quality can be assessed by studying root mean square errors (of calibration or prediction), or by studying scores, loadings and error matrix supplied by the model. Nevertheless, none of these results and parameters were able to estimate the confidence intervals of NIR tablet potency calculated by the model. To assess these intervals, an approach using the bootstrap of PLS residuals was tested.

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This paper describes and explains the steps to develop a whole tablet potency model for the laboratory and the production environment. A technique based on the bootstrap of the PLS residuals was evaluated to estimate confidence intervals of tablet potency estimations.

2. Materials and methods

2.1. General methodology

The aim of the study was the development of an alternative method to HPLC for tablet potency determination in the development and the production environment. The tablet potency estimations have been included in a confidence interval. The general methodology used for tablet potency determination by NIR spectroscopy (model created in the lab or in production) started with the selection of a set of calibration tablets with varied API content spanning the range of analysis. Spectra were collected with a NIR spectrometer, and the true API contents were established afterwards by a reference method (high performance liquid chromatography). The calibration model was developed by correlating NIR spectra with API content using a multivariate regression technique (partial least squares). Once the model was built from the research and development spectra, spectra were acquired with the production spectrometer and a transfer method was used to correct spectra differences. The last step consisted in determining the confidence interval for each tablet potency calculated by the model. The technique used was based on the bootstrap of the PLS residuals.

2.2. Instrument and data acquisition

Spectral dataset were acquired from two FT-NIR ABB Bomen MB160 series instruments (ABB Bomen, Québec, Canada), using the transmittance mode, a tungsten–halogen lamp, a quartz beamsplitter and an indium gallium arsenide detector. Even if these two instruments were supplied by the same company and were qualified properly and comparatively, there were still spectra differences between acquisitions. These variations were due to lamp intensity differences, or because of different distances between sample and detectors, or optical variations between instruments. These two spectrometers were called primary (research and development spectrometer) and secondary (production field spectrometer). A 30 positions tablet sampler accessory was used in order to collect spectra. This accessory ensured that tablets fit well on it. The light passed through the tablet to extract the whole tablet information thanks to the hole on the accessory. Background references were recorded on Spectralon® each time the detector was moved. Spectra were acquired with Gram's version 2.2 (Thermo Fischer Scientific Inc., Waltham, MA). Measurements were carried out at room temperature ($22 \pm 1\ ^{\circ}C$) with a resolution of $16\ cm^{-1}$ over the spectral range 10,000–7800 cm^{-1} and 128 scans were co-added. Data were analysed with Matlab R2008b (The Mathworks Inc., Natick, MA), PLS toolbox version 5.0.3 (Eigenvector Research Inc., Wanetchee, WA), and homemade toolboxes.

2.3. Samples

Stablon® is an anti-depressant commercialised by Les Laboratoires Servier. It is also known as Tianeptine (Sodium salt) and contains 12.5 mg of API in the commercial drugs. The API has only one known solid state form. Major core excipients are mannitol, talc, magnesium stearate and maize starch. The calibration set employed in this study was made up of 45 spectra collected from 45 tablets of Stablon®. A range from 70% to 130% of API in tablets was manufactured by the formulation department (5 spectra for 70%, 80%, 90%, 100%, 110%, 120%, 130% of API tablet potency) and to include the production variability, spectra of 10 tablets from production batches (each production was manufactured with different batches of API and excipients) were added to the calibration set. The NIR light went through the sugar coated drugs to record the whole tablet information. Two external test sets were used to challenge the performance of the model. The first one (called test set 1) was composed of 30 samples from a production batch. The second one (called test set 2) was composed of 26 tablets from a second production batch with different batches of API and excipients and 4 tablets from two batches of 70% and 130% of the 12.5 mg API tablets.

Reference drug content values of the individual tablets were measured off-line using an isocratic reversed-phase high-performance liquid chromatography with ultraviolet (UV) detection. The chromatographic conditions involved using a 4.6 mm × 50 mm column (Chromolith speedROD RP-18e, Merck KgaA, Darmstadt, Germany). The mobile phase was composed of a acetonitrile/phosphate buffer (pH 5.4)/water (37:40:23, v/v/v). An Agilent 1200 Series Rapid Resolution chromatographic system coupled to an Agilent 1200 Series multiple wavelength detector SL was used Agilent Technologies, France). The flow rate was set to 4.5 ml/min with 20 μl sample injections. The detection was centered at 220 nm. The reference method was validated in compliance with the requirements of the International Conference on Harmonisation (ICH) [10]. Table 1 shows the results of the HPLC validation performed with e-noval V2.0 Prod (Arlenda, Liège, Belgium). It fully complies with the ICH Q2(R1) regulatory documents as it integrates the required validation criteria such as accuracy, trueness, precision, limits of quantification, range and linearity.

2.4. Partial least squares

PLS regression [11] is a well-known chemometric technique used in spectroscopy to set up quantitative models. In this study, the model was built using a calibration set of 45 samples. The number of latent variables was optimised by studying root mean square error of calibration (RMSEC) and root mean square error of cross validation (RMSECV).

2.5. Piecewise direct standardization

The piecewise direct standardization [12] method is an improvement on the direct standardization (DS) method [13]. The PDS method transfers spectra from the secondary instrument to the primary instrument (where the calibration model was developed). Spectral intensity at a specific wavelength on the primary spectrometer is related to a spectral window containing the intensities (at the same wavelength and a few neighbouring wavelengths) on the secondary instrument.

A subset of samples (also called transfer calibration samples) was selected by the Kennard–Stone algorithm [14] to extract samples with a large influence within the calibration set.

Once spectra of the subset spectra were collected, each wavenumber response j from primary instrument S_1 were related to a specified window around j measured on the secondary instrument S_2:

$$S_{1,j} = S_{2[j-n,\ldots,j+n]} b_j \quad (1)$$

where S_1 is the response of the primary instrument at wavenumber j, S_2 is the response of the secondary instrument within the wavenumber window n and b_j is the vector of transformation coefficients for the jth wavelengths.

Local multivariate transfer models were established between spectral windows of the secondary instrument and the central point in each corresponding spectral window of the primary instrument.

Table 1
Validation results obtained for the dosage units of the drug substance.

Criteria	Conclusion		
Linearity	The linearity was assessed statistically for five calibration points between 70 and 130% of the theoretical drug substance content per tablet (70, 85, 100, 115, 130%) Recovery: 100.3% Bias: 0.3%		
Precision	The precision of the method was determined for each level of linearity		
	Level (%)	Repetability(RSD%)	Intermediate precision (RSD%)
	70	0.20	0.20
	85	0.15	0.39
	100	0.17	0.48
	115	0.16	0.60
	130	0.32	0.51
Accuracy profile	The method was validated on the range 0.0877–0.1597 mg/ml (corresponding from 70% to 130% of the Tianeptine content) at a risk of 5%		

RSD: relative standard deviation.

PLS or Principal Component Regression can be used in the modelling step. The number of eigenvalues to retain for local models was predetermined based on a tolerance value [15,16].

The values of b_j were assembled to form a diagonal matrix F:

$$F = \mathrm{diag}(b_1^T, \ldots, b_k^T) \quad (2)$$

where k is the number of wavenumber elements, and T is the transposition matrix of b.

Spectra from the secondary instrument can be projected to the primary instrument space:

$$\hat{X}_2 = X_2^T \cdot F \quad (3)$$

where X_2 is the spectra matrix of the secondary instrument.

Two parameters were set before using the PDS method: the window size and the tolerance value which was used in forming the local models. The advantages of PDS are the correction of wavelength shifts and intensity variations. One of the difficulties can be attributed to the bad quality of the spectra (hard frequency noise for example) which can be reduced by using preprocessing method as standard normal variate, multivariate scatter correction or derivatives.

2.6. Estimation of confidence intervals

Aji et al. [17] proposed a bootstrap method to determine confidence intervals of chemical properties of oil. In this paper, this approach was adapted to the pharmaceutical environment. The method was used to evaluate the lower and upper intervals of the tablet potency calculations. The confidence interval estimation for a calculated concentration is a real question in the pharmaceutical field and several approaches have been tested [18,19]. In this paper, the bootstrap [20] was used to resample residuals from PLS regression. This method consists in a random sampling with replacement of PLS residuals.

Once the PLS model was developed and optimised, residuals ε_i were calculated as follows:

$$\varepsilon_i = Y_i - \hat{Y}_i \quad (4)$$

where Y is the concentration established by the reference method and $\hat{Y}$ the concentration calculated by the model for a calibration sample i.

As the resampling method of PLS residuals will underestimate error variability, mean centered residuals were standardized by using the variance.

Standardized residuals are randomly sampled b times with replacement to obtain a matrix $\tilde{\varepsilon}_{h,i}^{*b}$ of standardized bootstrapped residuals.

Bootstrapped residuals $\tilde{\varepsilon}_{h,i}^{*b}$ are added to the PLS tablet potency calculations $\hat{Y}_i$ to obtain new estimated calculations Y_h^{*b}:

$$Y_h^{*b} = \hat{Y}_h + \tilde{\varepsilon}_{h,i}^{*b} \quad (5)$$

Once these new estimated calculations were established, the PLS projection of Y_h^{*b} on the PLS latent variables gave the bootstrap estimators. The entire development of the model and the estimation of intervals assumed that the non-linear iterative partial least squares algorithm [21] was used to set up the model. For this kind of model, a PLS regression model can be written as:

$$Y = t_1 c_1 + \cdots + t_h c_h + y_h \quad (6)$$

where Y is the estimation of tablet potency, t the component and c the regression coefficient associated to the hth latent variable.

The new regression coefficients from the new estimated calculation are determined as follows:

$$C_h^{*b} = (t_h' t_h)^{-1} t_h' Y_h^{*b} \quad (7)$$

where t_h is the score value of the PLS model for the latent variable h and Y_h^{*b} the new estimated calculations from Eq. (5).

The bootstrap estimator $\hat{\beta}_h^{*b}$ of the coefficient matrix is then calculated as:

$$\hat{\beta}_h^{*b} = W_h (P_h' W_h)^{-1} C_h^{*b} \quad (8)$$

where W_h and P_h are respectively the loading weight and loading of the PLS model for a specific latent variable h, and C_h^{*b} the regression coefficients calculated in (7).

The bootstrap estimator allows the calculation of new tablet potency values $\hat{Y}_{h,i}^{*b}$:

$$\hat{Y}_{h,i}^{*b} = X_i \hat{\beta}_h^{*\mathrm{b}} \quad (9)$$

where $\hat{\beta}_h^{*b}$ is the bootstrap estimator calculated in Eq. (8) and X_i the calibration set matrix.

Finally, the bootstrapped estimated error for each observation i is calculated:

$$y_{h,i}^{*b} = Y_{h,i}^{*b} - \hat{Y}_{h,i}^{*b} \quad (10)$$

where $Y_{h,i}^{*b}$ are the new estimated calculations determined in Eq. (5) and $\hat{Y}_{h,i}^{*b}$ the new tablet potency values calculated in Eq. (9).

The quantiles of the distribution of $y_{h,i}^{*b}$ are used to design the confidence interval. To obtain an individual confidence interval for each sample, the percentile-t method was used. For each bootstrap,

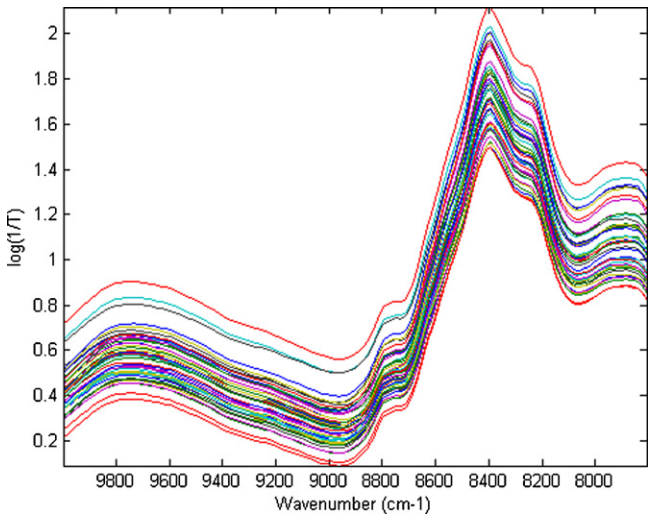

Fig. 1. Calibration set spectra. This figure shows the spectra of the 45 tablets from the calibration set.

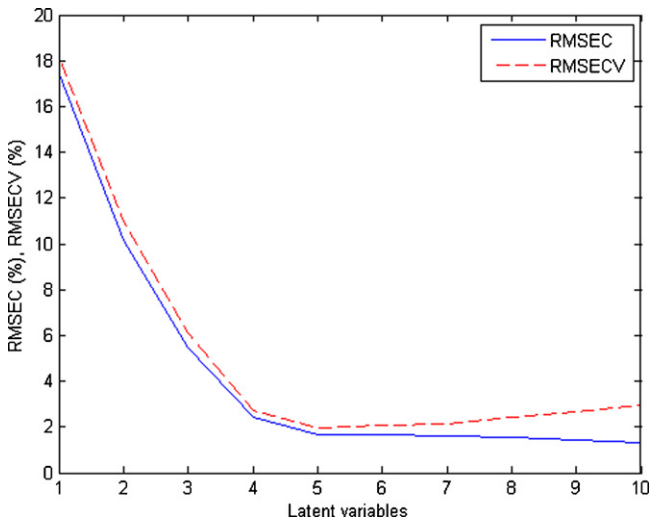

Fig. 2. Root mean square error of calibration (—) and root mean square error of cross validation (– –) calculated from the calibration set to select the number of latent variables. RMSEC and RMSECV are respectively equal to 1.7 and 2.0. This figure represents the evolution of calibration errors (RMSEC and RMSECV) according to the number of latent variables. The optimal number of latent variable was 5.

a statistical coefficient z is calculated as follows:

$$z_{h,i}^{*b} = \frac{y_{h,i}^{*b}}{s(y_{h,i}^{*b})} \tag{11}$$

where $y_{h,i}^{*b}$ is the result of Eq. (10) and s is calculated as follows:

$$s^2(y_{h,i}^{*b}) = \hat{\sigma}_h^{2*b}(1 - T_{h,i}(T_h'T_h)^{-1}T_{h,i}') \tag{12}$$

where T is the scores from the PLS model, h the latent variable, i the sample and σ calculated as follows:

$$\hat{\sigma}_h^{2*b} = \frac{1}{n-h}\left\|Y_h^{*b} - \hat{Y}_h^{*b}\right\|^2 \tag{13}$$

where Y_h^{*b} is the result of Eq. (5), Y_h^{*b} the result of Eq. (9), n is the number of samples and h the number of latent variables.

The quantiles of the z distribution, defined for a specified risk, were used to determine the confidence interval of tablet potency calculations. The confidence intervals are asymmetrical and specific to each sample. The PLS calculations of tablet potency are surrounded by lower and upper limits defined in Eq. (14).

$$[\hat{Y}_h - s(y_{h,i})q_{(1-\alpha)}, \hat{Y}_h - s(y_{h,i})q_{(\alpha)}] \tag{14}$$

where $\hat{Y}_h$ is the tablet potency value calculated by the model, s the square root of Eq. (12) and q the quantile at the specific risk α equal to 1% in this paper.

Estimations of confidence intervals can also be carried out with an external test set. In this case, the bootstrap estimator calculated from the calibration set is used for new tablet potency determination and the new bootstrapped estimated errors are defined as:

$$y_{h,i}^{*b} = \hat{Y}_{t,i} - X_{t,i} \cdot \hat{\beta}_h^{*b} \tag{15}$$

where $\hat{Y}_{t,i}$ is the tablet potency value calculated by the PLS model, $X_{t,i}$ spectra matrix of the external test set and $\hat{\beta}_h^{*b}$ the bootstrap estimator calculated in (8).

3. Results and discussion

3.1. Tablet potency model

Spectra of the 45 calibration samples were acquired with the research and development spectrometer between 10,000 and 7800 cm^{-1} (Fig. 1). Tablet potencies of API were then measured with high performance liquid chromatography to obtain reference values for each tablet. The wavelengths corresponding to the API were identified and selected to avoid the variations induced by different batches of excipients and data were mean centered. Five latent variables were chosen to build the PLS model (Fig. 2) resulting in an RMSEC equal to 1.7% and an RMECV equal to 2.0%. Fig. 3 shows the relation between the percentage of API measured by HPLC and the percentage of API calculated by the model. Root mean square error of calibration (RMSEC) and root mean square error of cross validation (RMSECV) were calculated as:

$$\mathrm{RMSEC} = \sqrt{\frac{\sum_{i=1}^{n}(\hat{y}_i - y_i)^2}{n}} \tag{16}$$

where $\hat{y}_i$ are the values of the predicted variable when all the samples are included in the model formation and n is the number of calibration samples. RMSEC is a measure of how well the model

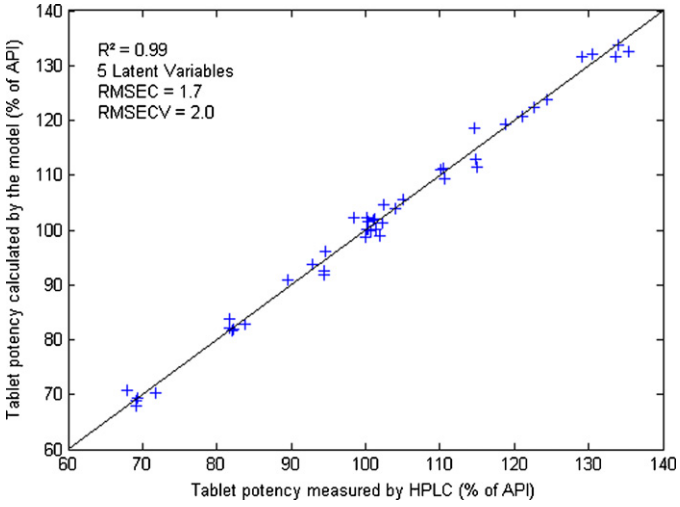

Fig. 3. Tablet potency percentages estimated by the model during the calibration step. This figure shows the relation between the tablet potencies measured by HPLC and the tablet potencies calculated by the model. The model used 5 latent variables, errors of calibration and cross validation were equal to 1.7% and 2.0%, respectively. This low values of errors associated with a R^2 close to 1 meant that the calibration model was optimized.

fits the data.

$$\mathrm{RMSECV}_k = \sqrt{\frac{\mathrm{PRESS}_k}{n}} \tag{17}$$

where k refers to the number of latent variables used in the model, and n is the number of calibration samples. PRESS_k (Predicted Residual Error Sum of Squares) is the sum of squared prediction errors for the model which includes k factors.

Linear regression was performed between the reference values (y) and the calculated model values ($\hat{y}$). To evaluate goodness of fit of the model and to measure how well the regression line approximates the real data points, the coefficient of determination R^2 was calculated as:

$$R^2 = 1 - \frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{\sum_{i=1}^{n}(y_i - \bar{y})^2} \tag{18}$$

where y_i is the measured value by the reference method, $\hat{y}_i$ the calculated value and $\bar{y}$ the mean of the measured value.

The model was evaluated by studying linearity and low error values of the calibration step. Spectra from two external test sets were collected by NIR to calculate the root mean square error of prediction (RMSEP) as:

$$\mathrm{RMSEP} = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{n}} \tag{19}$$

where y_i is the tablet potency determined by the reference method, $\hat{y}_i$ the tablet potency calculated by the model and n the number of observations.

The RMSEP calculated for test set 1 and test set 2 were equal to 2.0% and 2.7%, respectively.

3.2. Model transfer

Due to spectroscopic variability, spectra acquired with the production spectrometer were not usable with the PLS model developed in part 3.1. When using the model with the first external test set acquired on the production spectrometer, the RMSEP was equal to 4.0% which was considered too high for tablet potency determination. Even if the spectrometers were supposed to be identical, spectral variations were observed, which excluded the possibility of using the same model with these two spectrometers. Instead of developing a complete recalibration, the PDS transfer method was applied. To perform this transfer method, spectra (properly selected) from the calibration set were acquired from the two spectrometers. To explore the variability within the calibration set, a principal component analysis was executed on the data.

Fig. 4 shows the score plot corresponding to the first three principal components of the calibration set. The first component explained more than 99% of the variability which was essentially due to the light scattering effect. This effect could have been reduced by using preprocessing such as standard normal variate (SNV) or multivariate scattering correction (MSC) but the results of the model were not better than the results obtained with the mean centered preprocessing. It was decided to chose the preprocessing according to the best model errors and tablet potency calculations. The Kennard and Stone algorithm selected the sample marked with a circle as transfer samples (5 samples which represent 11% of the calibration set) to cover the variability of the data. As expected, transfer sample spectra acquired on the development spectrometer and the production spectrometer were different, mainly in terms of baseline variations (results not shown).

The window size parameter, essential to set up the PDS method, was optimised. Fig. 5 shows the impact of the window size parameter on the error of prediction of test set 1 (composed of 30 samples from a production batch). The effect of the window size was not obvious compared to the effect of the number of latent variables. The PDS window was not a critical choice as there were no or fewer wavelength variations between the two instruments. A window size of 11 was selected because it gave the lowest RMSEP with 5 latent variables.

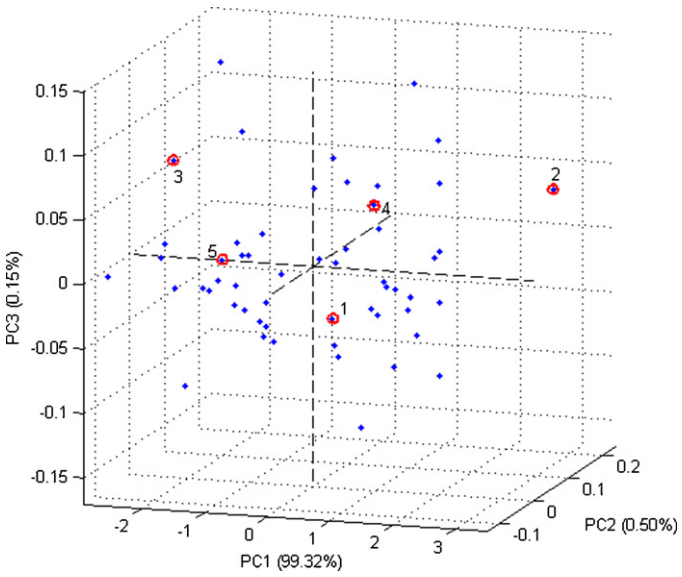

Fig. 4. Transfer samples numbered according to the order of selection by the Kennard et Stone algorithm (PC1, PC2 and PC3 explain more than 99.9% of the total variance). This figure represents the results of a PCA analysis on the calibration set. This 3D representation shows the dispersion of the 45 samples within the three first components of the PCA. Samples surrounded in red were used as transfer samples. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Before the calibration transfer, the tablet potency estimations of the external test set were not satisfactory with a RMSEP equal to 4.0%. By using the transfer function, differences between spectra acquired on development and production apparatus were decreased, and the tablet potencies were predicted with a RMSEP

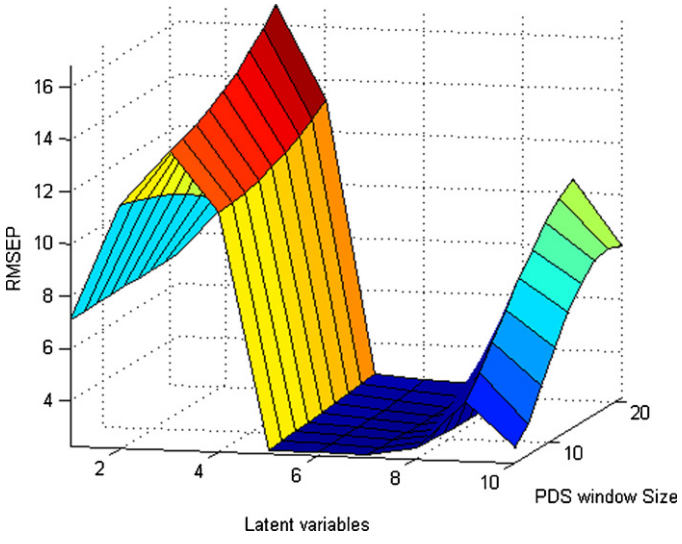

Fig. 5. RMSEP variation of the test set 1 according to the latent variable number and to the window size of the PDS algorithm. The evolution of the error of prediction depends on the number of latent variable selected and the window size of the PDS algorithm. This figure shows that the most important criteria was the number of latent variables. The window size of the PDS algorithm was not a critical parameter. The model was built with 5 latent variables and the PDS algorithm used a window size equal to 11.

Table 2
Influence of bootstrap number on the results variability.

Number of bootstrap	5	100	300	500	700	900	1000	2000
Standard deviation	2.17	1.61	0.85	0.72	0.52	0.45	0.37	0.42

equal to 2.4%. This calibration transfer technique was very useful in developing a model which can be used on two NIR spectrometer.

3.3. Estimation of confidence intervals

The bootstrap of PLS residuals technique was used to calculate the confidence interval of the tablet potency values calculated by the PLS model. The confidence interval was defined so that a HPLC measurement of tablet potency must be within the interval if a chemical analysis is performed. The first step of this approach was to calculate the PLS residuals corresponding to the difference between PLS calculation and HPLC measurement for each sample. Note that the PLS model must be fully optimised during the previous steps in order to obtain quality results.

The number of bootstrap was optimised to obtain the most reproducible results. This bootstrap number was chosen by studying the variability of repeated calculations. By increasing the number of bootstraps, the confidence intervals were decreased. Table 2 shows the results of the standard deviation for 10 repeated calculations. A number of bootstrap equal to 1000 was chosen for the study.

PLS residuals were bootstrapped and added to the PLS tablet potency calculations of the model to obtain new estimated calculations. Regression coefficients, bootstrap estimators and the bootstrap estimated error were calculated using this new set of calculations. The distribution of z, calculated from Eq. (11) made it possible to determine two quantiles with a risk of 1%.

These quantiles were the basics for confidence interval determination. For each sample, and then for each tablet potency calculation, two limits were established. The tablet potency obtained with the PLS model was surrounded by a upper and a lower limits defined by the interval (14).

An easy graphical interface was developed under the Matlab environment in order to facilitate the use of this algorithm and to compile all the steps presented in this paper. This interface includes the transfer of spectra (if spectra were acquired on the production spectrometer), tablet potency calculations and confidence interval estimations for each tablet.

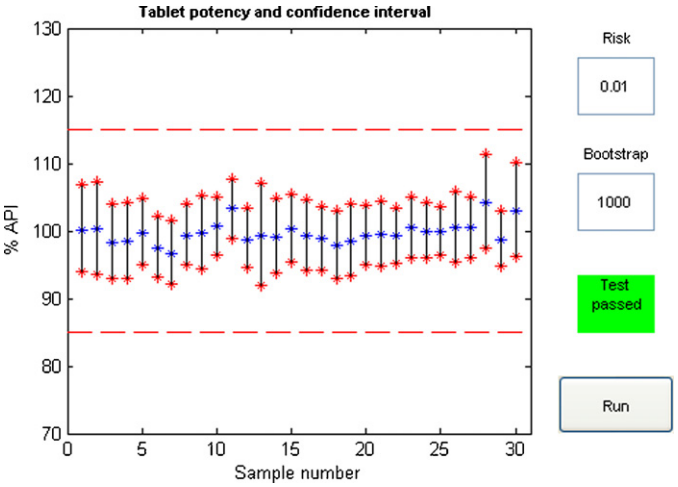

Fig. 6. Tablet potency and confidence interval of the external test set 1. This figure shows the results provided by the graphical interface. It gave the tablet potencies of each sample analysed by NIR. These tablet potencies were surrounded by a minimum and a maximum which defined a confidence interval for a specific risk. A green test passed message is displayed because all the tablet potencies and confidence intervals are within the content uniformity limits. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 6 shows the confidence interval calculation of test set 1. The graphical results show the tablet potency values surrounded by the upper and lower limits and the table at the bottom provides the numerical values of the predictions and limits. A green test passed message is displayed because all the predictions are in the first level

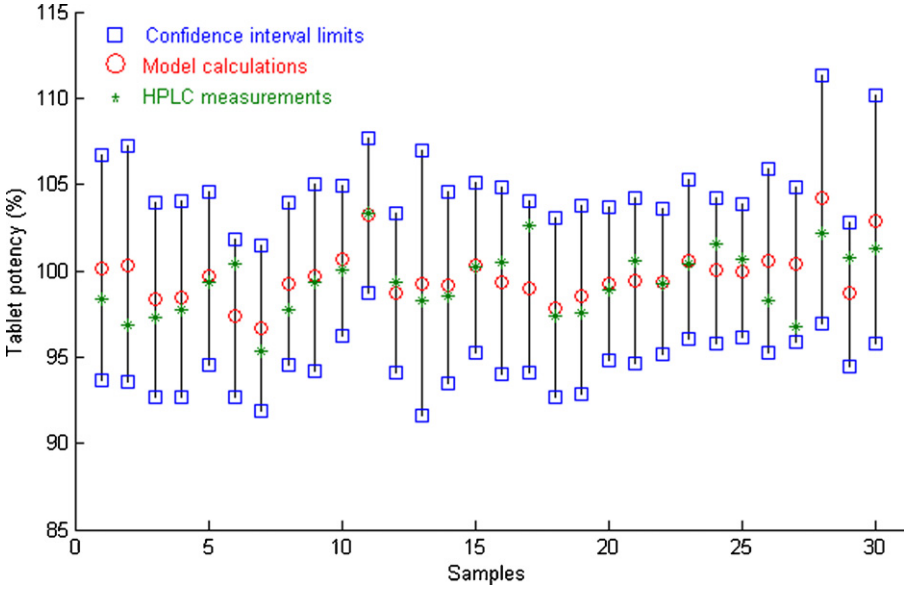

Fig. 7. Model calculations and HPLC measurements of tablet potency for test set 1. This figure represents the tablet potencies (red circles) surrounded by the confidence interval (blue squares) of each sample. The green cross represents the HPLC measurements of each sample. All the HPLC measurements were included in the confidence interval. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

of the European Pharmacopoeia specifications [22] (lower than 85% or upper than 115%).

To evaluate the whole model, HPLC measurements were performed on samples from test set 1 constituted by 30 samples from a production batch. As shown in Fig. 7, all the HPLC measurements (represented by the green cross in Fig. 7) were included in the confidence interval (represented by the blue squares in Fig. 7) defined by the bootstrap of PLS residual method.

4. Conclusions

Quantifying the content of API in a tablet is a real challenge in the pharmaceutical field as it is important to ensure that the correct quantity of substance is delivered to the patient. In this study, a PLS model for tablet potency determination was developed by using NIR spectroscopy. A calibration transfer method was carried out to improve the poor predictions obtained when the model was used with the spectra acquired at the production site. This method required the acquisition of transfer samples with the spectrometers from the different sites. The last part of this development, which consisted in the determination of a confidence interval, was based on residual bootstrapped calculations, and provided an answer on the error of the tablet potency estimation. A graphical interface, including all the steps of the development, was developed making it possible for production operators to use this approach.

This development ensures that the tablet potency value obtained by a classical chemical analysis is close to the model calculation and within the confidence interval determined by the bootstrap technique.

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