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Influence of physical factors on the accuracy of calibration models for NIR spectroscopy

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ABSTRACT

The quality of pharmaceutical drugs is strongly influenced by a number of physical and chemical factors that require careful control during the production process in order to ensure that the end-product will meet the specifications. Near infrared spectroscopy has proved effective for monitoring changes in such factors and is currently the most widely used technique for controlling drug manufacturing processes. In this work, the authors determined an active pharmaceutical ingredient (API) throughout its production process. The influence of particle size, galenic form, compaction pressure and coating thickness on NIR spectra was evaluated with a view to developing effective methodologies for constructing simple, accurate calibration methods affording API quantization at different stages of a drug production process. All calibration models were constructed from data for laboratory samples alone and NIR calibration models for determining the API determination by using product weights as reference values. The proposed models were validated by application to samples obtained at three stages of a drug manufacturing process and comparison of the predicted values with HPLC reference values. The RSEP values thus obtained never exceeded 1.5%.

1. Introduction

Near infrared (NIR) spectroscopy has been successfully used to determine the chemical composition and various physical properties of a number of pharmaceutical samples [1–5]. Multivariate calibration methods constitute essential tools for extracting quantitative information from NIR spectra. The use of calibration models in routine determinations is limited to the prediction of samples of nature and composition similar to those used in their construction. In addition, NIR models require using reliable reference methods [6] to both construct models and check their results.

Can the quality of a product at each step of its production process be assured by using a multivariate model constructed from laboratory samples alone? Properly answering this question requires a thorough knowledge of the production process, and also of the performance and constraints of the analytical methodology to be used to construct calibration models, which will obviously depend on those of the analytical measuring instrument.

Pharmaceuticals are subject to stringent national and international regulations as regards production and end-product characteristics compliance with which must be confirmed by using appropriate control analyses. In fact, a pharmaceutical end-product must not be released until it has been checked to meet each and every specification. This is a complex, time-consuming process that delays parametric release and can adversely affect productivity at a drug production plant. Also, a product failing to meet some quality specification must be rejected or reprocessed, which obviously has adverse economic implications.

Most drugs are available in solid form, whether as single doses, capsules or tablets. Their production process includes mixing of the raw materials and, frequently, granulation. These steps are used to homogenize the active principle and excipients in order to ensure dosing and mass uniformity in the end-product. Obtaining an appropriate particle size upon granulation increases the fluidity of the solid and avoids disaggregation losses during transport [6] – and hence inhomogeneity.

Tablet production processes involve a tableting step and, frequently, a coating step as well. Prior granulation of the mixture of ingredients facilitates compression. Tablets should be compacted at a high enough pressure to avoid subsequent breaking, but not so high as to prevent disaggregation when it enters the body. Tablets are most often cylindrical or oblong in shape and have rounded edges to facilitate swallowing.

The last step in the tablet production process involves coating with a thin film of lacquer usually consisting of sugars or polymers. The film is intended to protect tablets from aggressive environmental agents, masking some unpleasant odour or flavour, or making them resistant to gastric juices in order to facilitate controlled release of the active pharmaceutical ingredient (API).

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Some tablet production variables including grain size [1,7], compaction pressure [2], galenic form and coating [8,9] influence the properties of the end-product and thus require careful control. These variables have some effect on the NIR spectrum for the product and should therefore be considered in constructing a multivariate calibration model to determine its API content. This allows NIR spectroscopy to be used to monitor changes in these physical variables during the production process and quantify the API in each critical step.

Recent studies [10,11] have shown that NIR technology continues to effectively meet a number pharmaceutical challenges and be useful for determining a number of variables of pharmaceutical processes. Since the primary aim of this work was to develop effective calibration models for controlling the API in different steps of drug manufacturing processes with a view to facilitating their control from beginning to end, we examined various ways of developing simple, robust models for this purpose.

We assessed the potential of NIR spectroscopy for monitoring the API concentration during a drug production process and developed simple calibration models based on laboratory samples alone for quantifying the API in each step of the process. Since the physical factors influencing NIR spectra differ from stage to stage, their effects were evaluated on an individual basis with a view to their inclusion in the calibration set if judged significant. In this way, one can efficiently monitor a production process by using a simple calibration model that can be expanded as required by successive incorporation of additional sources of variability.

2. Experimental

2.1. Production samples

The pharmaceutical formulation studied contained a high proportion of API (63.5% ibuprofen) and the following four excipients: maize starch, avicel PH 102, aerosil and magnesium stearate. The major ingredients (ibuprofen and starch) were weighed in appropriate amounts and placed in the blender together with an appropriate amount of water before stirring to a homogeneous mixture that was then dried under a stream of hot air. The resulting granulate was sieved to obtain grains less than 2 mm in size, supplied with the other ingredients, all in dry form, mixed and re-sieved to obtain grains smaller than 1.5 mm. These granules were used to prepare two different types of cores in two galenic forms containing 400 and 600 mg of API, respectively (see Fig. 2). The cores were spray-coated with a lacquer dispersion to make the final, coated tablets, the most salient physical properties of which are shown in Table 1.

The lacquer was a dispersion of sepifilm, sepisperse and polyethylene glycol in water.

All samples were kindly supplied by Kern Pharma, S.L. (Terrassa, Spain).

2.2. Laboratory samples

2.2.1. Powder samples (set A)

Laboratory samples were prepared by mixing appropriate amounts of API and various placebos in order to span a wide enough concentration range for calibration. A total of 13 placebo mixtures at concentrations ±5% around the nominal content for each compound and exhibiting the lowest possible collinearity between concentration values were prepared by using a D-optimal experimental design.

Mixtures were prepared by weighing on an analytical balance and homogenizing in a solid blender.

A total of 34 API–placebo mixtures were prepared that spanned an ibuprofen concentration range of 80–120% the nominal value (*viz*. the drug concentration in production tablets).

Table 1
Characteristics of the production tablets.

	Type 1	Type 2
Shape	Cylindrical	Oblong
Weight by tablet (mg)	630	960
Weight of API (mg)	400	600
Pressure of compression (MPa)	120	155

2.2.2. Cores samples (set B)

Powder samples were compacted at pressures from 80 to 190 MPa to obtain laboratory cores. Two cores were obtained for each composition that were compacted at a variable, randomly selected pressure.

2.2.3. Cores samples (set C)

A set consisting of samples of production granulate was compacted at pressures from 35 to 260 MPa in order to determine the optimum compaction range. As with set B, the compaction pressure applied to each sample was randomly selected.

2.3. Spectrum for the lacquer coating

The average spectrum for the tablet coating was obtained by recording the individual spectra for 50 coated tablets from 5 production batches (10 tablets per batch) for each dose (400 and 600 mg). Then, each tablet was filed on one side and its NIR spectrum re-recorded. Subtracting the spectrum for the coated side (s_{coated}) from that for the filed side (s_{filed}) provided the difference spectrum (d_i) for each tablet. The average difference spectrum $\bar{d}_i$ for each of 5 batches of 400-mg tablets and 600-mg tablets was then calculated and used to modify the core spectra:

$$d_i = s_{\text{coated}} - s_{\text{filed}}$$

$$\bar{d}_i = \frac{\sum_{i=1}^{n} d_i}{n}$$

$$s'_{\text{coated}} = s_{\text{core}} + \bar{d}_i$$

where n is the number of difference spectra used, s'_{coated} the modified spectrum for the coated tablets and s_{core} the spectrum for a core.

The set of spectra thus obtained was taken to be the tablet sample set (D).

2.4. Hardware and software

Laboratory samples were homogenized in a Turbula T2C WAB shaker mixer and compacted in a cylindrical dye with a cross-sectional area of 132.7 mm^2 on a Perkin-Elmer 15.011 press. Sample spectra were recorded on a Foss NIRSystems 6500 spectrophotometer equipped with a Rapid Content Analyser (RCA) module. The instrument was governed via the Vision v. 2.51 software package, also from NIRSystems. The D-optimal design was developed by using the software Modde v. 6.0 from Umetrics. Dendrograms were obtained by cluster analysis with the software SPSS v. 15.0 for Windows. PCA and PLS models were constructed by using The Unscrambler v. 9.8 from Camo Process.

2.5. Recording of NIR spectra

The NIR spectra for powder and granulate samples were recorded in glass cells that were placed on the window of the RCA module. Each sample was analysed in triplicate, with turnover between recordings, in order to obtain an average spectrum.

The spectra for the tablets, both round and oblong, were recorded by direct placement on the instrument window and irradiation of the smooth, unmarked side. Each sample was analysed in duplicate and turned a right angle between recordings in order to obtain an average spectrum.

2.6. Reference values

The reference values for the laboratory-made samples were obtained by direct weighing of each mixture.

Production samples were analysed by HPLC. An average API value for each batch was obtained by analysing 20 milled tablets. To this end, an amount of mass equivalent to one tablet was supplied with 40 ml of mobile phase (a 60:40, v/v acetonitrile/water mixture buffered at pH 3), stirred to complete dissolution—which took about 30 min—and made to 50 ml with mobile phase. An aliquot of the resulting solution was centrifuged for 5 min and the supernatant injected into the chromatograph. Ibuprofen was quantified by interpolating the chromatographic measurement into a calibration curve previously constructed by using isobutylacetophenone as internal standard. The result was taken to be the batch content.

The same methodology was used to analyse granulate except that the amount of sample used was equivalent to one tablet.

All concentrations are given as percentages of the nominal value for the studied preparation, which was taken to be 100%.

Although the HPLC values were only compared with the NIR values, they were used to construct the models.

2.7. Construction of calibration models

Similarity between laboratory and production samples in each step of the production process was assessed by principal component analysis and/or cluster analysis (dendrograms).

PLS multivariate regression models were constructed at concentrations over the range 80.0–20.0% of the nominal value. One PLS model was constructed for each type of sample representing one step of process (*viz.* granulate, cores and tablets). The results were acquired over various wavelength ranges and subjected to different spectral treatments. The joint use of the whole wavelength range (1100–2500 nm) and the standard normal variate (SNV) treatment was found to provide the best results.

PLS calibration models were constructed by cross-validation, using the leave-one-out method. The optimum number of factors was selected in terms of the relative standard deviation (RSE):

$$\mathrm{RSE} = \sqrt{\frac{\sum_{i=1}^{m}(Y_i^{NIR} - Y_i^{REF})^2}{\sum_{i=1}^{m} Y_i^{REF2}}} \times 100$$

Thus, the best model (*viz.* the model with the highest predictive ability) was taken to be that leading to the lowest RSE for the prediction set of laboratory samples. Thereafter, the predictive ability of the model for granulate samples was assessed with 12 production batches; that for cores with 5 batches of each dose; and that

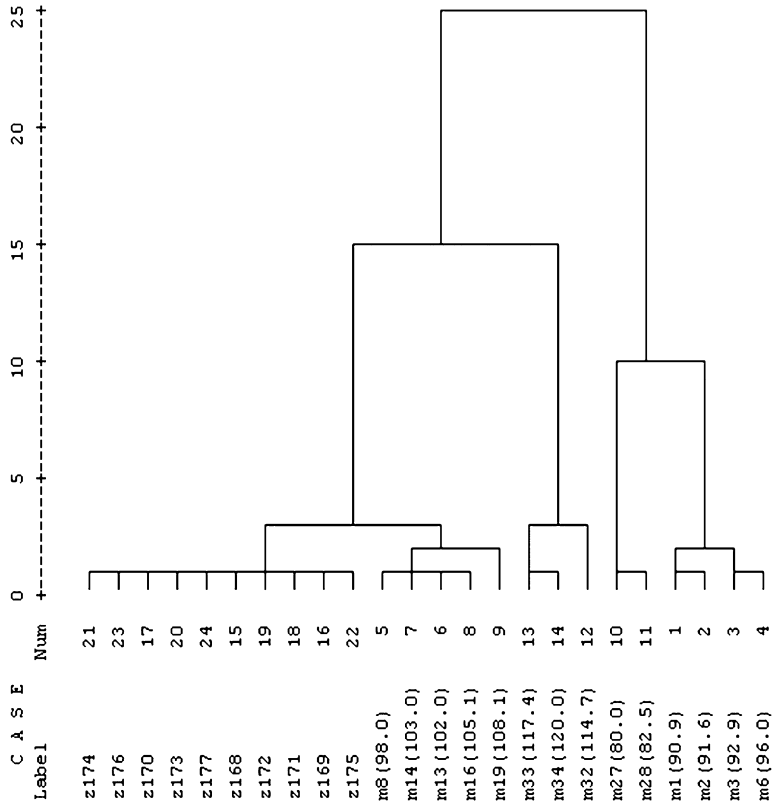

Fig. 1. Dendrogram for laboratory mixtures (m1–m34) and production granulates (z169–z177) constructed from the first two factors of a PCA (97.4% of explained variance) based on spectral data obtained over the wavelength range 1100–2500 nm and corrected with SNV. The API contents of the laboratory samples are given as percentages in brackets.

Table 2
Figures of merit for calibration models.

	Powder model			Cores model				Tablet model			
	Cal lab	Pred lab	Pred prod	Cal lab	Pred lab	Pred 400	Pred 600	Cal lab	Pred lab	Pred 400	Pred 600
Pretreatment	SNV			SNV				SNV			
Range (nm)	1100–2500			1100–2500				1100–2500			
No. of PC	2			4				5			
Variance *Y* (%)	99.2			99.7				99.7			
No. of samples	21	7	12	26	10	5[a]	5[a]	42	20	10[a]	18[a]
RSEC/P	0.88	0.69	1.75	0.69	1.23	1.47	1.12	0.68	1.18	1.34	1.23
Bias	1.1×10^{-6}	−0.16	1.33	2.3×10^{-6}	−0.58	−1.15	0.60	1.1×10^{-6}	−0.18	−0.66	−0.25

[a] Number of analysed batches. Each batch is an average of 10 tablets.

for tablets with 10 batches of the 400 mg formulation and 18 of the 600 mg formulation.

The average value for each production batch was obtained from the spectra for 10 tablets.

3. Results and discussion

The primary aim of this work was to construct models from laboratory samples alone (*i.e.* by using no reference method) with a view to predicting samples from various steps of the production process.

One of the major sources of variability to be considered in constructing a calibration set is the target concentration range. The ICH guidelines [12] recommend that the API concentration range spanned by models for assessing a pharmaceutical end-product be ±20% around the nominal value. This was the specific target adopted in our study. Also, placebos were prepared in such a way as to span a range of ±5% around the nominal value for each excipient in order to account for potential differences in their concentrations and minimize correlation between them with a view to ensuring robustness in the ensuing model.

3.1. Influence of particle size on NIR spectra. API determination in granulates

Success in developing an accurate calibration model relies heavily on the availability of a large enough set of calibration samples with characteristics similar to those to be predicted. The most salient difference between laboratory-made and production samples is that particle size; in fact, laboratory samples (set A) are powder mixtures whereas production samples are frequently granulated prior to processing. Properly processing spectral data can help reduce differences. The SNV treatment is known to be especially effective in reducing spectral differences due to particle size differences [13], which led us to adopt it for our spectral data.

In order to identify potential differences between spectra, the results for laboratory-made powder samples and granulate production samples were subjected to cluster analysis following application of the SNV treatment. The dendrogram was constructed by using average linkage in conjunction with the square of the Euclidean distance in the principal component space as similarity parameter. It was obtained from the first two PCs for whole spectra (1100–2500 nm) subjected to SNV, which jointly accounted for 97.4% of the total variance (see Fig. 1). The dendrogram revealed a high spectral similarity between production and laboratory samples (particularly in those with API contents near the nominal value); therefore, a model constructed from laboratory samples alone can be expected to provide accurate predictions.

Powder laboratory samples were split into two sets that were used to construct the PLS calibration model and assess its predictive ability, respectively. The two in combination spanned a concentration range ±20% around the nominal value.

Table 2 shows the figures of merit of the model, which is applicable to both powder and granulate samples. As can be seen from the RSEP values, the predictions differed very little from the values for the powder laboratory samples. Therefore, an SNV treatment suffices to suppress differences between powder (laboratory-made) samples and production granulate samples, and the NIR model is useful for both.

3.2. Influence of galenic form and compaction pressure on NIR spectra. API determination in cores

During the production process, the granulate is compacted to obtain two types of cores of different shape (Fig. 2) and weight but identical in composition. Predicting the API content in cores with the model for granulates led to systematic errors in the determination. In fact, the contents of the 400 and 600 mg formulations were both overestimated (by 1.1% and 5.0%, respectively). The latter error was large enough to justify constructing an alternative, more accurate model.

The batch cores differed from the laboratory-made cores (set B) in that the former were smaller and flat-surfaced, and also in their compaction pressure. Both types of production cores had a slightly curved surface that might affect diffuse reflectance measurements. Also, the laboratory cores (set B) were flat on both sides; because they were used as samples to construct the calibration model, checking that the differences in surface characteristics between the two types of cores would have no effect on measurements was an essential pre-requisite. To this end, 10 cores (uncoated tablets) containing 400 mg of API and another 10 containing 600 mg were filed as needed to leave the contact surface with the quartz window fully

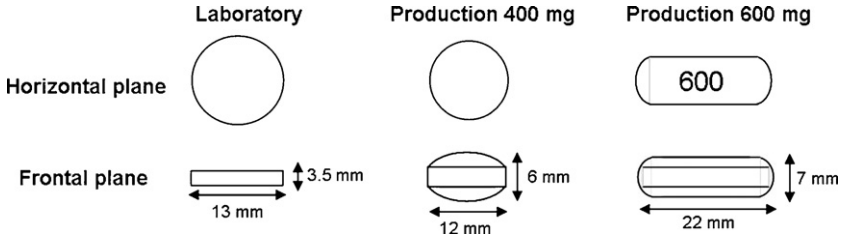

Fig. 2. Shape and dimensions of the three types of cores and tablets.

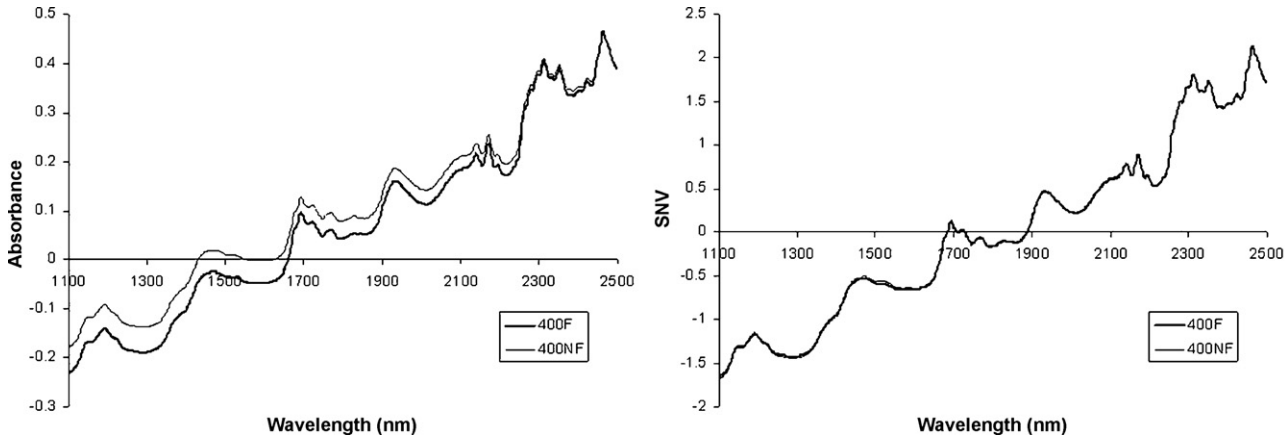

Fig. 3. Comparison of the absorbance and SNV-corrected spectra for a filed 400 mg core (400F) and an unfiled core with the same API content (400NF).

flat in order to make them as similar to the laboratory tablets as possible. NIR spectra for the cores were recorded before and after filing. Fig. 3 shows the absorbance and SNV-corrected spectra for a core prior to (400NF) and after filing (400F). As can be seen, the absorbance spectrum exhibited a shift that was efficiently corrected by the SNV treatment.

A dendrogram for laboratory cores, and filed and unfiled production cores, was obtained by using average linkage and the Euclidean distance squared in conjunction with the first two factors of a principal component analysis, which jointly accounted for 96.0% of the variance. Fig. 4 shows the dendrogram obtained by using the spectra for filed 400 mg cores (400F), unfiled 400 mg cores (400NF), and the ten 600 mg cores before (600NF) and after filing (600F). As can be seen, the production cores clustered together with the laboratory cores containing an API concentration near its nominal value. Both filed and unfiled cores lay close to the laboratory cores containing near 100% of the nominal concentration, which indicates that variability due to core curvature was uninfluential.

The tablet compression pressure is one other factor influencing NIR spectra: the higher it is, the greater is the shift in the NIR spectrum. One way of correcting this effect is by expanding a calibration set consisting of powder samples with production cores in order to introduce variability due to the compaction pressure and improve predictive ability—all at the expense of using a greater number of PLS components and making the model more complex as a result [14]. Because one of our aims was to avoid the need to use production samples for calibration, this entailed using a calibration set consisting of cores compacted at pressures similar to those for the production tablets. This required the prior determination of the compaction pressure for the production samples and preparing laboratory cores compacted at pressures over an appropriate range. To this end, the production granulate was used to prepare a series of cores (set C) that were compacted at 35–260 MPa. Fig. 5 shows the results of a PCA of the spectra for set C samples and the average spectra for several batches of 400 and 600 mg cores; spectra were recorded throughout the wavelength range and subjected to SNV treatment. The first PC contained the spectral variability due to the compaction pressure; based on the results, the 400 mg cores were pressed at a lower pressure than the 600 mg cores. All production cores were pressed at 80–190 MPa, which was thus the selected

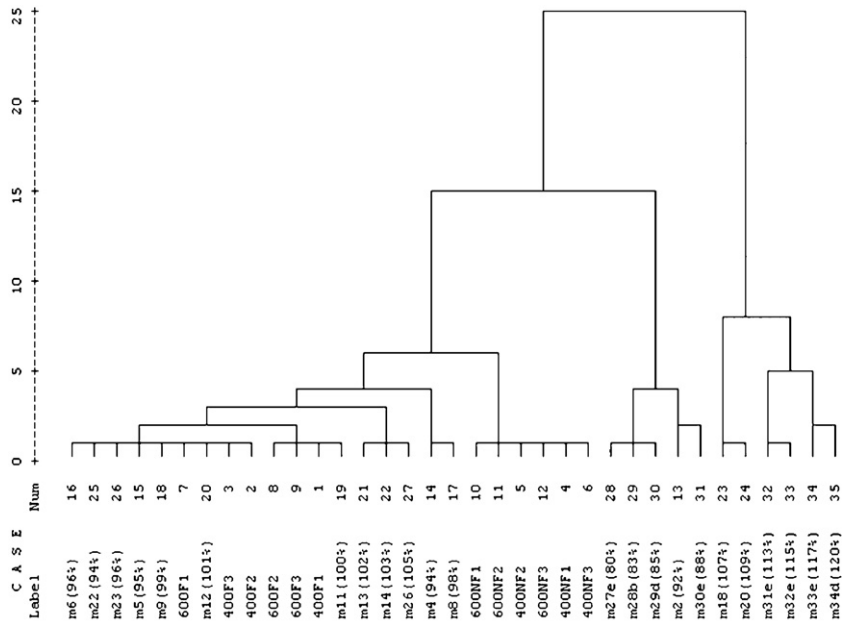

Fig. 4. Dendrogram for laboratory cores (m1–m34) and filed (400F and 600F) and unfiled production cores (400NF and 600NF) constructed from the first two factors of a PCA (96.0% of explained variance) based on spectral data obtained over the wavelength range 1100–2500 nm and corrected with SNV. The API contents of the laboratory samples are given in brackets.

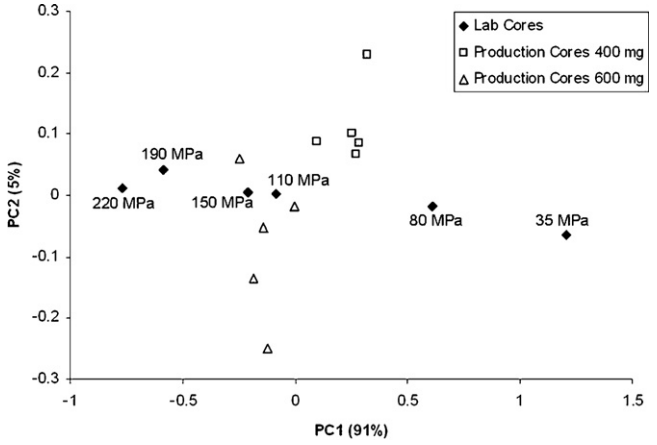

Fig. 5. Scores plot of a PCA based on spectral data acquired over the wavelength range 1100–2500 nm and corrected with SNV for production cores and laboratory cores pressed at variable compaction pressures (35–260 MPa).

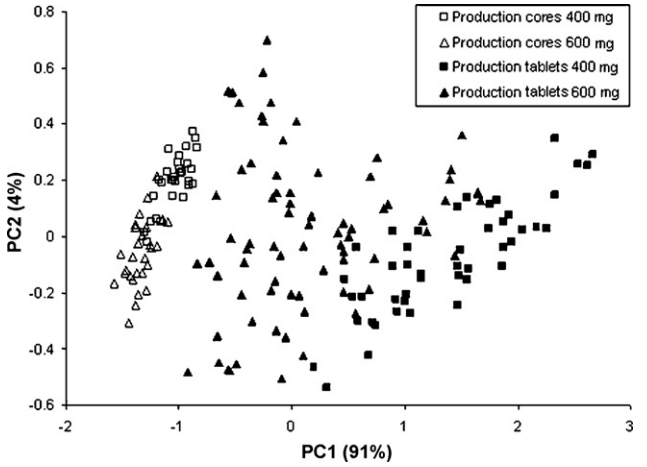

Fig. 6. Scores plot of a PCA based on spectral data acquired over the wavelength range 1100–2500 nm and corrected with SNV for production cores and coated tablets.

range for pressing the laboratory cores and constructing the API quantization model. Although differences in the second PC, which accounted for 5% of the variance, were not examined in depth, they can be ascribed to physical differences (*e.g.* geometric shape) or reflectance changes by effect of core geometry.

The calibration model for the production cores was constructed from the spectra for set B cores alone since, as shown before, tablet surface curvature had no substantial effect on the spectral results. Based on the data of Fig. 5, the calibration set was built from samples with API contents 80–120% the nominal value and pressed at 80–190 MPa.

Table 2 shows the figures of merit of the model used to quantify the cores. The RSEP values shown correspond to 5 batches of 400 mg cores and 5 of 600 mg cores; the RSEP values for 400 mg and 600 mg were 1.47% and 1.12%, respectively, and similar to those for the laboratory samples (1.23%), which confirms that the surface curvature of the production cores has absolutely no effect on their NIR spectra and also that the proposed model provides accurate predictions of their concentrations.

3.3. *Influence of the lacquer coating on NIR spectra. API determination in tablets*

In the last step of the drug production process, cores are coated with a thin film of lacquer to obtain the final tablets. The coating introduces three new chemicals in the formulation which together account for about 2% by weight of the 600 mg tablets and 5% of the 400 mg tablets. Using the core model to predict production tablets resulted in underestimation, with residuals of 19.3% for the 400 mg tablets and 7.6% for the 600 mg tablets. Therefore, the 400 mg tablets—those with the thicker lacquer coating—were quantified with greater errors than the 600 mg tablets. This can be ascribed to increased attenuation of radiation by effect of its crossing a thicker layer in the former formulation. The substantial influence of the coating film on the NIR spectra for the tablets led us to incorporate it into the API calibration model.

Differences in lacquer coating thickness can be quantified by visual inspection of the scores plot of a PCA for cores and coated tablets. As can be seen from Fig. 6, the 600 mg tablets, which were coated with a thinner film, were more similar to the cores than was the set of 400 mg tablets, which had a thicker coating. The cores clustered on the left of the scores graph and exhibited low dispersion; by contrast, the coated tablets scattered on the right and middle of the graph. This result confirms that coating leaves a lacquer film of variable thickness.

The high variability in coating thickness and the difficulty of accurately reproducing such variability in the laboratory led us to obtain 5 average spectra for the coating in 400 mg tablets —the thicker— and another 5 for that in 600 mg tablets —the thinner — which were obtained as described in Section 2.3. The average coating spectra were combined separately at random with those for the laboratory cores in order to obtain a new matrix of spectral data (set D) incorporating coating variability in addition to concentration and compaction pressure variability (80–120% of the API nominal value and 80–190 MPa, respectively). Fig. 7 shows the scores plot for PCA of SNV-treated spectra data recorded over the 1100–2500 nm wavelength range for the laboratory cores as corrected with the average spectrum for the lacquer coating and coated production tablets—each spectrum was the average of those for 10 production tablets from the same batch. As can be seen, the spectra for the coated production tablets clustered together with those for the laboratory cores as corrected for the coating spectrum.

Similarly to the previous models, set D was split into two that were used to construct the calibration model and assess its predictive ability, respectively. Finally, the model was used to predict production tablets and obtain the average API content for each batch. Table 2 shows the figures of merit of the calibration model. As can be seen, the RSEP values for the production samples differed little from those for the laboratory tablets. Therefore, the model constructed from laboratory-made samples can be used to accu-

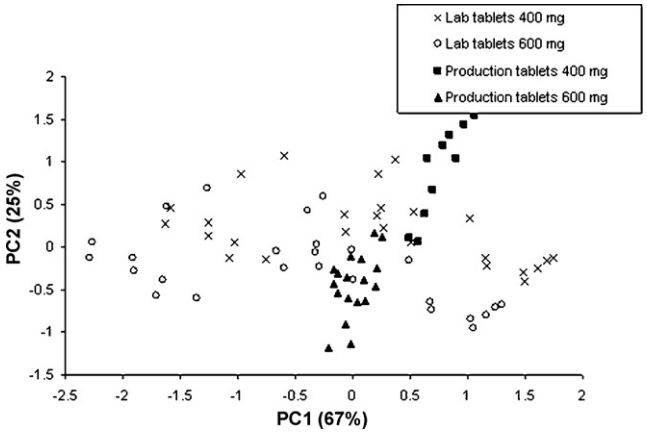

Fig. 7. Scores scatter plot for modified tablet spectra (set D, see the text) acquired over the wavelength range 1100–2500 nm and corrected with SNV for coated production tablets.

rately predict production samples differing in shape, compaction pressure and coating thickness without the need to include any production samples—or conduct any additional analysis to obtain reference values.

4. Conclusions

In this work, we furthered research into the variables affecting the production of drug tablets by constructing models incorporating the sources of variability that typically affect NIR spectra (particle size, tablet geometry, compaction pressure and coating thickness).

Principal component analysis and cluster analysis allow similarity between samples of disparate origin (laboratory and production), shape, compaction pressure and coating thickness to be assessed in order to anticipate the influence of these factors on calibration models. The SNV treatment significantly reduces their effects and facilitates construction of more robust predictive models. In this work, we used SNV to correct the effect of differences in particle size.

The core compaction pressure has a significant influence on NIR spectra. Compacting laboratory cores at pressures over an appropriate range allows the effect of this source of variability on calibration to be lessened and the API to be more accurately quantified as a result.

The effect of differences in coating thickness between production tablets was modelled by incorporating the average spectrum for the lacquer coating to the model for laboratory cores. The expanded model exhibited good predictive ability.

Calibration models were constructed from laboratory samples alone, the production samples being used to assess their predictive ability. The models were validated by determining the RSE values between their predictions and the HPLC reference values. Based on the results, the models afford efficient control of the drug production process.

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References

[1] A.J. O'Neil, R.D. Jee, A.C. Moffat, Measurement of the cumulative particle size distribution of microcrystalline cellulose using near infrared reflectance spectroscopy, Analyst 124 (1999) 33–36.
[2] M. Blanco, M. Alcalà, A process analytical technology approach based on near infrared spectroscopy: tablet hardness, content uniformity, and dissolution test measurements of intact tablets, J. Pharm. Sci. 95 (2006) 2137–2144.
[3] J.J. Moes, M.M. Ruijken, E. Gout, Application of process analytical technology in tablet process development using NIR spectroscopy: blend uniformity, content uniformity and coating thickness measurements, Int. J. Pharm. 357 (2008) 108–118.
[4] M. Blanco, A. Peguero, An expeditious method for determining particle size distribution by near infrared spectroscopy: comparison of PLS2 and ANN models, Talanta 77 (2008) 647–651.
[5] E.W. Ciurczak, J.K. Drenen III, Pharmaceutical and Medical Applications of Near-infrared Spectroscopy, Marcel Dekker Inc., New York, 2002.
[6] M.E. Aulton, Farmacia: La Ciencia del Diseño de las Formas Farmacéuticas, Elsevier, Amsterdam, 2004.
[7] A.J. O'Neil, J. Andrew, D. Roger, A.C. Moffat, The application of multiple linear regression to the measurement of the median particle size of drugs and pharmaceutical excipients by near-infrared spectroscopy, Analyst 123 (1998) 2297–2302.
[8] J.D. Kirsch, J.K. Drennen, Determination of film-coated tablet parameters by near-infrared spectroscopy, J. Pharm. Biomed. Anal. 13 (1995) 1273–1281.
[9] S.H. Tabasi, R. Fahmy, D. Bensley, C. O'Brien, S.W. Hoag, Quality by design, part II: application of NIR spectroscopy to monitor the coating process for a pharmaceutical sustained release product, J. Pharm. Sci. 97 (2008) 4052–4066.
[10] M. Cruz Sarraguça, J. Almeida Lopes, Quality control of pharmaceuticals with NIR: from lab to process line, Vib. Spectrosc. 49 (2009) 204–210.
[11] J.M. Amigo, C. Ravn, Direct quantification and distribution assessment of major and minor components in pharmaceutical tablets by NIR–Chemical imaging, Eur. J. Pharm. Sci. 37 (2009) 76–82.
[12] ICH Guidelines: Q2A Text on Validation of Analytical Procedures 1994. Q2B Validation of Analytical Procedures: Methodology 1996. http://www.ich.org/LOB/media/MEDIA417.pdf.
[13] R.J. Barnes, M.S. Dhanoa, S.J. Lister, Standard normal variate transformation and de-trending of near-infrared diffuse reflectance spectra, Appl. Spectrosc. 43 (1989) 772–777.
[14] M. Blanco, M. Alcalà, Content uniformity and tablet hardness testing of intact pharmaceutical tablets by near infrared spectroscopy, Anal. Chim. Acta 557 (2006) 353–359.