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Controlling individual steps in the production process of paracetamol tablets by use of NIR spectroscopy

M. Blanco*, R. Cueva-Mestanza, A. Peguero

Department of Chemistry, Faculty of Sciences, Universitat Autonoma de Barcelona, E-08193 Bellaterra, Barcelona, Spain

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ABSTRACT

Various physical and chemical parameters of interest to the pharmaceutical industry were determined by NIR spectroscopy with a view to assessing the potential of this technique as an effective, expeditious alternative to conventional methods for this purpose. To this end, the following two steps in the production process of tablets containing 1 g of paracetamol were studied: (1) intermediate granulation, which was characterized in terms of Active Principle Ingredient (API) content, average particle size and particle size distribution and (2) manufactured tablet, which was examined in relation to compaction pressure and API content of the tablets. The ultimate aim was to identify critical attributes of the process influencing the quality of the end-product. Based on the results, a new method for determining the API in the end-product was developed and validated for its quality control.

1. Introduction

Quality in a drug is assured by careful execution of every single step in its production process and optimization of any factors potentially affecting it. Determining some physical and chemical parameters of pharmaceutical interest over a production process can help one obtain useful information about its evolution and consistency. In fact, such parameters can provide a "snapshot" of the process at any time and allow one to act timely on it if necessary. This approach to the production process departs from the traditional strategies of the pharmaceutical industry, which has led US Food and Drug Administration (FDA) to propose the initiative PAT (Process Analytical Technology) involving the incorporation of new technologies to drug production in order to both improve the quality of end-products and cut manufacturing costs [1]. The yield of a production process can be adversely affected by the need to analyze large numbers of samples in order to assure quality in the end-product; in fact, the analyses involved are usually sluggish and expensive. The need to perform massive analyses detracts from industrial productivity, increases costs and reduces benefits. In order to circumvent these shortcomings and acquire a sound knowledge about each step of a production process, in this work we developed a Near-Infrared (NIR) analytical method as an alternative to traditional choices (UV/VIS, HPLC) for drug samples. Near infrared spectroscopy (NIRS) is an expeditious, user-friendly, non-destructive, reliable, flexible technique, which facilitates its use both in the laboratory and for controlling/monitoring individual steps of a production process. At present, NIRS is widely used to determine a number of physical and chemical quality-related parameters in a wide variety of materials. Its qualitative and quantitative potential in this respect is widely documented [2–7].

A tablet production process requires strict control of each individual step in it (reception of the raw material, blending, granulation, sieving and tableting).

Granulation increases the product particle size in order to facilitate uniform feeding to the pressing machines and reproducible filling of the tablet matrix. This results in uniform compaction of the product particles and ensures uniformity in tablet weight and constancy in the physico-mechanical properties (hardness, friability) of the product.

The fluidity of a powdered or granulated material depends on its average particle size, particle size distribution, particle shape, surface roughness and moisture content. As a rule, fine particles with a high surface area-to-mass ratio are more cohesive than are coarser particles. Thus, particles larger than 250 μm can usually flow relatively freely; by contrast, powders consisting of particles smaller than 10 μm are cohesive and scarcely fluid [8]; for this reason, the pharmaceutical industry usually employs granulates with a narrow size distribution (i.e. little variability in particle size with respect to its average value) [9,10].

By pressing powders or previously granulated substances, particles are brought very close to one another. Tablets must possess

* Corresponding author. Tel.: +34 93 58 1367; fax: +34 93 58 1367.
E-mail address: marcel.blanco@uab.es (M. Blanco).

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an adequate hardness (diametral breakage strength) in order to withstand mechanical shock from handling during production, packaging, distribution and usage [11]. Pressing extremely reduces the efficient surface of a drug, which can affect the dissolution rate of the API. The disintegration rate of a tablet depends on various mutually related factors including the nature of the drug it contains and its concentration, and the solvent, binder, disaggregant, lubricant, wetting agent and compaction pressure used [12]. Tablet hardness is influenced by surface area, cohesive strength, particle size distribution and moisture content, among other factors [13]. Based on the foregoing, particle size and compaction pressure are two essential pieces of information with a view to assuring quality in pharmaceutical products in as much as they have a direct impact on API bioavailability.

In addition to controlling the above-described factors, the pharmaceutical industry must determine the API content of each product in the intermediate steps of the process and also, unavoidably, in the end-product.

Some authors have studied individual factors during a specific step of a production process [14–18]; none, however, seems to have established their influence on the quality of the end-product. The primary aim of this work was to assess the potential of NIR spectroscopy for determining quality in the end-product from the physical and chemical parameters most strongly influencing it with a view to acquiring a comprehensive knowledge about the process as a whole and any critical points potentially affecting its outcome. The study was conducted in two parts. In the first, the use of NIR spectroscopy to quantify the API in granulates, and establishes their particle size distribution and average particle size, was examined. In the second, the potential of this technique for predicting the compaction pressure of tablets was assessed and the ensuing method for quantifying APIs validated.

2. Experimental

2.1. Tablet production process

The tablet production process studied involves the following steps, depicted in Fig. 1: weighing of the API and excipients (wei), mixing (mix), granulation (gra), drying (dry), sieving (sie) and tableting (tab). The product consists of uncoated white oblong tablets 20 mm long × 7 mm wide with a groove on one side and a nominal weight of 1111 mg that are pressed at 195–215 MPa.

2.2. Production samples

Production granulates and tablets consisted of the API (paracetamol, 898 mg/g), pregelatinized starch (87 mg/g) as major excipient, and stearic acid (5 mg/g) and povidone (10 mg/g) as minor excipients.

2.3. Laboratory samples

A total of 26 mixtures were prepared by weighing appropriate amounts of the formulation ingredients spanning API concentrations from 80 to 111%. The nominal paracetamol content (898 mg/g). ICH recommends a calibration range between 80 and 120% of nominal value. In this case the upper limit cannot reach because the 111% concentration represented pure paracetamol. The high content in API and low contents in the two minor excipients precluded using an experimental design to facilitate the preparation of samples with a low correlation between concentrations. The component mixtures were blended in a solid mixer for 30 min to ensure homogeneity.

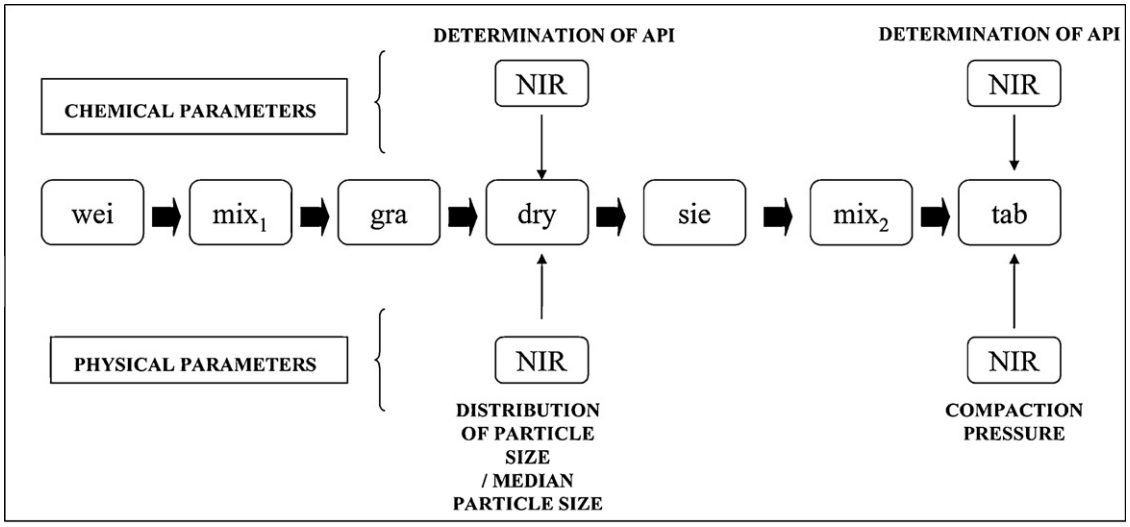
Laboratory granulates were prepared from powder mixtures, which were sprayed with water, blended with a spatula to obtain granules and dried in a vacuum stove at 60 °C for 3 h. Finally, the dry granules were ground in a mortar to a particle size similar to that of production granules.

The granulate samples were used to obtain laboratory tablets. To this end, an amount of ca. 1 g of powdered sample was compacted at 195–215 MPa on a Perkin–Elmer press.

In parallel, laboratory-made tablets were prepared from production granulate that was overdosed or underdosed to ±5% around the nominal API content and pressed at 74–370 MPa.

2.4. Particle size distribution

An amount of ca. 10 g of each granulate was sieved to obtain 5 fractions of different particle size (<200, 200, 300, 500 and 1000 μm) in order to determine the average size and distribution of particles. Each fraction was weighed in an analytical balance in



wei= weighed, mix=mixed, gra=granulation, dry=dried, sie= sieving, tab= compressed into tablet, NIR measurements (symbolized with NIR boxes).

Fig. 1. Overview of a manufacturing process for tablets.

order to calculate the proportion of sample passing through each sieve and obtain the particle distribution curve for the product. The average particle size was calculated from the following expression [19]:

$$\text{Average particle size} = \frac{\text{weight fraction} \times \text{particle size fraction}}{\text{total weight}}$$

2.5. Hardware and software

Laboratory samples were blended in a Turbula T2C WAB shaker mixer and pressed on a Perkin–Elmer 15.011 cylindrical press with a cross-sectional area of 132.7 mm^2. Production granulates were sieved through a BA100-N electromagnetic sieve shaker from CISA (Barcelona, Spain).

Near infrared spectra were recorded on a NIRSystems 6500 spectrophotometer from FOSS NIRSystems (Silver Springs, MD) equipped with a Rapid Content Analyser (RCA) module and governed via the software Vision 2.51, also from FOSS NIRSystems.

PCA, PLS and PLS2 models were constructed by using the software Unscrambler v. 9.2 from Camo Process (Trondheim, Norway).

2.6. Determination of API concentrations

The API concentration in each laboratory sample was obtained from the weights of its components. The API contents of the production tablets and granulated samples were determined by high performance liquid chromatography (HPLC) with UV/VIS detection, using a steel column 25 cm long × 4 mm ID packed with Spherisorb ODS-2 resin of 5 μm particle size, a mobile phase consisting of 70:30 (v/v) methanol/aqueous acetic acid flowing at 1.0 mL min^{-1}, an injected volume of 25 μL a maximum chromatographic run time of 10 min and a detection wavelength of 280 nm.

2.7. Recording of NIR spectra

Near infrared spectra were recorded at 2 nm intervals over the wavelength range 1100–2500 nm. Each spectrum was the average of 32 scans. The reference spectrum was obtained from the ceramic plate supplied with the instrument.

The spectra for the powders and granulates were obtained by placing the samples in a glass cell with a circular section around 3 cm of diameter. Two spectra per sample were recorded, with turnover between recordings, in order to obtain an average spectrum.

The spectra for the production tablets were recorded by direct measurement on the spectrophotometer quartz window; the entire sample is illuminated by the radiation beam and hence its analysis area corresponds to its cross-section. Each tablet was turned 90° to obtain a second spectrum for the opposite side which was averaged with the first. The spectra for the laboratory tablets were recorded identically.

2.8. Processing of NIR data

A calibration set and a prediction set incorporating spectral and parameter variability were constructed. The spectral data were subjected to various treatments including SNV, and first and second derivatives as obtained by using the Savitzky–Golay algorithm with an 11-point moving window and a second-order polynomial.

The quantitation models for granulates, production tablets, compaction pressure and average particle size were constructed by using the PLS algorithm. We intent use only samples from laboratory for the calibration set while the validation set is only constituted by production samples. Two types of model validation were performed: an internal validation using leave-one-out cross-validation for building of the model and an external validation using a production set of samples. The model for particle size distribution was based on PLS2. PLS2 models can be used for to calibrate and then predict simultaneously a set of variables (useful with variables strongly correlated); in this study a PLS2 model was used for determination of the percentages of 5 fractions of each particle size (distribution size) in the granules. The optimum number of factors for each model was taken to be that resulting in the lowest possible relative standard error (RSEC for calibration and RSEP for prediction), defined as:

$$\text{RSEC,RSEP}(\%) = \sqrt{\frac{\sum_{i=1}^{m}(Y_i^{\text{REF}} - Y_i^{\text{NIR}})^2}{\sum_{i=1}^{m} Y_i^{\text{REF}^2}}} \times 100$$

where m is the number of samples, and Y_i^{REF} and Y_i^{NIR} are the concentrations obtained with the reference and NIR method, respectively.

3. Results and discussion

The aim of this work was to develop an effective method for checking product quality by determining various parameters in different steps of the paracetamol production process, which starts with the granulate mixture and ends with the final control of the tablets. The specific steps studied were granulation and tableting, which were examined in terms of API content, particle size distribution and average particle size of the granulate, and compaction pressure of the tablets.

3.1. Determination of API contents in granulates and tablets

The calibration models for granulates and tablets were constructed from a set of samples spanning API contents from 80 to 111% the nominal value for paracetamol in the studied formulation. Fig. 2 shows the absorbance spectrum for a granulated, tablet, API and excipient majority (Gluten-free pregelatinized corn starch).

Prior to constructing the calibration model for the API in the granulates, the results for laboratory and production granulates were subjected to PCA in order to assess the similarity of the two types of samples with a view to selecting an appropriate set to develop the model. Fig. 3 shows the scatter plot of the scores for the first two PCs, which jointly accounted for 94% of the total variance.

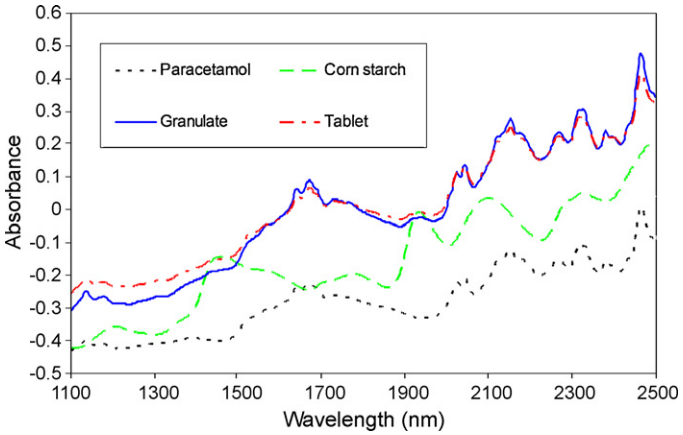


Fig. 2. NIR spectra for granulate, tablet, API (paracetamol) and excipient majority (corn starch).

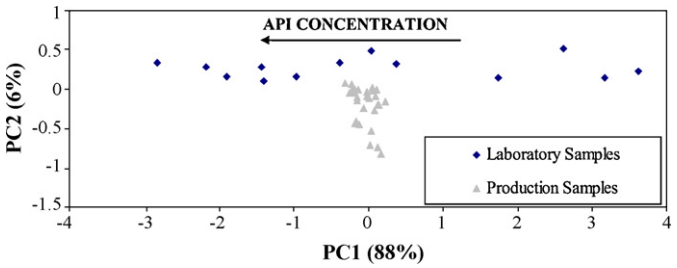


Fig. 3. PCA scores plot for granulated samples.

The laboratory samples spanned a broad range of values for PC1; on the other hand, the production samples clustered in the centre of the graph which is suggestive of close similarity between them and exhibited PC1 values very similar to that for the laboratory samples containing the nominal API concentration.

The similarity between the laboratory and production granulated samples revealed by the scatter plot of the scores led us to use a calibration set consisting solely of laboratory samples and a validation set containing production samples alone. The model for quantifying paracetamol in the granulate was established by testing various spectral treatments of which that based on SNV with two PLS factors was found to provide the best results. Excluding the regions around 1440 and 1940 nm, which correspond to the absorption of OH and are thus associated to moisture in the sample, provided a much simpler model with an improved predictive ability. Table 1 shows the figures of merit of the model.

The model for quantifying the API in tablets was developed in the same manner. Since the scatter plot for the PCA scores was suggestive of differences between the laboratory and production tablet samples, the calibration set was constructed with both, and so was the validation set. The best results were obtained with a spectral derivative treatment and 3 PLS factors (Table 1). The spectral ranges examined were 1100–1885 and 2000–2500 nm and thus excluded the zone around 1940 nm for the above-described reason. Not using the zone around 1440 nm resulted in no further improvement, however.

Accurately determining the API concentration at this step of the tablet production process can help assure the desired API content in the end-product or any required corrections in this respect to be made before the process is allowed to proceed.

3.2. Determination of the compaction pressure

The compaction pressure affects the hardness and ease of disintegration and dissolution of tablets. Pharmaceutical disintegration and dissolution tests provide a measure of API bioavailability. The compaction pressure also influences the API release rate, which should be identical across production batches. In addition, tablets should be hard enough to preserve their integrity during handling.

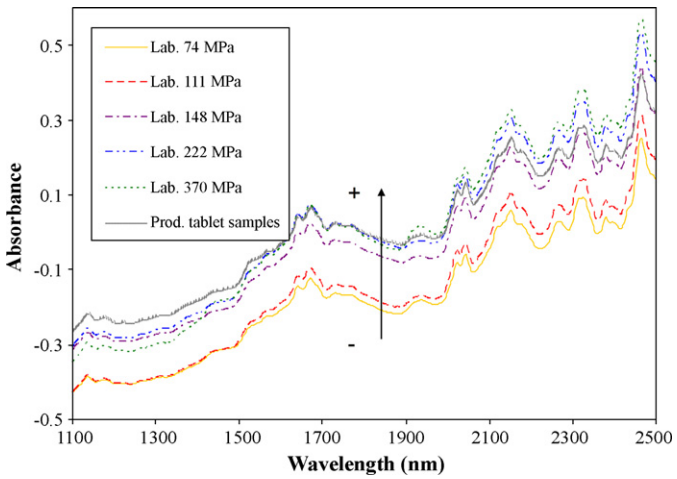


Fig. 4. Absorbance spectra for different compaction pressure of laboratory and production tablet samples.

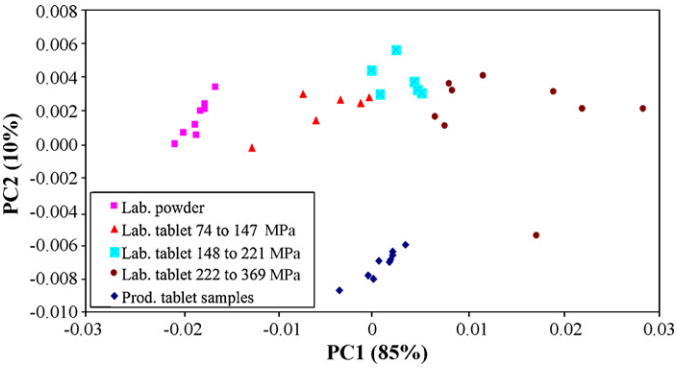


Fig. 5. PCA scores plot for laboratory samples (powder and compressed) and production tablets.

Laboratory tablets containing API concentrations ±5% around the nominal content and pressed at 74–369 MPa were split into three groups according to compaction pressure. As can be seen from Fig. 4, the pressure used to prepare the tablets caused a shift in the NIR bands. Fig. 5 is a scatter plot of the PCA scores for laboratory tablets, powder samples and production tablets. As can be seen, the compaction pressure was the strongest individual source of variability, PC1, which accounted for 85% of the total variance. On the other hand, the second component (PC2), which accounted for 10% of the total variance, represented differences between production and laboratory tablets [11]. As can also be seen, the production samples fell within the 148–221 MPa range for the laboratory samples, which suggests that the compaction pressure for the production tablets lay in that range.

Table 1
Relevant parameters of the models for PLS determination of API in granulated and tablet samples.

Samples	Granulated			Tablet		
	Calibration	Prediction		Calibration	Prediction	
	Laboratory	Laboratory	Production	Laboratory and production	Laboratory	Production
Pre-treatment	SNV			1st derivative		
Range (nm)	1550–1800 2050–2400			1100–1885 2000–2500		
Concentration (%label claim)	80.0–111.0	80.0–111.0	95.0–105.0	80.0–111.0	80.0–111.0	95.0–105.0
Factors	2			3		
Explained Variance Y (%)	99.5			99.5		
Samples	14	8	33	18 + 5	24	22
RSEC/P (%)	0.78	1.53	2.95	0.65	0.78	0.81

Table 2
Main figures for determination of physical parameters in granulated and tablet samples.

Samples	Compaction pressure			Particle size distribution		Average particle size	
	Calibration	Prediction		Calibration	Prediction	Calibration	Prediction
	Laboratory	Laboratory	Production	Production		Production	
Pre-treatment	1st derivative			2nd derivative		1st derivative	
Range (nm)	1110–2488			1110–2488		1110–2488	
Range of value	74–370 MPa		172–223 MPa	0–1000 μm			
Algorithm	PLS			PLS2		PLS	
Factors	4			5		5	
Explained Variance Y (%)	99.0			97.2		99.5	
Samples	16	10	90	12	6	13	8
RSEC/P (%)	3.5	8.6	[a]	2.7	7.5	1.0	6.2

[a] Not reference value is available to calculate RSEP.

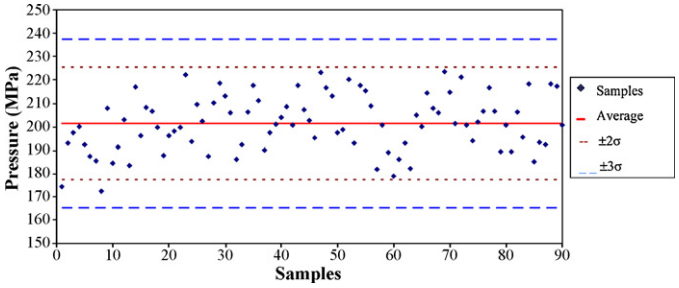


Fig. 6. Control chart of compaction pressure for production tablet.

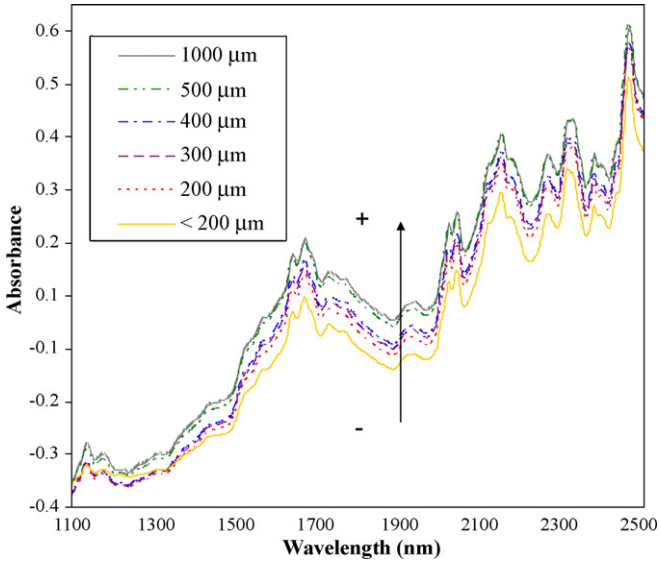


Fig. 7. Absorbance spectra of different particle size samples.

The compaction pressure for the tablets was determined by using a model constructed from laboratory samples. Table 2 shows the figures of merit of the model. No reference values for the compaction pressure were available with a view to validating the model; the sole information available for this purpose being the operating range of the press: 195–215 MPa. The ensuing model was used to predict the compaction pressure for 90 production tablets from 9 different batches and provided values from 172 to 223 MPa (average, 201 MPa).

Fig. 6 is the control plot for the predicted compaction pressure for each tablet. As can be seen, there were differences between individual tablets. In any case, pressure values clustered randomly around a central one (the average compaction pressure) and only 2 tablets had a pressure outside the range defined by the average value $\pm 2\sigma$.

Control plots provide an effective tool for controlling deviations and trends from individual values and confirming that the compaction process is under control.

3.3. Determination of particle size distribution and average particle size

Ensuring efficiency in the production process and a high quality in the end-product entails controlling the average particle size and particle size distribution of the product. In fact, an appropriate particle size ensures acceptable physical properties (hardness, disintegration, average weight) in the product.

Table 3
Determination of average particle size in granulated samples (comparison of PLS and PLS2 calibration models).

Samples	Particle size distribution (PLS2) Average particle size (μm)	Median particle size (PLS) Prediction of average particle size (μm)	Particle Size reference (μm)	PLS2 to particle size distribution Residual	PLS to average particle size Residual
1	684	683	623	−61	−60
2	676	704	648	−28	−56
3	599	668	672	72	4
4	606	654	633	27	−20
5	557	573	626	69	53
6	583	614	597	14	−17
			Average residual	15.7	−16.02
			s	52.86	41.71
			n	6	6
			t_{exp}	0.73	0.94
			t_{crit} [a]	2.57	2.57

[a] t critical ($\alpha = 0.05$, 5 degrees of freedom).

Table 4
Validation parameters of API determination in production tablets.

	Parameter	Result
Linearity	n	20
	Concentration range (% of nominal value)	80–111%
	Intercept	3 ± 4
	Slope	0.98 ± 0.04
	R	0.992
Accuracy	n	6
	Average difference (% of nominal value)	0.08
	s	0.72
	t_{exp}	0.27
	t_{crit}	2.571
Repeatability	Mean NIR (% of nominal value)	97.3
	CV%	0.1
Intermediate pre-ci-sion	ANOVA	
	Day (3)	
	F_{exp}	3
	F_{crit}	19
	Analyst (2)	
	F_{exp}	0.3
	F_{crit}	18.5
	s	0.1
	CV%	0.1
Robustness	n	26
	Average residual	0.41
	s	1.12
	t_{exp}	1.89
	t_{crit}	2.06

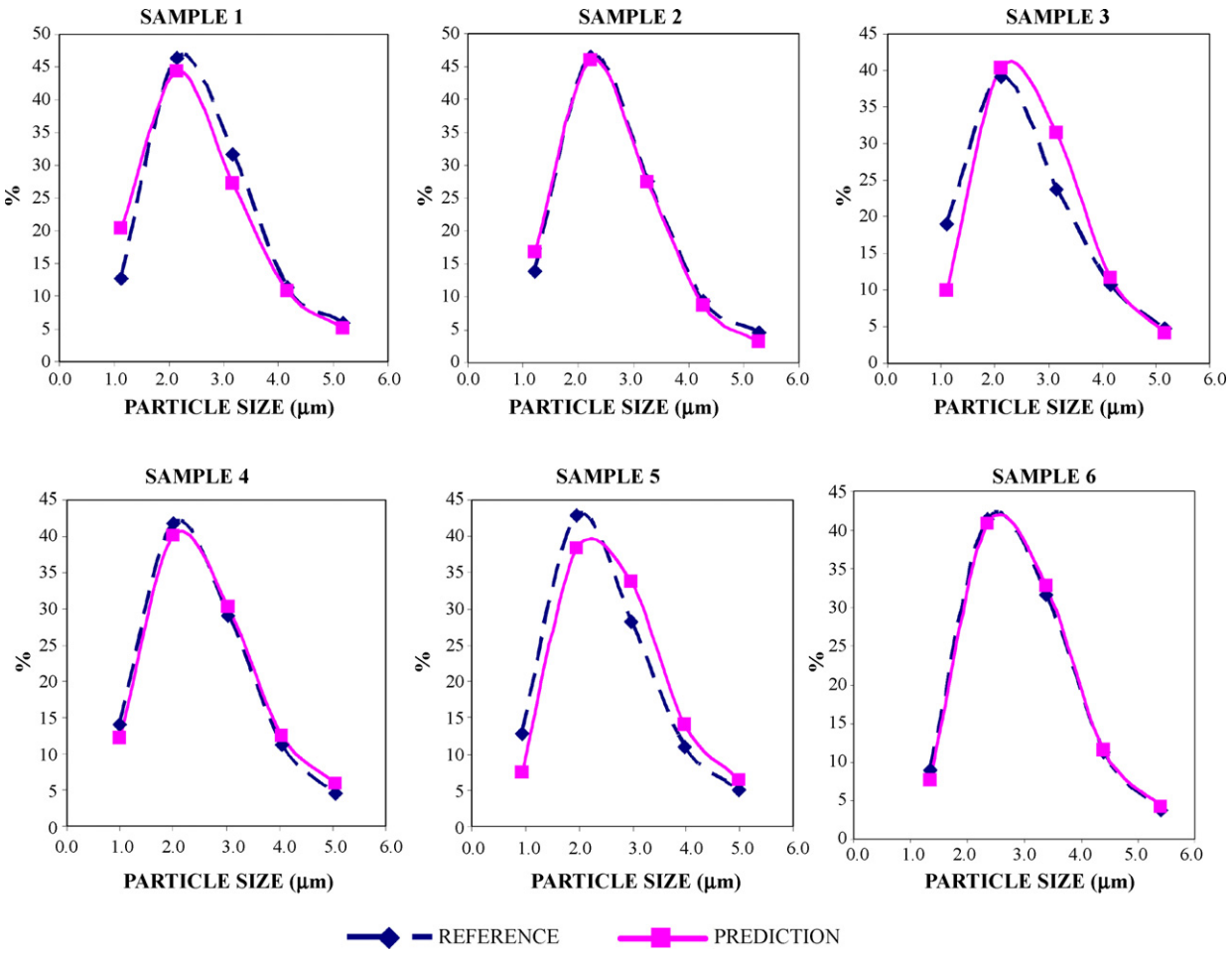


Fig. 8. Particle size distribution curves for different granulated samples obtained applying PLS2 calibration models.

The granulate samples studied were collected over a period of 2 years. This ensured a broad enough temporal distribution and hence good representativeness in the samples.

Fig. 7 shows the NIR spectrum for each sieving fraction. As can be seen, the bands shifted with increase in particle size. Particle size distribution was determined by using a PLS2 model. The PLS2 algorithm allows one to correlate the spectral data matrix with more than one variable and predict various particle sizes with a single calibration model [20]. The selected wavelength range was 1100–2500 nm and the model with the highest predictive ability one based on a second-derivative spectral treatment (Table 2).

The particle size distribution of a product is a measure of granulate heterogeneity and also of the particle size range it spans; particles larger than 250 μm but distributing closely around the average size are acceptably fluid [8]. As can be seen from Fig. 8, the predicted curves fitted those obtained from the reference values quite closely.

Another PLS model was constructed to determine the average particle size by using the whole wavelength range (1100–2500 nm). The best choice as regards predictive ability was a first-derivative model (see Table 2). A comparison of the average particle sizes provided by the PLS and PLS2 models with the theoretical value was made via a paired *t*-test. Based on the results, there were no significant differences in performance between the two models at a significance level $\alpha < 0.05$ (see Table 3).

3.4. Validation of the proposed method for quantifying the API in paracetamol tablets

The proposed NIR method for determining paracetamol (API) in tablets was validated in accordance with the ICH [21] and EMEA guidelines (ICH, 1994) [22]. This involved assessing the selectivity, linearity, accuracy, precision (as repeatability and intermediate precision) and robustness of the method. "The selectivity of a NIR method is established across the identification of the pharmaceutical preparation using spectral libraries constructed with spectra of the preparation and the possible confusions: excipients and other similar preparations. The identification of the preparation is a previous step for quantification of its API content".

Robustness was assessed by analyzing samples collected over a period of 6 months. A paired *t*-test at the 95% confidence level on the differences between the NIR and HPLC values revealed the absence of significant differences between the proposed and reference methods.

Table 4 shows the validation results for the proposed method.

4. Conclusions

This study testifies to the usefulness of NIR spectroscopy for assessing quality in a pharmaceutical product by determining various chemical and physical properties in several steps of the production process.

By using two different PLS calibration models to determine the API in intermediate granulates and the end-product one can control individual steps and the overall process before the product is released. The proposed model for determining the API in granulated samples require no production samples was used in content of API determinations with results not significantly different from those provided by the reference (HPLC) method. This can dramatically facilitate the development of effective prediction models and improve their accuracy since reference values can be obtained simply by weighing, without the need to use any special technique. The validation results obtained by applying the ensuing method to finished production tablets in accordance with the ICH guidelines testifies, these results show that this method is an effective alternative to conventional (HPLC) choices for this purpose.

The PLS2 model used to determine particle size distribution provides a more comprehensive knowledge of the particle size-related properties of the intermediate product, which facilitates assurance of an increased quality and uniformity in the physical properties (average weight, dissolution rate) of the tablets.

Using a NIR model to predict the compaction pressure of tablets provides a simplified, non-destructive alternative which additionally ensures fulfillment of other requirements associated to this variable.

All models used here produce results comparable to those obtained by the reference method and are thus potentially useful for routine analyses with a view to controlling critical points in the production of tablets and avoiding non-conforming batches and the need for re-processing as a result.

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