Monitoring the chemical and physical parameters used to assess quality in the pharmaceutical industry: an application of PAT for manufacturing

Juan G. Rosas¹, Manel Alcalá¹, Josep M^a. González² and Marcel Blanco^{1*}

 ¹Grupo de Quimiometría Aplicada, Departament de Química, Unitat de Química Analítica, Universitat Autònoma de Barcelona, E-08193 Bellaterra, Barcelona, Spain
 ²Laboratorios Menarini, Badalona, Spain.
 *corresponding author: marcel.blanco@uab.es

Introduction

The process analytical technology (PAT) initiative was developed by the United States Food and Drug Administration (US-FDA).^{1,2} The aim of the US-FDA was to encourage the pharmaceutical industry to include greater technical and scientific rigor in manufacturing processes. PAT approaches based on scientific knowledge and risk analysis allow efficient processes to be designed and developed, and consequently ensure the quality of the final product. Therefore, PAT can be considered a connection between analytical chemistry and pharmaceutical technology.

Near infrared (NIR) spectroscopy was used to monitor the pharmaceutical blending process. NIR is one of the more versatile vibrational spectroscopic techniques for analysing pharmaceuticals, owing to the compatibility of fibre-optic probes designed for at-line, in-line and on-line measurement of chemical and physical properties.³ In this work we present an application for real-time monitoring of active pharmaceutical ingredient (API) and excipient concentrations, particle size distribution, flowability and moisture as an in-line method at the end of the manufacturing process.

Materials and Methods

Samples

A pharmaceutical formulation manufactured as a granulate containing about 5 %w/w API was studied. A total of forty powder samples were prepared in the laboratory; appropriate amounts of API and excipients and were weighed, mixed and carefully homogenised.

Calibration Samples

The construction of calibration models was based on the method described by Blanco & Peguero⁴ and modified by using standard normal variate (SNV) transformation as a spectral pre-treatment. First, the spectrum of process (S_p) was calculated, which should incorporate the process variability (Equation 1):

$$S_p = S_t - S_{lab_ref} \tag{1}$$

where S_t is the spectrum for a production sample (API and excipients nominal concentration) and S_{lab_ref} is the reference spectrum (same concentrations).

The calibration set for moisture, particle size and flowability was prepared using samples from 12 batches which were moistened, dried and sieved.

Reference Methods

The reference methods used to obtain calibration values were previously validated by the pharmaceutical company. The quantitative determination of active ingredient (nimesulide) was performed with a high-performance liquid chromatography (HPLC) instrument (Agilent Technologies, Inc, Santa Clara CA, USA) at a wavelength (λ) of 300 nm (mobile phase, acetic acid 0.03 M:methanol (40:60% v/v)). The pH was determined by measuring a solution of 2% (w/v) of the granules with a pH meter (model 691; Metrohm AG, Herisau, Switzerland). The moisture content of samples was determined using the loss on drying (LOD) method with a LJ16 Moisture Analyzer Balance (Mettler-Toledo Intl. Inc, Polaris Parkway, Columbus, USA). The particle size distribution was calculated by sieving batches of final product in a sieve analyser Prufsieb Jel 200 (Hosokawa, Augsburg, Germany); three ranges of particle sizes (< 125 µm, 125–250 µm, and > 250 µm) were chosen. Flowability and angle of repose of granules were calculated using a Powder Characterisation Instrument GmbH PTG-2 (Pharma Test AG, Germany).

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Near infrared spectroscopy

NIR spectra were acquired in reflectance mode with a portable NIR LabSpec® Pro 5000 spectrophotometer (ASD Inc., Boulder, Colorado, USA); light was collected through the sapphire glass window of a specially designed accessory. Triplicate spectra were acquired without interfering with the blending process or the formulation.

Data processing

Spectral data were used to develop quantitative multivariate calibration models using the partial least squares (PLS1) algorithm. The reference data were obtained from the same samples following the on-site routine analytical methods. The spectral treatments used included the calculation of first and second derivatives with different moving window points and SNV transformation; principal component analysis (PCA) was used to evaluate the spectral data. Models were validated by full cross-validation. PLS models were constructed with The Unscrambler 9.8 (CAMO, Trondheim, Norway). Calibration and prediction were measured in terms of the root mean square error (RMSE).

Result and Discussion

Table 1 summarises the figures of merit for PLS calibration models calculated for the determination of API, pH and moisture. The API model was calculated using the combination of SNV + 1st derivative, explaining 99.4% of variance with 3 PLS factors. The S_p method has the advantage of determining physical parameters related to the concentration of some constituents in the formulation. The pH model was constructed using a combination of SNV + 2nd derivative, explaining 99.1% of variance with 3 PLS factors. The chosen spectral range mainly included citric acid absorption bands, whose concentrations were directly related to changes in pH. The same set of samples allowed the calculation of calibration models for the citric acid content and pH. The moisture model was calculated using Savitzky-Golay 1st derivative, explaining 97.79% of variance with 3 PLS factors. Although moisture concentration was low and difficult to model, the problem was solved by selecting the spectral range of water bands.

Modelling particle size and flow properties was difficult; the models needed a higher number of PLS factors to be fitted compared with the calibration models for chemical determinations. Table 2 summarises the figures of merit of the models for particle size (percentage corresponding to three sieve fractions). The fractions chosen were: particles less than 125 microns (< 125 µm), between 125 to 250 microns (125-250 μ m) and greater than 250 microns (> 250 μ m). Two models were calculated for flow properties of granules: flowability and angle of repose. The model for determining the angle of repose needed more PLS factors than the flowability model.

The evaluation of the robustness of the PLS models was performed by comparing the NIR predictions and reference values from 40 routine industrial batches (Table 3). Student's t-test (39 degrees of freedom) revealed no significant differences between the reference values and NIR determinations. The NIR method was therefore suitable for routine monitoring. The predictive ability was evaluated for the NIR determination of particle size and flow properties for 12 production batches and no significance difference was observed between NIR and reference data (Table 4). Prediction error (RMSEP) of the flowability was 0.54 g.s⁻¹ and the angle of repose was 0.94° while particle size determination errors were between 1.22 and 1.51%. Overall, the predictions were satisfactory for these physical parameters.

Table 1. Characteristics of PLS models for API content, pH and moisture							
Characteristics of model	Model API (mg/g)	Model pH	Moisture (%)				
Spectral pre-treatment	SNV+1st Dev. SG	SNV+2nd Dev. SG	1st Dev. SG				
Wavelength range (nm)	1000–2400	1000–2260	1300 – 1500; 1850–2050				
Calibration range*	34.11-66.15	2.87-3.31	0.10–1.21				
Nominal values (NOC)*	50 ± 2.5	3.00 ± 0.5	< 0.5				
Number of PLS factors	3	3	3				
Explained variance (Y) (%)	99.39	99.09	97.79				
Regression Yref vs YNIR							
Slope	0.99	0.99	0.98				
Offset	0.36	0.03	0.01				
RMSEC*	0.69	0.01	0.04				
RMSEP (External set)*	1.15	0.03	0.02				

* Results expressed in their respective units

NOC = Normal operating conditions; RMSEC/P = Root mean square error of calibration / prediction

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Table 2. Characteristics of PLS models for particle size parameters and flow properties (flowability and angle of repose) of granule

	Models for	or particle size pa	Models for flow properties			
Characteristics of model	< 125 µm (%)	125–250 μm (%)	> 250 µm (%)	Flowability (g.s ⁻¹)	Angle of repose (°)	
Spectral Pre-treatment	1st Dev.	SNV	SNV	1st Dev.	SNV+1st Dev.	
Wavelength range (nm)	1000–2400	1000–2400	1000–2400	1100–2330	1000–2400	
Calibration range*	16.60-25.00	35.50-43.50	37.10-48.00	4.41-9.32	30.30-36.30	
Target values**	19.09	38.62	42.30	6.80	33.45	
Number of PLS factors	5	5	5	5	6	
Explained variance (Y) (%)	99.97	99.44	98.97	97.89	99.59	
Regression Y ^{ref} vs Y ^{NIR}						
Slope	0.99	0.99	0.98	0.98	0.99	
Offset	0.01	0.22	0.44	0.15	0.14	
RMSEC*	0.04	0.18	0.31	0.18	0.11	
RMSEP (External Set)*	2.55	2.10	2.36	0.63	1.07	

** Average of 12 batches analysed on laboratory

* and ** Results expressed in their respective units; RMSEC/P = Root mean square error of calibration / prediction

Table 3. Statistics and t-test of residuals for prediction values of product quality responses from 40 production batches.

Statistical Parameters	API (mg.g ⁻)		рН		Moisture (%)		
Statistical Parameters	HPLC	NIR	Reference	NIR	Reference	NIR	
Batches number		40		40		40	
Nominal value*		50 ± 2.5		$\textbf{3.00} \pm \textbf{0.5}$		< 0.5	
Mean of batches*	50.12	50.40	3.08	3.08	0.24	0.24	
St. dev. of batches*	0.77	0.99	0.08	0.03	0.05	0.03	
Residuals t-test							
Mean*		0.28		0.00		0.01	
St.dev*.		1.13		0.09		0.05	
DF		39		39		39	
t _{crit (alpha=0.05)}		2.02		2.02		2.02	
t _{cal (alpha=0.05)}		1.59		0.02		0.55	
RMSEP*		1.15		0.08		0.05	
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* Results expressed in their respective units; RMSEP = Root mean square error of prediction

Table 4. Statistics and t-test of residuals for prediction values of product quality responses from 12 production batches.

		Flow properties				Particle Size				
Statistical Parameters	Flowability (g.s ⁻¹)		A. of repose (°)		< 125 µm		125 – 250 µm		> 250 µm	
	NIR	Ref.	NIR	Ref.	NIR	Ref.	NIR	Ref.	NIR	Ref.
Number of batches		12		12		12		12		12
Target values ^a	6.8	30 ± 1.5	33.	45 ± 3.2	19.	09 ± 4.7	38.	62 ± 5.4	42.	30 ± 7.2
Mean of batches*	6.87	6.80	33.23	33.45	19.92	19.09	38.52	38.62	41.85	42.30
St. dev. of batches*	0.67	0.50	0.95	1.07	1.63	1.57	1.79	1.81	2.29	2.40
Residuals t-test										
Mean*		0.06		-0.22		0.83		-0.10		-0.45
St. dev.*		0.60		0.96		1.32		1.27		1.37
DF		11		11		11		11		11
t _{crit(alpha=0.05)}		2.20		2.20		2.20		2.20		2.20
t _{cal (alpha=0.05)}		0.37		0.78		2.17		0.27		1.14
RSMEP*		0.57		0.94		1.51		1.22		1.39

^a Average of 12 batches analysed on laboratory

* Results expressed in their respective units; RMSEP = Root mean square error of prediction

Conclusion

This work is an excellent example of using NIR to improve the product and process knowledge in a pharmaceutical process. The NIR method allows the real time and non-invasive monitoring of chemical and physical quality parameters. The proposed strategy provides excellent results for assessing the homogeneity of a final blend. Consequently, it is demonstrated that the NIR technique is a highly suitable tool for process analytical technology (PAT).

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