Quality by design: foundation of design space and near infrared monitoring for a semi-solid pharmaceutical manufacturing process

Juan G. Rosas[1], Manel Alcalá[1], Josep Mª. González[2] and Marcel Blanco[1]*

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

Introduction

The philosophy behind quality by design (QbD) and design space (DS) is playing a prominent role in current thinking about the regulation of pharmaceutical production processes.[1] The DS concept represents the multi-dimensional combination and interaction of such variables and parameters. An adequate DS ensures that the manufactured product fulfils the quality requirements defined for the process within the prescribed framework.[1]

Near infrared (NIR) spectroscopy is widely used as an analytical tool for the fast determination of physical and chemical properties of drugs.[1,2] Very often, the analytical control of pharmaceuticals is time-consuming and delays the adoption of corrective measures during production processes. This problem is being solved more often and more efficiently with NIR spectroscopy, as new, more powerful analytical equipment and software becomes available. The usefulness of NIR spectroscopy for determining the composition of excipients,[3] raw materials[4] and active pharmaceutical ingredients (APIs) have enabled the development of fast, accurate and precise analytical methods for the pharmaceutical industry, exploiting the sampling flexibility and data processing capabilities. In addition, NIR spectroscopy has proved useful for determining various parameters including homogeneity,[5-7] moisture[8-10] and particle size in pure products, granulates,[11,12] tablet hardness[13] and polymorphism.[14-16]

NIR spectroscopy does not require sample treatment, which allows an analytical response to be obtained within a few seconds with minimal effort on the part of the analyst. This has fostered wide use in the monitoring of pharmaceuticals[17-19] and also in various other fields for purposes such as the determining ethanol content[20] and monitoring fermentation,[21] diol synthesis[22] and food manufacturing.[23] In this work, we used NIR spectroscopy as a process analytical technology (PAT) tool to determine physical (viscosity and pH) and chemical properties (API and excipient concentrations) of a pharmaceutical gel.

Materials and Methods

Samples

The studied material is a pharmaceutical gel containing 12.5 $mg.g^{-1}$ of active principal ingredient. A total of 60 laboratory samples were used to calculate the multivariate calibration models.

Near infrared spectroscopy

Data were collected with a portable NIR LabSpec® Pro 5000 spectrophotometer from ASD, Inc. (Boulder, Colorado, USA) furnished with a continuous-flow cell of 0.1 mm light path. Spectra were acquired with Indico Pro 5.2 (ASD, Inc). The spectrum for the empty cell in the absence of gel was used as spectral blank. Each NIR spectrum was the average of 32 scans performed at 1 nm intervals over the wavelength range 1000–2500 nm.

Experimental design of equipment and processes

Fifteen gel batches were prepared according to a D-optimal design gathering five factors (ethanol, water and carbomer content, acid neutralised fraction and reactor temperature). The batches were prepared in a stainless steel reactor model M-15L from IPROCOMSA (Badalona, Spain). Viscosity and pH were measured during the process with a Rheomat RM180 viscometer and a Metrohm 691 pH-meter respectively. Each gel batch was prepared as follows: the reactor was loaded with an appropriate amount of ethanol and API and the mixture was stirred to complete dissolution; the amount of water required was added after dissolution. After homogenisation, the mixture was supplied with carbomer (a polycarboxylic polymer) and stirred until complete dissolution. Total acidity in the solution was the combination of that of the API (a monocarboxylic acid) and the carbomer. The reactor mixture was finally supplied with a tris(hydroxymethyl)aminomethane (TRIS) solution in different fractions in order to neutralise the API and cause gelling. Each homogenisation

Reference paper as:
J.G. Rosas, M. Alcalá, J Mª. González and M. Blanco (2012). Quality by design: foundation of design space and near infrared monitoring for a semi-solid pharmaceutical manufacturing process, in: Proceedings of the 15th International Conference on Near Infrared Spectroscopy, Edited by M. Manley, C.M. McGoverin, D.B. Thomas and G. Downey, Cape Town, South Africa, pp. 159-162.

step was followed by withdrawal of appropriate samples for analysis. A total of 15 samples were withdrawn. The temperature in the reactor was recorded and each sample was allowed to cool to room temperature (21–23ºC) prior to NIR data collection and measurements of viscosity and pH.[24, 25]

Data processing

All multivariate models used to determine the physical (viscosity and pH) and chemical (concentrations) parameters were constructed with the partial least squares (PLS1) algorithm. The spectral treatments used included calculating first and second derivatives (with a moving window of 15, 21 or 29 points), standard normal variate (SNV) transformation and principal component analysis (PCA). Models were validated by full cross-validation. PLS models were constructed with The Unscrambler 9.8 (CAMO, Trondheim, Norway) and SIMCA-P+ 12.0 (Umetrics, Umeå, Sweden). Calibration and prediction quality were measured in terms of the root mean standard error of prediction (RMSEP).

Results and Discussion

The critical quality attributes (CQAs) for the process and product were identified and estimated. The critical process parameters (CPPs) were defined and examined in order to obtain a comprehensive knowledge and understanding of the gelling process. Figure 1 depicts the methodology used in this work. Implementing the proposed design of experiment (DoE) required reactor gel batches with variable amounts of reagents to be produced in a pilot plant, which led to variable viscosity and pH values. The production process was monitored by withdrawing samples to record their NIR spectra at 0, 10, 20, 30, 40, 50, 60, 75, 90, 105, 120, 135, 150, 170 and 190 minutes.

Multivariate models were constructed to determine the concentrations of the major components of the gel. Figure 2 shows the NIR spectra for a process sample (nominal batch), water, the API and ethanol. The low concentration of API and high absorptivity of the hydroalcoholic matrix (64:32 ethanol/water mixtures) masked the contribution of the API; this entailed using the maximum absorption bands for the API (1600–1800 nm) to construct the model in order to avoid the influence of the matrix. The water, ethanol and API contents were determined using calibration models based on the PLS1 algorithm. Principal component analysis (PCA) revealed spectral differences between batches and helped identify the experiments corresponding to the same population with a view to constructing appropriate models (Figure 3). The batches were designated B1–B13, the batches B9–B11 are the normal operating conditions (NOC) batches. Batches B2 and B4 were excluded owing to their strong spectral differences from the others (determined from PC scores values). The samples withdrawn for analysis from the different batches followed an identical trajectory (denoted by a start-to-end arrow; Figure 3). The separation between batches confirms that altering the composition of the gel modifies its properties.

Table 1 shows the figures of merit for the three PLS1 models, which used a small number of PLS factors and exhibited a very high predictive ability (prediction errors, as RMSEP, were all less than 0.7). We also conducted two calibration models to determine physical properties of the gel (viscosity and pH). Although these models required a greater number of factors than those for the chemical parameters, they also exhibited a very high predictive ability, with RMSEP < 0.4 for both viscosity and pH.

At-line monitoring of a process

The models described above were used to monitor physical and chemical parameters during a gelling process. A residuals t-test ($\alpha = 0.05$) was used to compare the NIR predictions with the reference values. Table 2 gives the figures of merit of the residuals t-test; the NIR predictions were not significantly different from the reference values ($t_{crit} > t_{obs}$). Predictions were accurate and errors were small (RMSEP was 0.48 for viscosity and 0.26 for pH) which shows that the NIR method is effective for at-line monitoring of pH and viscosity changes during the production of a pharmaceutical gel.

Reference paper as:
J.G. Rosas, M. Alcalá, J Mª. González and M. Blanco (2012). Quality by design: foundation of design space and near infrared monitoring for a semi-solid pharmaceutical manufacturing process, in: Proceedings of the 15th International Conference on Near Infrared Spectroscopy,
Edited by M. Manley, C.M. McGoverin, D.B. Thomas and G. Downey, Cape Town, South Africa, pp. 159-162.

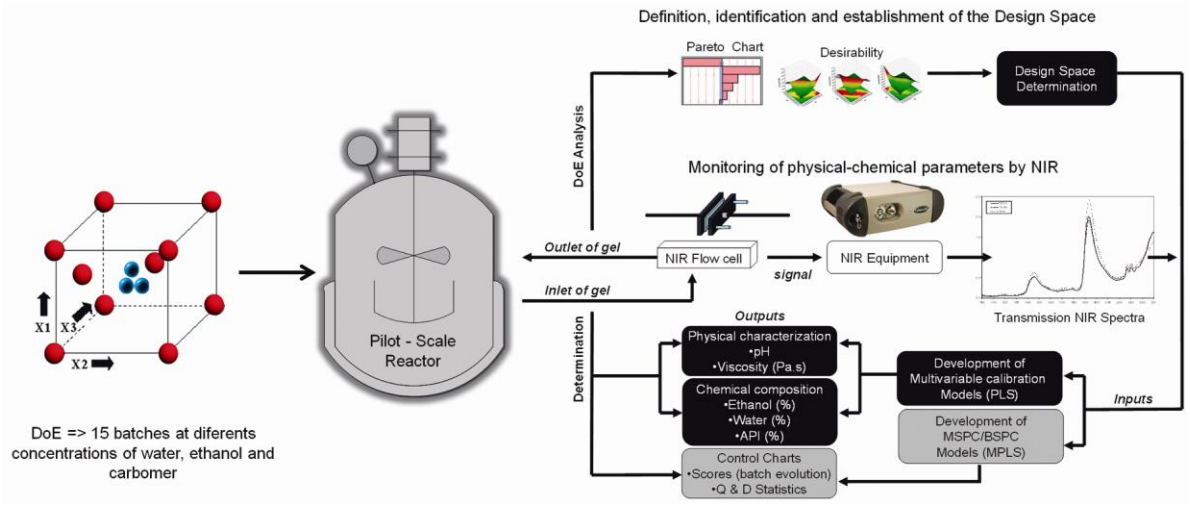

Figure 1. Strategy applied in the development of the experiments.

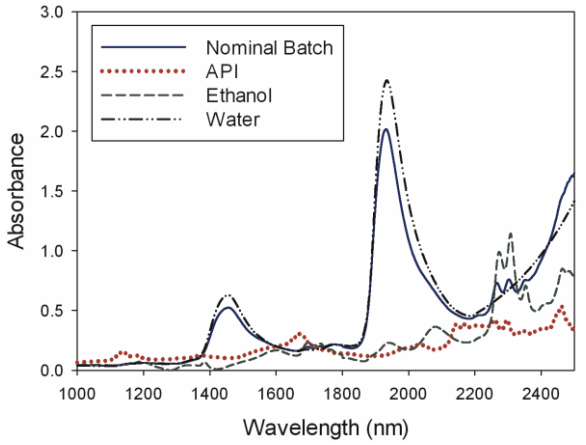

Figure 2. Near infrared spectra for a pharmaceutical gel sample (nominal), water, the API and ethanol.

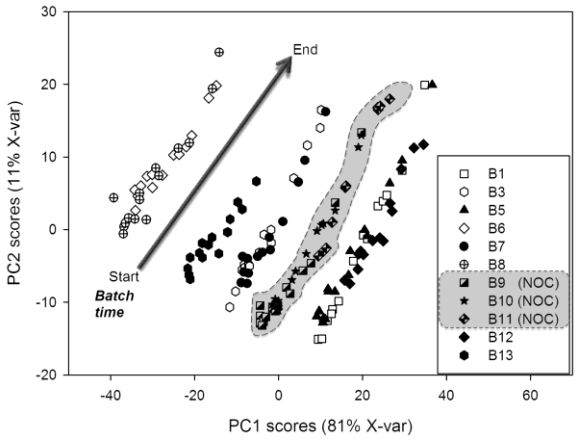

Figure 3. Scatter plots for DoE batches PC1 vs PC2 (B2 and B4 were excluded).

Table 1. Figures of merit of the models for the determination of chemical and physical parameters.

Parameter	Chemical Parameters			Physical Parameters	
	Ethanol (%)	**Water (%)**	**API (%)**	**Viscosity (Pa.s)**	**pH**
Spectral mode	1st derivative	1st derivative	1st derivative	1st derivative 29p + SNV	1st derivative 29p + SNV
Spectral range (nm)	1832–2100	1300–1642 1801–2100	1600–1800	1000–1796 1984–2112	1100–1796 1861–2400
Nº PLS factors	2	2	3	5	5
NOC target value *	33.60	63.09	1.21	3.00	6.22
Calibration set					
Nº samples (laboratory)	9	8	15	-	-
Nº samples (production)	10	3	30	41	42
Calibration range *	24.7–41.9	55.2–72.6	1.0–1.4	2.0–5.7	4.5– - 6.5
Prediction set					
Nº samples (laboratory)	14	13	26	34	34
Prediction range *	28.1–38.4	58.9–69.2	1.1–1.2	2.2–4.0	4.6–6.4
RMSEP*	**0.636**	**0.649**	**0.027**	**0.359**	**0.394**

*Results in respective unites

Reference paper as:
J.G. Rosas, M. Alcalá, J Mª. González and M. Blanco (2012). Quality by design: foundation of design space and near infrared monitoring for a semi-solid pharmaceutical manufacturing process, in: Proceedings of the 15th International Conference on Near Infrared Spectroscopy, Edited by M. Manley, C.M. McGoverin, D.B. Thomas and G. Downey, Cape Town, South Africa, pp. 159-162.

Table 2. Statistics of residuals of NIR predictions for a batch of pharmaceutical gel.

Statistical parameters	Chemical Parameters			Physical Parameters	
	Ethanol (%)	Water (%)	API (%)	Viscosity (Pa.s)	pH
Average of residuals*	-0.17	0.04	-0.01	-0.12	0.11
St. dev. of residuals*	0.32	0.31	0.06	0.46	0.23
$t_{crit\ (\alpha=0.05)}$	2.14	2.14	2.14	2.16	2.14
$t_{obs\ (\alpha=0.05)}$	2.12	0.51	0.43	0.98	1.86
Degrees of freedom	14	14	14	13	14
RMSEP*	**0.35**	**0.30**	**0.06**	**0.48**	**0.26**

*Results in respective unites

Conclusions

NIR spectroscopy is a highly suitable tool for process analytical technology when combined with multivariate chemometric methods. The combination of NIR spectroscopy and chemometrics can be used to develop an expeditious method for quantifying the composition of gel and assessing temporal changes in major physical factors affecting the quality of the product (specifically, viscosity and pH).

Acknowledgements

The authors are grateful to Spain's Ministry of Science and Technology for funding this research as part of Project CTQ2009-08312 and to Laboratorios Menarini (Badalona, Spain) for supporting the conduct of this work.

References

1. ICH. ICH-Topic Q8 (R1): *Pharmaceutical Development*, (2008).
2. M. Blanco and M. Alcala, *Process Analytical Technology: Spectroscopic Tools and Implementation Strategies for the Chemical and Pharmaceutical Industries*, ed by K. Bakeev, John Wiley & Sons Ltd, p. 463–491 (2010).
3. M. Ulmschneider, G. Barth and E. Trenka, *Drugs* **43**, 71–73 (2000).
4. M. Blanco and M.A. Romero, *Analyst* **126**, 2212–2217 (2001).
5. V.W. Uhl and J.B. Gray, *Mixing: Theory and Practice*. New York (1967).
6. R.E. Schirmer, *Modern Methods of Pharmaceutical Analysis*. 2nd Ed., CRC Press (1991).
7. J.K. Drennen and R.A. Lodder, *Pharmaceutical applications of near-infrared spectrometry*. JAI Press, Greenwich, CT (1993).
8. X. Zhou, P. Hines and M.W. Borer, *J. Pharm. Biomed. Anal.* **17**, 219–225 (1998).
9. J.A. Jones, I.R. Last, B.F. MacDonald and K.A. Prebble, *J. Pharm. Biomed. Anal.* **11**, 1227–1231 (1993).
10. M.S. Kamat, R.A. Lodder and P.P. DeLuca, *Pharm. Res.* **6**, 961–965 (1989).
11. E. Ciurczak, *Appl. Spectrosc. Rev* **23**, 147–163 (1987).
12. J.L. Ilari, H. Martens and T. Isaksson, *Appl. Spectrosc.* **42**, 722–728 (1988).
13. K.M. Morisseau and C.T. Rhodes, *Pharm. Res.* **14**,108–111 (1997).
14. P.E. Luner, S. Majuru, J.J. Seyer and M.S. Kemper, *Pharm. Dev. Technol.* **5**, 231–246 (2000).
15. M. Blanco, D. Valdes, M.S. Bayod, F. Fernandez-Mari and I. Llorente, *Anal. Chim. Acta* **502,** 221–227 (2004).
16. E.W. Ciurczak, *Am. Pharm. Rev.* **5**, 68–73(2002).
17. R.D. Maesschalck, F.C. Sanchez, D.L. Massart, P. Doherty and P. Hailey, *Appl. Spectrosc.* **52**, 725–731 (1998).
18. M. Blanco and M.A. Romero, *J. Pharm. Biomed. Anal*. **30**, 467–472 (2002).
19. M. Kemper, E. Magnuson, S. Lowry, W. McCarthy, N. Aksornkoae, D. Watts, J. Johnson and A. Shukla, *AAPS J.* **3**, 81–85 (2001).
20. R. Mackison, S.J. Brinkworth, R.M. Belchamber, R.E. Aries, D.J. Cutler, C. Deeley and H.M. Mould, *Appl. Spectrosc.* **46**, 1020–1024 (1992).
21. A.G. Cavinato, D.M. Mayes, Z. Ge and J.B. Callis, *Anal. Chem.* **62**, 1977–1982 (1990).
22. H.R. Bjørsvik, *Appl. Spectrosc.* **50**, 1541–1544 (1996).
23. A.M. Mouazen, J. De Baerdemaeker and H. Ramon, *Soil Tillage Res.* **80**, 171–183 (2005).
24. M. Islam, N. Rodríguez-Hornedo, S. Ciotti and C. Ackermann, *Pharm. Res.* **21**, 1192–1199 (2004).
25. M. Islam, N. Rodríguez-Hornedo, S. Ciotti and C. Ackermann, *AAPS J.* **6**, 61–67 (2004).

Reference paper as:
J.G. Rosas, M. Alcalá, J Mª. González and M. Blanco (2012). Quality by design: foundation of design space and near infrared monitoring for a semi-solid pharmaceutical manufacturing process, in: Proceedings of the 15th International Conference on Near Infrared Spectroscopy,
Edited by M. Manley, C.M. McGoverin, D.B. Thomas and G. Downey, Cape Town, South Africa, pp. 159-162.