Engineering Advances, 2022, 2(2), 201-210
https://www.hillpublisher.com/journals/ea/
ISSN Online: 2768-7961

PAT Monitoring of Coating Pan by NIR - PLS Method Calibration Approach

Andrea Umberto Gelain[1,*], Eleonora Mustorgi[2], Alice Melocchi[3], Emiliano Genorini[2], Giuseppe Buratti[1]

[1]Freund-Vector Corporation European Laboratory, Via Enrico Mattei 2, Villasanta (MB), Italy.
[2]VIAVI Solutions, Via Cernuschi 8, Monza (MB), Italy.
[3]Università degli Studi di Milano, Dipartimento di Scienze Farmaceutiche, Via G.Colombo 71, Milano (MI), Italy.
*

How to cite this paper: Andrea Umberto Gelain, Eleonora Mustorgi, Alice Melocchi, Emiliano Genorini, Giuseppe Buratti. (2022) PAT Monitoring of Coating Pan by NIR - PLS Method Calibration Approach. *Engineering Advances*, 2(2), 201-210.
DOI: 10.26855/ea.2022.12.012

Received: November 20, 2022
Accepted: December 18, 2022
Published: December 30, 2022

[*]**Corresponding author:** Andrea Umberto Gelain, Freund-Vector Corporation European Laboratory, Via Enrico Mattei 2, Villasanta (MB), Italy.
Email: andrea.gelain@freund-vector.com

Abstract

A process analytical technology (PAT) method relying on near infrared (NIR) diffuse reflectance spectrometry was developed to determine the average coating thickness applied and the weight gained by tablets during coating process. The NIR device was installed inside the pan directly in contact with the cores under processing and relevant spectra were recorded in real time during the entire coating process. The method required principal component analysis (PCA) and partial least squares regression (PLS). The primary methods to calibrate PLS are tablet weight gain and coating thickness, they were carried out using the chemometric methods. The PLS-model was employed as the calibration curve for an online process monitoring and was based on the spectra obtained from the tablets during coating, pretreated with SNV and first derivative, and ordered into one object. This way, the method developed could be advantageously used for in-line PAT monitoring. Additional characterization insights were attained by calibrating the spectra versus the weight gain data obtained from at-line tablet weighing.
Overall, the possibility to monitor multiple parameters using just one device and one spectrum was demonstrated.

Keywords

PAT, PAT Monitoring, Process Analytical Technology, Coating Pan, NIR, Coating

1. Introduction

Real-time control of the production process has gained increasing importance in the pharmaceutical industry, as it allows to ensure accurate reproducibility of the process itself and consistency of the quality of the finished product over time. This approach could be especially advantageous when dealing with products of large use, such as orally administered tablets, as it would reduce the associated manufacturing and quality control costs. Indeed, tablets currently represent one of the most common widespread dosage forms and ensures very high patient compliance, being present on the market both as coated and uncoated products. Tablets are often coated for various reasons. Coatings can be classified into functional and non-functional. Non-functional coatings are performed for cosmetic reasons, such as coloring the tablets (for branding reasons or to distinguish between different dosages), or to cover some appearance defects like a dark-colored component of the blend that might make the look of the tablet completely unappealing. Functional coatings are intended to improve taste masking and to control the drug release form the inner core ensuring pH-, rate- and time-dependent kinetics to be attained. Usually, the endpoint of this coating process is based on a calculation of the theoretical amount of coating material to be sprayed on. The precise control of the thickness of the coating layer is definitely important to assure the perfect functionality of the final-products, especially in the case of modified-release drug delivery systems and also, from a production point of view, to spare materials, reduce process time, thus overall enhancing sustainability and cost-saving.

The method presented in this paper is based on spectrometric measurements using a VIAVI Solutions MicroNIR PAT-U near infrared (NIR) diffuse reflectance spectrometer. Measurement by NIR spectrometry is rapid and simple method [1] for in-process or at-line monitoring controls and would be especially useful in the case of film coating. Near infrared (NIR) spectroscopy investigates the absorption of electromagnetic radiation in the wavelength range from 700 to 2500 nm (wavenumber from 14,300 cm− 1 to 4000 cm− 1). NIR region is situated before the mid infrared region (2500–10,000 nm) and far infrared region (10–1000 µm). In NIR spectroscopy, samples are irradiated with NIR light which brings molecules to a higher vibrational state when NIR radiation is absorbed. NIR light is absorbed only when induced vibration results in the change of molecule's dipole moment (Fig. 1). Therefore, two-atomic molecules require a permanent dipole to be IR active, while larger molecules with polyatomic structure require a dipole induced by vibration. O-H, N-H, C-H, and S-H bonds are known as strong NIR absorbers, since their dipole moment is high. On the other hand, H2 does not absorb NIR radiation because no change in a dipole moment occurs during its vibration. Absorption of the radiation can lead to vibration in 2 modes: stretching and bending. Stretching presents continuous change in the interatomic distance along the bond axis, while bending presents a change in bond angle [2]. In the near infrared region covered by the spectrometer (908 – 1676 nm), the information comes from the overtones of molecular vibrations [3, 4]. Because molecules differ in their vibrations, and hence in their vibrational overtone spectra, the near infrared region can be very useful in identifying the characteristics of chemical systems without the necessity of sample preparation [5]. The LVF design of the NIR device allows to install the probe in the process environment without being affected by vibrations [6]. These procedures are based on spectral changes occurring when the coating thickness varies, and the procedures make use of chemometrics to relate the spectral information to the amount or thickness of the coating [7]. The aim of the present study was to show how to quantify the amount of coating applied on the tablets**.** In this study, the coating process in coating pan was taken in consideration, different coating materials were tested, the process was monitored by NIR to determine simultaneously the weight gain and the coating thickness of the coated tablets in real time. To perform this, it was also necessary to establish the correlation between the physical properties of the tablets and spectra of the NIR device, to demonstrate the independency from the coating material used, and to find a mathematical approach to the in-process control using derivative method, PLS calibration and cross-validation method.

Figure 1. NIR and Spray bar setup.

2. Methods

Placebo tablets (round, biconvex, 8mm diameter, 4mm thickness, 250 mg) were used as coating cores in this study. The set of processes were performed in a coating pan (Freund-Vector LDCS Pilot) set up with 8L pan, Schlick 975 two ways spray gun and Viavi MicroNIR PAT U® device. The NIR device was positioned inside the coating pan through the front door, attached to the spray bar and mounted parallel to the spray gun. A VIAVI specifically designed 10cm extended probe was used to put the tip of the NIR device directly in contact with the tablets. The Freund-Vector pan is fully-perforated, in this configuration the airflow circuit is completely sealed in working conditions, the airflow is generated by a sucking main fan positioned at the end of the circuit and the heated air passes completely through the tablet bed; since the fan is pulling and not pushing air through the pan, the airflow produced is much less turbulent; the NIR device was positioned parallel to the airflow direction and this helped to keep the NIR window clean during the process. Moreover, the fully perforated pan houses just the spray bar through the pan door, there is no need to position the inlet and outlet air ducts, so there is much more space to install the NIR device and to ensure proper connections. A clearance of about 3 cm was set between the NIR device and the pan baffles.

The mass of dry cores was adjusted for the type of equipment to achieve appropriate product movement and the correct quantity was determined to be 4000 g. The process was repeated using two different coating formulations (Colorcon Opadry® Complete Film Coating System, white HPMC-based and Opadry® II High Performance Film Coating System, blue PVA-based) to demonstrate the independency of the measurements taken from the coating polymers employed (Table 1). Also, it was decided to use different colors to demonstrate the independency of the method under development from different dyes and colorants.

Table 1. Coating Agent Formulations

Coating Agent	Quantity (g)	% Suspension	Target Weight Gain (%)
Opadry I White	400	12	10
Opadry II Blue	400	12	10

Using the equipment configuration described above, two different processes (i.e. the former based on the HPMC formulation and the latter on the PVA one) were carried out by setting the same parameters, which were indicated as the most appropriate by the manufacturer of the selected coating formulations (Table 2).

Table 2. Process Parameters set

Coater Ariflow (m^3/hr)	Inlet Air Temp (°C)	Exhaust Air Temp (°C)	Pan Speed (RPM)	Atomization Press (bar)	Pattern Press (bar)	Spray Rate (g/min)
110	60	40	20	1.3	1.2	15

The process was monitored by VIAVI MicroNIR PAT-U device acquiring a spectrum every 10 seconds per 1000 repetitions for the entire length of the process without the need for stopping or pausing the process (Figure 2). Before performing an automatic online reading of the product parameters during the process, it is necessary to build a calibration curve for the NIR system, so 3 batches per each coating material were run to acquire at-line data and build the calibration curve. Specifically, 30 tablets were sampled at regular 15-minute intervals, they were weighted to calculate the mean weight value. The diameter and thickness of the coated tablets were measured individually using a manual high precision 3-point digital micrometer. From the values attained, the mean diameter and thickness were determined. In this respect, the uncoated tablets were used as a reference and the coating thickness was calculated by difference.

The data collected were analyzed and processed using CAMO Unscrambler® software.

The first transformation applied to the data matrix was Standard Normal Variate (SNV), this is a transformation usually applied to spectroscopic data in order to remove scatter effects by centering and scaling each individual spectrum (i.e. a sample-oriented standardization) (Figure 3). The practical result of SNV is that it eliminates both multiplicative interferences associated with scattering phenomena and particle size effects from spectral data, while, on the vertical scale, each spectrum resulted centered on zero. For the above-mentioned reason, SNV is typically used with diffuse reflectance spectrum.

After this, the First derivative of the spectra contained in the data matrix was calculated: this is generally done to correct for baseline effects in spectra for the purpose of removing nonchemical effects and creating robust calibration models. Derivatives may also aid in resolving overlapped bands which can provide a better understanding of the data, emphasizing small spectral variations not evident from the raw data.

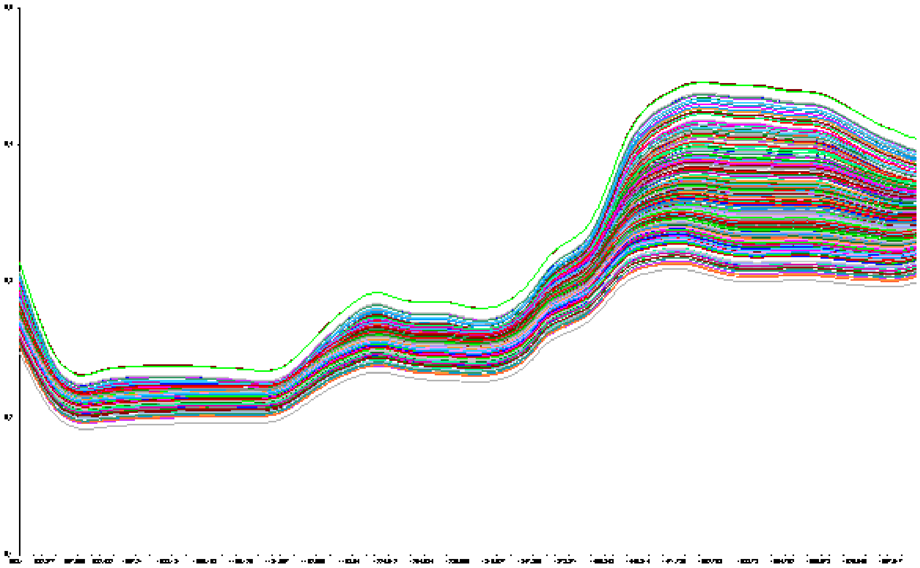

Figure 2. Raw Spectra of Batch 20190130-01- Opadry I White.

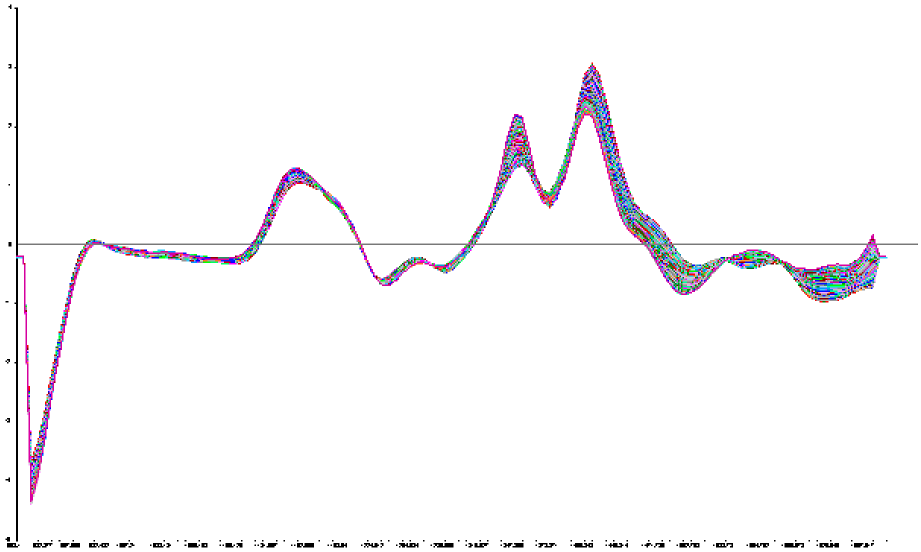

Figure 3. SNV and 1st Derivative Trasformation of the Spectra of Batch 20190130-01- Opadry I White.

After these transformations, the Principal Component Analysis (PCA) was performed after the transformations: PCA can be used to reveal the hidden structure within large data sets. It provides a visual representation of the relationships between samples and variables and provides insights into how measured variables cause some samples to be similar to, or how they differ from each other. In this respect, PCA method results very useful to have a glance on how the process is performing. If the process itself is coherent it will be possible to notice an alignment of the points on the PCA chart, indicating that the process is following a precise direction (process trajectory). It is also possible to distinguish between the different process phases represented by changes in the slope of the chart.

To analyze the results, the spectra treated in this way were correlated to the real values of the product parameters (weight and thickness) measured at-line, using the PLS (Partial Least Squares) regression method.

Data relevant to 3 batches prepared using the same coating formulation were combined together to verify the model robustness and to create the calibration curve.

Finally, a new batch for each coating agent considered was performed, during which the thickness and weight gain values of the processed tablets were monitored autonomously by the NIR device basing on the built calibration curve. Manual measurements were repeated anyway to collect the reference and have the possibility to verify the results given by the NIR system comparing it to the measured values.

3. Results

The target weight gain for a tablet coating process is usually around 3%, however, in this study, it was increased to 10%, too much for the common uses, to put better in evidence the growth of the coating film and to highlight the capabilities of the NIR probe to monitor the thickness in a wide range.

The results discussed in the following paragraphs mainly focused on the coating formulation containing HPMC as a coating agent, as the other polymer tested (i.e. PVA) gave results that were completely analogous in terms of NIR response.

3.1 Calibration of the NIR Probe

The NIR illuminates the sample using two tungsten lamp and measures the reflectance given by the sample itself that is the result of the portion of the irradiation reflected and the portion absorbed. The spectrum of the NIR is split in 125 wavelengths, and the response of the system is a table reporting all the 125 values of reflectance per each wavelength. The sum of the reflectance values represents the overall spectrum of the sample analyzed. During online monitoring, the NIR probe was set to perform, every 10 seconds, 1000 repetitions of the spectrum acquisition per each reading. The result is the average reflectance of 1000 repetitions of the acquiring done on the tablets moving in the coating pan. Since the movement of the tablets in the pan is random, this gives the possibility to monitor different tablets during the same acquisition and, above all, the possibility to monitor different spots along the surface of a single core could be evaluated during the same acquisition, ensuring, through the complete monitoring of the convex part, the lateral part and the edges, that a complete investigation of the coating applied was carried out.

As the NIR probe should be calibrated for every different material used, because the absorbance would be different in view of the chemical composition of the coating, a calibration curve was preliminarily built up.

Three different batches were run for each coating material, to ensure the consistency of the NIR readings. Each batch was run using the same process parameters and was monitored by NIR using the same settings. 30 tablets were sampled every 15 minutes, weighted, and measured to obtain the real data necessary to build the correlation with the spectra acquired. The mean value of weight and thickness was taken in consideration to build the calibration curve.

The Spectra acquired were imported in the Unscrambler software and the physical values were correlated to the corresponding spectrum.

3.2 PCA Analysis

First of all, the pretreatments (SNV and First derivative) were applied to the data collected, then the PCA analysis was performed. The PCA was employed to reveal the hidden path in the data set, showing an evident direction in which the process is moving. Specifically, it was possible to see a long slope corresponding to the coating phase and a sudden change of slope corresponding to the drying phase. This indicates that the NIR probe was able to correctly follow the different steps of the coating process (Figure 4).

It was used a 7-component PCA analysis; 95-99% of the Variance was explained by the PC1 and PC2 for all the considered batches.

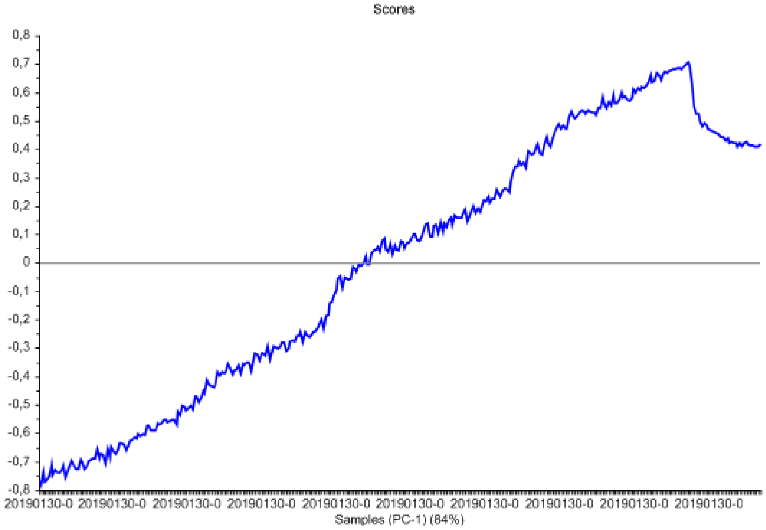

Figure 4. PCA analysis of batch 20190130-01 (Opadry I white).

3.3 PLS Analysis

Since the PCA demonstrated that the probe was capable to perfectly monitor the process, the PLS regression analysis was performed to test the correlation between the physical, measured values of thickness and weight gain and the spectra collected by the NIR.

First of all, every batch was analyzed separately, and the resulting R-square values turned out extremely high for each of them, both for calibration and validation test set (Figure 5-6). This showed a very good correspondence between the measured values and the data acquired by the NIR probe. The model was tested using cross validation, where the responses were the coating thickness and the weight gain of the tablets.

The cross validation was performed using the 'leave one out' method because all the calibration samples were derived from different times of the process.

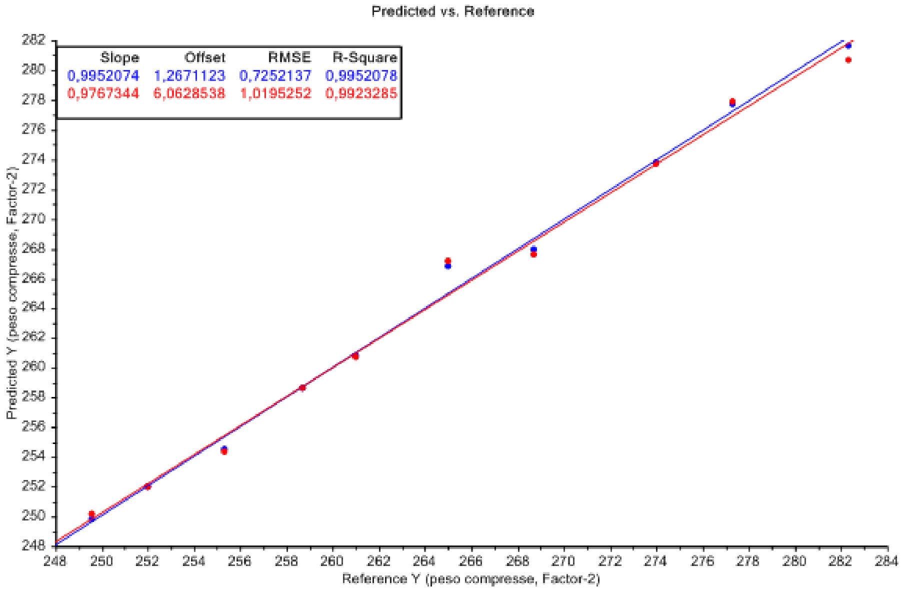

Figure 5. PLS weight analysis Batch 20190130-01- Opadry I White.

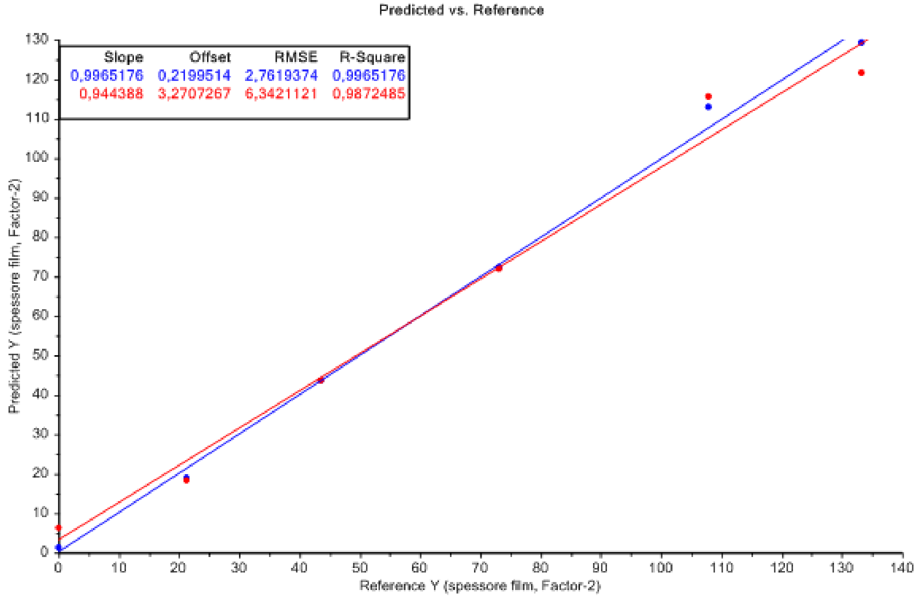

Figure 6. PLS Coating Thickness Analysis Batch 20190130-01- Opadry I White.

Due to the good correlation between the spectra and the measured data, the regression method was used to calculate all the values corresponding to the spectra recorded during the whole process. The results were extremely reliable, showing the monitoring of all the process during the coating phase with an error of less than ±1mg in the case of the weight gain and less than ±6microns when dealing with the coating thickness for all the batches considered (Figure 7). During the drying phase we observed an incremental loss of precision due to the uneven shrinking of the coating film on the tablets and to partial curing.

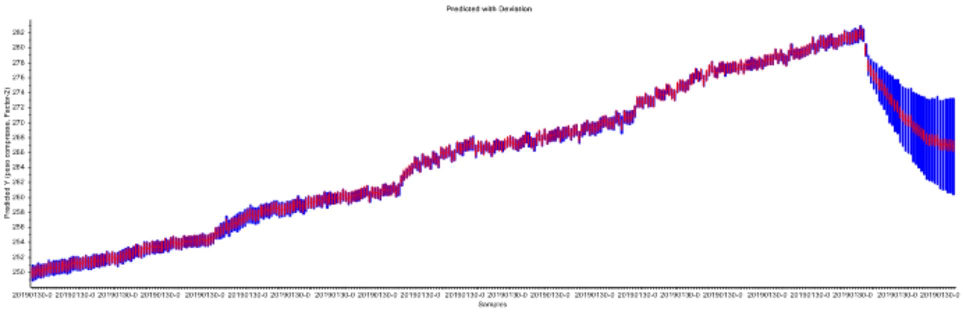

Figure 7. Weight Prediction with Standard Deviation for Batch 20190130-01- Opadry I White.

3.4 Calibration curve

Every compound analyzed using NIR spectroscopy reacts differently to the NIR signal, depending on its chemical characteristics, so the calibration curves must be built specifically for each coating material.

For this purpose, all the data generated by the 3 initial calibration batches were combined together to form a single data matrix, which was analyzed following the same steps previously described to ensure that the NIR readings were coherent (Figure 8 and 9).

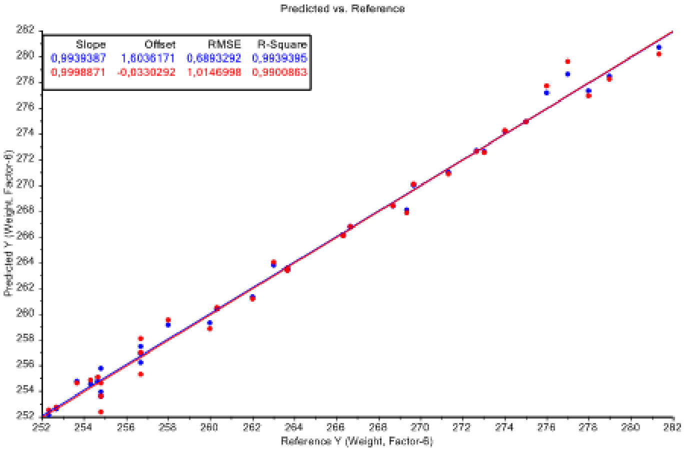

Figure 8. PLS Weight Analysis 3 combined batches - Opadry I Wite.

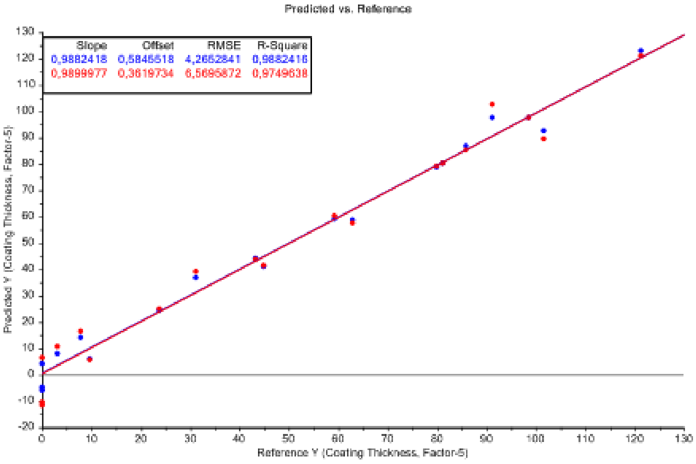

Figure 9. PLS Coating Thickness Analysis 3 combined batches - Opadry I white.

The PLS regression applied to the matrix comprising three batches showed a very good consistency of the readings, with an R-square of 0,988 in the calibration and 0,975 during the relevant validation, demonstrating the capability of the NIR probe to follow different processes in a very reproducible way. The combination of the 3 batches was used as a model for the subsequent online reading.

A new batch of tablets was thus coated to verify the model, the tablets under processing were sampled and measured as before described to have a reference to compare the results of the online reading with, the NIR probe was set to online reading and the previously built model was used as a calibration curve.

The data acquired were stored and compared with the manual measurements and the results were very positive: the values calculated by the NIR software, and the values measured at-line were almost identical for the whole length of the process.

Those positive results were achieved both for the HPMC based coating system and for the PVA based one, the precision of the NIR monitoring of the process was almost identical.

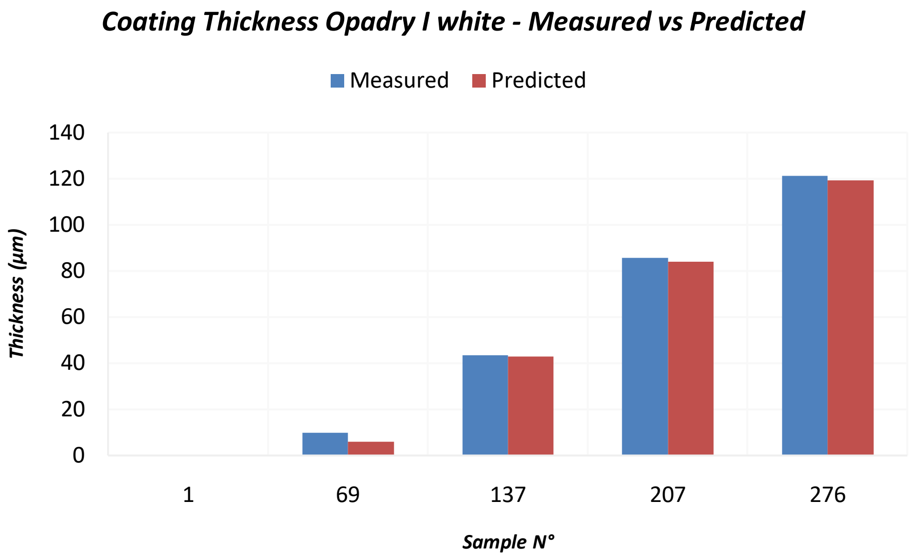

Figure 10. Opadry I white Coating Thickness.

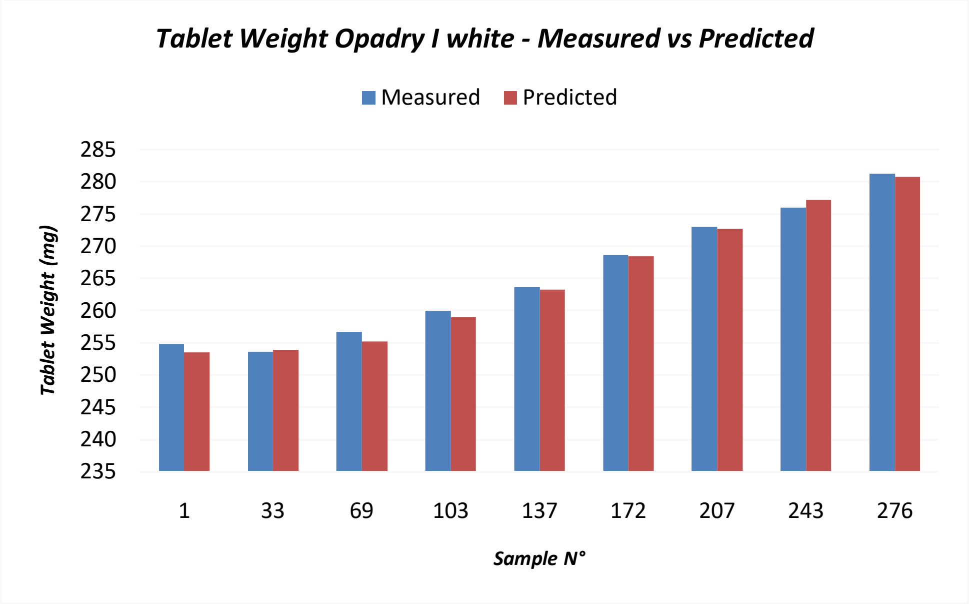

Figure 11. Opadry I white Tablet Weight.

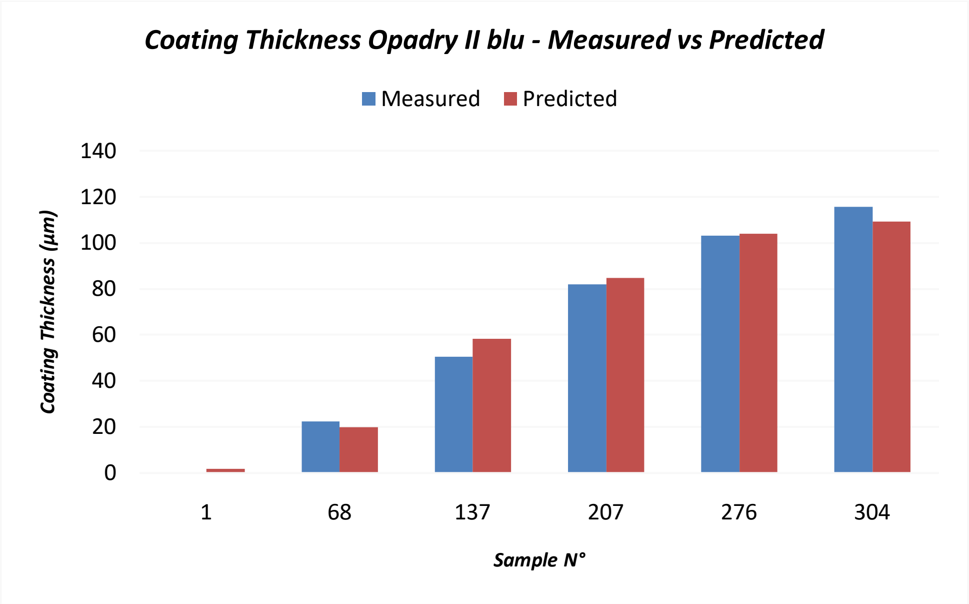

Figure 12. Opadry II blu Coating Thickness.

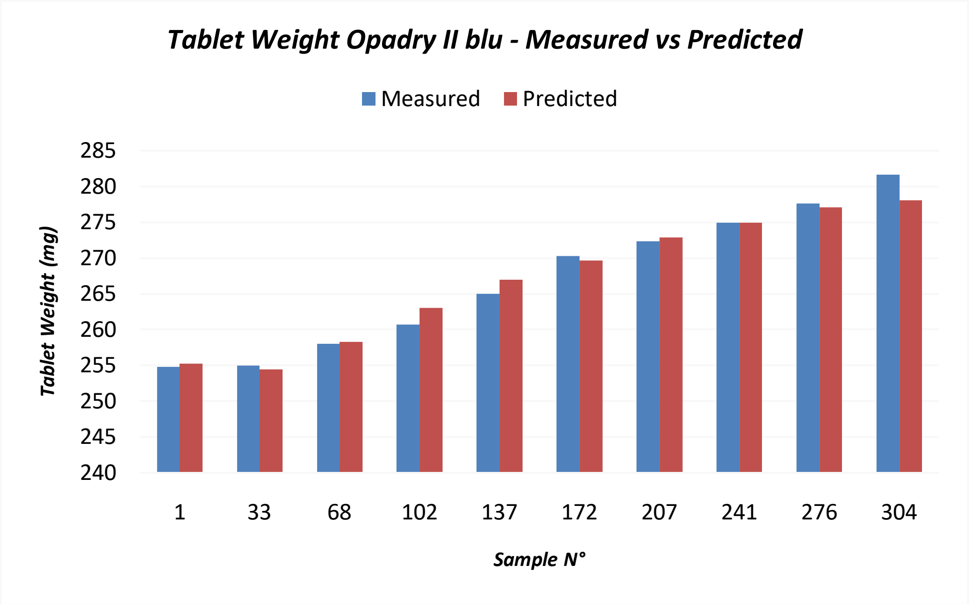

Figure 13. Opadry II blu Tablet Weight.

4. Conclusion

The process was characterized by a very solid correlation between the absorbance values read by the NIR instrument and the coating thickness and weight gain data collected. This indicated that the model was robust, reproducible, and consistent.

Reproducibility precision ensured by PAT monitoring would enable process control without the need for constant sampling and at-line analyses. This would allow high-quality real-time control over the product and provide the possibility to save time, energy and reduce the waste of raw materials.

This study also demonstrated the possibility to simultaneously control multiple product properties using just one device and one signal. This approach would be fundamental i) to define the endpoint of the process, directly measuring the critical quality parameters on the cores and not relying on approximations as well as calculations, and ii) to immediately recognize any deviations from the standard specs, thus implementing prompt corrections and avoiding discarding the whole batch.

In this respect, future development could be carried out to integrate the PAT technology with the control software of the coating pan. This way, a real-time control of product characteristics instead of process parameters could be performed. Such an integration can favor the development of a continuous manufacturing process that has to be kept constantly under control to guarantee the reproducibility of the final product.

References

[1] J.D. Kirsch, J.K. Drennen Appl. Spectrosc. Rev., 30 (1995), pp. 139-174.
[2] Klemen Korasa, FrancVrečer: Overview of PAT process analysers applicable in monitoring of film coating unit operations for manufacturing of solid oral dosage forms, 2017.
[3] L.G. Weyer Appl. Spectrosc. Rev., 21 (1985), pp. 1-43.
[4] I.M. Mills, in: I. Murray, I.A. Cowe (Eds.), Making Light Work: Advances in Near Infrared Spectrometry, VCH, Weinheim, 1991, pp. 67–80.
[5] Kim H. Esbensen, Andres D. Roman-Ospino, Adriluz Sanchez, Rodolfo J. Romanach: Adequacy and verifiability of pharmaceutical mixtures and dose units by variographic analysis (Theory of sampling) – A call for a regulatory paradigm shift, International journal of pharmaceutics, 2015.
[6] Nada O'Brien, Charles A. Hulse, Donald M. Friderich, Fred J Van Milligen, Marc K.vongunten, Frank Pfeifer, Heinz W Siesler: Miniature Near Infrared (NIR) Spectrometer Engine For Handheld Applications; Proceedings of SPIE – The International Society for Optical Engineering, 2012.
[7] M.Anderssona, M.Josefson, F.W.Langkilde, K.-G.Wahlund. (1999). Monitoring of a film coating process for tablets using near infrared reflectance spectrometry. *Journal of Pharmaceutical and Biomedical Analysis*, 20, 27-37.