IN-LINE FLUID BED GRANULATION MONITORING BY NIR SPECTROSCOPY. METHOD DEVELOPMENT AND VALIDATION

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Abstract

This study describes the development of an in-line NIR fluid bed granulation monitoring method, evaluating the capacities of a Viavi microNIR™ spectrometer during the process. For this purpose, an experimental design was set up, having binder spraying rate and inlet air temperature as independent inputs. NIR spectra were recorded continuously, the acquired data was pre-processed and principal component analysis was performed in order to develop a multivariate model. Applying the developed model, the evolution of each parameter could be well underlined, moreover the projected score line plots obtained from the data analysis enabled the capturing of the variance related to moisture content and granule growth throughout the granulation process. This allowed the ulterior time optimization by an accurate determination of the process end point. In order to evaluate the sensibility of the monitoring method, additional runs were performed varying the binder spraying rate and evaluating the registered moisture levels. The results showed that the in-line monitoring of moisture content facilitates the process control, increasing its reliability and leading to an optimum product. Furthermore, the NIR process analyser based on linear variable filter technology proved to be sensitive enough to clearly distinguish each step of the process.

Rezumat

Acest studiu descrie dezvoltarea unei metode infraroșu apropiat (NIR) *in-line* de monitorizare a granulării în pat fluidizat, evaluând pe această cale și capacitățile unui spectrometru Viavi microNIR™. În acest scop a fost conceput un plan experimental având ca variabile independente de proces, debitul de pulverizare al soluției de liant și temperatura aerului de intrare. Spectrele NIR au fost înregistrate continuu pe durata întregului proces, pentru fiecare determinare experimentală, datele obținute au fost pre-procesate și analiza componentelor principale (PCA) a fost aplicată în vederea dezvoltării unui model multivariat. În continuare, graficul de scoruri obținut pe baza modelului PCA a permis monitorizarea întregului proces de granulare pe baza variației umidității patului de pulbere și a creșterii granulometrice, oferind astfel posibilitatea optimizării și determinării punctului final al procesului. Pentru a valida metoda dezvoltată, au fost efectuate determinări experimentale adiționale în cadrul cărora a fost variat debitul de pulverizare, evaluând nivelul de umiditate. Rezultatele demonstrează faptul că monitorizarea în timp real a nivelului de umiditate facilitează controlul procesului, crescându-i fiabilitatea și furnizând un produs optim. În plus, spectrometrul NIR utilizat s-a dovedit a fi suficient de sensibil pentru identificarea clară a fiecărei etape a procesului de granulare în pat fluidizat.

Keywords: microNIR, in-line monitoring, process analytical technology, fluid-bed granulation, design of experiments

Introduction

According to the Food and Drug Administration [9] and the International Council for Harmonisation (ICH) Q8 [16] guidelines, the implementation of Quality by Design (QbD) and Process Analytical Technology (PAT) is highly recommended for the pharmaceutical manufacturing. Moreover, those two concepts are giving the pharmaceutical industry the opportunity to develop well-controlled manufacturing methods and to optimise the processes [23]. In order to do so, a science-based understanding of the critical process parameters (CPPs) is crucial for the control and assurance of the products critical quality attributes (CQAs) [25]. Real-time process monitoring is a promising solution that could improve the process understanding and allow its continuous optimisation,

yet to be suitable for in-line monitoring, the analytical method should be fast, non-invasive, process adaptable and should not interfere with the process itself. Near-infrared Spectroscopy (NIRs) owns all those characteristics, therefore being implemented in the pharmaceutical industry for a long period of time [3, 11].

Fluid bed granulation is a key manufacturing step that allows the production of granules by spraying a binder solution over a fluidized powder. The general purpose of granulation is to improve flow characteristics, blend uniformity, compression properties and to reduce the dust [4]. There are two critical parameters that should be observed during this process. The first one is the water level reached during the binder spraying, which is closely linked to the growth of the granules. The second parameter is the drying

time of the granules, especially in the case of a fluid bed process, the drying time should not be prolonged more than necessary [11, 20]. Several authors have already developed in-line NIR monitoring methods for water content assessment during granulation and end-point determination of the drying process [2, 10, 12, 14, 15, 18, 21, 22]. However, to the best author's knowledge, the use of an experimental design for the development of a monitoring method has not yet been described.

In this work, we describe the development of a NIR monitoring method by the means of an experimental design. Through systematic variations of process inputs and simultaneous evaluation of their effects, this chosen approach had the capacity to provide the largest amount of information from a relatively low number of experimental runs and to identify interactions between the studied process inputs [6]. The NIR spectrometer was mounted on the expansion vessel of a fluid bed granulator, avoiding any interferences between the spectrometer and the process or the product, and NIR spectra have been registered for all performed experimental runs. Based on the pre-treated spectral data, a Principal Component Analysis (PCA) was developed and specific statistical parameters were chosen as outputs of the experimental design. The parameters analysed and introduced as responses of the experimental design were the calculated PCA score values, this allowed a better understanding of the correlations between CPPs and CQAs of the final granulate. Furthermore, the analysis of the PCA model and the score line plot projections for each principal component enabled an exact observation of the powder beds water content and the granule growth, allowing a precise estimation of the process end-point. Therefore, the developed NIR monitoring method was found to be a powerful PAT tool considering its ability to provide real time information related to product characteristics and process behaviour.

Materials and Methods

Materials

The active pharmaceutical ingredient (API) chosen for the product formulation was a type that requires granulation to improve the flow properties, blend uniformity and to reduce the dust formation. Lactose monohydrate – Pharmatose 150M (DFE Pharma, Goch, Germany) and microcrystalline cellulose – Avicel PH102 (FMC BioPolymer, Philadelphia, USA) were used as diluents and polyvinylpyrrolidone – Kollidon 30 (BASF, Ludwigshafen, Germany) was used as granulation binder. In this formulation lactose was the main diluent, microcrystalline cellulose with larger particles was also introduced in order to increase the powder bed volume. The granules formulation was established after preliminary studies (data not shown) and the final formulation consisted of 25.65% API, 38.45% lactose, 32.05% microcrystalline cellulose and 3.85% binder, used as a 10% aqueous solution. The batch size for the laboratory scale granulator was 312 g.

Experimental design

In order to perform the study, a D-optimal quadratic experimental design was developed using the Modde 11.0 design of experiments software (Sartorius Stedim, Umea, Sweden). As independent variables of the experimental design, two process parameters, each with 5 levels of variation, were chosen. The first studied parameter was the binder solution spraying rate and the second one the inlet air temperature. Four responses were analysed during this study, the first three represented the values of the 1st principal component (PC) registered on the score plot of the later generated Principal Component Analysis (PCA) model and the fourth represented the period of time needed for each granulate to dry completely, assessed also from the PCA score plot. The symbols and levels of all the experimental design variables are presented in Table I.

Table I
Symbols and levels of the experimental design variables

Variables	Symbol	Levels	
		Low	High
Independent variables (factors)			
Binder spraying rate (g/min)	X_1	8	12.3
Inlet air temperature (°C)	X_2	40	60
Dependent Variables (responses)			
1 st PC score after 1/3 binder spraying	Y_1		
1 st PC score after 2/3 binder spraying	Y_2		
1 st PC score at the end of binder spraying	Y_3		
Drying time (sec)	Y_4		

PC: principal component

The partial least square (PLS) fitting of the experimental data was assessed using specific statistical parameters like R^2 , Q^2 and the Analysis of variance (ANOVA) test. R^2 – the goodness of fit – represents the variation

of the responses explained by the model and Q^2 – the goodness of prediction – represents the prediction capacities of the model. R^2 and Q^2 take values between 0 and 1, and the difference between those

two statistical parameters should not exceed 0.2 - 0.3, higher differences would indicate an inappropriate fitted model. High R^2 , Q^2 values indicate a very good model and together, these are the most reliable parameters that could be used for the description of the model validity [8].

After performing all experimental runs according to the developed design of experiments, the effects of each studied independent variable over the chosen responses were evaluated by analysing the coefficients and contour plots generated by the experimental design software.

Granulation process

All the granulations were performed in an Aeromatic Strea 1 (GEA, Düsseldorf, Germany) fluid bed granulator. The total process time was between 41 and 50 min and involved three different phases: blending and preheating (2 min), spraying of the binder solution (10 to 15 min, depending on the spraying rate) and drying (30 min).

The three phases of the process were performed in the same apparatus, using the same inlet air temperature. The binder solution was sprayed through a 0.8 mm nozzle, using an atomizing pressure of 0.75 atm, varying the spraying rate according to the experimental design, as described in the experimental design. After the end of binder spraying, the only active process was the drying of the granules which continued without the interruption of the process, the single modified parameter being the fluidization airflow rate which was reduced from 4 - 5 m³/min to 3 m³/min.

Granules characterization

In order to assess the flow properties of the granules, the Hausner Ratio (HR), Carr Index (CI) and repose angle were determined according to well-known methods, described in the European Pharmacopoeia and other literature [5, 20]. All analyzes were performed in triplicate and the average was reported.

The final moisture content of the granules was determined applying the loss on drying (LOD) method using an Ohaus MB45 (Ohaus, Parsippany, USA) humidity scale. A quantity of approximately 0.8 - 1 g of granulate was dispersed on the sample pan and dried at 80°C, total moisture percent was automatically calculated at the moment when the weight variation was lower than 0.2% over 10 min.

NIR measurements and data pre-processing

The aim of this study was to develop a NIR spectroscopic method using an experimental design approach and therewith to evaluate the Viavi MicroNIR capacities of in-line/real-time monitoring of the granulation and determination of the process end-point. This spectrometer model incorporates a Linear Variable Filter technology which, according to the producer's specifications, allows the miniaturisation and increases the robustness of the device. A quality in-line monitoring method will lead to an improved process understanding and a consistent final quality of

the end product, hence avoiding batch loss. In order to achieve this, the entire granulation process was monitored in-line *via* NIR reflectance measurements and the corresponding spectra was analysed.

For the in-line NIR measurements, a MicroNIR PAT-Wireless spectrometer (Viavi Solutions, Milpitas, USA) was used and controlled with its own MicroNIR PAT 1700 software. The spectrometer has the capacity to register data in the 950–1650 nm range with a resolution of 6.2 nm *per* pixel. Spectra were recorded in reflectance mode, continuously at 10 s intervals and each one was acquired by averaging 200 scans, with an integration time of 7 milliseconds *per* scan. As shown in Figure 1, the device was mounted directly on the expansion vessel wall, ensuring the direct contact of the NIR detector with the powder bed, but in the same time, avoiding any interferences with the process or the product.

Figure 1.

Schematic diagram of the employed equipment (1 - fluidization air, 2 - exhaust, 3 - filters, 4 - spray arm, 5 - spraying nozzle, 6 - microNIR spectrometer)

After acquisition, the spectral data was transferred and pre-processed using the Simca 14.0 multivariate analysis software (Sartorius Stedim, Sweden).

The spectral pre-treatment methods applied to construct a robust model included first and second derivatives (FD and SD), standard normal variate (SNV), multiple scatter correction (MSC) and combinations of those pre-treatments, like SD followed by SNV or SD followed by MSC. Principal component analysis (PCA) was performed in order to extract and describe the information transmitted by spectral variability related to modifications of the product properties. The developed PCA models were evaluated using the cumulative R^2 and Q^2 for the X matrix. R^2X is described as the percent of variation of all the X values explained by the model and Q^2X as the percent of the variation of all the X values that can be predicted by the model. Those parameters take values between 0 and 1, and for a good model, both criteria should register as high values as possible. Another statistical parameter used for the evaluation of model performance was the eigenvalue (EV). This parameter is obtained multiplying the minimum number of observations and variables by R^2X . A component is

considered significant if its normalized EV is greater than 4 [7]. The optimum number of PC (principal components) was taken to be the lowest number of PCs that could give the best possible R^2X and Q^2X values, reflecting in the same time a relevant EV. Later, information regarding the product properties were evaluated with the use of scores line plots of the PCs, generated by Simca based on the developed PCA model. Projecting and comparing the PCs score values of each registered spectra, the granules moisture level and the total drying time of the granules could be assessed, thus allowing using the developed method for the non-invasive monitoring of the entire fluid bed granulation processes.

Validation of the monitoring method

Three experimental runs were performed in order to evaluate the method's capacity of detecting moisture content changes and also to validate the developed method. For this purpose, the binder solution spraying rate was changed during the spraying phase, while the inlet air temperature was maintained at 50°C for all three performed runs. For the two first runs, extreme parameters were initially set in order to investigate the detection method limitations. In the first case, half of the binder solution was sprayed with a higher rate of 15.5 g/min and then this parameter was reduced to an average rate of 10.2 g/min. For the second run, the first half of the binder solution was sprayed with a lower rate of 5 g/min, and for the rest of it, the spraying was increased to the average rate. The third run was performed using parameters generated by the optimiser function of the Design of Experiments (DoE)

software, based on a set of constraints according to the desired product profile.

Results and Discussion

Granule characterization

The same formulation has been used in all experimental runs in order to observe the variation of product properties caused only by process parameters. The flow and compression properties of the granules were analysed according to the European Pharmacopoeia specifications. The tapped and untapped densities were determined and the HR and CI were calculated. For all granulates the registered HR was between 1.06 and 1.14 and the CI from 5.8 to 12.3%, these values stand for good to excellent flowability. The angle of repose was also analysed for the obtained products and values between 38° and 45° were registered, values which describe a good to acceptable flowability [20]. The moisture content was determined for each granulate at the end of the process applying the LOD method. The granules obtained after each experimental run registered low moisture content, with values between 1.06 and 1.67%.

Experimental design analysis

The matrix of the experimental design generated by the Modde software and the validation runs, including the responses obtained after conducting all experimental runs is presented in Table II. The obtained values showed that the developed monitoring method was sensitive enough to detect changes and to determine the end-point of the granulation process.

Table II

Matrix and validation runs of the experimental design

Experiment Code	X_1	X_2	$Y_1 (\times 10^{-2})$	$Y_2 (\times 10^{-2})$	$Y_3 (\times 10^{-2})$	Y_4 (sec)
N1	8.0	40	-0.0696	0.1624	0.4160	410
N2	9.1	40	-0.0317	0.2068	0.4521	500
N3	11.3	40	-0.0538	0.2255	0.5553	750
N4	12.3	40	-0.0534	0.2096	0.6004	820
N5	8.0	45	-0.0371	0.1083	0.1805	440
N6	11.3	45	-0.0111	0.2099	0.4373	590
N7	12.3	45	-0.0340	0.2241	0.4688	630
N8	10.2	50	-0.0071	0.1601	0.3806	530
N9	8.0	55	0.0081	0.1267	0.3814	400
N10	9.1	55	-0.0019	0.0991	0.2921	510
N11	11.3	55	-0.0177	0.0857	0.2811	450
N12	12.3	55	-0.0574	0.1064	0.3488	540
N13	8.0	60	0.0523	0.0875	0.1970	350
N14	9.1	60	0.0572	0.1215	0.1851	460
N15	11.3	60	-0.1340	0.0575	0.3189	410
N16	12.3	60	-0.0205	0.0783	0.3083	480
N17	10.2	50	0.0061	0.1283	0.3664	520
V1	15.5/10.2	50	0.1248	0.3456	0.4569	640
V2	5.0/10.2	50	-0.0225	0.0248	0.3057	340
V3 pred.			-0.0012	0.1386	0.3606	485
V3 reg.	9.0	50	-0.0084	0.1405	0.3875	500

$X_{1,2}$, $Y_{1,2,3,4}$: variables according to the experimental design; pred.: predicted by the experimental design software; reg.: experimentally registered

The model selected for the fitting of the experimental design showed excellent quality, with R^2 greater than 0.83 and Q^2 greater than 0.70 for the PC scores (Y_1 , Y_2 , Y_3) and R^2 of 0.93 and Q^2 of 0.81 for the drying time (Y_4).

A third statistical parameter used to evaluate the model validity was the ANOVA test which analyses the variance of the results. In the present case, for both studied responses, the ANOVA p values were lower than 0.001 for the model and higher than 0.237 for the lack of fit. These values describe a statistically good model with no lack of fit.

The following equation was used by the software to determine the PLS fitting of the experimental data and the regression coefficients:

$$Y_n = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 \quad \text{Eq. (1)}$$

In the displayed equation, Y_n is the dependent variable; b_0 is the model constant; b_1 and b_2 are

linear coefficients; b_{12} is the interaction coefficient between the two independent variables and X_1 , X_2 are the coded levels of the introduced variables. The influence of the studied factors is represented by the equation coefficients used to fit the data to the quadratic model. Regarding that the developed experimental design was not a complex one, only one significant interaction could be observed between the introduced factors [1, 19].

Based on the model, a scaled and focussed coefficient plot, shown in Figure 2, has been generated for the last two responses. This kind of plots enhances the understanding of the relationship between the studied inputs and outputs of the granulation process. The results of the coefficient plot analysis show that the score values of the developed PCA can be successfully used as experimental design outputs, to observe and assess changes of both studied CPPs, the binder spraying rate (X_1) and the inlet air temperature (X_2).

Figure 2.

The influence of the process inputs on (a) 1st PC score values registered at the end of the binder spraying and (b) drying time of the granules, presented as scaled and centred coefficient plots (X_1 - binder spraying rate; X_2 - inlet air temperature; PC - principal component)

According to the coefficient plot generated for the 1st PC score values registered at the end of the binder spraying process, displayed in Figure 2a, the maximum moisture level reached during the binder spraying phase of the process depends mostly on the inlet air temperature (X_2). By increasing the temperature of the introduced air flow, the drying of the granules is accelerated, phenomenon which reduces the granule's humidity levels during the whole process progress. Regarding the binder spraying rate (X_1), it is noticeable that higher moisture levels could be achieved by increasing this particular parameter. The design of experiments software has also calculated an interaction possibility between the two independent variables, which in this case was not statistically significant, its value being lower than the displayed error bar.

The moment when the moisture level of granules went under 2% was considered final drying point and was observed on the PCA score line plot. The factor influence over the process endpoint is displayed

in Figure 2b. As expected, the increase of inlet air temperature shortened the drying time. In the same time, the binder spraying rate influenced the reached humidity level of the powder bed, this factor also had a significant influence over the granules drying time. The two studied factors influenced the process in opposite directions with approximatively same intensity. In this case, the interaction registered between the two factors ($X_1 \cdot X_2$) was statistically significant and suggested that increasing both factors simultaneously, would lead to a decrease of the drying time [24].

Data pre-processing

All experimental runs were monitored in-line using the MicroNIR spectrometer and the same spectral analysis was applied for all the batches. To exemplify the applied pre-processing techniques, the spectral analysis of the N8 experimental run, performed using average process parameters, is described in the following section.

The second derivative pre-processing technique was performed on the NIR spectra and the obtained pre-processed data were decomposed into three principal components (PCs) explaining a cumulative variance of 98%, the 1st PC accounting for most of the spectral variability, 53.1%, while the 2nd PC accounting for 40.9% of the variability and the 3rd PC for only 3.97% respectively. As seen in Figure 3, which illustrates the variation of the absorption bands during a single batch performed in average parameters, a significant increase of the baseline is observed between the moments before and after adding the binding solution. The variation of particle size throughout the granulation

process could be accounted for this spectral variation, as previously reported [2, 14, 18].

Major spectral variations can be observed in the 1080 to 1250 nm domain, as the bands in this region changed markedly upon addition of the binder during the granulation step. Furthermore, the second major spectral variation is observed in the 1350 to 1510 nm domain (spectral range characteristic for the O-H stretching vibrations in water), where the intensity clearly increases after adding the binding solution, and decreases at the end of the drying, suggesting the end of the process.

Figure 3.

NIR spectra corresponding to three different steps of the granulation process
(PC - principal component, t - process time)

Figure 4 illustrates the 1st versus 2nd PC scores plot for the N8 granulation as a function of the three process steps. The blending and preheating process corresponds to the scores situated in the lower part of the figure; as can be seen, the scores clustered together and exhibited almost no change. Upon addition of the binder solution two min later, both 1st and 2nd PCs score values increased along the process. During the final drying the 1st PC scores decreased rapidly in the first part of the process, then remained relatively constant, clustering at

around 0,001. Towards the end of the granulation, the 2nd PC score values started to decrease, suggesting that some more changes of the particle properties occurred during the prolonged drying. Therefore, the scores plot could be used to check whether a batch is developing under normal operating conditions and if the granulation is being properly done [2]. A similar evolution of the score plot could also be observed for the rest of the experimental runs, using the same pre-processing model.

Figure 4.

Scores plot obtained from a principal component analysis (PCA) of the complete spectral data set for a single batch

The loadings for the PCs are illustrated in Figure 5, overlapped with the pre-processed spectra. The loading of the 2nd PC revealed a very good similarity with the spectra, as the correlation coefficient was greater than 0.9, confirming that the second component accounts for the variation in the spectra due to particle size changes. Analysis of the loadings of the 1st PC revealed one significant peak at 1430 nm, located in the spectral range characteristic for O-H stretching vibrations in water (1400 - 1480 nm). This suggests that the 1st PC accounts for variations in the spectra

due to changes of the absorption bands of water during the three different steps of the process. The 3rd PC was found to account for only 3.97% of the total explained variance, but according to its EV of 4.41, it still is a statistically significant model component. A significant peak could be observed on the loading of the 3rd PC (not shown in Figure 5) at around 1370 nm, which is characteristic for polyvinylpyrrolidone (Kollidon 30), suggesting that the last PC accounts for the binder addition.

Figure 5.

Loading plots generated for the principal component analysis (PCA) model (PC-principal component)

For a better visualization of the main stages of the granulation process, the 1st and 2nd PCs, as they accounted for most of the variability and therefore are most influential on the process outcome, were each plotted against time in Figure 6. Both loading plots exhibited distinct regions, marked with dotted delimitation bars, which could easily be associated with the steps of the process, i.e., 1 – blending and preheating, 2 – spraying of the binder solution, and 3 – drying of the granules.

As can be seen in Figure 6a, the variation of the 1st PC over time suggests that its scores increased during the binder solution addition, in the second step of the process and then decreased due to the drying effect in the third phase. The score value decrease after 13

min suggests a decrease in water content due to the evaporation of the water promoted by the high temperature air stream. After 24 min major changes could not be observed any more on the projected score plot, this point was marked on the figure through a dash-dot bar and suggests the drying was finished. In this case the process end point coincides with the moment when the scores become constant, indicating that no further moisture content changes are occurring any more. The capacity to establish the process end point allowed the shortening of the initially set drying time of 30 min, to only 12 min. Prediction of the granulation end point allowed the process optimisation in terms of efficiency, costs and overall quality of the granules.

Figure 6.

Score line plots of the principal component analysis (PCA) model plotted vs. process time: a) 1st principal component scores and b) 2nd principal component scores

The variation of the 2nd PC over time (Figure 6b) reveals that in the first phase which represents the blending and preheating of the sample, the spectral variation was relatively reduced. Immediately after the start of binder spraying, a considerably increase of the scores can be observed, most probable due to changes in particle size as the granules start to form. This increase was more significant in the beginning, then reached a plateau after approximately 12 min. After this moment, no more score changes could be noticed, marking the end of the granule growth process. Therefore, by observing the variation of the 1st and 2nd PCs scores, one can gain effective knowledge of the batch evolution, demonstrating that NIR spectroscopy combined with chemometry can be a useful tool for process analysis and control. This method allows us to identify and monitor each step of the granulation process by the interpretation of scores and loadings of a PCA model. Moreover, the use of multivariate analysis on NIR data enabled capturing variance related to moisture content throughout the entire granulation process, and this allowed us to determine the end point of the process and optimize the process time.

Validation

To confirm the validity of the developed monitoring method, the three validation experimental runs were also monitored and the recorded spectral data was pre-processed in the same way as the data recorded for the experimental design runs.

Considering that the 1st PC score values reflect the moisture level of the powder bed, in order to observe and analyse the sensitivity of the monitoring method, the generated validation score line plots of the 1st PC are highlighted in Figure 7. In Figure 7a can be noticed that for the first validation run (V1), performed by spraying the first half of the binder solution with a higher rate, the 1st PC score values increased sharply

and remained in a plateau even after 7 min when the spraying rate was reduced to average parameters. Also, due to the higher spraying rate, the maximum registered PC value was greater than the one obtained for the other experimental runs, which suggests a higher moisture level. Observing the evolution of the PC score values for the second validation run (V2), also illustrated in Figure 7a, it can be observed that the lower spraying rate set for the first half of the binder solution translates in an increase of the score value at a much slower pace. Only after the increase of the binder spraying rate, to average parameters, after 15 min, the score values increase steepens. It is clear that for both validation runs, the score values start to decrease immediately after the end of the binder spraying, suggesting a water content decrease. Regardless of the maximum registered PC score value, the decrease stops and the values stabilise after approximately 10 min of drying, suggesting the end of the drying process.

The process parameters for an ideal product were calculated by introducing a set of constrains into the optimiser function of the Modde software [13]. The target PC scores were set according to the values obtained in the experimental design and the drying time was minimised [17]. The process parameters that lead to the desired product, provided by the DoE software, are shown in Table II, together with the DoE predicted and experimentally registered response values. The generated score line plot of the 1st PC, obtained after the spectral data analysis of V3 was plotted in Figure 7b, together with the values predicted by the experimental design software. It is noticeable that the two plots overlap each other, fact confirmed by a calculated correlation coefficient of 0.98, suggesting that the developed monitoring method is stable and reproducible.

Figure 7.

Validation score line plots: a) V1, V2 and V3 reg., b) V3 reg. vs. V3 pred. (V1, V2, V3 - experimental runs according to Table I; V3 reg. - experimentally registered values; V3 pred. - values predicted by the experimental design software)

Conclusions

The present study described the development of a non-invasive method for the in-line monitoring of the fluid bed granulation processes. For the method calibration an experimental design was generated and,

for all the performed experimental runs, spectral data have been acquired using a microNIR spectrometer attached to the granulator expansion vessel. Based on the spectral data a PCA model was calculated and in order to analyse the method capacities and the

influence of critical process inputs, score values of the PCA model, which are specific statistical parameters, were chosen as experimental design outputs. Moreover, the use of multivariate data analysis, namely the projected score line plots, enabled the capturing of the variance related to granule growth and moisture content throughout the entire granulation process. This enhanced the process time optimization by accurately determining of the process end point. In order to test the sensibility of the monitoring technique, additional runs were performed varying the spraying rate of the binder solution and evaluating the registered moisture levels. Corresponding changes of the water content could be registered, proving the reliability of the method. Moreover, a granulation was performed using average parameters and the assessed moisture levels reached during the process were very similar to the ones obtained for an experimental run performed in the same conditions during the design of experiments, proving good reproducibility properties. This study described the successful development and evaluation of a versatile non-invasively monitoring method applying an experimental design approach in conjunction with multivariate data analysis of spectral data. The organized approach allowed the identification of putative interactions between studied parameters and provided a better understanding of the fluid bed granulation process.

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