Optimization of a Membrane Production Process according to PAT

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Abstract

The quality control of a polyethersulfone membrane production process is a time consuming procedure that involves the repeated measurement of its critical quality attributes (CQA) until they fit within specification. To optimize such delays, it has been proven that the combination of Process Analytical Technology (PAT) tools with near infra-red spectrometry can monitor the stability of critical process parameters (CPP) in a production line and even predict CQAs.
In the present thesis, it is proposed to independently apply this principle to membrane 15458, 15457, 15404-H and 15407. This study aims to evaluate the relationships between selected CPPs and membrane's CQAs, using design of experiments, and to build predictive models for each membrane. Through multivariate data analysis, these models were obtained by merging the NIR spectral data and the CQAs for each membrane.
This work showed a good correlation of the CQAs: bubble point (BP), thickness and air flux, with the most important CPPs. The fraction for the variation of the most important CQA, BP, was between 0,79 – 0,98 with a prediction ability between 0,64 – 0,9. For the model building, the standard error of prediction of all BP models appears to be within the same range (0,05 – 0,16 bar) and lower than half the standard deviation of the in-specification range. This study proves that this optimization can be expanded to different kinds of membranes, which contributes for the improvement of the monitoring of this type of manufacturing processes.

Keywords: Process analytical technology; monitoring; Design of Experiments; Near-Infrared Spectroscopy; membrane production;

1. Introduction

The development of powerful computers in last decades permitted a systematic management of large quantities of data. This allowed for the multivariate methods to be used in analysis, monitoring and diagnostics of processes [1], [2]. Typical multivariate data analysis (MVDA) included statistical methods such as Principal Component Analysis (PCA) and Partial Least Square regression (PLS) [1], [3]. All of this development allowed instrumentation like Near Infra-Red Spectroscopy (NIRS) to use chemometrics and MVDA in analytical chemistry and process monitoring. NIRS had its breakthrough starting from the 80s, when computers got fast enough to treat NIR spectra in a way that the chemical information could be extracted. NIR spectra produced can carry information on the physical and chemical constituents of samples. However, the NIR data is a complex spectra with overlapping bands of chemical bonds [4]. This makes interpretation impossible using univariable analysis. More recently, NIRS is becoming increasingly widespread in production processes in the biotechnology and pharmaceutical industries. [5]–[7]. It is not a surprise that lately, there have been numerous publications on applications of NIRS. For instance, in the pharmaceutical industry, NIRS is now used both to trace physical parameters [8] and determination of chemical content. Chemical components, such as active pharmaceutical ingredients (APIs) can now be measured. [7]. NIRS can also be used to detect polymorph structures that can modify the dissolution properties of the final drug. Among others, NIRS can trace moisture content in powders or granulates, tablets, capsules, as well as lyophilized vials or in solutions [7], [9]. Most recently it was reported that NIRS could also predict biogas yield by the analysis of the starting materials [10], [11]. NIRS has so far been applied only in a very limited application to the analysis of thin layers such as paper, films or membranes [1].

In 2010, Sartorius Stedim Biotech has planned to implement a Process Analytical Technology (PAT) approach in a membrane casting machine, as one of their projects. The objective of this project is to improve product quality control, through the use of spectroscopy, design of experiments (DoE) and MVDA. Since most of these membranes are used to assemble filter cartridges, deviations in the quality may compromise the proper functioning and final throughput of this component. Thus it may lead to

inappropriate aeration and sterilization of target environments. The quality of the final membranes relies on the production process, more specifically on critical process parameters (CPPs). The continuous production of Polyethersulfone (PES) membranes involves a condition step where the polymeric solution is placed and a precipitation step, where the membrane's pores acquire their final form. The CPPs have a special influence in the beginning of the process. So far the process control is only monitoring the stability of CPPs. No monitoring in product and process quality has been implanted. The quality control is only performed in a small fraction of the membrane roll in the end of the process. So far, the sampling practice is only performed in the end of a 180m roll. This raises a problem since there is not a fixed set of CPP for each membrane. These parameters may vary over lot and time. Therefore, if quality control traces a membrane that is out of specification (OSS), adjustments have to be made in CPP. The quality control also lies on the assumption that there is no variability within the roll. Therefore quality deviations within a roll may slip through, if the end of the roll fits within specification. OSS membranes have to be resend to quality control. This process is repeated until the membrane fits within specification. There is a substantial time delay between defining process parameters and the proper adjustment of critical quality attributes (CQA) of each membrane. The lack of full control raises the need to monitoring the process stability. This will significantly reduce the amount of samples that are sent to quality control, which reduces the time delay. Instead of sampling every roll, it is only necessary to sample in the beginning of each batch while monitoring the process stability. Considering that a batch can produce several rolls, the sampling process is significantly reduced. In case of detection of OSS parameters, additional samples need to be sent to quality control, which makes the sampling a guided practice.

In the beginning of this project, the main challenge was how to implement the process monitoring. Having this in mind, it is necessary to consider that initially the casting solution is applied to a band. Then it is immersed in a precipitation bath. After precipitation agent extraction, the membrane is washed and dried. A good control instrument has to be able to predict physical and/or chemical proprieties in the stages that are more influenced by CPPs. It has been shown that using Near Infrared Spectroscopy (NIRS) over the belt edge, makes it possible to trace the physical properties of the final membrane. As this instrument acquires more spectra, the more data is reintroduced in the system recalibrating the model. This contributes for an increasing robustness of the model.

Considering the present work, only 3 companies are able to produce this type of membrane worldwide. Therefore, it is very difficult to collect statistical data of production process that can be relevant for comparison. This is aggravated by the fact that each company protects its own data, which makes most of this information impossible to reach.

Feasibility studies for 1 membrane have been followed after this implementation. A good process monitoring has to be able to predict not only optimum CQA values but also deviations. Therefore it was necessary to put the system in different conditions. This feasibility study for a membrane showed that product and process stability can likely be monitored. It also unveiled that the prediction of that membrane quality might be feasible. It is needed to take in consideration that casting machine can produce a significantly sized range of different membranes. Therefore, more feasibility studies have to be performed. This will guarantee that the process monitoring is active as long as the machine is running.

It is proposed in the current thesis to make a feasibility study for membranes 15458, 15457, 15404-H and 15407. The choice of these types lies on the importance in terms of quantity of production. Each feasibility study starts by defining the most relevant CPP for each membrane. This will allow to generate four DoEs that considers the change of the chosen CPPs. Each DoE will be performed in casting machine. This will generate four sets of NIR spectral data. The NIR data is gathered using an automated data acquisition software. This data will be used in model building. To build these models, it is necessary to measure all CQA. This will allow to:

- Evaluate relationships between CPPs and CQAs for each membrane. Also it can expose less relevant CQAs relatively to the changes of the selected CPPs.
- Build models using MVDA for each CQA of each membrane. These models will be generated using pre-treatments and outlier detection.

Once models are built and automation completed, the results are displayed in process control software (SCADA). In order to reduce parameters variability (e.g. lot-to-lot variability) the data obtain must be acquired in the most uninterrupted way as possible. For this reason, each membrane will be considered as

a different system, which also makes the data gathering a more feasible process.

2. Experimental Procedure

The methodology performed for each the 4 membranes can be summarized in Figure 1 and described as follows:

1. *The prior knowledge is used in risk analysis (RA) to define CPPs;*

The CPPs defined for the membranes were the temperature of the band (T_{Band}), temperature of the precipitation bath (T_{PB}), casting speed (CSp), amount of casting solution ACS, temperature of the column T_{col} and coverage (Cov). The CQAs defined for the membranes were bubble point (BP), Thickness (Tk), Air Flux (AF) and Diffusion (Df). Each DoE map will have a unique structure with only the most important set of CPPs for each membrane. It is also important to notice that a relevant CPP for a type of membrane, can be irrelevant for another. Such fact can change the number of variables in the system, which it will be determined for the choice of model design and subsequent number of experimental trials. Prior knowledge predicts a high correlation between T_{Band}-BP and ACS/CSp-Tk. The respective CPPs used in DoE for each membrane can be summarized in Table 1.

Table 1 - Membrane CPPs used for DoE building for each membrane.

	T_{Band} (°C)	T_{PB} (°C)	CSp (m/h)	ACS (kg/m2)	T_{col} (°C)	Cov
15458	x	x	x			
15457	x	x	x	x	x	
15404-H	x	x	x			
15407	x	x		x		x

2. *The chosen CPPs are used to build a DoE Map that is implemented in the production line;*

All DoE were built using screening analysis. This will be sufficient to analyze CPP-CQA interactions and for the fusing between CQAs and NIR data. Each DoE requires a custom made design, especially for time optimization. This makes the Full Factorial design the best initial choice. This design may be redundant but it ensures correct models and guarantees the main influence of CPPs and CQA-CPP interactions are revealed. The DoE maps were rearranged depending on the minimum time transition between each experiment state. This will reduce the amount of discarded membrane. It will also maximize the number of experiment states reached in a feasible working period, which can lead ultimately to more data and subsequently a better model.

3. *The DoE implementation will generate membrane samples and NIR data;*

Each DoE state is introduced in the casting machine by changing the set-points of the selected CPPs. After these set-points are reached, the CQAs of the produced membranes are already affected by these changes. When these membranes reach the cleaning step in the process, they are marked with a pen for recognition in the roll-up. The time of this marking procedure is recorded for the NIR integration, for each membrane.

4. *The samples are referenced and used for evaluation of CPP/CQA relations;*

In the roll-up, each set of membranes is divided in several sets of 10-20 sheets. Each set of sheets will represent a moment where the CPPs were aligned according to the designed DoE. In order to reduce these measuring errors within the referencing, each CQA considered is an average of (at least) three measures.

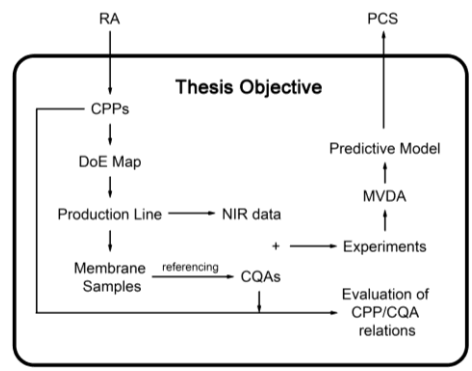

Figure 1– Overview of the thesis objective.

Each sheet is 53,8 cm in length and an average of 35 cm wide. The referencing protocol requires skilled personal that can operate with the instruments. Some of these measurements required previous sample preparation. The referencing process is divided in pre-referencing and refining referencing. The pre-referencing step is facultative for this project and it´s executed at-line by the operators with single measures. The refining referencing is performed later with triplets. BP and Df were measured with Sartocheck,

Tk was measured with a caliper and a digital optical microscope. Finally AF was measured with a PTA-Line Bendtsen.

3. Experimental Results and Data Analysis

For the membranes 15458 and 15457, it were gathered 23 and 24 samples, respectively. For the membrane 15404-H it were only gathered 14 samples. The lower number of samples for this last membrane is explained by the fact that the process failed to reach some CPP ranges, in the middle of performing the DoE. This forced to discard some of the initially planned DoE states. In the membrane 15407, it was only possible to obtained 10 experiments. This is because the stipulated casting solution for the current batch of this membrane was finishing, which reduced time to perform the DoE to only half a day. For model building this was not a problem, since this membrane was already modeled before. Therefore, this last DoE served as a validation procedure of the old model. The evaluation of CPP/CQA relations used Multiple Linear Regression (MLR) approach to create statistical models with CPPs and CQAs. This generated different statistical plots. Since the main objective is to analyze and evaluate the impact of CPPs on the process, the more relevant plots are the fit plot and coefficient correlation plots (data not shown). The statistical data obtained from correlation plots can be found in Table 2.

Table 2 - Statistic evaluation of each model. N_{Exp} is the number of experiments. Green marked values meet the specifications of a good model exposed ($R^2 \geqslant 0,80$; $Q^2 > 0,5$; MV > 0,25; Rep > 0,5). Red marked values do not meet such specifications.

	N_{Exp}	CQA	R^2	Q^2	MV	Rep
15458	23	BP (bar)	0,79	0,67	0,89	0,7
		Tk (µm)	0,88	0,82	0,31	0,99
		AF (L/m².s)	0,99	0,98	0,62	1
		Df (ml/min)	0,09	-0,2	0,73	0,53
15457	24	BP (bar)	0,87	0,76	-0,05	1
		Tk (µm)	0,97	0,94	0,79	0,99
		AF (L/m².s)	0,96	0,92	0,55	1
		Df (ml/min)	0,51	0,06	0,93	0,14
15404-H	14	BP (bar)	0,93	0,9	0,83	9,4
		Tk (µm)	0,74	0,59	0,63	0,91
		AF (L/m².s)	0,84	0,68	-0,2	1
15407	10	BP (bar)	0,98	0,84	0,73	0,98
		Tk (µm)	1	0,99	0,97	0,99
		AF (L/m².s)	0,99	0,86	0,85	0,98

The model building was performed with software SX-Center and SX-Plus from NIR Online. To obtain a predictive model, each set of measured CQAs are assigned to the respective spectral data. This combination is hereafter called experiment. Such merging is accomplished by attributing the marking time of each membrane to NIR spectral data with the same corresponding time.

After both sets of data are merged, the software uses a specified model to reduce the number of variables. For the building of these predictive models, it was used a modified version of PLS. The algorithm of this model is protected by NIR-Online and specifically designed to provide a better output when using spectral data.

After defining these initial parameters, the software could present a predictive model with the raw data. This is followed by deciding an initial number of principal components (nPC). Such requires to choose/analyze the most relevant plot in all statistical plots available in the software. The initial nPC can be established by using a Loadings Plot. This plot is often used in NIR spectroscopy to identify a spectral band of pure component in a sample. So it is expected that this plot is significantly relevant for the identification of chemical properties. Normally for physical parameters, like BP, there is not a specific band. Loadings for physical parameters will be based on scattering (background effects) without the need of specific bands. It is important to refer that the pores are a result of some organic compounds that are caught in the casting solution. Therefore chemical spectral bands can correlate with the BP. Nevertheless it is expected scattering as the main effect. After establishing an initial nPC, each model was evaluated using estimates and residues plot. The estimates plot puts the original CQA set against the predicted set. This plot provides statistical insight of the SEC and the fit of the prediction (R^2). The residues plot can expose the residues of the predicted data. It also highlights the data above standard deviation (SD) and two times the SD. Both these plots are fundamental when choosing the necessary pre-treatments and in outlier detection.

The cleaned model was validated using simple validation and/or cross-validation (CV). For this step, it is necessary to define a number (for validation (N_{Val}) or for cross-validation (N_{CV})). Afterwards the software takes out one experiment in every multiple of that number. Using estimates plot, it is possible to observe changes in standard error of calibration (SEC), cross-validation (SECV), prediction (SEP) and

their respective parameter of fit, R^2. Finally, using a Press plot it is possible to evaluate the initial number of principal components (nPC) chosen. Once finalized, the model is exported in a form of a calibration file. The model building for each CQA of each membrane is presented in the next sections.

Regarding the CPP-CQA relationship analysis, BP, Tk, AF data seen to have a good fit within the selected CPPs. BP is strongly correlated with T_{Band}, which corroborates with the prior-knowledge of the process. The T_{PB} correlation with pore size indicators, such as BP, seems to be a good indicator of in which step does the pore development is more relevant (condition or precipitation step). As predicted from pior-knowledge, it was also verified that Tk is highly affected by CSp and ACS. It was seen that Tk influeces T_{Band}. T_{col} and Cov don't appear to have a significant impact in the membranes where they were tested. Diffusion is irrelevant as a membrane CQA for the selected membranes and group of CPPs.

Regarding the model building, it is clear that the SEP and R^2 improved with the data pre-treatment (Figure 2). Therefore, it is possible to conclude that all models presented a good response to the data cleaning. The percentage improvement of these statistical parameters is in the same range of membranes 15457 and 15458. Such doesn't happen with membranes 15404-H and 15407 with ranges from 4-90% for SEP decrease and 3-30% for R^2 increase.

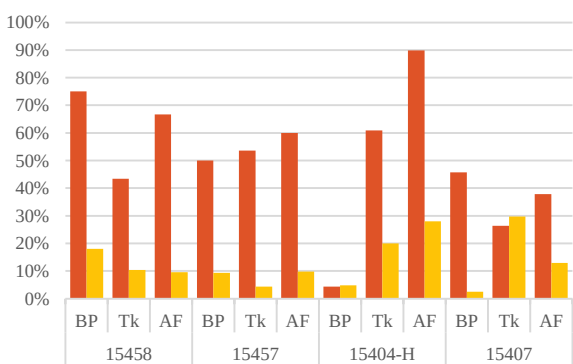

Figure 2 - Decrease of SEP (red bars) and increase of R^2 (yellow bars) for the membranes 15458, 15457, 15404-H and 15407.

When it comes to pre-treatments, extended multiplicative scatter correction (EMSC) appears to have a good effect on the models of membranes 15404-H and 15407. Although effective, the EMSC pre-treatment uses data already stored, which can create a "bias effect" that can induce errors in the model building. In fact, the high improvement in R^2 in some models of these membranes can reflect this fact.

The outlier detection removed up to 26% of the experiments. The low number of experiments in membranes 15404-H and 15407 conditioned other types of data cleaning such as cross-validation and outlier detection (15407 only). In the light of these facts, the use of EMSC was important to ensure a reasonable model. The model produced by the data with 10 experiments and pre-treated with EMSC proved to be fitted in a much larger data set.

The quality of the model seems to correlate differently when analyzing by CQAs and membrane type. When analyzing by CQAs (Figure 3), the SEP of all BP models appear be within the same range (0,05 – 0,16 bar), which is positive since this is the main CQA. Tk models for the membranes 15458, 15457 and 15404-H appear to be within the same range (0,47 – 3,52 µm). The errors for membrane 15407 are too high (SEC=18,04 µm and SEP=51,71 µm). Since it appears to exist no miscorrelation between Tk and the CPPs for this membrane (R^2=1, Q^2=0,99; MV=0,97; Rep=0,99), the problem must be possibly related to precipitation and stirring problems in casting solution tank and/or errors in the referencing. More data should be acquired in order to take further conclusions. When it comes to AF, the membranes 15458, 15457 and 15407 appears to be within the same range (0,02 – 0,42 L/m².s). The membrane 15404-H has a low SEC (0,19 L/m².s) but a high SEP (1,56 L/m².s). In fact, when evaluated the relation between Tk-CPPs of this membrane, the statistical parameters don't all appear to be relevant, with a very low value of MV (R^2=0,84, Q^2=0,68;MV=-0,2;Rep=1). In the light of these facts it is plausible to conclude that maybe AF is not a good CQA for this type of membrane. Although, models of 15404-H and 15407 were built with a low number of experiments.

Analyzing the quality of the model according to membrane type, models generated by 15404-H and 15407 seem to be very dependent on pre-treatments and lack consistent results. On the other hand, membranes 15458 and 15457 more reliable results. This can be directly associated with the size of each data sets. Evidently, bigger data sets carry more information about the system and prevent poor model building. Normally, small data sets translate in lower

range of variability which restricts the ability of predict better results.

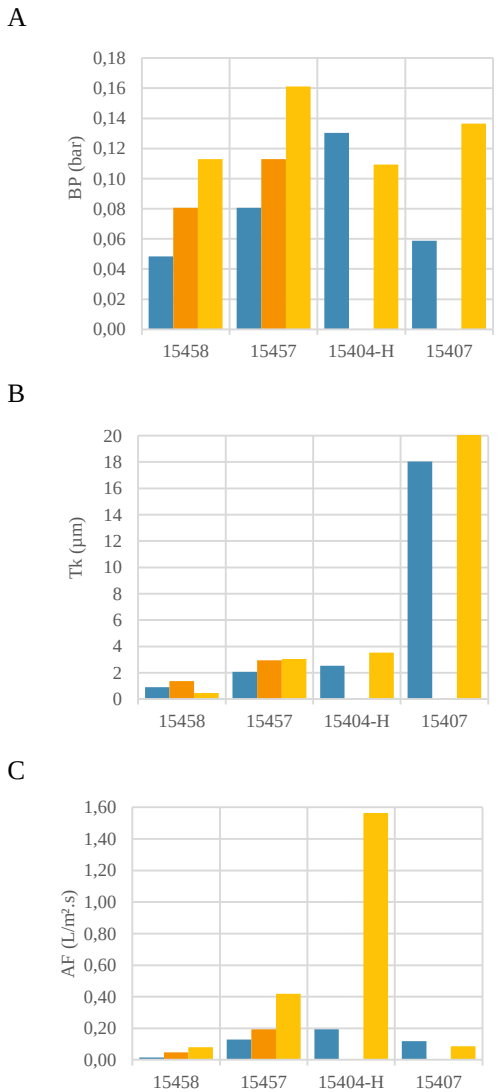

Figure 3 - Comparison between SEC (blue bars), SECV (orange bars) and SEP (yellow) for the models of the 4 membranes by CQA (Plot A – BP; Plot B – Tk; Plot C – AF). Due the low number of experiments, cross-validation was not used in membranes 15404-H and 15407 which explains the absent values. In the plot B, the Tk of 15407 is beyond the max value of the axis, 51,71 µm.

The model evaluation can also be complemented having in mind the final application of the process. Since this is an industrial process, this evaluation should consider standard in-specification limits used in the production line. Having in mind these ranges, it is possible to set limits with SD and SEP values for each membrane. These in-specification limits are documented for the BP, since it is the most important CQA. (Table 3).

Table 3 - In-specification limits used at the membrane production site to evaluate the process performance and their SD and SD/2

	BP Min (bar)	BP Máx (bar)	SD (bar)	SD/2 (Bar)
15458	4,031	4,999	0,484	0,242
15457	2,580	3,386	0,403	0,202
15404-H	1,451	2,096	0,322	0,161
15407	5,724	6,611	0,443	0,222

As showed in Figure 4, all the errors of all the BP models are lower than the SD and SD/2 of the each in specification range. This guarantees that it is possible to use the NIR spectrometer to predict if these 4 membranes stay inside specification. This will allow to use BP to monitor the process and to reduce the number of sampling. Of course when it comes to other CQAs, this monitoring may fail for some of the models like 15404-H and 15407.

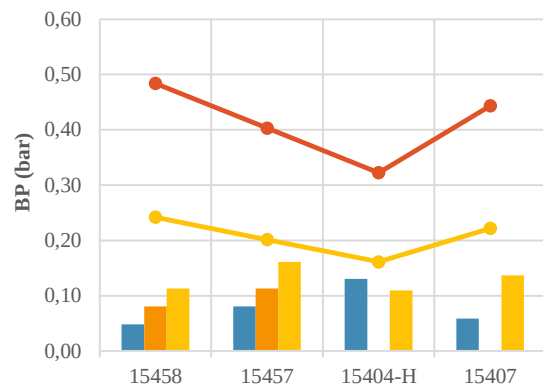

Figure 4 - Comparison between SEC (blue bars), SECV (orange bars) and SEP (yellow) for the models of the 4 membranes according to the BP. Due the low number of experiments, cross-validation was not used in membranes 15404-H and 15407 which explains the absent values.

4. Conclusions and future work

In sum, this study shows that is possible to identify the prior knowledge of these membranes from the main relations between CPP-CQAs. It also shows that is possible to expand model building into different kinds of membranes. Since Sartorius has other membranes produced by a precipitation process, this study

contributes for the improvement on the monitoring of this type of manufacturing processes.

Considering the results obtained, it is clear that to expand the monitoring for other CQAs than BP, the models of 15404-H and 15407 may require additional improvement. This can be done by adding samples to the existing model or performing an entirely new DoE. The last option is preferential since other CPPs and CPPs' range can be tested. Having in mind the models obtained from membranes 15458 and 15457, it is possible to think about a minimum number of samples to guarantee a good model. Although, this cannot be generalized since the number of samples for a DoE increases with the number of CPPs. Also each CPP has a different impact on the process which does not necessarily guarantee the building of a good model. For this reason it is difficult to establish a minimum number of experiments. Although it is worth notice that 15458 proved to successfully generate good models yielding 23 experiments with only 3 CPPs. Having in mind that both 15404-H and 15407 use 3 CPPs, it is plausible that the outcome would improve with 23 samples. Additional samples from membrane 15458 and 15457 can be gathered and added to the model for validation. This will increase the reliability on these models.

The next step of this project concludes by introducing this models in process control system (PCS) of NIRS, as soon as they are fully operational. These models can be used for monitoring for a long period. Of course, different process tweaks, such as different suppliers or lots of casting solution, may require for this models to be updated over time.

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6. Abbreviations

ACS	-	Amount of Casting Solution (kg/m^2)
AF	-	Air Flux ($L/m^2.s$)
API	-	Active Pharmaceutical Ingredient
BP	-	Bubble Point (bar/mbar)
Cov	-	Coverage
CPP	-	Critical Process Parameter
CQA	-	Critical Quality Attribute
CSp	-	Casting Speed (m/s)
CV	-	Cross Validation
Df	-	Diffusion (ml/min)
DoE	-	Design of Experiments
DOM	-	Digital Optical Microscope
EMSC	-	Extended Multiplicative Scatter Correction
MLR	-	Multiple Linear Regression
MSC	-	Multiplicative Scatter Correction
MV	-	Model Validation
MVDA	-	Multivariate Data Analysis
N_{CV}	-	Number used for cross-validation
N_{Exp}	-	Number of experiments (Initial)

NIR	-	Near Infra-Red
NIRS	-	Near Infra-Red Spectroscopy
nPC	-	Number of Principal Components
N_{Val}	-	Number used for validation
OOS	-	Out of Specification (Product)
PAT	-	Process Analytical Technology
PCA	-	Principle Component Analysis
PCR	-	Principle Component Regression
PCS	-	Process Control System
PES	-	Polyethersulfone
PLS	-	Partial Least Squares
Q^2	-	Percentage of the variation of the response predicted by the model. Predictive factor
R^2	-	Percentage of the variation of the response explained by the model.; correlation factor
RA	-	Risk Analysis
Rep	-	Reproducibility
SCADA	-	Supervisory Control and Data Acquisition
SD	-	Standard Deviation
SEC	-	Standard Error of Calibration
SECV	-	Standard Error of Cross Validation
SEP	-	Standard Error of Prediction
T_{Band}	-	Temperature of the band/belt (°C).
T_{col}	-	Temperature of the (Distillation) Column (°C).
Tk	-	Thickness (µm)
T_{PB}	-	Temperature of the precipitation bath (°C).