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Research paper

Design space approach in the optimization of the spray-drying process

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ABSTRACT

From a quality by design perspective, the aim of the present study was to demonstrate the applicability of a Bayesian statistical methodology to identify the Design Space (DS) of a spray-drying process. Following the ICH Q8 guideline, the DS is defined as the "multidimensional combination and interaction of input variables (e.g., materials attributes) and process parameters that have been demonstrated to provide assurance of quality." Thus, a predictive risk-based approach was set up in order to account for the uncertainties and correlations found in the process and in the derived critical quality attributes such as the yield, the moisture content, the inhalable fraction of powder, the compressibility index, and the Hausner ratio. This allowed quantifying the guarantees and the risks to observe whether the process shall run according to specifications. These specifications describe satisfactory quality outputs and were defined *a priori* given safety, efficiency, and economical reasons. Within the identified DS, validation of the optimal condition was effectuated. The optimized process was shown to perform as expected, providing a product for which the quality is built in by the design and controlled setup of the equipment, regarding identified critical process parameters: the inlet temperature, the feed rate, and the spray flow rate.

1. Introduction

Nowadays, there is an increasing demand from regulatory authorities calling for the pharmaceutical industries to gain a comprehensive understanding of their manufacturing processes together with an accurate estimation of their robustness and reliability. Instead of providing solutions to meet these demands and requirements, authorities such as the International Conference on Harmonization (ICH) have published guidelines establishing the overall methodology to achieve these expectations. In the ICH Q8 guideline on pharmaceutical development, the emphasis is put on the "Quality by Design" (QbD) concept, stating that quality should not be tested into products, but should be built in [1,2]. The Design Space (DS) concept is also introduced in this guideline, which is "the multidimensional combination and interaction of input variables (e.g., materials attributes) and process parameters that have been demonstrated to provide assurance of quality." Furthermore, ICH indicates that as long as the process and formulation parameters are kept within the defined DS, no regulatory post-approval change is needed. Thus, the DS of a process must also guarantee its reliability and robustness. In the US, the Food and Drug Administration has released the manual of policies and procedures for the effective application of several guidelines including ICH Q8 [3]. This is a strong indicator that industries must now be fully compliant with these QbD approaches.

Pulmonary delivery is an attractive administration route for the treatment or prophylaxis of airways diseases. It is also a reliable alternative to the subcutaneous and intravenous administration routes, especially for proteins and peptides. Indeed, the large surface area of the alveolar epithelial, the abundance of capillaries, and the low thickness of the air–blood barrier enable a drug delivery with systemic activity [4].

Optimal drug deposition in the lungs requires several criteria to be fulfilled in terms of morphological aspects and ventilatory parameters. In addition, the particle's size and geometry aspects are also crucial [5]. The optimum aerodynamic particle size for delivery is in the range of 1–5 μm [6]. Among the different particle processing techniques, spray-drying is known to produce particles that well fulfill the requirements for the pulmonary administration route. This processing technique offers many advantages, the first one being that the drying time of a droplet is only a fraction of a second, with a fast evaporation avoiding droplet overheating. The second one is that the final product has a large surface area and a uniform and controllable particle size [7]. Furthermore, spray-drying is a continuous drying process consuming less energy than

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a freeze-drying process, for example [8]. All the previous advantages make spray-drying an attractive manufacturing process for the pharmaceutical industry.

The aerodynamic properties of the powders obtained by spray-drying are determined by the particle size, density, and shape, which are influenced by spray-drying process parameters such as the inlet/outlet temperature, the air flow rate, and the feed flow rate [9]. Facing the previous considerations, it is obvious that a holistic approach is needed to map the process–parameters interactions. In this context, design of experiments is perfectly adapted to gather the data and translate how the combination of critical process parameters (CPPs) affects the product critical quality attributes (CQAs). It will eventually help defining the combinations of CPPs that will keep the product performance within the specifications with a quantified guarantee for the future use of the process: the design space [1]. For the present study, only three CPPs have been used for the sake of clarity.

In this context, the DS being identified is a region of reliable robustness, into the knowledge space. To provide guarantees of future quality, DS can be defined in a risk-based framework. The approach would finally be compliant with the QbD expectations. The results focus on the assessment of quality and on the guarantees (risks) that this quality could (could not) be achieved. Formally, design space is defined as

$$DS = \{x_0 \in \chi | E_\theta[P(\text{CQAs} \in \mathbf{\Lambda}) | X = x_0, \theta] \geqslant \pi\}.$$

In other words, we look for a region of an experimental domain χ (often called knowledge space) where the expected probability that the CQAs are within specifications $\mathbf{\Lambda}$, is higher than a specified quality level π, given the model parameters $\boldsymbol{\theta}$, that include the uncertainty estimated by the statistical model.

Predictive probability is central when dealing with concepts such as design space, as it allows quantifying the guarantees and risks that specifications will (or will not) be met in the future runs of the process, given the today's information. Specifications express the minimal satisfying quality that the experimenters want to obtain.

The optimization of multiple response surfaces usually involves the overlapping mean responses approach, which can be computed with commercially available software packages such as Modde, SAS-JMP, Minitab, Statistica. This approach is performed as follows: if, for example, a process response is influenced by three process parameters, then specific pieces of software can generally display the mean predicted process responses for any combination of the three process parameters within the defined parameter range. However, such approach does not take into account the model uncertainty: it will not provide any indication about how well and how often the process can meet the specifications with respect to the investigated CQAs [10]. This represents a major drawback since ICH Q8 is clearly asking for a level of assurance guaranteeing the product specifications will be met. In contrast to the overlapped mean response approach, a Bayesian predictive approach to define the DS takes into account the uncertainty of the process and of the analytical methods used to determine the CQAs and the uncertainties and correlations between the envisaged responses and the derived CQAs [10,11]. This approach integrates the uncertainty of parameters and the correlations between CQAs by propagating the multivariate error associated with the responses prediction. Consequently, the Bayesian predictive approach will significantly improve the model's prediction ability. We believe that this is the most efficient way for "demonstrating assurance of quality" as requested by the ICH Q8 definition of the DS. Within the pharmaceutical industry, the application of Bayesian statistics now begins to gain more interest and to be well accepted by authorities, especially in the field of clinical trials [12]. Among other qualities, the Bayesian approaches allow the incorporation of prior information into models, if available, and may ease the solutions toward the predictive risk assessment.

In a previous work, Baldinger et al. investigated the influence of the processing parameters inlet temperature, spray flow rate, and feed rate on the following critical quality attributes: yield, moisture content, particle size, and flowability by means of a design of experiment [13]. However, high uncertainty was observed on most of the model parameters and no DS was identified. In this context, however, the question is to know to what extend the uncertainty could impact the prediction reliability. Within the framework of that previous work, the aim of the present study was to extend the approach of Baldinger et al. to define the spray-drying process DS according to ICH Q8. To our knowledge, this represents the first truly QbD-compliant approach to a spray-drying manufacturing process.

2. Materials and methods

2.1. Materials

D(−)-mannitol and D(+)-trehalose dihydrate were purchased from BDH Prolabo (Leuven, Belgium). Spray-drying was performed using 100 mL of an aqueous solution containing 10 g of a mixture of mannitol and trehalose in a mass ratio 90/10. Products were stored in closed vials at 5% relative humidity at room temperature.

2.2. Spray-drying

A Büchi Mini Spray-Dryer B-290 (Büchi Labortechnik AG, Flawil, Switzerland) with a 0.7-mm two-fluid nozzle was used. The solution was sprayed in a co-current flow with air as drying medium. Relevant spray-drying parameters were varied as stated in the section "Design of experiment." The spray-dried particles were separated from the drying air by an improved cyclone [14]. Other key parameters were kept constant: The aspirator rates were set at 100% in all experiments, leading to a drying air flow of approximately 35 m^3/h. Spray-dried powders were collected, weighed, and stored in capped glass vials.

2.3. Inhalable fraction estimation by laser diffraction

To obtain an estimation of the inhalable fraction, a laser diffractometer Mastersizer 2000 connected with a Scirrocco 2000 powder feeder (both: Malvern Instruments, Malvern, UK) has been used, assuming spherical particles shape. For the measurement of the particles in air, a dispersion pressure of 1 bar was used.

2.4. Thermogravimetric analysis

The residual moisture content of the samples was investigated directly after spray-drying by using a TGA 7 (Perkin Elmer, Norwalk, CT). Powder samples between 3 and 12 mg were loaded onto a platinum sample pan and heated from 25 to 150 °C at a rate of 10 °C/min.

2.5. Bulk and tapped density

Bulk density and tapped density were obtained by following the Ph. Eur. procedure 2.9.34 [15]. Due to the small amount of sample, a 10-mL tarred graduated cylinder was used. The bulk volume used for the calculation of the bulk density was directly read from the cylinder. Triplicates were made, and the mean value has been taken to define the bulk density.

$$\text{Bulk density (g/ml)} = (\text{weight of powder})/(\text{bulk powder volume})$$

The tapped density is obtained by mechanically tapping a graduated measuring cylinder containing the powder sample [15]. The tapped density is read after 1250 taps corresponding to 5 min at a tapping height of 3 mm. The mean value of three replicates is recorded along with the observed variances among the experiments.

$$\text{Tapped density (g/ml)} = (\text{weight of powder})/(\text{tapped powder volume})$$

2.6. Softwares

An in-house computer program was developed to perform the statistical analysis. The coding was done with R 2.12, freely distributed at http://www.r-project.org and available for most operating systems [16]. The package `mvtnorm` has been used in order to sample from a multivariate Student's distribution [17].

3. Design of experiment

3.1. Critical process parameters

Three CPPs have been identified as having an impact on product quality. They are the inlet temperature, the spray flow rate, and the feed rate. Their range and unit are presented in Table 1.

For these three factors, a central composite face-centered design has been chosen, leading to 17 experiments comprising a center point in (independent) triplicates [18]. Other key process parameters such as the drying air flow, the aspirator rate, the product variables (raw material characteristics) are kept constant. A more usual DOE application would have consisted in a first screening of all the possible effects to identify the most interesting ones and to refine the knowledge space. In this study, the data are derived from the experimental plan presented by Baldinger et al. [13] and no experiment has been carried out to further explore the proposed knowledge space.

3.2. Critical quality attributes

On every experiment, CQAs are recorded or derived from other attributes. They are defined in order to allow numerical assessment of the quality of the output. For every CQA, a specification ($\mathbf{\Lambda}$) is given that indicates a minimal satisfactory level of quality. The knowledge about these specifications can be a hard task, but it is the key toward a thorough and sound understanding of the process. Economical, efficiency, and safety reasons help in the definition of specifications. The five CQAs that will be taken into account for further analysis are reviewed hereafter.

3.2.1. Yield

The yield of the process is taken as a first quality attribute. It is computed as the percentage of obtained powder to the use of raw material. The experimenter will naturally look for a high yield. A specification limit can be derived from economical reason, but also from practical process management, and leads to a yield that must not be inferior to 80%. A yield that is lower than this limit means that the use of the raw material is not optimal. In this case, the proportion of raw material that is not present in the obtained powder may be lost in the apparatus and more cleaning would be needed.

Table 1
The critical process parameters, their abbreviations, and ranges.

Critical process parameters	Abbreviation	Low level	High level
Inlet temperature (°C)	IT	110	220
Spray flow rate (L/h)	SFR	439	1744
Feed rate (ml/min)	FR	2.5	7.5

3.2.2. Moisture content

The residual moisture content of the obtained powder was analyzed using a thermogravimetric analysis. However, one can be easily convinced that a spray-dried powder has generally a very low level of moisture. Precision of the thermogravimetric apparatus is low in this case. For obvious quality reasons (conservation, non-aggregation of the powder), residual moisture of no more than 1% must be observed.

3.2.3. Inhalable fraction

The optimum aerodynamic particle size distribution for most inhalation aerosols has generally been recognized to be in the range of 1–5 μm [6]. Aerosols outside this range generally do not deposit in the lungs. The actual data consist of a mean of two analyses from the Mastersizer. The specification for the inhalable fraction is set to a minimum proportion of 60% of the particles that should have a size between 1 and 5 μm.

3.2.4. Compressibility index and Hausner ratio

Two final CQAs are taken into account, the compressibility index (sometimes referred as Carr's index) and the Hausner ratio. They quantify the flowability of the obtained powder. They are both computed on the basis of the bulk and tapped density of the obtained powder:

- Compressibility index (%) = 100 × (tapped density − bulk density)/tapped density.
- Hausner ratio = tapped density/bulk density.

Since the compressibility index and the Hausner ratio are the combinations of random variables, we do not envisage their direct modeling. Instead, it is preferable to model the tapped density and the bulk density and to derive the two CQAs from these two responses.

Table 2 illustrates some specifications about the compressibility index and the Hausner ratio [19].

Specifications for the compressibility index and the Hausner ratio have been chosen such as to have a good flowability, that is, the compressibility index must be lower than 15% and the Hausner ratio lower than 1.18.

The five CQAs are summarized in Table 3 together with their specifications. An optimized process should provide outputs satisfying all the five specifications simultaneously, with the highest level of quantified guarantee possible. The complete data of the experimental plan are also available in the online version of this manuscript.

Table 2
Specification for compressibility index and Hausner ratio.

Flowability	Compressibility index (%)	Hausner ratio
Excellent	0–10	1.00–1.11
Good	11–15	1.12–1.18
Fair	16–20	1.19–1.25
Passable	21–25	1.26–1.34
Poor	26–31	1.35–1.45
Very poor	32–37	1.46–1.59
Very, very poor	>38	>1.60

Table 3
The CQAs and their specifications.

CQA	Specification
Yield	>80
Moisture	<1
Fraction [1–5] μm	>60
Compressibility index	<15
Hausner ratio	<1.18

4. Results and discussion

4.1. Model

In this section, the statistical model and the related results are detailed.

4.1.1. Responses

From the analysis of the CQAs, five model responses are envisaged to allow analyzing the quality of the output (obtained powder): the *Yield*, the *Moisture* content, the inhalable *Fraction*, the *Bulk*, and the *Tapped* densities. As the yield and the inhalable fraction are percentage values, they should have a range constrained to a domain [0–1], i.e., [0–100]%. Indeed, during prediction, not only the mean values should be constrained in this domain, but also every sample from the predictive distribution of these responses. A logit transformation is a natural choice to ensure this property valid during the predictions:

- *LYield* = logit(*Yield*).
- *LFraction* = logit(*Fraction*).

For the 3 other variables, log transformations are applied to ensure positivity.

- *LMoisture* = log(*Moisture*).
- *LBulk* = log(*Bulk*).
- *LTapped* = log(*Tapped*).

Notice also that a good practice is to constrain the value of bulk and tapped densities so that the tapped density is always higher than the bulk density. Otherwise, the computation of the compressibility index and the Hausner ratio could lead to a negative value or value smaller than 1, respectively. Constraints can be applied during a Monte-Carlo simulation step, discarding the samples that do not fulfill them.

4.1.2. Multivariate multiple linear regression

To account for the correlations that will be observed between the responses, a multivariate multiple linear regression (MMLR) is adopted. Other statistical models are possible but MMLR has the advantage of simplicity for the identification of its predictive distribution. This model is fitted for every response jointly ($\mathbf{Y}$ = (*LYield*, *LFraction*, *LMoisture*, *LBulk and LTapped*)). Modeling the responses separately would not allow the estimation of the possible responses correlation. On the other hand, MMLR could suffer from under and over fitting for certain responses. Let the following model be applied

$$\mathbf{Y} = \boldsymbol{\beta}_0 + \mathrm{IT}\cdot\boldsymbol{\beta}_1 + \mathrm{IT}^2\cdot\boldsymbol{\beta}_2 + \mathrm{FR}\cdot\boldsymbol{\beta}_3 + \mathrm{FR}^2\cdot\boldsymbol{\beta}_4 + \mathrm{SFR}\cdot\boldsymbol{\beta}_5 + \mathrm{IT}\cdot\mathrm{SFR}\cdot\boldsymbol{\beta}_6 + \mathrm{IT}\cdot\mathrm{FR}\cdot\mathrm{SFR}\cdot\boldsymbol{\beta}_7 + \mathbf{E},$$

$$\mathbf{Y} = \mathbf{XB} + \mathbf{E}$$

with $\boldsymbol{\varepsilon}_n$, the nth line of $\mathbf{E}$, assumed to follow a multivariate Normal distribution, $\boldsymbol{\varepsilon}_n \sim N(0,\boldsymbol{\Sigma}), n = 1,\ldots,N$, with N the number of experiments. $\mathbf{X}$ is then the $(N \times F)$ centered and reduced design matrix and $\mathbf{B}$ is the $(F \times M)$ matrix containing the F effects for each of the M responses. The modeled effects have been chosen so that the model has the best properties for every response, jointly. $\boldsymbol{\Sigma}$ is the covariance matrix of the residuals.

In order to account for the variability of the parameters $\mathbf{B}$ and $\boldsymbol{\Sigma}$, a predictive density of new predicted responses can be obtained in the Bayesian framework, considering the non-informative prior distribution $p(\mathbf{B},\boldsymbol{\Sigma}) = |\boldsymbol{\Sigma}|^{-(M+1)/2}$ [20,21]. In this context, the predictive posterior density of a new predicted set of responses $(\tilde{\mathbf{y}}|\mathbf{X} = \mathbf{x}_0, \mathrm{data})$ at a new operating condition $\mathbf{x}_0 \in \chi$, is identified as a multivariate Student's t distribution, defined as follows:

$$(\tilde{\mathbf{y}}|\mathbf{X} = \mathbf{x}_0, \mathrm{data}) \sim T_M\left(\mathbf{x}_0\hat{\mathbf{B}}, \frac{\mathbf{A}}{\nu}\cdot 1 + \mathbf{x}_0(\mathbf{X}'\mathbf{X})^{-1}\mathbf{x}_0', \nu\right), \quad (1)$$

where $\hat{\mathbf{B}}$ is the least squares estimate of $\mathbf{B}, \hat{\mathbf{B}} = (\mathbf{X}'\mathbf{X})^{-1}(\mathbf{X}'\mathbf{Y})$; $\mathbf{A} = (\mathbf{Y} - \mathbf{X}\hat{\mathbf{B}})'(\mathbf{Y} - \mathbf{X}\hat{\mathbf{B}})$ is a scale matrix and $\nu = N - (M + F) + 1$ is the degrees of freedom.

4.1.3. Effects analysis

The analysis of the parameters effects is done using the marginal posterior density of the parameters $\mathbf{B}$ [20]. This density is centered on the ordinary least squares estimates $\hat{\mathbf{B}}$) and provides the credible intervals of the parameters, as shown on Fig. 1. It illustrates the high uncertainty observed on most of the regression parameters. The parameters for which the 95% credible intervals contain 0 are said to be nonsignificant (red), whereas the others differ significantly from 0 (green).

Briefly looking at Fig. 1, one may observe that the increase in feed rate and spray flow rate have a positive impact on the moisture content of the product. However, as the moisture remains limited whatever the condition, this may not have a strong impact on the overall quality. The same CPPs show a negative impact on both bulk and tapped densities. The squared term for the feed rate ($\mathrm{I(FR^2)}$) has been kept although not statistically significant. Indeed, it provided better fit for most responses. Next, the inlet temperature shows a negative impact on the yield. It might be due to the fact that more agglomerates are created at higher temperature, leading to a lower yield [12]. The same observation is done about

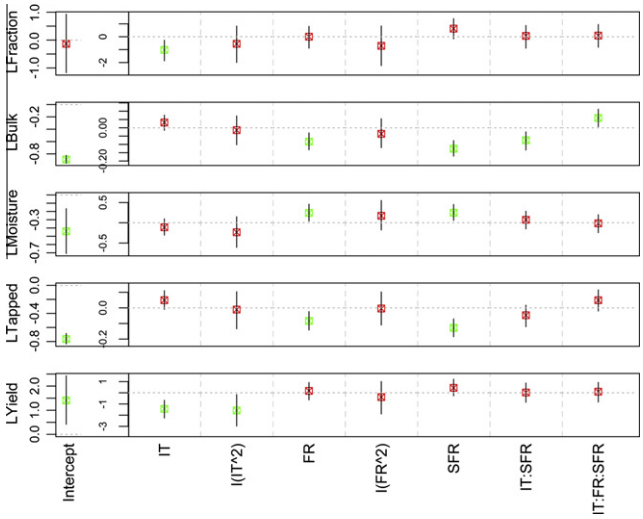

Fig. 1. Parameter estimates and 95% credible intervals. (Green) Parameters significantly different from 0. (Red) Parameters nonsignificantly different from 0. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

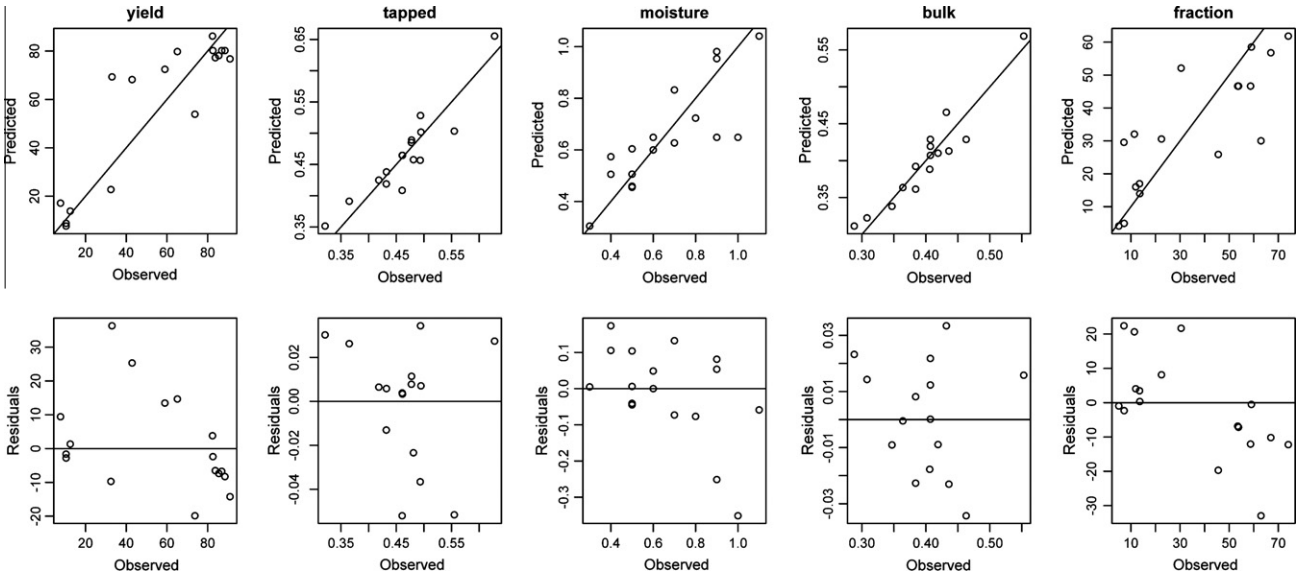

Fig. 2. Predicted vs. observed plots (top) and residuals plots (bottom) for every response.

the inhalable fraction. These types of results are the first keys toward a better understanding of the process.

Finally, Fig. 1 clearly emphasis the necessity in considering the uncertainties of the parameters when envisaging a risk-based approach. If checking their mean values and their distributions provide good insights into the process, it does not provide any direct valuable information on the quality of the output of the process, nor on the guarantee that this quality would be achieved.

4.1.4. Predicted vs. observed and residual analysis

Other model checks allow a better understanding of the model's capabilities. Firstly, it is advised to visualize the model suitability by plotting the mean (untransformed) predicted responses against the observed ones. The residuals have been graphically also checked, as illustrated in Fig. 2.

Fig. 2 illustrates the low quality of the multivariate model. Adjusted R^2 ranges from 0.40 (*LFraction*) to 0.82 (*LBulk*). Low model quality has clear explanations for responses like the moisture content (low precision of the measuring device for very low concentrations) or the tapped/bulk density (that are experimentally carried on small quantities of powder). Again, taking into account these residual uncertainties allows giving risk-based results even in the presence of poor model fit. This will have a direct impact on the quality level associated with the DS.

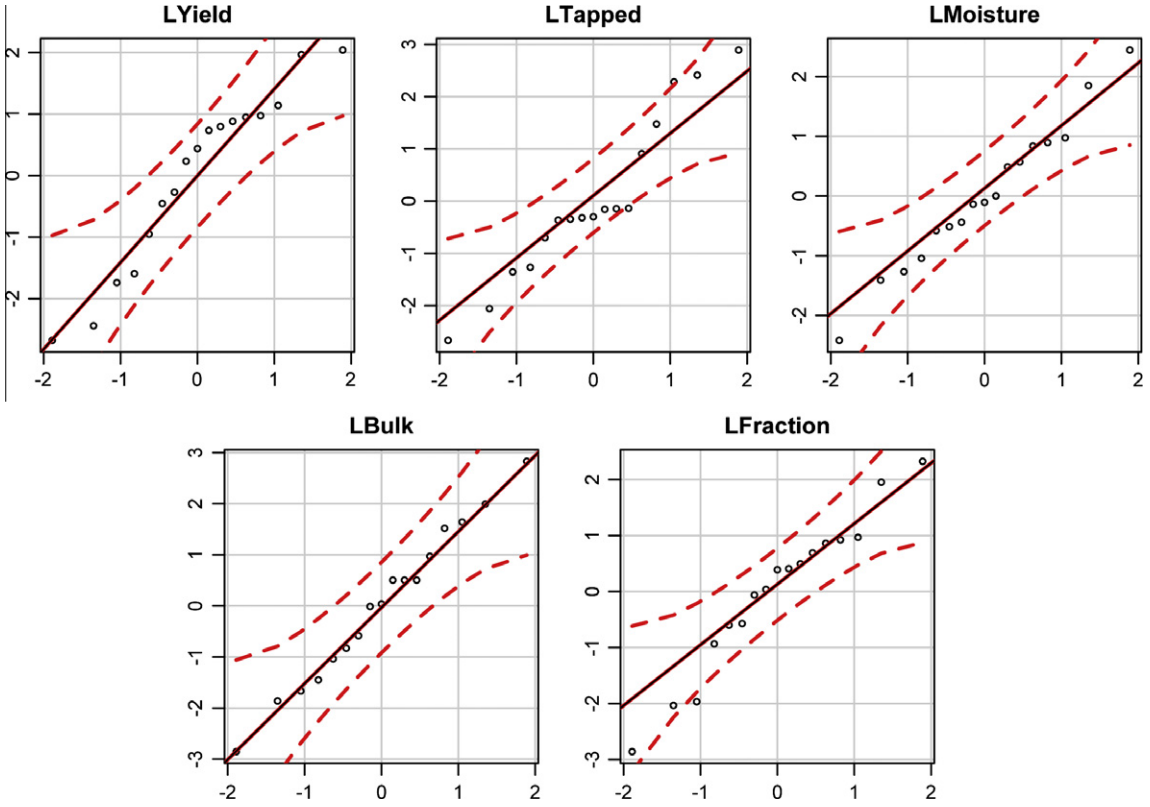

Fig. 3. Marginal Normal Q–Q plots of the residuals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 4
Estimated residuals correlations between the responses.

	LYield	LTapped	LMoisture	LBulk	LFraction
LYield	1				
Ltapped	−0.05	1			
Lmoisture	0.16	0.04	1		
LBulk	0.3	0.9	0.31	1	
LFraction	0.83	0.32	0.28	0.6	1

Finally, Q–Q plots are drawn to see whether the model residuals do not depart from Normality assumption. This is shown in Fig. 3. The hypothesis of Normality of the residuals seems acceptable.

4.1.5. Response correlations

From the model, one can estimate the correlations that exist between the responses by rescaling the matrix **A** into an estimated correlation matrix, by dividing its elements with the appropriate row and column standard deviations [22]. The correlations are given in Table 4.

A strong correlation (0.9) is observed between the bulk and the tapped densities meaning that these two values generally have a similar behavior. These similarities might be a result of the tapping process carried out on small quantities of powder. The observation is as follows: if the bulk density is low (high), this will give a proportionally low (high) tapped density. From a statistical point of view, not taking this correlation into account when deriving the compressibility index and the Hausner ratio would be harmful.

Next, there is an agreement between the yield and the inhalable fraction. In the present process, the higher the yield, the higher the inhalable fraction will be.

In addition, a correlation of 0.6 between the inhalable fraction and the bulk density can be observed. From a physical point of view, this can be explained by the fact that the lower the particle size is, the higher the bulk density will be. Moreover, the tapped density being correlated with the bulk density, the tapped density is also slightly correlated with the inhalable fraction. Nevertheless, this correlation is lower than the one between the inhalable fraction and bulk density because the inhalable fraction determination is based on the bulk powder and not on the tapped one.

4.1.6. Design space computation

Basically, the way to compute the DS is to use the joint predictive distribution of the CQAs, derived from Eq. (1) in every point of the experimental domain. When CQAs are transformations and/or combinations of the responses, Monte-Carlo simulations are envisaged to propagate the predictive uncertainty and interactions/correlations of the responses to the CQAs.

Randomly looking at a point $\mathbf{x}_{sub}$ of the knowledge space, for instance, Inlet Temperature = 180 °C, Feed Rate = 2.5 ml/min, Spray Flow Rate = 1744 L/h, one can analyze the sampled CQAs derived from the responses drawn from the multivariate Student's *t* distributions, as shown on Fig. 4.

The red lines indicate the specifications for each CQA, while the red regions of the densities illustrate the proportion of simulated points (i.e., the estimated predictive probability) that are within specifications. For instance, at operating condition $\mathbf{x}_{sub}$ and for the CQA *Yield*, the proportion is about 30%, meaning that there is a probability of about 0.3 to have, in the future, a yield higher than 80% ($P(Yield > 80\%) = 0.3$). This represents a high risk of 1–0.3 = 0.7 of being outside the specification. Taking into account the yield alone, this condition may thus be considered outside of the DS with a satisfying quality level. Regarding the moisture content, the probability to have this CQA within the specification is 0.8, so there is a risk of 0.2 of being outside specifications. Envisaging this CQA alone, $\mathbf{x}_{sub}$ could belong to the "design space" with a specified

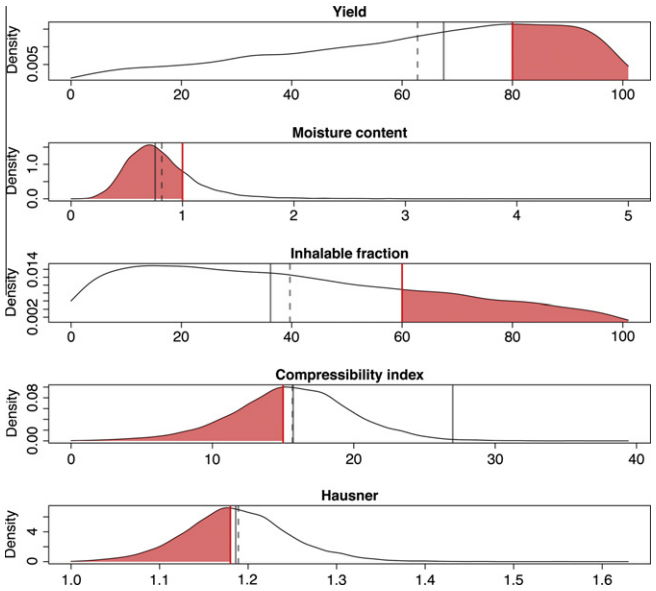

Fig. 4. Marginal predictive kernel density estimations of the critical quality attributes on a point $\mathbf{x}_{sub}$ of the experimental domain. The red lines are the specification limits, and the red regions are the estimated probabilities of achieving the specifications. The black lines are the medians (plain) and the means (dashed) of the distributions. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

minimal quality level π of, say, 0.6. However, going multivariate deteriorate the results. The joint probability to accept all the specifications is lower than 0.001. The $\mathbf{x}_{sub}$ input condition is then clearly not within any DS.

Next, the same computations are done, on every point of the experimental domain χ. To do so, a grid search is applied. For each operating condition, the estimated expected probability that the 5 CQAs are jointly within specifications is recorded. A probability map is then drawn, as shown in Fig. 5. A clear similarity with response surface is seen, but the interpretation of such maps is quite different. In each operating condition represented, the map gives the joint expected probability (i.e., the guarantees) to observe the process within specifications, on a future run. On the cuboid knowledge space, only three slices that include the optimal condition are represented.

The black-contoured region is the DS, i.e., the operating conditions where the joint probability to achieve all specifications on the CQAs is the highest over the experimental domain. A cuboid can be extracted, and the limit values for its vertices are given in Table 5.

In this application, a DS is found, for a specified minimal quality level of $\pi = 0.437$, chosen as 95% of the quality level of the optimal solution. However, one can be suspicious about the quality of the results. Indeed, the optimal expected probability is *only* about 0.45. Thus, within the DS, there is a risk of 0.55 not to be within all the specifications concurrently. A good insight for a better comprehension of what happens is to have a look at the marginal predictive distributions at the optimal point, which is: Inlet Temperature = 123.75 °C, Feed Rate = 4.69 ml/min, and Spray Flow Rate = 1744 L/h, as shown in Fig. 6.

Regarding Fig. 6, it is obvious that, marginally, the estimated expected probabilities for every CQA are quite satisfactory. The acceptance probability is higher than 0.7 for the yield ($P(Yield > 80\%) = 0.71$), 0.78 for the moisture content (<1%), 0.62 for the inhalable fraction (>60%), and 0.85 for both the compressibility index (<15) and the Hausner ratio (<1.18). Then, except for the inhalable fraction, the model provides us a satisfying confidence toward the future performance of the process.

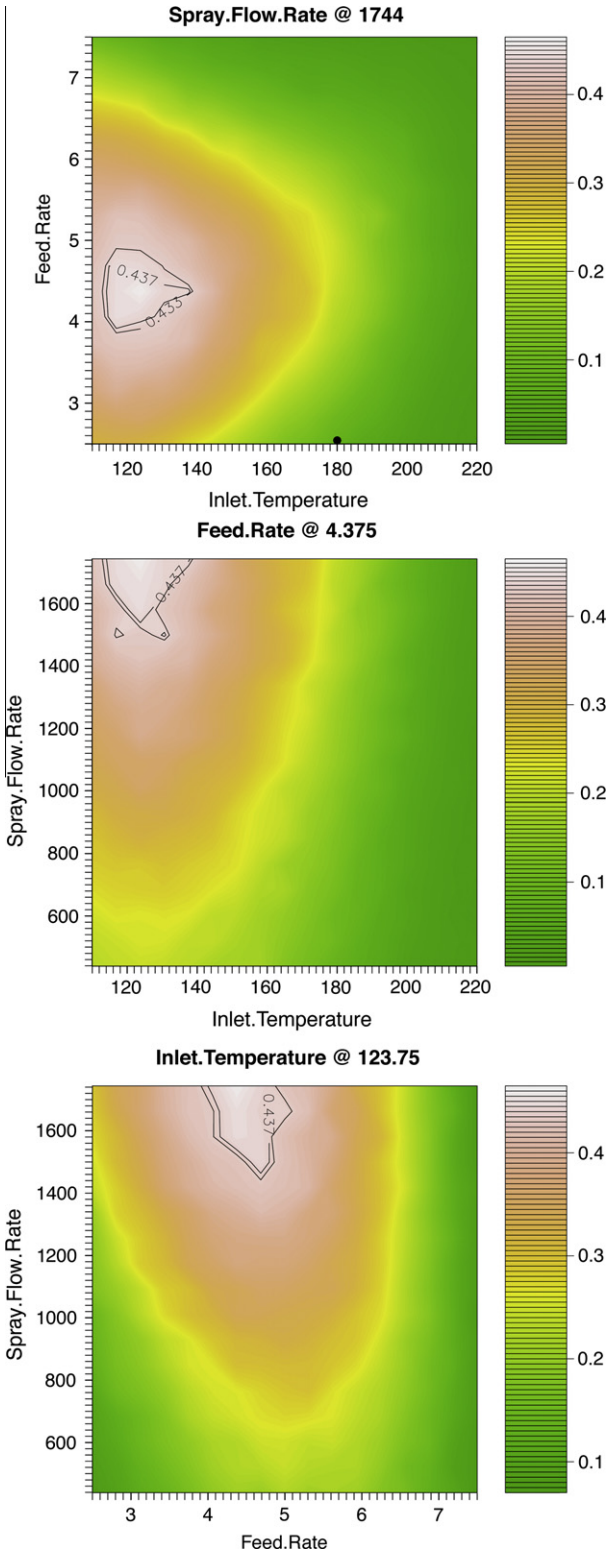

Fig. 5. Probability map that the CQAs satisfy the five specifications presented in Table 3. Inner black lines define the DS for the minimal quality level $\pi = 0.437$ The black point is the suboptimal condition $\mathbf{x}_{sub}$ presented in Fig. 4. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

From a probabilistic perspective, the addition of univariate specifications in a multivariate analysis logically leads to a decrease in the joint predictive probability of acceptance [23]. At optimal condition, the following decreasing probabilities illustrate this situation.

$P(Yield > 80\%) = 0.71$,
$P(Yield > 80\%$ and $Moisture < 1\%) = 0.56$,
$P(Yield > 80\%$ and $Moisture < 1\%$ and $Fraction > 60\%) = 0.48$,
$P(Yield > 80\%$ and $Moisture < 1\%$ and $Fraction > 60\%$ and $Hausner < 1.18) = 0.45$.

The definition of multivariate specifications may be seen as a remedy to this. In this context, desirability functions can be envisaged to aggregate the values of every individual predicted CQA into a single value, namely the desirability index, representing the desirability of the solution [24,25]. Monte-Carlo simulations can be used to propagate the predictive uncertainty and the correlations of the CQAs to the desirability index [26]. This index allows for certain trade-offs between the CQAs. A slightly bad result for one CQA could be compensated by a very satisfactory result for another.

In this 5-CQAs study with univariate specifications, it may not be surprising to observe the optimal joint estimated expected probability of acceptance being about 0.45. Of course, finding a DS with a higher minimal quality level and even stronger specifications would be an even more desirable situation.

Some estimates for each CQA are provided in Table 6, computed from the distribution presented in Fig. 6. The mean values (Fig. 6, dashed lines) or the medians (plain line) are the values expressing the central tendency one can expect to observe. Additionally, the 75% and 95% Bayesian predictive intervals are also provided as valuable information about the uncertainty of prediction.

For instance, the 75% predictive interval around the CQA *Inhalable fraction* is very large ([49–85]%). Then, the model is poorly informative regarding this CQA. A similar conclusion was reached when looking at the marginal acceptance probability for this CQA at the optimum, which was only 0.62.

Table 5
Design space of the process.

Critical process parameters	DS range
Feed rate (ml/min)	[4.2–4.8]
Spray flow rate (L/h)	[1614–1744]
Inlet temperature (°C)	[118–125]

4.2. Validation

The optimal solution has been carried out three times independently on the same apparatus to observe how the process performs within its 0.45 quality level DS. Table 7 summarizes the experimental results. They reinforce the statistics observed during the optimization process.

As expected, the process performs according to the predictions. Most batches are within specifications. The inhalable fraction is seen as acceptable (higher than 60%) except in the third batch (red). However, on average (bold), the process corroborates the results of the joint expected probability, which was about 0.45. Obviously, a longer-term study would be necessary to plainly assess the routine performance of the process.

Finally, Table 7 provides the indication of the variability observed in the three independent batches. This variability is low compared to the predictive uncertainty that was observed (see Fig. 6 and Table 6). This indicates that the residuals predictive uncertainty is not only due to the noise of the process. The poor model fit is also a concern. A possible explanation is that more complex interactions and higher order or non-linear effects are present. Unfortunately, the central composite face-centered design used in the experimental part is too light to detect such effects.

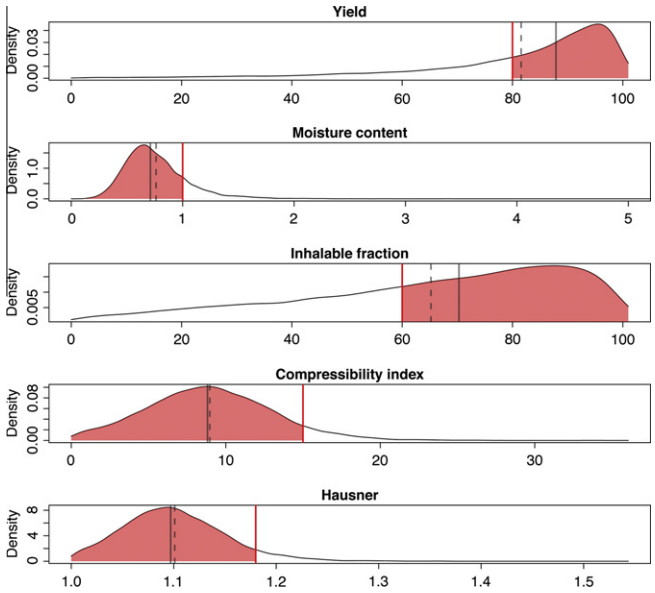

Fig. 6. Marginal predictive kernel density estimations of the critical quality attributes on at the optimum. See Fig. 4 for colors and legend. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 6
Statistics on the CQAs at the optimal input condition.

CQA	Lower 95%	Lower 75%	Median	Mean	Upper 75%	Upper 95%
Yield (%)	42	75	**88**	**81**	94	~100
Moisture content (%)	0.26	0.57	**0.71**	**0.76**	0.89	1.31
Inhalable fraction (%)	17	49	**70**	**65**	85	100
Compressibility index	0.4	6.2	**8.8**	**9**	11.5	16.1
Hausner ratio	1	1.07	**1.09**	**1.1**	1.13	1.19

Indeed, the design allows only the estimation of the main and quadratic effects and the principal interactions. This underlines the need to define more informative designs when little is known about the process, even if the price that must be paid is the carrying out of more experiments.

5. Conclusions

When setting up a QbD-compliant ICH Q8 design space for a process such as spray-drying, the use of the mean response surface optimization methodology is not recommended due to the inevitable uncertainties and interactions that are encountered. Accordingly, the data gathered through a well-designed experimental plan have been analyzed using a risk-based Bayesian predictive approach allowing the uncertainties and interactions to be integrated into a multivariate statistical model.

These variabilities result in a minimal quality level that has been kept relatively low in order to be able to define a design space, i.e., the guarantee of jointly observing the critical quality attributes within their acceptance limits is low. Even with this situation, these guarantees are quantified along with the risks of not observing such quality, jointly or marginally. The specifications have been designed such as to provide a minimal satisfying quality for whole process. In this way, the quality of the resulting product

Table 7
Results of the validation experiments.

Batches	Yield (%)	Moisture content (%)	Inhalable fraction (%)	Compressibility index	Hausner ratio
1	88	<0.2	63	11.6	1.13
2	89	<0.2	62	12	1.14
3	88	<0.2	59	11.5	1.13
Mean	**88.7**	**<0.2**	**61.18**	**11.76**	**1.13**
Standard deviation	0.61	NA	1.82	0.22	0.01

is built in by the design and controlled setup of the spray-drying equipment.

Validation of the optimal condition within the design space has been carried out, and these experiments provided a product compliant with the predicted quality. To better assess how the guarantees of quality prediction perform, one would consider analyzing longer-term process data.

In addition, the validation experiments carried out independently provided supplementary information concerning the statistical model. Indeed, the good repeatability of the process seems to indicate that the causes of the poor model fit were not solely due to the noise present in the data. Instead, more complex interactions or non-linearity of the responses can be present. In cases where nothing or little is known about a specific process, defining a more informative though labor-intensive design of experiments should be envisaged.

Finally, the definition of a low guarantee design space could be seen as the very first step toward a quality by design methodology. The results presented are of great interest for the spray-drying manufacturers and experimenters in order to improve quality. For instance, the causes of variation could be identified, such as poorly controlled factors. Furthermore, the effect of the key process parameters that have been kept constant during this study could be analyzed in a more detailed way through a new experimental plan.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejpb.2011.09.014.

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