Guaranteeing a Quality Scale-up

Enric Jo at Reig Jofré Group provides a detailed account of a first approach for applying quality by design in a scale-up of a lyophilisation cycle for an antiviral product

As explained in the FDA Guidance for Industry Q8, Q9 and Q10 Questions and Answers, it is possible to develop a design space for existing products and also for scale-up processes (1). Working with quality by design (QbD) means, basically, a guarantee of the safety and efficacy of the product. To reach that goal we need to start from the quality target product profile (QTPP) established during the first steps of the development. In the case presented here we will discuss a well-known antiviral product already on the market. Having processed a variety of batches with different equipment, it is debatable whether the process involved – in this case lyophilisation – would be able to withstand a QbD process to establish its design space. To begin with, the critical quality attributes and the critical process parameters have been initially selected through a careful process of risk assessment. Using PAT tools available in a pilot plant, and by means of multi-dimensional data analysis, an acceptable range of responses allows us to obtain the limits to carry out a rational design of experiments. Modifying the main input variables – chamber pressure (P_c), shelf temperature (T_s) and time (t) – it is possible to determine the limits of the design space and, most importantly, apply them to the scale-up, or even in technology transference processes.

THE QTPP – FIRST APPROACH

The target product profile is usually described throughout the key sections in the product's labelling (2). Based on this profile we can identify the QTPP as its natural extension for product quality. Regarding the product that we are studying to select for the intended critical quality attributes, the following can be established based on these three QTTP elements:

- Appearance – the critical quality attribute is correct
- Moisture content – the critical quality attribute is less than six per cent
- Reconstitution time – the critical quality attribute is less than two minutes

One of the most common problems during lyophilisation is the appearance of a crumbled cake, indicating that the front of sublimation has reached a temperature which is above the product collapse temperature (T_{co}).

QUALITY BY DESIGN

The three constituent elements of QbD are the following (3):

- Quality target product profile
- Critical quality attributes: A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality
- Risk assessment: Linking material attributes and process parameters to the drug product's critical quality attributes. This tool allows us to identify and rank parameters with a potential to have an impact on product quality, based on prior knowledge and initial experimental data

In the design space we have to describe the relationship between the process inputs (material attributes and process parameters) and the critical quality attributes.

MATERIAL ATTRIBUTES & PROCESS PARAMETERS

The key material attributes for the product are shown in Table 1. A key parameter or attribute may eventually be designated as 'critical' depending on severity, probability of failure and its ability to be detected (4). Some of those attributes can be considered critical when conditioning the input variables to set up the process. We select those which are related to critical parameters in the process. As a result, only the following will become relevant: T_{ts}, T_g', T_{co} and T_{max}. Table 2 shows the critical process parameters already selected.

During the process a different set of parameters is relevant. During the freezing

Table 1: Key material attributes

Key attribute	Analytical source	Rank
(1) Temperature of total solidification (T_{ts})	DSC/FDM	<-26°C
(2) Glass transition temperature (T_g')	DSC	[-72:-32]°C
(3) Collapse temperature (T_{co})	FDM	[-58:-56]°C
(4) Melting temperature (T_m)	DSC/FDM	[-20:-13]°C
(5) Height of the solution (inside the vial)	Measure	10mm
(6) Solid material content	Defined (TPP)	10.5 per cent
(7) Maximum temperature of exposition allowed (T_{max})	Stability studies	<35°C
(8) Volume (to ensure the API dose)	Defined (TPP)	2.8 ± 0.1ml

Table 2: Critical process parameters

Critical process parameter	Related variable	Process step
Set point shelf temperature	T	**Freezing**
Freezing rate	Fr	
Freezing time	Ft	
Set point shelf temperature	T	**Primary drying**
Heating rate	HRa	
Chamber pressure	P	
Primary drying time	PDt	
Set point shelf temperature	T	**Secondary drying**
Heating rate	HRa	
Chamber pressure	P	
Secondary drying time	SDt	

step, the product temperature has to reach a value below the T_{ts} found in the previous thermal studies. If we measure it using a probe during sublimation, it does not indicate a clear response because it gives the average of three temperatures – the dry layer temperature, the frozen layer temperature, as well as the sublimation front temperature. Nevertheless, this temperature gives information on the evolution of the process and, although it is expendable in the industrial process, in the scale-up studies it can be used as a PAT tool. Other PAT tools have also been applied.

RISK ASSESSMENT

Let us link the critical quality attributes with the critical process parameters. First of all, we have to define the scope of the lyophilisation process, and for this we build a process flow diagram (see Figure 1). The risk assessment has to analyse how the variations in the critical process parameters can affect the critical quality attributes, based on the material attributes and on the previous product knowledge. The Ishikawa diagram (see Figure 2) provides a graphical representation of the relationship between process operating parameters and unit operation outcomes. An appropriate analysis of the risk assessment allows us to establish the design of experiment that will frame our study.

CASE STUDY

The subject of this case study is an antiviral, lyophilised in 10ml vials with 250mg of active pharmaceutical ingredient (API) in 2.8ml of solution.

Quality Target Product Profile

We have established three main elements for the QTTP:

- Appearance: Prior knowledge of the product indicates a range of appearances that are either correct or incorrect. Some

Figure 1: Process flow diagram linking critical material attributes, critical process parameters and critical quality attributes

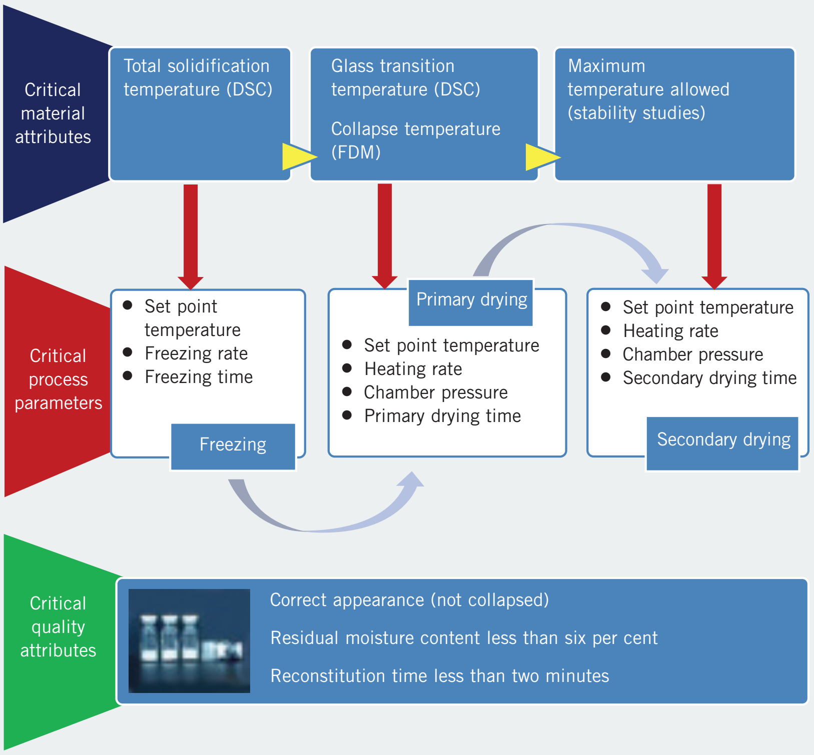
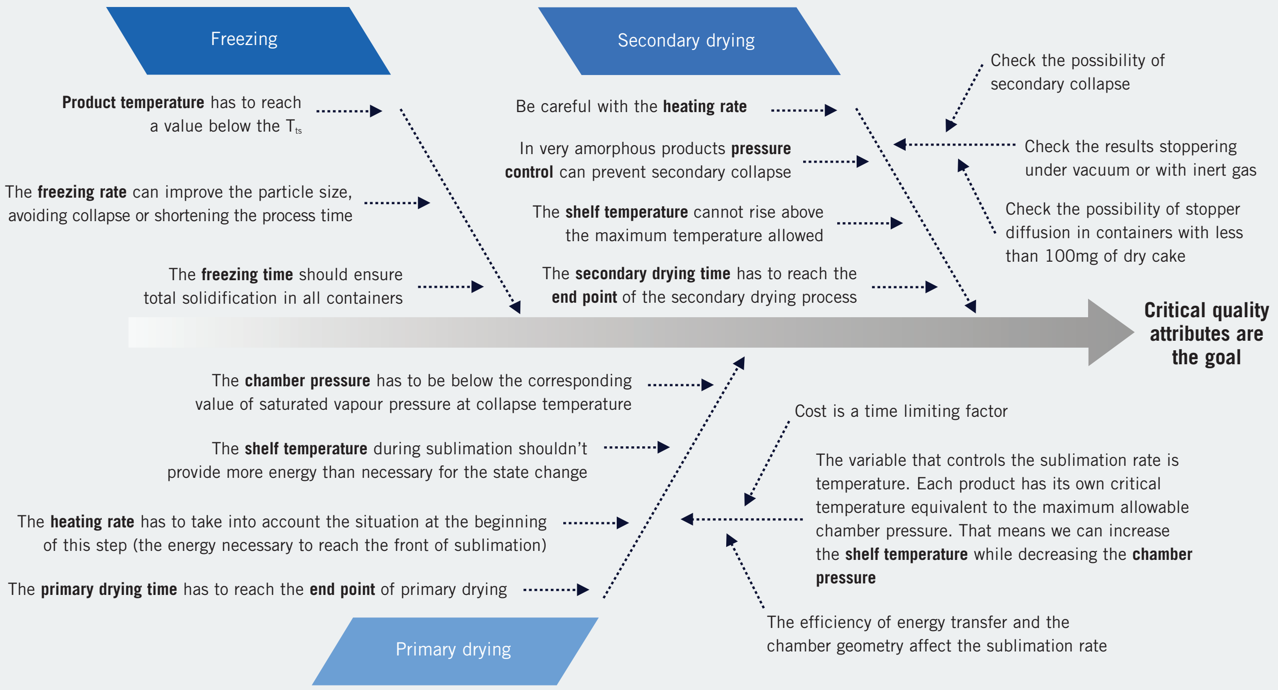


Figure 2: Ishikawa diagram for freeze-drying process



Product temperature has to reach a value below the T_{ts}

The **freezing rate** can improve the particle size, avoiding collapse or shortening the process time

The **freezing time** should ensure total solidification in all containers

Be careful with the **heating rate**

In very amorphous products **pressure control** can prevent secondary collapse

The **shelf temperature** cannot rise above the maximum temperature allowed

The **secondary drying time** has to reach the **end point** of the secondary drying process

Check the possibility of secondary collapse

Check the results stoppering under vacuum or with inert gas

Check the possibility of stopper diffusion in containers with less than 100mg of dry cake

The **chamber pressure** has to be below the corresponding value of saturated vapour pressure at collapse temperature

The **shelf temperature** during sublimation shouldn't provide more energy than necessary for the state change

The **heating rate** has to take into account the situation at the beginning of this step (the energy necessary to reach the front of sublimation)

The **primary drying time** has to reach the **end point** of primary drying

Cost is a time limiting factor

The variable that controls the sublimation rate is temperature. Each product has its own critical temperature equivalent to the maximum allowable chamber pressure. That means we can increase the **shelf temperature** while decreasing the **chamber pressure**

The efficiency of energy transfer and the chamber geometry affect the sublimation rate

Figure 3: Photo of collapse obtained by freeze drying microscope

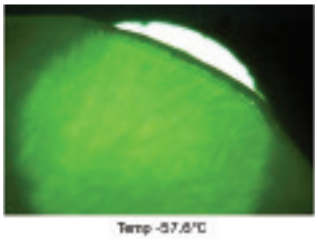


Figure 4: Categories of appearance for collapse

authors have described a decreased physical stability in collapsed cakes (5). Considering the conclusions from published investigations, structural collapse leads to a variety of changes in the cake's properties, resulting in both aesthetic and stability concerns (6,7)

- Residual moisture content: The specification is under six per cent in most of the formulations. Some dossiers have been presented in different agencies describing the specification as under four per cent. Obtaining a value from two to three per cent at time = zero, does not produce stability problems at the expiry date (which is currently three years)
- Reconstitution time: Less than two minutes. It is also possible to reach values less than one minute

Critical Material Attributes

Total solidification temperature (T_{ts}): Obtained by means of differential scanning calorimetry (DSC). The exothermic event reaches a security value below -45ºC. Some authors speak about the necessity of lowering the product temperature below the lowest of both T_g' and T_{co} (8). Nevertheless, taking into account the often already very low T_g' values, this is not always possible.

Glass transition temperature (T_g'): Obtained by means of DSC. The endothermic process indicates different glass transitions in a range between -72 and -32ºC.

Collapse temperature (T_{co}): From the selected photos obtained by freeze drying microscope, shown in Figure 3, it is possible to observe that the collapse started at -57ºC.

Maximum temperature allowed by the product (T_{max}): The stability studies, regarding the impurities generated, marked the maximum temperature the product can withstand as 35ºC.

Risk Assessment and First Approach to Design of Experiment

The risk assessment analyses the critical process parameters versus the critical quality attributes. The historical data let us detect a strong relationship between the set points established for the temperature, pressure and time (critical process parameters), and the collapse and RMC (critical quality attributes). Different considerations have been taken into account. The attempts to avoid the collapse by means of annealing turned out not to be useful. The range of T_g' & T_{co} is too low for the equipment's capabilities. Nothing can be done during the freezing step.

During primary drying, the sublimation front temperature is controlled by the chamber pressure. Taking this value as the critical temperature, several strategies can be carried out to establish the previous design of experiment. In any case, the sublimation rate is controlled by the shelf temperature (9). The initial design of experiment will analyse the variations of two factors at a time: pressure and temperature, taking five different critical temperatures for the product, from the more aggressive criteria (cycle 1) to the more conservative (cycle 5).

The time only justifies the attainment of the end point. In order to guarantee the outcome of the process, the chamber pressure will be set at 50 per cent of the pressure corresponding to the critical temperature.

A certain time interval will be needed until the energy supplied by the shelves reaches the sublimation front of the frozen product. The secondary drying does not show any collapse problems. A complex matrix of risk assessment has been established to link the critical process parameters and the critical quality attributes. Table 3 shows the initial design of experiment. The critical quality attributes are the following:

- Appearance: A ranking of four categories has been established in Figure 4
- Moisture: Under six per cent; ideal results between two and three per cent
- Reconstitution time: less than two minutes. Ideal results less than one minute

RESULTS

Figure 5 (page 66) shows the graphic for the more conservative cycle (5). Table 4 shows the quality attributes obtained for each cycle.

Design Space

The design space allows us to redefine the design of experiment in order to finely adjust the limits for the critical process parameter. To tackle it, several different cycles processed in the pilot plant have been selected. Initially 18 different

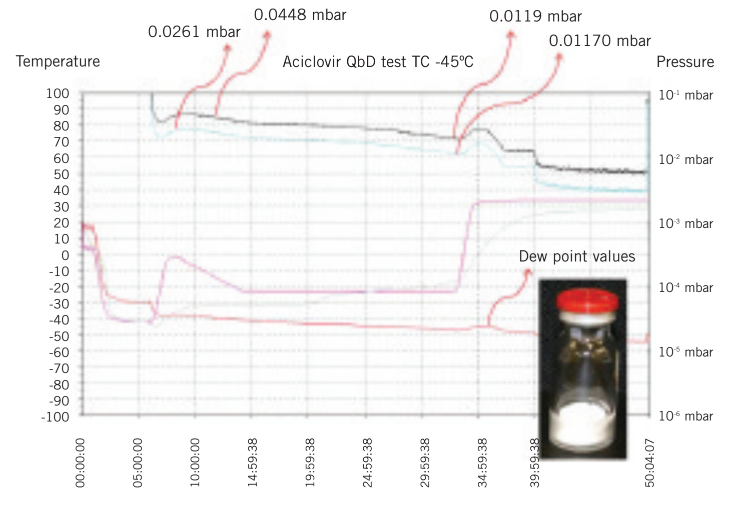
Table 3: Initial design of experiment

Process parameter	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5
Critical temperature (°C)	-25	-30	-35	-40	-45
Corresponding pressure (Pirani) (mbar)	9.7 x 10^{-1}	5.8 x 10^{-1}	3.4 x 10^{-1}	2.0 x 10^{-1}	1.1 x 10^{-1}
Set points in the equipment					
Shelf temperature (°C)	-5	-10	-15	-20	-25
PD time (hours)	18	22	26	30	34
Chamber pressure (Pirani) (mbar)	4.8 x 10^{-1}	2.9 x 10^{-1}	1.7 x 10^{-1}	1.1 x 10^{-1}	4.5 x 10^{-2}
Total process time (hours)	34	38	42	46	50

Table 4: Quality attributes obtained

Quality attribute	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5
Appearance (aspect)	Unacceptable	Poor	Acceptable	Correct	Correct
RMC (Hr) (per cent)	7.16	5.13	3.08	1.92	1.82
Reconstitution time (seconds)	No	Partial	45	30	30

Figure 5: Cycle 5 (correct) – critical temperature: 45ºC



variables of pressure and temperature were selected, also including the data collected from the dew point probe. The data were processed by means of the statistics software Unscrambler X from CAMO Software AS (Oslo, Norway).

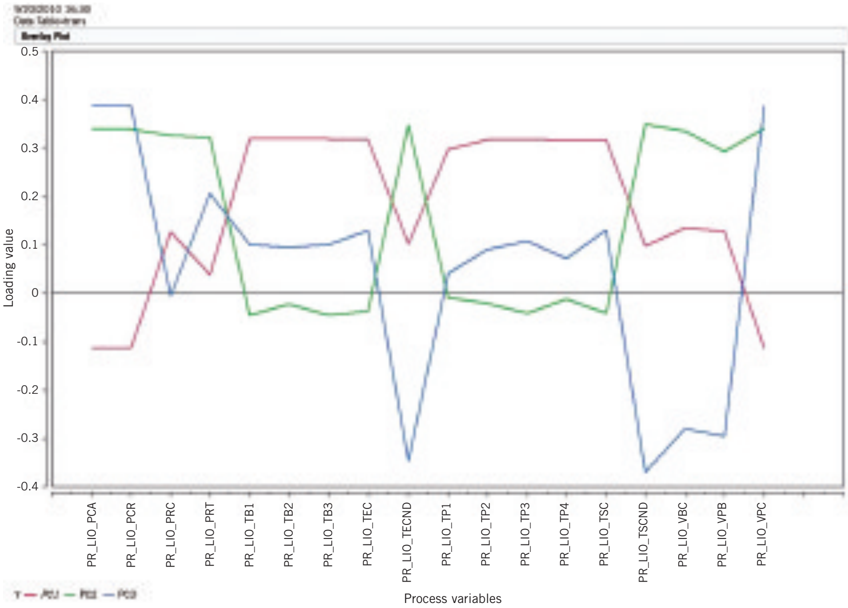
Data Transformation for the Fitting

To carry out the first approach, a matrix of 18 columns (process variables) and more than 30,000 rows (data) was built, where each row corresponds to one value taken at each minute in the pilot plant. Two situations should be controlled before starting the chemometric analysis. With regard to autoscaling, the statistical treatment understands nothing about the units, so it is necessary to give the same weight for all the data when comparing the different variables. This transformation was done in order to be able to carry out the treatment of the data by means of a multivariable tool – principal components analysis. The process consists of a method of centred values using a new function that will transform each data. The expression for the function is the following:

$$f(x) = \frac{x_{i,A} - x_{\bar{A}}}{\sigma_A}$$

Here, each one of the values for the variable A is $x_{i,A}$, $x_{\bar{A}}$ is the average of the values and σ is the standard deviation for the values of the variable A. That means given weight to σ.

Figure 6: Loadings graphic



Noise

From the previous transformation we obtained a new matrix whose eigen vectors, along with its eigen values, continue to point in the same direction (10,11). Nevertheless, the instrumental and electrical noise produced by the equipment limitations should still be reduced. Four different techniques in order to reach this reduction were assayed: moving average, median filter, Savitsky-Golay and Gaussian filter, with the last one being the most effective. The data window tested was one of either 9, 15 or 21 data points, with 21 being selected. The simple expression of the fitting, within the Gaussian filter is, the following:

$$g(x) = \frac{1}{\sqrt{2\pi}\sigma} e^{-\frac{x^2}{2\sigma^2}}$$

Principal Component Analysis

The risk in the treatment could be to establish a function that fits the data in a complex mathematic function but without giving an explanation to the physical process. To avoid it, different analytical methods have been applied for the principal component analysis:

Method of the Explained Variance

The fitting determines an analysis of seven principal components, each one grouping the 18 variables, giving different weight for each variable, in different fitting functions. It is discovered that the first principal component explains 53 per cent of the fitting; the second one explains 33 per cent and the third one explains nine per cent. Thereby, with the three first principal components, we can explain 95 per cent of the fitting.

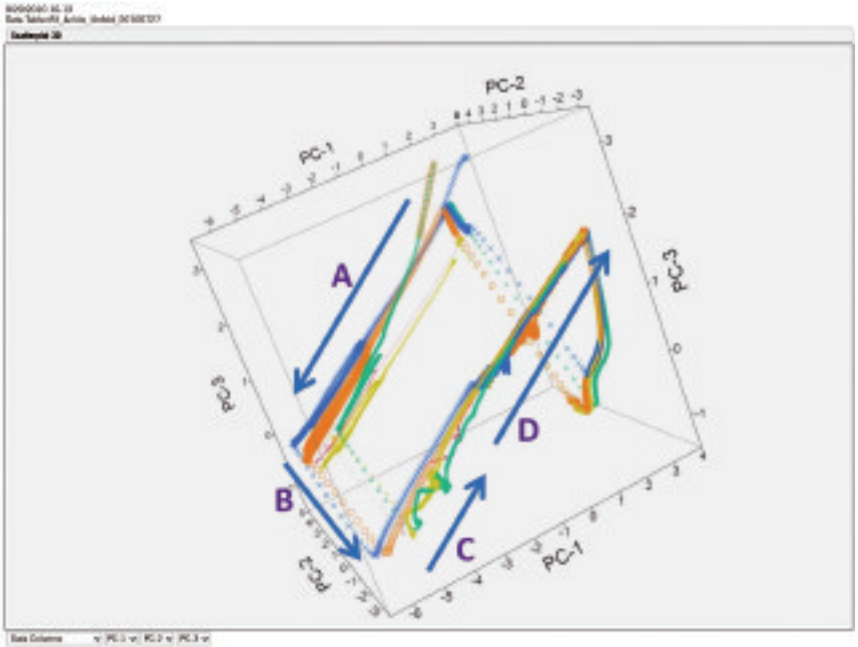
Loadings Graphic

This graphic represents in two dimensions the contribution of the variables and their correlation for the principal components: PC1, PC2 and PC3. Regarding each principal component, the further from zero the variables are, the more contribution is given to those variables to build the PC. Also, the closer the variables are among them, the more correlated they are. Figure 6 shows these contributions.

Graphic of Scores

This graphic represents the frame of our 33,000 data. This is the established three-dimensional space from the advised PC1,

Figure 7: Graphic of scores (3D)



PC2 and PC3 to reach 95 per cent of the explained variance (see Figure 7).

The stretch marked by arrow A in Figure 7 indicates the freezing step; the one marked by B corresponds to the transition from freezing to primary drying; C is the primary drying; and D is the secondary drying. From D to A the system turns back to the initial conditions.

CONCLUSION

Upon reaching this point we can establish the following conclusions. The process can be explained by means of the used statistical tool. A further step should be done using cycles whose corresponding parameters are between the third and fifth tested. The second approach would be carried out with at least three cycles. Fewer variables should be selected from the 18; using just 12 or less can really help to define the design space. More variables can be added from the use of other PAT techniques, such as NIR. Therefore, a new design of experiment will be built, whose results will be tackled with the matrix corresponding to the critical quality attributes in order to obtain an operator that will establish the correlation between critical process parameters and critical quality attributes to reach the golden batch (process signature) for the product. That treatment will be carried out by means of a mathematic treatment using partial least squares-discriminate analysis (PLS-DA).

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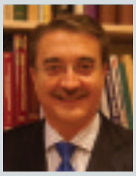

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