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Design space of the micronization process
based on the Quality by Design (QbD)

KEYWORDS: Design of Experiment, Critical Quality Attributes, Critical Process Parameters, Micronization, Particle Size Distribution, D90.

Abstract Since the FDA and EMS have actively begun sponsoring the Quality by Design (QbD), this has started to be a more and more active philosophy in the development of new drugs. Pharmaceutical companies have grasped the real value and the benefits that this new approach can produce and have started to introduce it in the projects they deem as the most important. In order for the QbD to be successfully implemented, it is necessary to develop an in-depth and consolidated knowledge of the involved processes, from the production of the active ingredient to the production of the finished pharmaceutical form. A single company, however big, can't manage all the project's stages and needs to outsource a part of it. Thus it becomes critical, in order to implement the QbD, that a clear and direct communication channel is opened between the customer and the service supplier, so that the latter can help the former in the elaboration of the QbD connected to the supplied service.

INTRODUCTION

Jetpharma is a company specialized in micronization services of active ingredients and highly active molecules. Through our Jet mills, designed and developed thanks to more than forty years of experience, we are able to reach PSD of between 1 and 5µm, guaranteeing our customers an excellent scalability and an exceptional process performance. In order to constantly improve and always support our most demanding clients, we have decided to implement the Quality by Design concept into our micronization processes. The following case history shows in detail how this modern approach can produce benefits since its very first development.

THE QbD

The QbD is a modern scientific approach to develop and produce drugs, based on international guidelines (ICH Q8 «Ph. Development»; Q9 «Quality Risk Management»; Q10 «Ph. Quality System»), which starts out, first, with the definition of the final product's qualitative goals and then progresses through the understanding of the process and framework aspects influencing the Critical Quality Attributes (CQAs). Furthermore, it uses the Process Analytical Technology (PAT), in other words, the on-line analytical instruments which in real time collect and transmit data on the raw material behaviour during the process. The result of the QbD implementation is to reach the development of a production method capable of always guaranteeing a successful achievement of the qualitative characteristics of a drug.

Through a previous knowledge of production operations, the use of a statistical method, the risk analysis and the PAT implementation, it is possible to identify and study the most critical variables of the production process and to understand how these influence each other. Such knowledge, as a consequence, leads to an improved management of deviations which, for companies, results in a remarkable savings and in a higher security when identifying causes and eventual solutions.

WHY?

In the past, a fair amount of time has not been devoted to the understanding of the variables at work during a drug development, thus this lack of knowledge has lead to a scarce capacity of reaction to the problems which could be met during a production process.

Nowadays, thanks to the active participation of EMA and the FDA, pharmaceutical companies admit the necessity to exhaustively investigate the whole production process and to enforce a control not only aimed at checking whether the final product complies with the settled specifications, but also at live monitoring the process.

By implementing the QbD, not only will companies be able to more quickly and more safely uncover the causes of an eventual deviation, but it will be also possible to obtain a deeper knowledge about the process.

The FDA and EMA have realized that the present regulation system does not support innovation inside production processes and it's often the cause of delays in the registration procedure due to lack of information. For this reason, both authorities – FDA and EMA – have been insisting for many years that every new drug is to be developed according to the Quality by Design; although the initial cost of such a development is high and demands a team of people with a very different backgrounds, advantages for the companies that will decide to implement it will be numerous and include the following benefits:

– A reduction of the time necessary to get the approval from the Authorities themselves;
– An easier process of identifying the causes generating non conforming production lots;
– A net reduction of the non conforming production lots: at present, a non conforming production lot costs pharmaceutical companies approximately 500,000 Euros;
– An easier achievement and maintaining of the regulation requisites;
– The possibility to optimize the production process;

Critical Quality Attribute	Failure mode	Consequence	Rating
Particle size distribution	Too wide distribution; Size too small; Size too Big;	Bioavailability; Spreadability; Penetration; Rheological behaviour; Dose uniformity	5
Morphology	Changed morphology;	Penetration; Stability; Efficacy; Can affect analytical results;	4
Crystallinity	Formation of amorphic API;	Stability; Bioavailability; Spreadability; Rheological behaviour	5
Water content and water appearance	Too much water; Too low water content; Undesired water appearance	Stability of the API and the Formulation; High electrostatic charges;	4
Chemical purity (HMWP, other product related impurities, secondary structure)	Too high content of impurities;	Safety; Stability;	4
Powder Properties: - Bulk density; - Segregation; - Flowability; - Hygroscopicity; - Electrostatic properties; - Adhesion/cohesion; - Agglomeration;	Too wide variation in powder properties;	Variation in filling volume important for variability in fine particle dose;	3

Table 1. Critical quality attributes.

CASE STUDY: DESIGN OF EXPERIMENT

We frequently happen to interconnect with customers who, once identified the PSD as a CQA (Critical Quality Attribute), need to define a design space for the micronization process.

Made strong by our experience, we are always glad to collaborate with our partners and to help them to successfully implement the QbD also into the micronization phase.

The Case Study we present here represents Jetpharma's involvement in the development of a NCE meant for a topical formulation. As it often happens in the topical area, the PSD becomes a critical factor both at the formulation level and in terms of bioavailability. Thus, once the customer identified the PSD as a CQA, we were consulted to inspect and study which micronization process variables could more critically influence it.

In order to identify the CQAs, first the customer had to define the TPP, in other words, to identify the product profile; the TPP generally provides: methods of administration, the quantity of active ingredient, the method of release, pharmaceutical characteristics such as dissolution or dispersion. Then, after defining the TPP, it's possible to define the CQAs, that is, all the chemical, physical, microbiological and biological aspects that have to be within certain limits: this identification can be carried out through the risk analysis process described by the guidelines ICH Q9.

Table 1 illustrates the identified CQAs, which can be influenced by the micronization process.

GOAL OF THE CASE STUDY

It was decided to analyse the way the micronization process can influence the PSD. The main purpose was to:

- Collect more data on how the PSD is influenced by the process variables;
- Develop a PSD predictive model as a function of the variables under consideration;
- Understand whether different process conditions can generate the same PSD;
- Inspect how different process conditions can cause a different impact, at a chemical/physical level, on the API and, as a consequence, on the formulation performance;
- Identify which critical process parameter (CPP) has a larger influence to obtain the required PSD;

STUDY PLAN

In a first stage of the study, we carried out a risk analysis applied to the micronization process and, through the use of FMEA (Failure Mode and Effects Analysis), we were able to:

- List the parameters describing the process;
- List all the eventual problems connected with the process;
- List all the possible consequences connected with such problems;
- List the controls or the detection methods concerning a problem;

Later, we gave a value (Risk Number) to each variable, taking into consideration three factors:

- Probability of Occurrence;
- Gravity of the Effect;
- Possibility of Detection through Controls;

A value between 1 and 10 was given to each of the three CPPs; as to the Probability of Occurrence, we gave 1 when it was remote, and we gave 10 when it was high; as to the Gravity of the Effect, we gave 1 when the effects were not serious, while 10 showed that gravity was maximum; as to Detection, we gave 1 when controls proved to be adequate and 10 in the absence of controls.

Then, implementing the formula «PxGxDx», we singled out the most critical parameters as shown in Figure 1.

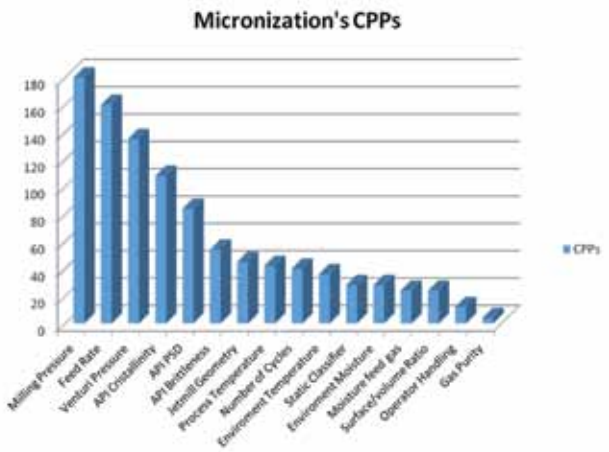

Figure 1. Pareto chart: CPPs trend with the change of the Risk Number.

After this first analysis, we decided to start investigating the three main CPPs (Table 2):
Milling Pressure (MP) – Energy used to micronize the product: its increase determines a superior micronization effect;
Feed Rate (FR) – Energy used to introduce the active ingredient into the milling chamber;
Venturi Pressure (VP) – Concentration of product introduced into the micronization chamber; the higher is the concentration, the less is the micronization effect;

Variable	Lower limit	Intermediate limit	Upper limit
Feed Rate (FR) - A1	20 g/30"	40 g/30"	60 g/30"
Milling Pressure (MP) -A2	2 bar	5 bar	10 bar
Venturi Pressure (VP) - A3	3 bar	7 bar	12 bar

Table 2. Upper, intermediate and lower limits of the investigated critical process parameters.

The interactions between the three variables were studied (a quadratic equation) using, as a model, a linear regression in which Q (Answer) is the result of a linear combination of the analysed variables (Figure 2):

$$Q = A0 + (A_1Y_1 + A_2Y_2 + A_3Y_3) + (A_{12}Y_1Y_2 + A_{13}Y_1Y_3 + A_{23}Y_2Y_3) + (A_{11}X_1^2 + A_{22}X_2^2 + A_{33}X_3^2)$$

Q	Response
A0	Constant
$A_1Y_1 + A_2Y_2 + A_3Y_3$	Linear terms
$A_{12}Y_1Y_2 + A_{13}Y_1Y_3 + A_{23}Y_2Y_3$	Interaction terms
$A_{11}X_1^2 + A_{22}X_2^2 + A_{33}X_3^2$	Quadratic terms

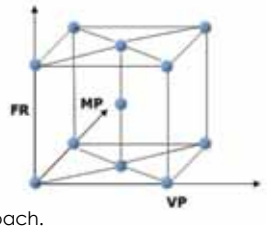

Figure 2. Design of Experiment Approach.

Excluding all the situations in which VP is less than MP, 74 was the number of possible combinations between VP and MP remaining. Also taking into account the 3 different selected FR (20g/30"; 40g/30"; 60g/30"), the experiments necessary to exhaustively investigate the 3 variables would be 222.

Through our experience and the implementation of an algorithm, we were able to reduce the number of experiments from 222 to 27 (Table 3).

Run	Feed Rate (gr/30")	Milling Pressure (Bar)	Venturi Pressure (Bar)	D90 (um) Sample 1	D90 (um) Sample 2
1	20	1	3	10,1	10,5
2	20	4	6	7,49	7,45
3	20	2	3	9,18	9,52
4	20	2	5	8,72	8,65
5	20	5	7	6,34	6,19
6	20	7	9	4,28	4,23
7	20	3	4	8,23	8,34
8	20	8	10	3,28	3,37
9	20	9	11	3,21	3,31
10	40	2	3	10,77	10,6
11	40	3	4	9,98	10,09
12	40	1	4	12,34	12,54
13	40	1	3	11,23	11,19
14	40	7	8	4,58	4,64
15	40	9	11	4,23	4,41
16	40	5	7	5,34	5,01
17	40	3	7	5,98	5,67
18	40	10	12	4,03	3,98
19	60	1	3	12,01	11,89
20	60	1	7	11,08	11,23
21	60	1	12	9,28	9,05
22	60	3	6	9,01	8,79
23	60	5	12	6,74	6,66
24	60	5	12	6,32	6,29
25	60	3	4	10,28	9,75
26	60	2	7	10,25	10,27
27	60	10	12	5,04	5,00

Table 3. Process conditions of experiments.

Using the data collected during the experiments (D90) and their subsequent analysis, we were able to develop a predictive model (Figure 3, 4).

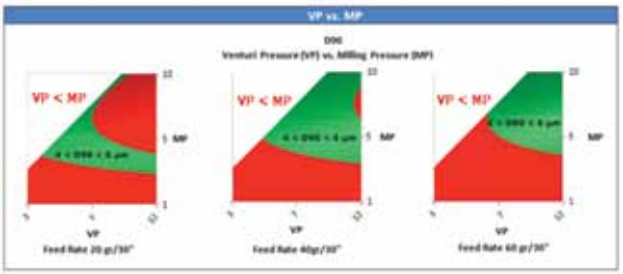

Figure 3. Design space.

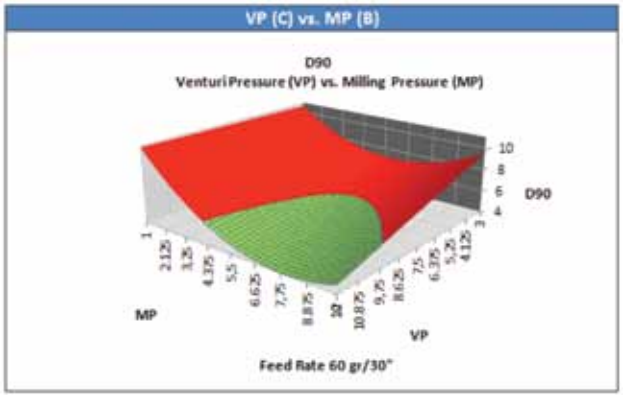

Figure 4. Surface chart of the design space at a Feed Rate 60gr/30".

Following the obtained results and in order to test the developed mathematic model, we attempted to estimate the PSD of two samples processed under different conditions.

The test result was positive and the model proved to be satisfying.

The samples (A and B) generated during the test are to be used by the customer to develop the topical formulation and to test whether the different production conditions implemented will have an impact on the formulation itself and its efficacy (Table 4).

				Expected		Experimental
Conditions	Feed Rate	Milling Pressure	Venturi Pressure	D90	Analytical Replicate	D90
A	60 g/30"	10 bar	12 bar	5.00 ± 0.9	1	5.16
					2	4,92
B	40 g/30"	5 bar	7 bar	5,35 ± 0,5	1	4,86
					2	5,42

Table 4. Process conditions in which the samples A and B were produced.

CONCLUSION

This study allowed us to collect an exhaustive amount of information about how the PSD is critically influenced by the Feed Rate, Milling Pressure and Venturi Pressure, and to develop a solid mathematical model capable of reliably estimating the D90.

After this first study, our customer also decided to investigate how API characteristics (morphology, hardness and initial PSD) can influence the process and, consequently, the final result.

Finally, the result of framework studies on samples A and B is currently being evaluated to understand whether the different implemented process conditions can have an impact on the formulation.

We are glad to inform you that, also this year, we will be at the CPhI WorldWide, Madrid 2016, Booth n. 6D60. To learn more about the Quality by Design, please visit us for our speech on October 14th, h. 15.00, at conference room 12F40.

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