APPROACH TO DESIGN SPACE FROM RETROSPECTIVE QUALITY DATA

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ABSTRACT

CONTEXT

Nowadays, the entire manufacturing process is based on the current GMPs, which emphasize the reproducibility of the process, and companies have a lot of recorded data about their processes.

OBJECTIVE

The establishment of the design space (DS) from retrospective data for a wet compression process.

MATERIALS AND METHODS

A design of experiments (DoE) with historical data from four years of industrial production has been carried out using as experimental factors the results of the previous risk analysis and eight key parameters (quality specifications) that encompassed process and quality control data.

RESULTS

Software Statgraphics 5.0 was applied and data were processed to obtain 8 design spaces as well as their safe and working ranges.

DISCUSSION AND CONCLUSION

Experience shows that it is possible to determine design spaces retrospectively, being the greatest difficulty the handling and processing of high amounts of data; however, the practicality of this study is very interesting as it let have the design space with minimal investment in experiments since actual production batch data are processed statistically.

1. INTRODUCTION

Nowadays, the entire manufacturing process is based on the current GMPs, which emphasize the reproducibility of the process. Once validated, the process is "frozen" and activities are reduced to the control of the parameters that may influence the process, resulting in a gathered process data which is never used subsequently. Product release depends on the analytical results of quality control, which show that the product meets previously approved regulatory specifications.

Since the appearance in 2003 of the so-called GMPs for the 21st century (US FDA, 2003) by the FDA, it can be said that the vision of both the administration and the industry has expanded up to a more practical pharmaceutical and industrial quality approach based on data which ensures, at least, the prior same level of quality based on validation and process controls.

The concepts introduced by the International Conference of Harmonization (ICH) in its guidelines Q8: Pharmaceutical Development (ICH Q8, 2005), Q9: Quality Risk Management (ICH Q9, 2005) or Q10: Pharmaceutical Quality System (ICH Q10, 2008), or ICH guideline Q11 on the Development and Manufacture of Drug Substances (ICH Q11, 2012) (chemical entities and biotechnological/biological entities), refer to a new understanding of pharmaceutical quality compared to pharmaceutical development and industrial production.

The concept of "design space" has been proposed in the ICH Q8 guideline and it has been defined as "the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality". (ICH Q8, 2005) Process characterization studies are performed primarily at laboratory scale with the purpose of defining the "design space" within which the process can operate and still perform in an acceptable fashion with respect to product quality and process consistency. In this sense, decision-taking based on deep scientific knowledge of the product and its process is sought; removing the causes of major deviations and forcing the incorporation of the process into a cycle of continuous improvement as a way of minimizing the risk of variability of product quality and as a contribution to the continuous improvement of the process.

This approach pursues product Quality by Design versus the current concept of complying uniquely with the registered specifications (Quality by Evidence). The objective is to build quality in the product and not to rely on end product testing. A highly detailed instance is the example of "QbD IR tablets" published in 2011 for generic drugs that points which would be the best approach during the development of the pharmaceutical dosage form (US FDA, 2012). According to ICH recommendations, all critical sources of variability must identified and explained, the intervals within which you can work freely (Design Space or DS) must be set with the certainty of obtaining an end product of the desired quality. QbD requires statistical methods to be used in pharmaceutical formulation and process development. Tools such as FMEA, scale-down modeling, and DOE have been shown to be effective for performing an efficient examination of process robustness (Charoo and Ali, 2012). For quality and productivity improvement, the most cost beneficial of these methods is statistical Design of Experiments (DoE). A trial-and-error search for the few vital factors that most affect quality is costly and time-consuming, as many authors who have worked in this field (Baum, 2007; Beneyto, 2007; Raju, 2003; Rudd, 2002) have affirmed.

Although the ICH Q8 refers primarily to the pharmaceutical development stage, our hypothesis is that the establishment of the design space (DS) may also be considered in existing products retrospectively. In this case the DS is established as a work frame based on process and product historical data, confirming the previously conducted risk analysis according to the premises of the guideline ~~guidelines of the~~ ICH Q9. The ICH document of questions and answers about QbD (ICH working group, 2010) already considered this possible application; the ICH response leaves the door open to possibilities “for manufacturing operations run under narrow operational ranges in fixed equipment, an expanded ~~region~~ range of operation and an understanding of multi-parameter interactions may not be achievable from existing manufacturing data alone and additional studies may provide the information to develop a design space. Sufficient knowledge should be demonstrated and the design space should be supported

experimentally to investigate interactions and establish parameter/attribute ranges" (ICH working group, 2010). A number of ~~Numerous~~ papers have been published for the development of the design space from the earliest stages of development for both drug and biopharmaceutical products (Adam et al., 2011; Baldinger et al., 2012; Charoo et al., 2012; Cook et al., 2007; García-Muñoz et al., 2010; Harms et al., 2008; Huang, 2011; Huang et al., 2009; Johnson et al., 2007; Kirdar et al., 2008; Kirdar et al., 2007; Konold et al., 2009; Kozlowski and Swann, 2006; Lebrun et al., 2012; Peterson, 2008; Rathore and Winkle, 2009); however, QbD implementation for new products is well documented but it is not for existing products. The key drivers for the Implementation of QbD into existing products are to reduce variability in the product quality, improve yield, reduce cycle time, solve manufacturing issues, reduce quality costs and the introduction of real time release testing for manufacturing processes (Garcia et al., 2008; Gautam et al., 2012; Johnson et al., 2007; Lourenço et al., 2012; Potter, 2009; Yu, 2008).

Despite the future possibilities (process characterization studies can serve as a foundation for a successful process validation, regulatory filing/approval, and subsequent manufacturing during the product lifecycle), few studies have been found (Gautam et al., 2012; Potter, 2009; Rathore and Winkle, 2009; Rathore et al., 2009) published on the subject that demonstrate this applicability. However, Potter's work is not fully developed in the article and does not provide any graphics, and Rathore's actually applies the Six Sigma concepts and in the second example, it shows through ~~it does show via~~ small scale experiments that all lots meet the design space proposed by the DoE carried out. Gautam's case is also exemplary, concerning a chemical process which managed to reduce the variability of the dimer impurity and reduce costs, properly implementing QbD to an existing chemical process.

This paper presents a stepwise approach in order to define the design space process for an existing product, which has been manufactured industrial-scale during four years. So, it provides a perspective of QbD application for tablet manufacturing using an example from a previous manufacturing process.

The objective of this work is to identify the critical points for inclusion in the design space proposed for the process, which will be established retrospectively. This goal will be achieved through the study and knowledge of the process and thanks to the incorporation of risk analysis and statistical analysis tools. The method to establish a retrospective design space involves the management of the retrospective data of 23 industrial batches, both in terms of process parameters and finished product specifications. As it is an initial approximation, it has been carried out with the first part of a coated tablet production process, that is, the compression process but not the coating process design space was carried out.

2. MATERIALS AND METHODS

The product selected for the study belongs to the portfolio of a multinational pharmaceutical company and it is already marketed. From the pharmaceutical technology standpoint, the product can be characterized as a solid dosage form, obtained by wet granulation, fluid bed drying and subsequent compression. It then undergoes a stage of tablet coating and screen-printing, as a preliminary stage to packaging.

The proposed study is retrospective, based on documentary records of batches produced in the same site for the first four years of production (2003-2006). In addition, the equipment and facilities used are the same, as it is the equipment used for analysis in quality control laboratory. During the study period, no significant change controls were registered for the established manufacturing process. Therefore, the report will also be valid to obtain the product PQR.

The overall approach toward process characterization involved four key steps:

- First, risk analysis via FMEA (Failure Mode and Effects Analysis) was performed to identify parameters for process characterization.

- Second, data from 23 batches manufactured for four years were collected, as much analytical results from API and finished product as process control (analytical results and manufacturing parameters).
- Third, statistical studies were designed using DoE in order to define the design space and to analyze the results for deciding on the criticality of the parameters as well as on establishing design space.
- Fourth, the design space for the compression process was established. These steps will be discussed in more detail in the following sections.

3. RESULTS

Below the results of the execution of the established stages for the study of the manufacturing process are described.

Following the guidelines set out in ICH Q9, a series of stages needed for a proper study of the process are executed. In the VII stage, the FMEA (Failure Mode and Effects Analysis) tool has been selected as it is the most widespread in the European Pharmaceutical Industry. The stages are:

3.1 SCOPE OF ANALYSIS DEFINITION ~~DEFINE THE SCOPE OF ANALYSIS~~

3.2 ~~ESTABLISH THE~~ SOURCES OF INFORMATION ESTABLISHMENT

3.3 PROCESS STEPS DEFINITION ~~DEFINE PROCESS STEPS~~ ("Process Mapping").

3.4 ~~ESTABLISH THE~~ ANALYSIS MATRICES ESTABLISHMENT (for FMEA)

3.5 FAILURES IDENTIFICATION ~~IDENTIFY FAILURES~~

3.6 FAILURES EFFECTS IDENTIFICATION ~~IDENTIFY THE EFECTS OF FAILURES~~ (for product quality)

3.7 RISK ASSESSMENT (using FMEA).

3.8 SELECTION OF PRODUCT REAL DATA

3.9 COLLECTION OF INFORMATION

3.10 RISK MITIGATION MEASURES IMPLEMENTATION ~~ESTABLISH RISK MITIGATION MEASURES~~ (if required)

3.11 STATISTICAL ANALYSIS OF DATA TO ESTABLISH THE PROCESS DESIGN SPACE

3.1 SCOPE OF ANALYSIS DEFINITION ~~DEFINE THE SCOPE OF ANALYSIS~~

The first step to define the design space for the manufacturing process was to identify CQAs (Critical Quality Attributes). Obvious CQAs are defined as a drug substance characteristic that has a direct or indirect impact on the safety and efficacy of the drug product. In this regard, the ~~work~~ paper of Yu (Yu, 2008) provide us with a list of process parameters and quality attributes for the compression process and the ~~work~~ paper of Garcia (Garcia et al., 2008) offer a worked example that is similar to ours.

According to the product quality dossier, the available quality parameters of the formula are: dissolution, assay on the mixture and on the tablet, and impurities in the tablet.

The process for obtaining the finished pharmaceutical product, ready for being distributed, is divided into the following stages:

- Preparation of tablets:
    1. Wet granulation
    2. Compression→Coating→ Screen-printing
- Packaging: blister and cartoning

The work is focused on the study of the wet granulation process and in the obtention of the final mixture, as these stages are considered to be critical for subsequent steps of compression and coating. Obtaining a good mixture and subsequent granulation is considered critical for product quality attributes such as content uniformity and the quantification ~~appearance~~ of degradation products.

The final granulate is compressed in a Fette 3090 model machine, which has a process capacity (Cp) of greater than 2.5 (equivalent to ± 6σ), and so the variability it contributes to the overall process is very low. The tablets are coated in a Glatt coating pan; finally they are screen-printed with a small anagram and packaged. During the first stage of the coating process, an insulating layer is generated which

prevents the tablet from moisturizing during coating and therefore the impact of moisture on the final tablet is not considered relevant. Also, because the tablets are dried, the temperature rise that occurs during coating it is not considered a major impact. Hence, it has been considered that all modifications of impurity values are associated to the stages of granulation and fluid bed drying.

3.2 ~~ESTABLISH THE~~ SOURCES OF INFORMATION ESTABLISHMENT

The information to be used in this study comes from:

- Manufacturing process data: Batch Record with the values of the process parameters recorded during manufacture, either in line or through automated control systems.
- Data from laboratory quality control certificates: active substance, intermediate and finished products.
- All data on product pharmaceutical development are also ~~are~~ available for consultation.

3.3 PROCESS STEPS DEFINITION ~~DEFINE PROCESS STEPS~~ ("Process Mapping")

The process map provides a visual understanding of the process to study, explaining and unfold the complex processes into simpler stages. In our case, the process map would be limited to the highlighted area in Figure 1.

3.4 ~~ESTABLISH THE~~ ANALYSIS MATRICES ESTABLISHMENT

The first thing is to define the scales to be used in the FMEA during the risk assessment stage. For this, the correlation between the values used in rating scales and descriptions of their meanings were determined. Tables 1A and 1B specify the ones chosen for the study.

Then all possible combinations within the values of severity, probability and detection (from equation 1) are developed, which can be used to establish all possible Risk Priority Numbers (RPN) and thus establish a number of courses of action based on the risk posed to product quality; table 2 shows the ones selected for the study.

$$RPN = SEVERITY * PROBABILITY * DETECTION \qquad \text{Eq (1)}$$

3.5 FAILURES IDENTIFICATION ~~IDENTIFY FAILURES~~ & 3.6 FAILURES EFFECTS IDENTIFICATION ~~IDENTIFY THE EFECTS OF FAILURES~~ & 3.7 RISK ASSESSMENT.

Once the evaluation matrices have been drawn up, we proceed to develop the FMEA work method. The first step is to establish all possible failure modes for each of the steps described in the "process mapping". Then proceed to describe the effects that can be produced by these failures on product quality. In Figure 2 is represented a “qualitative” risk analysis for our compression process, as a Qualitative Risk Analysis (multivariable causes and effects relationship) for process and API. Finally, failure assessment is carried out following the tables drawn up in point IV.

~~Having completed~~ By having all these tasks completed, a table ~~is~~ was drawn up containing all the information issued on ~~generated~~. One way of displaying this data is the one presented in Table 3 and in the Pareto chart (Figure 3).

This Pareto chart shows the eight factors [Binding liquid quantity (granulation), Drying time (fluid bed), Power consumption on endpoint kneading (granulation), Moisture at the end of drying (fluid bed), Moisture at the end of cooling (fluid bed), Particle size (API), Mean Particle size (Excipients), Impurities content (API)], that produce most risk to the process and which should be studied to determine whether their influence in the process is statistically significant or not.

3.8 SELECTION OF PRODUCT REAL DATA & 3.9 COLLECTION OF INFORMATION

According to estimated failure modes, and to corroborate the performed approach to the significance of each one, data from real industrial batches ~~are~~ were reviewed. Data were collected from 23 batches manufactured over 4 years, as much analytical results from API and finished product as process control (analytical results and manufacturing parameters).

Quality parameters ~~are~~ were reviewed in the batch documentation to obtain information about possible failures and their effects; this is shown in detail in Table 4.Although the percentage of impurities (A, B,

C, others and total) of API batches were analyzed, they could not be used as process variables because data were available neither for the 23 batches analyzed nor for the excipients particle size.

Within these real data, the variable parameters of the process are given in bold and italics in Table 4 (therefore they will be treated as potential factors for the experimental design) and product specifications.

3.10 RISK MITIGATION MEASURES IMPLEMENTATION ~~ESTABLISH RISK MITIGATION MEASURES~~

Risk mitigation measures are not applied as it is a retrospective process. However, the process controls themselves are already risk mitigation actions.

3.11 STATISTICAL ANALYSIS OF DATA TO ESTABLISH PROCESS DESIGN SPACE

Statistical studies were designed using DoE in order for the data to be amenable for ~~use in defining~~ using to define the design space, the results analyzed for decisions on the criticality of the parameters as well as on establishing design space.

For the construction of the design space retrospectively, we proceeded as follows:

1. - Statgrafics 5.0, statistical software ~~was used~~ and ~~real~~ raw data ~~of~~ from production were used. The outcome of quality risk assessment has identified 7 factors as potential critical process parameters that may significantly ~~affect~~ impact the stability of tablet dissolution. These critical factors were introduced in the Doe, except for the particle size of the excipients, because ~~it could not be collected~~ raw data was not available from the laboratory records) plus a further 3, firstly no identified as critical, but having the data we have considered interesting for inclusion in the study: water content of the API, % of API particles greater than 500µm and blending time. Also the critical responses (product specifications) are shown in Table 4.

For the following 9 factors, that are continuous variables, data are available:

- Amount of binder liquid: must be added to form a mass among different excipients and active substance. Range between: 2.1-2.785 L. Specification: 2.1-2.8 L.
- Consumption during kneading: marks the endpoint of blending. Range between: 6.06-6.7 Kw. Specification: 5-7 Kw.
- Drying time: varies from 5-15 minutes. Specification: 5-15 minutes
- API particle size (<125 microns). Varies between 31-90 microns.
- Retained API fraction greater than 500 microns (<1%). Range between 0-1%
- API relative humidity. Range from 0.1 to 0.2%. Specification: ≤ 0.5%
- End blending time: range from 1152 to 1171 seconds. Specification: 1150-1200 seconds.
- Moisture, drying phase: % range from 0.53 to 0.9 %. Specification: ≤ 1%
- Moisture, cooling phase: % range from 0.48 to 0.81 %. Specification: ≤ 1%

At last 12 parameters were available as responses; ~~in~~ Table 5 lists all of them ~~are listed~~ with the specification and the range found in the 23 batches studied.

2. - Once the data are entered into the program, design is analyzed and those factors that are not significant are removed from the model.

~~In~~ Table 6 lists ~~,~~ factors with a significance level of 5% ~~have been listed~~, meaning that the probability that the effect attributed to the factor is by chance is less than 5%. The boxes marked grey correspond to effects with a probability greater than 5%, namely that the probability that their influence is due to chance is more than 5%, and so it can be assumed that there is no significant relationship between the factor and the response analyzed. Nevertheless, the possibility of the existence of other relationships of co-linearity between the factors studied has been taken into account, the existence of a significant relationship between the response and a factor that prevents introducing in the model a second factor which considered individually have a significant relationship with the response but which, being

correlated with another factor already introduced in the model, its additional contribution to the variation of the response is not significant.

3. - The relationship between critical factor and critical response is determined and also the best combination of factors to produce the industrial batch is established.

Based on the data in Table 6, it can be assumed ~~deduced~~ that **only one factor does not significantly influence** (probability level of 95%) in any of the responses studied; that is the "I" factor or relative humidity during cooling. The rest have a significant influence on one or more of the responses. Therefore any factor level within the range will be suitable for obtaining a correct product.

Similarly, only one response is not significantly influenced by any of the factors studied that is impurity B. It can thus be concluded that it is probably due to the raw material (API).

~~Also in table~~ Table 6 ~~it can be seen~~ shows that the most important factors influencing the final specifications are those relating to the characteristics of the API: particle size, % retained in the 500 micron sieve (both significantly influence in 4 responses) and water content API (influences significantly in 3 responses). These relationships are discussed below.

4. DISCUSSION

4.1. ANALYSIS OF THE MAIN FACTORS WITH SIGNIFICANT INFLUENCE ON THE PRODUCT SPECIFICATIONS

4.1.1. STUDIED RESPONSE ~~STUDIED~~: INTERNAL PHASE YIELD

According to Table 6, only one factor (drying time) significantly influences this response. By increasing the drying time, the internal performance of the granulate increases. The specification of this response is 80-105%, and so between 10 and 15 minutes (design space) will be required for the specified performance and nearly at 100%.

Logically this drying time will depend on the moisture during drying. In graph (Figure 4) the area is marked that ensures a correct product (work or control space).

4.1.2. STUDIED RESPONSE ~~STUDIED~~: API CONTENT

In this case the theoretical content is 12.5 mg and should be between 11.9-13.1 mg, Figure 5 shows the space studied and it can be observed that by working on the area to the right we will always obtain tablets within specifications and so we should preferably work in the area between 70 and 91 microns and between 0 and 0.4% retention. It can be seen from the graph that although these ranges are exceeded, the product is still correct, except when working with a very small particle size and the % retention is high, and so its design space could be 47-91 microns (API particle size) and from 0 to 0.7% (% retention of API).

4.1.3. STUDIED RESPONSE ~~STUDIED~~: RSD CONTENT IN API

In this case we are interested in obtaining low percentages of (or) near-to-zero variation, corresponding to the area (left of the graph, Figure 6), that is, the control interval would be to work between 2.1-2.35 L of amount of binder and between 0.1- 0.2% of API water content (area shown on the left side of Figure 6), although the entire graph is within specifications, and so design space would be the entire area between 2.1 and 2.9 L of amount of binder and 0.1 to 0.2% of API water content.

4.1.4. STUDIED RESPONSE ~~STUDIED~~: PERCENTAGE DISSOLUTION AFTER 15 MINUTES

Figure 7 shows that all batches meet the specifications (≥ 80%), with just the area on the left remaining without. Therefore, the work zone would be for the amount of binder of between 2.35 to 2.9 L, although as a working range it would be advisable to work between 2.35 and 2.7 L. For drying moisture, we ensure dissolution provided we work below 0.73%. Clearly our concern is for both factors to be at their low level. See Figure 8 of the main effects, maximum dissolution levels are obtained when the factors are at their lowest level for both the amount of binder and for the moisture drying factor (left side of the line). For particle size factor, the best level would be the largest size, although the difference between the two levels is not very large (low gradient of the line).

4.1.5. STUDIED RESPONSE ~~STUDIED~~: IMPURITY A

In the case of impurity A (specification of <0.1%) only the particle size of the API appears as a significant factor. The whole graph would give a correct product (Figure 9). However to find the optimal point (lowest possible impurity) it is best for the API to have the lowest particle size as it will give the minimum impurity level.

4.1.6. STUDIED RESPONSE ~~STUDIED~~: IMPURITY B

As mentioned, impurity B is not influenced by any studied preparation factor. It can be seen in the graph (Figure 10) that it does not vary; it must be an impurity that comes with the API and the preparation of the tablet does not influence the level.

4.1.7. STUDIED RESPONSE ~~STUDIED~~: IMPURITY C

For impurity C three factors appear which have a significant influence: the % of particles retained > 500 microns, consumption during kneading, and blending time. The specification also is <0.1%. In this case, the graphs (Figures 11, 12 and 13) only relate two factors at the same time, but it can be seen that all areas give a correct product, below 0.1%, and the maximum impurity obtained in the three figures is 0.04%. To introduce the third factor it is worth consulting figure 14 in which the combination of factors and levels which give a higher level of impurity C is marked.

Therefore it would be best to work at maximum consumption, maximum mixture time and maximum % retention. Regarding the control space it would be 6.6 to 6.8 Kw for kneading consumption and 0.3-1% for particles of 500 microns and 1162-1174 seconds blending time.

4.1.8. STUDIED RESPONSE ~~STUDIED~~: OTHER IMPURITIES

Regarding the other impurities response, the only significant factor was drying moisture. It can be seen in the graph (Figure 15) that when it is at a high level between 0.80% and 0.93%, minimum levels are reached, which is proposed as control space, and the entire area is design space.

4.1.9. STUDIED RESPONSE ~~STUDIED~~: TOTAL IMPURITIES

The specification in this case is ≤ 0.5% and the two factors significantly influencing (Table 6) are API particle size and % of the particles retained > 500 microns. In this case the minimum levels are found when working with particle sizes of between 31–71 µm, as long as that the retained particles are between 0.6 and 1%, so that this will be the work or control space and the entire interval gives a level within specifications which will be the design space (figure 16).

4.1.10. STUDIED RESPONSE ~~STUDIED~~: MIXTURE CONTENT

The theoretical specification in this case is 121.4 mg/g granulate or between 115.3-127.5 mg/g. It can be seen in Table 6 that the content will depend on the characteristics of the API (particle size and % particles greater than 500 microns) and the amount of binder.

In the graph of two factors (Figure 17) the area is marked representing the control space for the API particle size which would be between 60 and 91 microns and % retention > 500 microns would be between 0 and 0.6%.

To study the third factor another graph (Figure 18) has been devised in which it can be seen that the amount of binder at the level between 2.6 and 2.9 L for any level of % particles retained will give a product within specifications.

As we are dealing with three factors, the design and control space is detailed in Table 7.

4.1.11. STUDIED RESPONSE ~~STUDIED~~: RSD BLEND CONTENT

In this case (Figure 19) it is clear that the area of interest is the right-hand side with the lowest RSD, and therefore it will be preferable to work between 0.16 and 0.2 % API water content at any blending time. The entire area is the design space since it meets specifications

4.1.12. STUDIED RESPONSES ~~STUDIED~~: BLEND WATER CONTENT

In this case we require the granulate not to be excessively dry and so it must be in the upper clearer zone. The most influential factor is API moisture (at higher moisture of the API, higher moisture of the final mixture); in fact the entire area of the graph would meet the specifications (Fig. 20). However, as a control area it could be recommended with the drying moisture between 0.69 to 0.93% to obtain a granulate that is not excessively moist.

4.2. SUMMARY OF FACTORS AND OPTIMAL LEVELS FOR THE QUALITY OF THE TABLET: CONTROL SPACE DURING MANUFACTURING

The experimental design conducted gives optimal conditions that will depend on each response and sometimes they can be contrasted and so some recommendations of commitment should be established. Now, the established intervals are tabulated with the previous graphs (Figures 4-20) analyzing the data of Table 8 to ascertain what would be the final conditions of the design space. However, although there is a statistically significant relationship between impurities (impurity A and total impurities) and particle size of the API, technically it does not seem to be consistent, and it should be studied with supplier data to see if the different particle sizes of the API relate to process conditions or incidents, as detected by the statistical analysis performed.

4.3. PROPOSED DESIGN SPACE

The fourth and final step is to establish the design space for the compression process; the intervals are shown in the last row of Table 8. It can be seen that the intervals forming the design space are

narrower than the previous specifications, which does not affect the regulatory aspects of the product, since they are included. The advantage is that if you work within these ranges, the product will always be within specifications for the 8 responses studied and these are always around the theoretical specification, a clear improvement given that by reviewing the raw data of the 23 batches, variability was detected especially for specifications such as dissolution (average of 23 batches: 95.7%, 4.9% RSD, with the maximum average value obtained standing at 104% and the minimum at 87%), which means that variability would decrease.

5. CONCLUSIONS

Process understanding is the major goal of a QbD program. A process is well understood when all the critical sources of variability are identified and explained; when variability is managed by the process, and when product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, manufacturing, environmental and other conditions (US FDA, 2004). The QbD principles provide a structured approach for gaining process knowledge and developing a robust manufacturing process. Based on process understanding a design space has been developed to consistently ensure tablet quality. However the application of the QbD principles for the existing products is very limited. In this case it has been applied successfully to the first stage of an industrial process for producing coated tablets. On the basis of process understanding, it has been demonstrated that the process can ensure correct tablet production and focus on the specifications (particularly on impurities and dissolution) by controlling the critical process variables.

Risk analysis was successfully utilized to identify operating parameters for process characterization. So 9 factors were examined in process characterization studies. Using the design of experiments (DoE), characterization studies were performed. Of all operating parameters characterized, 8 factors were identified as key operating parameters. Only one parameter was non-key or non-critical: relative humidity during cooling.

Finally, based on the results of small-scale studies, acceptable ranges were set for the characterized operating parameters to define the design space for the product. The approach presented here is not specific to the illustrated case study. The method can be extended to other pharmaceutical unit operations and processes that can be characterized at industrial scale.

In the case of this study, it is determined that the incorporation of methodologies or hardware to improve the current process is not required. The process is robust and capable of obtaining a product that meets all the quality attributes recorded.

As a result of the failure modes evaluated and after verification with production data, the most important and obvious conclusion that can be drawn is that the process is stable and the possible incorporation of improvements to mitigate the existing risks will have a minimal impact on to ~~improving~~ improve the current quality assurance, since it is very high for the ~~present~~ current process.

Because of the great robustness of the API and of the manufacturing method under study, a priori any additional control plan to the existing ones can be ruled out since the variability of the process does not warrant any extra investment in the current process.

In view of the information supplied by the factory and laboratory data it can be assumed ~~deduced~~ that the way of eliminating risks in this process involves a decrease in the severity of the failures and a reduction of unnecessary steps to reduce the number of risk stages (such as those responsible for increased degradation impurities, namely impurity C, which is directly affected by the API water content; the greater the moisture, the more impurity C).

Finally, despite the limitations of applying the concept of QbD for existing products, it should be noted that the strategy implemented helps the "the improvement in life" of the product since additional data to industrial development data, when well studied, will help to go deeper into the process and its continuous improvement. Following this working line of process understanding, it could be interesting to

study the granulation process (from the point of view of the solid-liquid transitions). This could be a good starting point for further studies to improve the knowledge of the current process.

Declaration of interest

The authors report no declaration of interest.

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Figure legends:

Figure 1: Process Map

Figure 2: Qualitative Risk Analysis (multivariable causes and effects relationship) for process and API

Figure 3: Pareto analysis

Figure 4: Surface contours of internal phase yield (Design space and control space)

Figure 5: Surface contours of API content (Design space and control space)

Figure 6: Surface contours of RSD final blend content (Design space and control space)

Figure 7: Estimated response surface of dissolution (Design space and control space)

Figure 8: Main effect chart for dissolution

Figure 9: Surface contours of Impurity A

Figure 10: Estimated response surface of Impurity B

Figure 11: Estimated response surface of Impurity C (factors studied kneading consum & part>500 µm).

Figure 12: Estimated response surface of Impurity C (factors studied part>500 µm& blending time).

Figure 13: Estimated response surface of Impurity C (factors studied kneading consum & blending time)

Figure 14: Cube graph of impurity C

Figure 15: Estimated response surface of other impurities

Figure 16: Estimated response surface of Total impurities

Figure 17: Surface contours of blend content

Figure 18: Estimated response surface of blend content

Figure 19: Surface contours of RSD blend content

Figure 20: Surface contours of blend water content

Table 1: Part A: Scales for the assessment of Severity, Occurrence and Detectability. Part B: Scales for the assessment of the risk analysis.

SEVERITY		
10	Severe impact on quality. It generates OOS without possibility of expert report	
7	Significant impact on the quality. It can generate OOS, no stability data available, it is possible an expert report	
3	Minor impact on quality. It can be OOS, stability data available	
1	Minor impact or no impact on quality. Product within the specifications	
OCCURRENCE		
4	Frequent	
2	Occasional	
1	Improbable or single event	
DETECTABILITY		
4	Can not be detected	Without manual control, failure detected as a "discovery"
2	Usually detected	Manual control, it is worked with statistical control or it's detected at a later stage of the process
1	Always detected	Always detected. 100% Control: Automated or Manual

		SEVERITY			
		10	7	3	1
OCCURRENCE x DETECTABILITY	16	160	112	48	16
	8	80	56	24	8
	4	40	28	12	4
	2	20	14	6	2
	1	10	7	3	1

Table 2: Classification of risk levels and actions planned

Action Level	Actions to take
Level 3	It's unacceptable to keep the current process. You must to act on one (or more) of the parameters to mitigate the situation.
Level 2	It is necessary to evaluate the current process and act on any of the factors. It is established the action level at R.P.N. ≥ 16
Level 1	The current process risk is acceptable. It's not priority to act on these failures.

Table 3: Risk analysis results obtained for all studied process steps.

FAILURE	PROCESS	FAILURE MODE	FAILURE EFFECT	S (10<7<3<1)	O (4<2<1)	D (4<2<1)	RPN (S*O*D)
1.	INGREDIENT (API)	Particle size	Does not meet specification: dissolution profile, content and content uniformity	10	2	1	20
2.	INGREDIENT (API)	Water content	Does not meet specification: water content and stability	7	1	1	7
3.	INGREDIENT (API)	Impurities content	Does not meet specification: related substances	7	2	1	14
4.	INGREDIENT (EXCIPIENTS)	Particle size	Does not meet specification: dissolution profile	10	2	1	20
5.	INGREDIENT (EXCIPIENTS)	Water content	Does not meet specification: water content and stability	3	1	1	3
6.	PRE-BLEND	Blending time	Does not meet specification: content and uniformity content	10	1	1	10
7.	PRE- BLEND	Blending speed	Does not meet specification: content and uniformity content	10	1	1	10
8.	PRE- BLEND	Addition order of components	Does not meet specification: content and uniformity content	1	1	1	1
9.	GRANULATION	Binding liquid quantity	Does not meet specification: dissolution profile, water content and stability	10	2	2	40
10.	GRANULATION	Binding solution addition rate	Does not meet specification: dissolution profile	10	1	1	10
11.	GRANULATION	Power consumption on endpoint kneading	Does not meet specification: dissolution profile	10	2	1	20
12.	MILL	Rotation speed	Does not meet specification: water content and stability	3	1	1	3
13.	MILL	Product inlet	Does not meet specification: water content and stability	1	2	1	2
14.	FLUID BED (DRYING)	Air flow	Does not meet specification: dissolution profile, related substances and stability	10	1	1	10
15.	FLUID BED (DRYING)	Drying air temperature	Does not meet specification: dissolution profile, water content, related substances and stability	10	1	1	10
16.	FLUID BED (DRYING)	Drying time	Does not meet specification: dissolution profile, water content, related substances and stability	10	2	2	40
17.	FLUID BED (DRYING)	Moisture at the end of drying	Does not meet specification: related substances and water content	10	2	1	20
18.	FLUID BED (DRYING)	Cooling air temperature	Does not meet specification: related substances and water content	3	2	1	6
19.	FLUID BED (DRYING)	Moisture at the end of cooling	Does not meet specification: related substances and water content	10	2	1	20
20.	FINAL SIEVING	Sieve size	Does not meet specification: de dissolution profile, content and uniformity content	10	1	1	10
21.	FINAL SIEVING	Product inlet	Does not meet specification: content and uniformity content	1	2	2	4
22.	FINAL BLEND	Addition order of components	Does not meet specification: content and uniformity content	1	1	1	1
23.	FINAL BLEND	Blending time	Does not meet specification: content and uniformity content	10	1	1	10

FAILURE	PROCESS	FAILURE MODE	FAILURE EFFECT	S (10<7<3<1)	O (4<2<1)	D (4<2<1)	RPN (S*O*D)
24.	FINAL BLEND	Speed	Does not meet specification: content and uniformity content	10	1	1	10
25.	ROOM CONDITIONS	Pressure	Cross contamination of contiguous rooms	1	2	1	2
26.	ROOM CONDITIONS	Temperature	Impact on drying conditions and time	1	2	1	2
27.	ROOM CONDITIONS	Humidity	Impact on drying conditions and time	1	2	1	2

Table 4: Data available for the DOE analysis, potential process variables (factors to be studied for significance) have excelled in bold and italics and data from available responses to be studied in black.

AVALAIBLE DATA FROM QUALITY CONTROL LABORATORY			AVALAIBLE DATA FROM PRODUCTION (phase I).
API	**FINAL BLEND**	**FINISHED PRODUCT**	**PROCESS DATA**
Particle size >500 µ (%)	API Content (mg/g)	Assay (mg/comp)	***Addition of binding liquid (L)***
Average particle size (µ)	RSD (%)	Dissolution test (%)	***Power consumption on endpoint kneading (Kw)***
Water Content (%)	Water Content (%)	RSD (%)	***Drying time (min)***
		Related Substances (%)	***Drying Moisture (%)***
		Impurity A	***Cooling Moisture (%)***
		Impurity B	***Blending time (seconds)***
		Impurity C	
		Other Impurities	
		Total Impurities	

Table 5: Responses (based on the finished product: coated tablet and final blend)

Responses	Minimum value obtained	Maximum value obtained	Specification to meet
Internal phase Yield	86.4	101.7	80-105%
API content (mg/tablet)	12.4	13	12.5 mg (11.9-13.1)
Uniformity content RSD	0.7	2.5	≤4%
Dissolution test	88	104	≤80%
Impurity A (tablet)	0	0.05	≤ 0.1%
Impurity B (tablet)	0	0.04	≤ 0.1%
Impurity C (tablet)	0	0.04	≤ 0.1%
Other impurities (tablet)	0	0.05	≤ 0.1%
Total Impurities (tablet)	0.03	0.1	≤ 0.5%
Final blend content	117.9	127.4	121.4 mg/g 115.3-127.5 mg/g
RSD final blend content	0.4	3.6	≤4%
Final blend water content	0.7	1.5	≤1.5%

Table 6: Significant relationships found between the studied factors and responses for the preparation of tablets. Numbers no underlined: factors that have a negative effect on the response (decrease) by increasing factor. Numbers in italics, bold and underlined those that have a positive effect on the response (increase) by increasing factor. The grey box means that there is no statistically significant relationship between factor and response ($p<0.05$). The numbers inside the grey boxes means that there is a relationship between factor and response but no statistically significant ($p>0.05$).

FACTORS→	BINDING LIQUID	BINDING CONSUM	DRYING TIME	PARTIC. API	PARTICLES > 500 MICRONS	API WATER CONTENT	BLENDING TIME	DRYING MOISTURE	COOLING MOISTURE
RESPONSES ↓	A	B	C	D	E	F	G	H	I
Internal phase Yield			***0,0052***						
API Content		0.0700		0.0084	***0.0147***				
Dissolution	0.0014			***0.1460***				0.0017	
RSD Content	***0.0234***					***0.0328***			
Imp. A				***0.0288***					
Imp. B					0.0926				
Imp. C		0.0079			0.0033	***0.0716***	0.0170		
Other Imp.				***0.0613***				0.0039	
Total Imp.		***0.0900***		0.0264	***0.0295***				
Blend content	0.0095			0.0069	***0.0012***				
RSD Blend content						0.0176			
Blend water content						0.0102		***0.0016***	

Table 7: Combination of the three factors that provide an optimized response of the content of blend before compression.

	Control or work space	Design space
Retained particles greater than 500 microns (%)	0-0.2	0-0.6
API particle size (µm)	71-91	61-91
Binding liquid quantity (L)	2.8-2.9	2.6-2.9

Table 8: Final ranges obtained for the process. In the last row of the table are highlighted intervals that optimize the responses of studied process.

	BINDING LIQUID (2.1-2.8L)	KNEADING CONS. (6.06-6.7 Kw)	DRYING TIME (5-15 MIN)	PART API (<125µ m)	% RET 500 µm (<1%)	API WATER CONTENT (<0.5%)	BLENDING TIME (1150-1200 s)	DRYING MOISTURE (<1%)	COOLING MOISTURE (<1%)
RESPONSE	A	B	C	D	E	F	G	H	I
Internal phase Yield			10-15						
API Content				47-91	0-0.7				
RSD Content	2.1 - 2.8					0.1-0.15			
Dissolution	2.35 - 2.8							0.53-0.73	
Imp. A				31-90					
Imp. B									
Imp. C		6 - 6.7			0 -1		1150.1170		
Other Imp.								0.53-0.93	
Total Imp.				31-91	0-1				
Blend content	2.6-2.8			61 -91	0-0.6				
RSD Blend content						0.1- 0.2			
Blend water content						0.1 -0.14		0.69-0.93	
Final recommendation	**2.6-2.8**	**6 - 6.7**	**10 -15**	**31 - 91**	**0 - 1**	**0.1-0.2**	**1150-1170**	**0.53-0.93**	**Whatever**