Quality risk management of top spray fluidized bed process for antihypertensive drug formulation with control strategy engendered by Box-behnken experimental design space

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Abstract

Introduction: Lacidipine (LCDP) is a very low soluble and highly biovariable calcium channel blocker used in the treatment of hypertension. To increase its apparent solubility and to reduce its biovariability, solid dispersion fluid bed processing technology was explored, as it produces highly dispersible granules with a characteristic porous structure that enhances dispersibility, wettability, blend uniformity (by dissolving and spraying a solution of actives), flow ability and compressibility of granules for tableting and reducing variability by uniform drug-binder solution distribution on carrier molecules. Materials and Methods: Main object of this quality risk management (QRM) study is to provide a sophisticated “robust and rugged” Fluidized Bed Process (FBP) for the preparation of LCDP tablets with desired quality (stability) and performance (dissolution) by quality by design (QbD) concept. Results and Conclusion: This study is principally focusing on thorough mechanistic understanding of the FBP by which it is developed and scaled up with a knowledge of the critical risks involved in manufacturing process analyzed by risk assessment tools like: Qualitative Initial Risk-based Matrix Analysis (IRMA) and Quantitative Failure Mode Effective Analysis (FMEA) to identify and rank parameters with potential to have an impact on In Process/Finished Product Critical Quality Attributes (IP/FP CQAs). These Critical Process Parameters (CPPs) were further refined by DoE and MVDA to develop design space with Real Time Release Testing (RTRT) that leads to implementation of a control strategy to achieve consistent finished product quality at lab scale itself to prevent possible product failure at larger manufacturing scale.

Key words: Critical process parameter, critical quality attribute, failure mode effective analysis, fluidized bed process, quality by design, quality risk management, scale-up.

INTRODUCTION

Lacidipine (LCDP) is a very low soluble and highly biovariable calcium channel blocker used in the treatment of hypertension. To increase its apparent solubility and to reduce its biovariability,
and height of the spray nozzle from the bed.\(^6\) Each of this process parameter is a very high risk for the development of robust and rugged fluid bed process (FBP), thus it should be optimized and managed properly in precise manner to reduce its impact on overall quality of end product irrespective of scale.\(^7\)\(^9\) Quality risk management (QRM) is a systematic process for the assessment, control, communication, and review of any process-related risks to the quality of the drug product across the product lifecycle. An ideal model for QRM is outlined in the Figure 1.

A) **Risk assessment** consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. Quality risk assessments begin with a well-defined problem description or risk question. As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

- What might go wrong?
- What is the likelihood (probability) it will go wrong?
- What are the consequences (severity)?

Risk identification addresses the “What might go wrong?” question, including identifying the possible consequences. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders.

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms with the ability to detect the harm (detectability).

Risk evaluation is a quantitative estimate of risk through multivariate data analyzed by conducting series of Design of Experiments (DoEs) for evaluating actual significant effect of individual factor and interaction factors on response in test. When risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as “high”, “medium”, or “low”.

B) **Risk control** includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. Risk control might focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks, and resources?

Risk reduction might include actions taken to mitigate the severity and probability of harm by implementing design space (DS)-based control strategy. Processes that improve the detectability of hazards [i.e. Process Analytical Technology (PAT) tools for Real Time Release Testing (RTRT)] might also be used as part of a risk control strategy.

Risk acceptance can be a formal decision to accept the residual risk.

C) **Risk communication** is the sharing of information related to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability, or other aspects of risks between the industry and regulators.

D) **Risk Review**: The output/results of the risk management process should be reviewed to take into account of new knowledge and experience.

Thus, main object of this QRM study is to provide a sophisticated robust and rugged FBP for the preparation of LCDP Tablets with desired quality (stability) and performance (dissolution) by Quality by Design (QbD) concept. This study is principally focusing on thorough understanding of the process by which it is developed and scaled up with a knowledge of the critical risks involved in manufacturing process analyzed by Risk assessment tools like: IRMA (Initial Risk-based Matrix Analysis) and FMEA (Failure Mode Effective Analysis) to identify and rank parameters with potential to have an impact on In Process/Drug Product Critical Quality Attributes (IP/DP CQAs), based on prior knowledge and initial experimental data; which were refined further to determine the significance of individual variables and interactions by developing DS with DoE and MVDA for critical process parameters that leads to mechanistic understanding for individual critical process parameter(s) to implement a control strategy to achieve consistent finished product quality at pilot-scale developmental stage itself.
to prevent possible product failure at larger commercial manufacturing scale.

### MATERIALS AND METHODS

#### Materials

LCDP was procured from Cadila Pharmaceuticals limited, India. Polyvinyl Pyrrolidone (Plasdone® K29/32) was purchased from ISP Technologies. Lactose Monohydrate (Pharmatose® 200M and DCL 11)® were purchased from DMV International used as an intragranular diluent cum powder substrate. Absolute Alcohol (Ethanol 99.6%/v/v) was procured from CVKUSML, India. Magnesium Stearate of vegetable grade was purchased from Ferro Synpro. Film Coating material, Opadry® White was purchased from Colorcon Asia limited, India.

#### Experimental methods

LCDP is an, once-a-day, orally administered, 1, 4-dihydro pyridine derived “Calcium channel blocker”, antihypertensive with an intrinsically slow onset of activity ensuing in a lack of reflex tachycardia with a long duration of action and a high degree of vascular selectivity.[10] But the quandary is that LCDP is a biopharmaceutics (BCS) class IV drug with low solubility and highly variable permeability presenting a challenge to the formulation scientists.[11] Thus, solvent evaporation by FBP was selected as a method of choice for formulation by Solid Dispersion; as it improves wettability with simultaneous increase in porosity of granules. Moreover it also decreases the crystalline structure of drug and promotes its conversion in to more soluble amorphous form.[12] Optimized formulation having desired disintegration and dissolution rate comprises of LCDP, carrier (PVP), diluent and lubricant; wherein the weight ratio of LCDP to carrier is 1:10, with definite intra-granular lactose (Pharmatose 200M) to extra-granular lactose ratio (DCL 11) of 80:20 and magnesium stearate with adjusted weight gain of 2%w/w film coating is mentioned in Table 1a. Moreover, as LCDP is highly variable drug product, thus fluidized bed processing parameters should be precisely controlled to produce intended robust product as per predefined QTPP.

#### Development of SD-FBP technology

At pilot scale, for FBP (Pam-Glatt®-GPCP2); LCDP was first dissolved in ethanol (99.6%/v/v) with stirring at slow speed until a clear solution was obtained. In this solution, PVP-K29/32 was slowly added with continuous stirring until a clear yellow-colored solution was obtained. To carry out Top spray fluidized bed granulation, 40# sifted Lactose Monohydrate (Pharmatose-200M) was loaded in fluidized bed processor and granulated by spraying of drug carrier solution (LCDP-PVP K29/32) for moistening of lactose powder substrate using top spray mechanics on fluidized bed as per Table 1a, while peristaltic pump RPM, spray rate, and atomization air pressure were very slowly increased up to optimum and recorded intermittently in every 10 minutes.

After completion of granulation, fluidized bed drying was carried out in the same FBP at parameters declared in Table 1b, until desired constant LOD specifically from 1.5 to 2.5% w/w at 105°C was achieved. Dried granules were sifted through 20# screen in mechanical sifter. Dried sifted granules were mixed in double cone blender for 5 minutes at 10 ± 2 RPM with 40# presifted spray-dried Lactose (Pharmatose DCL-11) and lubricated with 60# presifted magnesium stearate. Lubricated granules were compressed using 12.7 × 7.1-mm oval-shaped punches at parameters revealed in Table 1c in 16 station rotary tablet compression machine (RIMEK®). Film Coating was carried out at inlet temperature of 60 ± 10°C with Opadry® white suspension in 24” Auto-coater (Ganscoater®) until desired weight gain was achieved.

#### Optimization of SD-FBP parameters as per enhanced QBD

According to ICH Q8 Guideline “Quality cannot be tested into products; quality should be built-in by design”. In all cases, the product was designed to meet patients’ needs and the intended product quality and performance. A more systematic enhanced QbD approach for development included incorporation of prior knowledge, results of studies using design of experiments (ICH Q8),[13] use of QRM (ICH Q9)[14] and use of knowledge management (ICH Q10)[15] throughout the lifecycle of the product. A greater understanding of the product and its manufacturing process created a basis for more flexible regulatory approaches. Thus, for pharmaceutical development of stable product with robust process by enhanced QbD approach included following steps in succession:
**Delineation of quality target product profile**
The quality target product profile (QTPP) formed the basis of design for the development of the product. Considerations for the QTPP included intended use, route of administration, dosage form, strength, container closure system, attributes affecting pharmacokinetic characteristics, purity, and stability appropriate for the intended product.

**Identification of critical quality attributes**
A CQA is 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. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials), and drug product. For drug substances, raw materials and intermediates, the CQAs can additionally include those properties (e.g. particle size distribution, density, and flow properties) that affect drug product CQAs. Potential drug product CQAs derived from the QTPP and/or prior knowledge was used to guide the product and process development. For drug product, CQAs of solid oral dosage forms are typically those aspects affecting product purity, strength, drug release and stability. The list of potential CQAs was modified when the formulation and manufacturing process were selected and as product knowledge and process understanding increased. Relevant CQAs were identified and prioritized by an iterative process of QRM and experimentation that assessed the extent to which their variation had an impact on the quality of the drug product.

**Critical quality risk analysis of critical process parameters by quality risk management**
Risk assessment is a valuable science-based process used in QRM (ICH Q9) that aided in identifying which material attributes and process parameters potentially had an effect on product CQAs as represented in Figure 2. Risk assessment was typically performed early in the development stage and was repeated as more information and greater knowledge was obtained. Risk assessment tools i.e. matrix analysis and failure mode effective analysis were concisely used to identify and rank parameters with potential to have an impact on IP/DP CQAs, based on prior knowledge and initial experimental data. This list was refined further through experimentation to determine the significance of individual variables and potential interactions through a combination of DOEs, mathematical models or studies that lead to mechanistic understanding to achieve a higher level of process understanding.
Optimization of processing parameters and establishment of design space

Depending on IRMA and FMEA results, process understanding experiments [Design of Experiments (DoE) and Multi-Variate Data Analysis (MVDA)] were developed for FBP and Compression parameters having higher risk priorities i.e. more than 15 among all processes involved in product development. The effect of each independent CPPs on dependent product quality (e.g. average granule size and tablet hardness) were analyzed for establishment of DS to design, analyze, and control manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials, which were modeled out with the goal of ensuring product quality. Here, for establishment of DS for CPPs, full factorial 3^m designs was used for optimization procedure, because it was suitable for investigating the quadratic response surfaces for constructing a second-order polynomial model, thus enabling optimization of liquid spraying rate and atomization air pressure to achieve desired average granule size i.e. NMT 400 µm without possibility of lump formation and to decide a desired range of tablet thickness at optimum turret speed to achieve anticipated hardness for prerequisite dissolution. Response surface methodology (RSM) was performed by engaging Design-Expert® software (Version 8.0, Stat-Ease Inc., Minneapolis, MN). Scaling factors were also included for DS intended to span multiple operational scales. Dimensionless numbers for scaling was included as part of the DS description.

Pivotal scale-up considering prior pilot scale QbD

Scale-up of FBP from small laboratory units to large commercial machines has been a continuing activity in pharmaceutical industry. Traditional approach of product development included limited development and scale-up work with final confirmation by validation of 3 batches at pivotal scale. Moreover, there was also a possibility of ‘Worst-case’ scenarios supposed to be included “Market recalls” and “underutilization of capacity” indicated limited success. While in QbD, complete understanding of product and process with monitoring, corrective and preventive actions of all critical steps were taken care at pilot-scale developmental stage to prevent product failure at larger scale. Henceforth, acceptable quality of the product would be ensured with “no recalls” and maximize utilization of capacity. Fluid bed scale-up is a mix of mathematics, engineering and personal judgment. Equipment variables, such as the type and size of the equipment and key process variables such as spray rate, atomization pressure, and inlet air temperature affect the product quality attributes. Control of such parameters to yield a consistent product at a large batch size, thereby constituted a successful scale-up strategy. Consistent quality of incoming raw material was also very important i.e., active pharmaceutical ingredients and excipients.

Among the three steps involved in fluid-bed agglomeration (dry mixing, spray agglomeration, and drying) the spray agglomeration stage was the most critical phase to monitor. During this phase, dynamic granule growth and breakdown takes place, along with solvent evaporation. Thus by QbD, risk associated with scale-up was considered in control strategy of pilot-scale development itself to maximize the probability of effectiveness at larger scale with utilized QRM tools to guide activities. Proposed DS is subject to regulatory assessment and working within the space is not a change. Movement out of DS is considered to be a change and requires scale-up post-approval change process. The relevance of a DS developed at small or pilot scale to the proposed production scale manufacturing process was justified and discussed with the potential risks in the scale-up operation with predetermined edges of failure for process parameters or material attributes, beyond which the relevant quality attributes, could not be met.

RESULTS AND DISCUSSION

Pilot-scale process optimization by QbD

Definition of QTPP with reference to Ip/Dp CQAs

First, QTPP with reference to IP CQA and FP CQA was identified as it relates to quality, safety and efficacy, considering e.g., the route of administration, dosage forms, bioavailability, and stability as represented in Table 2.

Risk identification by knowledge space and matrix investigation of critical process variables affecting CQAs

A cross-functional team of authors has worked together for brainstorming to develop an Ishikawa (fishbone) diagram as represented in Figure 3 that identified potential formulation and FBP factors in knowledge which can have an impact on the desired quality attribute. The variables were then ranked qualitatively in Matrix Analysis (i.e., having low, medium, or high impact) based on prior knowledge and initial experimental data as mentioned in Table 3. Then after DoE was used to evaluate the impact of the higher ranked variables, to gain greater understanding of the process, and to develop a proper control strategy.

![Figure 3: Ishikawa (Fish Bone) Diagram illustrating factors in knowledge for involved Processing steps affecting Finished Product Critical Quality Attributes (CQAs)](image-url)
As compared to other processing steps (i.e., sizing, blending, compression, and film-coating) involved in the manufacturing of LCDP tablets, fluidized bed granulation is the most critical step involving high risk possessing scale-up parameters, which have high impact on one or more in-process and finished product CQA(s). i.e., (i) Liquid Spraying Rate: Higher liquid flow rate will produce larger droplet and larger granules (ii) Atomization Air Pressure: Higher pressure will produce finer droplet, resulting in smaller granules (iii) Fluidization Air Velocity: Higher air flow will cause attrition and rapid evaporation, generating smaller granules and fines. Proper air flow should fluidize the bed without clogging the filters, which can affect process efficiency in terms of %yield.

Risk assessment by failure mode effective analysis
Risk included severity of harm, probability of occurrence, and detects ability, and therefore the level of risk was evaluated quantitatively by FMEA in the term of Risk Priority Number as a result of QRM as summarized critically in Table 4.

Risk evaluation by generation of DoE based design space and multivariate data analysis
Depending on IRMA and FMEA results, process understanding experiments [Design of Experiments (DoE) and Multi-Variate Data Analysis (MVDA)] were developed for FBP having higher risk priorities i.e. more than 25. The effect of CPPs on product quality were analyzed by one of the RSM i.e. 3-level Box-Behnken Experimental Design for establishment of DS to design, analyze and control manufacturing through timely measurements of critical CPPs, which were modeled out with the goal of ensuring product quality in terms of CQAs as revealed in Table 5. The Box-Behnken design (BBD) utilized in this QRM study provides strong coefficient near the center of the DS, where the presumed optimum is located. 2D

Table 2a: Definition of quality target product profile with reference to in-process critical quality attributes

| IP CQAs       | Quality target product profile                                                                 |
|---------------|-----------------------------------------------------------------------------------------------|
| Appearance    | White to off-white free flowing granules                                                         |
| Assay         | 95-105% of the label claim of composite blend sample                                            |
| Blend uniformity | 95-105% of the label claim for Individual blend sample. Mean value: 97-103%, acceptance value:  |
| Average granule size | NMT 15.0, RSD: NMT 5.0%                                                                       |
| Bulk density  | NLT 0.40 g/cc                                                                                    |
| Tapped density| NLT 0.50 g/cc                                                                                    |
| Carr’s index  | NMT 20                                                                                          |
| Hausners ratio| NMT 1.25                                                                                         |
| Angle of Repose | NMT 35°                                                                                        |
| %Loss of drying | NMT 2.0% w/w at 105°C/4 min                                                                    |

IP CQAs: In process critical quality attributes

Table 2b: Definition of quality target product profile with reference to finished product critical quality attributes

| DP CQAs       | Quality target product profile                                                                 |
|---------------|-----------------------------------------------------------------------------------------------|
| Appearance    | White to off-white, oval-shaped, coated tablets having embossed with “C” and “P” on one side with break line on both side. |
| Assay         | 95-105% of the label claim                                                                       |
| Impurities    | Impurity A: NMT 0.5%; Impurity B: NMT 2.0%; Any Other impurity: NMT 0.5% Total impurities: 2.5% |
| Uniformity    | Acceptance value: NMT 15.0 RSD: NMT                                                              |
| Dissintegration| Not more than 15 minutes                                                                        |
| Dissolution   | Not less than 75% (Q) of the labeled amount dissolved in 45 minutes                              |

DP CQAs: Drug product critical quality attributes

Table 3a: Initial qualitative risk-based matrix analysis for critical process parameters affecting in-process critical quality attributes

| IP CQAs     | FB Process | Sizing | Blending | Compression | Film coating |
|-------------|------------|--------|----------|-------------|--------------|
| Appearance  | High       | Medium | Low      | Medium      | Low          |
| Assay       | High       | Low    | Low      | Low         | Low          |
| LOD         | High       | Low    | Low      | Medium      | Low          |
| Blend uniformity | High    | Medium | Medium   | Low         | Low          |
| Flow properties | High     | Medium | Medium   | Low         | Low          |

IP CQAs: In process critical quality attributes, FB: Fluidized bed

Table 3b: Initial risk-based matrix analysis for critical process parameters affecting finished product critical quality attributes

| FP CQAs    | FB Process | Sizing | Blending | Compression | Film coating |
|------------|------------|--------|----------|-------------|--------------|
| Appearance | High       | Medium | Low      | Medium      | Low          |
| Assay      | High       | Low    | Low      | Low         | Low          |
| Impurities | High       | Low    | Low      | Medium      | Low          |
| Cont. uniformity | High  | Medium | Medium   | Low         | Medium      |
| Dis integration | High  | Low    | Low      | Medium      | Low          |
| Dissolution| High       | Low    | Medium   | Medium      | Low          |

FP CQAs: Finished product critical quality attributes, FB: Fluidized bed, Low: Broadly accepted risk, no further investigation is required, Medium: Risk is acceptable. Further investigation may be needed in order to reduce the risk, High: Risk is unacceptable. Further investigation is required to reduce the risk, overview of qualitative relative risk ranking system
Contour plots between one independent variable versus another holding magnitude of response and other variables constant of CPPs; with proven acceptable ranges and edges of failure were clearly revealed with defined margins in Figure 4. 3D Response Surface Plots (a graphical representation of a response variable plotted against two independent variables) and Cube plots (representing the effects of three factors at a time) were represented for both the responses in Figure 5.

Table 4: Quantitative failure mode effective analysis of critical process parameters affecting In process/finished product critical quality attributes

| Unit Operations | Critical process parameter | Failure mode (Critical event) | Effect on IP and FP CQAs with respect to QTPP (Justification of failure mode) | Severity (S) | Probability (P) | Detectability (D) | Risk priority No (RPN=S*P*D) |
|-----------------|---------------------------|-------------------------------|--------------------------------------------------------------------------------|-------------|-----------------|-------------------|-------------------------------|
| Fluid bed granulation | Liquid spraying rate | Higher RPM | Produce larger granules (lump)= Disintegration and dissolution can be affected | 03 | 03 | 03 | 27 |
| Atomizing air pressure | Lower pressure | Unevenly distributes drug binder solution=Content uniformity can be affected | 02 | 02 | 03 | 12 |
| Product temperature | Very high Inlet/Product/ exhaust temperature | Rate of degradation may be affected=Impurity profile may be affected | 02 | 02 | 03 | 12 |
| Fluidizing air flow rate | Higher CFM | Attrition and evaporation produces fines by which process efficiency (%yield) can be impacted | 03 | 03 | 01 | 09 |
| Total RPN for FBP | | | | | | | 60 |
| Sizing | Sifting | Increase in sieve no. | Larger granules=dissolution may be affected | 02 | 02 | 01 | 04 |
| Milling | Increase in Screen size | Uneven PSD=Content Uniformity can be affected | 02 | 02 | 01 | 04 |
| Total RPN for sizing | | | | | | | 04 |
| Blending | Blender RPM | Higher RPM | Increase No. of total Revolutions=Disintegration and dissolution can be affected | 02 | 02 | 01 | 04 |
| Blending time | Longer time | | | | | | 04 |
| Total RPN for blending | | | | | | | 08 |
| Compression | Press speed | High speed | Weight Variation=Content Uniformity may be affected, but in the case of FBP, individual particle coating gives very less deviation in CU | 03 | 03 | 01 | 09 |
| Thickness adjustment | Higher hardness | Disintegration=Dissolution may be affected, but once range was set at pilot scale then there will be no effect at large scale | 03 | 03 | 01 | 09 |
| Total RPN for compression | | | | | | | 18 |
| Film coating | Bed temperature | Very high temperature | Impurity profile affected | 02 | 02 | 03 | 12 |
| Spraying rate | Higher rate | Appearance affected | 02 | 02 | 01 | 04 |
| Atomizing air pressure | Lower pressure | Appearance affected | 01 | 02 | 01 | 02 |
| Total RPN for film-coating | | | | | | | 18 |

Total risk priority number (RPN) more than 25 seek critical attention for DoE for possible failure
*Probability: likelihood of occurrence of harm to the quality, **Severity: Measure of the possible consequence of harm to the quality, ***Detect ability: Ability to discover or determine the existence, presence, or fact of harm to the quality.

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Actual Equation for Response Y1: Granule size (D90) in Terms of Coded Factors:
Granule Size = +398.40 + 115.50*A -21.25*B - 14.25*C -42.50*A*B -26.50*A*C + 35.30*A^2 -6.20*B^2 + 17.80*C^2 (1)

The Model F-value of 24.82 implies the model is significant. There is only a 0.02% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, B, AB, A2 are significant model terms as mentioned in Table 6. Values greater than 0.1000 indicate the model terms are not significant. Here there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve this model.

So, Reduced Equation for Response Y1: Granule size (D90) in Terms of Coded Factors:
Average Granule Size = +398.40 + 115.50*A -21.25*B -42.50*A*B +35.30*A^2 (2)

Actual Equation for Response Y2: Process Efficiency (in %) in Terms of Coded Factors:

Figure 4a: Interaction plot & 2D surface plot for the effect of Fluidized Bed Processing Factors (A: Liquid Spraying Rate & B: Atomization Air Pressure) on the Response Y1: Granule Particle Size (D90) (in µm)

Figure 4b: Interaction plot & 2D surface plot for the effect of Fluidized Bed Processing Factors (A: Liquid Spraying Rate & D: Fluidization Air Velocity) for the Response Y2: Process Efficiency (in %)
Figure 5a: 3D Surface plots & 4D Cube plots for FBP for the response Y1: Granule Particle Size (D90) (in um)

Figure 5b: 3D Surface plots & 4D Cube plots for FBP for the Response Y2: Process Efficiency (in %)

Table 6: Multivariate data analysis by ANOVA for response surface Quadratic model [Partial sum of squares- Type III] of response Y1: Granule size (D90) (in %) with effects from variables: A=Liquid spraying rate, B=Atomizing air pressure, C=Fluidization air velocity

| Source          | Sum of squares | Degree of freedom | Mean square | F value | P value | P value prob>F | Model       |
|-----------------|----------------|-------------------|-------------|---------|---------|----------------|-------------|
| Model           | 1.289E+005     | 9                 | 14324.00    | 24.82   | 0.0002  | Significant    |             |
| A-Liquid spraying rate | 1.067E+005 | 1                 | 1.067E+005  | 184.91  | <0.0001 |                |             |
| B-Air atomization pressure | 3612.50   | 1                 | 3612.50     | 6.26    | 0.0409  |                |             |
| C-Fluidization air velocity | 1624.50   | 1                 | 1624.50     | 2.81    | 0.1373  |                |             |
| AB              | 7225.00        | 1                 | 7225.00     | 12.52   | 0.0095  |                |             |
| AC              | 2809.00        | 1                 | 2809.00     | 4.87    | 0.0632  |                |             |
| BC              | 0.000          | 1                 | 0.000       | 0.000   | 1.0000  |                |             |
| A^2             | 5246.69        | 1                 | 5246.69     | 9.09    | 0.0195  |                |             |
| B^2             | 161.85         | 1                 | 161.85      | 0.28    | 0.6128  |                |             |
| C^2             | 1334.06        | 1                 | 1334.06     | 2.31    | 0.1722  |                |             |
| AB              | 7225.00        | 1                 | 7225.00     | 12.52   | 0.0095  |                |             |
| AC              | 2809.00        | 1                 | 2809.00     | 4.87    | 0.0632  |                |             |
| BC              | 0.000          | 1                 | 0.000       | 0.000   | 1.0000  |                |             |
| A^2             | 5246.69        | 1                 | 5246.69     | 9.09    | 0.0195  |                |             |
| B^2             | 161.85         | 1                 | 161.85      | 0.28    | 0.6128  |                |             |
| C^2             | 1334.06        | 1                 | 1334.06     | 2.31    | 0.1722  |                |             |
| Residual        | 4040.20        | 7                 | 577.17      | 8.10    | 0.0357  |                |             |
| Lack of fit     | 3469.00        | 3                 | 1156.33     | 8.10    | 0.0357  |                |             |
| Pure error      | 571.20         | 4                 | 142.80      |         |         |                |             |
| Cor total       | 1.330E+005     | 16                |             |         |         |                |             |

Table 7: Multivariate data analysis by ANOVA for response surface Quadratic model [Partial sum of squares- Type III] of response Y2: Process efficiency (in %) with effects from variables: A=Liquid spraying rate, B=Atomizing air pressure, C=Fluidization air velocity

| Source          | Sum of squares | Degree of freedom | Mean square | F value | P value | P value prob>F | Model       |
|-----------------|----------------|-------------------|-------------|---------|---------|----------------|-------------|
| Model           | 149.71         | 9                 | 16.63       | 6.45    | 0.0112  | Significant    |             |
| A-Liquid spraying rate | 50.00  | 1                 | 50.00       | 19.39   | 0.0031  |                |             |
| B-Air atomization pressure | 0.13    | 1                 | 0.13        | 0.048   | 0.8320  |                |             |
| C-Fluidization air velocity | 36.12  | 1                 | 36.12       | 14.01   | 0.0072  |                |             |
| AB              | 1.00           | 1                 | 1.00        | 0.39    | 0.5532  |                |             |
| AC              | 4.00           | 1                 | 4.00        | 1.55    | 0.2530  |                |             |
| BC              | 2.25           | 1                 | 2.25        | 0.87    | 0.3813  |                |             |
| A^2             | 9.16           | 1                 | 9.16        | 3.55    | 0.1014  |                |             |
| B^2             | 0.21           | 1                 | 0.21        | 0.083   | 0.7820  |                |             |
| C^2             | 43.79          | 1                 | 43.79       | 16.98   | 0.0045  |                |             |
| Residual        | 18.05          | 7                 | 2.58        |         |         |                |             |
| Lack of fit     | 15.25          | 3                 | 5.08        | 7.26    | 0.0427  |                |             |
| Pure error      | 2.80           | 4                 | 0.70        |         |         |                |             |
| Cor total       | 167.76         | 16                |             |         |         |                |             |
Process Efficiency = 97.20 + 2.50 \cdot A - 0.12 \cdot B - 2.13 \\
\cdot C - 0.50 \cdot A \cdot B - 2.22 \cdot C \cdot A^2 - 0.22 \cdot B^2 - 3.22 \cdot C^2 \quad (3)

The Model F-value of 6.45 implies the model is significant. There is only a 1.12% chance that a "Model F-value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, C, C$^2$ are significant model terms as mentioned in Table 7. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve this model.

![Figure 6: Overlay plots of studied factors to achieve optimum responses “sweet spots”](image)

### Table 8a: Constraints and 30 possible solutions of factors and responses

| Factors: Process variables | Levels of factors studied |
|---------------------------|---------------------------|
| A Liquid spraying rate (g/min) | -1 0 +1 |
| B Air atomization pressure (bar) | 1 2 3 |
| C Fluidization air velocity (cfm) | 50 75 100 |

**Responses**

- **Y1 Granule particle size**
  - Goal with acceptable ranges
  - To achieve D90 in the range from 380 to 420 µm
- **Y2 Process efficiency**
  - To achieve %yield in the range from 95% to 100%

### Table 8b: “Numerical Optimization” Constraints & 30 possible Solutions for combinations of Factors to achieve goal within acceptable ranges

| Number | Liquid spraying rate (g/min) | Air atomization pressure (bar) | Fluidization air velocity (cfm) | Granule particle size (D90) (µm) | Process efficiency (%yield) | Desirability |
|--------|-----------------------------|-------------------------------|-------------------------------|----------------------------------|---------------------------|--------------|
| 1      | 4.25                        | 1.47                          | 56.08                         | 391.695                          | 96.0738                   | 1.000        |
| 2      | 4.30                        | 2.53                          | 55.04                         | 383.393                          | 96.6143                   | 1.000        |
| 3      | 4.89                        | 1.64                          | 84.86                         | 397.973                          | 95.8669                   | 1.000        |
| 4      | 4.95                        | 2.31                          | 86.41                         | 387.124                          | 95.3498                   | 1.000        |
| 5      | 5.05                        | 1.36                          | 86.75                         | 408.7                            | 95.7522                   | 1.000        |
| 6      | 5.58                        | 2.02                          | 86.08                         | 388.516                          | 95.53                    | 1.000        |
| 7      | 4.37                        | 1.12                          | 57.27                         | 397.068                          | 96.0253                   | 1.000        |
| 8      | 6.32                        | 2.75                          | 86.57                         | 414.493                          | 95.8998                   | 1.000        |
| 9      | 4.35                        | 1.03                          | 62.88                         | 389.197                          | 96.4216                   | 1.000        |
| 10     | 5.71                        | 2.69                          | 88.72                         | 397.219                          | 95.1419                   | 1.000        |
| 11     | 6.33                        | 2.83                          | 81.47                         | 413.612                          | 96.7656                   | 1.000        |
| 12     | 5.97                        | 2.85                          | 64.00                         | 418.739                          | 97.897                    | 1.000        |
| 13     | 5.66                        | 2.97                          | 70.99                         | 393.513                          | 97.5759                   | 1.000        |
| 14     | 5.28                        | 1.66                          | 90.59                         | 413.845                          | 95.0911                   | 1.000        |
| 15     | 4.45                        | 1.10                          | 64.03                         | 393.106                          | 96.638                    | 1.000        |
| 16     | 5.05                        | 1.21                          | 67.71                         | 419.807                          | 97.3748                   | 1.000        |
| 17     | 4.16                        | 2.71                          | 50.48                         | 382.863                          | 96.0956                   | 1.000        |
| 18     | 4.74                        | 1.26                          | 62.68                         | 408.688                          | 96.9473                   | 1.000        |
| 19     | 4.94                        | 2.36                          | 61.45                         | 400.786                          | 97.4424                   | 1.000        |
| 20     | 5.52                        | 2.82                          | 81.28                         | 388.197                          | 96.4156                   | 1.000        |
| 21     | 4.38                        | 1.98                          | 67.27                         | 380.562                          | 97.0238                   | 1.000        |
| 22     | 5.38                        | 2.56                          | 65.98                         | 405.543                          | 97.7719                   | 1.000        |
| 23     | 5.70                        | 2.67                          | 73.75                         | 404.712                          | 97.552                    | 1.000        |
| 24     | 4.26                        | 1.21                          | 56.29                         | 392.351                          | 95.8764                   | 1.000        |
| 25     | 5.41                        | 1.78                          | 89.66                         | 416.059                          | 95.3657                   | 1.000        |
| 26     | 5.28                        | 2.98                          | 51.86                         | 409.611                          | 96.8323                   | 1.000        |
| 27     | 5.28                        | 1.40                          | 85.72                         | 416.594                          | 96.1739                   | 1.000        |
| 28     | 4.33                        | 1.41                          | 62.90                         | 387.157                          | 96.6604                   | 1.000        |
| 29     | 5.38                        | 1.64                          | 87.76                         | 418.047                          | 98.809                    | 1.000        |
| 30     | 4.97                        | 2.91                          | 59.25                         | 388.958                          | 97.3752                   | 1.000        |
After analyzing experimental data by ANOVA and getting the final equation, the desired goal for each factor and response were chosen using "Numerical Optimization" option in Design Expert software. The goal seeking begins at a random starting point and proceeds up the steepest slope to a maximum as mentioned in Table 8a. By starting from several points in the design space chances improve for finding the “best” local maximum. The default is 30 starting points as mentioned in Table 8b.

With multiple responses, it was required to find regions where requirements simultaneously meet the critical properties, the “sweet spot”. By superimposing or overlaying critical response contours on a contour plot, visually search for the best compromise was possible by “Graphical Optimization option” in Design Expert Software. Graphical optimization displayed the area of feasible response values in the factor space in yellow color. Regions that did not fit the optimization criteria were gray shaded as represented in Figure 6, constituted a DS for robust and rugged FBP.

Risk reduction by implementation of control strategy irrespective of scale

On the basis of overall development by QbD, a control strategy was designed to ensure that a product of required quality would be produced consistently by proposed process without probability of failure at larger scale. The elements of the control strategy described and justified how in-process controls and the controls of input materials (drug substance and excipients), intermediates (in-process materials), drug products container and closure system contributed to the final product quality. These controls were based on product, formulation and process understanding and include, at a minimum, control of the critical process parameters and material attributes. Sources of variability that impact product

![Diagram of Fluidized Bed Processing, Sizing & Blending, Compression, and Film-Coating processes.](image-url)

**Figure 7:** Outlined Controlled pertinent strategy for Robust & Rugged Manufacturing Process of Lacidipine Tablets
A final control strategy included the following as pointed out in Figure 7:

- Control of input material attributes especially risky formulation variables (e.g. drug substance, excipients, primary packaging materials) based on an understanding of their impact on process ability or product quality for reducing probability of risk;
- Product specification(s);
- Controls for unit operations especially risky process variables as per that have an impact on downstream processing or product quality (e.g. the impact of temperature on degradation, particle size distribution of the granulate on dissolution) for reducing probability of risk;
- In-process or real-time testing in lieu of end-product testing (e.g. measurement and control of in process CQAs inline monitored by PAT tools: in situ Focused Beam Reflectance Measurement (FBRM) for inline Particle Size measurement during granulation and in situ Fourier Transform Infra-Red Spectroscopy (FTIR) for inline Blend Uniformity at Blending stage and Content Uniformity in Finished Product, which ensure that Fluidized Bed Granulation process is working as anticipated to deliver product quality attributes as predicted by the DS) for increasing detectability of harm;
- A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models.

**Pivotal scale-up considering prior pilot-scale QbD**

Following section illustrated how a product was scaled up from 5 to 120 kg in equipment supplied by Glatt when scaling up as revealed with “scale independent” fixed parameters in Figure 8. Scale-dependent variable parameters at large production (pivotal) scale were calculated as per following with reference to QbD optimized parameters at small laboratory (pilot) scale.

**Batch size and equipment selection**

Scale-up from small laboratory sized fluid-bed machines can be made much easier if the same line of equipment is to be used. However, efforts were in need to be spent on modifying process parameters, because of differences in air flow pattern, expansion chamber geometry, gun spray pattern, etc., Thus, for Top Spray equipment minimum and maximum batch size could be approximated as per equation no.(5) and (6)

\[
S_{\text{min}} = [V \times 0.3 \times BD] = [500 \times 0.3 \times 0.4] = 60 \text{ kg} 
\]

\[
S_{\text{max}} = [V \times 0.7 \times BD] = [500 \times 0.7 \times 0.4] = 140 \text{ kg} 
\]

Where;
- \( S \) is batch size in kilograms,
- \( V \) is the product bowl working volume in liters
- \( BD \) is the bulk density of finished granules in g/cc;
- 0.3 = Minimum occupancy of 30% in product bowl
- 0.7 = Maximum occupancy of 70% in product bowl

**Fluidization air flow scale-up**

To maintain the same fluidization velocity, the air volume in a larger unit was increased, based upon the cross-sectional area of the product bowl. In this case, the cross-sectional area of the base of the larger container was 0.64 m² and the smaller was 0.02 m². Thus, correct air flow was calculated as per equation no. (7)

\[
AF_2 = [AF_1 \times (A_2/A_1)] = [80 \times (0.64/0.02)] = 2560 \text{ CMH} 
\]

Where;
- \( AF_1 \) is Fluidization air flow in the laboratory scale equipment,
- \( A_1 \) is cross-sectional area of the laboratory scale equipment,
- \( A_2 \) is cross-sectional area of the scaled-up equipment.

**Spray rate and atomization air pressure scale-up**

Spray rate scale-up was determined by the drying capacity of the equipment which is directly proportional to cross-sectional area of the air distribution plate rather than by the increase in batch size. At a given atomization pressure and air flow volume, change in liquid spray rate directly affects droplet size which in turn impacts particle agglomeration and may cause lumping. Thus, cross-sectional areas of the air distribution plate were used for approximation of scale-up spray rate as per equation no (8).

\[
SR_2 = [SR_1 \times (A_2/A_1)] = [5 \times (0.64/0.02)] = 160 \text{ g/min.} 
\]

Where;
- \( SR_1 \) is spray rate in the laboratory scale equipment,
- \( SR_2 \) is spray rate in the scaled-up equipment,
A₁ is cross-sectional area of the laboratory scale equipment, A₂ is cross-sectional area of the scaled up equipment.

To maintain the same particle size, the “triple-headed nozzle” in scale up could spray at the same pilot-unit spray rate at a same atomization air pressure. However, this could result in a longer process time. So another approach to maintain a similar droplet size was utilized to achieve granule size D₉₀ of 400 μm with maintenance of the mass balance of spray rate and the atomization pressure by increasing the atomization pressure to 2*3 = 6 bar, the spray rate could be increased to 160*(3) = 480 ~ 500 grams per minute at production scale (where 3 indicates number of nozzle heads) keeping the same droplet size and hence obtaining granulation with desired CQAs as revealed in Table 9 and 10.

### Table 9: In process results for laboratory batch and scaled-up batch

| IP CQAs                  | Laboratory batch results | Scaled up batch results |
|--------------------------|--------------------------|-------------------------|
| Appearance               | White to off white free flowing granules | White to off white free flowing granules |
| Assay                    | 98.6%                    | 99.3%                   |
| Blend uniformity (n=11)  | Mean: 99.4%             | Man: 101.5%             |
|                          | Min: 96.6%              | Min: 97.1%              |
|                          | Max: 102.2%             | Max: 104.2%             |
|                          | RSD: 1.5%               | RSD: 1.6%               |
| Average granule size     | D₅₀: 360 μm             | D₅₀: 360 μm             |
| Bulk density             | 0.45 g/cc               | 0.47 g/cc               |
| Tapped density           | 0.54 g/cc               | 0.55 g/cc               |
| Carr’s index             | 16.67                   | 14.54                   |
| Hausners ratio           | 1.20                    | 1.17                    |
| Angle of repose          | 34°                     | 33°                     |
| %Loss of drying          | 1.85%                   | 1.72%                   |

### Table 10: Finished drug product results for laboratory batch and scaled-up

| FP CQAs                  | Laboratory batch results | Scaled up batch results |
|--------------------------|--------------------------|-------------------------|
| Appearance               | White to off-white, oval-shaped coated tablets having embossed with “C” and “P” on one side with break line on both side. | White to off-white, oval-shaped coated tablets having embossed with “C” and “P” on one side with break line on both side. |
| Assay                    | 99.2%                    | 99.7%                   |
| Impurities (Related Substances) | Impurity A: 0.31% | Impurity A: 0.55% |
|                          | Impurity B: 0.22%        | Impurity B: 0.82%       |
|                         | Any Other Impurity: 0.20% | Any Other Impurity: 0.35% |
|                          | impurities: 0.72%       | impurities: 1.72%      |
| Content Uniformity (n=20) | Mean: 96.9% Max: 102.7% RSD: 1.4% | Mean: 97.7% Max: 103.8% RSD: 1.5% |
| Disintegration (n=6)     | 10 minutes              | 10 minutes              |
| Dissolution (n=12)      | 98%                     | 99%                     |

FP CQAs: Finished product critical quality attributes

### CONCLUSIONS

From exhaustive use of risk “assessment” tools: Qualitative Matrix Analysis and Quantitative Failure Mode Effective Analysis (based on Probability, Severity, and Detectability), it was unquestionable that Fluid Bed Granulation is the most critical step for achieving consistent QTPP in case of formulation of poorly soluble and highly biovariable drug LCDP by solid dispersion approach. To reduce “control” risk irrespective of the scale, detailed experimental study of CPPs was carried out by BBD to develop DS with acceptable proven ranges, which reduce probability of risk respected CPPs affecting quality and/or performance of In Process/Finished Product (IP/FP) CQAs, which reduces probability of risk irrespective of scale. To increase detectability of risk, performance of FBP could be inline monitored by Process Analytical Technology (PAT) tools: in situ FBRM for inline particle size measurement during granulation and in situ FTIR for inline blend uniformity at blending stage and content uniformity in finished product, which ensure that fluidized bed granulation process is working as anticipated to deliver product quality attributes as predicted by the DS. Thus, understanding sources of variability of CPPs and “review” of impact of individual CPP on downstream processes or processing and finished product quality during pilot scale development stage provided flexibility for shifting of controls upstream at large scale and minimize the need for end-product testing and maximize the probability of process effectiveness at larger scale.

From the result of this QRM study of top spray FBP for antihypertensive drug formulation with Control Strategy engendered by “Box-Behnken Experimental Design Space”, it has been proved that QRM, along with DoE and PAT tools of QbD can be a systematic process for the “assessment, control, communication, and review of any process-related risks to the quality of the drug product across the product lifecycle”.

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