**Recent Advances in Pharmaceutical Science Research**
**www.rapsr.com**
**Vol-1 | No-1 | 2012 | 39-59**

*Original Research Article*

# Development and Scale-Up of SD-FBP Formulation Technology in line with parametric QbD

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## ABSTRACT

Main objective of this study is to provide a sophisticated robust process for the preparation of oral dosage form of poorly soluble anti-hypertensive drug by Quality by Design (QbD) concept with focusing on thorough understanding of the product and process by which it can be developed and scaled up with outlined control strategy at pilot scale developmental stage itself to prevent product failure at larger scale. Proper selection & optimization of formulation, equipment & process related variable in Fluidized bed granulation only can lead to successful scale up of Fluid-bed processing technology from the laboratory to commercial production successfully. Thus, risk assessment tools were used 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 through DOE that lead to mechanistic understanding to achieve a higher level of process understanding. Proposed design space with proven acceptable ranges of CPPs & predefined edges of failure is subjected to regulatory assessment. Working within the space is not a change, but movement out of design space is considered to be a change and requires scale up post-approval change process.

**KEY WORDS:** Solid Dispersion (SD), Fluidized Bed Process (FBP), Quality by Design (QbD), Critical Quality Attribute (CQA), Critical Process Parameter (CPP), Failure Mode Effective Analysis (FMEA), Scale– up.

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## 1.0. Introduction

At the stage of drug discovery and development, experimental operations are carried out in bench top or small pilot-scale equipment. Process knowledge in the form of raw data obtained from these experiments is specific to that scale. While, Scale-up is normally identified with an incremental increase in batch size until a desired level of production is obtained. It is generally recognized that many NDAs and ANDAs contain provision for multiple manufacturers of the drug products and all manufacturers cannot produce equivalent material. So, there is a need for material quality control to assure the performance and reproducibility of the finished product. Furthermore, the process should be controlled by employment of a validation protocol, which defines the critical in process parameters and also establishes the acceptance criteria for the granulation; which may include sieve analysis, moisture content, flow properties, density, uniformity, and compressibility etc. In those- cases where the manufacturing process has been controlled and validated, batch scale-up, changes in site of manufacture, allowance for equipment change (where the operating principle is the same), minor formulation changes, etc., should be determined on the basis of the comparability of both the granulation and the final product, as assured by: appropriate tests, specifications, process validation and comparative accelerated stability or by QbD developed control strategy at pilot scale[1].

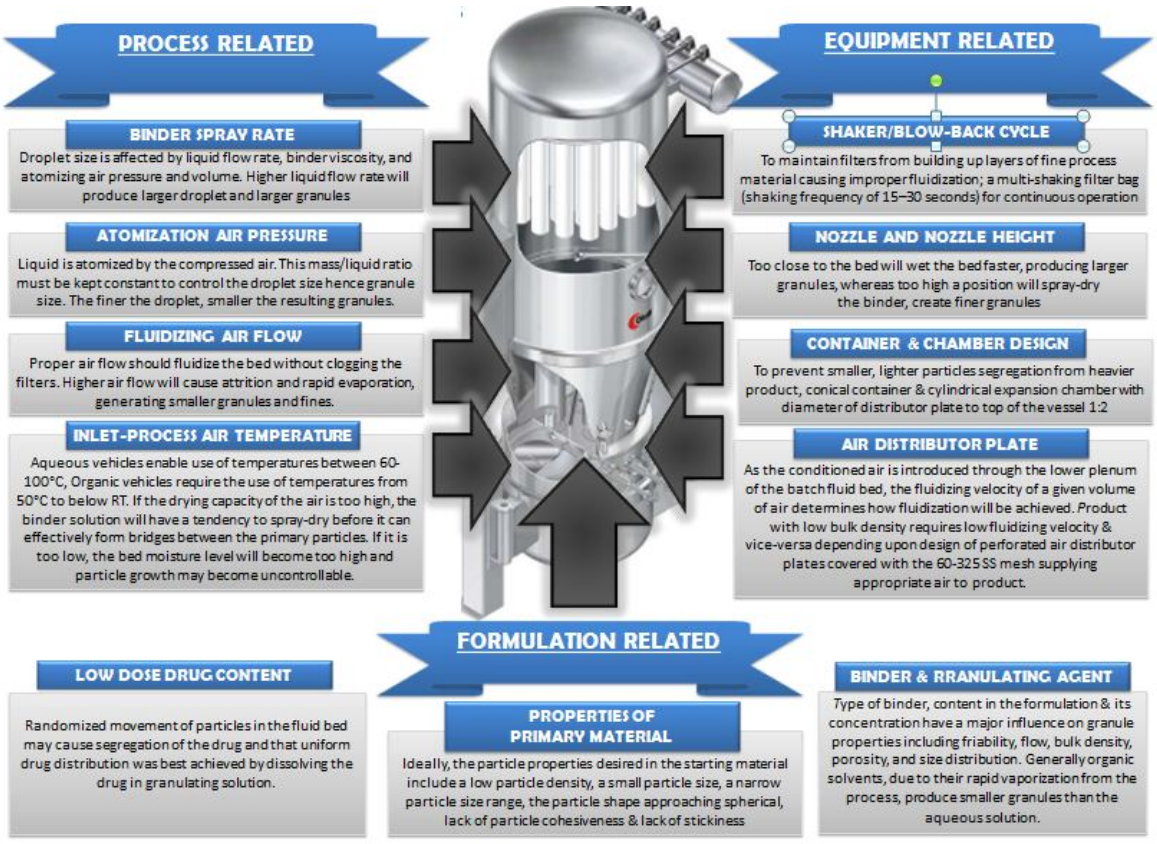



**Figure 1.** A Comprehension scheme for factors affecting FBP Development

The fluid bed agglomeration process is a combination of three steps: dry mixing, spray agglomeration and drying to a desired moisture level or to a desired granule size. The scale-up from laboratory equipment scale to production-size units is dependent on equipment design, which may or may not have been scalable as far as its selected dimensional features or components is concerned[2,3]. Quality of the granules is determined during the spraying stage only where constant building of granules and evaporation of binder solvent is taking place [4]. Authors found that the processing factors that most affect granule characteristics were rate of binder addition, degree of atomization of the binder liquid, process-air temperature and height of the spray nozzle from the bed. Since the higher air flow along with the temperature in a larger unit, provides a higher evaporation rate, one must maintain the drying capacity in the larger unit such that the bed temperature is similar to the smaller unit's bed temperature. This can be accomplished either by increased spray rate, increased air temperature, increased air flow or a combination of these variables to obtain suitable results. Since the ratio of bed depth to the air distributor increases with the size of the equipment, the fluidization air velocity is kept constant by increasing the air volume [5]. Important Critical Process Parameters (CPPs) having impact on Critical Quality Attributes [6, 7] were precisely summarized in **Figure 1.** In summary, when scaling up, the following processing conditions should be similar to those in the pilot-scale studies: 1) Fluidization velocity of the process air through the system [8-12] 2) Ratio of granulation spray rate to the drying capacity of the fluidization air volume [8-12] 3) Droplet size of the binder spray liquid proportional to atomizing air pressure [8-12]. Each of these values must be calculated based on the results of the operation of the pilot-size unit to determine the allowable operating range for the process by QbD.

In the past, scale-up was carried out by selecting best-guess process parameters, while the recent trend is to employ the factorial and modified factorial designs and search methods. These statistically designed experimental plans can generate mathematical relationships between the independent variables, such as process factors and the dependent variables, such as product properties. Main object of this study is to provide a sophisticated robust process for the preparation of said pharmaceutical dosage form by Quality by Design (QbD) concept focusing on thorough understanding of the product and process by which it is developed and scaled up along with a knowledge of the risks involved in manufacturing by IRMA (Initial Risk based Matrix Analysis) and FMEA (Failure Mode Effective Analysis) study of the product with process and how best to mitigate those risks by developing design space with DoE and MVDA with outlined control strategy at pilot scale developmental stage itself to prevent product failure at larger scale. Thus, risk assessment tools were used 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 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.

## 2.0. Materials and methods

### 2.1. Materials

Lacidipine was procured from Cadila Pharmaceuticals limited, India. Polyvinyl Pyrrolidone (Plasdone® K29/32) was purchased from ISP Technologies. Lactose Monohydrate (Pharmatose® 200M & DCL 11®) was purchased from DMV International and was used as an intra-granular 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. Premixed Film Coating material, Opadry® White was purchased from Colorcon Asia limited, India.

### 2.2. Experimental methods

Lacidipine (LCDP) is an, once-a-day, orally-administered, 1, 4 –dihydro pyridine derived "Calcium channel blocker", categorized as an anti-hypertensive 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. But the quandary is that LCDP is a low dose potent drug with low solubility and highly variable permeability presenting a challenge to the formulation scientists. Thus, solvent evaporation by Fluidized Bed Process (FBP) was selected as a method of choice for formulation by Solid Dispersion, as it improves wettability with simultaneous increase in porosity of granules & uniform distribution of drug particles within formulation to achieve content uniformity [13-16]. Moreover it also decreases the crystalline structure of drug & promotes its conversion in to more soluble amorphous form [17]. Optimized formulation having desired disintegration & 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 & magnesium stearate with adjusted weight gain of 2%w/w film coating as in **Table 1(a).** Moreover, as LCDP is Highly Variable Drug Product [HVDP] whose intra-subject variability for a bioavailability parameter is larger than 30% [18, 19], thus FBP parameters should be precisely controlled to produce intended robust product as per predefined Quality Target Product Profile.

#### 2.2.1. Development of SD-FBP technology

At pilot scale, for FBP (Glatt®-GPCP5); 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-$K_{29/32}$ 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 & granulated by spraying of drug carrier solution for moistening of lactose powder substrate using top spray mechanics on fluidized bed as per **Table 1(a),** while peristaltic pump RPM, spray rate and atomization air pressure were very slowly increased up to optimum & 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 1(b)**, until desired 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# pre-sifted spray dried Lactose (Pharmatose DCL-11) & lubricated with 60# pre-sifted magnesium stearate. Lubricated granules were compressed using 12.7 X 7.1 mm oval shaped punches at parameters revealed in **Table 1(c)** in 16 station rotary tablet compression machine (RIMEK®). Film Coating was carried out at inlet temperature of 60 ± 10ºC with Opadry® white suspension in 24" Auto coater (Ganscoater®) until desired weight gain was achieved.

### 2.2.2. 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 patient needs and the intended product quality & performance. A more systematic enhanced QbD approach for development included incorporation of prior knowledge, results of studies using design of experiments (ICH Q8) [20], use of quality risk management (ICH Q9) [21] and use of knowledge management (ICH Q10) [22] 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:

**Table 1(a).** Optimized LCDP Formulation

| No | Intra granular (IG) | mg/unit |
|---|---|---|
| 1 | Lacidipine | 4.00 |
| 2 | Plasdone K29/32 | 40.00 |
| 3 | Pharmatose 200M | 204.80 |
| | **Extra granular (EG)** | |
| 4 | Pharmatose DCL11 | 50.45 |
| 5 | Magnesium Stearate | 0.75 |
| 6 | Unit Weight of core tablet (in mg.) | 300.00 |
| | **%Weight gain in coating** | **2%** |
| 7 | Unit Weight of coated tablet (in mg.) | 306.00 |

**Table 1(b).** Fluidized Bed Process Parameters

| No | FBP Parameters | Limit |
|---|---|---|
| 1 | Inlet Temperature | 50±10ºC |
| 2 | Outlet Temperature | 40±10ºC |
| 3 | Product Temperature | 30±10ºC |
| 4 | Atomization air pressure | 1-3 bar |

**Table 1(c).** Compression Parameters

| No | Compression Parameters | Limits |
|---|---|---|
| 1 | Target Weight | 300 mg |
| 2 | Hardness | 50 to 70 Newton |
| 3 | Disintegration Time | NMT 15 minutes |

**2.2.2.1. Delineation of Quality Target Product Profile (QTPP)**
The quality target product profile formed the basis of design for the development of the product. Considerations for the quality target product profile included intended use, route of administration, dosage form, strength, container closure system, attributes affecting pharmacokinetic characteristics, purity and stability appropriate for the intended product.
**2.2.2.2. Identification of Critical Quality Attributes (CQAs)**
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 & flow properties) that affect drug product CQAs. Potential drug product CQAs derived from the quality target product profile 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 & prioritized by an iterative process of quality risk management and experimentation that assessed the extent to which their variation had an impact on the quality of the drug product.
**2.2.2.3. Critical Quality Risk Analysis of CPPs by QRM**
Risk assessment is a valuable science-based process used in Quality Risk Management (QRM) (ICH Q9) that aided in identifying which material attributes and process parameters potentially had an effect on product CQAs. Risk assessment was typically performed early in the development stage & was repeated as more information & greater knowledge was obtained. Risk assessment tools i.e. matrix analysis & Failure Mode Effective Analysis (FMEA) 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. 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. The ability to detect the harm (detectability) also factors in the estimation of risk. Risk evaluation compares the identified and analyzed risk against given risk criteria. 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.
**2.2.2.4. Optimization of processing parameters & Establishment of Design space:** Depending on IRMA & FMEA results, process understanding experiments [Design of Experiments (DoE) & Multi-Variate Data Analysis (MVDA)] were developed for FBP & 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 & tablet hardness) were analyzed for establishment of Design Space (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 design space for CPPs, full factorial $3^2$ 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 & atomization air pressure to achieve desired average granule size i.e. NMT 400 um 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 design space intended to span multiple operational scales. Dimensionless numbers for scaling was included as part of the design space description.

**2.2.3. Pivotal Scale-Up Considering Prior Pilot Scale QbD**

Scale-up of fluid-bed process 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 design space is subject to regulatory assessment and working within the space is not a change. Movement out of design space is considered to be a change and requires scale up post-approval change process. The relevance of a design space 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.

## 3.0. Results and discussion

### 3.1. Pilot scale process optimization by QbD

#### 3.1.1. Definition of QTPP with reference to IP/DP CQAs:

First, Quality Target Product Profile (QTPP) with reference to in process critical quality attributes (IP CQA) & Drug Product Critical Quality Attribute (DP 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**.

#### 3.1.2. Identification of formulation variable CQAs

Critical Quality Attributes (CQA) of the Active Pharmaceutical Ingredients (API) and Excipients having an impact on product quality were identified and summarized in **Table 3** (highlighted red for higher impact & highlighted green for lower impact) to study & control those product characteristics. Among all physicochemical properties of API, crystallinity, solubility, stability & purity has high impact on final drug product quality attribute as compared to others. While in case of excipients (inactive ingredients), Particle size of Lactose monohydrate which act as a substrate (for intra granular & extra granular) as well as API to PVP ratio for the desired solid dispersion was the most critical parameter, those have most prominent effect on final quality of drug product. While choice of appropriate solvent plays a major role in impurity generation in finished product.

#### 3.1.3. Identification and quality risk analysis of process variable affecting IP/DP CQAs by IRMA & FMEA

An appropriate manufacturing process was established and Critical Process Parameters (CPPs) using prior knowledge & Risk management tools [Initial Risk based Matrix Analysis (IRMA) & Failure Mode Effective Analysis (FMEA)] were critically analyzed as per **Table 4**. Risk included severity of harm, probability of occurrence, and detectability, and therefore the level of risk changed as a result of risk management.

#### 3.1.4. Selection and optimization of appropriate process parameters by DOE & MVDA

Depending on IRMA & FMEA results, process understanding experiments [Design of Experiments (DoE) & Multi-Variate Data Analysis (MVDA)] were developed for FBP & Compression having higher risk priorities i.e. more than 15. The effect of CPPs on product quality (e.g. average granule size & tablet hardness) were analyzed for establishment of Design Space (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 as revealed in **Table 5**.

#### 3.1.5. Establishment of design space (DS)

The relationship between the process inputs (material attributes and process parameters) and the critical quality attributes were described in the design space.

**3.1.5.1. Selection of Variables:** The risk assessment and process development experiments could lead to an understanding of the linkage and effect of process parameters and material attributes on product CQAs and helped to identify the variables and their ranges within which consistent quality could be achieved.

**Table 2(a). Definition of QTPP with reference to IP CQAs**

| IP CQAs | Quality Target Product Profile (QTPP) |
|---|---|
| Appearance | White to off white free flowing granules |
| Assay | 95% to 105% of the label claim of Composite Blend sample |
| Blend uniformity | 95% to 105% of the label claim for Individual Blend sample. Mean value: 97% to 103%, Acceptance Value: NMT 15.0, RSD : NMT 5.0% |
| Average Granule size | D50:NMT 400um |
| Bulk Density | NLT 0.40 gm/cc |
| Tapped Density | NLT 0.50 gm/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 |

**Table 2(b). Definition of QTPP with reference to DP CQAs**

| DP CQAs | Quality Target Product Profile (QTPP) |
|---|---|
| Appearance | White to off white, oval shaped, coated tablets having embossed with "C" & "P" on one side with break line on both side. |
| Assay | 95% to 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% |
| Content Uniformity | Acceptance Value: NMT 15.0 RSD : NMT 5.0% |
| Disintegration | Not more than 15 minutes |
| Dissolution | Not less than 75% (Q) of the labeled amt dissolved in 45 minutes |

**Table 3(a). Identification of API CQAs with impact on DP CQAs**

| | API CQAs | | | | | | |
|---|---|---|---|---|---|---|---|
| **DP CQAs** | Particle size | Moisture content | Solvent content | Crystal linity | Salt form | Solubility | Stability |
| Appearance | Low | High | High | Low | Low | Low | High |
| Assay | Low | High | High | Low | Low | Low | High |
| Impurities | Low | Low | Low | Low | Low | Low | High |
| Content Uniformity | Low | Low | Low | Low | Low | High | Low |
| Disintegration | Low | Low | Low | High | High | High | Low |
| Dissolution | High | Low | Low | High | High | High | Low |

Green colored boxes indicated lower impact of unit operation on drug product CQA, while Red colored box indicates higher impact of unit operation on drug product CQAs. From initial matrix analysis, solubility & stability of API had found higher impact on drug product quality as per Target product profile.

**Table 3(b).** Identification of Excipient CQAs with impact on DP CQAs

| | **EXCIPIENT CQAs** | | | | | |
|---|---|---|---|---|---|---|
| **DP CQAs** | Plasdone® K29/32 – Polyvinyl Pyrrolidone | Pharmatose® 200M -Lactose Monohydrate | Absolute Alcohol – Ethanol 99.6%v/v | Pharmatose® DCL11 -Lactose Spray Dried | Magnesium Stearate – Vegetable grade) | Opadry White |
| Appearance | Low | Low | Low | High | High | High |
| Assay | Low | Low | Low | Low | Low | Low |
| Impurities | Low | Low | High | Low | Low | Low |
| Content Uniformity | Low | High | Low | Low | Low | Low |
| Disintegration | High | Low | Low | High | High | Low |
| Dissolution | High | Low | Low | High | High | Low |

Green colored boxes indicated lower impact of unit operation on drug product CQA, while Red colored box indicates higher impact of unit operation on drug product CQAs. From initial matrix analysis, Plasdone® K29/32 –Polyvinyl Pyrrolidone & Pharmatose® DCL11-Lactose Spray Dried had found higher impact on drug product quality as per Target product profile.

**Table 4(a).** Initial Risk based Matrix Analysis for CPPs affecting IP CQAs

| | **Unit Operations relating to CPPs** | | | | |
|---|---|---|---|---|---|
| **IP CQAs** | FB Process | Sizing | Blending | Compression | Film Coating |
| Appearance | High | High | Low | High | High |
| Assay | High | Low | Low | Low | Low |
| LOD | High | High | Low | Low | High |
| Blend Uniformity | High | High | High | Low | Low |
| Flow Properties | High | High | High | Low | Low |

**Table 4(b).** Initial Risk based Matrix Analysis for CPPs affecting DP CQAs

| | **Unit Operations relating to CPPs** | | | | |
|---|---|---|---|---|---|
| **DP CQAs** | FB Process | Sizing | Blending | Compression | Film Coating |
| Appearance | High | High | Low | High | High |
| Assay | High | Low | Low | Low | Low |
| Impurities | High | Low | Low | Low | High |
| Content Uniformity | High | High | High | Low | Low |
| Dis integration | High | Low | Low | High | Low |
| Dissolution | High | Low | High | High | Low |

Green colored boxes indicated lower impact of unit operation on drug product CQA, while Red colored box indicates higher impact of unit operation on drug product CQAs. From initial matrix analysis, Fluidized bed process and compression process had found highest impact on drug product quality as per Target product profile.

**Table 4(c).** Failure Mode Effective Analysis (FMEA) of CPPs affecting IP/DP CQAs

| Unit Operations | Critical Process Parameter (CPPs) | Critical Event | Effect on IP/ DP CQAs with respect to QTPP | Severity (S) | Probability (P) | Detectability (D) | Risk Priority No (RPN=S*P*D) |
|---|---|---|---|---|---|---|---|
| **Fluidized Bed Process (Granulation & Drying)** | Temperature | Very High Inlet/ Temperature | Finer Granules, Higher rate of degradation = Assay & Impurity profile affected | 03 | 02 | 01 | 06 |
| | Spraying rate | Higher Rate | Larger granules (lump)= Disintegration & Dissolution affected | 03 | 03 | 03 | 27 |
| | Atomizing air pressure | Lower Pressure | Uneven distribution of Drug binder solution = CU | 02 | 02 | 02 | 08 |
| | Fluidizing Air Flow rate | Higher CFM | Attrition &evaporation produces fines | 02 | 02 | 02 | 08 |
| **Total RPN for FBP** | | | | | | | **49** |
| **Sizing** | Sifting | Increase in Sieve No. | Larger granules = Dissolution affected Uneven PSD = Content Uniformity | 02 | 02 | 01 | 04 |
| | Milling | Increase in Screen size | | 02 | 02 | 01 | 04 |
| **Total RPN for Sizing** | | | | | | | **08** |
| **Blending** | Blender RPM | Higher RPM | Increase No. of total Revolutions = Disintegration & Dissolution affected | 01 | 02 | 01 | 02 |
| | Blending Time | Longer Time | | 01 | 02 | 01 | 02 |
| **Total RPN for Blending** | | | | | | | **04** |
| **Compression** | Press Speed | High Speed | Weight Variation = Content Uniformity | 02 | 02 | 02 | 04 |
| | Thickness adjustment | Higher Hardness | Disintegration= Dissolution affected | 03 | 03 | 02 | 18 |
| **Total RPN for Compression** | | | | | | | **22** |
| **Film Coating** | Temperature | Very High Temperature | Impurity profile affected | 01 | 02 | 01 | 02 |
| | 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** | | | | | | | **08** |

| Severity | Score | Probability | Score |
|---|---|---|---|
| Minor | 01 | Very Unlikely | 01 |
| Major | 02 | Remote | 02 |
| Critical | 03 | Occasional | 03 |
| Catastrophic | 04 | Probable | 04 |
| | | Frequent | 05 |

Total Risk Priority Number (RPN) more than 10 seek critical attention for DoE for possible failure

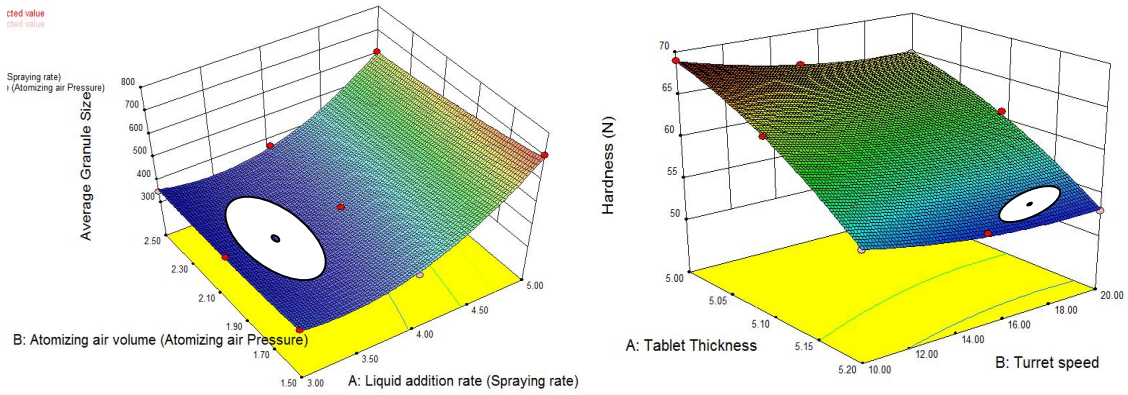
**Table 5.** Design of Experiments (DoEs) & Multi-Variate Data Analysis (MVDA)
(a) For Fluidized Bed Process

| **(a) DoE & MVDA for Fluidized Bed Process** | | | |
|---|---|---|---|
| **Run** | **Spraying rate (in gm/min)** | **Atomizing Air Pressure (bar)** | **Average Granule size: D50 (um)** |
| 1 | 3.00 | 1.50 | 375 |
| 2 | 4.00 | 1.50 | 395 |
| 3 | 5.00 | 1.50 | 710 |
| 4 | 3.00 | 2.00 | 360 |
| 5 | 4.00 | 2.00 | 380 |
| 6 | 5.00 | 2.00 | 630 |
| 7 | 3.00 | 2.50 | 350 |
| 8 | 4.00 | 2.50 | 370 |
| 9 | 5.00 | 2.50 | 615 |

(b) for compression.

| **(b) DoE & MVDA for Compression** | | | |
|---|---|---|---|
| **Run** | **Adjusted Thickness (in mm)** | **Press Speed (in RPM)** | **Tablet Hardness (in Newton)** |
| 1 | 5.00 | 10 | 69 |
| 2 | 5.10 | 10 | 64 |
| 3 | 5.20 | 10 | 56 |
| 4 | 5.00 | 15 | 66 |
| 5 | 5.10 | 15 | 61 |
| 6 | 5.20 | 15 | 54 |
| 7 | 5.00 | 20 | 65 |
| 8 | 5.10 | 20 | 61 |
| 9 | 5.20 | 20 | 53 |

**3.1.5.2. Design Space versus Proven Acceptable Ranges:**
A combination of proven acceptable ranges did not constitute a design space. Proven acceptable ranges based on multi-variate experimentation provided useful knowledge about the process parameters as represented by white circle encountering “least risky” violet colored portion of VIBGYOR in **Figure 2** representing 3D surface plot. However, “most risky” red colored portion of 3D surface plot indicated risky boundary levels of Critical Process Parameters (CPPs).
Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and initiate a regulatory post approval change process in case of any change in process parameter required after approval from regular authority during commercial manufacturing at larger scale.




(a) For FBP CPPs (b) For Compression CPPs

**Figure 2.** 3D surface plots for Establishment of Design Space with QbD.

Final Equation of design space in terms of coded factor for FBP is:

Average Granule Size = $+373.00+145.00A_1-24.17B_1-17.50A_1B_1+125.00A_1^2+12.50B_1^2$…… **(1)**

| Response For Average Granule Size where $A_1$= Liquid Spraying rate) & $B_1$= Atomizing Air Pressure | | | | | | |
|---|---|---|---|---|---|---|
| ANOVA for Response Surface Quadratic Model [Partial sum of squares- Type III] | | | | | | |
| **Source** | **Sum of squares** | **Degree of Freedom** | **Mean Square** | **F Value** | **p Value Prob>F** | **Model** |
| **Model** | 1.642E+005 | 5 | 32488.33 | 120.58 | 0.0012 | Significant |
| **$A_1$** | 1.261E+005 | 1 | 1.261E+005 | 468.19 | 0.0002 | |
| **$B_1$** | 3504.17 | 1 | 3504.17 | 13.01 | 0.0366 | |
| **$A_1B_1$** | 1225.00 | 1 | 1225.00 | 4.55 | 0.1228 | |
| **$A_1^2$** | 31250.00 | 1 | 31250.00 | 115.98 | 0.0017 | |
| **$B_1^2$** | 312.50 | 1 | 312.50 | 1.16 | 0.3604 | |
| **Residual** | 808.33 | 3 | 268.44 | | | |
| **Core Total** | 1.633E+005 | 8 | | | | |

Final Equation of design space in terms of coded factor for Compression is:

Tablet Hardness = $+61.33 – 6.17A_2 + 1.67B_2+0.25A_2B_20-1.50A_2^2+1.00B_2^2$**…….. (2)**

| Response For Hardness of Compressed Tablet | | | | | | |
|---|---|---|---|---|---|---|
| ANOVA for Response Surface Quadratic Model [Partial sum of squares- Type III] | | | | | | |
| **Source** | **Sum of squares** | **Degree of Freedom** | **Mean Square** | **F Value** | **p Value Prob>F** | **Model** |
| **Model** | 251.58 | 5 | 50.32 | 362.28 | 0.0002 | Significant |
| **$A_2$** | 228.17 | 1 | 228.17 | 1642.80 | <0.0001 | |
| **$B_2$** | 16.57 | 1 | 16.67 | 120.00 | 0.0016 | |
| **$A_2B_2$** | 0.25 | 1 | 0.25 | 1.80 | 0.2722 | |
| **$A_2^2$** | 4.50 | 1 | 4.50 | 32.40 | 0.0107 | |
| **$B_2^2$** | 2.00 | 1 | 2.00 | 14.40 | 0.0321 | |
| **Residual** | 0.42 | 3 | 0.14 | | | |
| **Core Total** | 252.00 | 8 | | | | |

From the equation 1, it could be predicted that spraying rate ($A_1$) has synergistic effect on average granule size, while atomizing air pressure ($B_1$) has antagonistic action on average granulae size. A higher spraying rate resulted in a larger average granule size, while an increase in atomization air pressure resulted in a decrease in average granule size. The F value of 120.58 implies the design space for "FBP" model is significant and there is only a 0.12% chance that "Model F-value" this large could occur due to noise. In this case $A_1$, $B_1$ & $A_1^2$ , having values of "Prob>F" less than 0.05, are significant model terms; while values greater than 0.1 indicate that the model terms are not significant.

From the equation 2, it could be predicted that thickness ($A_2$) has antagonistic effect on tablet hardness, while turret speed ($B_2$) has synergistic action on tablet hardness.The F value of 362.28 implies the design space for "compression" model is significant and there is only a 0.02% chance that "Model F-value" this large could occur due to noise. In this case $A_2$, $B_2$ & $A_2^2$, $B_2^2$, having values of "Prob>F" less than 0.05, are significant model terms; while values greater than 0.1 indicate that the model terms are not significant.

**3.1.5.3. Design Space and Edge of Failure:**

From 2D contour plots of critically analyzed CPPs; proven acceptable ranges having violet color in VIBGYOR and edges of failure having red color in VIBGYOR could be clearly defined as revealed with defined margins in contour plots of **Figure 3.**

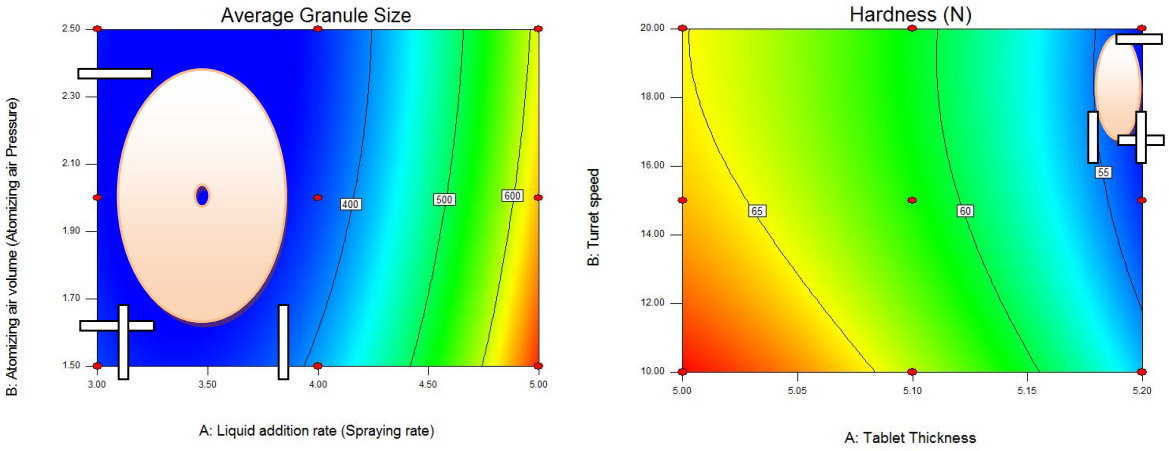


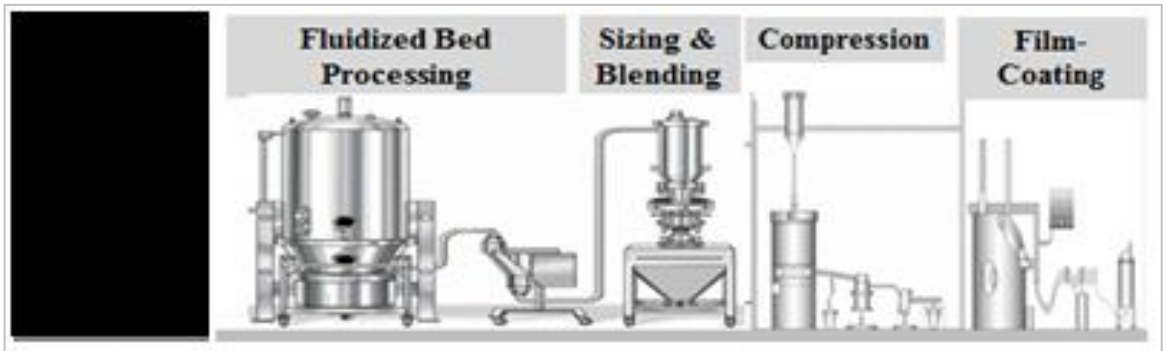

**Figure 3**: Design Space & Edge of Failure: (a) for FBP (b) for Compression

**3.1.6. OUTLINE OF CONTROL STRATEGY (CS)**

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 quality were identified, appropriately understood and subsequently controlled. Understanding sources of variability and their impact on downstream processes or

processing, in-process materials and drug product quality provided an opportunity to shift controls upstream and minimized the need for end product testing.
A final control strategy included the following as pointed out in **Figure 4**:

1. Control of input material attributes (e.g. drug substance, excipients, primary packaging materials) based on an understanding of their impact on process ability or product quality;
2. Product specification(s);
3. Controls for unit operations that have an impact on downstream processing or product quality (e.g. the impact of drying on degradation, particle size distribution of the granulate on dissolution);
4. In-process or real-time release testing in lieu of end-product testing (e.g. measurement and control of CQAs during processing);
5. monitoring program (e.g. full product testing at regular intervals) for verifying multivariate prediction models




| Unit Operations | FBP | Sizing & Blending | Compression | Film-Coating |
|---|---|---|---|---|
| CQAs of input materials (API & Excipients) | API: PVP ratio; API & PVP solubility, stability & purity; ethanol purity | Level of Magnesium stearate & Pharmatose 200M & DCL11 | API solubility; Level of Magnesium stearate | % of Opadry white per tablet |
| QTPP (Product specification) | Assay: 95 to 105%; Total Impurities: 2.5%; Content Uniformity: AV: NMT 15.0 & RSD: NMT 5.0%; Disintegration time: NMT 15 minutes; Dissolution: NLT 75% of the labeled amount dissolved in 45 minutes. | | | |
| CPPs Controls for unit operation | Spraying rate & Aatomizing air pressure | Screen size & Blender total revolutions | Press speed & Adjusted Thickness | % weight gain during coating |
| In Process or real time release testing | Average Granule size by PSD | Particle size distribution, Blending time & Blending RPM | Uniformity of weight, Tablet Hardness | Tablet Appearance |
| A monitoring program | Assay, Impurities, Disintegration & Dissolution | Content Uniformity & Dissolution | Disintegration & Dissolution | Impurities & Final Description |

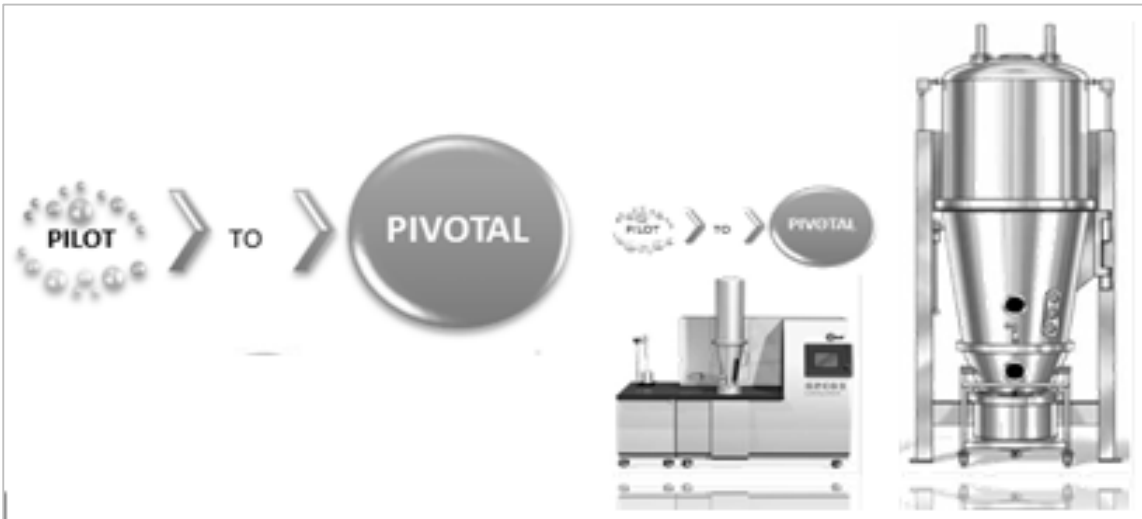
**Figure 4.** Outlined controlled pertinent strategy

### 3.2. Pivotal scale-up considering prior pilot scale QbD

Following section illustrated how a product was scaled up from 5kg to 120kg in equipment supplied by Glatt® when scaling up as revealed with parameters in **Figure 5.**

#### 3.2.1. 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. Though 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.(1) and (2)




| Process Parameters | Glatt GPCG®-2 | Glatt GPCG®-120 |
|---|---|---|
| Batch Size capacity (in Kg) | 2 kg | 120 kg |
| Cross sectional area of the base ($m^2$) | 0.02 | 0.64 |
| Mixing Air Flow (CMH) | 60 | 2000 |
| Spraying Air Flow (CMH) | 80 | 2600 |
| Inlet Air Temperature (°C) | 50 | 50 |
| Outlet Air Temperature (°C) | 40 | 40 |
| Bed Temperature (°C) | 30 | 30 |
| For Scale UP from "Single headed nozzle" to " Single headed nozzle" | | |
| Atomization Spray Rate (gm./min) | 04 | 130 |
| Atomization air pressure (bar) | 02 | 02 |
| For Scale UP from "Single headed nozzle" to " Triple headed nozzle" | | |
| No of Atomizing nozzle | 01 | 03 |
| Atomization Spray Rate (gm./min) | 04*01=04 | 130*03=390 |
| Atomization Air Pressure (bar) | 02*01=02 | 02*03=06 |
| Drying Air Flow (CMH) | 100 | 3200 |

**Figure 5.** FBP Parameters from small scale to large scale

**Smin = [V x 0.3 x BD] = [500 x 0.3 x 0.4] = 60 kg……..…….. (1)**
**Smax = [V x 0.7 x BD] = [500 x 0.7 x 0.4] = 140 kg ……..……. (2)**

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 gm/cc;
0.3= Minimum occupancy of 30% in product bowl
0.7= Maximum occupancy of 70% in product bowl

**3.2.2.Fludization 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$m^2$ and the smaller was 0.02 $m^2$. Thus, correct air flow was calculated as per equation no. (3)

**$AF_2$ = [$AF_1$ x ($A_2$/$A_1$)] = [80 x (0.64/0.02)] = 2560 CMH ~ 2600 CMH ……..… (3)**

Where; $AF_1$ is Fluidization air flow in the laboratory scale equipment,
$AF_2$ Fluidization air flow in the scaled-up equipment,
$A_1$ is cross-sectional area of the laboratory scale equipment,
$A_2$ is cross-sectional area of the scaled up equipment.

**3.2.3. 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 (4).

**$SR_2$ = [$SR_1$ x ($A_2$/$A_1$)] = [4 x (0.64/0.02)] = 128gm/min ~ 130 gm/min.....(4)**

Where; $SR_1$ is spray rate in the laboratory scale equipment,
$SR_2$ is spray rate in the scaled-up equipment,
$A_1$ is cross-sectional area of the laboratory scale equipment,
$A_2$ 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 mean granule size of 400um 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 **130* (3) = 390~400 grams per minute** (where 3 indicates number of nozzle heads) keeping the same droplet size and hence obtaining granulation with desired characteristics as final In Process Critical Quality Attributes (IP CQAs) and Finished Drug Product Critical Quality Attributes (DP CQAs) for larger scale batch as reveled in Table 6.

**Table 6.** In Process & Finished Drug Product Results for Laboratory batch & Scaled-up batch of optimized formulation as per QTPP

| **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%<br>Min: 96.6%<br>Max: 102.2%<br>RSD: 1.5% | Man: 101.5%<br>Min: 97.1%<br>Max: 104.2%<br>RSD: 1.6 |
| Average Granule size | D50:360 um | D50: 380 um |
| Bulk Density | 0.45 gm/cc | 0.47 gm/cc |
| Tapped Density | 0.54 gm/cc | 0.55 gm/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% |

| **DP CQAs** | **Laboratory Batch Results** | **Scaled up Batch Results** |
|---|---|---|
| Appearance | White to off white, oval shaped, coated tablets having embossed with "C" & "P" on one side with break line on both side. | White to off white, oval shaped, coated tablets having embossed with "C" & "P" on one side with break line on both side. |
| Assay | 99.2% | 99.7% |
| Impurities (Related Substances) | Impurity A: 0.31%<br>Impurity B: 0.22%<br>Any Other Impurity:0.20%<br>Total impurities:0.72% | Impurity A: 0.55%<br>Impurity B: 0.82%<br>Any Other Impurity:0.35%<br>Total impurities:1.72% |
| Content Uniformity (n=20) | Mean: 99.4%<br>Min: 96.9%<br>Max: 102.7%<br>RSD: 1.4% | Mean: 100.9%<br>Min: 97.7%%<br>Max: 103.8%%<br>RSD: 1.5% |
| Disintegration (n=6) | 10 minutes | 10 minutes |
| Dissolution (n=12) | 98% | 99% |

## 4.0. Conclusion

With proper selection of equipment design, operating conditions and suitable quality excipients, it has been shown that SD-FBP technology can be scaled-up from the laboratory to commercial production. When a formulation and process were optimally developed with critical risk analysis of all CQAs & CPPs in fluid-bed technology by QbD, prepared granules ultimately imparted superb quality to the end product.

From exhaustive FMEA risk analysis, it was decided that FBP and Compression are the two risky barriers for achieving QTPP in case of formulation of poorly soluble & highly bio-variable drug LCDP. Thus, detailed study of these two processes was carried out with resulting design space employed with acceptable proven ranges & predefined edge of failures for respected CPPs (i.e. Liquid spraying rate & Atomizing air pressure in case of Fluidized Bed Granulation and Turret speed & Tablet thickness in case of compression stage) related to IP/DP CQAs (Average Granule Size for Fluidized Bed Granulation & Tablet Hardness in case of Compression). Concerning statistical analysis, it was revealed that $3^2$ Full Factorial Experimental Design (FFED) and optimization technique can be successfully used in the development of robust process of SD-FBP technology for predicated QTPP achievement. Performance of Fluidized Bed Process could be monitored to ensure that it is working as anticipated to deliver product quality attributes as predicted by the design space. This monitoring could include trend analysis of the manufacturing process as additional experience gained during routine manufacture. For certain design spaces using mathematical models, periodic maintenance could be useful to ensure the model's performance. The model maintenance was an example of activity that can be managed within an internal quality system provided the design space is unchanged. Thus, understanding sources of variability and their impact on downstream processes or processing and finished product quality during pilot scale development stage could provide flexibility for shifting of controls upstream at pivotal scale manufacturing stage and minimize the need for end-product testing and maximize the probability of effectiveness at larger scale.

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