International Journal of Research and Development in Pharmacy and Life Sciences
Available online at http//www.ijrdpl.com
June -July, 2012, Vol. 1, No.2, pp.72-89
ISSN: 2278-0238

Research Article

FUNCTIONALITY ADVANCEMENT OF POORLY SOLUBLE BIOVARIABLE ANTI HYPERTENSIVE DRUG BY SOPHISTICATED SD-FBP TECHNOLOGY AS PER ENHANCED QbD

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(Received: April 29, 2012; **Accepted:**May18, 2012**)**

ABSTRACT

Lacidipine (LCDP) is a dihydropyridine derivative categorized as an Anti-hypertensive Ca^{+2} channel blocker belonging to BCS class IV drug with low solubility and low permeability which presents a challenge to the formulation scientists. The development of a solid dispersion by solvent evaporation is a practically viable method to enhance dissolution of LCDP from oral dosage form. Solvent evaporation by Fluidized Bed Process (FBP) was the method of choice for SD as it improves wettability with simultaneous increase in porosity of granules resulting enhanced surface area producing higher dissolution rate and bioavailability of poorly water-soluble drug. Thus, the main object of the present invention is to provide stable pharmaceutical dosage form of LCDP with desired dissolution rate i.e. at least 80% drug release within 45 minutes, without use of disintegrant(s) and/or surfactant(s) or without micronization of the active ingredient *per se*. One more object of this invention 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 manufactured along with a knowledge of the risks involved in manufacturing by IRMA & FMEA study of the product with process and how best to mitigate those risks by developing design space with DoE & MVDA with outlined control strategy.

Keywords: Lacidipine (LCDP), Solid Dispersion (SD), Fluidized Bed Process (FBP), Critical Quality Attribute (CQA), CPP (Critical Process Parameter), Failure Mode Effective Analysis (FMEA), Design of Experiment (DoE), Quality by Design (QbD).

INTRODUCTION

Lacidipine (LCDP) is chemically a "1, 4 - Dihydropyridine derivative", which is pharmacologically a "Calcium channel blocker" used as an anti-hypertensive drug. LCDP works by blocking 'calcium channels' in the muscle cells those are found in the arterial walls. Calcium is needed by muscle cells in order for them to contract; so by depriving them of calcium, LCDP causes the muscle cells to relax. Relaxing and widening of the small arteries decreases the resistance that the heart has to push against in order to pump the blood around the body, which reduces the pressure within the blood vessels[1]. LCDP is completely absorbed from the GIT providing its complete dissolution[2]. But the quandary is that LCDP is a Bio-pharmaceutics (BCS) class IV drug with low solubility and low permeability[3]. The formulation of poorly soluble drugs for oral delivery presents a challenge to the formulation scientists. When an active agent is administered orally, it must first dissolve in gastric and/or intestinal fluids before it permeate the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. In case of poorly water soluble drugs, dissolution may be the rate-limiting step in the process of drug absorption. Drug with poor water -

solubility have been shown to be unpredictably and slowly absorbed compared with drugs of higher solubility[4].Among the relevant prior arts in this field, WO1995/08987 discloses compositions comprising one or more 1, 4 dihydropyridine derivatives; a carrier such as water-soluble derivatives of saccharides; a "disintegrant" selected from polacrilin potassium, sodium starch glycolate and/or cross-linked carboxy methylcellulose and "surfactant" selected from sodium lauryl sulfate, poloxamers and/or higher fatty acidspolyoxyethylenesorbitan ester[5]. Whereas, WO2006/113309 discloses the preparation of agglomerated particles of LCDP having smaller particle size[6].All the above mentioned prior art disclosed pharmaceutical composition comprising of lacidipine by using surfactant(s) and/or disintegrant(s) or micronized lacidipine. Thus, it would be significant improvement in the art to provide pharmaceutical dosage form of lacidipine without the use of surfactant(s) and/or disintegrant(s) or without micronization of Lacidipine*per se*. The development of solid dispersion is a practically viable method to enhance bioavailability of poorly water-soluble-size reduction. In case of solid dispersion, drug is dispersed in the hydrophilic matrix with enhanced wettability & porosity[7]. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs[8-10].The main object of the present invention is to provide pharmaceutical dosage form of lacidipine with desired dissolution rate (at least 80% drug release within 45 minutes), without the use of disintegrant(s) and/or surfactant(s) or without micronization of the active ingredient *per se*. Another object of this invention is to provide a sophisticated robust process for the preparation of said pharmaceutical dosage form with Quality by Design (QbD) concept focusing on thorough understanding of the product and process by which it is developed and manufactured along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks related to product quality and/or performance.

MATERIALS & METHODS

Materials

Intragranular Ingredients [Manufacturer/supplier]	Application
Lacidipine BP [Cadila Pharmaceuticals limited, India]	Active Pharmaceutical Ingredient (API)
Plasdone® K29/32 (Polyvinyl Pyrrolidone) [ISP Technologies,]	Carrier cum Binder
Pharmatose® 200M (Lactose Monohydrate) [DMV International]	Diluent cum substrate
Absolute Alcohol (Ethanol 99.6%v/v) [CVKUSML, India]	Solvent cum Granulating Agent
Extragranular Ingredients	
Pharmatose® DCL11 (Lactose Spray Dried) [DMV International]	Diluent cum flow promoter cum disintegrant
Magnesium Stearate (Vegetable grade) [Ferro Synpro]	Lubricant
Film Coating	
Opadry White (A premix powder of Hydroxy Propyl Methyl Cellulose (HPMC) Polyethylene glycol & Titanium Dioxide (TiO_2)) [Colorcon Asia limited]	HPMC as a film forming agent& TiO_2 as a opacifying agent

Experimental Methods

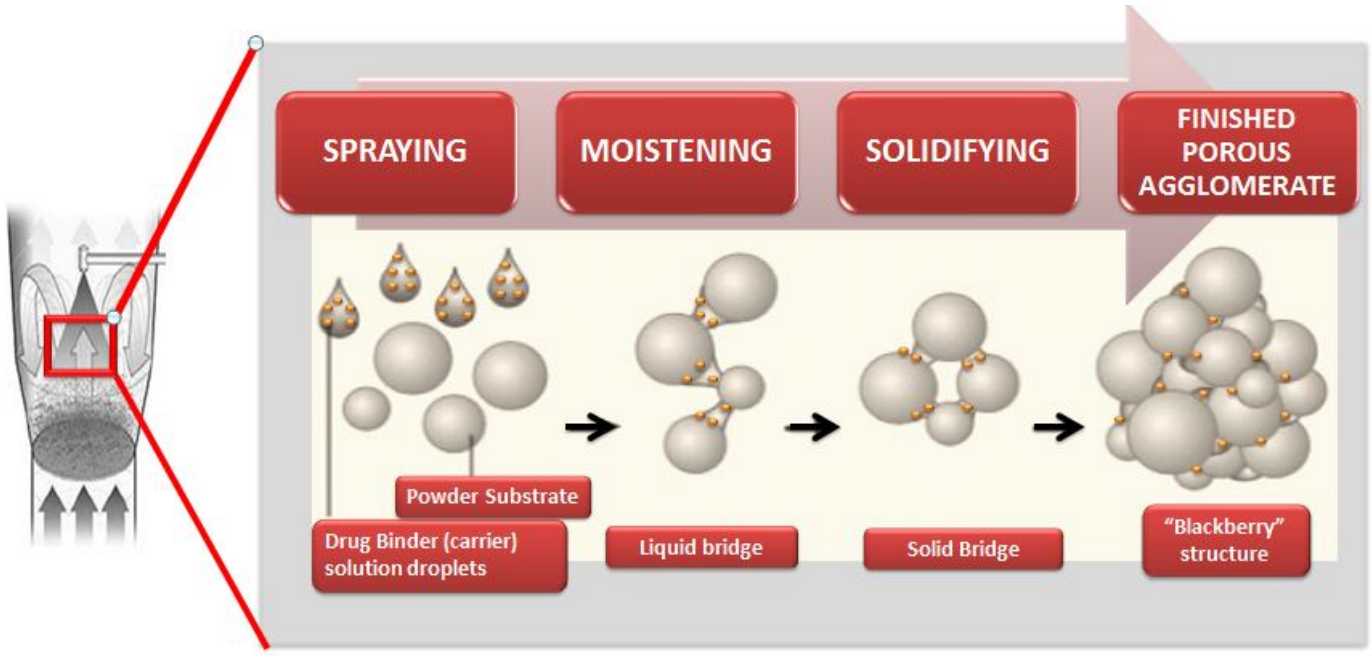


Figure 1 Schematic representation of SD-FBP Technology

Formulation development (Solid Dispersion)

The term Solid Dispersion (SD) is defined as "the dispersion of one or more active ingredients in an inert carrier or matrix (hydrophilic) at solid state, prepared by the melting (fusion), solvent evaporation or melting-solvent method". Solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. Among all methods, solvent evaporation by Fluidized Bed Process (FBP) was the method of choice for SD as it improves wettability with simultaneous increase in porosity of granules. Because of the simplicity of manufacturing and scale up processes, the popularity of the solid dispersion systems to solve difficult bioavailability issues with respect to poorly water-soluble drugs will grow rapidly. Moreover it also decreases the crystalline structure of drug & promotes its conversion in to more soluble amorphous form[11]. The first step in this method includes the formation of clear solution containing mixture of the drug i.e. LCDP and carrier i.e. Poly Vinyl Pyrrolidone (PVP), dissolved in a common solvent and second step involves the removal of solvent resulting the formation of solid dispersion. This enables to produce a solid solution of the drug in the highly water soluble carrier. Selection of carrier for SD matrix & common solvent for drug & carrier were two challenges in front of formulators. In this solvent-based spray drying process, PVP was selected as a carrier for SD, as it forms homogenous glass solution, a glassy system in which a solute dissolves in a glassy solvent. The glassy or vitreous state is usually obtained by an abrupt quenching of melt, which is characterized by transparency & brittleness below the glass transition temperature Tg. i.e. a function of homogenously mixed SD composition[12]. The next challenge was to mix both drug & carrier in one common solvent, which is difficult when they differ in polarity. Use of water to dissolve both drug & carrier requires evaporation of tremendous amounts of solvent during Fluidized Bed Process; making the process expensive, time consuming & impractical. Chloroform[13] (Betageri&Makarla, 1995) & Dichloromethane[14] (Damian et al. 2002) may be used to dissolve both drug & carrier PVP simultaneously, but according to ICH guidelines (Q3C)[15], these are classified under class I (most toxic) solvents. Therefore, use of these solvents is unacceptable & impractical because the amount of residual solvent present in SD after drying has to be below 1500 ppm. Thus, in this study Ethanol (commonly available ICH Class III solvent)[16]was selected as it shows higher solubility of drug as well as carrier for solid dispersion.

Table 1 Compression parameters

No	Compression parameters	In House Specification Limits
1	Target Weight.	300 mg
2	Thickness	5.1 mm ± 0.1 mm (5.0 mm to 5.2 mm)
3	Hardness	40 to 80 Newton
4	Friability	Not more than 0.5 % w/w
5	Disintegration Time	Not more than 15 minutes

For drug: carrier solution preparation; LCDP was 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 and stirring was continued until a clear yellow colored solution was obtained. To carry out solvent evaporation method, fluidized bed processor (Pam-Glatt®) was utilized. In 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 represented in Figure 1. Inlet, Product & outlet temperatures was set at 55±10°C, 35±10°C & 30±10°C respectively; whileFilm Coating was carried out for protection of core from heat, light & moisture. For film-coating,Opadry® White was added in purified water with continuously stirring for 45 minutes until a uniform suspension is formed. Coating was carried out with this suspension in 24" Auto coater (Ganscoater®) at parameters mentioned in Table 2 until desired weight gain was achieved.

In formulation optimization study, first LCDP to PVP ratio was optimized for SD depending upon desired solubility & dissolution profile as mentioned in formulation No. F**1** to F**6** i.e. from 1:4 to 1:14. Intra granular lactose (Pharmatose® 200M) functions as a diluent, while extra granular lactose (Pharmatose® DCL 11) promotes disintegration by wicking mechanism[17]. Thus, ratio of intra granular lactose & extra granular lactose was optimized to attain desired disintegration & corresponding dissolution profile as mentioned in formulation No. F**7** to F**9**. This formulation was sticky in its physical nature due to higher proportion of PVP, thus level of lubricant in formulation was optimized depending upon desired flow property which would not affect desired dissolution profile as mentioned in Formulation No. F**10** to F**12**. Film coating was required to protect core tablet from direct exposure of temperature, light & moisture. Finally, essential %weight gain per tablet was optimized as per optimum film strength without affecting desired dissolution profile as mentioned in Formulation No. F**13** to F**15**. All formulations optimization are summarized in **Table 3**.Peristaltic pump RPM, spray rate and atomization air pressure were recorded intermittently in every 10 minutes.After completion of Granulation, Fluidized bed drying wasperformed in the same FBP at inlet temperature of 40° to 55°C, until desired LOD i.e1.5 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 embossed with "C" & "P" on each side of break line with below mentioned parameters in Table 1 in 16 station compression machine (RIMEK®), India

Table 2 Film Coating Parameters

No.	Coating Parameters	In House Specification Limits
1	Inlet temp	55 ± 10°C
2	Outlet temp	50 ± 10°C
3	Bed temperature	40± 5°C
4	Pan Speed	2-8 RPM
5	Peristaltic pump speed	2-10 RPM
6	Compressed air pressure	2 – 3 kg /cm^2

Table 3A. Drug : Carrier ratiooptimization for LCDP formulation

	F1	F2	F3	F4	F5	F6
Drug : Carrier Ratio	**1:04**	**1:06**	**1:08**	**1:10**	**1:12**	**1:14**
Intragranular (IG)						
Lacidipine	4	4	4	4	4	4
Plasdone K29/32	16	24	32	40	48	56
Pharmatose 200M	280	272	264	256	248	240
Unit Weight of core tablet (in mg.)	**300**	**300**	**300**	**300**	**300**	**300**

Table 3B. Intra to Extra-granular Lactose ratiooptimization for LCDP formulation

	F7	F8	F9
Drug : Carrier Ratio	**1:10**	**1:10**	**1:10**
Optimization of Intra to Extragranular Lactose ratio	**(90:10)**	**(80:20)**	**(70:30)**
Intragranular (IG)			
Lacidipine	4	4	4
Plasdone K29/32	40	40	40
Pharmatose 200M	230.4	204.8	179.2
Extragranular (EG)			
Pharmatose DCL11	25.6	51.2	76.8
Unit Weight of core tablet (in mg.)	**300**	**300**	**300**

Table 3C. Lubricant level& % weight gain in coating optimization for LCDP formulation

	F10	F11	F12	F13	F14	F15
Drug : Carrier Ratio	**1:10**	**1:10**	**1:10**	**1:10**	**1:10**	**1:10**
Intragranular to Extragranular Lactose ratio	**(80:20)**	**(80:20)**	**(80:20)**	**(80:20)**	**(80:20)**	**(80:20)**
Optimization of Level of Lubricant	**0.25%**	**0.50%**	**1.00%**	**0.25%**	**0.25%**	**0.25%**
Intragranular (IG)						
Lacidipine	4	4	4	4	4	4
Plasdone K29/32	40	40	40	40	40	40
Pharmatose 200M	204.8	204.8	204.8	204.8	204.8	204.8
Extragranular(EG)						
Pharmatose DCL11	50.45	49.7	48.2	50.45	50.45	50.45
Magnesium Stearate	0.75	1.5	3	0.75	0.75	0.75
Unit Weight of core tablet (in mg.)	**300**	**300**	**300**	**300**	**300**	**300**
%Weight gain in film coating				1%	2%	3%
Unit Weight of coated tablet (in mg.)				**303**	**306**	**309**

Table 4. Definition of QTTP 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 amount dissolved in 45 minutes

Process Optimization (Fluidized Bed Granulation) by QbD

According to ICH Q8 Guideline "Quality cannot be tested into products; quality should be built-in by design". In all cases, the product should be designed to meet patients' needs and the intended product performance. A more systematic enhanced QbD approach to development includes incorporation of prior knowledge, results of studies using design of experiments (ICH Q8)[18], use of quality risk management (ICH Q9)[19] and use of knowledge management (ICH Q10)[20]throughout the lifecycleof 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:

Definition of Quality Target Product Profile (QTPP):First, Quality Target Product Profile (QTPP) 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 4.***Identification of API& Formulation Critical quality Attribute (CQAs):*** Potential drug product CQAs derived from QTPP & prior knowledge were used for product and process development. Thus, CQA of the AP) and Excipients having an impact on product quality were identified and summarized in **Table 5** to study & control those product characteristic

Table 5 Identification of API& Excipient CQAs impact on DP CQAs

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

	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

Quality Risk analysis of CPPs by IRMA & FMEA: 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 as summarized in Table 6A & Failure mode effective analysis as summarized in Table 6B were concisely used to identify and rank parameters with potential to have an impact on 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 mechanistic understanding.

Table 6A. Initial Risk based Matrix Analysis for CPPs (IRMA)

	UNIT OPERATIONS RELATING TO CPPS				
DP CQAs	**FB Process**	**Sizing**	**Blending**	**Compression**	**Film Coating**
Appearance	Low	High	Low	High	High
Assay	High	Low	Low	Low	Low
Impurities	High	Low	Low	Low	High
Content Uniformity	High	High	Low	Low	Low
Disintegration	High	Low	High	High	Low
Dissolution	High	Low	High	High	Low

As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Risk identification addresses the "What might go wrong?" question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process. 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. In some risk management tools, 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. Risk evaluations consider the strength of evidence for all three of the fundamental - questions. In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output. Revealing assumptions and reasonable sources of uncertainty will enhance confidence in this output and/or help identify its limitations. Uncertainty is due to combination of incomplete knowledge about a process and its expected or unexpected variability. Typical sources of uncertainty include gaps in knowledge gaps in pharmaceutical science and process understanding, sources of harm (e.g., failure modes of a process, sources of variability), and probability of detection of problems. The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of a range of risk. When risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as "high", "medium", or "low", which should be defined in as much detail as possible. Sometimes a "risk score" is used to further define descriptors in risk ranking. In quantitative risk assessments, a risk estimate provides the likelihood of a specific consequence, given a set of risk-generating circumstances. Thus, quantitative risk estimation is useful for one particular consequence at a time.

Table 6B. Failure Mode Effective Analysis (FMEA)

Unit Operations	Critical Process Parameter (CPPs)	Critical Event	Effect on 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/ Product/ Exhaust Temperature	Higher rate of degradation = Assay & Impurity profile affected	03	02	01	06
	Spraying rate	Higher Rate	Larger granules = Disintegration & Dissolution affected	03	03	03	27
	Atomizing air pressure	Lower Pressure	Uneven distribution of Drug binder solution = Content Uniformity affected	02	02	02	08
Total RPN for FBP							**41**
Sizing	Sifting	Increase in Sieve No.	Larger granules = Dissolution affected Uneven PSD = Content Uniformity affected	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

Selection of appropriate manufacturing process 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. morethan10. 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.

Table 7. Design of Experiments (DoEs) &Multi-Variate Data Analysis (MVDA)

(a) For Fluidized Bed Process (b) for compression.

(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) 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

Outline of pertinent control strategy: Finally pertinent Control Strategies were outlined for ensuring consistent final product quality & process robustness i.e. ability of process to tolerate variability of materials and changes of the process and equipment without any negative impact on product quality.

Packaging Materialistic Study with Accelerated Stability

Optimized formulation prepared by optimized process having desired QTPP was packed in two different types of packaging material 1) HDPE (High Density Poly Ethylene) bottle with child resistant closure containing cotton and silica gel 2) ALU-ALU 10's Blister; Final packed tablets were charged at different storage condition of Temperature (°c) and Relative humidity (%RH) for long term (real time), Intermediate and Accelerated stability testing. Stability samples on pre-decided time points were withdrawn from stability chamber and analyzed for Assay, Related substances, Disintegration & Dissolution by methods specified in British Pharmacopoeia.

RESULTS & DISCUSSION

Formulation Optimization with desired disintegration & dissolution profile

Table 8A. Drug: carrier ratio optimization inLCDP Formulation

	F1	F2	F3	F4	F5	F6
Drug : Carrier Ratio	**1:04**	**1:06**	**1:08**	**1:10**	**1:12**	**1:14**
Assay	97.1	97.4	98.6	99.2	99.2	99.2
Related Substances (Impurities)						
Impurity A	0.31	0.30	0.30	0.31	0.31	0.31
Impurity B	0.22	0.22	0.20	0.22	0.22	0.21
Unknown Max	0.23	0.23	0.23	0.20	0.20	0.19
Total Impurities	0.76	0.75	0.73	0.72	0.72	0.70
Disintgration Time						
N=6 (Min:Sec)	30:00	23:10	17:50	12:00	11:30	11:10
Dissolution Profile (N=12) in BP official media						
10 min	29	33	39	40	42	46
15 min	31	49	56	65	66	68
20 min	42	58	67	76	78	80
30 min	56	71	87	95	96	99
45 min	71	85	93	99	99	100
60 min	94	96	99	100	100	101

Table 8B. Intra to Extra-granular Lactose ratio optimization inLCDP Formulation

	F7	F8	F9
Drug : Carrier Ratio	**1:10**	**1:10**	**1:10**
Optimization of Intragranular to Extragranular Lactose	**(90:10)**	**(80:20)**	**(70:30)**
Assay	99.2	99.2	98.8
Related Substances (Impurities)			
Impurity A	0.30	0.31	0.31
Impurity B	0.20	0.22	0.27
Unknown Max	0.18	0.20	0.22
Total Impurities	0.70	0.72	0.90
Disintgration Time			
N=6 (Min:Sec)	12:10	9:40	8:20
Dissolution Profile (N=12) in BP official media			
10 min	39	41	44
15 min	62	66	68
20 min	73	76	77
30 min	93	96	98
45 min	96	98	100
60 min	99	101	100

Table 8C. Lubricant level optimization inLCDP Formulation

	F10	F11	F12
Drug : Carrier Ratio	**1:10**	**1:10**	**1:10**
Intragranular to Extragranular Lactose	**(80:20)**	**(80:20)**	**(80:20)**
Optimization Level of Lubricant	**0.25%**	**0.50%**	**1.00%**
Assay	99.2	99.2	99.2
Related Substances (Impurities)			
Impurity A	0.31	0.32	0.34
Impurity B	0.22	0.23	0.25
Unknown Max	0.20	0.2	0.19
Total Impurities	0.72	0.75	0.78
Disintgration Time			
N=6 (Min:Sec)	9:50	11:10	12:40
Dissolution Profile (N=12) in BP official media			
10 min	40	38	35
15 min	65	62	60
20 min	75	71	71
30 min	95	94	91
45 min	98	96	93
60 min	100	99	97

Table 8D. Optimization of %Weight gain in coating inLCDP Formulation

	F13	F14	F15
Drug : Carrier Ratio	1:10	1:10	1:10
Intragranular to Extragranular Lactose	(80:20)	(80:20)	(80:20)
Level of Lubricant	0.25%	0.25%	0.25%
Optimization of %Weight gain in coating	1%	2%	3%
Assay	99.2	99.2	99.1
Related Substances (Impurities)			
Impurity A	0.30	0.31	0.3
Impurity B	0.20	0.22	0.2
Unknown Max	0.20	0.20	0.2
Total Impurities	0.70	0.72	0.8
Disintgration Time			
N=6 (Min:Sec)	10:10	10:20	11:10
Dissolution Profile (N=12) in BP official media			
10 min	40	41	36
15 min	68	66	61
20 min	76	75	72
30 min	97	96	91
45 min	99	98	95
60 min	99	100	98

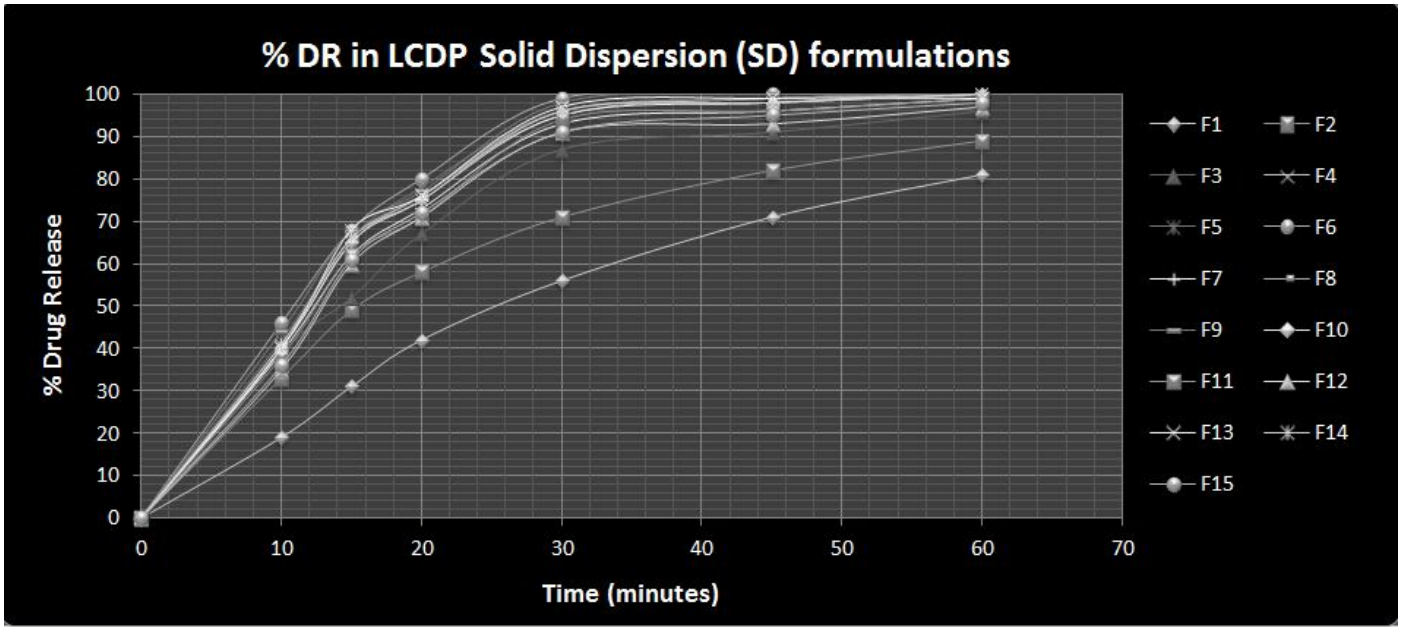


Figure 2. Dissolution Profiling of LCDP Formulations

In accordance with; optimized formulation with desired disintegration & dissolution rate comprises of LCDP, carrier, diluent and lubricant; wherein the weight ratio of LCDP to carrier is 1:10 (as shown in Formulation F4 out of Formulation F1 to F6) in Table 8A, with specific intra-granular lactose to extra-granular lactose ratio of 80:20 (as shown in Formulation F8 out of Formulation F7 to F9) in Table 8B& magnesium stearate (0.25%, as shown in Formulation F10 out of Formulation F9 to F11)in Table 8C with optimized weight gain of 2% in coating (as shown in Formulation F14 out of Formulation F13 to F15) in Table 8D; formulation No. F14 is the optimized final formulation in terms of QTPP.Dissolution profiling of individual formulation i.e. from batch no F1 to F15 was represented graphically in **figure 2.**

Process Optimization with QbD by DoE & MVAEstablishment of Design Space (DS) The relationship etween the process inputs (material attributes and process parameters) and the critical quality attributes were described in the design space.

When describing a design space, the applicant should consider the type of operational flexibility desired. A design space can be developed at any scale. The applicant should justify the relevance of a design space developed at small or pilot scale to the proposed production scale manufacturing process and discuss the potential risks in the scale-up operation. The risk assessment and process development experiments described in section 2.2 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. 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 violet colored portion of VIBGYOR in **Figure3** representing 3D surface plot. However, red colored portion indicates risky boundary level of CPPs. Working within the design space is not considered as a change.

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

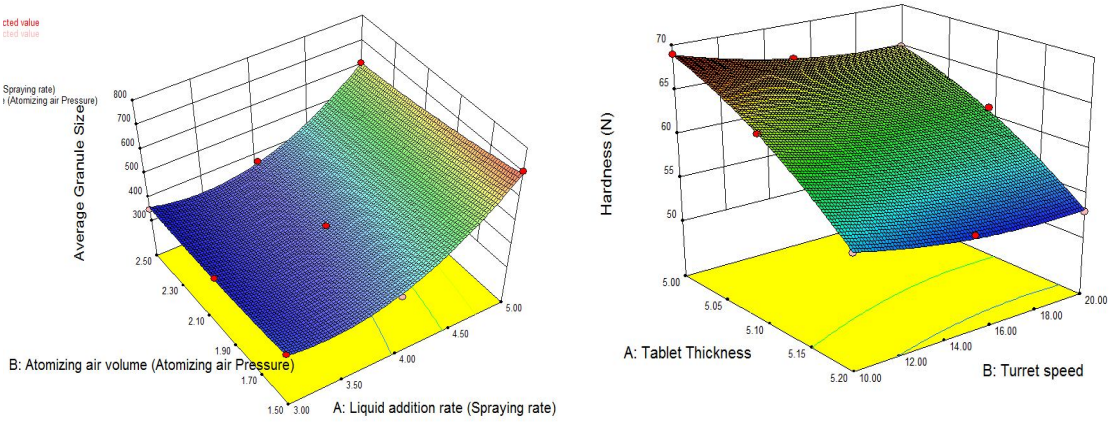


Figure 3. 3D surface plots for Establishment of Design Space with QbD.

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**1**B**1**+125.00A**1**^{2}+12.50B**1**^{2}**(1)**

Response 1 Hardness (N)

ANOVA for Response Surface Quadratic Model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	251.58	5	50.32	362.28	0.0002	significant
A-Tablet Thi	*228.17*	*1*	*228.17*	*1642.80*	*< 0.0001*	
B-Turret spe	*16.67*	*1*	*16.67*	*120.00*	*0.0016*	
AB	*0.25*	*1*	*0.25*	*1.80*	*0.2722*	
A²	*4.50*	*1*	*4.50*	*32.40*	*0.0107*	
B²	*2.00*	*1*	*2.00*	*14.40*	*0.0321*	
Residual	0.42	3	0.14			
Cor Total	252.00	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**2**B**2**0-1.50A**2**^{2}+1.00B**2**^{2}..... ..... **(2)**

Response 1 Average Granule Size

ANOVA for Response Surface Quadratic Model

Analysis of variance table [Partial sum of squares - Type III]

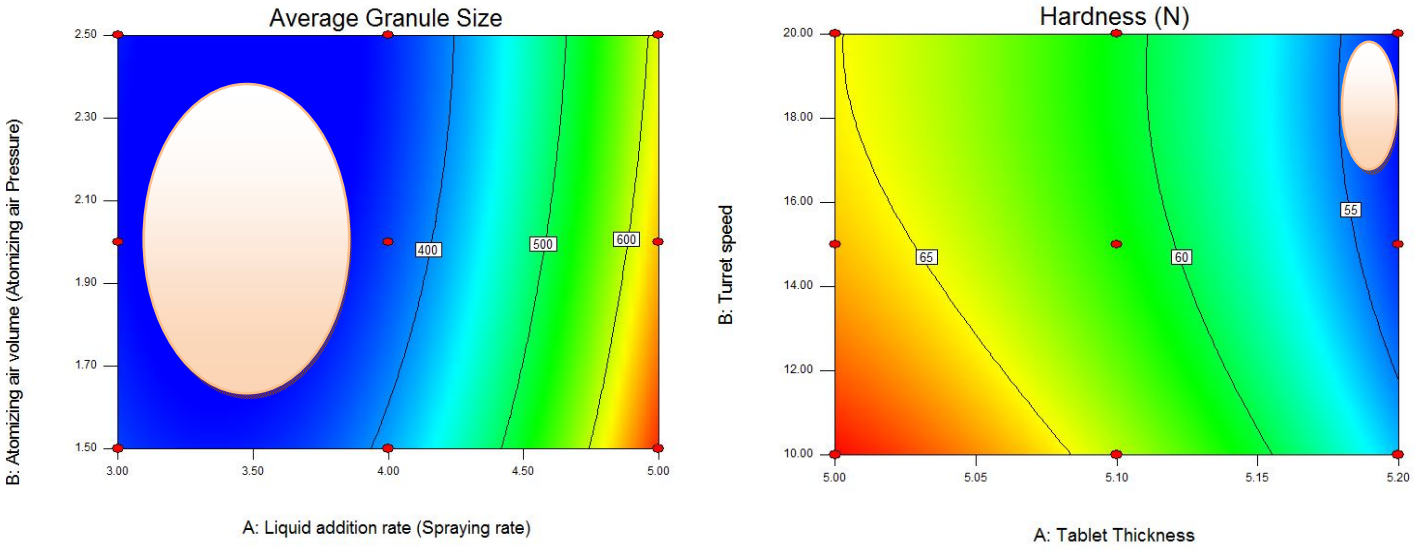
Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	1.624E+005	5	32488.33	120.58	0.0012	significant
A-Spraying ra	*1.261E+005*	*1*	*1.261E+005*	*468.19*	*0.0002*	
B-Atomizing	*3504.17*	*1*	*3504.17*	*13.01*	*0.0366*	
AB	*1225.00*	*1*	*1225.00*	*4.55*	*0.1228*	
A²	*31250.00*	*1*	*31250.00*	*115.98*	*0.0017*	
B²	*312.50*	*1*	*312.50*	*1.16*	*0.3604*	
Residual	808.33	3	269.44			
Cor Total	1.633E+005	8				

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 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 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. 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.

Design Space and Edge of Failure:

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 4 representing 3D surface plot. However, "most risky" red colored portion of 3D surface plot indicated risky boundary levels of 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.

Figure 4: Design Space & Edge of Failure: (a) for FBP (b) for Compression



Outline of Control Strategy (CS)

A control strategy was designed to ensure that a product of required quality will be produced consistently. 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), container closure system and drug products 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 5**:

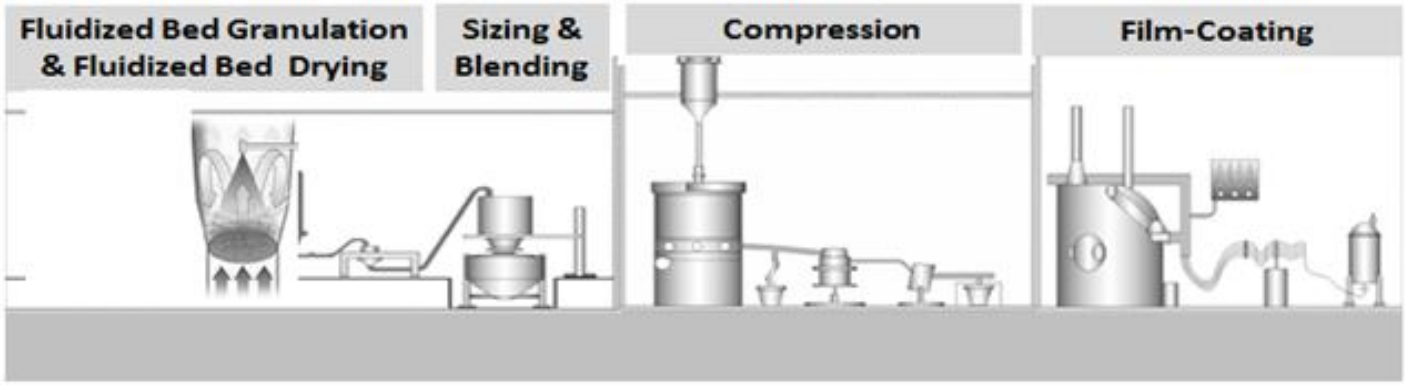
1. Control of input material attributes (e.g. drug substance, excipients, primary packaging materials) based on an understanding of their impact on process ability or product quality;

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. A 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 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 & atomizing 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 5 Outlined controlled pertinent strategy

A control strategy can include different elements. For example, one element of the control strategy could rely on end-product testing, whereas another could depend on real-time release testing. The rationale for using these alternative approaches should be described in the submission.

Adoption of the principles in this guideline can support the justification of alternative approaches to the setting of specification attributes and acceptance criteria as described in Q6A and Q6B guidelines by international control of harmonization.

Packaging Material vs. Stability profile

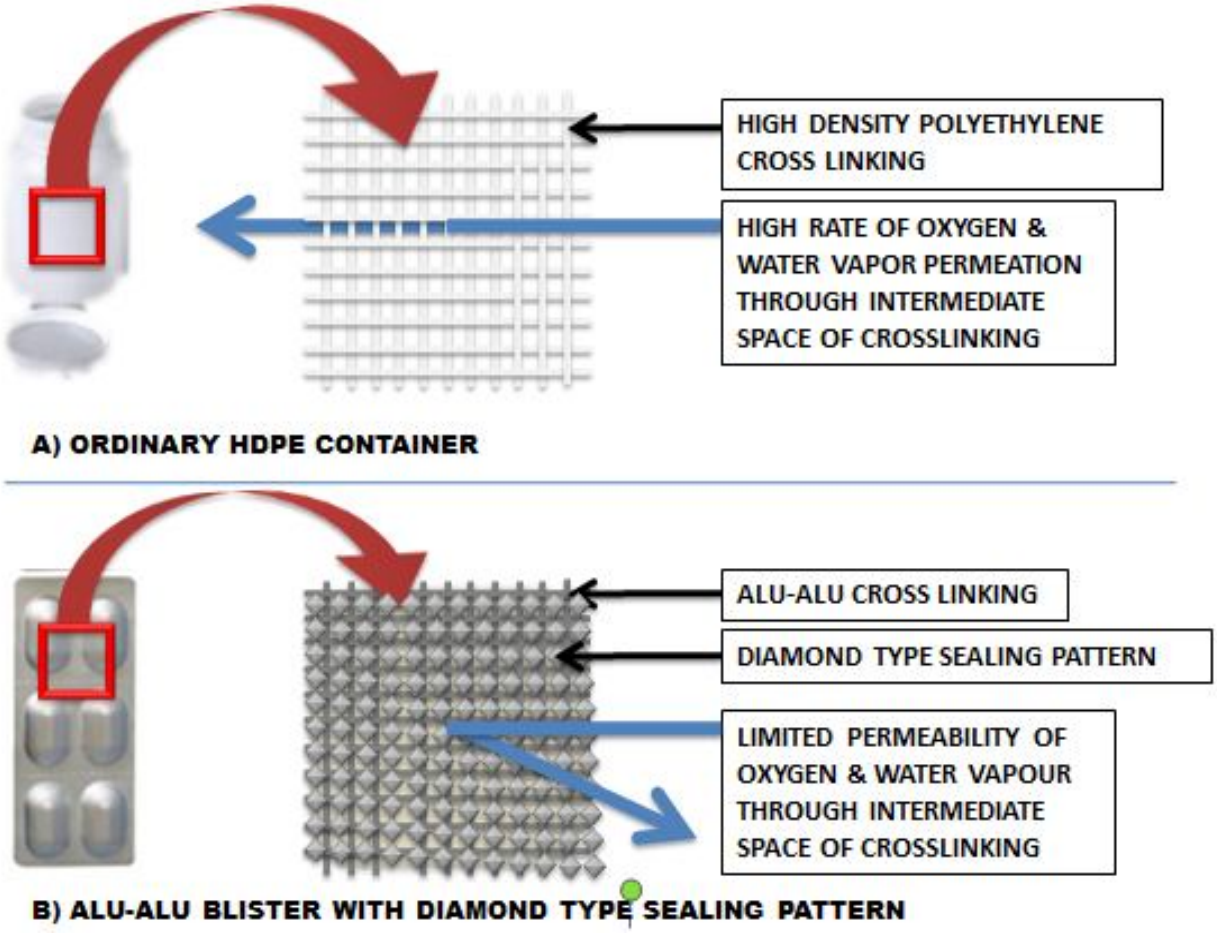


Figure 6. Schematic representation of Packaging materialistic study

Optimized formulation showed very good accelerated stability as shown in Table 10, in fompackedAlu-Alu blister (cold formed foil: made up of 25 micron OPA(Oriented Poly Amide) Film /Adhesive/45 micron Aluminium foil/ Adhesive/60 micron PVC (Poly Vinyl Chloride) with diamond type sealing pattern film having least void space) that resist moisture, temperature, oxidation & all kinds of gases; as compared to HDPE container (having higher void space and higher permeability as compared to Alu-Alu Blister) as represented in Figure 6.

Table 10. Stability evaluation of LacidipineTablets, 4mg for 3 months,packed in HDPE (High density poly ethylene) container with CRC (Child resistant container) closure as well as Alu-Alu 10's blister. Shaded area indicates failing in physicochemical evaluation.

Storage Conditions / Parameters	Initial	25°±2°C /60±5%RH		30°±2°C/65±5%RH		40°±2°C /75±5%RH	
		HDPE	Alu-Alu	HDPE	Alu-Alu	HDPE	Alu-Alu
Total Impurities	0.72%	0.85	0.80	1.10	0.96	1.94	1.72
Assay	100%	99.10	99.20	98.6	98.9	94.6	98.2
Disintegration	10 min	10 min	10 min	11 min	10 min	12 min	10 min
Dissolution profile in 45 min	99%	98%	99%	96%	98%	91%	98%

CONCLUSION

From results, it can be concluded that optimized solid oral pharmaceutical composition with desired disintegration & dissolution rate comprises of lacidipine, carrier, diluent and lubricant wherein the weight ratio of lacidipine to carrier is 1:10, with specific intra-granular lactose to extra-granularlactose ratio of 80:20 & magnesium Stearate (0.25%); without size reduction and without use of any surfactant(s) and/or disintegrant(s). All formulation optimizations with respect to QTPP were represented in Table 9. Out of all formulations, formulation no. F**14** is the optimized final formulation in terms of QTPP. Optimized formulation showed very good accelerated stability in fom-packed Alu-Alu Blister as compared to HDPE container.

Process performance can 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 is 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 is an example of activity that can be managed within an internal quality system provided the design space is unchanged. Expansion, reduction or redefinition of the design space could be desired upon gaining additional process knowledge. Thus, understanding sources of variability and their impact on downstream processes or processing, intermediate products and finished product quality can provide flexibility for shifting of controls upstream and minimize the need for end-product testing.

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