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Review on Scale Up and Process Validation of Lacidipine Tablets

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ABSTRACT

Objective: The objective of this protocol is to define the procedure for process validation and to establish documented evidence that the manufacturing process is in state of control. Review the definition and types of validation. Understand the requirements for documentation and key stages in process validation. It is essential part of GMP. Definition of desirable attributes of the drug product. Determination of the controls or testing parameters that will be measured or tested.

Method: Concurrently 3 batches were taken and all critical parameters evaluated for fixing optimum process parameters for process validation.

Results: The risk assessment was done for each step, and the critical parameters were validated. All the tests was found to be within the limits, and validated. Physicochemical parameter of tablets compressed with granules obtained at final impeller amperage of 11.5 to 12.5 amps, which comply with specification. The parameters in granulation stage are suggested for binder addition time, kneading time and discharge time. In the coating process all the parameters in critical steps were found within the specified limits. The sieve analysis was done for all the three batches. The sieve used and % retains are found to be within the specified limits. In the hopper study, all the parameters were found to be within the specified limits and hence the critical steps were validated. The dissolution studies for all three batches and it complies with the specification.

Conclusion: The manufacturing of three batches of common blend for Lacidipine tablets 6 mg was conducted for a batch size of 94.50 kg (210,000 tablets). The study involved validating the process variables of this transferred product to show that the process is under control. The study includes the validation of critical steps of manufacturing such as blending, drying, granulation, compression and coating. The process validation of Lacidipine tablets showed that there was no significant batch-to-batch variation. Therefore it can be concluded that the process stands validated and the data can be used in regulatory submission for obtaining marketing authorization for the Lacidipine tablets.

Keywords: Process validation, Lacidipine, Parameters, GMP

INTRODUCTION

The basic principle of quality assurance is that a drug should be produced that is fit for its intended use. In order to meet this principle, a good understanding of process and their performance is important. Quality should be built into the manufacturing process. These processes should be controlled in order that the finished product meets all quality specifications [30].

DEFINITION OF VALIDATION

WHO (World Health Organization)

The validation in the same way but elaborates considerably on the concept "Validation studies are essential part of good manufacturing practice and should be conducted in according with predefined protocols [30]. A Written report summarizing results and conclusions should be recorded, prepared and stored. Process and procedures should be established based upon the validation study and undergo periodic revalidation to ensure that they remain capable of

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achieve the intended results [31]. Particular attention should be accorded to the validation of processing, testing and cleaning procedures. Critical process should be validated, prospectively or retrospectively. When any new master formula or method of preparation is adopted, steps should be taken to demonstrate its stability for routine processing [2]. The defined process, using the materials and equipment specified should be shown to yield a product consistently of the required quality [3]. Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and or reproducibility of the process, should be validated [7].

Why to validate the processes?

There are many reasons in addition to the regulatory requirements for validating processes. A manufacturer can assure through careful design of the device and packaging careful design and validation of processes and process controls that there is a high probability that all manufactured units will meet specifications and have uniform quality [11]. The dependence on intensive in-process and finished device testing can be reduced [4]. However, in-process and finished product testing still play an important role in assuring that products meet specifications. A properly validated and controlled process will yield little scrap or rework resulting in increased output. Consistent conformance to specifications is likely to result in fewer complaints and recalls. Also whenever needed the validation file will contain data to support improvements in the process or the development of the next generation of the process [5].

IMPORTANCE OF PROCESS VALIDATION

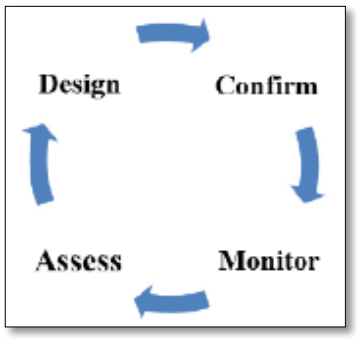
1) Reduction of Quality cost 2) Process optimization 3) Assurance of quality 4) Safety

Validation protocol

Definition: A document stating how validation will be conducted, including test parameters, product characteristics, manufacturing equipment and decision points on what constitutes acceptable test results [11].

Contents of validation protocol: 1) General information; 2) Objective, Label claim; 3) List of equipment and their qualification status; 4) Facilities qualification; 5) Process flow charts; 6) Manufacturing procedure narrative; 7) List of critical processing parameters and critical recipients; 8) Sampling, tests and specifications; 9) Acceptance criteria [17].

Process validation lifecycle



Process design: GMP, requirements for process design: 1) Design of facility; 2) Design of equipment; 3) Design of production and control procedures; 4) Design of laboratory controls; 5) Propose process steps (unit operations) and process variables (operating parameters) that need to be studied; 6) Identify sources of variability each unit operation is likely to encounter; 7) Consider possible range of variability for each input into the operation; 8) Evaluate process steps and variables for potential criticality; 9) Select process steps and variables for test in representative models; 10) Development studies to identify critical operation parameters and operating ranges; 11) Designed experiments; 12) Lab scale, pilot scale and/or full scale experimental batches to gain process understanding; 13) Establish mechanisms to limit or control variability based on experimental data; 14) Aim for a "robust process", i.e., one that can tolerate input variability and still produce consistent acceptable output [12].

Confirmation of process: 1) Transfer developmental knowledge to Production, i.e., technology transfer; 2) Batch record and operating SOPs in place, equipment and facilities equivalency established; 3) Raw materials approved; 4) Measurement systems qualified (QC lab as well as production floor test instrumentation); 5) Personnel training completed; 6) Environment controlled as necessary; 7) Execution of confirmed batches with appropriate sampling points and sampling level; 8) First evidence that process can function at commercial scale by production personnel; 9) Demonstrates reproducibility [8].

Types of process validation

A) Prospective Validation

B) Concurrent Validation

C) Retrospective Validation

D) Revalidation

E) Periodic revalidation

Phases in process validation

A) Phase 1. (Pre-validation phase)

B) Phases 2 (Pre-validation phase)

C) Phase 3 (Process validation phase/Process qualification phase)

D) Phase 4 (Validation maintenance phase)

In-process quality control test includes

1) Uniformity of weight 2) Uniformity of content 3) Disintegration time 4) Friability

PROCESS PARAMETERS FOR STANADARDIZATION

Granulation

These variables affect the: 1. Granule strength; 2. Bulk density of blend; 3. Flow characteristics of granules [26].

Semi-drying and milling

1) Dust free; 2) Round, uniform shape; 3) Good flow behavior; 4) Easy to dose; 5) Good dispersibility; 6) Good solubility; 7) Compact structure; 8) Low hygroscopicity; 9) High bulk density; 10) Dense surface; 11) Narrow grain size distribution; 12) Low abrasion; 13) Visual attractiveness [9].

Drying

Moisture content in granules which determined in terms of LOD is important factor. If moisture content is more in granules it will lead to poor flow and sticking problem. If moisture is less it will lead to capping, high friability and chipping. During drying the desired LOD will be maintained in the granules which will influence the quality parameters like flow properties of granules, physical properties during compression like tablet hardness. Inlet temperature of FBD is most critical variable for the same. LOD is checked periodically to establish the same during drying [12].

Blending

1. Bulk Density; 2. Angle of Repose; 3. Sieve analysis; 4. Compressibility Index.

Compression

Following physical parameters are to be checked to establish the above-mentioned variables at regular intervals. 1. Appearance; 2. Individual Weight variation; 3.Group Weight variation; 4. Hardness; 5. Thickness; 6. Friability [16].

Film coating

The Eight Critical Parameters for film Coating: 1. Gun geometry; 2. Automising/pattern air; 3. Pan pressure; 4. Pan speed; 5. Spray rate; 6. Inlet outlet air temperature; 7. Total air volume; 8. Adhesion of particles to the gun surface [13].

Packing

Following parameters influences speed of the machine: 1. Proper forming of blister pockets; 2. Proper sealing of blister pack; 3. Configuration of blister pack.

MATERIALS AND METHODS

Materials

Name: LACIDIPINE

Classification: Belongs to the class of dihydropyridine derivative selective calcium-channel blockers with mainly vascular effects.

Categories: Calcium antagonist.

Weight: 422.911 g/mol

Chemical formula: $C_{26}H_{33}NO_6$

IUPAC name: 3,5-diethyl4-{2-[(1E)-3-(tert-butoxy)-3-oxoprop-1-en-1-yl]phenyl}-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

Absorption: Well absorbed, the systemic bioavailability of Lacidipine is approximately 33%.

Protein binding: >95%

Metabolism: Extensive first pass metabolism.

Route of elimination: The metabolites are mainly eliminated by the biliary route and excreted via the feces.

Half-life: 13 to 19 h.

Plasma concentration: 1.6 to 5.7 μg/L

Toxicity: Hypotension and tachycardia; Bradycardia could occur from parasympathetic (vagal) stimulation, LD50=1000 mg/kg (orally in rat).

Bioavailability: 2 to 52%

Melting point: 183.5-184.5°C

State: Solid

Water solubility: 0.82 mg/L

Methods

Procurement and authentication of drug Lacidipine under study: Evaluation of three batches considering parameters listed below for I.P.Q.C tests.

1. Optimization of granulation end points
2. Evaluation of granules
3. Compression of granules into tablet
4. Evaluation of Tablet
5. Film coating of compressed tablets
6. Evaluation of coated tablets
7. Sampling of strips
8. Preparation of the validation report.

RESULTS (FIGURES 1 AND 2 AND TABLES 1-15)

Table 1. Risk assessment.

Critical process step	Risk	Critical parameter	Degree	Critical Response
Granulation	Major	Impeller speed	High	Loss on drying
		Occupancy	Moderate	
		Mixing time	High	
		Fluid uptake	High	
		Binder addition rate & time	High	
		Kneading time	High	
Drying	Medium	Inlet temperature	Moderate	Loss on drying
		Product temperature	High	
Milling/Sifting	Minor	Screen size	High	Pre blend uniformity dissolution assay
		Speed of milling	Moderate	
Blending	Medium	Blender Occupancy	Moderate	Blend uniformity dissolution assay
		Sequence of addition	Moderate	
		Mixing time	High	
		Mixing speed	High	

Steps mentioned above are the critical steps in the in the tablet formulation. The risk assessment was done for each step and the critical parameters were validated

Table 2. Comparative sampling and testing plan for submission, validation and commercial batches.

Stage		Test	Submission Batch	Validation Batch	Commercial Batch
Pre-lubrication (from Octagonal blender)	Unit dose sample	Blend uniformity	+	+	NA
Lubrication (from Octagonal blender)	Unit sample	Blend uniformity	+	+	NA
	Pooled sample	Particle size distribution, tapped density, bulk density	+	+	NA
Lubrication (from Bins)	Unit sample	Blend uniformity	+	+	NA
	Pooled sample	Assay, Particle size distribution, water by kf, residual solvent	+	+	+

Table 3. Acceptance criteria for critical in-process controls and sampling plan.

Stage	Time	Test	Sample Size	Acceptance criteria
Pre-lubrication (from OGB)	25 min interval	Blend Uniformity	149.25 mg to 447.75 (3 × 10)	As per specification
Lubrication (from OGB)	5 min interval	Blend Uniformity	150 to 450 mg (3 × 10)	As per specification
		Particle size distribution, tapped density, bulk density	250 g	
Lubrication (from bins)	NA	Blend Uniformity	150 to 450 mg (3 × 10)	As per specification
		Particle size distribution, tapped density, bulk density	250 g	

Table 4. Physicochemical parameter of tablets compressed with granules.

Batch no.	**B 1**		**B 2**		**B 3**	
Lot no.	**I**	**II**	**I**	**II**	**I**	**II**
Dry mixing time (s) Impeller slow and chopper off	300	300	300	300	300	300
Binder addition time (s) Impeller slow and chopper slow	300	300	300	300	300	300
Kneading time (s) Impeller slow and chopper slow	30	30	30	30	30	30
Discharge time (s) Impeller slow and chopper off	30	30	30	30	30	30
Impeller speed at all stages	Slow	Slow	Slow	Slow	Slow	Slow
Final impeller amperage	11.5	11.7	11.9	12.2	12.2	12.2
Final chopper amperage	3.9	3.8	3.7	3.7	3.8	3.7

Table 5. Coating parameters.

Parameter	Specification	B 1		B 2		B 3	
		Lot I	Lot II	Lot I	Lot II	Lot I	Lot II
Inlet temperature	55°C	55	55	55	55	55-60	55
Outlet temperature	-------	39.44	39-41	34-44	35-45	33-40	34-40
Product temperature	-------	43-51	41-51	40-51	40-52	38-44	38-43
Final LOD	NMT 20%	1.57	1.76	1.72	1.51	1.66	1.88
Time taken	-------	100	100	100	100	100	100

Table 6. Time interval studies.

Initial blending (Pre lubrication)	25 min
Final blending (Lubrication)	05 min
Bin sample (Lubrication)	10 sample

Table 7. Blend uniformity results.

Batch no.	B 1			B 2			B 3		
Sample	Pre lubrication (25 min)	Lubrication (5 min)	Sample from bins	Pre lubrication (25 min)	Lubrication (5 min)	Sample from bins	Pre lubrication (25 min)	Lubrication (5 min)	Sample from bins
1	99.4%	95.4%	98.4%	98.5%	99.0%	97.6%	94.5%	99.7%	99.1%
2	99.5%	95.6%	98.6%	99.1%	97.2%	98.1%	97.3%	100.4%	97.3%
3	97.4%	96.1%	98.2%	96.5%	98.4%	97.6%	94.3%	98.3%	98.9%
4	95.8%	96.5%	97.4%	97.1%	94.8%	97.7%	99.9%	97.1%	97.6%
5	95.5%	95.9%	98.3%	98.7%	96.6%	98.2%	97.2%	96.8%	95.8%
6	96.1%	97.5%	98.1%	98.3%	97.0%	98.6%	94.6%	96.9%	98.1%
7	96.2%	96.5%	97.0%	97.2%	98.1%	9.1%	98.8%	99.2%	98.8%
8	96.6%	96.4%	97.7%	98.1%	97.4%	97.4%	98.1%	99.4%	94.3%
9	96.0%	94.4%	97.0%	96.2%	97.8%	96.7%	93.6%	99.3%	98.7%
10	97.9%	98.0%	96.9%	95.8%	98.0%	96.6%	104.0%	96.8%	93.0%
Min	99.5%	94.4%	96.9%	95.8%	94.8%	96.6%	93.6%	96.8%	93.0%
Max	99.5%	98.0%	98.6%	99.1%	99.0%	98.2%	104.0%	100.4%	99.1%
Avg	97.0%	96.2%	97.8%	97.6%	97.4%	97.2%	97.2%	98.4%	97.2%
% RSD NMT 5.0%	1.5%	1.1%	0.7%	1.2%	1.2%	0.6%	3.3%	1.3%	2.2%

Table 8. Physical parameter of blend and sieve analysis.

Batch no.	B 1	B 2	B 3
%Retains on #30	27.429%	30.347%	40.679%
%Retains on #40	43.782%	44.082%	54.245%
%Retains on #60	59.136%	57.057%	66.423%
%Retains on #80	65.373%	62.565%	71.448%
%Retains on #100	68.452%	65.553%	74.046%
Bulk density	0.667 g/ml	0.668 g/ml	0.676 g/ml
Tapped density	0.927 g/ml	0.927 g/ml	0.927 g/ml
Compressibility index	28.000%	28.000%	28.027%

Table 9. Quantity of residual solvents.

Batch no.	B 1	B 2	B 3
Residual solvents	Ppm	Ppm	Ppm
Acetone	13	71	91
IPA	585	1965	2358

Table 10. Yield details.

Batch no.	Actual yield
B 1	99.46%
B 2	99.33%
B 3	99.35%

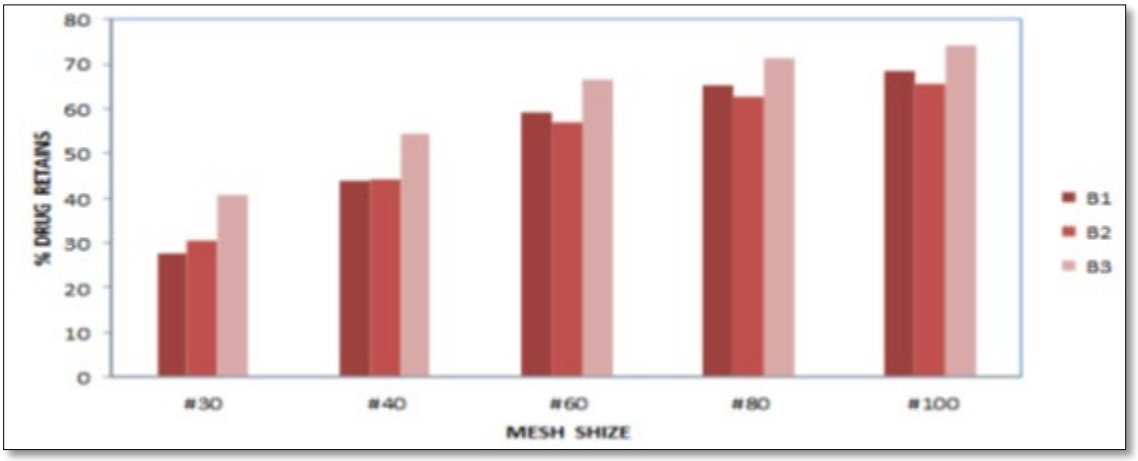


Figure 1. Graphical representation of sieve analysis.

Table 11. Acceptance criteria for critical in-process control and sampling.

Stage		Quantity of sample	Test to be performed
Compression (Hopper study)		30 tab	Appearance
		20 tab	Group weight
		30 tab	Individual weight
		6 tab	Hardness
		6 tab	Thickness
		6 tab	Disintegration time
		6 tab	Friability
		3 × 10 at each hopper level	Uniformity of dosage unit
		One pooled sample 50 tab	Dissolution, Assay
Coating	Lot I	20 tab	Description
	Lot II		
	Lot III		
	Lot IV		
Reference sample (Lacirex Italy)		20 tab	Dissolution profile on 12 tab
		120 tab	Description
			Assay
			Related substance
			Average weight
			Water by kf
			Disintegration time
			Dissolution

Table 12. Comparative sampling and testing plan for submission, validation and commercial batches.

Stage	**Test**		**Submission batch**	**Validation batch**	**Commercial batch**
Periodic online in process testing during tablet compression (pooled sample testing will be recorded in BPR, there will be no separate analysis	Description Weight variation Weight of 20 tablet Hardness Thickness Friability Disintegration time		+	+	+
Core tablet	Initial and end cycle	Appearance Group weight variation Hardness Thickness Disintegration time Friability Uniformity	+	+	NA
	Pooled sample	Description Assay Dissolution	+	+	NA
Coating	Lot I II III IV	Description	+	+	NA
	Pooled sample	Finished analysis	+	+	+
	Pooled sample	Dissolution profile of 12 tab	+	+	NA
Reference sample (Lacirex Italy)	Dissolution profile of 12 tab		+	NA	NA

Table 13. Physical parameter at different hopper levels/cycles during compression.

Parameter and Specification	Hopper level	B 1 (6 mg)	B 2 (6 mg)	B 3 (6 mg)
Appearance (White to pale yellow, oval shaped)	Full (initial cycle)	Complies	Complies	Complies
	Middle (initial cycle)	Complies	Complies	Complies
	Middle cycle	Complies	Complies	Complies
	Near end hopper level	Complies	Complies	Complies
Group weight variation (9.000 ± 3.0% g)	Full (initial cycle)	9.080	9.014	9.046
	Middle (initial cycle)	9.064	9.017	9.045
	Middle cycle	9.056	9.026	9.026
	Near end hopper level	9.063	9.015	9.062
Individual weight variation (427.5-472.5 mg)	Full (initial cycle)	450.8-459.1	441.6-462.5	449.6-463.7
	Middle (initial cycle)	447.1-458.2	438.3-462.6	445.8-465.7
	Middle cycle	444.2-456.7	444.2-458.8	448.9-461.6
	Near end hopper level	449.4-457.5	440.8-463.2	448.2-460.5
Hardness (8-16 kp)	Full (initial cycle)	11.4-13.2	12.4-13.4	11.8-13.2
	Middle (initial cycle)	11.5-13.0	12.0-3.4	12.4-13.2
	Middle cycle	12.2-13.9	12.0-13.2	11.8-12.6
	Near end hopper level	12.8-14.0	11.9-13.0	12.0-13.4
Thickness (5.1-5.9 mm)	Full (initial cycle)	5.46-5.52	5.42-5.52	5.44-5.50
	Middle (initial cycle)	5.46-5.52	5.46-5.51	5.44-5.52
	Middle cycle	5.46-5.52	5.45-5.52	5.44-5.51
	Near end hopper level	5.46-5.52	5.44-5.51	5.46-5.52
% Friability (NMT 0.8%w/w)	Full (initial cycle)	0.03%	Nil	Nil
	Middle (initial cycle)	0.02%	Nil	Nil
	Middle cycle	Nil	Nil	Nil
	Near end hopper level	Nil	Nil	Nil
Disintegration time (NMT 20 min)	Full (initial cycle)	17 min 15 s	17 min 40 s	17 min 38 s
	Middle (initial cycle)	17 min 20 s	17 min 38 s	17 min 40 s
	Middle cycle	17 min 30 s	17 min 36 s	17 min 36 s
	Near end hopper level	17 min 30 s	17 min 40 s	17 min 39 s

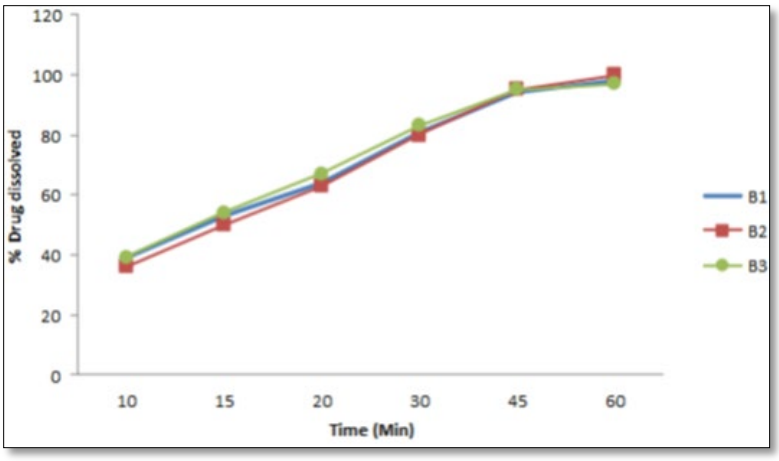


Figure 2. Dissolution graph of batch no. B 1, B 2, B 3.

Table 14. Film coating description.

Test	Specification	Results	Remark
Description	White colored oval shaped debosed with (symbol like Dr. Reddy's logo) on one side and 226 on other side	White colored oval shaped debosed with (symbol like Dr. Reddy's logo) on one side and 226 on other side	Pass

Table 15. Yield details (limit 90-100% at all stages).

Stage	% Yield of Batch		
	B 1	B 2	B 3
Compression	97.31	96.51	99.68
Film coating	90.82	92.68	92.70

Finished product report

The finished product report for all the three batches was collected. All the tests for finished product were passed as per the specification **(Figure 3 and Tables 16-19)**.

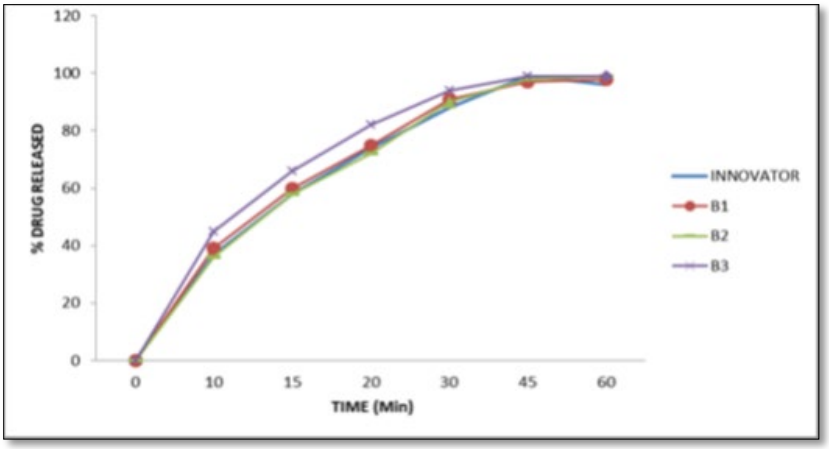


Figure 3. Comparison of dissolution profile of film coated tablet with innovator batch.

Table 16. Packing yield details.

Batch no.	Actual yield (%)	
B1	94.31%	99.87%
B 2	95.86%	99.22%
B 3	94.64%	99.57%

Table 17. Finished product report for packing.

Test	Specification	Result		
		B 1	B 2	B 3
Related substance by HPLC impurity A	NMT 0.15%	0.019%	0.023%	0.025%
Related substance by HPLC impurity B	NMT 0.50%	0.206%	0.204%	0.204%
Related substance by HPLC impurity C	NMT 0.20%	0.005%	0.013%	0.015%
Related substance by HPLC maximum unknown unspecified impurity	NMT 0.20%	0.013%	0.017%	0.016%
Related substance by HPLC total impurities	NMT 1.00%	0.26%	0.26%	0.27%

Table 18. Reference sample results.

Test	Specification	Lacirex 6 mg
Description	White colored, oval shaped, film coated tablet debosed with GXCX3 on one side and plain on other side	White colored, oval shaped, film coated tablet debosed with GXCX3 on one side and plain on other side
Assay by HPLC	For information	97.9%
Related substance by HPLC impurity A	For information	Less than log (0.012)
Related substance by HPLC impurity B	For information	0.497%
Related substance by HPLC impurity C	For information	0.017%
Related substance by HPLC maximum unknown unspecified impurity	For information	0.063%
Related substance by HPLC total impurities	For information	0.63
Water by kf	For information	5.2%
Average weight	For information	462.58 mg
Disintegration time	For information	13 min 4 s
Dissolution	For information	Unit S 1 94 2 94 3 94 4 95 5 95 6 93
Uniformity	For information	5.2%

Table 19. Comparison of dissolution profile of Innovator versus exhibit batches.

Batch no.	0 min	10 min	15 min	20 min	30 min	45 min	60 min
Innovator	0	37	58	74	88	99	96
B 1	0	39	60	75	91	97	98
B 2	0	36	58	72	90	98	99
B 3	0	45	66	82	94	99	99

DISCUSSION

The common blend 94.50 kg was divided into three different strengths viz. 19.50/130,000 tab for 2 mg strength 30.00 kg/100,000 tab for 4 mg and 45.00 kg/100,000 tab for 6 mg tab.

Dry mixing and granulation

Dry mix was done for 5 min at impeller slow speed (75 rpm) to match Froude number with tablet batches. Granulation was carried out at slow speed of impeller and chopper slow speed with addition of granulating solution as per manufacturing instruction which produced satisfactory granules so the binder addition time and kneading time is recommended as mentioned in manufacturing instructions.

Wet milling

Wet milling was done in Quadro co-mill using 250Q screen to break wet mass and facilitate uniform drying to keep residual solvents within specified limits.

Drying

Drying was carried out at controlled inlet temperature of 55°C and desired loss on drying of NMT 2.0% w/w at 105°C achieved. LOD of dried granules achieved between NMT 2.0% w/w. Hence the drying process was found to comply the predefined specification for 3 batches

Pre lubrication and lubrication

The pre lubrication time of 25 min is to match number of revolution with that of tablet batches and found satisfactory at blender fast speed. The blend uniformity results were found to comply with the predefined specification. Lubrication time of 5 min at blender fast speed shows satisfactory results. Blend uniformity results found to be complied with predefined specification for all three batches. The process validation of Lacidipine tablets 6 mg was conducted for a batch size of 45.00 kg (100,000 tab) which included the validation of critical steps of manufacturing such as compression and film coating which were found satisfactory.

Compression

Compression was carried out on 30 station Fette press. All physical parameter such as individual weight variation, thickness, friability, disintegration time are well within the acceptance limit at full hopper, middle hopper and end hopper. Hopper study data shows no segregation during compression and uniformity of dosage unit at full hopper; middle hopper and end hopper are found satisfactory. On the basis of all analytical and physical parameter data found that compression stands validated.

Film coating

Coating had been performed with the parameters as mentioned in manufacturing instructions in order to obtain the desired film coating buildup of 3.0 ± 0.5% w/w. Film coating inlet temperature is recommended as 65°C-75°C. Finished product report shows that final product meets the finished product specification.

Deviation and incidents: Nil.

Compression: Stands validated as per parameters specified in manufacturing instructions.

Film coating: Stands validated as per parameter specification in manufacturing instructions.

CONCLUSION

The manufacturing of three batches of common blend for Lacidipine tablets 6 mg was conducted for a batch size of 94.50 kg (210,000 tablets). The study involved validating the process variables of this transferred product to show that the process is under control. The study includes the validation of critical steps of manufacturing such as blending, drying, granulation, compression and coating. The Process validation of Lacidipine tablets showed that there was no significant batch-to-batch variation. Therefore it can be concluded that the process stands validated and the data can be used in regulatory submission for obtaining marketing authorization for the Lacidipine tablets.

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