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%

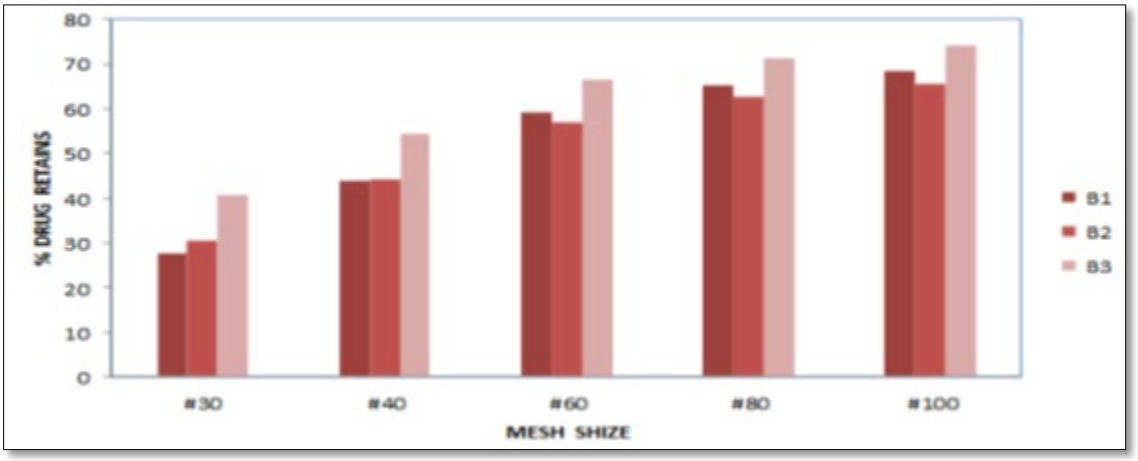

Figure 1. Graphical representation of sieve analysis.

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

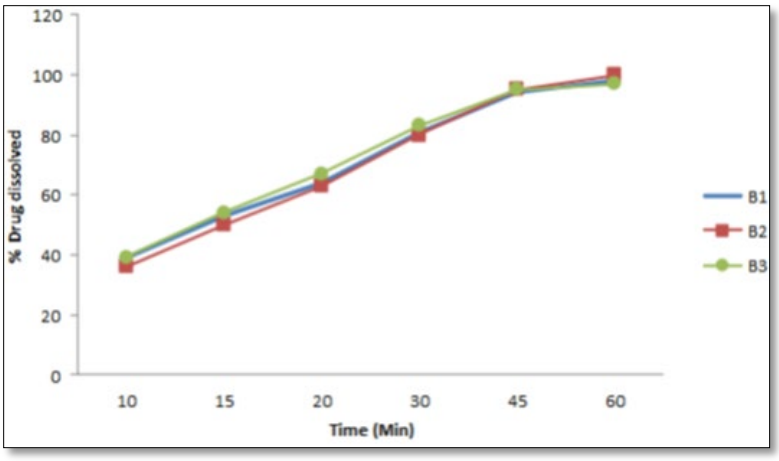

Figure 2. Dissolution graph of batch no. B 1, B 2, B 3.

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)**.

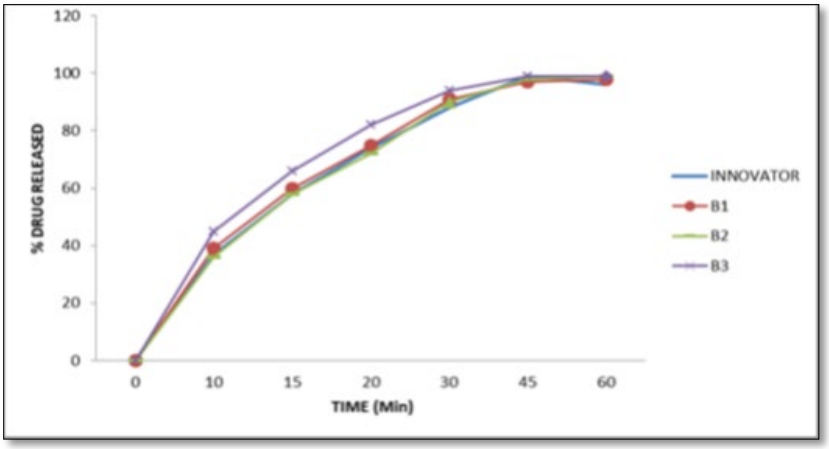

Figure 3. Comparison of dissolution profile of film coated tablet with innovator batch.

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.

REFERENCES

1. USFDA (2004) Guideline for industry – Sterile drug product produced by aseptic process cGMP.
2. USFDA (2011) Guidelines on process validation: General principle and practice. WHO: Guidelines on GMP requirement: Part 2 - Validation.
3. TGA Guidelines (2002) Australian code of good manufacturing practice for medicinal products, pp: 103-109.

4. Beaty NA, Narlin B (1978) Aseptic vial and syringe filling. Am Chem Soc, pp: 123-128.
5. Watler P, Rathore AP, Joseph F, Edward R, Arling GS (2002) Process validation - How much to do and when to do it. BioPharm, pp: 18-28.
6. Woodcock J (2004) The concept of pharmaceutical quality. Am Pharm, pp: 1-3. (Available on: http://americanpharmaceuticalreview.com/ViewArticle.aspx ContentID
7. McBurnie L, Bardo B (2004) Validation of sterile filtration. Pharm Technol 2004: s13-s23.
8. Stockdale D (2005) Overview of aseptic fill/finish manufacturing. Part 2: Regulatory requirements. Am Pharm Rev, pp: 123-129.
9. Brett M, Belongia S (2006) Characterization, qualification and validation of disposable final filling process for parenteral and ophthalmic drug. Pharm Technol.
10. Spurgeon T (2006) Aseptic process validation is a new FDA guidance imminent? Contact Pharma. Available at: http://www.fda.gov/cber/faq/sanofiqa.htm
11. http://www.fda.gov/ICECI/EnforcementActions/WarningLetter
12. http://www.fda.gov/cber/faq/sanofiqa.htm
13. Siddiqui MS (2010) Monitoring of aseptic environments and processes in sterile facility. Available on: http://www.askaboutvalidation.com
14. Parenteral Drug Association (2011) Technical Report No. 22. Process simulation for aseptically filled products, pp: 1-40.
15. Chaurasia S, Golani S, Jain NP, Goyal M, Verma S (2011) Comprehensive review on aseptic fill/finish manufacturing as per regulatory guidelines. J Curr Pharm Res 5: 19-27.
16. Dubey SK, Basia A (2011) cGMP requirement for process control. Int J Curr Pharm Res 3: 58-63.
17. Grege G (2011) Basic requirements for aseptic manufacturing of sterile medicinal products: A comparison between Europe and USA.
18. EU Guidelines to Good Manufacturing Practice (2008) Manufacture of sterile medicinal products. Annex 1. 4: 1-16.
19. James FJ (2006) Validation of Pharmaceutical Processes. 2nd Edn. Mercel Dekker Inc., pp: 1555-1561.
20. Guidance for Industry (2004) Sterile products produced by aseptic processing current good manufacturing practices. U.S. FDA, pp: 1-63.
21. Agalloco J (2005) Importance of background microbial levels in the manufacture and testing of sterile products. Pharm Technol 74.
22. ISO 13408-1. Aseptic processing of health care products. General Requirements, pp: 1-35.
23. ISO 14644-1. Clean rooms and associated controlled environments, classification of air cleanliness.
24. Savant DA (2007) The Pharmaceutical Sciences. Pharma Pathway, 4th Edn. Pragati books Pvt. Ltd., pp: 1.91-1.99.
25. Scott B (2010) Process validation of oral solids dosage form. Part 1: General principles. Available on: http://www.ikev.org/haber/bozzonejune1.pdf
26. Syed IH (2006) Pharmaceutical Master Validation Plan. 1st Edn. St. Lucie Press, pp: 2-27.
27. White E (2009) Risk management for aseptic processing [online] pharmaceutical technology. Available from: http://www.bioline.org.br/pdf?pr02016
28. Work group of the Scottish QA Specialist Interest Group (2004) Guideline on test method for environmental monitoring for aseptic dispensing. pp: 35-40.
29. Guidance for Industry Process Validation (2008) General principle and practices. Available at: http://www.fda.gov./Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf
30. Guidance for Industry Process Validation (1987) U.S. FDA. Available at: http://www.fda.gov./Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124720.htm
31. Nash Robert A (2000) Pharmaceutical process validation. 3rd Edn. 129: 159-185.