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Research Article

PROCESS VALIDATION OF FINASTERIDE TABLETS

Rahul Paruchuri*, Shagun Trivedi, Gargeyi Pavuluri, Prasanthi B and Senthil Kumar M

Annai Veilankanni's Pharmacy College, Saidapet, Chennai, Tamilnadu, India.

ABSTRACT

Validation is one of the important steps in achieving and maintaining the quality of the final product. If each step of production process is validated we can assure that the final product is of the best quality. Validation of the individual steps of the processes is called the process validation. Different dosage forms have different validation protocols. Here this article concentrates to provide assurance that the manufacturing procedure is suitable for intended purpose and consistently meet predetermined specifications and quality attributes, as per specified master formula record. It also provides a documented evidence for the operation sequence and schedule of manufacturing process and to determine the critical parameters and variables in the process of manufacturing of the tablets. It gives a higher degree of assurance that the manufacturing process consistently meet the pre-determined specifications and quality products output can be used to increase productivity, its consistent quality and decreasing the need for processing/market complaints.

Keywords: Process validation, Tablets, Quality, Protocol, Manufacturing process.

INTRODUCTION

The prime objective of any pharmaceutical plant is to manufacture products of requisite attribute and quality consistently, at the lowest possible cost. Although validation studies have been conducted in the pharmaceutical industry for a long time, there is an ever-increasing interest in validation owing to their industry's greater emphasis in recent years on quality assurance and productivity improvement. Validation is a necessary part of a quality assurance program and is fundamental to an efficient production operation. Process validation establishes the flexibility and constraints in the manufacturing process controls in the attainment of desirable attributes in the drug product while preventing undesirable properties. This is an important concept, since it serves to support the underlying definition of validation, which is a systematic approach to identifying, measuring, evaluating, documenting, and re-evaluating a series of critical steps in the manufacturing process that require control to ensure a reproducible final product.[1,2] USFDA defined process validation as "establishing documented evidence which provides high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics."[3]Solid dosage forms include tablets and capsules.

TYPES/ METHODS OF VALIDATION

Prospective Validation

It is defined as the established documented evidence that a system does what it purports to do based on a pre-planned protocol. This validation usually carried out prior to distribution either of a new product or a product made under a revised manufacturing process. Performed on at

least three successive production-sizes. (Consecutive batches).[4]

Concurrent Validation

Similar to prospective validation, except the fact the operating firm will see the product during the qualification runs, to the public at its market place, and also similar to retrospective validation.

This validation moves in process monitoring of critical processing steps and product testing. This helps to generate and document evidence to show that the production process is in a state of control.

Retrospective Validation

It is defined as the established documented evidence that a system does what it purports to do on review and analysis of historical information. This is achieved by the review of the historical manufacturing testing data to prove that the process has always remained in control. This type of validation of a process is done for a product already in distribution[5].

PHASES IN PROCESS VALIDATION

The activities relating to validation studies may be classified into three phases:

Phase 1

Pre-Validation Phase or the Qualification Phase, which covers all activities relating to product research and development, formulation, pilot batch studies, scale up studies, transfer of technology to commercial scale batches, establishing stability conditions, storage and handling of in-process and finished dosage forms, Equipment qualification, Installation Qualification, master production documents, Operational Qualification, Process Capability.

Phase 2

Process Validation Phase (Process Qualification phase) designed to verify that all established limits of the Critical Process Parameters are valid and that satisfactory products can be produced even under the "worst case" conditions.

Phase 3

Validation Maintenance Phase requiring frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications to the production process, and that all Standard Operating Procedures have been followed, including Change Control procedures.

At this stage the Validation Team also assures that there have been no changes, deviations that should have resulted in Requalification and Revalidation[6].

VALIDATION LIFE CYCLE

Validation is a continuing and evolving process. The validation process which extends from the very basic to a very broad theological and methodical investigation if how the system and processes perform. Its scope encompasses documentation revision control, training and maintenance of the system and process. Evidence of validation should be seen at the corporate level, and be reflected in the management structure. Validation is a method for building and maintaining quality[7].

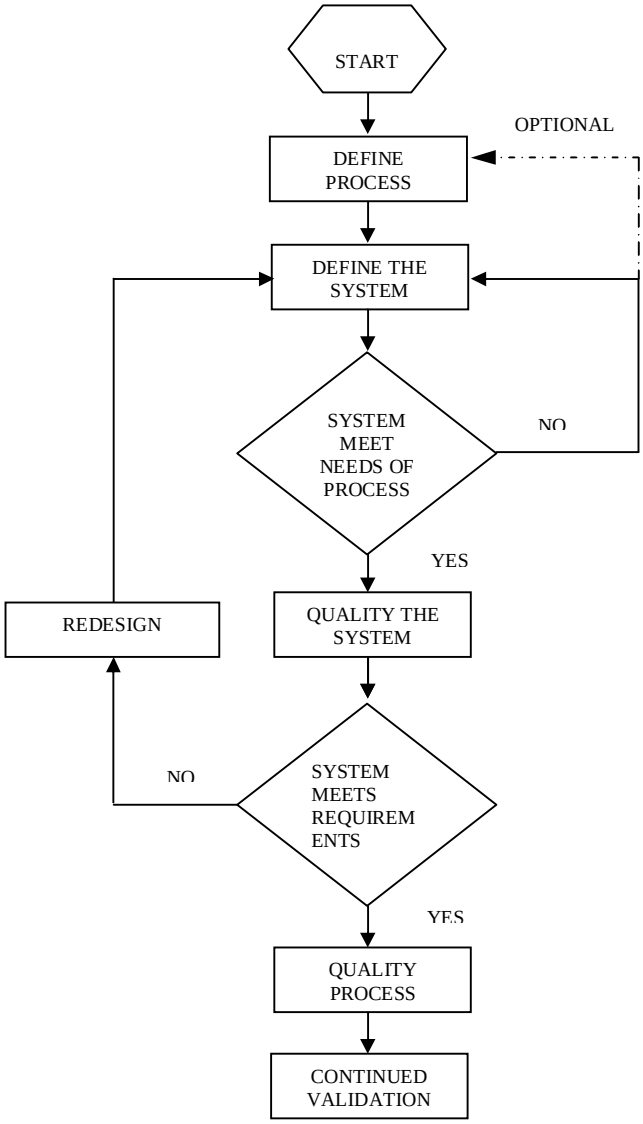

Fig. 1: Validation Life Cycle

VALIDATION PROTOCOL

A written plan of actions stating how process validation will be conducted; it will specify who will conduct the various tasks and define testing parameters; sampling plans, testing methods and specifications; will specify product characteristics, and equipment to be used. It must specify the minimum number of batches to be used for validation studies; it must specify the acceptance criteria and who will sign/approve! Disapprove the conclusions derived from such a scientific study.

An ideal validation protocol contains the followings:

a) Objective and General Information.
b) Background I revalidation activities.
c) List of equipment's and their qualification status.
d) Facilities qualification.
e) Manufacturing formula & manufacturing procedure narrative.
f) Process flow diagram
g) Label claim
h) Process flow chart.
i) List of critical processing parameters and critical excipients.
j) Sampling, tests and specification.
k) Acceptance criteria[8].

METODOLOGY

Validation procedure

1. Three batches of 0.50 million tablets batch size to be manufactured as described in the batch manufacturing record.
2. Current version of standard operating procedures to be followed.
3. Record the observations at compression stage in the below specified data sheets.
4. Record the yield after compression.

Sampling procedures at different stages

Compression

Compression to be carried out as per batch manufacturing record using 7.3mm normal concave with FIN logo on upper side 7.3mm normal concave plain on lower side of dies.
No. of stations: 45
Type of tooling: 'D' type.

Physical parameters as mentioned in the below table

Table 1: Physical parameters

S. No.	Parameter	Standard	No. of Tablets to be Taken for Each Time Testing(L.H.S & R.H.S)
1	Description	white to off-white colored, round biconvex tablets with 'FIN' deposing on one side and plain surface on the other side	50 tablets
2	Weight of 20 tablets	2.50g ±20%(2.450g-2.550g)	20 tablets
3	Individual wt variation	125.0mg+5.0%(118.75mg to 131.25mg)	50 tablets
4	Hardness	NLT 2.5kg/cm²	6 tablets
5	Thickness	2.90±0.1mm(2.80mm-3.00mm)	50 tablets
6	Disintegration time	NMT 10minutes	6 tablets
7	Friability	NMT 1.0% w/w	20 tablets

Run the compression machine at different speeds and check the samples for all above physical parameters.

Note: Approximately one third of the compression to be carried out at each speed and record the speed and timings in the BMR.

Acceptance criteria for critical inprocess controls and sampling plan

The below table gives the stage wise critical process variables and inprocess control limits of different tests with sample size and also gives the names of the department responsible for that particular stage.

Note: The physical parameter samples have to be collected from both LHS & RHS and all the analytical parameter sample have to be collected from pooled samples. Collect the sample for uniformity of dosage limits in 3 sets. One set of sample to be taken for analysis and other two sets are to be kept as a reserve sample. In case of failure of the result, use the reserve sample for analysis, otherwise, discard the reserve sample test.

Table 2: Acceptance Criteria

Stage	Process Variables	Sampling Frequency	Tests to be Performed	Appropriate Sample Size	Acceptance criteria	Responsibility
Pre compression studies	Machine speed-optimum speed	At lower & higher thickness	Dissolution	3×6 tablets at different thickness levels	As per current finished product specification	TTG/production QA/QC
Compression Studies	Machine speed(maximum, optimum & minimum)	At different speeds	Description	50 tablets	As per BMR	
			Group wt variation	20 tablets	2.50g±2.0%(2.450g-2.550g)	
			Hardness	6 tablets	NLT 2.5kg/cm²	
			Individual wt variation	50 tablets	125.0mg± 5.0%(118.75mg to 131.25mg)	
			Thickness	50 tablets	2.90±0.1mm(2.80mm-3.00mm)	
			Disintegration Time	6 tablets	NMT-10min	
			Friability	20 tablets	NMT 1.0% w/w	
			Uniformity of dosage units & RSD	3 x 10 tablets at each speed	As per current Finished product specification.	
			Dissolution	3 x 6 tablets at each speed		

Stage	Process Variable	Sampling Frequency	Tests to be Performed	Appropriate Sample Size	Acceptance criteria	Responsibility
Compression Studies (Continued)	Hopper study at maxi speed	Full, middle and low levels of the hopper	Uniformity of dosage units and RSD	3×10 tablets at each hopper level	As per current finished product specification	TTG/production QA/QC
			Individual weight variation	50 tablets	125.0mg+5.0% (118.75mg to 131.25mg)	
			Group weight variation	20 tablets	2.50g±2.0% (2.450g-2.550g)	
			Thickness	50 tablets	2.90±0.1mm (2.80mm-3.00mm)	
			Hardness	6 tablets	NLT 2.5kg/cm²	
			Disintegration time	6 tablets	NMT 10minutes	
			Friability	20 tablets	NMT 1.0% w/w	
		Pooled sample	All the tests as per product release specification	Pooled sample of 200 tablets	As per current product release specification	
Coating		Pooled sample	Dissolution profile (at 5,15,20,30 & 45 min.)	3×12 tablets	As per current product specification	TTG/production QA/QC

Prerequisites of process validation

1. The batches shall be manufactured as per batch manufacturing record.
2. The equipment utilized for manufacturing and processing of these batches shall be as per list of equipment.
3. The raw material used for manufacturing shall be from approved vendors and shall be released for manufacturing by QC.
4. The critical process parameters shall be evaluated with respect to quality attributes of the products.
5. Sampling for in-process control samples shall be carried out as per sampling procedure and plan.
6. Critical in-process controls shall conform to the specification.
7. Product of these batches shall conform to specifications.

Process validation report

The process validation report shall be prepared by compiling the analytical results and raw data generated during validation. Analytical results and raw data shall be verified against acceptance criteria. A comparative report of validation data obtained shall be prepared and checked by TTG. Production, RA and quality assurance shall approve this report.

Deviation

If there is any deviation with respect to the procedure mentioned in the protocol/BMR it shall be recorded in BMR and validation report.

Revalidation

The manufacturing process of Finasteride shall be revalidated in one or more of following cases:

1. Change in formulation, procedure or quality of pharmaceutical ingredients.
2. Change of equipment, addition of new equipment and major breakdowns/maintenance, which affect the performance of equipment.
3. Major change of process, parameters.
4. Change in site.
5. On appearance of negative quality trends.
6. On appearance of new findings based on current knowledge.
7. Batch size change implementation of these changes shall be carried out as per change control system.

RESULTS AND DISCUSSIONS

Compression stage

Variables considered for study

Machine speed (6-8 RPM)

Measured response

Appearance, group weight variation, individual weight variation, hardness, thickness, friability, disintegration time and uniformity of dosage units & dissolution.

Acceptance criteria

As per finished product specification.

Batch taken for study

A100204, A100240 & A100256

Table 3: Dissolution of Finasteride tablets at different thickness levels

% of Finasteride (limit: NLT 75% (Q) of labeled amount dissolved in 45 min)						
Batch No.	**A100204**		**A100240**		**A100256**	
Thickness	**Lower**	**Higher**	**Lower**	**Higher**	**Lower**	**Higher**
AR No.	**N1FV0077**	**N1FV0078**	**8900000283942**	**890000289341**	**890000290444**	**890000290445**
1	83.9%	93.9%	89.7%	93.3%	86.4%	90.4%
2	87.1%	93.0%	89.6%	99.2%	85.8%	88.0%
3	87.8%	96.0%	91.1%	88.7%	85.5%	86.3%
4	83.9%	94.2%	93.4%	87.7%	87.4%	87.0%
5	85.2%	94.3%	92.1%	87.3%	85.5%	86.1%
6	86.2%	95.0%	88.3%	89.8%	86.7%	88.5%
Min.	83.9%	93.0%	88.3%	87.3%	85.5%	86.1%
Max.	87.8%	96.0%	93.4%	99.2%	87.4%	90.4%
Avg.	85.6%	94.4%	90.7%	91.0%	86.4%	87.71%

Observation

The dissolution results of lower and higher thickness are found within the specification limits for the batches A100204, A100240, A100256

Table 4: Uniformity dosage units of Finasteride tablets at different speeds for the batches A100204 & A100240

BatchNo.	A100204			A100240		
Speed of the m/c	6RPM	7RPM	8RPM	6RPM	7RPM	8RPM
A.R. No.	890000283380	890000283381	890000283382	890000289348	890000289348	890000289349
1	93.4	97.5	94.2	98.1	94.5	95.8
2	92.6	93.2	96.0	99.8	95.8	95.1
3	94.1	92.6	92.7	97.4	94.4	96.5
4	94.8	94.2	96.1	96.2	95.5	94.8
5	96.2	94.8	95.3	97.5	95.1	99.7
6	92.2	98.2	101.5	98.5	93.5	98.7
7	100.5	92.5	98.9	96.5	94.6	96.4
8	98.4	94.3	96.2	91.3	97.1	99.4
9	96.9	94.1	96.9	98.2	94.6	101.1
10	95.1	101.2	96.3	96.8	95.0	95.8
Min.	92.6	92.5	94.2	91.3	93.5	94.5
Max.	100.5	101.2	101.5	99.8	97.1	101.1
Avg.	95.42	95.26	96.41	97.0	95.0	97.3
RSD	2.8%	3.0%	2.5%	2.3%	1.0%	2.3%

Table 5: Uniformity dosage units of Finasteride tablets at different speeds for the batch A100256

Batch No.	A100256		
Speed of the m/c	6 RPM	7 RPM	8 RPM
A.R. No.	890000290449	890000290450	890000290451
1	97.7	99.9	99.4
2	97.6	97.6	99.2
3	97.4	100.1	96.7
4	94.9	96.4	96.5
5	96.8	97.5	95.2
6	96.1	98.1	99.1
7	98.5	97.8	99.1
8	97.4	98.7	99.1
9	96.3	99.1	100.4
10	95.5	99.5	99.1
Min.	94.9	96.4	95.2
Max.	98.5	100.1	100.4
Avg.	96.82	98.47	98.38
RSD	1.2%	1.2%	1.7%

Observation

The uniformity of dosage units results at different speeds are found within the specification limits for all the three batches. Hence at the specified machine speed, the compression stage is validated & reproducible when performed on 45 station compression machine was proven statistically at 95% confidence level. The average of uniformity of dosage units of all the 3 runs were subjected to single factor-ANOVA to determine the intra-batch similarity. The results of ANOVA were presented in Table 14.

The calculated F-value for uniformity of dosage units is less than the theoretical F-value of 5.1 as shown in Table 14 at 5% level of statistical significance. This shows that there is insignificant difference in the uniformity of dosage units of the FINASTERIDE tablets at different speeds. Batch shows intra-batch similarity for uniformity of dosage units at greater than 95% confidence level.

Table 6: Uniformity of dosage units (average) of the FINASTERIDE tablets at all the 3 speeds for batch no. A100204

SPEEDS	6 RPM	7 RPM	8 RPM
Uniformity of dosage units of Finasteride in FINASTERIDE tablets of B.No.A100204	93.4	97.5	94.2
	92.6	93.2	96.0
	94.1	92.6	92.7
	94.8	94.2	96.1
	96.2	94.8	95.3
	92.2	98.2	101.5
	100.5	92.5	98.9
	98.4	94.3	96.2
	96.9	94.1	96.9
	95.1	101.2	96.3
Average	95.42	95.26	96.41

Table 7: Uniformity of dosage units (average) of the FINASTERIDE tablets at all the 3 speeds for batch no. A100240

SPEEDS	6 RPM	7 RPM	8 RPM
Uniformity of dosage units of Finasteride of FINASTERIDE tablets of B.No.A100240	98.1	94.5	95.8
	99.8	95.8	95.1
	97.4	94.4	96.5
	96.2	95.5	94.8
	97.5	95.1	99.7
	98.5	93.5	98.7
	96.5	94.6	96.4
	91.3	97.1	99.4
	98.2	94.6	101.1
	96.8	95.0	95.8
Average	97.0	95.0	97.3

Table 8: Uniformity of dosage units (average) of the FINASTERIDE tablets at all the 3 speeds for batch no. A100256

SPEEDS	6 RPM	7 RPM	8 RPM
Uniformity of dosage units of Finasteride of FINASTERIDE tablets of B.No.A100256	97.7	99.9	99.4
	97.6	97.6	99.2
	97.4	100.1	96.7
	94.9	96.4	96.5
	96.8	97.5	95.2
	96.1	98.1	99.1
	98.5	97.8	99.1
	97.4	98.7	99.1
	96.3	99.1	100.4
	95.5	99.5	99.1
Average	96.82	98.47	98.39

Table 9: ANOVA TEST-single factor (for average of Finasteride uniformity of dosage units)

GROUPS	COUNT	SUM	AVERAGE	VARIANCE
6 RPM	3	287.09	95.69666667	0.3880333
7 RPM	3	289.37	96.45666667	1.5921333
8 RPM	3	294.67	98.22333333	1.7740333

Table 10: ANOVA

Source of variation	SS	df	MS	F	P-value	F crit
Between speeds	10.08275556	2	5.041377778	4.0285902	0.077760509	5.143253
Within all 3 batches	7.5084	6	1.2514	-	-	-
Total	17.59115556	8	-	-	-	-

Table 11: Dissolution of Finasteride tablets at different speeds for the batches A100204 & A100240

% of Finasteride (Limit: NLT 75%(Q) of labelled amount dissolved in 45min)						
Batch No.	A100204			A100240		
Speed of the m/c	6RPM	7 RPM	8 RPM	6 RPM	7 RPM	8 RPM
AR NO.	890000283380	890000283381	890000283382	890000289347	890000289348	890000289349
1.	85.7	82.8	86.3	86.3	83.3	92.4
2.	85.3	86.0	84.9	84.5	91.6	88.0
3.	85.9	82.2	85.9	83.2	89.4	87.4
4.	84.8	84.9	81.2	84.5	89.9	87.5
5.	85.2	83.9	81.3	83.8	89.1	92.9
6.	84.2	81.4	86.2	81.3	93.5	89.2
Min.	84.2	81.4	81.2	81.3	83.3	87.4
Max.	85.7	86.0	86.3	86.3	93.5	92.9
Avg.	85.18	83.53	84.3	83.9	89.5	89.6

Table 12: Dissolution of Finasteride tablets at different speeds for the batch A100256

% of Finasteride (Limit: NLT 75%(Q) of labeled amount dissolved in 45min)			
Batch No.	A100256		
Speed of the m/c	6RPM	7 RPM	8 RPM
AR NO.	890000290449	890000290450	890000290451
1.	86.6	93.9	82.4
2.	86.7	81.3	88.5
3.	82.6	82.1	85.5
4.	81.5	90.0	86.2
5.	83.6	87.6	86.5
6.	81.3	92.2	82.2
Min.	81.3	81.3	82.2
Max.	86.7	93.9	88.5
Avg.	83.71	87.85	85.21

Observation: The Dissolution results at different speeds are found within the specification limits for the batch A100204, A100240, A100256.

Table 13: Physical parameters of Finasteride tablets at 3 different speeds for A100204

Parameter	Limit	Machine speed					
		6RPM		7RPM		8RPM	
		LHS	RHS	LHS	RHS	LHS	RHS
Description	White to off-white colored, round biconvex tablets with FIN' debossing on oneside and plain surface on the other side.	Complies	Complies	Complies	Complies	Complies	Complies
Group weight variation	2.50g ± 2.0% (2.450g – 2.550g)	Min: 2.490g Max: 2.525g	Min: 2.500g Max: 2.528g	Min: 2.490g Max: 2.520g	Min: 2.490g Max: 2.520g	Min: 2.490g Max: 2.515g	Min: 2.490g Max: 2.520g
Individual weight variation	125.0mg + 5.0% (118.75mg to 131.25mg)	Min: 122mg Max: 130mg	Min: 121mg Max: 130mg	Min: 122mg Max: 129mg	Min: 124mg Max: 128mg	Min: 122mg Max: 128mg	Min: 122mg Max: 129mg
Hardness	NLT 2.5 kg/cm^2	Min: 2.6 kg/cm^2 Max:3.2 kg/cm^2	Min: 2.6 kg/cm^2 Max: 3.2 kg/cm^2	Min: 2.8 kg/cm^2 Max: 3.2 kg/cm^2	Min: 2.8 kg/cm^2 Max: 3.2 kg/cm^2	Min: 2.8 kg/cm^2 Max: 3.1 kg/cm^2	Min: 2.8 kg/cm^2 Max: 3.1 kg/cm^2
Thickness	2.90 ± 0.1mm (2.8-3.0 mm)	Min:2.82mm Max:3.00Mm	Min:2.83 mm Max:3.00mm	Min:2.85 mm Max:2.96 mm	Min:2.85 mm Max:2.99mm	Min:2.86mm Max:2.99mm	Min:2.89mm Max:2.99mm
Friability	NMT 1.0% w/w	0.08% - 0.20%	0.07% - 0.59%	0.07% - 0.23%	0.04% - 0.23%	0.07% - 0.19%	0.07% - 0.20%
Disintegration time	NMT 10 minutes	2'45'' – 2'59''	2'32'' – 2'59''	2'47'' – 2'52''	2'45'' – 2'50''	2'48'' – 2'52''	2'45'' – 2'52''

Table 14: Physical parameters of Finasteride tablets at three different speeds for the batch no. A100240

Parameter	Limit	Machine speed					
		6RPM		7RPM		8RPM	
		LHS	RHS	LHS	RHS	LHS	RHS
Description	White to off-white colored, round biconvex tablets with FIN' debossing on oneside and plain surface on the other side.	Complies	Complies	Complies	Complies	Complies	Complies
Group weight variation	2.50g ± 2.0% (2.450g – 2.550g)	Min: 2.495g Max: 2.518g	Min: 2.490g Max: 2.528g	Min: 2.500g Max: 2.509g	Min: 2.500g Max: 2.512g	Min: 2.495g Max: 2.520g	Min: 2.490g Max: 2.510g
Individual weight variation	125.0mg + 5.0% (118.75mg to 131.25mg)	Min: 122mg Max: 128mg	Min: 121mg Max: 128mg	Min: 122mg Max: 130mg	Min: 122mg Max: 130mg	Min: 122mg Max: 128mg	Min: 122mg Max: 129mg
Hardness	NLT 2.5 kg/cm^2	Min: 2.8 kg/cm^2 Max:3.5 kg/cm^2	Min: 2.7 kg/cm^2 Max: 3.4 kg/cm^2	Min: 2.7 kg/cm^2 Max: 3.6 kg/cm^2	Min: 2.6 kg/cm^2 Max: 3.6 kg/cm^2	Min: 2.8 kg/cm^2 Max: 3.4 kg/cm^2	Min: 2.6 kg/cm^2 Max: 3.14kg/cm^2
Thickness	2.90 ± 0.1mm(2.8 – 3mm)	Min:2.80 mm Max:2.91mm	Min:2.82 mm Max:2.92mm	Min:2.81 mm Max:2.95 mm	Min:2.82 mm Max:2.93 mm	Min:2.80mm Max:2.94mm	Min:2.80mm Max:2.94mm
Friability	NMT 1.0% w/w	0.08% - 0.20%	0.07% - 0.59%	0.07% - 0.23%	0.04% - 0.23%	0.07% - 0.19%	0.07% - 0.20%
Disintegration time	NMT 10 min	2'38'' – 2'51''	2'39'' – 2'54''	2'42'' – 2'51''	2'40'' – 2'52''	2'42'' – 2'50''	2'30'' – 2'50''

Table 15: Physical parameters of Finasteride tablets at three different speeds for the batch no. A100256

Parameter	Limit	Machine speed					
		6RPM		7RPM		8RPM	
		LHS	RHS	LHS	RHS	LHS	RHS
Description	White to off-white colored, round biconvex tablets with FIN' debossing on oneside and plain surface on the other side.	Complies	Complies	Complies	Complies	Complies	Complies
Group weight variation	2.50g ± 2.0% (2.450g – 2.550g)	Min: 2.498g Max: 2.509g	Min: 2.497g Max: 2.510g	Min: 2.501g Max: 2.510g	Min: 2.501g Max: 2.511g	Min: 2.500g Max: 2.510g	Min: 2.500g Max: 2.511g
Individual weight variation	125.0mg + 5.0% (118.75mg to 131.25mg)	Min: 120mg Max: 130mg	Min: 120mg Max: 128mg	Min: 121mg Max: 129mg	Min: 120mg Max: 130mg	Min: 121mg Max: 130mg	Min: 121mg Max: 130mg
Hardness	NLT 2.5 kg/cm^2	Min: 2.6 kg/cm^2 Max:3.2 kg/cm^2	Min: 2.6 kg/cm^2 Max: 3.2 kg/cm^2	Min: 2.6 kg/cm^2 Max: 3.2 kg/cm^2	Min: 2.6 kg/cm^2 Max: 3.2 kg/cm^2	Min: 2.6 kg/cm^2 Max: 3.2 kg/cm^2	Min: 2.6 kg/cm^2 Max: 3.1 kg/cm^2
Thickness	2.90 ± 0.1mm (2.80mm – 3.00mm)	Min:2.81 mm Max:2.89 mm	Min:2.81 mm Max:2.90mm	Min:2.81 mm Max:2.91 mm	Min:2.81 mm Max:2.91 mm	Min:2.82mm Max:2.92mm	Min:2.81mm Max:2.91mm
Friability	NMT 1.0% w/w	0.08% - 0.16%	0.08% - 0.20%	0.08% - 0.16%	0.08% - 0.16%	0.08% - 0.16%	0.08% - 0.12%
Disintegration time	NMT 10 minutes	3'32'' – 3'40''	3'42'' – 3'51''	3'25'' – 3'52''	3'15'' – 3'49''	3'40'' – 3'55''	3'36'' – 3'51''

Observation

The physical parameters at different speeds of the machine of 6, 7 & 8 RPM were found within the limits of acceptance criteria for all the three batches.

Table 16: Uniformity of dosage units of Finasteride tablets at different hopper levels for the batch no. A100204, A100240

% of Finasteride (90.0% to 110% of the label claim)						
Batch No.	**A100204**			**A100240**		
Hopper level	**Full**	**Middle**	**Near End**	**Full**	**Middle**	**Near End**
A.R. No.	**890000283383**	**890000283384**	**890000283385**	**890000289343**	**890000289344**	**890000289346**
1.	95.8	94.0	92.7	96.9	95.1	99.0
2.	95.9	98.9	93.8	95.0	96.2	95.8
3.	92.0	93.8	93.8	94.9	95.5	97.2
4.	95.5	96.3	92.7	96.1	98.1	92.3
5.	94.6	92.9	93.3	98.0	93.9	98.2
6.	92.9	95.3	94.4	96.3	94.4	97.9
7.	94.1	94.6	95.2	95.9	94.3	95.1
8.	92.2	92.9	94.5	95.9	96.6	99.3
9.	92.7	101.4	93.5	93.1	94.2	94.0
10.	97.8	95.9	92.6	94.3	92.7	94.0
Min.	92.0	92.9	92.6	93.1	92.7	92.3
Max.	97.8	101.4	95.2	98.0	98.1	99.3
Avg.	94.26	95.6	93.65	95.6	95.1	96.3
RSD.	2.0%	2.8%	0.9%	1.4%	1.7%	2.5%

Table 17: Uniformity of dosage units of Finasteride tablets at different hopper levels for the batch no. A100256

% of Finasteride (90.0% to 110% of the label claim)			
Batch No.	**A100256**		
Hopper level	**Full**	**Middle**	**Near end**
A.R. No.	**890000290446**	**890000290447**	**890000290448**
1.	98.2	96.3	97.2
2.	100.3	98.7	98.7
3.	100.4	101.9	97.7
4.	100.7	97.5	95.2
5.	99.6	97.8	100.1
6.	98.4	98.7	96.9
7.	100.0	98.2	96.3
8.	99.1	96.9	100.
9.	100.9	100.2	95.8
10.	99.6	99.7	98.5
Min.	98.2	96.3	95.2
Max.	100.9	101.9	100.3
Avg.	99.72	98.59	97.67
RSD	0.9%	1.7%	1.8%

Observation

The uniformity of dosage units at different hopper levels were found within the specification limits for the batches A100204, A100240, A100256

Table 18: Physical parameters of Finasteride tablets at full, middle & near end hopper for the batch no. A100204

Parameter	Specification	Full		Middle		Near end	
		LHS	RHS	LHS	RHS	LHS	RHS
Group weight variation	2.50g ± 2.0% (2.450g – 2.550 g)	Min:2.490g Max:2.520g	Min: 2.490g Max: 2.520g	Min: 2.490g Max: 2.520g	Min: 2.490g Max: 2.520g	Min: 2.490g Max: 2.515g	Min: 2.490g Max: 2.520g
Individual weight variation	125.0 mg + 5.0 % (118.75 mg – 131.25mg)	Min:122mg Max:129mg	Min:124mg Max: 128mg	Min:122mg Max: 129mg	Min:124mg Max: 128mg	Min:122mg Max: 129mg	Min:124mg Max: 128mg
Hardness	NLT 2.5 kg/cm²	Min:2.8 kg/cm² Max:3.2 kg/cm²	Min: 2.8 kg/cm² Max: 3.2 kg/cm²	Min: 2.8 kg/cm² Max: 3.2 kg/cm²	Min: 2.8 kg/cm² Max: 3.2 kg/cm²	Min: 2.8 kg/cm² Max: 3.2 kg/cm²	Min: 2.8 kg/cm² Max: 3.2 kg/cm²
Thickness	2.90 ± 0.1mm (2.80mm – 3.00 mm)	Min:2.85mm Max:2.96mm	Min: 2.85mm Max: 2.99mm	Min: 2.85mm Max: 2.96mm	Min: 2.85mm Max: 2.99mm	Min: 2.85mm Max: 2.96mm	Min: 2.85mm Max: 2.99mm
Disintegration time	NMT 10 minutes	2'49''- 2'52''	2'45'' – 2'50''	2'48" – 2'50''	2'45'' – 2'50"	2'47'' – 2'52''	2'45'' – 2'50"
Friability	NMT 1.0% w/w	0.08%- 0.16%	0.07% - 0.16%	0.07% - 0.20%	0.04% - 0.15%	0.12% - 0.23%	0.15% - 0.23%

Table 19: Physical parameters of Finasteride tablets at full, middle & near end hopper for the batch no. A100240

Parameter	Specification	Full		Middle		Near end	
		LHS	RHS	LHS	RHS	LHS	RHS
Group weight variation	2.50g ± 2.0% (2.450g – 2.550 g)	Min:2.504g Max:2.506g	Min: 2.500g Max: 2.510g	Min: 2.505g Max: 2.509g	Min: 2.505g Max: 2.512g	Min: 2.490g Max: 2.508g	Min: 2.500g Max: 2.515g
Individual weight variation	125.0 mg + 5.0 % (118.75 mg – 131.25mg)	Min:123mg Max:130mg	Min:122mg Max: 131mg	Min:123mg Max: 129mg	Min:123mg Max: 130mg	Min:122mg Max: 128mg	Min:124mg Max: 128mg
Hardness	NLT 2.5 kg/cm²	Min:2.8 kg/cm² Max:3.2 kg/cm²	Min: 2.8 kg/cm² Max: 3.2 kg/cm²	Min: 2.8 kg/cm² Max: 3.5 kg/cm²	Min: 2.8 kg/cm² Max: 3.5 kg/cm²	Min: 2.9 kg/cm² Max: 3.6 kg/cm²	Min: 2.8 kg/cm² Max: 3.6 kg/cm²
Thickness	2.90 ± 0.1mm (2.80mm – 3.00 mm)	Min:2.82mm Max:2.99mm	Min: 2.80mm Max: 2.91mm	Min: 2.82mm Max: 2.90mm	Min: 2.82mm Max: 2.90mm	Min: 2.81mm Max: 2.94mm	Min: 2.85mm Max: 2.91mm
Disintegration time	NMT 10 minutes	2'45''- 2'51''	2'40'' – 2'52''	2'40'' – 2'52"	2'40'' – 2'45''	2'42" – 2'50''	2'45'' – 2'50''
Friability	NMT 1.0% w/w	0.15%- 0.19%	0.23% - 0.32%	0.01% - 0.19%	0.01% - 0.23%	0.19% - 0.24%	0.15% - 0.19%

Table 20: Physical parameters of Finasteride tablets at full, middle & near end hopper for the batch no. A100256

Parameter	Specification	Full		Middle		Near end	
		LHS	RHS	LHS	RHS	LHS	RHS
Group weight variation	2.50g ± 2.0% (2.450g – 2.550 g)	Min:2.491g Max:2.511g	Min: 2.469g Max: 2.508g	Min: 2.504g Max: 2.510g	Min: 2.501g Max: 2.511g	Min: 2.501g Max: 2.509g	Min: 2.503g Max: 2.506g
Individual weight variation	125.0 mg + 5.0 % (118.75 mg – 131.25mg)	Min:121mg Max:129mg	Min:120mg Max: 130mg	Min:121mg Max: 129mg	Min:120mg Max: 130mg	Min:120mg Max: 129mg	Min:120mg Max: 129mg
Hardness	NLT 2.5 kg/cm^2	Min:2.6 kg/cm^2 Max:3.2 kg/cm^2	Min: 2.6 kg/cm^2 Max: 3.2 kg/cm^2	Min: 2.8 kg/cm^2 Max: 3.1 kg/cm^2	Min: 2.8 kg/cm^2 Max: 3.2 kg/cm^2	Min: 2.6 kg/cm^2 Max: 3.2 kg/cm^2	Min: 2.8 kg/cm^2 Max: 3.2 kg/cm^2
Thickness	2.90 ± 0.1mm (2.80mm – 3.00 mm)	Min:2.81mm Max:2.91mm	Min: 2.81mm Max: 2.91mm	Min: 2.80mm Max: 2.87mm	Min: 2.81mm Max: 2.89mm	Min: 2.81mm Max: 2.89mm	Min: 2.81mm Max: 2.89mm
Disintegration Time	NMT 10 minutes	3'36''	3'46''	3'25'' – 3'52''	3'15'' – 3'49''	3'41''- 3'46''	3'38'' – 3'40''
Friability	NMT 1.0% w/w	0.16%	0.12%	0.12%	0.11% - 0.12%	0.08%	0.16%

Observation

The physical parameters of Finasteride tablets in three different hopper levels are complying with specifications and met with the acceptance criteria defined for all the three batches.

Table 21: Finished product Pooled Sample Results as per Specification F0-200000020-00 (Dissolution Profile)

S.No.	Test	Specification	Results					
			A100204		A100240		A100256	
			AR No. NIFV0112		AR No.AIFV0154		AR No.A1	
1.	Description	White colored, round biconvex film coated tablets with 'FIN' debossing on one side and plain surface on other side	Complies		Complies		Complies	
2.a)	**Dissolution 10 min**	For Information	D1	54.0%	D1	50.7%		
			D2	58.2%	D2	60.4%		
			D3	41.1%	D3	54.1%		
			D4	52.1%	D4	50.2%		
			D5	61.3%	D5	36.8%		
			D6	35.2%	D6	52.4%		
			D7	55.0%	D7	50.9%		
			D8	52.7%	D8	46.2%		
			D9	49.4%	D9	52.4%		
			D10	56.3%	D10	67.3%		
			D11	57.7%	D11	35.4%		
			D12	58.1%	D12	28.9%		
b)	**15 min**		D1	86.7%	D1	75.4%		
			D2	81.7%	D2	75.7%		
			D3	75.9%	D3	75.9%		
			D4	82.1%	D4	74.4%		
			D5	85.5%	D5	72.4%		
			D6	77.6%	D6	76.8%		

			D7	82.1%	D7	
			D8	88.8%	D8	
			D9	79.6%	D9	76.5%
			D10	85.2%	D10	75.2%
			D11	81.4%	D11	72.6%
			D12	85.9%	D12	84.5%
						74.0%
						69.6%
			D1	88.0%	D1	80.9%
			D2	85.8%	D2	80.9%
			D3	83.8%	D3	79.6%
			D4	87.6%	D4	78.3%
			D5	89.4%	D5	78.2%
2.	**Dissolution**	For Information	D6	85.4%	D6	80.7%
c)	**20 min**		D7	87.0%	D7	81.5%
			D8	95.5%	D8	79.9%
			D9	87.0%	D9	78.5%
			D10	89.7%	D10	87.7%
			D11	85.8%	D11	79.0%
			D12	91.1%	D12	77.3%
			D1	94.0%	D1	83.9%
			D2	89.2%	D2	83.4%
			D3	89.4%	D3	83.9%
			D4	91.4%	D4	81.2%
			D5	92.2%	D5	84.2%
			D6	92.5%	D6	83.3%
d)	**30 min**		D7	92.7%	D7	84.9%
			D8	92.9%	D8	83.1%
			D9	92.65	D9	83.7%
			D10	92.8%	D10	90.3%
			D11	92.7%	D11	84.3%
			D12	92.9%	D12	83.6%
			D1	95.4%	D1	85.8%
			D2	89.3%	D2	85.6%
			D3	90.6%	D3	84.4%
			D4	92.2%	D4	84.2%
			D5	92.1%	D5	86.6%
			D6	94.4%	D6	85.9%
e)	**45 min**		D7	91.0%	D7	86.2%
			D8	99.2%	D8	85.2%
			D9	95.6%	D9	84.7%
			D10	93.1%	D10	89.6%
			D11	89.4%	D11	85.7%
			D12	95.3%	D12	86.2%

YIELD DETAILS

Table 22: Compilation of yield details of Finasteride tablets at compression stage for the batch Nos. A100204, A100240 & A100256

Batch No.	Yield in %
	Compression
A100204	92.00%
A100240	91.2%
A100256	98.88%

Table 23: Finished Product analytical report for the batch No. A100204, A100240 & A100256

Batch No. / TEST	Specification	A100204	A100240	A100256
		890000283090	890000289631	890000290571
Description	White to off-white colored, round biconvex tablets with FIN' debossing on one side and plain surface on other side.	Complies	Complies	Complies
Identification test by HPLC	The retention time of the major peak in the chromatogram of the test preparation corresponds to that in the chromatogram of the standard preparation, as obtained in the assay.	Complies	Complies	Complies
Disintegration Time	NMT 12 minutes	Complies 3 min	Complies 3 min	Complies 3 min
Uniformity of weight	When 20 tablets are weighed not more than 2 tablets should deviate from the average weight by more than ± 7.5% w/w & no tablet deviates by more than ± 15.0% w/w	Complies	Complies	Complies
Uniformity of content	When 10 tablets are tested for their contents, the content of each tablet is between 90.0% and 110% of the label claim	Unit-1 96.7 Unit-2 95.5 Unit-3 91.9 Unit-4 100.3 Unit-5 94.7 Unit-6 93.9 Unit-7 91.7 Unit-8 96.3 Unit-9 94.1 Unit-10 95.9	Unit-1 96.2 Unit-2 97.4 Unit-3 94.1 Unit-4 96.5 Unit-5 94.3 Unit-6 92.9 Unit-7 98.1 Unit-8 94.1 Unit-9 96.8 Unit-10 94.1	Unit-1 100.2 Unit-2 99.2 Unit-3 99.4 Unit-4 99.0 Unit-5 98.5 Unit-6 99.8 Unit-7 98.3 Unit-8 100.2 Unit-9 98.5 Unit-10 95.2
RSD	NMT 6.0%	2.6%	1.8%	1.5%

Batch No. / TEST	Specification	A100204	A100240	A100256
		890000283090	890000289631	890000290571
Dissolution	NLT 75% (Q) of labelled amount dissolved in 45 min	STAGE S1 UNIT-1 81.3 UNIT-2 90.6 UNIT-3 93.5 UNIT-4 90.1 UNIT-5 96.1 UNIT-6 92.6	STAGE S1 UNIT-1 92.4 UNIT-2 87.4 UNIT-3 91.9 UNIT-4 92.0 UNIT-5 93.7 UNIT-6 92.4	STAGE S1 UNIT-1 88.1 UNIT-2 84.8 UNIT-3 87.9 UNIT-4 91.0 UNIT-5 86.6 UNIT-6 84.4
Assay	NLT 4.75 mg and NMT 5.25 mg	4.84 mg	4.90 mg	5.08 mg
Diameter	7.40 mm ± 0.20 mm	7.42 mmMin: 7.39 mm Max: 7.46 mm	7.44 mmMin: 7.42 mm Max: 7.48 mm	7.44mmMin: 7.40 mm Max: 7.48 mm
Thickness	2.90 mm ± 0.20 mm	2.90 mm	3.00 mm	2.98 mm
Hardness	NLT 6.0 % w/w	2.93 kpMin:2.68 kp	2.72 kpMin: 2.55 kp	2.90 kpMin: 2.54 kp
Average weight	129.0 mg ± 3.0 %	127.2 mg	127.92 mg	128.7mg
Water	NMT 6.0%w/w	4.74%w/w	4.86%w/w	4.88%w/w
Related substances by HPLC i) Impurity A	NMT 0.3%	0.000%	0.000%	0.056%
ii) Impurity B		0.000%	0.000%	0.000%
iii) Impurity C		0.095%	0.07%	0.110%
iv) Maximum single unknown impurity	NMT 0.1%	0.000%	0.000%	0.000%
v) Total impurities	NMT 0.6%	0.095%	0.07%	0.165%

DISCUSSION

The validation of FINASTERIDE tablets was conducted for a batch size of 5,00,000 tablets for compression stage due to change in the compression machine from 16 station single rotary to 45 station double rotary machine as per change control no.200006024. Hence the compression stage was validated for the batches no. A100204, A100240 & A100256.

CONCLUSION

The compression was done considering the aspects of compression process. The physical parameters checked include individual weight variation, thickness, hardness, friability and disintegration time in both LHS & RHS.

The analytical data on content uniformity & Dissolution of compressed tablets arte found to be well within the limits of acceptance criteria as described in the specification. From the above, it is concluded that compression process for FINASTERIDE tablets is validated.

The finished product report of the batch no.A100204 (A.R. No. 890000283090), A100240 (AR No.890000289631) & A100256 shows that the product meets the acceptance criteria.

The report overall summarizes the data of three batches of Finasteride tablets 5 mg. the following were observed during the processing of these validation batches and the same parameters were recommended for the subsequent commercial batches.

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