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Research Article

PROCESS VALIDATION OF TERBINAFINE 250MG TABLETS

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ABSTRACT

In the present work simultaneous process validation of Terbinafine tablet was completed. Process validation is the mean of guaranteeing and giving narrative confirmation that procedure inside their predefined outline parameter are prepared to do over and over and dependably delivering a completed result of required quality. The procedure approval of Terbinafine HCL tablets of dosage 250mg was completed for 3 back to back bunches of Batch no.1, Batch no.2, Batch no.3 which incorporate the validation of basic strides of assembling constituting apportioning, filtering, Dry blending, Granulation, Drying, Blending, Compression and Packing. Disintegration of the three successive validation clusters were contrasted and the reference test. All previously mentioned process was approved amid the procedure approval. The outcome got of the three clumps were found inside the points of confinement. In this way the item with required particular can be reliably acquired.

Keywords: Heating ventilation and air conditioning system, Standard operating procedures, Validation master plan, Disintegration time, Quality management system, Over the counter, New Drug Application, Quality Assurance, Design Qualification, Operational Qualification, Installation Qualification, Performance Qualification.

INTRODUCTION

Validation is the way toward setting up narrative proof showing that a technique, process, or movement completed in testing and afterward creation keeps up the coveted level of consistence at all stages. In the pharmaceutical business, it is vital that notwithstanding last testing and consistence of items, it is likewise guaranteed that the procedure will reliably create the normal outcomes.[1]

Validation mainly Based on, FDA regulations describing current good manufacturing practice (CGMP) for finished pharmaceuticals are provided in 21 CFR parts 210 and 211.

a wide variety of procedures, processes, and activities need to be validated, the field of validation is divided into a number of subsections including the following:

Equipment validation, Facilities validation, HVAC system validation, Process Validation, Analytical method validation, Computer system validation, Packaging validation, Cold chain validation.
Similarly, the activity of qualifying systems and equipment is divided into a number of subsections including the following:
Design qualification (DQ), Component qualification (CQ), Installation qualification (IQ), Operational qualification (OQ), Performance qualification (PQ)
Process Validation is the analysis of data gathered throughout the design and manufacturing of a product in order to confirm that the process can reliably output products of a determined standard. Regulatory authorities like EMA and FDA have published guidelines relating to process validation.[2]

DEFINITIONS [2-5]

Process Validation is the analysis of data gathered throughout the design and manufacturing of a product in order to confirm that the process can reliably output products of a determined standard. Regulatory authorities like EMA and FDA have published guidelines relating to process validation.

European commission

1991 –Validation-"Act of proving, in accordance of GMPs that Any…" process actually leads to expected results.
2000 -"Documented evidence that the process, operated within established Parameters, can perform effectively and reproducibly to produce a Medicinal product meeting its predetermined specifications and quality attributes".

US FDA Definition

"Process validation is establishing documented evidence which provides a high degree of assurance that a specified process will consistently produce a product meeting its pre-determined specifications and quality characteristics."

ICH Definition

"Process Validation is the means of ensuring and providing documentary evidence that processes within their specified design parameters are capable of repeatedly and reliably producing a finished product of the required quality."

WHO Definition

"The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to expected result."

MAJOR PHASES IN VALIDATION

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

Phase 1: **Pre-validation Qualification Phase** – This stage is otherwise called process configuration stage concentrating solely on capability endeavors. This stage predominantly covers all exercises identifying with item RnD, detailing pilot bunch thinks about, scale-up examines, innovation exchange to business scale clusters, setting up strength conditions and capacity, and treatment of in-process and completed measurement shapes, gear capability, establishment capability, ace item report, operational capability and process limit. Additionally, this the phase in which the foundation of a strategy for the procedure control is occurring utilizing collection learning and comprehension of the procedure.

Phase 2: **Process qualification-** Amid this stage the procedure which is outlined in process configuration stage is assessed whether the procedure is equipped for reproducible business producing. It affirms that all the set-up points of confinement of basic process parameters are legitimate and attractive items can be delivered.

There are 2 aspects of process qualification;
1. Design of facilities and qualification equipment and utilities- Activities perform to assure proper facilities design and that the equipment and utilities are suitable for their intended use and perform properly.

2. Process Performance Qualification- It involves defining performance criteria and deciding what to collect when, how much data, and appropriate analysis of data. Manufacturer must scientifically determine suitable criteria and justify it.

Phase 3: **Continued process verification-**This is known as the Validation Maintenance Phase, it requires visit survey of all archives identified with the procedure, including approval of review answers, to guarantee that there have been no progressions, deviations, disappointments and alterations to the generation procedure and that all standard working techniques (SOPs), including change control strategies, have been taken after. At this stage, the approval group containing people speaking to every single real division additionally guarantees that there have been no progressions/deviations that ought to have brought about requalification and revalidation. A cautious plan and approval of frameworks and process controls can set up a high level of certainty that all parcels or clumps created will meet their expected determinations. It is accepted that all through assembling and control, activities are led as per the guideline of good assembling practice (GMP) both as a rule and in particular reference to sterile item make. [6, 7]

Based on the stage of the production lifecycle at which process validation is performed, it can be of four types:

1. Prospective Validation
This kind of approval is performed before creation; amid an item's improvement organize. A hazard examination is performed to survey the creation procedure by separating it into discrete advances. These are exclusively assessed and in light of past involvement, the probability of every one prompting basic circumstances is resolved.

- Once you've recognized the basic sub-forms, these are the means you ought to take after: Evaluate singular hazard for every one
- Investigate and survey

1. Potential causes
2. Probability of circumstances emerging
3. The degree of their belongings

- Draw up the preliminary designs
- Set needs for the approval

After this, you can start with the preliminaries and make an over appraisal. Forthcoming approval is basic for restricting the danger of value failures and blunders happening amid the genuine generation.

2. Concurrent Validation
You should screen the initial three clusters delivered on a creation scale as nearly as would be prudent. The information accumulated through this progression can give a top to bottom understanding of the basics, which extraordinarily impacts the viability of simultaneous approval.
Together with thorough pattern examination, which incorporates different viewpoints like security, you ought to perform simultaneous approval all through an item's life to whatever degree it is required.

3. Retrospective Validation
As the name recommends, review approval is fairly similar to approval looking back. It includes inspecting the past encounters of the procedure and assessing the last control tests. This assessment is done while accepting that the strategies, piece and gear stays unaltered. To decide how well the procedure parameters stick to the allowable range, you can likewise lead a pattern examination.
Review approval ought not be viewed as a quality affirmation measure, rather it ought to be performed just in specific conditions, similar to when you're presenting approval necessities out of the blue. It is more helpful for building up needs for approval, so maintain a strategic distance from this procedure for new items or procedures.

4. Revalidation
Revalidation is fundamental for guaranteeing that any progressions made to the procedure or its condition have not brought about unfriendly consequences for item quality or process attributes. It can be separated into two sub-types:

- Revalidation after Changes – Whenever you've presented any new components in the assembling procedure, revalidation should be performed to learn their belongings. There can be various changes in the assembling or standard working methods that effect item quality. These can be:
- Changes in Starting Materials – Changes in physical traits can modify the mechanical properties of mixes and materials, which can thusly effectively affect the item or the procedure.
- Changes in Packaging Material – If you switch bundling materials, you may likewise be compelled to roll out improvements to the methods took after amid bundling, which can affect item strength.
- Changes in Process – Any time you change the assembling procedure, the consequent advances can be influenced and subsequently, the item quality as well.
- Changes in Equipment – Repairs, support and substitution of key segments is unavoidable, however make sure to survey whether quality is influenced and how much.
- Changes in Support System or Production Area – Rearrangement of emotionally supportive networks or

creation zones can likewise influence item quality, particularly basic frameworks like ventilation.

Periodic Revalidation-Similar to general upkeep, alignment and other centre prerequisites, revalidation at booked interims encourages you guarantee that your frameworks and checks are performing inside the required norms. [8]

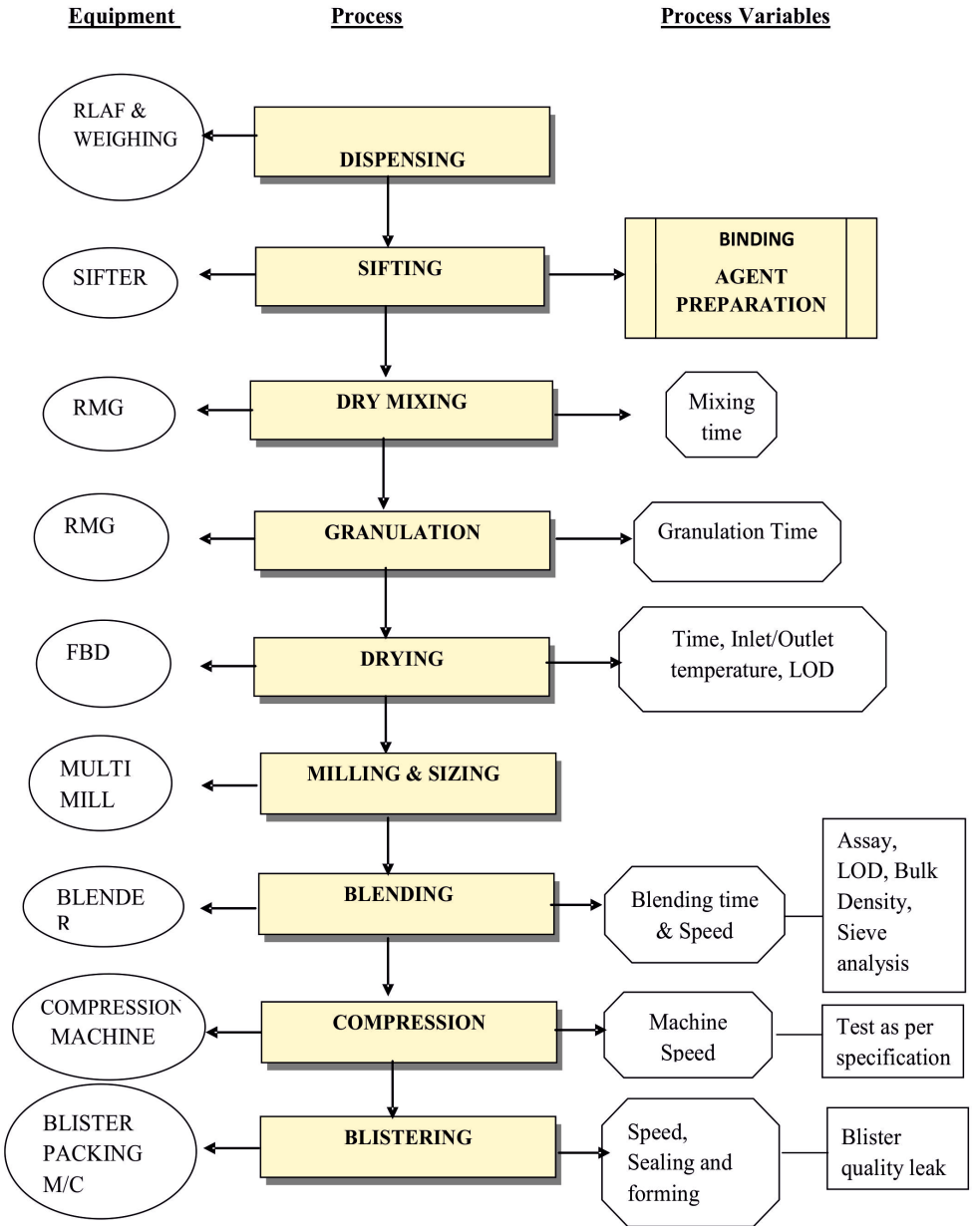
MATERIALS AND METHODS

Terbinafine Hydrochloride, Crosscarmilose Sodium (Ac-di-sol), Micro crystalline cellulose, Colloidal silicon dioxide (Aerosil), Lactose, Betacyclodextrin, PVPK-30, Magnesium Stereate, Purified Talcum, Sodium starch Glycolate, Iso Propyl alcohol.

Table 1: Machineries

Name of the Equipment	Size / Capacity
Vibro Sifter	30"
Multimill	750 to 2200 RPM
RMG	400 Ltr.
FBD	120kg/Drying through steam heating
Octagonal Blender	750 Ltr.
Compression Machine (35 station)	80000 Tablets/hr
Tablets Inspection Machine	Standard GMP Model
Blister packing machine	45cuts/minute

Process Flow Diagram



Manufacturing process & critical control parameters

1. Sifting- Material was passed through specified sieve using vibro sifter
Machine & Equipments- Vibro Sifter & Multimill
Process Description- Machine was set, Terbinafine HCl, Microcrystalline Cellulose (MCC), Lactose, Betacyclodextrin & Cross carmellose Sodium was shifted.
Control Points- Sieve integrity was checked before & after sifting.

2. Binder preparation: Binder Paste preparation.
Machine & Equipments- Paste Kettle
Process Description-25ltr IPA and 3.5 Kg PVPK-30 was taken in s.s vessels with constant stirring up to clear solution. Obtained and pas through 100♯ nylon cloth.

3. Dry-mixing: Sifted materials was loaded into the Rapid Mixer Granulator for 15 minutes at about 13 to 15 Amp.
Machine & Equipments- Rapid Mixer Granulator
Process Description- sifted material was loaded in to the RMG.& Operated for 15 minutes. Amp. load about 10 to 15 Amp. The material was unloaded in plastic containers lined with double polybags.
Control Points- Mixing time & Amp. load.

4: Granulation: The material was granulated
Machine & Equipments- RAPID MIXER GRANULATOR
Process Description- The binder paste was added into it within 2 minutes and mixed for about 15 minutes till a consistent cohesive mass was obtained. Remaining quantity of Isopropyl Alcohol & additional quantity was added
(if required).
Control Points- Mixing time & Amp. load.

5. Drying: Sifted material was dried through Fluidized Bed dryer (FBD)
Machine & Equipments- Fluidized Bed Dryer (FBD)
Process Description- The granules were loaded in FBD bowl, Drying temperature was maintained 50-55°C. The material was dried for 40 minutes with hot air or till desired moisture was achieved. The reading of moisture content at the end of operation of each lot was recorded.
Control Points- Drying Time, vacuum & temperature

6. Sizing & milling: Dried granule sized & milled
Machine & Equipments- Multimill/ Vibro Sifter
Process Description- Dried granules were shifted though #14 sieve fitted with vibro sifter and collected in double polythene bag.
Over size material to be re-sized by passing through Multi mill fitted with 3.0mm Screen.
Control Points- Sieve size

7. Final mixing (lubrication)- The required materials are loaded in octagonal blender & operated for an specified time to obtain uniform blend.
Machine & Equipments- Octagonal Blender
Process Description- Compacted & re-sized materials was loaded in Octagonal blender. Octagonal blender was operated for 20 minutes at 12 rpm to obtain homogenous mass with even distribution of ingredients.
Control Points- Blending time & blender speed. Store material in tightly closed containers below 25^0C.

8. Compression
Machine & Equipments- Compression Machine 35 Station
Process Description- Approved blended granules was brought to compression to make into compressed tablets by using Rotary Compression machine. Parameters, was checked and adjusted to meet specified criteria. In-process check was carried out concomitantly at defined intervals as defined.
Control Points- Speed of machine (15 to 25 rpm).

EVALUATION OF TABLETS

Table 2

Process stage	Variables	Justification	Sampling	Acceptance Criteria
Dry Mixing	• Speed of RMG • Time	Homogenous mixing of all materials	Each 5 gm sample from different locations Top Left, Top Right, Middle, Bottom Left, Bottom Right and one composite sample From RMG After 10 & 15 min. mixing interval.	Assay: Terbinafine HCl equivalent to Terbinafine: 90.0 % to 110.0% RSD = NMT 3%
Drying	• Temperature • Time	Uniformly dry the Granules	From FBD Bowl.	LOD of Granules between 1.0 to 3.0% w/w
Lubrication	• Speed of blender • Time	Uniform dough mass to form Distribution of lubricants in homogenous mixing with dry Granules	Physical verification. Each 5 gm sample from 10 different locations Top right, Top Left, Top middle, Middle left, Middle Center, Middle bottom, Bottom left, Bottom right, Bottom middle, discharge bottom from octagonal Blender after 10, 20 & 30 min. mixing interval.	Assay: Terbinafine HCl equivalent to Terbinafine: 90.0 % to 110.0% RSD = NMT 2%
			100 gm composite sample from octagonal Blender	Bulk density, Taped density, angle of repose, sieve Analysis, compressibility index (for information) & Loss on Drying between 1.0 – 3.0% w/w
Compression	• Initial • middle • end of Compression	All compressed core tablet complies with specification of core tablets	Initial, middle, End of compression. Different speed of machine & Low & high pressure of compression machine	As per specification (Table 3)

Blister sealing	• Speed • Temperature	Physical appearance. To get proper sealing and cutting, over coding details and other physical properties	At sealing Temp.160 to 180^{0}C & forming Temperature 140^{0}C to 160^{0}C & collect 8 Blister at different rpm	- Blister should have aesthetically good appearance, proper sealing, cutting, Intactness and legible over coding batch details - Leak Test: No one tablet should leak or wet.

Table 3: Compressed tablet specifications

Sr. No.	Test/Parameter	Specifications	Frequency
1.	Description	White, Round, biconvex, scored on one side uncoated tablets.	Every hour
2.	Avg. Wt.	430mg±2% (421.40mg to 438.60mg)	Every half hour
3.	Uniformity of weight	± 5% of avg. weight	Every hour
4.	Hardness	NLT 3.0 Kg/cm^2	Every hour
5.	Diameter	11.0mm±0.2mm	Every hour
7.	Thickness	4.80mm ±0.2mm	Every hour
8.	Friability	NMT 1.0%	Every hour
9.	Disintegration Time	NMT 10 minutes	Every hour
Other tests:			
Low & high Hardness: Diameter, thickness, hardness, Friability & disintegration test shall be performed.			
Low speed & high speed: Collect 50 tablets for Avg. weight of tablets, uniformity of weight, Diameter, thickness, Hardness, Friability & disintegration test shall be performed.			
Remarks: Collect 50 tablets for each point & 20 tablets for group weight.			

RESULTS AND DISCUSSION

All the results are found satisfactory and within the predetermined quality attributes and are tabulated in Tables from 4-18.

1. SIFTING STAGE-Whole material was passed through the given mesh size no foreign material was found on the sieve.

Table 4

Batch No.	Test/activity	Specifications/Requirements	Observations
Batch no. 1	Physical Observation for residue on sieve & foreign matter	Whole qty of given material should pass easily through given mesh and No foreign matter should observed	Whole material passed through given mesh and no foreign material found
Batch no. 2	Physical Observation for residue on sieve & foreign matter	Whole qty of given material should pass easily through given mesh and No foreign matter should observed	Whole material passed through given mesh and no foreign material found
Batch no. 3	Physical Observation for residue on sieve & foreign matter	Whole qty of given material should pass easily through given mesh and No foreign matter should observed	Whole material passed through given mesh and no foreign material found

2. DRY MIXING STAGE- All the materials were mixed properly, and the content uniformity results was found within the limit.

Table 5: Mixing uniformity after dry mixing

Location		Batch no.1		Batch no.2		Batch no.3	
		10 Min.	**15 Min.**	**10 Min.**	**15 Min.**	**10 Min.**	**15 Min.**
TR, assay%		100.46%	98.17%	101.58%	98.75%	99.46%	100.85%
TL, assay%		103.11%	101.69%	99.00%	99.13%	99.15%	100.04%
MI, assay%		101.83%	99.70%	98.86%	100.33%	100.77%	99.25%
BR, assay%		105.83%	101.44%	99.57%	98.47%	99.85%	100.56%
BL, assay%		102.91%	101.62%	101.68%	99.25%	98.37%	101.21%
composite		103.74%	104.34%	99.44%	98.76%	99.67%	99.65%
Average		102.98%	101.16%	100.02%	99.15%	99.55%	100.25%
RSD%		1.75%	2.06%	1.28%	0.66%	0.79%	0.74%
Acceptance Criteria	**Assay**	**90%-110% of Claim**					
	RSD%	**NMT 3%**					

3. DRYING STAGE: All the material was dried completely and LOD was performed and results were found within the limits.

Table 6: Loss on drying after drying

Location	Batch no.1	Batch no.2	Batch no.3
TL, LOD%	1.40%	1.60%	1.50%
TR, LOD%	1.60%	1.60%	1.60%
M, LOD%	1.80%	2.00%	1.70%
BL, LOD%	1.60%	1.40%	1.45%
BR, LOD%	1.40%	1.40%	1.70%
Average	1.56%	1.60%	1.59%
Acceptance Criteria	**1.0% to 3.0%**		

4. BLENDING (LUBRICATION)-Assay of the blended material was performed, and results was found satisfactory within the limit.

Table 7: Percentage assay after Lubrication

Location	Batch no.1			Batch no.2			Batch no.3		
	10 Min	**20 Min**	**30 Min**	**10 Min**	**20 Min**	**30 Min**	**10 Min**	**20 Min**	**30 Min**
TL, assay%	101.42%	100.85%	98.60%	100.20%	100.68%	100.14%	98.98%	98.62%	98.94%
TR, assay%	100.95%	100.12%	98.41%	99.44%	99.93%	99.80%	100.03%	101.66%	98.40%
TC, assay%	99.07%	101.60%	99.12%	98.86%	100.09%	102.95%	98.41%	99.37%	100.72%
ML, assay%	100.03%	100.08%	98.17%	99.25%	100.51%	101.60%	98.24%	98.99%	99.74%
MR, assay%	99.04%	102.00%	99.44%	100.28%	99.39%	101.40%	98.60%	99.80%	100.07%
MC, assay%	100.02%	101.42%	101.46%	101.89%	99.68%	100.74%	102.35%	98.93%	99.48%
BL, assay%	98.41%	100.68%	98.28%	101.44%	100.20%	101.08%	100.62%	101.98%	98.56%
BR, assay%	98.38%	101.53%	99.28%	98.26%	99.37%	100.55%	100.02%	99.73%	99.70%
BC, assay%	98.67%	101.33%	101.01%	100.39%	99.41%	101.90%	102.50%	100.42%	102.95%
DB, assay%	99.01%	101.18%	98.65%	100.64%	100.43%	102.70%	99.05%	101.34%	101.69%
Composite	98.93%	99.17%	98.58%	102.25%	100.79%	101.31%	98.71%	99.62%	99.00%
Average	99.45%	100.91%	99.18%	100.26%	100.04%	101.29%	99.77%	100.0%	99.93%
RSD%	1.01%	0.83%	1.10%	1.25%	0.53%	0.97%	1.51%	1.11%	1.38%
Acceptance criteria	**Assay %**		**90%-110% of claim**						
	RSD%		**NMT 2.0%**						

5. BLEND UNIFORMITY

Table 8

Tests	**Observations**			**Acceptance Criteria**
Description	**Batch no.1**	**Batch no.2**	**Batch no.3**	White colored granular powder
	White granular powder	White granular powder	White granular powder	
Assay of Terbinafine HCl	99.66%	99.87%	99.33%	95.0% to 105.0%
Bulk Density (un-tapped)	0.532 g/ml	0.526 g/ml	0.527 g/ml	For Informatory purpose
Bulk Density (Tapped)	0.658 g/ml	0.653 g/ml	0.659 g/ml	For Informatory purpose
Compressibility Index	19.14%	19.47%	20.00%	NMT 25 %
Moisture content	1.0% w/w	1.4% w/w	1.6% w/w	1.0% to 3.0%
Angle of Repose	42.55º	42.61 º	42.70º	For Informatory purpose

6. COMPRESSION STAGE- All the in process checks at different sampling condition was performed and the results found satisfactory and within the predetermined limits.

Table 9: (Initial, Middle & Final sample) (L.H.S.)

Test	**Specifications/ Requirements**	**Observations**								
		Batch no.1			**Batch no.2**			**Batch no.3**		
		Initial	**Middle**	**End**	**Initial**	**Middle**	**End**	**Initial**	**Middle**	**End**
Description	White, round, biconvex, scored on one side, uncoated tablets.	complies	complies	complies	complies	complies	complies	complies	complies	Complies
Avg. Wt.	430mg ±2%	428.44	435.2	431.96	429.82	433.65	430.26	432.71	428.36	427.72
Wt. Uniformity	±5% of Avg. wt.	-0.52 to +2.51	-1.99 to +1.15	-3.18 to +1.21	-0.96 to +2.74	-1.56 to +1.12	-1.54 to +1.83	-1.34 to +1.80	-1.25 to +2.27	-1.71 to +2.85
Diameter	11.0 mm±0.2mm	11.09 to 11.14	11.11 to 11.16	11.11 to 11.17	11.10 to 11.15	11.00 to 11.15	11.08 to 11.14	11.09 to 11.13	11.08 to 11.15	11.08 to 11.12
Thickness	4.8mm ± 0.2mm	4.86 to 4.99	4.85 to 4.87	4.92 to 5.00	4.88 to 5.00	4.85 to 4.94	4.84 to 5.95	4.81 to 4.93	4.81 to 4.91	4.77 to 4.85
Friability	NMT 1.0%	0.665	0.757	0.767	0.662	0.619	0.564	0.587	0.575	0.604
Hardness	NLT 3.0Kg	3.0 to 3.4	3.2 to 3.6	3.0 to 3.6	3.0 to 3.2	3.2 to 3.6	3.2 to 4.0	3.0 to 3.4	3.0 to 3.8	3.2 to 3.8
DT	NMT 10 minutes	6.0	7.0	6.30	6.30	7.05	6.47	6.31	7.10	7.13
Dissolution	NLT- 80% of label claim	96.34 to 100.82	98.36 to 104.68	96.95 to 101.06	96.63 to 105.16	98.89 to 102.68	97.71 to 101.66	94.01 to 96.59	99.36 to 101.12	99.99 to 104.57
Assay	237.50mg to 262.50mg (95.0% to 105.0%)	246.99	245.55	256.09	251.08	245.96	249.54	248.89	246.48	247.96
RSD % of Assay	NMT 3.0%	2.29%			1.05%			0.49%		

Table 10: (Initial, Middle & Final sample) (R.H.S.)

Test	Specifications/ Requirements	Observations								
		Batch no.1			Batch no.2			Batch no.3		
		Initial	Middle	End	Initial	Middle	End	Initial	Middle	End
Description	White, round, biconvex, scored on one side, uncoated tablets.	compli es	compli es	compli es	compli es	compli es	compli es	compli es	compli es	Compli es
Avg. Wt.	430mg ±2%	432.46	431.81	429.65	430.46	429.58	432.56	431.44	433.83	428.35
Wt. Uniformity	±5% of Avg. wt.	-1.47 to +1.07	-2.82 to +1.13	-1.73 to +0.92	-1.33 to +1.55	-1.43 to +2.08	-1.22 to +2.01	-1.38 to +1.91	-1.66 to +0.80	-1.34 to +1.93
Diameter	11.0 mm±0.2mm	11.09 to 11.13	11.10 to 11.14	11.11 to 11.15	11.11 to 11.14	11.09 to 11.17	11.11 to 11.16	11.09 to 11.12	11.10 to 11.13	11.07 to 11.14
Thickness	4.8mm ± 0.2mm	4.85 to 4.90	4.90 to 5.00	4.88 to 4.94	4.88 to 4.94	4.77 to 4.86	4.73 to 4.87	4.85 to 4.94	4.87 to 4.96	4.78 to 4.84
Friability %	NMT 1.0%	0.586	0.708	0.742	0.615	0.813	0.697	0.489	0.661	0.503
Hardness	NLT 3.0Kg	3.2 to 3.6	3.2 to 4.0	3.0 to 3.6	3.0 to 3.6	3.2 to 3.8	3.0 to 3.8	3.2 to 4.2	3.2 to 3.6	3.2 to 4.4
Disintegration	NMT 10 minutes	7.30	6.15	8.10	6.10	6.00	7.20	6.00	6.15	7.10
Dissolution	NLT- 80% of label claim	98.33 to 104.06	97.75 to 103.61	98.89 to 103.73	98.28 to 102.27	98.46 to 103.22	95.87 to 100.39	95.21 to 99.36	97.93 to 102.05	98.25 to 102.81
Assay	237.50mg to 262.50mg (95.0% to 105.0%)	250.88	249.06	257.76	253.70	245.55	247.99	251.63	248.51	248.50
RSD % of Assay	NMT 3.0%	1.81%			1.67%			0.72%		

Table 11: I.P.Q.A. Observations

Test	Specifications/ Requirements	Observations					
		Batch no.1		Batch no.2		Batch no.3	
		LHS	RHS	LHS	RHS	LHS	RHS
Description	White, round, biconvex, scored on one side, uncoated tablets.	Complies	Complies	Complies	Complies	Complies	Complies
Avg. Wt.	430mg ±2%	428.6 to 433.0	428.6 to 433.2	428.6 to 434.2	427.2 to 433.9	427.9 to 432.9	427.9 to 432.2
Wt. Uniformity	±5% of Avg. wt.	-0.91 to +1.87	-1.04 to +1.59	-0.91 to +1.88	-0.81 to +1.47	-0.76 to +1.54	-0.81 to +1.65
Diameter	11.0 mm±0.2mm	11.09 to 11.13	11.10 to 11.14	11.06 to 11.12	11.04 to 11.15	11.03 to 11.12	11.08 to 11.14
Thickness	4.8mm ± 0.2mm	4.85 to 4.90	4.86 to 4.90	4.86 to 4.90	4.85 to 4.90	4.87 to 4.92	4.84 to 4.91
Disintegration	NMT 10 minutes	2.25 to 2.40	2.15 to 2.40	2.05 to 2.20	1.50 to 2.10	2.00 to 2.15	1.55 to 2.10
Friability %	NMT 1.0%	0.38 to 0.49	0.42to 0.54	0.33 to 0.45	0.31to 0.43	0.34 to 0.46	0.38to 0.46
Hardness	NLT 3.0Kg	4.0 to 4.2	4.0 to 4.1	4.0 to 4.5	4.0 to 4.5	4.0 to 4.8	4.0 to 4.3

Table 12: Composite samples

Test	Specifications/ Requirements	Observations		
		Batch no.1	Batch no.2	Batch no.3
		Composite	Composite	Composite
Description	White, round, biconvex, scored on one side, uncoated tablets.	Complies	Complies	Complies
Avg. Wt.	430mg ±2%	431.21	432.50	432.92
Wt. Uniformity	±5% of Avg. wt.	-2.11 to +2.41	-2.54 to +2.20	-1.97 to +1.31
Diameter	11.0 mm±0.2mm	11.11 to11.15	11.09 to11.13	11.08 to11.11
Thickness	4.8mm ± 0.2mm	4.87 to 4.95	4.87 to 4.96	4.80 to 4.86
Friability %	NMT 1.0%	0.699	0.845	0.439
Disintegration	NMT 15 minutes	6.30	7.23	7.10
Hardness	NLT 3.0Kg	3.2 to 3.6	3.0 to 3.4	3.0 to 4.6
Dissolution	NLT- 80% of label claim	98.58 to 99.79	97.43 to 105.33	98.06 to 106.35
Assay Terbinafine HCl Eq. to Terbinafine	237.50mg to 262.50mg (95.0% to 105.0%)	249.55	248.80	247.57

Table 13: Result at different sampling condition of Batch no. 1

Test	Specifications/ Requirements	Observations Batch no.1					
		High hardness	Low hardness	Full hopper	Near Empty hopper	High speed (25 RPM)	Low speed (15 RPM)
Description	White, round, biconvex, scored on one side, uncoated tablets.	Complies	Complies	Complies	Complies	Complies	Complies
Avg. Wt.	430mg ±2%	429.66	431.12	431.30	429.50	429.77	430.22
Wt. Uniformity	±5% of Avg. wt.	-1.31 to +1.12	-2.12 to +2.31	-2.38 to +2.01	-2.21 to +1.97	-2.21 to +2.38	-1.21 to +1.36
Diameter	11.0mm ± 0.2mm	11.06	11.08	NA	NA	11.08	11.04
Hardness	NLT 3.0Kg/cm^2	7.0	3.2	NA	NA	4.0	4.2
Thickness	4.8mm ± 0.2mm	4.84	4.90	NA	NA	4.86	4.88
Friability %	NMT 1.0%	0.42	0.67	NA	NA	0.47	0.41
Disintegration	NMT 10 minutes	2.50	1.50	NA	NA	2.35	2.24

Table 14: Result at different sampling condition if Batch no.2

Test	Specifications/ Requirements	Observations Batch no.2					
		High hardness	Low hardness	Full hopper	Near Empty hopper	High speed (25 RPM)	Low speed (15 RPM)
Description	White, round, biconvex, scored on one side, uncoated tablets.	Complies	Complies	Complies	Complies	Complies	Complies
Avg. Wt.	430mg ±2%	430.66	430.12	429.85	430.90	429.35	430.61
Wt. Uniformity	±5% of Avg. wt.	-1.31 to +1.12	-1.13 to +1.08	-1.82 to +1.89	-1.60 to +1.87	-1.21 to +1.12	-1.33 to +1.14
Diameter	11.0mm ± 0.2mm	11.06	11.07	NA	NA	11.06	11.08
Hardness	NLT 3.0Kg	7.0	3.2	NA	NA	4.0	4.1
Thickness	4.8mm ± 0.2mm	4.80	4.89	NA	NA	4.86	4.88
Friability %	NMT 1.0%	0.38	0.46	NA	NA	0.42	0.44
Disintegration	NMT 15 minutes	2.55	1.40	NA	NA	2.15	2.20

Table 15: Result at different sampling condition of Batch no.3

Test	Specifications/ Requirements	Observations Batch no.3					
		High hardness	Low hardness	Full hopper	Near Empty hopper	High speed (25 RPM)	Low speed (15 RPM)
Description	White, round, biconvex, scored on one side, uncoated tablets.	Complies	Complies	Complies	Complies	Complies	Complies
Avg. Wt.	430mg ±2%	429.65	430.86	430.90	429.75	431.22	429.65
Wt. Uniformity	±5% of Avg. wt.	-1.43 to +1.21	-1.67 to +1.86	-2.52 to +2.57	-1.80 to +1.91	-2.31 to +2.12	-1.63 to +1.81
Diameter	11.0mm ± 0.2mm	11.04	11.06	NA	NA	11.04	11.06
Hardness	NLT 3.0Kg	7.0	3.2	NA	NA	4.0	4.4
Thickness	4.8mm ± 0.2mm	4.84	4.88	NA	NA	4.86	4.87
Friability %	NMT 1.0%	0.40	0.68	NA	NA	0.42	0.38
Disintegration	NMT 15 minutes	2.55	2.10	NA	NA	2.25	2.20

7. BLISTERING STAGE: - Blistering at high sealing temperature and low speed, high sealing temperature at high speed, low sealing temperature at low speed and high sealing temperature at low speed is performed and all the parameters are checked and found satisfactory.

Table 16

BATCH NO. 1, 2, 3					
Condition	**Leak Test**	**Sealing**	**Cutting**	**Knurling**	**Coding**
Specification	Should Pass	Proper sealing	Proper cutting	Proper knurling	Legible & sharp coding
Low speed at low sealing temperature 160^0C	Should Pass	Proper sealing	Proper cutting	Proper knurling	Legible & sharp coding
High speed & high sealing temperature 175^0C	Pass	Proper sealing	Proper cutting	Proper knurling	Legible & sharp coding
Low speed & high sealing temperature 175^0C	Pass	Proper sealing	Proper cutting	Proper knurling	Legible & sharp coding
High speed & low sealing temperature 160^0C	Pass	Proper sealing	Proper cutting	Proper knurling	Legible & sharp coding
At low forming temperature 140^0C	Pass	Proper sealing	Proper cutting	Proper knurling	Legible & sharp coding
At high forming temperature 155^0C	Pass	Proper sealing	Proper cutting	Proper knurling	Legible & sharp coding

8. FINISHED PRODUCT ANALYSIS: The finished product was analyzed as per finish product specification and all the test was found within the limits.

Table 17

Test	**Specifications/Requirements**	**Observations**		
		Batch no.1	**Batch no.2**	**Batch no.3**
Description	White coloured, round, biconvex scored on one side, uncoated tablets, and packed 7 tablets in blister	Complies	Complies	Complies
Identification (by HPLC)	It Should be Positive for Terbinafine HCl	Positive for Terbinafine HCl	Positive for Terbinafine HCl	Positive for Terbinafine HCl
Avg. Wt.	430mg ± 3.0% w/w	431.21	432.50	432.92
Uniformity of dosage unit	It should be within + 5.0% of avg. weight	Complies	Complies	Complies
Thickness	4.80mm±0.3mm	4.87 to 4.95	4.89 to 4.96	4.83 to 4.93
Diameter	11.00mm±0.3mm	11.11 to 11.15	11.08 to 11.13	11.11 to 11.16
Hardness	NLT 3.0kg/cm^2	3.2 to 3.6	3.2 to 3.8	3.2 to 4.4
Friability	NMT 1.0 % w./w	0.699	0.672	0.439
Dissolution	NLT 80% (Q)	98.58 to 99.79	97.43 to 104.56	98.06 to 106.35
Impurities				
*Organic impurity				
N-Methyl-1-(Nepthalen-1-y1) Methanamine	NMT 0.20% w/w	Not Detected	Not Detected	Not Detected
Any Single unspecified impurity	NMT 0.20%	0.07%	0.01%	0.01%
Total impurity	NMT 0.70% w/w	0.12%	0.01%	0.02%
*Limit of Terbinafine Dimer	NMT 0.05% w/w	Not Detected	Not Detected	Not Detected
Assay: Each uncoated tablets contains – Terbinafine HCl Eq. to Terbinafine 250 mg	225.0 mg to 275.0 mg	249.55 mg	248.80 mg	247.57 mg

SECONDARY PACKING STAGE

Table 18

Batch No.	**Tablets available in each pocket**	**Blister available in carton**	**Text matter on sec. packing material**	**Coding detail on Sec. packing material**	**Defect in tablets (Chipped/ broken/ missed)**
Specifications	Should available in each pocket	Should available	Sharp & legible as per approved specimen	Should be Sharp & legible	Should be none of defect
Batch no.1	Available	Available	Sharp & legible as per approved specimen	Sharp & legible	None
Batch no.2	Available	Available	Sharp & legible as per approved specimen	Sharp & legible	None
Batch no.3	Available	Available	Sharp & legible as per approved specimen	Sharp & legible	None

CONCLUSION

Validation of sifting process-Raw materials used in validations batches are sifted using specified sieve (#40), Validation of dry mixing stage-Results for dry mixing : 98.17% to 105.83% (Limit: 90%-110% of the claim) and RSD value was found between 0.66% to 2.06% (Limit : not more than 3%)**,** Validation of drying stage-Results of the drying stage: 1.40% to 2.00% (Limit 1% to 3%)**,** Validation of blending stage-Results for the blend uniformity : 98.38% to 102.95% (Limit 90% to 110% of the claim)**,** RSD value was found between 0.53% to 1.51% (Limit not more than 2%)**,** Assay: 99.66%, 99.87%, 99.33% (Limit 90% to 110%)**,** %LOD : 1%, 1.4%, 1.6% (Limit : 1% to 3%)**,**Validation of the compression stage-Average weight of initial, middle and final sample of RHS and LHS, composite sample, IPQA sample and at different sampling condition was found within limits i.e., 430mg ±2%, Thickness was found within limits i.e., 4.80mm to ±0.2mm, Hardness was found within limit i.e., NLT 3.0 Kg/cm^2 **,** Friability was found within limit i.e., NMT 0.1%, Disintegration time was found within the limit that is NMT 15mins, Validation of finished product-Average weight -431.21mg, 432.50mg, 432.92mg (Limit-430±3%)**,** Assay-249.55 mg, 248.80 mg, 247.57 mg(Limit- 250±5%)**,** Dissolution-98.58 to 99.79, 97.43 to 104.56, 98.06 to 106.35 (Limit- NLT 80%)**,** Based on the data, various physiochemical test parameters it was summarized that the process, parameters, specifications and control have been adequate to show the total conformance of the product to the specifications. So, present study show that the set process parameters could be reproduced during the process resulting in the product meeting the specifications.

Process validation study on the three consecutive batches of Terbinafine HCL 250mg was successfully completed and manufacturing critical process parameters were validated in this process validation study.

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