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Process Validation of Terbinafine Hydrochloride Tablets and Blend

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Abstract

Quality is the primordial intention for 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 required quality. In this study process validation is carried out for tablet dosage form Terbinafine Hydrochloride. The process validation of Terbinafine HCl Tablets of dose 250 mg was carried out for three consecutive batches of BN - 1, BN - 2, and BN - 3 which includes the validation of critical steps of manufacturing constituting Dispensing, Sifting, Dry mixing, Granulation, Drying, Blending and Compression. Dissolution profile of the three consecutive validation batches viz., BN-1, BN - 2 and BN - 3 were compared with the reference sample (XYZ). All the above mentioned processes have been validated during the process validation. The results obtained for the three validation batches viz., BN-1, BN-2 and BN-3 were found to be within the limits. Therefore, the product with required specifications can be consistently obtained.

Keywords: Terbinafine Hydrochloride, Quality, Process validation, blending.

Contents

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1. Introduction

Process validation incorporates the understanding that the conditions exist viz., Quality, safety and efficacy are designed or built into the product. Quality cannot be adequately assured merely by in-process and finished product inspection or testing each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes including specifications. After the manufacturing process is validated, current good manufacturing practice also requires that a well-written procedure for process controls is established to monitor its performance. [1-3]. 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. Validation is an integral part of quality assurance; it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and

consistently as specified. A validated process is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications and has therefore been formally approved [4-6]. Terbinafine is chemically it is (E)-N-(6,6-dim ethyl-2-hepten-4-ynyl)-N-methl-1-naphthalene methanamine hydrochloride [7]. It is used as an antifungal drug belongs to allylamine group. This inhibits ergosterolsynthesis by inhibiting squaleneepoxidase, an enzyme that is part of the fungal cell membranesynthesis pathway [8 and 9]. Literature survey reveals very few guideline general principles of process validation are mentioned [10 and 11]. The present paper describes a process that meets its predetermined characteristics in its tablet formulation and blend.

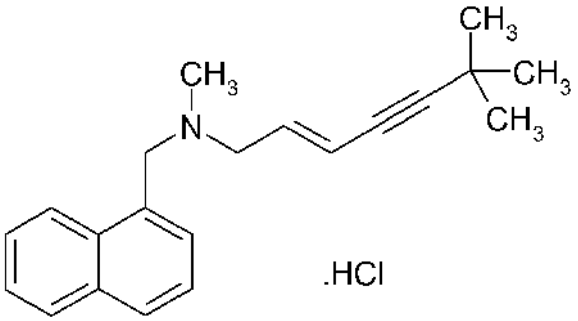

Figure 1: Structural formula of Terbinafine HCl

2. Materials and Method

Process validation was carried for three consecutive batches. For all the three consecutive batches, viz., BN – 1, BN – 2 and BN – 3, the materials used for the formulation were Terbinafine Hydrochloride was a gift sample from MSN labs, Hyderabad. The reagents of AR Grade Colloidal Silicon Dioxide (Aerosil 200), Sodium Starch Glycollate (Primojel), Microcrystalline 101, HPMC (Methocel E5 Premium LV), Magnesium stearate were procured from SD fine chemicals, Mumbai, India. Distilled water was used in entire experiment.

Formulation details

The materials that are needed for the formulation of Terbinafine HCl 250 mg tablets were clearly mentioned in the table 1.

Methods for in process checks and controls:

Sifting: Sifting is an in process method done by weighing the material retained on the sieve and observing the flow of the material through the sieve. Sieve integrity was checked before and after sifting and the suitability of sieves selected for each raw material is shown in table 2.

Dry mixing:

Samples are drawn after mixing for 5, 10 & 15 min from nine sampling points i.e., Top right, Top middle, Top left, Centre right, Centre middle, Centre left, Bottom right, Bottom middle, Bottom left of Planetary mixer and analyzed for blend uniformity. Each sampling contains about 365mg to 1095mg (in triplicate manner). Terbinafine HCl is calculated for the content of active ingredients and must be 90-110% and RSD must be not more than 5.0%. The results are shown in the table 3.

Wet Granulation: Consistent wet mass (granules) is obtained to get the required particle size distribution. Speed of beater during addition of binder solution is maintained slow and faster after complete addition of binder. Time taken for granulation and for addition of binder is recorded.

Drying: From each sampling point samples are collected weighing about 3-5 g at different intervals and Loss on Drying (LOD) is evaluated. Sampling must be done from 3 different locations i.e., top, middle, bottom trays at every 30 min. loss on drying should not be more than 2.5 % w/w. Rate of drying for the samples was shown in the tables 4 to 6.

Pre–lubrication and lubrication:

From 10 sampling points, samples are collected weighing about 380.0mg to 1140.0 mg at different intervals of pre-lubrication and lubrication. Validation is done for the process of pre-lubrication at 5, 10 and 15 min and the process of lubrication at 5 min.

Blend Uniformity: Terbinafine HCl is calculated for each of the ten samples. Content of API was found within 90.0 % - 110.0 % for each of the 10 samples and % RSD not more than 5.0% shown in the table 7 to 9. The optimized characteristics for the samples are mentioned in table 10.

Compression:

This step involves Conversions of blended material into tablets as per specifications. Speed of machine, tablet thickness and hopper level are the major variables. Samples to be collected at 3 different powder level in the hopper - Full hopper, half hopper and almost empty hopper. Characterization of Terbinafine HCl 250 mg dose Tablets of BN-1, BN-2 and BN - 3 during compression at optimum speed was shown in the table 11.

Dissolution: Comparative dissolution profile of three consecutive validation bathes, viz. BN - 1, BN - 2 and BN - 3 with reference sample was done. The chemicals Citric acid monohydrate, Sodium citrate dehydrate are of analytical grade and purified water were used in the procedure.

Preparation of Citrate buffer pH: 3.0: Dissolve 221.06 g of citric acid monohydrate and 5.82 g of sodium citrate dehydrate in 6000 ml de ionized water. If necessary adjust pH to 3.0±0.05 with citric acid. Heat the medium to 41°C and filter the medium through 0.45 µ nylon 66 membrane filter and degas.

Standard preparation:

Weigh and transfer accurately about 56.3 mg of Terbinafine HCl working standard into a 100 ml volumetric flask, add 75 ml of dissolution medium and sonicate to dissolve with intermittent shaking and dilute to volume with dissolution medium and mix well. Dilute 3 ml of the above solution to 25 ml volumetric flask with dissolution medium and mix well. The values obtained are shown in table 12. The comparative dissolution profile for the samples shown in the fig. 2

Dissolution parameters:

Set the parameters of dissolution apparatus as mentioned above. Place one tablet into each of the twelve dissolution jars. At the specified time point (10, 15, 20, 30 and 40 min) withdraw 10 ml of aliquot from each vessel and replace with 10ml of fresh dissolution medium (temperature 37±0.5°C). Centrifuge the sample at 3000 rpm for 15 min Dilute 3 ml of centrifuged aliquot into 25 ml volumetric flask with dissolution medium and mix well.

Procedure:

Measure the absorbance of the standard preparation and sample preparation in 0.5 cm cell on UV spectrophotometer at about 283 nm using dissolution medium as blank. Record the absorbance and calculate.

3. Results and Discussion

Based on the validation study data, it can be concluded that the proposed method is accurate and precise for the analysis of drug. No interference was found from excipients used in Tablets formulation and hence the method is suitable for analysis of blend and tablet formulation. Process validation samples, blend uniformity was found to be good within and between all three validation batches as shown in Table 7 to 9. Formation of tablets, sample for content uniformity were collected at three stages (initial, mid, end) for all three validation batches, results for which show that there is uniformity in dosage units within batch and similarity between batches as shown in Table 3.

Table 1: List of materials used in tablet formulation

Raw material Name	Quantity/Unit (Mg)	Quantity/ batch (Kg)
Terbinafine HCl (Eq. to 250 mg)	281.285	42.913
Colloidal Silicon Dioxide (Aerosil 200)	1.000	0.150
Sodium starch Glycollate (Primojel)	15.000	2.250
Microcrystalline Cellulose (Cyclocel 101)	67.715	10.157
Hydroxyl propyl Methyl Cellulose	15.000	2.250
Magnesium Stearate	4.000	0.600
Purified water	Q.S	24.997
Total weight	400.0	60.000

Table 2: Sieve integrity during sifting of raw materials of BN-1, BN-2 and BN-3 by sieve.no.20

Ingredients	Sieve integrity	
	Before	After
Terbinafine HCl	Good	Good
Colloidal Silicon Dioxide	Good	Good
Sodium Starch Glycollate	Good	Good
Microcrystalline Cellulose	Good	Good
Hydroxyl propyl Methyl Cellulose	Good	Good
Magnesium stearate	Good	Good

Table 3: Content Uniformity* (% Assay for Each Sample)

Parameter	Batch 1 (min)			Batch 2 (min)			Batch 3 (min)		
	10	15	20	10	15	20	10	15	20
Min	98.81	99.69	99.81	99.01	99.04	99.05	98.2	99.98	99.99
Max	100.46	102.12	101.46	98.15	100.44	101.4	99.8	100.24	101.1
Mean	98	100.6	99.89	97.51	98.46	99.51	96.5	97.0	98.8
% RSD	2.27	1.37	1.80	0.71	0.73	0.84	0.85	0.96	0.95

Table 4: Rate of drying (%) from tray dryer of BN – 1

Time (min)	Tray Numbers					
	1	**12**	**24**	**25**	**36**	**48**
Initial	22.31	22.00	22.30	22.66	22.18	22.22
After 60	18.24	18.00	18.48	18.38	18.50	18.13
After 120	14.67	14.11	14.75	14.74	14.50	14.52
After 180	10.24	10.32	10.30	10.40	10.28	10.22
After 240	6.06	6.22	6.08	6.13	6.10	6.16
After 300	2.64	2.59	2.53	2.76	2.44	2.46
After 360	1.74	1.47	1.70	1.66	1.53	1.68

Table 5: Rate of drying (%) from tray dryer of BN – 2

Time (min)	Tray Numbers					
	1	**12**	**24**	**25**	**36**	**48**
Initial	21.84	21.69	21.92	21.78	21.76	21.35
After 60	17.96	17.78	17.76	17.36	17.69	17.40
After 120	13.35	13.56	13.30	13.60	13.36	13.38
After 180	9.16	9.20	9.35	9.24	9.16	9.22
After 240	6.76	6.78	6.84	6.69	6.96	6.69
After 300	2.28	2.14	2.32	2.25	2.20	2.28
After 360	1.82	1.74	1.86	1.66	1.68	1.78

Table 6: Rate of drying (%) from tray dryer of BN – 3

Time (min)	Tray Numbers					
	1	**12**	**24**	**25**	**36**	**48**
Initial	21.68	21.76	21.64	21.84	21.74	21.88
After 60	17.64	17.78	17.68	17.66	17.86	17.84
After 120	13.16	13.40	13.28	13.24	13.38	13.22
After 180	9.13	9.26	9.20	9.18	9.16	9.23
After 240	5.24	5.26	5.24	5.30	5.32	5.16
After 300	2.34	2.30	2.38	2.28	2.34	2.26
After 360	1.88	1.96	1.90	1.84	1.88	1.94

Table 7: Blend Uniformity* (% Assay for Each Sample)

Parameter	Batch 1	Batch 2	Batch 3
Min.	97.58	99.08	98.38
Max	100.21	101.24	100.51
Mean	97.84	99.88	99.69
SD	0.77	0.78	0.51
% RSD	0.65	0.77	0.51

Table 8: Blend Uniformity* (% Assay for Each Sample)

Parameter	Batch 1	Batch 2	Batch 3
Min.	96.37	98.05	97.93
Max	101.31	101.25	101.25
Mean	98.6	99.98	99.69
SD	1.69	0.69	0.65
% RSD	1.69	0.69	0.65

Table 9: Blend Uniformity after unloading (% Assay for Each Sample)

Parameter	Batch 1	Batch 2	Batch 3
Min.	96.03	98.08	99.20
Max	100.28	100.76	101.32
Mean	98.6	99.89	100.26
SD	1.66	0.52	0.5
% RSD	1.66	0.52	0.5

Table 10: Characterization of granules of BN-1, BN - 2 and BN-3 at the end of blending process

Various parameters evaluated	Values Obtained		
	BN-1	**BN-2**	**BN-3**
Particle Size (#20) (%)	8.9	8.6	8.6
Loss on Drying (%)	1.48	1.59	1.47
Weight of Blend (gm)	50	50	50
Volume before tapping (ml)	110	100	100
Volume after tapping (ml)	95	85	85
Untapped bulk density (g/ml)	0.34	0.36	0.36
Tapped bulk density (g/ml)	0.45	0.46	0.46
Hausner's ratio	0.75	1.17	1.17
Compressibility Index	14	15.0	15
Assay of Terbinafine Hydrochloride (mg/tab)	240	249.75	246.75

Table 11: Characterization of Terbinafine Hydrochloride 250 mg dose Tablets of BN-1, BN-2 and BN - 3 during compression at optimum speed

Various parameters evaluated	Values Obtained		
	BN-1	**BN-2**	**BN-3**
Compression Machine Speed RPM	20	20	20
Appearance ***	Complies	Complies	Complies
Average Wt. (mg) **	399.1± 5	400.09±5	400.07±5
Thickness (mm) ***	4.18±0.6	4.06±0.6	4.05±0.6
Hardness (Kp) ***	10.3± 0.8	10.2±0.8	9.4±0.8
Disintegration time *	5'23"±10	5'14"±10	5'05"±10
Friability (%) **	0.05±0.01	0.09±0.01	0.08±0.01
Uniformity of weight (%)	-2.1 to + 2.36	- 0.45 to + 1.05	- 0.69 to + 2.05

All values mentioned as mean ±S.D; number of trials (n):-*=6; **=10;***=20

Table 12: Comparative Dissolution Profiles of the 3 Validation Batches BN - 1, BN - 2 and BN - 3 Including Reference Sample

Time (min)	Reference Sample	Test samples		
	XYZ (%)	**BN.1 (%)**	**BN.2 (%)**	**BN.3 (%)**
10	95.5 ± 2.5	99.2 ± 3.20	99.4 ± 3.23	99.6 ± 3.16
20	99.8 ± 2.0	103.6 ± 2.42	102.0 ± 2.50	102.0 ± 2.30
30	103.2 ± 1.84	108.2 ± 1.94	107.2 ± 1.94	108.1 ± 1.90
40	105.6 ± 1.76	109.0 ± 1.86	110.2 ± 1.86	110.3 ± 1.82

All values mentioned as mean ±S.D; number of trials (n)=3

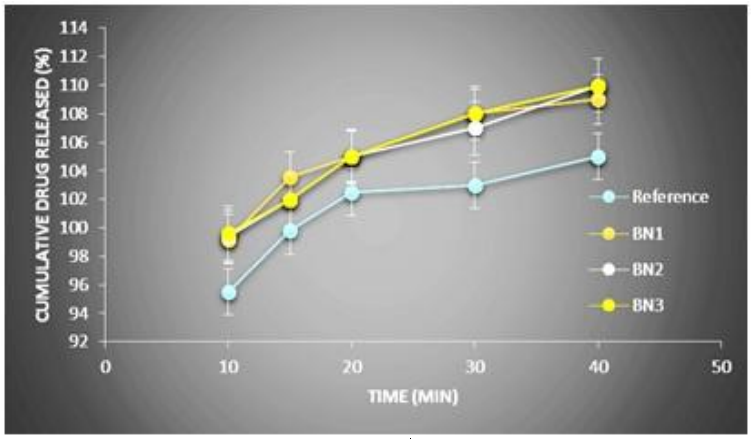

Figure 2: The comparative dissolution profile of three validation batches BN -1, BN -2 and BN - 3 including the reference sample was given graphically below

4. Conclusion

Process validation of Terbinafine HCl 250 mg tablets was conducted for a batch, which included the validation of critical steps of manufacturing such as blending and compression. The blending was performed and the samples at the designated locations were drawn after 5, 10 and 15 min of blending for determination of the content uniformity and RSD values. The RSD the values meet the acceptance criteria at the all the 3 blending intervals. From the analytical results it is clear that the drug distribution pattern in the blend is almost homogeneous. The compression was carried out between the speed limits and physical parameters of the tablets were studied at this speed. The parameters checked included appearance, individual weight variation, group weight variation, thickness of tablets, hardness of tablet, tablet friability and tablet disintegration time. The parameters are well within the limits of acceptance criteria at the speed is studied. Hence the compression stage of terbinafine hydrochloride is consistent and reproducible when the compression was carried out at the speeds of 20 rpm of the turret. Content uniformity and dissolution of compressed tablets are found to be uniform and well within the limits of acceptance criteria. Hopper study was carried out for full hopper, half hopper and near end hopper to establish the segregation of the blend during compression. The results obtained for the three validation batches viz., BN-1, BN-2 and BN-3 were found to be within the limits. The product with required specifications can be consistently obtained.

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