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Manufacturing Process Optimization of Anti-fungal Drug Product Itraconazole Capsules by Wet Granulation Approach

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ABSTRACT:
The manufacturing process optimization study untaken here assures that the optimized manufacturing process is suitable for the intended purpose and the product consistently meets predetermined specifications and quality attributes. It gives detailed information on various steps involved in the manufacturing process like Sifting, Dry Mixing, Wet granulation, Drying, Sizing, Mixing, Blending, Capsule filling, Packing, and analysis of process challenges samples at various critical stage of manufacturing, in-process tests and finished product testing.
During this study, Critical Process Parameters (CPPs) involved in Sifting, Dry Mixing, Wet granulation, Drying, Sizing, Mixing, Blending, Capsule filling and packing were identified with the help of developmental study and evaluated during manufacturing process optimization study batch. During this process, all the Critical Quality Attributes (CQA) were observed such as Blend Uniformity (BU), Water content, Physical characteristics of blend, physical parameters of Capsules, Description, Water content (Finished product) Dissolution, Uniformity of Dosage Unit, Assay, Degradation products and Microbial examination.
After the evaluation of analytical results and discussion, it can be concluded that this optimized manufacturing process is capable of producing the product consistently meeting with quality attributes and its predetermined specification. Hence the manufacturing process of drug product is optimized and can be used for process validation batches of Itraconazole Capsules 100 mg.
Key words: Process Optimization, Critical Process Parameters, Critical Quality Attributes, Sampling plan, and Testing plan, Acceptance criteria, finished product, Process Validation.

INTRODUCTION:

The range for process parameters shall be proposed given compliance of commercial batches run during continuous commercial manufacturing of the batches because there can be minor variation in subsequent batches due to variability in the input raw material physical attributes of the API / excipients lots within approved specifications (like bulk density, tapped density and particle size distribution), variations in environmental conditions like temperature and relative humidity of manufacturing area and variation in equipment drive motor efficiency over a period of time[1,2,3]. Such minor variations do not have an impact on the product quality as the critical product parameters (like LOD, disintegration time, dissolution, assay, etc.) are within limit[4,5]. The range of the process parameters can be rounded off to the nearest value. Optimized ranges of process parameters proposed for exhibit/process validation/ commercial batches should be within the qualification range of the equipment. In-process critical quality attributes like the individual weight of the capsules, disintegration time, and locking length of the capsules are optimized in the optimization batch[6,7,8].

Critical Quality Attributes (CQA): A CQA is a physical, chemical, biological, or microbiological property or characteristic of a semi-finished or finished product that should be within an appropriate limit, range, or distribution to ensure the desired product quality[9].

Critical Process Parameter (CPP): It is a process parameter whose variability has an impact on CQA and therefore should be monitored or controlled to ensure the process produces the desired quality of the finished drug product[10].

Machine Operating Parameters: These are the machine parameters that are adjusted/controlled on a machine to get the desired product parameters e.g. compression machine speed, force feeder speed, compaction force parameters of compression which are adjusted on a machine to get the desired product parameters (viz. weight, hardness, and thickness) of tablets[11].

Manufacturing Process Optimization: It is the process of fixing the values and limits of the manufacturing process/machine/product parameters based on review, evaluation and recommendations of scale-up/Pre-validation batches data[12].

Optimization batch: Batch is defined as the batch taken for optimization of process/machine/product parameters during manufacturing of drug product before process validation batches. These batches are not meant for commercial distribution. After the manufacturing optimization study, these bathes can be destroyed[12].

Exhibit Batches: Batches taken for stability study data generation and submission to regulatory agency.

Commercial Batches: Batches taken for sale in the market for commercial purposes.

Quality by Design (QbD): A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management[14,15].

MATERIAL AND METHOD:

Itraconazole Capsules 100 mg is an immediate-release solid dosage form consisting of a solid dispersion of Itraconazole by using Methocel E3 LV as a carrier for enhanced dissolution. Each capsule consists of 100 mg of Itraconazole as active ingredient. The proposed formulation comprises of commonly used excipients in the design of a solid oral dosage form.

The generic formulation process enhances the water-insoluble nature of Itraconazole API by granulating it with HPMC (Methocel E3 LV) used in the formulation is a water-soluble polymer and also acts as a dispersion carrier for solid dispersion to enhance the dissolution profile of Itraconazole.

The drug Itraconazole dissolves in Glacial Acetic Acid at 45^{O}C and granulates with the following ingredients HPMC (Methocel E 3 LV), Pearlitol 25C was grade of Mannitol chosen as a diluent, Aerosil 200 (Colloidal silicon dioxide), in Extra granulation stage use of Croscarmellose Sodium(Ac-di-sol) as disintegrating agent, with Silicified Microcrystalline Cellulose (Prosolv 50) as diluent.

List of API, Raw Materials, and their Functions: Table 1 indicates raw material used for manufacturing of the process optimization batch.

Table 1: Raw material used for manufacturing of the process optimization batch

Sr. No.	Raw Material	Function	Stage of Use of material	Manufacturer/ Vendor	Quantity mg/Capsule
Granulating solution					
1	Itraconazole EP	Active Pharmaceutical Ingredient	Wet Mixing	Hetero Drugs Limited. / MSN Pharma Chem	100.000

Sr. No.	Raw Material	Function	Stage of Use of material	Manufacturer/ Vendor	Quantity mg/Capsule
2	Glacial Acetic Acid USP	Solvent to solubilize Itraconazole API (Granulating Agent)	Wet Mixing	Oasis Alcohol	170.000
Dry Mixing					
3	Mannitol (Pearlitol 25 C) USP/NF	Diluent	Dry Mixing	Roquette	50.000
4	Hydroxy Propyl Methyl Cellulose USP/EP (Methocel E3 LV)	Carrier for Solid Dispersion	Dry Mixing	Nutrition & Bioscience	290.000
5	Colloidal Silicon Dioxide USP/NF (Aerosil 200)	Glidant/Adsorbent	Dry Mixing	Evonik	10.000
Extra granular Material					
6	Croscarmellose Sodium NF (Ac-di-sol)	Disintegrating Agent	Blending	International N & H MFG.	50.000
7	Silicified Microcrystalline cellulose (Prosolv 50)	Diluent	Blending	Sigachi Industries limited	50.00
Unit weight of filled content of Capsule.					**550.000**

List of Packing Materials and their Functions: Table 2 shows packing materials used for manufacturing of the process optimization batch.

Table 2: Packing materials used for manufacturing of the process optimization batch

Sr. No.	Packing Material	Function	Stage of Use of Material	Manufacturer/ Vendor
1	50 CC Round Opaque White HDPE Bottle (HW/SP73 /33MM) HDPE Container	Primary Packing Material	Primary Packing	Triveni Polymers
2	33-400 ARGUS-LOC Child Resistant Closure HS123 (0.035")Closure	Primary Packing Material	Primary Packing	BPREX Pharma
3	Silica Gel Sachet 1g	Primary Packing Material	Primary Packing	Multisorb Technologies

Equipment: Table 3 shows the equipments used for manufacturing of the process optimization batch.

Table 3: Equipment used for manufacturing of the process optimization batch.

Stage of Manufacture	Equipment / Utility Name	Make
All applicable stages	Weighing Balance	Jay-Pan

Sifting	Vibratory Sifter	Gansons
Binder Preparation	Binder preparation vessel	Fluidyne
Dry Mixing / Wet Granulation	Rapid Mixer Granulator(RMG)	Saral Engineering
Drying	Fluid Bed Dryer (FBD)	Saral Engineering
Milling	Co Mill	R P Product
Blending	Pillar Blender Bin	RP Product
Capsule Filling	Capsule Filling Machine	PAM AF 90
	Tablet Deduster	Omega Pharma
	Metal Detector	Technofour

Method:

Solid Dispersion method was selected as the manufacturing process as it involves the following steps i.e. granulating drug solution preparation, dry mixing, granulation, drying, milling, blending, capsule filling and packing. Itraconazole Capsules 100 mg formulation contains Hydroxypropyl methyl cellulose (Methocel E3 LV) as carrier for Solid Dispersion and Glacial Acetic Acid as vehicle to solubilize Itraconazole API. Colloidal Silicon Dioxide (Aerosil 200) was added as adsorbent. Croscarmellose Sodium (Ac-Di-sol) as disintegrant, Silicified Microcrystalline cellulose (Prosolv 50) as Diluent to enhances the density of capsule.

Manufacturing process.

Step 1: Preparation of Drug Solution: Placed Glacial Acetic Acid in a container equipped with a propeller mixer. Dissolved Itraconazole API at 45^0 C in Glacial Acetic Acid by stirring till get the clear solution. (Store the drug solution in a closed S.S. Container).

Step 2: Sifting: Sifted Mannitol (Pearlitol 25 C), Hydroxypropyl Methyl Cellulose (Methocel E3 LV Premium) through 40 mesh sieve. Collected it HDPE drums lined with double polythene bags.

Step 3: Dry mixing: Loaded the Step 2 material into a Rapid Mixer Granulator (RMG) and mixed for 10 minutes as slow speed of impeller and chopper off.

Step 4: Wet granulation: Added Drug Solution of Step 1 to Step 3 material in 3 minutes with impeller at slow speed and copper off. Mixed the wet material for 2 minutes with impeller and chopper at slow speed. Scrapped the wet mass. Then again mixed the wet material for 2 minutes with impeller and chopper at fast speed. Required the consistency of the wet mass was observed.

Step 5: Drying: Placed the wet granules into a Fluid Bed Dryer (FBD) bowl and dried wet mass at Inlet temperature 65.0 ± 5.0°C and until the Outlet temperature was observed 52°C. The sample was withdrawn for LOD determination and checked LOD at 105°C. Limit- NMT 1.0%.

Step 6: Milling: Sifting of dried granules was performed though 20 mesh S.S. Sieve and retention on 20 mesh was passed through 1.5 mm S.S. Screen of Co mill again passed through 20 mesh S.S. sieve. Milling process continued till 1.0 mm S.S. Screen of Co mill till all granules passed through 20 mesh S.S. sieve.

Step 7 Extra Granular material: Sifted Croscarmellose Sodium and Silicified Microcrystalline cellulose (Prosolv 50) through 40 mesh S.S Sieve. Collected it HDPE drums lined with double polythene bags.

Step 8: Mixing: Added material of Step 7 in Step 6 and mixed for 2, 5, 8 minutes at 5 rpm in Pillar Blender Bin.

Step 9: Capsule filling and Polishing: Filled the blend from Step 8 in hard gelatin capsules, Size 0-EL size with a fill weight of 550 mg. Samples were withdrawn at slow speed and high speed to check impact of Capsules Filling Machine speed on CQA of the drug product.

Samples were withdrawn full hopper blend level, half hopper blend level and low hopper blend level to check

impact of low blend level and high blend level in hopper of Capsule filling machine on CQA of the drug product. Polished the capsules using polishing machines. Inspected the filled capsules visually and discard any defective capsules.

Step 10: Packing: Capsules are filled in HDPE containers.

Stability study: After packing batch was charged for stability study.

Utilities: HVAC System (ABB), Compressed Air System (Ingersollrand) and Purified Water System (Christnisotec).

Instruments used for analysis: UV Spectrophotometer (Perkin Elmer), HPLC (Aglent), Disintegration Apparatus (Electro Lab), Sieve Shaker (Elactron Pharma), Tap Density Tester (Electrolab), Weighing Balance (Mettler Toledo). Table 4 depicts critical and non-critical process parameters used in the manufacturing process optimization of anti-fungal drug products by wet granulation approach.

Table 4: Critical/Non-Critical Process Parameters

Sr. No.	Manufacturing Process Stage	Process Parameters	Observed in Optimization batch	Recommended range for Process Validation/ commercial batches	Classification (Critical/ Non critical)	Justification
1.	Sifting of Excipients	Sieve used for sifting (mesh)	40	40	Non Critical	Sifting has been incorporated to break the lumps observed in the material and to remove foreign particles if any.
2.	Dry Mixing	Dry Mixing (Minutes: Seconds)	10:00	10:00	Non Critical	Dry Mixing stage does not contain the API, hence Dry mixing time and Impeller speed unlikely have impact on CQA of Drug product.
		Impeller speed (RPM)	Slow	Slow		
		Chopper Speed (RPM)	Off	Off		
3.	Wet Granulation	Drug solution addition time (Minutes: Seconds)	03:00	03:00 ± 00: 30	Critical	Drug Solution Addition time, impeller speed, and kneading time are likely to have impact on homogeneity of granulation
		Impeller speed (RPM)	Slow	Slow		
		Chopper Speed (RPM)	Slow	Slow		

		Mixing time (Minutes: Seconds)	2:00	2:00		process and physical properties of granules such as particle size distribution and flow ability.
		Impeller speed (RPM)	Slow	Slow		
		Chopper Speed (RPM)	Slow	Slow		
		Mixing time (Minutes: Seconds)	2:00	2:00		
		Impeller Speed (RPM)	Slow	Slow		
		Chopper Speed (RPM)	Slow	Slow		
4.	Drying of wet mass	Inlet air temperature (°C)	69	65.0 ± 10.0 (55.0 to 75)	Critical	Inlet, outlet temperature and FCD will have impact on % LOD/physical parameters of the granules and residual solvent.
		Outlet Temperature (°C)	49	35 to 60		
		Fluidization control damper (FCD) (%)	35 to 45	40 ± 10 (30 to 50)		
5	Sifting of dried granules	Sieve used for sifting (mesh)	20	20	Critical	
6	Milling and sifting of Oversized Granules	Screen used for milling of oversized granules (mm)	1.5	1.5	Critical	Milling screen and speed likely have impact on the bulk density, tapped density, compressibility index, Hausner ratio and particle size distribution granules and physical parameters of the capsules.
		Speed of Co-mill (Hz)	22 to 28	25 ± 5 (20 to 30)	Critical	
		Sieve used for sifting of milled granules (mesh)	20	20	Critical	
		Screen used for milling of oversized granules (mm)	1.0	1.0	Critical	
		Speed of Co-mill (Hz)	20 to 27	25± 5 (20 to 30)	Critical	
7	Milling and sifting of oversized	Sieve used for sifting of milled granules (mesh)	20	20	Critical	Milling screen and speed likely have impact on

	granules	Screen used for milling of oversized granules (mm)	1.0	1.0	Critical	the bulk density, tapped density, compressibility index, Hausner ratio and particle size distribution granules and physical parameters of the capsules.
		Speed of Co-mill (Hz)	51 to 59	55 ± 5 (50 to 60)	Critical	
		Sieve used for sifting of milled granules (mesh) (Till all granules passed)	20	20	Critical	
8	Sifting of Extra granular material	Sieve used for sifting (mesh)	40	40	Non Critical	Sifting has been incorporated to break the lumps observed in the material and to remove foreign particles if any.
9	Mixing of Sized granules	Blending time (Minutes: Seconds)	10:00	10:00	Critical	Mixing time and Blender RPM likely have impact on the blend uniformity of the blend and Particle size distribution of blend.
		Pillar Blender Speed (RPM)	05	05		
10	Blending	Blending time (Minutes: Seconds)	02:00,5:00 & 08:00	5:00	Critical	Blending time and Blender RPM likely have impact on the blend uniformity of the blend and Particle size distribution of blend.
		Pillar Blender Speed (RPM)	05	05		
11	Capsule filling	Capsule Filling Machine Speed (Capsules/hour)	Slow Speed: 50,000. High Speed: 90,000.	50,000 to 90,000	Critical	The parameters like capsule filling machine speed likely have impact on physical and Critical Quality Attribute like Assay and CU of

						the capsules.
12	Bulk Packing	Capsules counting and filling machine speed (Bottles per minute)	55	20 to 90	Critical	To verify the accuracy of set count.
		Capping machine Torque (lbin)	22	15 to 25	Critical	To ensure the proper tightening of cap.
		Power %	95	94 to 100	Critical	To ensure the intactness of bottle.
		Travel Time (Seconds)	05	05 to 06	Critical	
		Height (mm)	03	02 to 04	Critical	
13	Strip Pack	Sealing temperature (°C)	126	110 to 150	Critical	It likely have impact on stability of the product.
14	Blister Pack	Sealing temperature (°C)	134	110 to 150	Critical	It likely has impact on stability of the product.
		Forming temperature (°C)	178	160 to 200	Critical	

SAMPLING AND TESTING PLAN: Table 5 shows the sampling and testing plan with acceptance criteria defined for the process optimization batch.

Table 5: Sampling and testing plan

Process stage	**Sampling procedure**	**Sample quantity**	**Test(s)**	**Acceptance criteria**
Drying of Wet mass	Collect the sample from each sampling location comprising of top, middle and bottom layer of FBD bowl. **(Note:-For sampling points - Refer Sampling Diagram Figure No.1)**	Approx. 3.0 g from each location	Loss on drying	NMT 1.0% at 105 °C
		Approx. 20 gm	1.Description	1. White to off-white granular Powder.
			2.Residual Solvent	2.NMT 5000 PPM

Process stage	Sampling procedure	Sample quantity	Test(s)	Acceptance criteria
Sized Granuls mixing	Three-unit dose samples each shall be withdrawn from 10 different locations/points of the blender comprising of upper, middle and lower layer and bottom of the blender after blending for 10 minutes. (**Note: For sampling points Refer sampling location Diagram figure. 2)**	1-3 x Unit dose quantity from each sampling point. 450.000 mg to 1350.000 mg/ vial in triplicate. (Use suitable die for sampling)	Blend Uniformity	1.All values should be within ± 10 % of mean value. 2.Mean Value shall be within 95 to 110 % of Label Claim. 3.RSD NMT 5.0 %
Blending	Three-unit dose samples each shall be withdrawn from 10 different locations/points of the blender comprising of upper, middle and lower layer and bottom of the blender after blending for 02,05 and 08 minutes. (**Note: For sampling points Refer sampling location Diagram figure. 2)**	1-3 x Unit dose quantity from each sampling point. 550.000 mg to 1650.000 mg/ vial in triplicate. (Use suitable die for sampling)	Blend Uniformity	1.All values should be within ± 10 % of mean value. 2.Mean Value shall be within 95 to 110 % of Label Claim. 3.RSD is NMT 5.0 %
Blending	Composite sample of blend to be sampled for physical characteristics evaluation.	Approx.20 g	1.Description 2. Water Content	1.White to off-white granular Powder. 2.NMT:5.0%
		Approx. 300 g	1.Bulk Density 2.Tapped Density 3.Compressibility Index. 4.Hauner Ratio 5.Angle of repose. 6.Particle Size Distribution by sieve analysis	For information and recording.

Process stage	Sampling procedure	Sample quantity	Test(s)	Acceptance criteria
Capsule filling [Speed Challenge Study of capsule filling machine] [Low Speed and High speed]	Samples to be collected from capsule filling machine at Low Speed and High Speed.	100 Capsule at each speed.	1. Description 2. Weight of 10 intact capsules 3. Uniformity of weight (intact capsules) 4. Content weight variation (by opening the capsule) 5. Capsule length after filling and sealing 6. Disintegration Time	Refer result and discussion section for acceptance criteria.
		144 Capsules (72 Capsules at each speed)	Dissolution on 6 capsules at each speed.	Not less than 70% (Q) of the labeled amount of Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) is dissolved in 90 minutes.
		60 Capsules at each speed	Uniformity of dosage units.(By content uniformity)	Acceptance value: Not more than 15.0.
Capsule filling (Hopper Challenges study of capsule filling machine)	Filled capsule samples to be collected from full hopper blend level, half hopper blend level and low hopper blend level at capsule filling machine.	100 Capsule at each Hopper challenge study.	1. Description 2. Weight of 10 intact capsules 3. Uniformity of weight (intact capsules) 4. Content weight variation (by opening the capsule) 5. Capsule length after filling and sealing 6. Disintegration Time	Refer result and discussion section for acceptance criteria.
		216 Capsules (72 Capsules at each Hopper challenge study)	Dissolution on 6 capsules at each Hopper challenge study	Not less than 70% (Q) of the labeled amount of Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) is dissolved in 90 minutes.

Process stage	Sampling procedure	Sample quantity	Test(s)	Acceptance criteria
		60 Capsules at each Hopper challenge study.	Uniformity of dosage units.(By content uniformity)	Acceptance value: Not more than 15.0.
Capsule filling (Optimum Run)	Samples to be collected from capsule filling machine at Optimum Speed.	100 Capsule shall be collected through out capsule filling process.	1. Description 2. Weight of 10 intact capsules 3. Uniformity of weight (intact capsules) 4. Content weight variation (by opening the capsule) 5. Capsule length after filling and sealing 6. Disintegration Time	Refer result and discussion section for acceptance criteria.
		216 Capsules (72 each from start, middle and end stage of Capsule filling process)	Dissolution on 6 capsules each from start, middle and end stage of Capsule filling Process.	Not less than 70% (Q) of the labeled amount of Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) is dissolved in 90 minutes.
		60 Capsule shall be collected through out capsule filling process.	Uniformity of dosage units. (By content uniformity)	Acceptance value: Not more than 15.0.
Finished product Analysis (Composite Sample)	Composite sample for finished product analysis shall be collected after completion of Capsule Filling Process.	200 Capsules	Description, Water content, Assay, Dissolution, Related substance, Residual Solvent.	As per mentioned in result and discussion section.
			[12 units Dissolution Profile at 10,15,20, 30,45, 60 & 90 Minutes]	For Comparison with Reference Product.

Sampling tools: Sampling rod and dies were used in blending while S.S. container and scoop were used in capsule filling as a sampling tool.

Product Storage: Store at a controlled room temperature 15^0 - 25^0 C (59^0-77^0 F). Protect from light and

moisture.

Sampling Location Diagram of Bowl of FBD (Fluid Bed Dryer): Figure 1 indicates the sampling location in a fluidized bed dryer. Upper layer (U), Middle layer (M), and Lower layer (L) were selected as sampling locations as shown in figure 1.

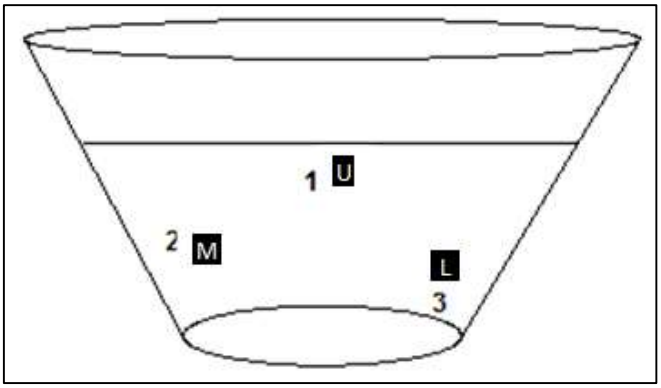

Figure 1: Sampling location in FBD

Sampling Location Diagram of Pillar Blender Bin: Figure 2 shows sampling location in pillar blender bin. Ten samples were withdrawn from various location i.e. upper (3)- U1, U2 and U3, middle (3)- M1,M2 and M3, lower (3)- L1, L2 and L3 and Bottom 1 sample as shown in figure.

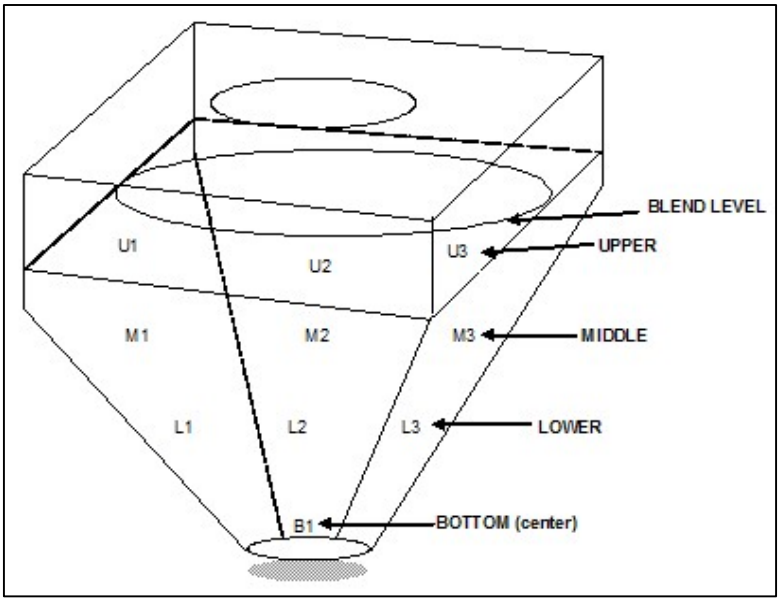

Figure 2: Sampling location in Pillar Blender Bin

RESULTS AND DISCUSSION.

Loss on drying and residual solvent analysis: % LOD of dried granules comprising of Top, Middle, Bottom layers & composite sample of FBD bowl of optimization batch was found 0.84 %, 0.73 %, 0.69 % and 0.79 %

respectively, and complies as per acceptance criteria. A residual solvent of dried granules optimization batch was found 1480 ppm and complies as per acceptance criteria.

Blend Uniformity at Sized Granules at mixing Stage (10 minutes): The Blend uniformity (Individual samples) of sized granules (10 minutes) for the optimization batch was found in the range of 96.5 to 101.3 %, respectively, and complies with per acceptance criteria. The mean value of Blend uniformity (Average) of sized granules (10 minutes) for the optimization batch was found 99.01 %, and complies as per acceptance criteria. % RSD at the blending stage (10 minutes) for optimization batch was found 1.32 %. The results are compiled in table 6.

Table 6: Blend Uniformity at Sized Granules at mixing Stage

Test (s)	**Acceptance criteria**		**Results (%) at 10 Minutes**	**Remarks**
Blend Uniformity (%)	1. All values should be within ± 10% of mean value. 2. Mean Value shall be within 95 to 110% o Label Claim. 3.RSD is NMT 5.0 %	Upper Left: 1	98.7	Complies
		Upper Centre: 2	96.5	
		Upper Right: 3	99.6	
		Middle left: 4	98.3	
		Middle Centre: 5	101.3	
		Middle Right: 6	99.1	
		Lower Left: 7	97.8	
		Lower Centre: 8	99.2	
		Lower Right: 9	100.2	
		Bottom Centre: 10	99.4	
		Minimum	**96.5**	
		Maximum	**101.3**	
		Average	**99.01**	
		RSD (%)	**1.32**	

Blend uniformity of lubricated blend at lubrication stage: The blend uniformity for the optimization batch was found to be 99.2 to 102.0, 98.8 to 99.8, and 95.8 to 100.0, which complies with acceptance criteria. The mean and average values were 100.8 to 99.2%, 99.4%, and 99.2%, respectively. Results are compiled in table 7.

Table 7: Blend uniformity of lubricated blend at lubrication stage

Test (s)	**Acceptance criteria**		**Results (%) in min.**			**Remarks**
			02	**05**	**08**	
Blend Uniformity (%)	1.All values should be within ± 10 % of mean value. 2.Mean Value	Upper Left: 1	99.2	99.4	99.6	Complies
		Upper Centre: 2	101.3	99.1	100.0	
		Upper Right: 3	101.1	99.8	95.8	
		Middle left: 4	100.6	99.6	99.7	
		Middle Centre: 5	101.5	99.6	100.0	
		Middle Right: 6	99.7	98.8	99.0	

	shall be within 95 to 110 % of Label Claim. 3.RSD is NMT 5.0 %	Lower Left: 7	101.2	99.7	99.6	
		Lower Centre: 8	100.8	99.4	99.6	
		Lower Right: 9	102.0	99.1	99.8	
		Bottom Centre: 10	100.1	99.7	99.0	
		Minimum	**99.2**	**98.8**	**95.8**	
		Maximum	**102.0**	**99.8**	**100.0**	
		Average	**100.8**	**99.4**	**99.2**	
		RSD (%)	**0.9**	**0.33**	**1.25**	

Water Content of Final Blend: The water content of the optimization batch was found 0.39 and complies as per acceptance criteria.

Physical Characteristics of Final Blend: Bulk density, tapped density, and particle size distribution of the final blend were found satisfactory. The Compressibility Index, Hausner Ratio and Angle of Repose were compiled for the optimization batch as per acceptance criteria. Table 8 shows the results of the physical characteristics of the final blend.

Table 8: Results of physical characteristics of the final blend

Test(s)		**Acceptance Criteria**	**Results**	**Remarks**
Bulk Density (gm/mL)		For Information	0.72	Satisfactory
Tapped Density (gm/mL)			0.81	Satisfactory
Compressibility Index (%)		NMT 25	18.27	Complies
Hausner Ratio		NMT 1.34	1.17	Complies
Angle of Repose (º)		25 To 40	31.00	Complies
Particle Size Distribution (% Cumulative retention)	Over 20 #	For Information	1.10	Satisfactory
	Over 40 #		48.40	
	Over 60 #		62.78	
	Over 80 #		69.67	
	Over 100 #		89.20	
	Below 100 #		8.70	

In-process checks of filled capsules during low and high speed of capsule filling machine: All in-process checks (physical parameters) performed during low speed and high speed of Capsule filling machine complied with acceptance criteria. Results of In-process checks of filled capsules during low and high speed of capsule filling machine are compiled in Table 9.

Table 9: In-process checks of filled capsules during the low and high speeds of capsule capsule-filling machine

Test(s)	**Acceptance criteria**	**Results**		**Remarks**
		Low Speed (50,000 caps/ Hour)	**High Speed (90,000 caps/ Hour)**	

Description	White to off White granules containing Opaque white (cap) and Opaque White (body) colored capsules		Complies	Complies	Complies
Weight of 10 intact capsules (g)	6.550 ± 3% (6.354 to 6.746)	Min	6.398	6.384	Complies
		Max	6.570	6.610	
		Avg.	6.480	6.450	
Uniformity of weight (intact capsules) (mg)	655.000 ± 5 % (622.250 to 687.750 mg)	Min	631.000	629.000	Complies
		Max	679.000	677.000	
		Avg.	655.240	651.100	
Content weight variation (by opening the capsule) (mg)	550.000 ± 5 % (522.500 to 577.500 mg)	Min	534.100	532.200	Complies
		Max	553.400	551.000	
		Avg.	552.600	556.400	
Capsule length after filling and sealing (mm)	21.5 mm ± 0.5 mm (21 to 22 mm)	Min	21.18	21.23	Complies
		Max	21.56	21.69	
		Avg.	21.38	21.46	
Disintegration Time	NMT 15 minutes	Min	02 min 34 sec.	03 min 14 sec.	Complies
		Max	05 min 14 sec.	05 min 51 sec.	

Uniformity of dosage unit (by content uniformity) of filled capsules during capsule samples collected at low and high speed of capsule filling machine: The uniformity of dosage units in filled capsule samples was found to be 99.6% to 107.4%, 97.8 to 103.4%, and a mean of 103.0% and 99.8%, meeting acceptance criteria. The results are compiled in table 10.

Table 10: Uniformity of dosage unit

Tests	**Acceptance criteria**		**Results**		**Remarks**
			Low Speed	**High Speed**	
Uniformity of dosage units by content uniformity (%)	Individual assay values are within 75% to 125% and AV value is ≤ 15.0	Unit:1	03.3	97.8	Complies
		Unit: 2	04.5	98.3	
		Unit: 3	00.5	98.0	
		Unit: 4	99.9	103.0	
		Unit: 5	99.6	98.4	
		Unit: 6	02.1	98.4	
		Unit: 7	07.4	99.2	
		Unit: 8	02.4	102.4	
		Unit: 9	07.1	99.2	
		Unit: 10	03.4	103.4	
		Minimum	99.6	97.8	
		Maximum	07.4	103.4	
		Mean	03.0	99.8	
		AV	2.6	2.2	

Dissolution of filled capsules at capsule filling process during capsule samples collected at low and high

speed of capsule filling machine: The dissolution results of capsules filled at low and high speeds in the optimization batch were found to be 89-94% and 87-93%, respectively as shown in table 11.

Table 11: Dissolution of filled capsules

Test(s)	Acceptance criteria		Results		Remarks
			Low Speed	High Speed	
Dissolution (%)	Not less than 70% (Q) of the labeled amount of Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) is dissolved in 90 minutes.	**1**	91	90	Complies
		2	93	92	
		3	94	93	
		4	89	89	
		5	92	88	
		6	94	87	
		Min	**89**	**87**	
		Max	**94**	**93**	
		Avg	**92**	**90**	

In process checks of filled capsules during full hopper, half hopper and end hopper of capsule filling machine: All in process checks (physical parameters) performed during full hopper, half hopper and end hopper blend level were complying as per acceptance criteria as depicted in table 12.

Table 12: In-process checks of filled capsules

Test(s)	Acceptance criteria		Results			Remarks
			Full Hopper	Half Hopper	End Hopper	
Description	White to off White granules containing Opaque white (cap) and Opaque White (body) colored capsules.		Complies	Complies	Complies	Complies
Weight of 10 intact capsule (g)	6.550 ± 3% (6.354 to 6.746)	Min	6.410	6.421	6.398	Complies
		Max	6.614	6.688	6.648	
		Avg	6.580	6.528	6.458	
Uniformity of weight (intact capsules) (mg)	655.000 ± 5 % (622.250 to 687.750 mg)	Min	634.000	631.000	630.000	Complies
		Max	675.000	668.000	665.000	
		Avg	648.240	650.200	654.100	
Content weight variation (by opening the capsule) (mg)	550.000 ± 5 % (522.500 to 577.500 mg)	Min	530.000	538.100	533.200	Complies
		Max	560.200	554.000	565.000	
		Avg	548.600	565.400	558.200	
Capsule length after filling and sealing (mm)	21.5 mm ± 0.5 mm (21 to 22 mm)	Min	21.28	21.28	21.29	Complies
		Max	21.68	21.78	21.78	
		Avg	21.52	21.50	21.58	
Disintegration Time (at 37 ± 0.5℃) with disc	NMT 15 minutes	Min	03:45	02:36	02:22	Complies
		Max	05:48	05:40	05:55	

Uniformity of dosage unit (by content uniformity) of filled capsules during collected at half hopper, middle hopper, and end hopper of capsule filling machine: Individual values of uniformity of dosage units' test (by content uniformity) of filled capsules samples collected at half hopper, middle hopper, and end hopper blend level were found in the range of 97.8% to 102.3%, 97.7 to 104.4% and 98.9 to 105.4 % respectively complying with acceptance criteria (Limit: 75% to 125%). The mean of Uniformity of dosage units of filled capsules of these samples were found as 99.65 %, 99.99 %, and 102.38 respectively. AV value is found 1.3, 2.3, and 2.2 respectively and complies as per acceptance criteria, as shown in table 13.

Table 13: Uniformity of dosage unit

Tests	Acceptance criteria		Results			Remarks
			Full Hopper	Half Hopper	End Hopper	
Uniformity of dosage units by content uniformity (%)	Individual assay values are within 75% to 125% and AV value is ≤ 15.0	Unit:1	99.6	97.7	103.4	Complies
		Unit: 2	98.3	98.3	104.6	
		Unit: 3	101.3	98.4	100.7	
		Unit: 4	99.1	103.2	98.9	
		Unit: 5	97.8	99.4	99.8	
		Unit: 6	99.2	99.6	103.1	
		Unit: 7	100.2	99.2	104.4	
		Unit: 8	99.4	101.5	105.4	
		Unit: 9	102.3	98.2	102.1	
		Unit: 10	99.3	104.4	101.4	
		Minimum	97.8	97.7	98.9	
		Maximum	102.3	104.4	105.4	
		Mean	99.65	99.99	102.38	
		AV	1.3	2.3	2.2	

Dissolution results of filled capsules during collection at half hopper, middle hoper and end hopper of capsule filling machine: Dissolution results of filled capsules at half hopper, middle hoper and end hopper at capsule filling of optimization batch were found in the range of 90 to 97 %, 89 to 94 % and 90 to 99 %, respectively and complies as per acceptance criteria, shown in table 14.

Table 14: Dissolution results of filled capsules during the collection at half hopper, middle hoper and end hopper of capsule filling machine

Test(s)	Acceptance criteria		Results			Remarks
			Half Hopper	Middle Hopper	End Hopper	
Dissolution (%)	Not less than 70% (Q) of the labeled amount of Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) is dissolved in 90 minutes.	1	94	92	90	Complies
		2	93	93	93	
		3	92	94	99	
		4	90	91	96	
		5	97	89	92	
		6	96	89	91	

		Min	90	89	90	
		Max	97	94	99	
		Avg	94	91	94	

In-process checks of filled capsules during the optimum speed of the capsule filling machine: All in-process checks (physical parameters) were performed during the Optimum speed and are shown in Table 15.

Table 15: In-process checks of filled capsules during the optimum speed of the capsule-filling machine

Test(s)	**Acceptance criteria**		**Results**	**Remarks**
			Optimum Speed (70,000 caps/ Hour)	
Description	White to off White granules containing Opaque white (cap) and Opaque White (body) colored capsules.		Complies	Complies
Weight of 10 intact capsule (g)	6.550 ± 3% (6.354 to 6.746)	Min	6.388	Complies
		Max	6.680	
		Avg	6.480	
Uniformity of weight (intact capsules) (mg)	655.000 ± 5 % (622.250 to 687.750 mg)	Min	627.000	Complies
		Max	681.000	
		Avg	655.240	
Content weight variation (by opening the capsule) (mg)	550.000 ± 5 % (522.500 to 577.500 mg)	Min	533.100	Complies
		Max	563.300	
		Avg	542.400	
Capsule length after filling and sealing (mm)	21.50 mm ± 0.50 mm (21.00 to 22.00 mm)	Min	21.16	Complies
		Max	21.78	
		Avg	21.55	
Disintegration Time	NMT 15 minutes	Min	03 min 46 sec	Complies
		Max	04 min 05 sec	

Uniformity of dosage unit (by content uniformity) of filled capsules during capsule samples collected at optimum speed of capsule filling machine: Individual values of uniformity of dosage units' test (by content uniformity) of filled capsules samples collected at Optimum speed were found in the range of 99.3% to 105.2% respectively complying with acceptance criteria. Mean of Uniformity of dosage unit of filled capsules of these samples were found as 101.1% respectively. AV Value found 1.8 and complies as per acceptance criteria as shown in table 16.

Table 16: Uniformity of dosage units in filled capsules during sample collection at the optimal speed

Tests	**Acceptance criteria**		**Results**	**Remarks**
			Optimum Speed (70,000 caps/ Hour)	
Uniformity of dosage units by content uniformity	Individual assay values are within 75% to 125%	Unit:1	101.2	Complies
		Unit: 2	100.3	
		Unit: 3	99.4	
		Unit: 4	102.5	

(%)	and AV value is ≤ 15.0.	Unit: 5	101.3	
		Unit: 6	99.5	
		Unit: 7	99.3	
		Unit: 8	105.2	
		Unit: 9	102.2	
		Unit: 10	100.2	
		Minimum	99.3	
		Maximum	105.2	
		Mean	101.1	
		AV (%)	1.8	

Dissolution results of filled capsules at capsule filling process start, middle, and end-stage of optimum run: Dissolution results of filled capsules at start, middle, and end-stage of optimum speed at capsule filling of optimization batch was found in the range of 88 to 95 %, 87 to 98 % and 89 to 98 %, respectively and complies as per acceptance criteria, as shown in Table 17.

Table 17: Dissolution of filled capsules at the start, middle, and end stages of the optimum run capsule filling process

Test(s)	**Acceptance criteria**			**Results** **Optimum Speed (70,000 caps/ Hour)**	**Remarks**
Dissolution (%)	Not less than 70% (Q) of the labeled amount of Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) is dissolved in 90 minutes.	Start	1	88	Complies
			2	95	
			3	94	
			4	91	
			5	90	
			6	93	
			Min	88	
			Max	95	
			Avg.	92	
		Middle	1	94	
			2	91	
			3	89	
			4	87	
			5	98	
			6	90	
			Min	87	
			Max	98	
			Avg.	91	
		End	1	89	
			2	92	
			3	98	
			4	94	

			5	96	
			6	94	
			Min	89	
			Max	98	
			Avg.	94	

Yield of Optimized Batch: This is the tentative yield limit for the optimization batch. The yield of the optimization batch complies as per tentative limit. % yield after Capsule Filling was 93.78%, % yield after Capsule Inspection was 91.92% and % yield at Capsule Packing Stage was 90.50% and all values were within acceptable limit.

Finished product analytical results of optimization batch: Analytical results of finished product of optimization batch found complying with Acceptance Criteria, as shown in table 18.

Table 18: Finished product analytical results of optimization batch

Sr. No.	Test(s)	Observation	Acceptance Criteria
1.	Description	Complies	White to off White granules containing Opaque white (cap) and Opaque White (body) colored capsules.
2.	Identification		
	By HPLC	Complies	The retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation, as obtained in the assay.
	By UV	Complies	The UV absorption spectra of sample preparation exhibit the maxima and minima at the same wavelengths as that of standard preparation in dissolution.
3.	Dissolution (by HPLC)%	Min: 90.87%	Not less than 70% (Q) of the labeled amount of Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) is dissolved in 90 minutes.
		Max: 99.80%	
4.	Uniformity of dosage units (By content uniformity)	2.8	The acceptance value (AV) of 10 dosage units is less than or equal to 15.0.
5.	Water content	1.6 %	Not more than 5.0 %
6.	Related substances (By HPLC, %w/w)		
	Any individual impurity	0.07 %	Not more than 0.15%
	Total Impurities	1.4 %	Not more than 2.0%
7.	Assay (By HPLC, %)	99.8	Not less than 95.0% and not more than 110.0% of the labeled Claim of Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$)
8.	Residual Solvents	Complies	To comply USP<467>
9.	Microbial enumeration tests and Tests for specified microorganisms		
	Total viable Aerobic Microbial Count	Absent	Not more than 1000 cfu/g

	Total combined Molds and Yeast count	Absent	Not more than 100 cfu/g
a	Pathogens	Absent	Absent
b	Staphylococcus aureus	Absent	Absent
c	Pseudomonas aeruginosa	Absent	Absent
d	Escherichia coli	Absent	Absent
e	Salmonella Candida Albicans	Absent	Absent

Dissolution profile of reference product and optimization batch: The dissolution profile of optimization batch is faster than the reference product as is depicted in Table 19 at various time intervals.

Table 19: % Cumulative Drug Release of reference product and optimization batch

Time points (Min.)	Reference Product (Sporanox Capsules)	Optimization batch
10	25.4	53.6
15	30.2	64.3
20	38.3	76.2
30	57.3	84.3
45	69.6	88.2
60	81.1	91.3
90	95.2	99.5

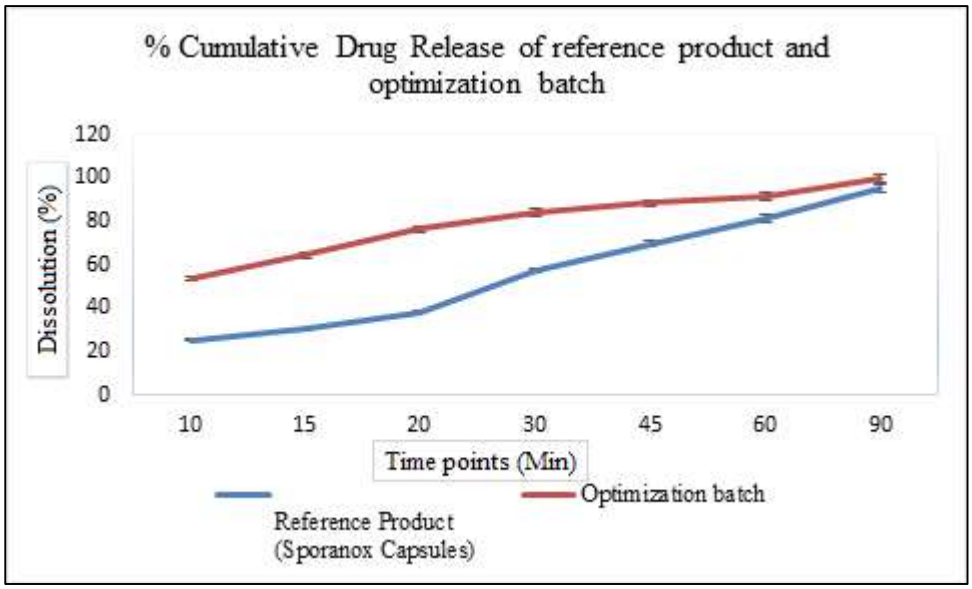

Figure 3: Comparison of the dissolution profile of the Optimization batch with reference product

Stability Study of Process Optimization batch: The stability study of the Process Optimization batch is shown in table 20, 21 and 22.

Pack Details: 50 CC HDPE Bottle.

Table 20: Stability Data Compilation for Itraconazole Capsules 100 mg.

Parameters	Specifications	40°C/ 75% RH			
		Initial	1M	2M	3M
Description	White to off-white pellets filled in size "0" White opaque cap & blue transparent body hard gelatin capsule.	Complies	Complies	Complies	Complies
Drug Release (%) (By HPLC)	Not less than 70 %(Q) of the labeled amount of Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) is dissolved in 90 minutes.	94.8 [89.7-99.3]	84.8 [81.9-89.7]	88.5 [86.4-93.8]	90.5 [88.3-94.6]
Water content (%)	Not more than 6.0%	1.52	1.68	1.74	1.87
Related Substances (%)	Any individual impurity (NMT 0.2%)	0.012	0.049	0.053	0.063
	Total Impurity (NMT 2.5%)	0.21	0.27	0.41	0.39
Assay (%)	Not less than 90.0% and not more than 110.0% of the labeled amount of Itraconazole (C35H38Cl2N8O4)	100.6	99.74	98.53	97.89

Pack Details: Strip Pack.

Table 21: Stability Data Compilation for Itraconazole Capsules 100 mg.

Parameters	Specifications	40°C/ 75% RH			
		Initial	1M	2M	3M
Description	White to off-white pellets filled in size "0" White opaque cap & blue transparent body hard gelatin capsule.	Complies	Complies	Complies	Complies
Drug Release (%) (By HPLC)	Not less than 70% (Q) of the labeled amount of Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) is dissolved in 90 minutes.	91.6 [85.6-97.3]	89.3 [83.6-95.3]	91.3 [84.5-96.2]	89.6 [82.3-95.8]
Water content (%)	Not more than 6.0%	1.24	1.46	1.74	1.95
Related Substances (%)	Any individual impurity (NMT 0.2%)	0.010	0.023	0.046	0.063
	Total Impurity (NMT 2.5%)	0.14	0.35	0.43	0.39
Assay (%)	Not less than 90.0% and not more than 110.0% of the labeled amount of Itraconazole (C35H38Cl2N8O4)	99.6	100.3	99.4	98.60

Pack Details: Alu/Alu Blister Pack.

Table 22: Stability Data Compilation for Itraconazole Capsules 100 mg.

Parameters	Specifications	40°C/ 75% RH			
		Initial	1M	2M	3M
Description	White to off-white pellets filled in size "0" White opaque cap & blue transparent body hard gelatin capsule.	Complies	Complies	Complies	Complies
Drug Release (%) (By HPLC)	Not less than 70% (Q) of the labeled amount of Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) is dissolved in 90 minutes.	93.6 [89.6-98.1]	88.7 [83.6-95.5]	88.3 [82.8-93.5]	89.6 [83.5-93.5]
Water content (%)	Not more than 6.0%	1.46	1.53	1.63	1.94
Related Substances (%)	Any individual impurity (NMT 0.2%)	0.022	0.038	0.043	0.074
	Total Impurity (NMT 2.5%)	0.23	0.34	0.43	0.64
Assay (%)	Not less than 90.0% and not more than 110.0% of the labeled amount of Itraconazole (C35H38Cl2N8O4)	99.60	98.36	97.36	96.7

CONCLUSION.

During manufacturing process challenges at different critical stage are performed. At blending stage, mixing time challenges are performed and results are complying as per acceptance criteria. At Capsule filling stage, Capsule filling machine speed is challenged and results of critical quality attributes like CU and dissolution are complies as per acceptance criteria. Also hopper blend level study challenged are critical quality attributes like CU and dissolution are complies as per acceptance criteria. The results of all stages were found within acceptance criteria mentioned in sampling plan. Results of finished products are complying as per acceptance criteria. Manufacturing Critical Process Parameters are optimized and recommendation of the process parameters are given. On the basis of data generated from manufacturing of the optimization batch it is concluded that the manufacturing process of Itraconazole Capsules 100 mg is optimized and capable of producing a product meeting its quality attributes and predetermined specification.

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