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Manufacturing Process Optimization of Anti-fungal Drug Product by Drug Coating and Seal Coating Method Approach

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The manufacturing process optimization study untaken here assures that the optimized manufacturing process is suitable for the intended purpose and that the product consistently meets predetermined specifications and quality attributes. It gives detailed information on various steps involved in the manufacturing process like Sifting, Drug Coating, Seal Coating, Drying, Lubrication, Capsule filling, Packing and analysis of process challenges samples at various critical stages of manufacturing, in-process tests, and finished product testing.

During this study, Critical Process Parameters (CPPs) involved in Sifting, Drug Coating, Seal Coating, Drying, Lubrication, Capsule filling, and packing were identified with the help of a developmental study and evaluated during the 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 lubricated blend, physical parameters of Capsules, Description, Water content (Finished product) Dissolution, Uniformity of Dosage Unit, Assay, Degradation products and Microbial examination.

After evaluating the analytical results and discussing them, it can be concluded that this optimized manufacturing process is capable of consistently producing the product meeting quality attributes and its predetermined specifications. Hence, the drug product manufacturing process is optimized and can be used for process validation batches of Itraconazole Capsules 100 mg.

Keywords: Process Optimization, Critical Process Parameters (CPPs), Critical Quality Attributes (CQAs), Sampling plan, and Testing plan, Acceptance criteria, finished product, Process Validation, Itraconazole Capsules 100 mg.

1. Introduction

The proposed process parameters range is based on compliance with commercial batches, allowing for minor variations in subsequent batches due to input raw material physical attributes, environmental conditions, and equipment efficiency. These minor variations do not affect product quality as critical parameters remain within the limit (Sangshetti et al., 2017).

The optimization batch optimizes process parameters for exhibit/validation/commercial batches, ensuring they are within the equipment qualification range while focusing on critical quality attributes like capsule weight and disintegration time (Baumann et al., 2021).

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 (Mitchell, 2013).

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 (Yu et al., 2014).

Machine Operating Parameters: These are the machine parameters that are adjusted/controlled on the 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 in-process parameters (viz. weight, hardness, and thickness) of tablets (Su et al., 2018).

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 (Lee et al., 2010).

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 (Alam, 2012).

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 (Mishra et al., 2018).

2. MATERIAL AND METHOD:

The 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 by using Drug Coating and Seal Coating method. Each capsule consists

of 100 mg of Itraconazole as the active ingredient. The proposed formulation comprises commonly used excipients in the design of a solid oral dosage form.

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

Table 1: Raw materials used for manufacturing of the optimization batch

Sr. No.	Raw Material	Function	Stage of Use of material	Manufacturer/ Vendor	Quantity mg/Capsule
Drug Coating Material					
1	Sugar Spheres (25#/30# mesh ASTM)	Base pellets	Drug Coating	Hanns G. Werner GmbH	200
2	Itraconazole	Active Pharmaceutical Ingredient	Drug Coating	Hetero Drugs Limited. / MSN Pharma Chem	100
3	Hypromellose 5 cps (Methocel E 5 Premium LV)	Solubility enhancing carrier	Drug Coating	Nutrition & Bioscience	150
4	Poloxamer 188 (Lutrol F 68)	Solubilizer	Drug Coating	BASF	4
5	Absolute Ethanol	Solvent	Drug Coating	S D Fine Chemical	Q.S.
6	Methylene chloride	Solvent	Drug Coating	Chemplast Sanmar Limited	Q.S.
Seal Coating Material					
7	Polyethylene Glycol 20,000	Solubilizer	Drug Coating	BASF	20
8	Absolute Ethanol	Solvent	Drug Coating	S D Fine Chemical	Q.S.
9	Methylene chloride	Solvent	Drug Coating	Chemplast Sanmar Limited	Q.S.
Lubrication Material					
10	Talc	Glidant	Lubrication	Luznac	3
11	Colloidal Silicon Dioxide	Glidant	Lubrication	Evonik	3
Weight of Lubricated Pellets:480 mg					

List of Packing Materials and their Functions: Table 2, shows a list of packing material used for packing of the optimization batch.

Table 2: List of packing material used for packing of the 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: The manufacturing process involves various stages, including weighing, sifting, drug dispersion preparation, seal coating, sifting, lubrication, capsule filling, tablet deduster, metal detector, and packing machines. Equipment used includes Jay-Pan weighing balance, Gansons vibratory sifter, Fluidise vessel, ACG FBP, Colloidal Silicon Dioxide and Talc sifter, Pillar Blender Bin, and Techno four metal detector.

Manufacturing Process:
Step 1: Sifting of Materials: Sugar spheres were sifted through #25 ASTM sieve, discarded, and collected. Passed sugar spheres were sifted through #30 ASTM, discarded, and retained in HDPE containers (Ramu et al., 2015).

Step 2: Drug Coating: The process involved mixing ethanol and methylene chloride, adding Poloxamer 188, Itraconazole, and Hypromellose, passing the drug solution through a sieve, setting the Fluidized Bed Processor (FBP), loading the bowl with pre-sifted sugar spheres, and spraying the drug solution to achieve the desired target weight gain. Additional coating operations were performed as needed (Hirun et al., 2022). The process parameters include input temperature, product temperature, exhaust temperature, atomization pressure, spray rate, winder height, air distribution plate, and filter bag in PC satin. After drug coating, the final drug loaded pellets at inlet temperature of 40°C -50°C under low fluidization for 10 minutes.

Step 3: Drying and Sifting: The drug-loaded pellets were dried at 60-80°C and 4-24 hours in a tray dryer. The LOD was determined at 105°C and the material was raked intermittently. The pellets were sifted and discarded. The #18 ASTM passed pellets were sifted through #25 ASTM, and the retained pellets were collected for analysis. The composite sample was withdrawn for physical characteristic evaluation and residual solvent analysis.

Step 4: Seal Coating: Preparation of Seal Coating Solution: The process involved mixing ethanol, methylene chloride, and Polyethylene Glycol 20,000 in a solution. The solution was then used to coat drug-loaded pellets, and the pellets were dried at different temperatures. The LOD was then determined, with the limit of detection (LOD) being 1.0%. The process parameters include input, product, exhaust, atomization pressure, spray rate, winder height, air distribution plate, and filter bag in PC satin.

Seal-coated pellets were sifted through sieves, and a composite sample was withdrawn for physical characteristic evaluation and analysis, followed by a description and residual solvent analysis.

Step 5: Lubrication of Seal Coated Pellets: Colloidal Silicon Dioxide and Talc were sifted and collected, then loaded into a blender bin. Lubricated for various durations, uniformity sampling was done, and a composite sample was withdrawn for description, water content, and physical characteristics evaluation.

Step 6: Capsule Filling: The lubricated pellets were filled into Size '0' capsules, and samples were withdrawn at different speeds to assess the impact of the capsule filling machine speed on the drug product's quality assurance.

Step 7: Packing: Capsules are filled in HDPE containers, Strip and Blister pack.

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: Weighing Balance (Mettler Toledo), Tap Density Tester (Electrolab), Disintegration Apparatus (Electro Lab), Sieve Shaker (Elactron Pharma), HPLC (Aglent), UV Spectrophotometer (Perkin Elmer).

Critical/Non-critical process parameters: The manufacturing process of a drug product involves critical parameters such as sifting sugar spheres, drug coating, drying, sealing coating, sifting of Colloidal Silicon Dioxide and Talc, lubrication of seal-coated pellets, packing, and capsule filling machine speed. These parameters affect the quality of the product and its assay, ensuring batch-to-batch consistency and uniformity.

Sampling, Testing Plan, and Acceptance Criteria: The process optimization batch involves drying drug-coated pellets at different temperatures and times, resulting in white to off-white pellets with a water content of 4.0%. Three unit dose samples are withdrawn from 10 sampling locations, resulting in an average weight of 454 mg. Lubricated pellets are analyzed for physical characteristics and particle size.

The study examines capsule filling machines' performance under various speed and speed challenges, including a Hopper Challenge and a composite sample of 200 capsules. The results will be compared with an innovative product to improve efficiency and ensure uniformity in dosage units, ultimately enhancing the efficiency of capsule filling machines.

Sampling Tools: Sampling rod and dies were used during lubrication while SS Container and Scoop were used during capsule filling as a sampling tool.

Rational for Sampling Plan/Points: The process involves drying drug coating pellets, sifting them, and filling capsules. Samples are collected from different locations to ensure uniform drying. Blending for various durations ensures uniform drug coating. Capsules are collected to check their quality throughout the filling process.

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

A] Sampling Location Diagram of Bowl of FBP (Fluid Bed Processor): 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.

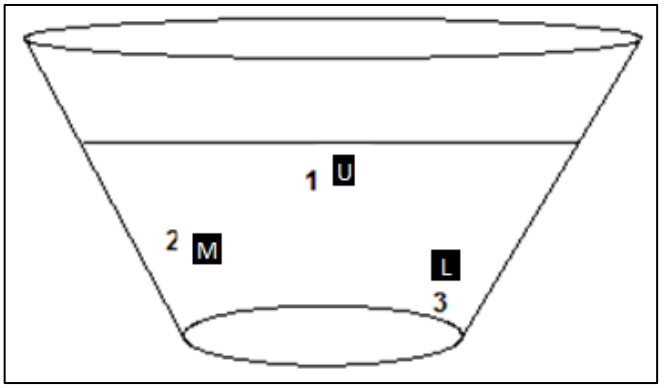

Figure 1: Sampling location in FBD

B] Sampling Location Diagram of IPC/Pillar Blender Bin:

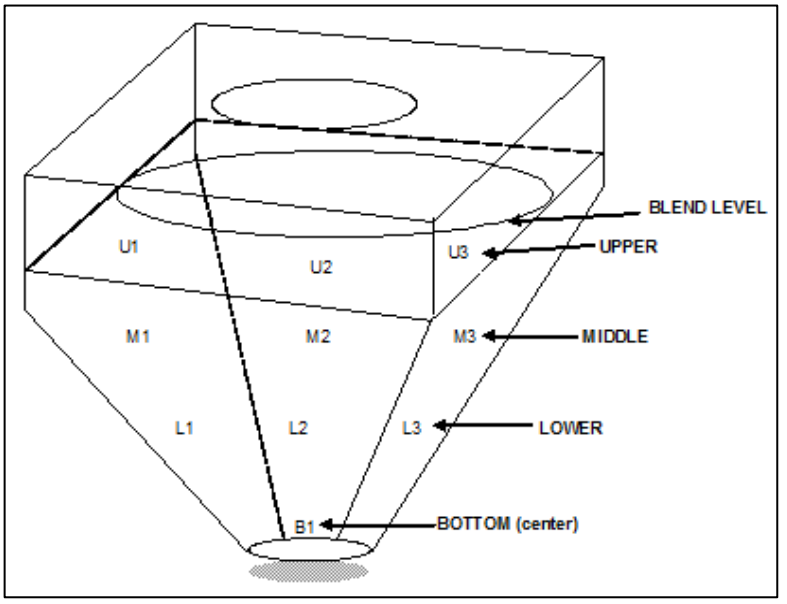

Figure 2: Sampling location in IPC/ Pillar Blender Bin

3. RESULTS AND DISCUSSION:

Loss on drying of Drug-Coated dried granules (LOD): The study revealed that the dried granules in the FBD bowl of the process optimization batch at 16 hours, 20 hours, and 24 hours met the acceptance criteria.

Related Substances for dried drug-coated pellets: Drying of drug-coated pallets at 60°C & 80°C at initial, 4, 8, 12, 16, 20, and 24 hrs does not show a significant increase in total impurity and other impurity.

Residual Solvent for dried drug-coated pellets: The tray dryer report complies with

specifications at 80°C and 24 hours, with the highest impurity at 0.067°C. The initial temperature was 60°C, followed by 0.012 to 0.67°C.

Description and Water Content of Drug-Coated Pellets: The Optimization Batch's dried drug-coated pellets meet acceptance criteria, with a water content of 0.43 %w/w, suitable for compounds with water content between 4.0 and 0.43.

Pellets Uniformity of Drug-Coated Pellets: The Optimization batch's Drug Coated Pellets met acceptance criteria with uniformity ranging from 95.7 to 99.4%, with a mean of 97.8% and a % RSD of 1.20%.

Assay of Drug-Coated Pellets (%): The optimization batch's assay yielded a 98.2% compliance rate, indicating that the drug-coated pellets, containing between 93.0 and 110.0 mg of Itraconazole, meet the acceptance criteria.

Physical Characteristics of Sifted Drug-coated Pellets: The Sifted drug-coated Pellets showed satisfactory bulk density and particle size distribution, with a cumulative retention of 97.56 over 18 mesh and 72.13 over 20 mesh.

Description and Residual Solvent of Dried Seal Coated Pellets: The Optimization batch meets acceptance criteria with an ethanol content of 1320 ppm and a methylene chloride content of 402 ppm.

Loss on drying of seal-coated dried granules (LOD): The study reveals that the dried granules in the FBD bowl of the process optimization batch at 20 minutes, 30 minutes, and 40 minutes met acceptance criteria, as shown in Table 3.

Table 3: Loss on drying of seal-coated dried granules

Test(s)	Acceptance criteria		Observations			Remark(s)
			20 Mins.	30 Mins.	40 Mins.	
LOD	NMT 1.0 % w/w at 105°C for 10 minutes	Top Layer	0.89	0.86	0.75	Complies
		Middle Layer	0.79	0.79	0.72	
		Bottom Layer	0.82	0.75	0.63	
		Composite	0.83	0.79	0.74	

Description and Water Content of Lubricated Pellets: The lubricated pellets from the Optimization batch met the acceptance criteria, with a water content of 0.26%w/w, results of water content are shown in Table 4.

Table 4: Description and water content of lubricated pellets

Test(s)	Acceptance criteria	Results	Remarks
Description	White to off- white pellets.	White to off- white pellets	Complies
Water content (%w/w)	Not more than 4.0	0.26	Complies

Pellets Uniformity of Lubricated Pellets: The Pellets Uniformity (Individual samples) and Mean Pellets Uniformity (Mean) of the Lubricated Pellets of Optimization batch at 05 minutes, 10 minutes, and 15 minutes were found to be 98.3%, 97.6-101.4%, and 96.4-101.3% respectively.

Assay of Lubricated Pellets: The percent of drug present in the optimization batch was found to be 98.4% accurate and meet the acceptance criteria which is Each 480 mg of pellets contains Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) between 93.0 mg and 110.0 mg (between 93.0% and 110.0% of the labeled amount of Itraconazole) as per the standards.

Physical characteristics of lubricated pellets: Lubricated pellets showed satisfactory bulk density, tapped density, and particle size distribution, with over 18 mesh having 100.0% cumulative retention and over 20 mesh having 97.16%, and over 25 mesh having 99.22%.

In process checks of filled capsules during low and high speed of capsule filling machine: Lubricated pellets showed satisfactory bulk density, tapped density, and particle size distribution, with over 18 mesh having 100.0% cumulative retention and over 20 mesh having 97.16% and over 25 mesh having 99.22%.

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 98.4% to 107.0% at low and high speed, and 102.4% to 99.6% at high speed. The mean uniformity was 102.4% and 99.6%, meeting acceptance criteria. Table 5 indicates, the uniformity of dosage units.

Table 5: Uniformity of dosage unit

Test(s)	Acceptance criteria		Results		Remarks
			Low Speed (40,000 caps/ Hour)	High Speed (80,000 caps/ Hour)	
Uniformity of dosage units by content uniformity (%)	Individual assay values are within 75% to 125% and AV value is ≤ 15.0	Unit:1	102.1	97.5	Complies
		Unit: 2	104.3	98.6	
		Unit: 3	99.6	97.0	
		Unit: 4	98.4	102.0	
		Unit: 5	99.3	99.5	
		Unit: 6	101.4	97.7	
		Unit: 7	105.4	99.4	
		Unit: 8	102.5	101.6	
		Unit: 9	107.0	99.1	
		Unit: 10	103.6	103.5	
		Minimum	98.4	97.0	
		Maximum	107.0	103.5	
		Mean	102.4	99.6	
		RSD (%)	2.7	2.1	

Dissolution results of filled capsules at low and high speed of capsule filling machine: The Optimization batch capsule dissolution results, filled at low and high speeds, met the acceptance criteria, with 88-96% and 86-94% respectively, as shown in table 6.

Table 6: Dissolution of filled capsules at low and high speed of capsule filling machine

Test(s)	Acceptance criteria		Results		Remarks
			Low Speed (40,000 caps/hr.)	High Speed (80,000 caps/hr.)	
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	92	91	Complies
		2	95	94	
		3	91	87	
		4	88	90	
		5	90	86	
		6	96	91	
		Min	88	86	
		Max	96	94	
		Avg.	92	90	

In-process checks of filled capsules during full hopper, half hopper, and end hopper of capsule filling machine: The physical parameters of the Full Hopper, Half Hopper, and End Hopper blend levels were checked and complied with the acceptance criteria, as shown in Table 7.

Table 7: In-process checks of filled capsules during full hopper, half hopper, and end hopper of capsule filling machine

Test(s)	Acceptance criteria		Results			Remarks
			Full Hopper	Half Hopper	End Hopper	
Description	White to off-white pellets filled in size "0" White opaque cap & blue transparent body hard gelatin capsule.		Complies	Complies	Complies	Complies
Weight of 10 intact capsule (g)	5.750 ± 3% (5.578 to 5.923) g	Min	5.580	5.585	5.588	Complies
		Max	5.810	5.720	5.884	
		Avg.	5.686	5.643	5.688	
Uniformity of weight (intact capsules) (mg)	575.000 ± 7.5 % (531 to 618 mg)	Min	535.000	541.000	550.000	Complies
		Max	572.000	576.800	583.100	
		Avg.	551.780	564.140	567.720	
Content weight variation (by opening the capsule) (mg)	480.000 ± 7.5 % (444 to 516 mg)	Min	447.000	452.000	448.500	Complies
		Max	472.400	481.200	488.000	
		Avg.	460.620	467.080	471.940	
Capsule length after filling and sealing (mm)	21.5 mm ± 0.5 mm (21 to 22 mm)	Min	21.0	21.1	21.0	Complies
		Max	21.9	21.7	21.9	
		Avg.	21.5	21.4	21.5	
Disintegration Time	NMT 15 minutes	Min	02:52	02:28	02:04	Complies
		Max	06:20	05:56	06:32	

Uniformity of dosage unit (by content uniformity) of filled capsules during collection at full hopper, half hoper, and end hopper blend level of capsule filling machine: The uniformity of dosage units in filled capsule samples at Full Hopper, Half Hopper, and End Hopper was found to be 97.4% to 102.1%, 97.3 to 104.2%, and 97.8 to 105.2%, all meeting acceptance criteria, as mentioned in table 8.

Table 8: Uniformity of dosage unit (by content uniformity) of filled capsules during collected at full hopper, half hoper and end hopper blend level of capsule filling machine

Test(s)	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	99.1	97.3	102.1	Complies
		Unit: 2	97.5	99.3	101.6	
		Unit: 3	100.2	98.6	100.4	
		Unit: 4	99.3	101.4	97.8	
		Unit: 5	97.4	99.1	99.5	
		Unit: 6	99.1	99.4	103.2	
		Unit: 7	100.5	98.6	104.1	
		Unit: 8	98.6	103.2	105.2	
		Unit: 9	102.1	97.6	101.3	
		Unit: 10	98.4	104.2	103.4	
		Minimum	97.4	97.3	97.8	
		Maximum	102.1	104.2	105.2	
		Mean	99.2	99.9	101.9	
		AV	1.4	2.3	2.2	

Dissolution results of filled capsules during collection at full hopper, half hoper, and end hopper blend level of capsule filling machine: The dissolution results of filled capsules in the Optimization batch were found to be 91-98%, 88-97%, and 90-97%, meeting acceptance criteria and are listed in table 9.

Table 9: Dissolution results of filled capsules during collected at full hopper, half hoper, and end hopper blend level of capsule filling machine

Test(s)	Acceptance criteria		Results			Remarks
			Full Hopper	Half 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	91	90	92	Complies
		2	95	94	94	
		3	93	97	97	
		4	92	92	95	
		5	98	88	94	
		6	94	96	90	
		Min	91	88	90	
		Max	98	97	97	
		Avg.	94	93	94	

In-process checks of filled capsules during the optimum speed of capsule filling machine: The optimal speed for optimization batch is 60,000 caps/hour, with hard gelatin capsules with a blue translucent body and white opaque cover. Disintegration time, length, and content weight change are consistent.

Uniformity of dosage unit (by content uniformity) of filled capsules during capsule samples collected at optimum speed of capsule filling machine: The uniformity of dosage units in filled capsule samples collected at optimal speed ranged from 97.4% to 105.1%, meeting acceptance criteria. The mean uniformity was 100.8%, and the AV value was 2.1, confirming the acceptance criteria. The results are presented in a table.

Dissolution results of filled capsules at capsule filling process start, middle and end stage of optimum run: The optimal speed at capsule filling in the Optimization batch was achieved with dissolution results of 89-94%, 88-97%, and 87-97%, meeting acceptance criteria as shown in table 10.

Table 10: Dissolution of filled capsules at capsule filling process start, middle and end stage of optimum run

Test(s)	Acceptance criteria			Results Optimum Speed (60,000 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	89	Complies
			2	93	
			3	92	
			4	94	
			5	91	
			6	90	
			Min	89	
			Max	94	
			Avg.	92	
		Middle	1	92	
			2	88	
			3	90	
			4	94	
			5	97	
			6	91	
			Min	88	
			Max	97	
			Avg.	92	
		End	1	87	
			2	91	

			3	96	
			4	95	
			5	97	
			6	93	
			Min	87	
			Max	97	
			Avg.	93	

Yield of optimization batch: The tentative yield limit for the optimization batch has been met, and the results have been recorded in table 11.

Table 11: Yield of optimization batch

Sr. No.	Manufacturing Stage	% Yield Limit*	% Yield Observed
1	% Yield after Lubrication	NLT 91	95.65
Capsule Filling			
2	% Yield after Capsule Filling	NLT 90	94.82
Inspection			
3	% Yield after Capsule Inspection	NLT 89	92.80
Packing			
4	% Yield at Capsule Packing Stage	NLT 89	90.60

Finished product analytical results of optimization batch: The analytical results of the optimization batch's finished product were found to meet the Acceptance Criteria and are listed in table 12.

Table 12: Finished product analytical results of optimization batch

Sr. No.	Test(s)	Observation	Acceptance Criteria
1.	Description	Complies	White to off-white pellets filled in size “0” White opaque cap & blue transparent body hard gelatin capsule.
2.	Identification		
i)	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.
ii)	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: 91 % Max: 99 %	Not less than 70% (Q) of the labeled amount of Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) is dissolved in 90 minutes.
4.	Uniformity of dosage units (By content uniformity)	4.6	The acceptance value (AV) of 10 dosage units is less than or equal to 15.0.
5.	Water content	1.8 %	Not more than 5.0 %

6.	Related substances (By HPLC, %w/w)		
i	Any individual impurity	0.04 %	Not more than 0.15%
ii	Total Impurities	1.6 %	Not more than 2.0%
7.	Assay (By HPLC, %)	99.5	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		
i	Total viable Aerobic Microbial Count	Absent	Not more than 1000 cfu/g
ii	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 the optimization batch is faster than the reference product, results are shown in table 13.

Table 13: Dissolution profile of reference product and optimization batch

% Cumulative Drug Release Profile		
Time points (min.)	Reference Product (Sporanox Capsules)	Optimization batch
10	25.4	55.3
15	30.2	66.9
20	38.3	76.2
30	57.3	85.3
45	69.6	89.2
60	81.1	93.3
90	95.2	100.2

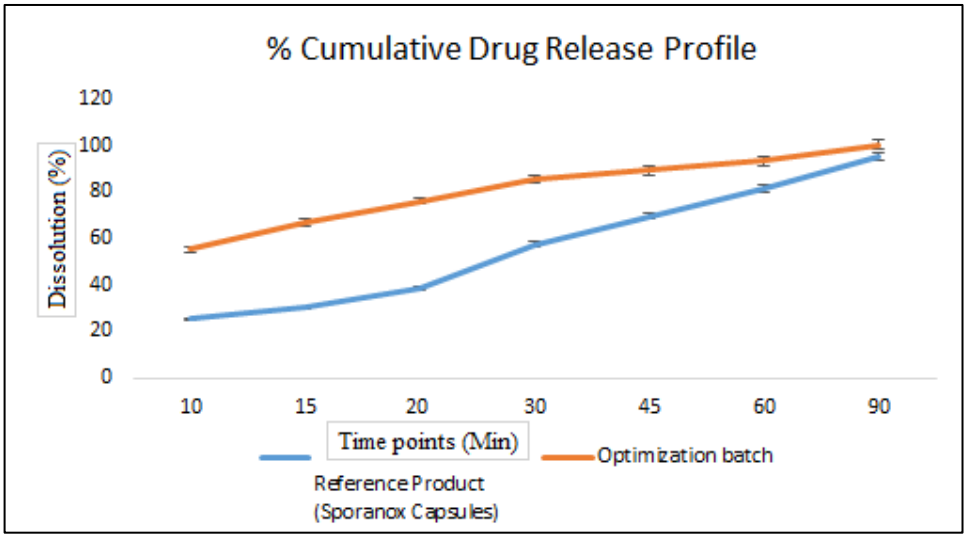

Figure 3: Comparison of the dissolution profile of optimization batch with reference product

Stability Study of Process Optimization Batch: The stability study of the Process Optimization batch is shown in table 14, 15 and 16.

Pack Details: 50 CC HDPE Bottle

Table 14: 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.	94.6 [88.5-102.3]	89.6 [85.3-96.5]	88.3 [84.3-95.3]	88.7 [84.9-94.7]
Water content (%)	Not more than 6.0%	1.46	1.59	1.53	1.78
Related Substances (%)	Any individual impurity (NMT 0.2%)	0.010	0.036	0.049	0.061
	Total Impurity (NMT 2.5%)	0.16	0.18	0.32	0.38
Assay (%)	Not less than 90.0% and not more than 110.0% of the labeled amount of Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$)	101.6	99.2	98.8	97.73

Pack Details: Strip Pack

Table 15: 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.	94.6 [88.5-102.3]	93.6 [84.4-96.4]	92.3 [83.2-97.2]	89.9 [81.6-96.2]
Water content (%)	Not more than 6.0%	1.46	1.51	1.63	1.84
Related Substances (%)	Any individual impurity (NMT 0.2%)	0.010	0.018	0.039	0.058
	Total Impurity (NMT 2.5%)	0.16	0.38	0.58	0.63
Assay (%)	Not less than 90.0% and not more than 110.0% of the labeled amount of Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$)	101.6	100.4	99.6	98.3

Pack Details: Alu/Alu Blister Pack.

Table 16: 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.	94.6 [88.5-102.3]	91.3 [87.7-96.6]	89.3 [83.4-94.6]	88.3 [84.6-93.6]
Water content (%)	Not more than 6.0%	1.46	1.59	1.69	2.07
Related Substances (%)	Any individual impurity (NMT 0.2%)	0.010	0.021	0.039	0.054
	Total Impurity (NMT 2.5%)	0.16	0.23	0.43	0.53
Assay (%)	Not less than 90.0% and not more than 110.0% of the labeled amount of Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$)	101.6	99.43	98.63	97.84

4. CONCLUSION:

During the manufacturing process challenges at different critical stages are performed. At the drying stage and blending stage, challenges are performed and results comply with per acceptance criteria. At the Capsule filling stage, the Capsule filling machine speed is challenged and results of critical quality attributes like CU and dissolution comply with per acceptance criteria. Also, Hopper blend-level study challenges are critical quality attributes like CU and dissolution are comply as per acceptance criteria. The results of all stages were found within the acceptance criteria mentioned in the sampling plan. The results of finished products comply with per acceptance criteria. Manufacturing Critical Process Parameters are optimized and recommendations of the process parameters are given. Based on data generated from manufacturing of the optimization batch it is concluded that the manufacturing process of Itraconazole Capsules 100 mg is optimized by Drug coating and seal coating approach and capable of producing a product meeting its quality attributes and predetermined specification.

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