RESEARCH ARTICLE

Process Validation of Itraconazole Capsules 100 mg Immediate Release Solid Oral Drug Product by Drug Coating and Seal Coating method

Shinde NK[1], Mane DV [1*]

PG and Research Center, Shri Chhtrapati Shivaji Mahavidhlay, Umarga, Tal: Umarga, District Dharashiv-413603, Maharashtra, India

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ABSTRACT

A crucial component of pharmaceutical manufacturing is process validation, which offers written proof that a production method regularly produces goods with predetermined quality standards and specifications. This study focused on the process performance qualification (PPQ) of Itraconazole Capsules 100 mg, an immediate-release dosage form, employing the solid dispersion technique through drug coating and seal coating methods. The research provides an in-depth analysis of each stage involved in the manufacturing process, including Sifting, Drug Coating, Seal Coating, Drying, Lubrication, Capsule Filling, Packing, and the assessment of in-process as well as finished product quality. Each of these steps was meticulously evaluated to ensure adherence to stringent quality standards. As part of the validation study, Critical Process Parameters (CPPs) associated with Sifting, Drug Coating, Seal Coating, Drying, Lubrication, Capsule Filling, and Packing were identified through developmental studies and further assessed during the process validation phase. The study also monitored Critical Quality Attributes (CQAs), including Blend Uniformity (BU), moisture content, physical characteristics of the lubricated blend, capsule weight variation, dissolution profile, uniformity of dosage units, assay, degradation products, and microbial examination. Each of these attributes was analyzed to ensure compliance with regulatory standards and product specifications. Based on the evaluation of analytical data and thorough discussion of results, it was concluded that the manufacturing process is robust, reproducible, and capable of consistently producing Itraconazole Capsules 100 mg that meet all required quality attributes and specifications. Consequently, the process was deemed validated, confirming its suitability for routine commercial manufacturing of the drug product.

Keywords: Process Validation, Critical Process Parameters, Itraconazole, Capsules, Critical Quality Attributes, Finished product

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INTRODUCTION

The pharmaceutical industry is driven by the need to produce high-quality, safe, and effective drug products that meet regulatory standards. Process validation plays a pivotal role in achieving these objectives, because it creates recorded proof that a manufacturing process reliably yields goods that satisfy predetermined standards and quality characteristics. Regulatory authorities, including the USFDA, ICH, WHO, emphasize the criticality of process validation for ensuring product consistency, safety, and efficacy.[1]

Aspergillosis, histoplasmosis, and onychomycosis are among the superficial and systemic fungal diseases that are commonly treated with itraconazole, a triazole antifungal medication. Due to its poor aqueous solubility and low bioavailability, formulating Itraconazole as an immediate-release oral dosage form poses significant challenges. To overcome these limitations, the use of advanced formulation strategies, such as solid dispersion technology, has become a preferred approach. When medications are poorly soluble in water, solid dispersion improves their solubility, rate of dissolution, and bioavailability by incorporating the active pharmaceutical ingredient (API) into a solid carrier matrix. In the case of Itraconazole, the drug coating and seal coating methods are widely employed to achieve a stable, effective, and reproducible immediate-release dosage form.[2]

The process validation of Itraconazole Capsules 100 mg is a critical aspect of pharmaceutical production. It entails evaluating and managing every stage of the production process, including material handling, sifting, drug coating, seal coating, drying, lubrication, capsule filling, and packing. The objective is to ensure that every batch of the drug product consistently meets the intended quality attributes such as blend uniformity, moisture content, disintegration, dissolution, and content uniformity. Failure to maintain these attributes can lead to batch rejections, regulatory non-compliance, and potential risks to patient safety.[3]

The process validation study for Itraconazole Capsules 100 mg requires a meticulous approach that includes identifying and controlling CPPs and CQAs. Critical Process Parameters are the key operational variables that have a direct impact on the quality of the final product.

**Author for Correspondence: dvmane11@gmail.com*

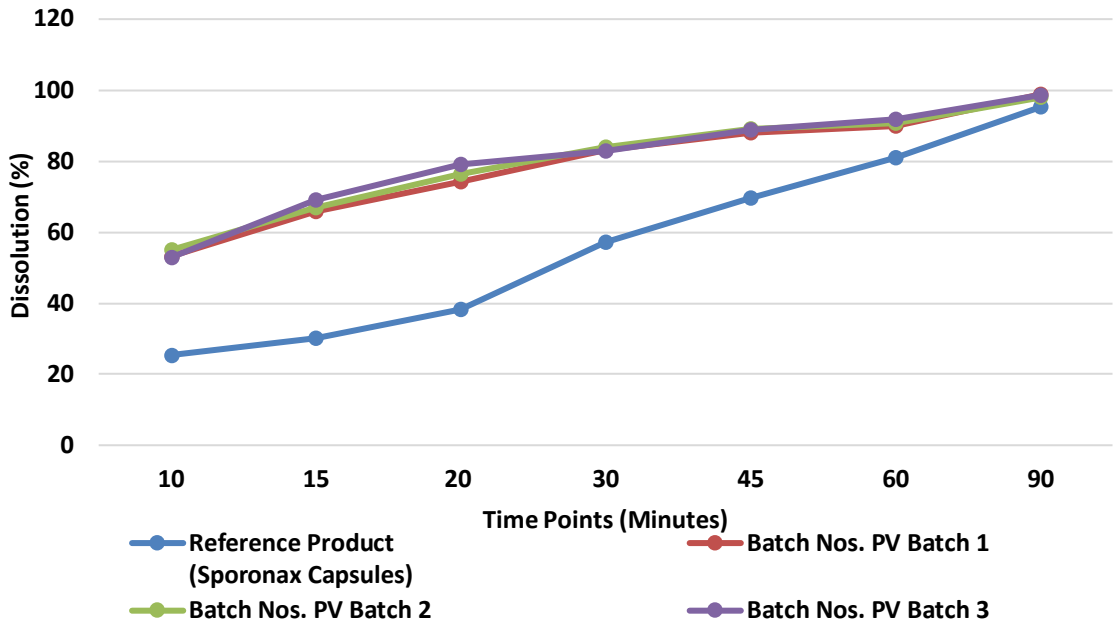

Figure 1: Dissolution results of batches.

Examples include mixing time, coating pan speed, drying temperature, and capsule filling weight variation. In contrast, critical quality attributes are those aspects of a product that need to be kept within certain bounds, whether they be chemical, biological, microbiological, or physical. For Itraconazole capsules, key CQAs include blend uniformity, water content, particle size distribution, capsule weight, and disintegration time.[4]

The drug coating and seal coating processes are particularly important for ensuring the stability and effectiveness of Itraconazole Capsules. The drug coating process involves the application of a homogenous drug layer over the carrier, ensuring uniform distribution of the active ingredient. The seal coating step provides an additional protective barrier to enhance the mechanical strength of the coated particles and prevent the migration of moisture, which can compromise product stability. Process validation of these stages ensures that every batch consistently adheres to predefined specifications, thereby reducing the likelihood of process deviations, product failures, and regulatory issues.[5]

In this research, the primary objective is to conduct the PPQ for the manufacturing of Itraconazole Capsules 100 mg using the drug coating and seal coating methods. The study aims to assess the robustness and reproducibility of the process, ensuring that it meets regulatory requirements and consistently produces high-quality drug products. This involves the identification and control of CPPs, the assessment of CQAs, and the evaluation of process capability through the validation of three consecutive commercial-scale production batches. In order to find possible process failure spots and reduce related risks, the validation research will also make use of quality risk management methods like FMEA.[6]

The outcomes of this research will provide a scientific basis for the validation of Itraconazole Capsules 100 mg and establish a standardized manufacturing process for routine production. This will not only enhance operational efficiency but also ensure regulatory compliance with cGMP guidelines. It is anticipated that the study's conclusions will benefit the larger pharmaceutical sector by providing a validation framework that can be adapted for other immediate-release solid oral dosage forms produced via solid dispersion technology.

MATERIAL AND METHOD

Materials

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 act as dispersion carrier for solid dispersion to enhance dissolution profile of Itraconazole by using Drug Coating and Seal Coating method.

List of API, Raw Materials and their Functions

Following raw material were used for manufacturing of the Process Validation batches by using Solid Dispersion technique by Drug Coating and Seal Coating Method. The manufacturing of process validation (PV) batches using the Solid Dispersion technique by the Drug Coating and Seal Coating method involved various raw materials (**Table 1**). Each material was selected based on its specific role in achieving the desired formulation characteristics, ensuring product stability, and maintaining compliance with quality standards. Below is an elaborated list of active pharmaceutical ingredients (APIs) and excipients used, along with their respective functions:

List of Packing Materials and their Functions

Following packing material were used for packing of the Process Validation batches. The packing materials utilized

for the Process Validation (PV) batches were carefully selected to ensure product protection, stability, and compliance with regulatory standards. Proper packaging plays a crucial role in maintaining the integrity of the product throughout its shelf life, during transportation, and in storage conditions (**Table 2**). Below is a detailed list of packing materials and their respective functions:

Table 1: Raw materials employed.

S. 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 engancing 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					

Table 2: Packing Materials used.

S. 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

Table 3: Equipments used.

Stage of Manufacture	Equipment / Utility Name	Make
All applicable stages	Weighing Balance	Jay-Pan
Sifting	Vibratory Sifter	Gansons
Preparation of Drug Dispersion	Portable S.S. vessel	Fluidyne
	Portable Stirrer	
Drug Coating and Drying of drug coated pellets	ssor (FBP)	ACG
Preparation of Seal Coating Solution	Portable S.S. vessel	Fluidyne
	Portable Stirrer	Anchor Mark
Seal coating	Fluid Bed Processor (FBP)	ACG

Sifting of Colloidal Silicon Dioxide (Aerosil-200) and Talc	Vibratory Sifter	Gansons
Lubrication	Pillar Blender Bin	RP Product
Capsule Filling	Capsule Filling Machine	PAM AF 90
	Tablet Deduster	Omega Pharma
	Metal Detector	Technofour

Table 4: Loss on Drying (LOD) of dried granules.

Manufacturing stage	Acceptance Criteria		Results (%w/w)			Remarks
			PV Batch 1	PV Batch 2	PV Batch 3	
Dried Drug Coated Pellets	NMT 1.0 % w/w at 105°C for 10 minutes	Top Layer	0.78	0.82	0.81	Complies
		Middle Layer	0.70	0.72	0.78	
		Bottom Layer	0.68	0.84	0.69	
		Composite sample	0.59	0.62	0.58	

Table 5: Water Content of Drug Coated Pellets.

Manufacturing stage	Test(s)	Acceptance Criteria	Results			Remarks
			PV Batch 1	PV Batch 2	PV Batch 3	
Dried Drug Coated Pellets	Description	White to off-white pellets.	White to off- white pellets.	White to off-white pellets.	White to off- white pellets.	Complies
	Water content (%w/w)	Not more than 4.0	0.23	0.31	0.26	Complies

Table 6: Pellets Uniformity of Drug Coated Pellets.

Manufacturing stage	Test	Acceptance Criteria	Results (%)			
			Sampling Location	PV Batch 1	PV Batch 2	PV Batch 3
Drug Coated Pellets	Pellets Uniformity (%)	1.Mean of test results: Between 90.0% to 110.0% of label claim of Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$). 2.Individual test results: ± 10% of mean. 3.Relative standard deviation: Not more than 5.0 %	Upper Left : 1	98.5	99.2	99.2
			Upper center:2	94.2	96.2	98.2
			Upper Right :3	93.6	99.2	98.3
			Middle Left : 4	98.5	97.1	92.3
			Middlecenter:5	97.2	95.3	99.8
			Middle Right:6	98.3	93.2	98.5
			Lower Left :7	95.2	100.2	96.9
			Lower center:8	97.2	95.1	99.2
			Lower Right:9	101.2	99.2	100.1
			Bottom center:10	95.6	100.5	99.3
			Min.	93.6	93.2	92.3
			Max.	101.2	100.5	100.1
			Avg.	97.0	97.5	98.2
			% RSD	2.3	2.5	2.3

Table 7: Assay of Drug Coated Pellets.

Manufacturing stage	Test(s)	Acceptance Criteria	Results (%)			Remarks
			PV Batch 1	PV Batch 2	PV Batch 3	
Dried Drug Coated Pellets	Assay (%)	Each 480 mg of pellets contains Itraconazole (C35H38Cl2N8O4) between 93.0 mg and 110.0 mg (between 93.0% and 110.0% of the labeled amount of Itraconazole)	98.6	97.9	99.2	Complies

Table 8: Residual Solvent of Dried Seal Coated Pellets.

Manufacturing stage	Test(s)		Acceptance Criteria	Results			Remarks
				PV Batch 1	PV Batch 2	PV Batch 3	
Dried Seal Coated Pellets	Description		White to off-white pellets.	White to off- white pellets.	White to off- white pellets.	White to off- white pellets.	Complies
	Residual Solvent	A) Ethanol	Not more than 5000 ppm	1488	1330	1688	Complies
		B) Methylene Chloride	Not more than 600 ppm	438	422	388	Complies

Table 9: Water Content of Lubricated Pellets.

Manufacturing stage	Test(s)	Acceptance Criteria	Results			Remarks
			PV Batch 1	PV Batch 2	PV Batch 3	
Lubricated Pellets	Description	White to off-white pellets.	White to off- white pellets.	White to off-white pellets.	White to off- white pellets.	Complies
	Water content (%w/w)	Not more than 4.0	0.19	0.28	0.22	Complies

Table 10: Assay of Lubricated Pellets.

Manufacturing stage	Test(s)	Acceptance Criteria	Results (%)			Remarks
			PV Batch 1	PV Batch 2	PV Batch 3	
Lubricated Pellets	Assay (%)	Each 480 mg of pellets contains Itraconazole between 93.0 mg and 110.0 mg (between 93.0% and 110.0% of the labeled amount of Itraconazole)	99.1	98.2	99.6	Complies

Table 11: Pellets Uniformity of Lubricated Pellets.

Manufacturing stage	Test	Acceptance Criteria	Results (%)			
			Sampling location	PV Batch 1	PV Batch 2	PV Batch 3
Lubricated Pellets	Pellets Uniformity (%)	1.Mean of test results: Between 90.0% to 110.0% of label claim of Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$). 2.Individual test results: ± 10% of mean. 3.Relative standard deviation: Not more than 5.0%	Upper Left : 1	97.6	98.8	93.3
			Upper center:2	95.4	97.4	98.2
			Upper Right :3	93.2	98.6	95.9
			Middle Left : 4	98.6	96.8	93.3
			Middlecenter:5	95.4	94.3	94.6
			Middle Right:6	99.2	92.8	95.7
			Lower Left :7	96.4	93.9	96.9
			Lower center:8	95.7	94.1	95.4
			Lower Right:9	93.2	95.3	95.9
			Bottom center:10	94.3	93.3	98.7
			Min.	93.2	92.8	93.3
			Max.	99.2	98.8	98.7
			Avg.	95.9	95.5	95.8
			% RSD	2.1	2.2	1.8

Table 12: Bulk Density of lubricated pellets.

Manufacturing Stage	Test	Results (gm/mL)			Remarks
		PV Batch 1	PV Batch 2	PV Batch 3	
Lubricated Pellets	Bulk Density (gm/mL)	0.85	0.84	0.87	Satisfactory

Table 13: Particles Sieve Distribution of Lubricated Pellets.

Lubricated Pellets	**Results (%)**			**Remarks**
	PV Batch 1	**PV Batch 2**	**PV Batch 3**	
Sieve size	**% Sieve Distribution**			
# 18 ASTM (Pass)	100	100	100	Satisfactory
# 20 ASTM (Retention)	97.97	98.1	97.6	
# 25 ASTM (Retention)	99.5	99.67	98.5	

Table 14: In process checks of filled capsules of three PV batches.

Stage	**Test(s)**	**Acceptance criteria**		**Results**			**Remarks**
				PV Batch 1	**PV Batch 2**	**PV Batch 3**	
Capsule filling	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**	5.710	5.723	5.730	Complies
			Max	5.820	5.870	5.85	
			Avg	5.765	5.796	5.79	
	Uniformity of weight (intact capsules) mg)	575.000 ± 7.5 % (531 to 618 mg)	**Min**	565	570	560	Complies
			Max	595	605	608	
			Avg	580	587	584	
	Content weight variation (by opening the capsule) (mg)	480.000 ± 7.5 % (444 to 516 mg)	**Min**	470	475	465	Complies
			Max	500	510	513	
			Avg	485	492	489	
	Capsule length after filling and sealing (mm)	21.5 ± 0.5mm (21.0 to 22.0)	**Min**	21.44	21.41	21.43	Complies
			Max	21.57	21.58	21.53	
			Avg	21.50	21.49	21.48	
	Disintegration Time (Minutes: Second)	NMT 15 minutes	**Min**	03:12	02:55	03:05	Complies
			Max	05:35	05:10	05:40	

Equipment

Following equipment were used for manufacturing of the Process Validation batches. The manufacturing of Process Validation (PV) batches involves the use of specialized equipment to ensure precise processing, consistency, and adherence to quality standards (**Table 3**). Each piece of equipment plays a critical role in various stages of production, contributing to the efficiency and robustness of the manufacturing process. Below is a detailed list of equipment used and their respective functions:

Manufacturing Process

Step 1: Sifting of Materials

Sifted Sugar Spheres (Pharm - a- Spheres 25-30 ASTM) through the sieve # 25 ASTM, discarded the retained Sugar Spheres and collect the Sugar Spheres and record the details. Again Sifted the #25 ASTM passed Sugar Spheres through #30 ASTM, discarded the passed Pellets and collected the retained pellets in double polythene bags lined HDPE container.

Step 2: Drug Coating

Mixed Ethanol Absolute and Methylene Chloride under constant stirring for 5 minutes. Added Poloxamer 188 (Lutrol F68) to the above solution under constant stirring and continue the stirring till clear solution is obtained. Itraconazole was added to the aforesaid solution while being continuously stirred, and the stirring was continued until a clear solution was achieved. To the aforesaid solution, hypromellose (Methocel E5 Premium LV) was added while being continuously stirred until a clear solution was achieved. Passed the Drug solution obtained above through 100 # S.S. Sieve. Setting of the Fluidized Bed Processor (FBP) was performed as per the setting parameters mentioned below in below Table. Loaded the FBP bowl with the pre sifted 25#pass and 30# retention Sugar Spheres (Pharm - a- Spheres 25-30ASTM). Started spraying of drug solution, if required continue the coating operation with the extra drug solution to obtain the required target weight gain. After drug coating, dried the final drug loaded pellets at inlet temperature 40°C -50°C under low fluidization for 10 minutes.

Step 3: Drying and Sifting

Operated the Tray Drier and dried the Drug loaded pellets at inlet temperature of 80 ℃ and continued the drying of the drug loaded pellets for 24 hrs. Raking of the material was done intermittently. Unloaded the dried pellets from tray dryer and pack in double polyethylene bag. Then sifted the drug loaded pellets through sieve No. 18 #ASTM, discarded the retained pellets. Again Sifted the

#18 ASTM passed pellets through #25 ASTM, discard the passed pellets and collected the retained pellets.

Step 4: Seal Coating

Preparation of Seal Coating Solution

Mixed the Ethanol Absolute and Methylene Chloride under constant stirring for 5 minutes. Added Polyethylene Glycol 20,000 to the above solution and continued the stirring till clear solution is obtained. Passed the seal coating solution obtained above through 100 S. S. Sieve and use this solution for spraying on drug loaded pellets. Setting of the Fluidized Bed Processor (FBP) was done as per the setting parameters mentioned in following Table. Seal coated the drug loaded pellets using the seal coating solution of above step. After coating, dried the seal coated pellets at temperature 40°C under low fluidization for 30 minutes.

Step 5: Lubrication of Seal Coated Pellets

Sifted Colloidal Silicon Dioxide (Aerosil-200) and Talc through sieve 25# sifter and collected in double Polythene lined labeled containers. Loaded the seal coated pellets in a blender bin. Lubricated the above seal coated pellets with sifted Colloidal Silicon Dioxide (Aerosil-200) and Talc for 10 minutes at 05 RPM.

Step 6: Capsule Filling

Filled the lubricated pellets in Size '0' capsules.

Step 7: Packing

Capsules are filled in HDPE containers.[7-9]

RESULTS AND DISCUSSION

Variability in Critical Quality Attributes between three process validation batches

Loss on Drying of Drug Coated Pellets

% LOD of dried Drug Loaded Pellets comprising of Top, Middle, and Bottom layers of FBP bowl and composite sample of PV Batch 1 was found 0.78 %, 0.70 %, 0.68 % and 0.59 % respectively and complies as per acceptance criteria. % LOD of dried Drug Loaded Pellets comprising of Top, Middle, Bottom layers of FBP bowl and composite sample of PV Batch 2 was found 0.82 %, 0.72 %, 0.84 % and 0.62 % respectively and complies as per acceptance criteria. % LOD of dried Drug Loaded Pellets comprising of Top, Middle, Bottom layers of FBD bowl and composite sample of PV Batch 3 was found 0.81 %, 0.78 %, 0.69 % and 0.58 % respectively and complies as per acceptance criteria (**Table 4**).[10]

Water Content of Drug Coated Pellets

Description of three PV batches complies as per acceptances criteria. Water content of PV batch 1, PV Batch 2 and PV Batch 3 was found 0.23 %, 0.31 %, and 0.26 % respectively and complies as per acceptance criteria. The water content of drug-coated pellets from three process validation (PV) batches was analyzed to ensure that it complied with the specified acceptance criteria. This parameter is critical in maintaining the stability, integrity, and performance of the pellets, as excess moisture can impact drug release, shelf life, and overall product quality (**Table 5**).[11]

Pellets Uniformity of Drug Coated Pellets

The Pellets Uniformity (Individual samples) of Drug Coated Pellets of three PV batches was found in the range of 93.6 to 101.2 %, 93.2 to 100.5 % and 92.3 to 100.1 % respectively and complies as per acceptance criteria. Mean value of Pellets Uniformity (Mean) of three PV batches was found 97.0%, 97.5 % and 98.2 % respectively and complies as per acceptance criteria. % RSD of three PV batches was found 2.3 %, 2.5 % and 2.3 % respectively and complies as per acceptance criteria (**Table 6**).[12]

Assay of Drug Coated Pellets (%)

Assay of PV batch 1, PV Batch 2 and PV Batch 3 was found 98.6 %, 97.9 %, and 99.2 % respectively and complies as per acceptance criteria. The assay of drug-coated pellets was conducted for all three process validation (PV) batches to determine the amount of active pharmaceutical ingredient (API) present relative to the labeled claim. This critical quality parameter ensures the uniformity, potency, and consistency of the drug product, confirming that the manufacturing process is in control and compliant with regulatory standards (**Table 7**).

Residual Solvent of Dried Seal Coated Pellets

Description of three PV batches complies as per acceptances criteria. Ethanol content in PV Batch 1, PV Batch 2 and PV Batch 3 was found 1488 ppm, 1330 ppm, 1688 ppm respectively and complies as per acceptance criteria. Methylene Chloride content in PV Batch 1, PV Batch 2 and PV Batch 3 was found 438 ppm, 422 ppm and 388 ppm respectively and complies as per acceptance criteria (**Table 8**).

Water Content of Lubricated Pellets

Description of three PV batches complies as per acceptances criteria. Water content of PV batch 1, PV Batch 2 and PV Batch 3 was found 0.19 %, 0.28 %, and 0.22 % respectively and complies as per acceptance criteria. The water content of lubricated pellets for three process validation (PV) batches was evaluated to ensure compliance with the predefined acceptance criteria. Monitoring the water content at this stage is critical as it directly affects the flowability, compressibility, stability, and overall performance of the pellets during downstream processes, such as capsule filling or tableting (**Table 9**).

Assay of Lubricated Pellets (%)

The assay values for all three PV batches fall within the predefined limits, indicating minimal batch-to-batch variability. These results affirm that the blending and lubrication processes are well-controlled and capable of producing pellets with consistent API content. Assay of PV batch 1, PV Batch 2 and PV Batch 3 was found 99.1 %, 98.2 %, and 99.6 % respectively and complies as per acceptance criteria (**Table 10**).

Pellets Uniformity of Lubricated Pellets

The Pellets Uniformity (Individual samples) of Lubricated Pellets of three PV batches was found in the range of 93.2 to 99.2 %, 92.8 to 98.8 % and 93.3 to 98.7 % respectively and complies as per acceptance criteria. Mean value of Pellets Uniformity (Mean) of Lubricated Pellets of three PV batches was found 95.9 %, 95.5 % and 95.8 % respectively and complies as per acceptance criteria. % RSD of three PV batches was found 2.1 %, 2.2 % and 1.8 %, respectively and complies as per acceptance criteria (**Table 11**).

Physical characteristics of lubricated pellets

Bulk Density of lubricated pellets

Bulk density of PV batch 1, PV Batch 2 and PV Batch 3 was found 0.85 %, 0.84 %, and 0.87 % respectively and it is performed for information and recording purpose (**Table 12**).

Particles Sieve Distribution of Lubricated Pellets

The particle size distribution of lubricated pellets was analyzed and recorded as part of the process validation to ensure that the physical characteristics of the pellets were consistent and met the requirements for optimal downstream processing. Although, this test was conducted for informational and documentation purposes, it provides valuable insights into the quality and uniformity of the pellets. (**Table 13**).

In process checks of filled capsules of three PV batches

In process checks (physical parameters) performed during capsule filling process of three PV batches was found within acceptance criteria. During the capsule filling process, comprehensive in-process checks were conducted for all three process validation (PV) batches to ensure that the physical parameters of the capsules met the predefined acceptance criteria. These checks play a vital role in maintaining product quality, consistency, and regulatory compliance throughout the manufacturing process. (**Table 14**).

Finished Product Analytical results of three PV batches

Analytical results of finished product of three PV batches found complying with Acceptance Criteria. The quality control testing for the three process validation (PV) batches of the drug formulation was conducted with results aligning with the specified acceptance criteria for each parameter. The physical description of all three PV batches complied with the expected standards, consisting of white to off-white pellets encapsulated in size “0” white opaque caps with blue transparent bodies, consistent with the reference. Identification tests by High-Performance Liquid Chromatography (HPLC) and UV spectroscopy both showed compliance across all batches, with the main peak’s retention time matching that of the standard preparation in HPLC, and the UV absorption spectra of the sample exhibiting maxima and minima at the same wavelengths as the standard in dissolution testing. Dissolution testing by HPLC demonstrated that all batches met the required dissolution criteria, with results ranging from 89% to 102%, surpassing the minimum threshold of 70% dissolution in 90 minutes. Uniformity of dosage units was assessed by content uniformity, with all batches demonstrating acceptable values well within the limit of 15.0, ensuring consistent dose distribution. Water content, as determined by Karl Fischer titration, remained below the upper limit of 5.0%, with values ranging from 1.4% to 1.9%. Related substance analysis by HPLC showed no individual impurity exceeding 0.15%, and total impurities for all batches remained below 2.0%, with values ranging from 1.0% to 1.3%, well within acceptable limits. Assay results by HPLC confirmed that the active ingredient, Itraconazole, was present within the acceptable range of 95.0% to 110.0% of the labeled claim, with batch values between 97.1% and 98.6%. Residual solvents, analyzed by Gas Chromatography (GC), were also within permissible limits, with ethanol levels well below 5000 ppm and methylene chloride levels staying below the 600 ppm threshold. Microbial testing confirmed the absence of any pathogens, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella*, and *Candida albicans*, with total viable aerobic microbial and combined mold and yeast counts within the acceptable limits of 1000 cfu/g and 100 cfu/g, respectively. These results collectively indicate that all PV batches meet the rigorous quality control specifications, ensuring the formulation's safety, efficacy, and compliance with pharmacopeial standards.

Dissolution Profile of three PV batches

The cumulative drug release profile for the process validation (PV) batches of the formulated product was evaluated and compared with the reference product, Sporanox® capsules, at multiple time intervals. The release pattern demonstrated a significant improvement in the drug release rate for all PV batches compared to the reference product. At the 10-minute mark, the reference product showed a release of 25.4%, while PV Batch 1, PV Batch 2, and PV Batch 3 exhibited higher releases of 53.2%, 55%, and 52.9%, respectively. A similar trend was observed at 15 minutes, where the drug release from the reference product reached 30.2%, whereas PV Batch 1, PV Batch 2, and PV Batch 3 showed enhanced releases of 65.8%, 66.9%, and 69%, respectively. The 20-minute time point displayed a cumulative release of 38.3% for the reference product, in contrast to 74.3%, 76.4%, and 79.2% for PV Batch 1, PV Batch 2, and PV Batch 3, respectively. By the 30-minute interval, the drug release for the reference product reached 57.3%, whereas PV Batch 1, PV Batch 2, and PV Batch 3 demonstrated markedly higher releases of 83.2%, 84%, and 82.8%, respectively. Further, at the 45-minute mark, the reference product achieved a cumulative release of 69.6%, which was significantly lower than the releases observed for PV Batch 1 (87.9%), PV Batch 2 (89%), and PV Batch 3 (88.9%). By 60 minutes, the release from the reference product was 81.1%, while PV Batch 1, PV Batch 2, and PV Batch 3 demonstrated cumulative releases of 89.9%, 90.6%, and 91.8%, respectively. At the 90-minute mark, the reference product exhibited a release of 95.2%, whereas PV Batch 1, PV Batch 2, and PV Batch 3 exhibited near-complete releases of 98.8%, 97.9%, and 98.6%, respectively. These findings suggest that the process validation batches exhibited faster and more complete drug release than the reference product at all time points, indicating the robustness and efficiency of the optimized formulation process (**Figure 1**).

CONCLUSION

The manufacturing critical process parameters were confirmed in the process validation study, which was successfully finished on three batches of 100 mg itraconazole capsules. The outcomes of every phase fell within the sampling's specified acceptability standards.

Based on the information gathered from the three batches (PV Batch 1, PV Batch 2, and PV Batch 3), it can be said that the production process for 100 mg Itraconazole Capsules may provide a product that satisfies its quality attributes and predefined specifications.

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