RESEARCH ARTICLE

Development and Evaluation of Antifungal Drug Product by Solid Dispersion Technique using Drug Coating and Seal Coating Approach (Itraconazole Capsules 100 mg)

Shinde NK, Mane DV*

PG and Research Center, Shri Chhtrapati Shivaji Mahavidhlay, Umarga, Dharashiv, Maharashtra, India

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ABSTRACT

A very important stage in developing and preserving the quality of any pharmaceutical drug product is validation. Drug product validation creates the written proof that offers a high level of certainty that a manufacturing process will reliably provide a product with predefined standards and quality features. Studying the process performance certification of the drug product Itraconazole Capsules 100 mg Immediate Release Capsule dosage form was the primary goal of my research. The research conducted here guarantees that the production process is appropriate for the intended use and that the final product continuously satisfies predefined requirements and quality standards. Sifting, dry mixing, wet granulation, drying, sizing, blending, lubrication, capsule filling, packing, and analysis of in-process tests and final product are only a few of the processes in the production process that are covered in depth. This study used developmental research to identify Critical Process Parameters (CPPs) that were involved in sifting, dry mixing, wet granulation, drying, sizing, blending, and capsule filling. The CPPs were then assessed during the process validation study. All of the critical quality attributes (also known as critical control parameters) were monitored during this process, including blend uniformity (BU), water content, blend physical characteristics, capsule physical parameters, description, water content (final product), dissolution, dosage unit uniformity, assay, degradation products, and microbiological examination. Following discussion and analysis of the analytical data, it may be said that this manufacturing process can reliably produce a product that satisfies its predefined specifications and quality features. As a result, the medicinal product's manufacturing method has been verified and is suitable for regular production of 100 mg Itraconazole Capsules.

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

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INTRODUCTION

Specifically, one of the key GMP concepts highlighted is validation. The process of confirming via analysis and objective evidence that the particular requirements for a particular intended use can be consistently satisfied is known as validation. Validation requires documentation of this proof in addition to demonstrating (or ensuring) that the method meets its criteria. The method used to document a validation attempt is called a protocol. Clinical testing, manufacturing, and medicines in all their forms are all impacted by the complex and wide-ranging regulatory issue of validation.[1] A medical product is developed through a number of steps, such as drug discovery, laboratory testing, preclinical research on animals, clinical trials on humans, formulation and development, registration with a regulatory authority, and related legislation. The quality of the finished product is greatly influenced by the facilities and processes utilized in drug development. Therefore, in order to further improve the drug product's efficacy and safety, regulatory authorities need the producer to test the product for identity, strength, quality, purity, and stability before releasing it for commercial use, even after regulatory approval. Pharmaceutical validation becomes an essential step in putting this into practice. In the United States, the idea of validation first appeared formally. USFDA officials were the first to propose the "Process Validation (PV)" idea in the pharmaceutical business because they thought it would assist to enhance the quality of pharmaceutical goods.[2] The modern definition of validation emerged from the necessity of upholding consistency, quality, and most importantly, public safety. The idea of validation is one that is expanding and changing quickly. The rate of technological advancement is the cause of this development. It is in charge of giving the product a better level of assurance. The basis of validation, the process of validation, and the necessity of validation will probably continue to be important elements of the sector.[3] Process validation is a journey rather than a one-time event that involves just finishing the three process validation runs or batches, according to the current life cycle approach to "process validation." The life cycle method to process validation encompasses all stages of a product's life cycle, from original creation to marketing to discontinuance. A scientific, risk-based approach that follows the principles of

*Author for Correspondence: dvmane11@gmail.com

Table 1: Raw materials employed.

S. 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
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
Extragranular 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

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

"Quality by Design" is the Enhanced Process Validation technique. An strategy that links product and process development, verifies the commercial manufacturing process, and controls the process inside the change management system is used to make sure that the process is kept under control during regular commercial production.[4] This study's main goal is to develop a strong process validation procedure for the wet granulation method of producing an antifungal medication product in the form of an immediate-release oral solid dose. For pharmaceutical products to consistently be safe, effective, and of high quality, process validation is essential. By focusing on the validation of critical process parameters, this study aims to achieve process robustness, minimize variability, and ensure regulatory compliance with current Good Manufacturing Practices (cGMP). To achieve this aim, the study is guided by the following objectives: (1) to identify and optimize CPPs and CQAs that significantly impact the quality of the final product, (2) to develop a VMP that outlines the scope, strategy, and acceptance criteria for the validation process, (3) to perform process qualification through three consecutive commercial-scale production batches, ensuring batch-to-batch consistency, (4) to assess process capability and establish control limits for key parameters such as granule size, moisture content, drying time, blending uniformity, and compression force, (5) to analyze and document in-process and finished product testing data, including assay, disintegration time, dissolution profile, and microbial limits, (6) to identify and mitigate potential risks in the manufacturing process using tools such as FMEA, and (7) to ensure that the entire process complies with regulatory guidelines provided by the USFDA, WHO, and ICH Q8, Q9, and Q10. Through these objectives, the study aims to establish a standardized and reproducible manufacturing process that guarantees the

production of high-quality, safe, and effective anti-fungal drug products.

Table 3: Equipments used.

Stage of Manufacture	Equipment / Utility Name	Make
All applicable stages	Weighing Balance	Jay-Pan
Sifting	Vibratory Sifter	Gansons
Drug Solution Preparation	Drug Solution Preparation	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
	Deduster	Omega Pharma
	Metal Detector	Technofour

MATERIALS AND METHODS

The Drug product is an immediate release capsules consisting of a solid dispersion of Itraconazole by using Methocel E3 LV as a carrier for enhance 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 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. The drug Itraconazole dissolve in Glacial Acetic Acid at 45°C, and granulate with following ingredients HPMC (Methocel E 3 LV), Pearlitol 25 C was the 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

The following active pharmaceutical ingredients (API) and excipients were used in the manufacturing of process validation batches through the wet granulation method. Each raw material plays a critical role in ensuring the stability, functionality, and efficacy of the final product (Table 1).

List of Packing Materials and their Functions

The following packing materials were utilized in the manufacturing of process validation batches. These materials play an essential role in ensuring the protection, stability, and presentation of the final pharmaceutical product. The selection of appropriate packing materials is critical to maintaining product quality throughout its shelf life (Table 2).

Equipments

The following equipment was employed during the manufacturing of process validation batches. Each piece of equipment is essential to ensuring the consistency, quality, and efficiency of the manufacturing process. The equipment was selected based on the requirements of the wet granulation method and subsequent processing steps (Table 3).

Method

Solid Dispersion method was selected as the manufacturing process as it involves following steps; i.e. Granulating solution preparation, Dry mixing, Granulation, Drying, Milling, Blending and Capsule Filling. 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. Colloidal Silicon Dioxide (Aerosil 200) was

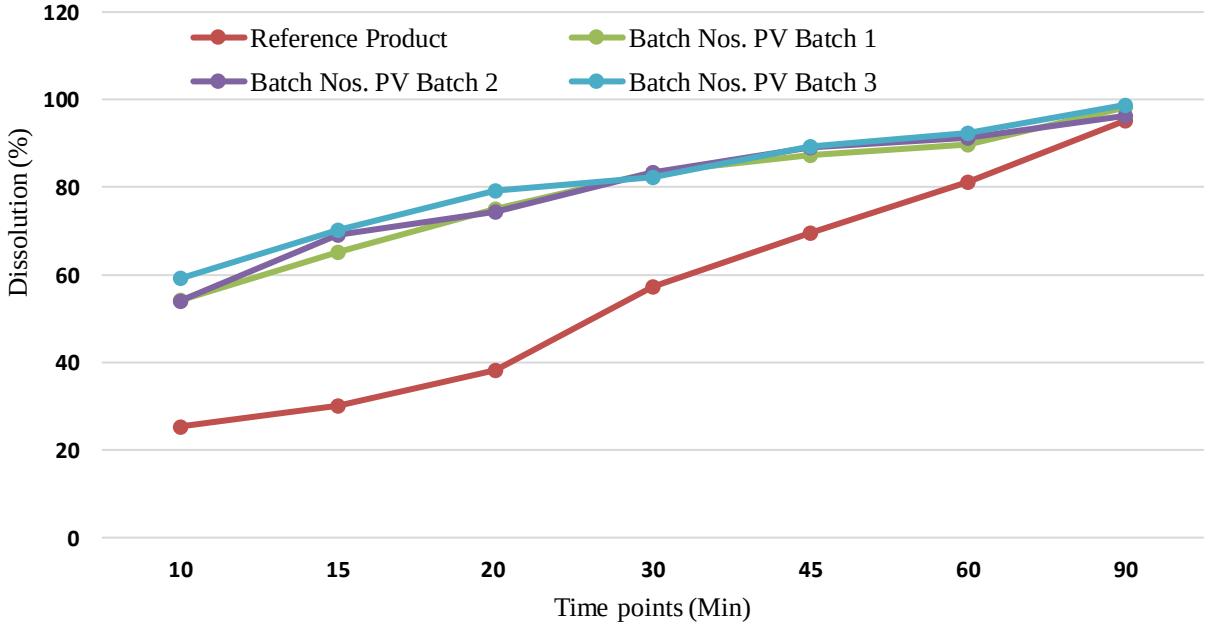

Figure 1. Dissolution profile.

added as adsorbent. Croscarmellose Sodium (Ac-Di-sol) as disintegrant, Silicified Microcrystalline cellulose (Prosolv 50) as Diluent to enhances the density of capsule. However, in contact with water it causes disintegration of the capsule which can cause rapid drug release.[5]

Manufacturing process

Preparation of Drug Solution

Placed Glacial Acetic Acid in a container equipped with a propeller mixer. Itraconazole API was dissolved at 45°C in Glacial Acetic acid by stirring till get the clear solution. (Store the drug solution in a closed S.S. Container).

Sifting

Sifted Mannitol (Pearlitol 25 C), Hydroxypropyl Methyl Cellulose (Methocel E3 LV Premium) through 40 mesh

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

Manufacturing stage	Acceptance Criteria		Observations			Remark(s)
			PV Batch-1	PV Batch-2	PV Batch-3	
Dried granules	NMT 1.0 % w/w at 105°C for 10 minutes	Top Layer	0.75	0.79	0.73	Complies
		Middle Layer	0.68	0.82	0.76	
		Bottom Layer	0.78	0.75	0.80	
		Composite	0.71	0.72	0.69	

Table 5: Description and residual solvent of dried granules.

Manufacturing stage	Test(s)	Acceptance Criteria	Results			Remarks
			PV Batch-1	PV Batch-2	PV Batch-3	
Dried granules	Description	White to off-white granular Powder.	White to off-white granular Powder.	White to off-white granular Powder.	White to off-white granular Powder.	Complies
	Residual Solvent (ppm)	Ethanol : NMT 5000	1310	1505	1482	Complies

Table 6: Water content of final blend.

Manufacturing stage	Test(s)	Acceptance Criteria	Results (% w/w)			Remarks
			PV Batch-1	PV Batch-2	PV Batch-3	
Final Blend	Description	White to off-white granular Powder.	Complies	Complies	Complies	Complies
	Water Content (% w/w)	NMT5.0%	0.23	0.46	0.33	Complies

Table 7: Blend uniformity.

Manufacturing stage	Test(s)	Acceptance Criteria	Results (%)			
			Sampling Location	PV Batch-1	PV Batch-2	PV Batch-3
Bending (05 Minutes)	Blend Uniformity (%)	1.All values should be within ± 10 % of mean value.	Upper Left : 1	97.2	94.5	96.9
			Upper center:2	96.7	97.2	97.3
			Upper Right :3	98.9	98.2	94.9
			Middle Left : 4	98.2	96.8	95.6
		2.Mean Value shall be within 95 to 110 % of Label Claim.	Middlecenter:5	97.9	96.2	95.8
			Middle Right:6	96.8	99.0	98.2
			Lower Left :7	96.4	95.4	96.9
			Lower center:8	98.5	96.9	97.8
		3.RSD is NMT 5.0 %	Lower Right:9	94.9	95.8	98.2
			Bottom center:10	99.0	97.5	98.7
			Min.	94.9	95.4	94.9
			Max.	99.0	99.0	98.7
			Avg.	97.5	97.0	97.0
			% RSD	1.33	1.38	1.30

Table 8: Physical characteristics of final blend.

Process Stage	Test(s)	Acceptance Criteria	Results			Remarks
			PV Batch-1	PV Batch-2	PV Batch-3	
Bending	Bulk Density (gm/mL)	For	0.64	0.66	0.63	Satisfactory
	Tapped Density (gm/mL)	Information	0.76	0.79	0.75	Satisfactory
	Compressibility Index (%)	NMT 25	17.19	20.00	18.33	Complies
	Hausner Ratio	NMT 1.34	1.21	1.22	1.32	Complies
	Angle of Repose (º)	25 to 40	32.0	31.66	31.56	Complies
	Particle Size Distribution	Over 20#	1.20	1.23	1.50	Satisfactory
	(% Cumulative retention)	Over 40#	52.06	51.23	53.26	
		Over 60#	65.78	66.51	63.40	
		Over 80#	70.75	70.30	73.50	
		Over 100#	92.05	90.53	94.35	
		below 100 #	7.95	9.47	5.65	

Table 9: In process checks of filled capsules.

Stage	Test(s)	Acceptance criteria		Results			Remarks
				PV Batch-1	PV Batch-2	PV Batch-3	
Capsule filling	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 g ± 3 % (6.354 to 6.746 g)	Min	6.440	6.490	6.510	Complies
			Max	6.620	6.625	6.640	
			Avg	6.540	6.538	6.563	
	Uniformity of weight (Intact capsules) (mg)	655.000 ± 5 % (622.250 to 687.750 mg)	Min	639.000	642.000	648.000	Complies
			Max	669.000	671.000	673.000	
			Avg	654.300	653.900	655.200	
	Content weight variation (by opening the capsule) (mg)	550.000 ± 5% (522.500 to 577.500 mg)	Min	535.200	536.400	539.300	Complies
			Max	563.100	564.000	559.100	
			Avg	551.200	553.500	551.000	
	Capsule length after filling and sealing (mm)	21.5 ± 0.5 mm (21 to 22 mm)	Min	21.36	21.29	21.25	Complies
			Max	21.74	21.73	21.71	
			Avg	21.54	21.52	21.53	
	Disintegration time (Min:Sec)	NMT 15 minutes	Min	03:40	02:35	02:12	Complies
			Max	05:43	05:36	05:35	

sieve. HDPE was collected from drums lined with double polythene bags.

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.

Wet granulation

The drug solution prepared in Step 1 was gradually incorporated into the material from Step 3 over a span of 3 minutes, ensuring a controlled addition with the impeller operating at a gentle speed and the chopper in an inactive state. The resulting wet mixture was thoroughly blended for 2 minutes using both the impeller and chopper at a slow, uniform speed to achieve homogeneity. The wet mass was subsequently scraped to prevent any adherence to the vessel surface, after which it was re-mixed for an additional 2 minutes with the impeller and chopper running at an accelerated speed. The process was carefully monitored to attain the desired uniformity and optimal consistency of the wet mass.

Drying

Placed the wet granules into a bowl of Fluid Bed Dryer. Dried wet mass at Inlet temperature 65.0 ± 5.0°C and until the Outlet temperature was observed 52°C. Sample was withdrawn for LOD determination. LOD was checked at 105°C with limit- NMT 1.0%.

Sifting and 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.

Extra Granular material

Sifted Croscarmellose Sodium and Silicified Microcrystalline cellulose (Prosolv 50) through 40 mesh

Table 10: Dissolution results of filled capsules.

Stage	Test(s)	Acceptance criteria			Results			Remarks
					PV Batch-1	PV Batch-2	PV Batch-3	
Capsule filling	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	99	98	98	Complies
				2	97	95	95	
				3	95	96	94	
				4	96	98	96	
				5	98	97	96	
				6	99	94	98	
				Min	95	94	94	
				Max	99	98	98	
				Avg	97	96	96	
			Middle	1	98	95	95	
				2	98	94	98	
				3	95	92	94	
				4	94	96	97	
				5	96	97	96	
				6	97	95	98	
				Min	94	92	94	
				Max	98	97	98	
				Avg	96	95	96	
			End	1	98	96	95	
				2	94	98	96	
				3	97	98	92	
				4	95	94	95	
				5	96	97	97	
				6	98	96	95	
				Min	94	94	92	
				Max	98	98	97	
				Avg	96	97	95	

S.S Sieve. It was collected it HDPE drums lined with double polythene bags.

Mixing

Added material of Step 7 in Step 6 and mixed for 5 minutes at 5 rpm in Pillar Blender Bin.

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. The capsules were polished using polishing machines. Inspected the filled capsules visually and discard any defective capsules.

Packing

Capsules are filled in HDPE containers.[6-9]

Instruments used for analysis

UV-Vis Spectrophotometer (Perkin Elmer), Weighing Balance (Mettler Toledo), Sieve Shaker (Electron Pharma), Tap Density Tester (Electrolab), HPLC (Agilent), Compressed Air System (Ingersollrand), Disintegration Apparatus (Electro Lab), Purified Water System (Christnisotec), and HVAC System (ABB) were utilized.

RESULTS AND DISCUSSION

Loss on Drying (LOD) of Dried Granules

% LOD of dried granules comprising of top, middle, bottom layers, and composite sample of FBD bowl of PV Batch-1 was found 0.75%, 0.68%, 0.78% and 0.71%, respectively and complies as per acceptance criteria. % LOD of dried granules comprising of top, middle bottom layers, and composite sample of FBD bowl of PV Batch-2 was found 0.79%, 0.82%, 0.75%, and 0.72%, respectively and complies as per acceptance criteria. % LOD of dried granules comprising of top, middle and bottom layers, and composite sample of FBD bowl of PV Batch-3 was found 0.73%, 0.76%, 0.80%, and 0.69%, respectively and complies as per acceptance criteria (Table 4).[10]

Residual Solvent of Dried Granules

The residual solvent levels in the dried granules of the process validation (PV) batches were assessed to ensure compliance with the predefined acceptance criteria. For PV Batch-1, the residual solvent content was found to be 1310 ppm, while PV Batch-2 showed a slightly higher level of 1505 ppm. Similarly, PV Batch-3 exhibited a residual solvent content of 1482 ppm. All three batches were well within the acceptable limits, demonstrating the effectiveness of the drying process employed. Additional analysis conducted on retained samples from these batches confirmed consistent results, with variations remaining within a permissible range, thereby reinforcing the robustness of the manufacturing process. This compliance ensures the quality and safety of the product, adhering to regulatory standards for residual solvents in pharmaceutical formulations (Table 5).[11]

Water Content of Final Blend

Description of three PV batches complies as per acceptances criteria. Water content of three PV batches was

Table 11: Uniformity of dosage units.

Manufacturing Stage	Acceptance criteria	Stage of Capsule filling	Uniformity of dosage units		
			PV Batch-1	PV Batch-2	PV Batch-3
Capsule Filling	Acceptance value: Not more than 15.0.	Start	5.8	4.1	2.8
		Middle	4.9	4.3	3.8
		End	5.3	5.7	4.2

fond 0.23, 0.46, and 0.33, respectively and complies as per acceptance criteria. The water content of the final blend was evaluated for all three PV batches to ensure compliance with the predefined acceptance criteria. Maintaining the correct water content in the final blend is critical for ensuring proper granule compressibility, flowability, and stability of the formulation (Table 6).

Blend Uniformity at Blending Stage (05 Minutes)

The blend uniformity (Individual samples) at blending stage (05 minutes) for three batches was found in the range of 94.9 to 99.0 %, 95.4 to 99.0 %, and 94.9 to 98.7 %, respectively, and complies as per acceptance criteria. Mean value of blend uniformity (Mean) at blending stage (05 minutes) for three batches was found 97.5 %, 97.0 %, and 97.0 %, respectively, and complies as per acceptance criteria. % RSD at blending stage (5 minutes) for three batches was found 1.33 %, 1.38 %, and 1.30 %, respectively, and complies as per acceptance criteria (Table 7).[12]

Physical Characteristics of Final blend

Bulk density and tapped density of final blend was found satisfactory. Compressibility Index, Hausner Ratio, and Angle of Repose were complying for all three PV batches as per acceptance criteria. Particle size distribution of final blend was found satisfactory. The physical characteristics of the final blend were thoroughly evaluated to ensure its suitability for subsequent manufacturing processes, such as compression or encapsulation. These parameters are essential for determining the blend's flowability, compressibility, and uniformity, which directly influence the quality of the final product. The analysis was conducted for all three process validation (PV) batches, and the results were satisfactory, meeting the predefined acceptance criteria (Table 8).

In process checks of filled capsules

During the capsule filling stage, in-process checks of physical parameters were conducted to ensure the quality and consistency of the filled capsules for three process validation batches. These checks are essential for verifying that the capsules meet predefined acceptance criteria and comply with regulatory standards for pharmaceutical manufacturing. Overall, the in-process checks conducted during the capsule filling stage demonstrated compliance with the acceptance criteria for all three batches. These results reflect the robustness of the manufacturing process and ensure that the filled capsules meet the required quality, safety, and efficacy standards (Table 9).

Dissolution results of filled capsules

Dissolution results of filled capsules at start, middle and end stage of capsule filling of PV Batch-1 found in the range of 95 to 99%, 94 to 98%, and 94 to 98%, respectively and complies as per acceptance criteria. Dissolution results of filled capsules at start, middle and end stage of capsule filling of PV Batch-2 found in the range of 94 to 98 %, 92 to 97 %, and 94 to 98 %, respectively and complies as per acceptance criteria. Dissolution results of filled capsules at start, middle and end stage of capsule filling of PV Batch-3 found in the range of 94 to 98 %, 94 to 98 %, and 92 to 97 %, respectively and complies as per acceptance criteria (Table 10).

Uniformity of dosage units (by content uniformity)

AV of Content uniformity results of filled capsules at start, middle and end stage of capsule filling of PV Batch-1 found 5.8, 4.9, and 5.3%, respectively and complies as per acceptance criteria. AV of Content uniformity results of filled capsules at start, middle and end stage of capsule filling of PV Batch-2 found 4.1, 4.3, and 5.7%, respectively and complies as per acceptance criteria. AV of Content uniformity results of filled capsules at start, middle and end stage of capsule filling of PV Batch-3 found 2.8, 3.8, and 4.2%, respectively and complies as per acceptance criteria (Table 11).

Finished Product Analytical results of three PV batches

The pharmaceutical validation of three process validation (PV) batches was conducted through a series of critical quality control tests to ensure compliance with established standards. The description test for PV Batch-1, PV Batch-2, and PV Batch-3 showed that all batches complied with the acceptance criteria, confirming the presence of white to off-white granules contained in opaque white (cap) and opaque white (body) colored capsules. For identification tests, both HPLC and UV spectrophotometric methods were employed. The chromatograms of the assay preparations exhibited prominent peaks with retention times identical to those of the standard preparation, while the UV absorption spectra showed congruent peaks and minima at similar wavelengths as the standard, thereby demonstrating compliance for all three batches. The dissolution test (by HPLC) revealed that the percentage of Itraconazole released ranged from 91.3% to 100.2% for PV Batch-1, 90.2% to 102.4% for PV Batch-2, and 92.6% to 101.7% for PV Batch-3. All these values met the acceptance criteria of at least 70% (Q) of the labeled Itraconazole content being dissolved within 90 minutes. The uniformity of dosage units (by content uniformity) yielded acceptability values (AV) of 5.6, 4.3, and 3.9 for PV Batch-1, PV Batch-2, and PV Batch-3, respectively, well within the required limit of 15.0 or below. The water content (measured by Karl Fischer titration) was 1.8%, 1.5%, and 2.1% for PV Batch-1, PV Batch-2, and PV Batch-3, respectively, all conforming to the specified limit of not more than 5.0% w/w.[14] The related substances test (by HPLC) examined individual and total impurities. The maximum individual impurity levels were 0.08%, 0.06%, and 0.08% for PV Batch-1, PV Batch-2, and PV Batch-3, respectively, all below the acceptance criterion of not more than 0.15%. The total impurities were 1.1%,

0.9%, and 0.8% for PV Batch-1, PV Batch-2, and PV Batch-3, respectively, satisfying the limit of not more than 2.0%. The assay (by HPLC) confirmed the active pharmaceutical ingredient (API) content of Itraconazole as 98.9%, 99.6%, and 99.1% for PV Batch-1, PV Batch-2, and PV Batch-3, respectively, which all lie within the range of 95.0% to 110.0% of the labeled claim.

Dissolution Profile of three PV batches

The cumulative drug release profile of the reference product was compared with the profiles of three process validation (PV) batches, PV Batch-1, PV Batch-2, and PV Batch-3 — at specific time intervals of 10, 15, 20, 30, 45, 60, and 90 minutes. At the 10-minute mark, the reference product exhibited a 25.4% release, while PV Batch-1, PV Batch-2, and PV Batch-3 demonstrated significantly higher releases of 54.2%, 54.1%, and 59.2%, respectively. By 15 minutes, the cumulative release for the reference product increased to 30.2%, whereas PV Batch-1, PV Batch-2, and PV Batch-3 showed notable increases to 65.2%, 69.1%, and 70.3%, respectively. At 20 minutes, the reference product released 38.3% of the drug, whereas PV Batch-1, PV Batch-2, and PV Batch-3 exhibited releases of 75.1%, 74.3%, and 79.3%, respectively, reflecting a more rapid release from the validation batches. At the 30-minute mark, the reference product achieved a 57.3% cumulative release, while PV Batch-1, PV Batch-2, and PV Batch-3 showed considerably higher releases of 83.5%, 83.3%, and 82.3%, respectively. This trend continued at 45 minutes, with the reference product reaching 69.6% drug release, while PV Batch-1, PV Batch-2, and PV Batch-3 exhibited 87.3%, 89.2%, and 89.4% release, respectively. By the 60-minute mark, the reference product had released 81.1% of the drug, compared to 89.8% from PV Batch-1, 91.2% from PV Batch-2, and 92.3% from PV Batch-3. Finally, at 90 minutes, the reference product exhibited a maximum drug release of 95.2%, while PV Batch-1, PV Batch-2, and PV Batch-3 showed higher releases of 98.2%, 96.3%, and 98.8%, respectively.[15] Overall, the cumulative drug release profile reveals a consistently faster and more complete drug release from the PV batches compared to the reference product at each time point. The PV batches demonstrated similar and uniform release patterns, indicating consistency and reproducibility in drug release behavior, which is essential for ensuring batch-to-batch uniformity and therapeutic efficacy (Figure 1).

CONCLUSION

Three batches of 100 mg itraconazole capsules were the subject of a successful process validation study, which also verified the manufacturing critical process parameters. Every stage's findings fell within the acceptable range specified in the sampling strategy. It is established that the production process of Itraconazole Capsules 100 mg is capable of generating a product that satisfies its quality characteristics and predetermined specification based on the data produced from the three batches (PV Batch-1, PV Batch-2, and PV Batch-3).

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