RESEARCH ARTICLE

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

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Received: 9th Aug, 2024; Revised: 04th Oct, 2024; Accepted: 27th Nov, 2024; Available Online: 25th Dec, 2024

ABSTRACT

Itraconazole Capsules 100 mg were formulated utilizing the Solid Dispersion Technique with Drug Coating and Seal Coating Approach in order to make the formulation as economical as possible. The formulation comprised of Sugar Spheres as base pellets, Hypromellose 5 cps as Solubility enhancing carrier, Poloxamer 188 (Lutrol F 68) as Solubilizer, Absolute Ethanol and Methylene chloride as solvent, Polyethylene Glycol 20,000 as Solubilizer, Talc and Colloidal Silicon Dioxide as Glidant. The improved formulation's in-vitro dissolution research revealed 100% release at 90 minutes, whereas the RLD formulation demonstrated 95% release. The formulation of Itraconazole Capsules 100 mg employing the solid dispersion technique with drug coating and seal coating approach has resulted in a stable and economical formulation, according to this finding.

Keywords: Solid Dispersion, Drug Coating, Seal Coating approach, Itraconazole, Capsules; In-vitro release

How to cite this article: Shinde NK, Mane DV. Development and Evaluation of Antifungal Drug Product by Solid Dispersion Technique using Drug Coating and Seal Coating Approach (Itraconazole Capsules 100 mg) International Journal of Pharmaceutical Quality Assurance. 2024;15(4):2250-58. doi: 10.25258/ijpqa.15.4.19

Source of support: Nil.

INTRODUCTION

Generic Itraconazole Capsules 100 mg, a BCS class II is developed by QbD approach and it is therapeutically equivalent to SPORANOX ™ (Itraconazole) Capsules 100 mg, a Reference Listed Product. The RLD pills are used to treat fungal infections. According to in vitro research, itraconazole prevents ergosterol, an essential component of fungal cell membranes, from being synthesized in a cytochrome P_{450}-dependent manner.[1]

QTPP was first defined based on the properties of the therapeutic component, the description of the Reference Product, and the RP label. CQAs were identified based on the extent of patient harm (safety and efficacy) caused by a pharmaceutical product's failure to meet that quality feature. Pharmaceutical development focused on CQAs that might be impacted by a useful change to the way CPPs are produced or how the medication is formulated. These CQAs covered Assay, Dissolution, Water Content, and Degradation Products for 100 mg Itraconazole Capsules.[2]

Given that drug-layered beads frequently possess lower particle size distributions and better surfaces, a drug layering (drug coating) technique was chosen for formulation development. According to BCS, itraconazole is essentially a medication with low water solubility, hence these characteristics are crucial for the next stages of bead coating. The drug-layered beads were created by dissolving the drug material and solubility enhancer carriers, Poloxamer 188 and Hypromellose 5 cps, in Methylene Chloride and Ethanol Absolute, and using a bottom-spray Fluid Bed coating technique to spray the chosen beads. In order to preserve the physical integrity of the drug-layered bead during further processing, a binder was added to the organic coating because there was little intrinsic binding property in the medication ingredient. However, in this formulation, Hypromellose 5 cps has both binding property and solubility-enhancing capabilities. Then process followed by seal coating by using Polyethylene Glycol 20,000. Excipient selection was based on the Reference Product Composition, IIG limits and Drug-excipient compatibility studies.[3]

Optimization of formulation is done by using Solubility enhancer carrier and other excipients at different concentration and ratio. Bead selection (type/size) identified, Drug substance particle size, Solubility enhancer Carrier lot-to-lot variability, Drug substance to Solubility enhancer Carrier Ratio, and Viscosity of drug layering solution.[4]

The weakly basic chemical itraconazole (pKa = 3.7) has very limited water solubility and can only be ionized at low pH and LogP of 5.66 at 8.1 pH, it is likewise highly

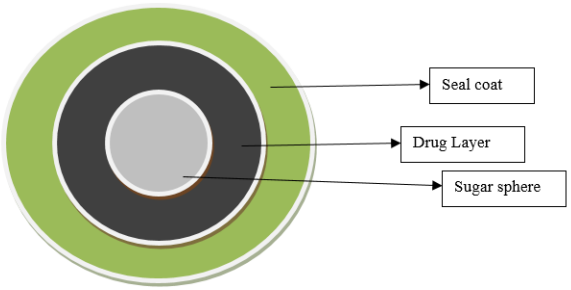

Figure 1: Design of the Seal Coated beads.

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lipophilic. The medication is highly soluble in acidic pH environments and exhibits a pH-dependent dissolution. Itraconazole exhibits pH dependent solubility and it can be classified as low soluble drug according to BCS.[5]

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 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 formulation of Process Validation (PV) batches using the Solid Dispersion technique, combined with Drug Coating and Seal Coating Methods, involves a variety of raw materials (**Table 1**). These raw materials play critical roles in enhancing the drug's solubility, bioavailability, stability, and release characteristics. Below is a detailed list of the Active Pharmaceutical Ingredients (APIs) and excipients used in the manufacturing process, along with their specific functions:

List of Packing Materials and their Functions

Following packing material were used for packing of the Process Validation batches. The packing materials used for the packing of the Process Validation (PV) batches are crucial in ensuring the stability, safety, and efficacy of the pharmaceutical product. Each material plays a specific role in maintaining the product's integrity during storage, handling, and transportation. Below is a detailed list of the packing materials used and their respective functions (**Table 2**).

Table 1: List of API and Raw Materials.

S. No.	Raw Material	Function	Stage of Use of material	Manufacturer/ Vendor	Prototype unit formula (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: List of Packing Materials.

S. No.	Packing Material	Function	Stage of Use of material	Manufacturer/ Vendor
Bulk HDPE Bottles Pack				
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
Strip pack				
1	Plain Aluminium Foil 242 MM 0.04 MM NC Free	Primary Packing Material	Primary Packing	Raviraj Foils
Aluminium – Aluminium Foil Blister (Alu/Alu Blister Pack)				
1	Cold Forming Alu/Alu 328 mm (50MIC)	Primary Packing Material	Primary Packing	Amcor Flexibles
2	Plain 0.030 mm Alu Lid Foil 328 mm	Primary Packing Material	Primary Packing	Raviraj Foils

Table 3: List of equipments employed.

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
Packing Machines	Bulk Packing Machine	CVC
	Strip Pack Machine	Hemson
	Blister Pack Machine	Elmach

Table 4: Drug–Excipient Compatibility Studies.

S. No.	Drug + Excipients	Ratio (Drug: Excipient)	Name of Impurity	Initial	Storage Condition	
					40°C/75% RH	40°C/75% RH
					2nd Week	4th Week
1	Itraconazole (Drug)	NA	Single Highest Unknown Impurity	0.024	0.027	0.026
			Total Impurity	0.204	0.217	0.227
2	Drug + Hypromellose 5 cps	1:1.5	Single Highest Unknown Impurity	0.032	0.024	0.039
			Total Impurity	0.182	0.204	0.240
3	Drug + Polyethylene Glycol 20,000	1:0.18	Single Highest Unknown Impurity	0.024	0.024	0.029
			Total Impurity	0.191	0.224	0.204
4	Drug + Sugar Spheres 25#-30#	1:2	Single Highest Unknown Impurity	0.029	0.024	0.027
			Total Impurity	0.205	0.190	0.289
5	Drug + Poloxamer 188	1:0.05	Single Highest Unknown Impurity	0.015	0.008	0.023
			Total Impurity	0.214	0.216	0.254
6	Drug + Talc	1:0.50	Single Highest Unknown Impurity	0.027	0.054	0.029
			Total Impurity	0.0175	0.213	0.201
7	Drug + Colloidal Silicon dioxide	1:0.5	Single Highest Unknown Impurity	0.027	0.026	0.029
			Total Impurity	0.180	0.206	0.204

Table 5: Qualitative and Quantitative Composition of Itraconazole Capsule 100 mg (mg/capsule) of the different formulation trials.

S. No.	Ingredient Name	Qualitative and quantitative composition of Itraconazole Capsule (mg/capsule)							
		Formulation Code							
		DPF1	DPF2	DPF3	DPF4	DPF5	DPF6	DPF7	DPF8
Drug Coating Material									
1	Sugar Spheres (25#/30# mesh ASTM)	200	200	200	200	200	200	200	200
2	Itraconazole	100	100	100	100	100	100	100	100
3	Hypromellose 5 cps (Methocel E 5 Premium LV)	150	140	160	150	150	150	150	150
4	Poloxamer 188 (Lutrol F 68)	0	4	4	2.5	5.5	4	4	4
5	Absolute Ethanol	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
6	Methylene Chloride	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Seal Coating Material									
7	Polyethylene Glycol 20,000	20	20	20	20	20	20	24	16
8	Absolute Ethanol	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
9	Methylene chloride	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Lubrication Material									
10	Talc	3	3	3	3	3	3	3	3
11	Colloidal Silicon Dioxide	3	3	3	3	3	3	3	3
Weight of Lubricated Pellets		476	470	490	478.5	481.5	480	484	476

Table 6: Physical Parameters and Particle Sieve Distribution of Lubricated blend of the different formulation trials.

Drug Coated Pellets	BD, CI, HR, and Angle of repose							
	Formulation Code							
	DPF1	DPF2	DPF3	DPF4	DPF5	DPF6	DPF7	DPF8
Bulk Density (g/mL)	0.85	0.86	0.85	0.86	0.86	0.85	0.85	0.86
Compressibility Index(%)	14	13	12	13	11	14	12	11
HR	1.18	1.13	1.12	1.14	1.13	1.15	1.14	1.15
Angle of repose (Degrees)	33	34	32	31	32	34	32	35
Sieve size	**% Sieve Distribution**							
# 18 ASTM (Passing)	100	100	100	100	100	100	100	100
# 20 ASTM (Retention)	93.5	99.2	95.78	98.5	95.3	99.9	98.5	98.6
# 25 ASTM (Retention)	98.2	99.7	97.7	99.7	99.4	99.6	99.2	99.5

Table 7: Physical Parameters of Capsules of the different formulation trials.

Filled capsules Parameters	Formulation Code							
	DPF1	DPF2	DPF3	DPF4	DPF5	DPF6	DPF7	DPF8
Group weight of capsules (10 Capsules) (g)	5.750	5.678	5.885	5.736	5.820	5.767	5.739	5.705
Average weight of filled capsules (mg)	569	567	588	573	577	576	573	570
Average weight of empty Capsules (mg)	94	95	96	93	93	95	94	93
Net content of filled capsules (mg)	475	472	492	480	484	481	479	477
Capsule Size	‘0’	‘0’	‘0’	‘0’	‘0’	‘0’	‘0’	‘0’
Locking length (mm)	21.41	21.42	21.4	21.44	21.38	21.37	21.4	21.39

Table 8: Dissolution profile of Capsules of the different formulation trials.

Time points (Min.)	Reference Product (Sporanox Capsules)	Formulation codes							
		DPF1	DPF2	DPF3	DPF4	DPF5	DPF6	DPF7	DPF8
10	25.4	27.4	53.9	53.7	56.5	61.3	60.2	52.8	52.6
15	30.2	32.8	66.5	68.3	69.6	71.2	72.5	67.3	66.5
20	38.3	45.5	74.1	75.2	76.5	78.1	80.1	75.2	74.2
30	57.3	52.6	82.3	84	80.7	83.2	87.3	83.1	85.2
45	69.6	60.3	86.2	88.7	83.2	86.1	90.5	85.1	87.7
60	81.1	65.5	89.5	90.5	86.2	89.1	95.7	87.2	91.2
90	95.2	70.7	96.1	97.8	88.9	98.2	99.8	95.8	96.8

Table 9: Manufacturing Formula Optimization trials to check the effect of Polyethylene Glycol 20,000 Concentration on dissolution profile of the drug product.

S. No.	Ingredient Name	Qualitative and quantitative composition of Itraconazole Capsule (mg/capsule)			
		Formulation Code			
		DPF9A	DPF9B	DPF9C	DPF9D
		Without PEG	PEG-16 mg	PEG-20 mg	PEG-24 mg
Drug Coating Material					
1	Sugar Spheres (25#/30# mesh ASTM)	200	200	200	200
2	Itraconazole	100	100	100	100
3	Hypromellose 5 cps (Methocel E 5 Premium LV)	150	150	150	150
4	Poloxamer 188 (Lutrol F 68)	4	4	4	4
5	Absolute Ethanol	Q.S.	Q.S.	Q.S.	Q.S.
6	Methylene Chloride	Q.S.	Q.S.	Q.S.	Q.S.
Seal Coating Material					
7	Polyethylene Glycol 20,000	0	**16**	**20**	**24**
8	Absolute Ethanol	Q.S.	Q.S.	Q.S.	Q.S.
9	Methylene Chloride	Q.S.	Q.S.	Q.S.	Q.S.
Lubrication Material					
10	Talc	3	3	3	3
11	Colloidal Silicon Dioxide	3	3	3	3
Weight of Lubricated Pellets		460	476	480	484

Table 10: Physical Parameters of Drug Coated Pellets trials to check the effect of Polyethylene Glycol 20,000 Concentration on dissolution profile of the drug product.

Drug Coated Pellets	BD, CI, HR, and Angle of repose			
	Formulation Code			
	DPF9A	DPF9B	DPF9C	DPF9D
Bulk Density (g/mL)	0.86	0.85	0.85	0.86
Compressibility Index (%)	13	12	15	14
HR	1.14	1.16	1.14	1.16
Angle of repose (Degrees)	30	32	31	33

Table 11: Particle Sieve Distribution of Drug Coated Pellets trials to check the effect of Polyethylene Glycol 20,000 Concentration on dissolution profile of the drug product.

Drug Coated Pellets	Formulation code			
	DPF9A	DPF9B	DPF9C	DPF9D
Sieve size	**% Sieve Distribution**			
# 18 ASTM (Pass)	100.00%			
# 20 ASTM (Retention)	97.95%			
# 25 ASTM (Retention)	99.50%			

Table 12: Physical Parameters Capsules of the different formulation trials to check the effect of Polyethylene Glycol 20,000 Concentration on dissolution profile of the drug product.

Filled capsules Parameters	Formulation Code			
	DPF9A	DPF9B	DPF9C	DPF9D
Group weight of capsules (10 Capsules)(gm)	5.396	5.522	5.623	5.873
Average weight of filled capsules (mg)	539	552	562	585
Average weight of empty Capsules (mg)	94	95	94	96
Net content of filled capsules (mg)	445	457	468	489
Capsule Size	‘0’	‘0’	‘0’	‘0’
Locking length (mm)	21.45	21.48	21.4	21.5

Table 13: Dissolution profile of Capsules of the different formulation trials to check the effect of Polyethylene Glycol 20,000 Concentration on dissolution profile of the drug product.

Time points (Min.)	Reference Product (Sporanox® Capsules)	Formulation codes			
		DPF9A	DPF9B	DPF9C	DPF9D
10	25.4	4.8	52.1	55.4	44.3
15	30.2	7.2	65.3	66.4	67.1
20	38.3	11.5	83.1	87.5	82.3
30	57.3	23.2	87.2	95.1	88.1
45	69.6	38.4	93.6	96.3	94.1
60	81.1	48.5	97.2	98.1	96.3
90	95.2	65.8	98.2	98.5	97.2

Table 14: Manufacturing Formula Optimization trials to check the effect of Talc and Colloidal Anhydrous Silica Concentration on dissolution profile of the drug product.

S. No.	Ingredient Name	Qualitative and quantitative composition of Itraconazole Capsule (mg/capsule)			
		Formulation Code			
		DPF10A	DPF10B	DPF10C	DPF10D
		Without Talc and Colloidal Silicon Dioxide	Talc 0.4 % and Silicon Dioxide 0.4 %	Talc 0.6 % and Silicon Dioxide 0.6 %	Talc 0.8 % and Silicon Dioxide 0.8 %
Drug Coating Material					
1	Sugar Spheres (25#/30# mesh ASTM)	200	200	200	200
2	Itraconazole	100	100	100	100
3	Hypromellose 5 cps (Methocel E 5 Premium LV)	150	150	150	150
4	Poloxamer 188 (Lutrol F 68)	4	4	4	4
5	Absolute Ethanol	Q.S.	Q.S.	Q.S.	Q.S.
6	Methylene chloride	Q.S.	Q.S.	Q.S.	Q.S.
Seal Coating Material					
7	Polyethylene Glycol 20,000	20	20	20	20
8	Absolute Ethanol	Q.S.	Q.S.	Q.S.	Q.S.
9	Methylene chloride	Q.S.	Q.S.	Q.S.	Q.S.
Lubrication Material					
10	Talc	0	**2**	**3**	**4**
11	Colloidal Silicon Dioxide	0	**2**	**3**	**4**
Weight of Lubricated Pellets		474	478	480	482

Table 15: Physical Parameters of Drug Coated Pellets to check the effect of Talc and Colloidal Anhydrous Silica Concentration on dissolution profile of the drug product.

Drug Coated Pellets	BD, CI, HR, and Angle of repose			
	Formulation Code			
	DPF10A	DPF10B	DPF10C	DPF10D
Bulk Density (g/mL)	0.85	0.85	0.86	0.86
Compressibility Index (%)	12	13	12	14
HR	1.15	1.15	1.14	1.16
Angle of repose (Degrees)	34	33	31	32

Table 16: Particle Sieve Distribution of Drug Coated Pellets trials to check the effect of Talc and Colloidal Anhydrous Silica Concentration on dissolution profile of the drug product.

Drug Coated Pellets	Formulation code			
	DPF10A	DPF10B	DPF10C	DPF10D
Sieve size	**% Sieve Distribution**			
# 18 ASTM (Pass)	100.00%			
# 20 ASTM (Retention)	97.40%			
# 25 ASTM (Retention)	98.70%			

Table 17: Physical Parameters Capsules of the different formulation trials to check the effect of Talc and Colloidal Anhydrous Silica Concentration.

Filled capsules Parameters	Formulation Code			
	DPF10A	DPF10B	DPF10C	DPF10D
Group weight of capsules (10 Capsules) (g)	5.772	5.739	5.778	5.779
Average weight of filled capsules (mg)	570	573	577	573
Average weight of empty Capsules (mg)	93	94	93	95
Net content of filled capsules (mg)	477	479	484	478
Capsule Size	'0'	'0'	'0'	'0'
Locking length (mm)	21.45	24.4	24.46	24.44

Table 18: Dissolution profile of the different formulation trials to check the effect of Talc and Colloidal Anhydrous Silica Concentration on dissolution profile of the drug product.

Time points (Min.)	Reference Product (Sporanox® Capsules)	Formulation codes			
		DPF10A	DPF10B	DPF10C	DPF10D
10	25.4	55.4	59.3	58.3	49.3
15	30.2	60.1	64.2	65.4	63.7
20	38.3	78.9	83.4	85.3	87.2
30	57.3	89.5	88.2	92.6	91.3
45	69.6	92.3	95.3	94.5	95.6
60	81.1	97.5	98.3	98.2	98.4
90	95.2	101.5	99.9	100.5	100.6

Equipment used

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 the production process adheres to quality standards and regulatory requirements (**Table 3**). The following equipment was employed at various stages of the manufacturing process, each serving a critical function in maintaining consistency, precision, and product quality. Below is a detailed list of the equipment used and their respective functions:

Pre-formulation study

Active Pharmaceutical Ingredient

Itraconazole API is almost white powder having molecular weight 705.63 and having Molecular Formula- $C_{35}H_{38}Cl_2N_8O_4$. Melting Point: 167°C to 169°C. pKa: 3.70. Isomerism: Racemic Mixture. Polymorphisam: Crystalline form. Bulk Density of the Itraconazole API is approximately 0.208 gm/mL. Since the Itraconazole is very poor aqueous soluble drug substance so finished product solubility was increased by dissolving the API with Hypromellose 5 cps and Poloxamer 188 in organic solvents, hence there is no impact of particle size on the drug substance solubility at proposed concentration/limit.

Excipients

In addition to the active substance, the dosage form contained other excipients. The following factors were taken into account when choosing the excipients. compatibility tests between drugs and excipients, as well as those found in the reference product, Spornox® Capsules. The amount of excipients utilized complies with the USFDA's Inactive Ingredient Guideline (IIG). Excipients have a well-established safety and effectiveness record. Only excipients that complied with the USP-NF were used.

Drug-Excipients Compatibility Studies

Through HPLC examination of binary combinations of excipient and drug component, such as itraconazole, at varying ratios in the solid form, the compatibility of the excipients was evaluated. For a maximum of four weeks, the samples were kept at 40°C/75% RH. The excipient compatibility research assessed lubricant, glidant, base pellets, and solubility-enhancing carriers (**Table 4**). Itraconazole is considered compatible with the respective excipients, if the impurities are less than or equal to three folds of initial impurities of API. From the above study it is observed that the level of impurities is within the specification limit, hence all excipients showed adequate compatibility.

Formulation Development Strategy

Formulation development of Itraconazole Capsules 100 mg was concentrated on assessing the factors of the vulnerable composition and effect of their concentration on the dissolution profile of the drug product: Effect of Hypromellose Concentration; Effect of Poloxamer Concentration; Effect of Total Polyethylene Glycol Concentration; Effect of Talc Concentration; and Effect of Colloidal Silicon Dioxide Concentration. Formulation development study was carried out to determine the optimum concentration of the Hypromellose, Poloxamer and Polyethylene Glycol in the drug product. For this study the concentration of the Talc and Colloidal Silicon Dioxide is kept fixed at 3.00 mg per capsule at lubrication stage. The concentration of the Hypromellose varies in

between 140 mg to 160 mg per capsules, concentration of the Poloxamer varies in between 2.5 mg to 5.5 mg per capsules of total capsule weight, whereas in seal coating stage concentration of Polyethylene glycol 20,000 varies between 16.0 mg to 24.0 mg per capsule of the total capsule weight. The concentration of Talc and Colloidal Silicon Dioxide varies in between 2.0 mg to 4.0 mg per capsules of total capsule weight and other excipients concentration kept fixed.

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. The aforementioned solution was mixed with Poloxamer 188 (Lutrol F68) while being continuously stirred until a clear solution was achieved. Stirring continuously, Itraconazole was added to the aforesaid solution until a clear solution was achieved. added Hypromellose (Methocel E5 Premium LV) to the aforementioned solution while stirring continuously until a clear solution was achieved. Drug solution obtained above was passed through a 100 # S.S. sieve. Setting the Fluidized Bed Processor (FBP) was done using the settings shown in the table below. 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 continues 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°C 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 Talc and Colloidal Silicon Dioxide (Aerosil-200) 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.

Seal Coated Beads

RESULTS AND DISCUSSION

Based on the dissolution profile results, it is observed that Hypromellose 5 cps and Polyethylene Glycol 20,000 concentration had no discernible effect on the Itraconazole Capsules dissolution but by different concentration of Poloxamer having significant impact on dissolution. As all the capsules shows rapid dissolution and results are complying with dissolution specification as more than 70% (Q) drug dissolution in 90 minutes. Based on the dissolution profile results, Hypromellose and Poloxamer concentration impacts the dissolution of Itraconazole Capsules, which is required to enhance the dissolution. Hence, optimum concentration of Poloxamer and Hypromellose is required to meet the dissolution criteria (**Table 5** to **Table 8**). From the above physicochemical parameters, it is concluded that physical properties of Drug Loaded Pellets and filled capsules by the change in total Polyethylene Glycol 20,000 concentration. Further, the change in total Polyethylene Glycol 20,000 concentration from 16.00 mg/Capsules to 24.00 mg/Capsules does not show the substantial effect on the Itraconazole medication release. But in trial without Polyethylene Glycol 20,000 (Formulation code-DPF9A) show the significant impact on drug release of Itraconazole Capsules. The reason of drug release only 65.8% because of during dissolution study drug loaded pellets were agglomerate/stick to each other. To resolve this problem in formulation Polyethylene Glycol 20,000 was finalized 20.0 mg/capsule (**Table 9** to **Table 14**). From the above physicochemical parameters it is concluded that physical properties of lubricated pellets and filled capsules with and without not getting impacted by the Talc and Colloidal Silicon Dioxide concentration. With and without Talc, Colloidal Silicon Dioxide does not show the significant impact on the drug release. To reduce the charging of pellets in final formulation, Talc 3 mg/Capsule and Colloidal silicon dioxide 3 mg/Capsule was finalized. The Ratio between the Itraconazole and Hypromellose 5 cps, Poloxamer 188, Polyethylene Glycol 20,000, Talc and Colloidal Silicon Dioxide concentration were finalized based on the experimental trial batches data (**Table 15** to **Table 18**). Based on the manufacturing formula optimization study data formulation code DPF6 and DP10C is finalized as prototype formula as dissolution

profile data is satisfactory and no any agglomeration found during dissolution profile study.

CONCLUSION

Itraconazole Capsules 100 mg was formulated by using solid dispersion technique using Drug Coating and Sealing Coating approach. Dissolution profile of Generic Itraconazole Capsules 100 mg is compared with RLD and it is observed that profiling of generic developed drug product is faster than the RLD. Stability study of the formulation is performed for three months and it found complies as per proposed shelf life limit. Hence it can be concluded that Itraconazole Capsules 100 mg is developed by employing solid dispersion technique using Drug Coating and Sealing Coating approach in the formulation resulted in a low-cost, stable, pharmaceutically similar formulation with better quality.

Acknowledgments

The authors express sincere thanks to college management for their continuous support. The authors would like to thank parents and family for their support in all stages of life.

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