ORIGINAL ARTICLE

Design and Optimization of Itraconazole Tablet Employing Solid Dispersion Approach

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Abstract

Introduction: The present research was envisaged for the development of ternary solid dispersion for enhancement of solubility and dissolution rate of itraconazole, a highly hydrophobic antifungal agent. **Materials and Methods:** The objective was strived through spray drying technique amalgamated with experiment design approach. Initially, trials were taken with different hydrophilic carriers to prepare binary amorphous system; however, selected levels of polymers were found to be incompetent to offer desired drug solubility or dissolution rate. Hence, combinations of different hydrophilic carriers were explored for development of spray dried ternary amorphous system employing full factorial design as an experimental tool. **Results and Discussion:** The developed ternary system was found to be completely amorphous as demonstrated by spectral and thermal analyses and substantially enhanced drug solubility and dissolution rate. Finally, the developed amorphous system was formulated into a tablet dosage form with substantially enhanced drug dissolution rate as compared to that of the crystalline form and found to be stable under both accelerated and controlled storage condition with statistically predicted shelf life of more than 60 months. **Conclusion:** The research evidently exemplifies enhancement of solubility and dissolution rate of stated model drug through spray drying technique and emphasizes criticality of ternary system in the formulation of amorphous solid dispersion.

Key words: Design of experiment, full factorial design, itraconazole, solid dispersion, spray drying

INTRODUCTION

Drug solubility remains one of the prime criteria for design and development of pharmaceutical formulations since a long time. A drug needs to be in solubilized form to get absorbed into blood circulation and exhibiting systemic effect.[1] Indeed, a large number of drugs suffer from bioavailability hitch on account of poor aqueous solubility.[2] Apparently, a significant rise in bioavailability can be achieved by enhancement of solubility and dissolution rate of poorly soluble drugs, especially BCS Class II drugs.[3] Itraconazole is a triazole class of antifungal drug with very low aqueous solubility.[4,5] The aqueous solubility of itraconazole varies from 1 ng/mL (at neutral pH) to 4 µg/mL (at pH 1) across physiological pH range.[6]

Itraconazole is insoluble in water, very slightly soluble in alcohols and freely soluble in dichloromethane. Its pharmacokinetic parameters including absorption and permeability are also well studied and reported.[7] Itraconazole is one of the classic examples of BCS Class II compound, having low solubility and high permeability. This suggests that oral bioavailability of itraconazole is solely governed by solubility and dissolution rate from the formulation, while permeability is not a hindrance for achieving the required bioavailability of itraconazole.[8,9] Development of any formulation of itraconazole will pose the challenge of improving the solubility and hence the dissolution rate.

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Formulations of itraconazole have been developed for oral, parenteral and topical use.[10-12] For oral itraconazole formulation therapeutically effective plasma levels of itraconazole can be maintained for about 24 h due to its long half-life of approximately 60 h. The immediate release formulation of itraconazole can be very helpful to augment its penetration into plasma. The absorption of dissolved itraconazole from stomach is in itself not a problem. In other words, the main problem with the administration of itraconazole in therapeutically effective amount is concerned with ensuring that a sufficient amount of itraconazole remains in solution for sufficiently long period to allow it to get into circulation and that it does not convert into a form that is not readily bioavailable; in particular into crystalline itraconazole, as itraconazole precipitates in an aqueous medium.

There are reports of various attempts for improvement of solubility of itraconazole using techniques such as preparation of eutectic mixture,[13] phase inclusion complexes with β-cyclodextrin,[14] cocrystal,[15] solid dispersion using aerosol solvent extraction system,[16] self-emulsifying formulations,[17,18] nano-suspension,[19] nanoemulsions,[20] solid dispersion using high shear pelletization,[21] evaporative precipitation,[22] thin film freezing,[23] cogrinding,[24] and hot stage extrusion.[25] However, it should be contemplated that quite often increase in solubility of a drug also increases its rate of degradation. Although a significant amount of literature has been published for solubility enhancement of various drugs, very few of them can succeed to enter into market either due to stability issue, specifically related substances or non-viability of developed formulation. There is a need for better formulation of itraconazole.[26]

With the aim of formulating a tablet dosage form, the solubility enhancement of itraconazole was initiated. Various approaches can be employed for improvement of solubility of poorly water soluble drugs.[27,28] Solid dispersion is one of the most promising techniques for solubility enhancement of poorly soluble compounds. The approach involves amorphization of crystalline structures by interacting them with hydrophilic carriers. Various hydrophilic carriers such as povidones, copovidones, hypromelloses, macrogols, and sugars are employed for the preparation of solid dispersions.[29,30] In addition, assessment of drug stability in a developed solid dispersion was thoroughly evaluated with an apt contemplation of related substances that may succumb product approval at final stages of development.

The present work describes the product development of itraconazole tablet, suitable for patients suffering from a fungal infection. The development aspects have been segregated into two steps which are solubility enhancement of itraconazole by solid dispersion and incorporation of solid dispersion into tablet formulation.

MATERIALS AND METHODS

Materials

Itraconazole (Hetero Drugs Ltd., Hyderabad, India), hydroxypropyl methylcellulose (HPMC) E3 and E5 (Dow, Mumbai, India), povidone (polyvinylpyrrolidone [PVP]) K30 and povidone K25 (BASF, Mumbai, India), polyethylene glycol (PEG) 6000 and 20000 (Polyglykol, Clariant, Mumbai, India), hydroxypropyl cellulose (HPC) (Klucel LF, Ashland, Mumbai, India), lactose monohydrate (Pharmatose 200M, DFE, Mumbai, India), microcrystalline cellulose (MCC) (Avicel PH101, FMC, Mumbai, India), mannitol (Perlitol SD 200, Roquette, Ahmedabad, India), sodium starch glycolate (SSG) Type A (Primojel, DFE, Mumbai, India) and crospovidone (Polyplasdone XL, Ashland, Mumbai, India), colloidal silicon dioxide (Aerosil 200, Evonik, Mumbai, India), magnesium stearate (MgS) (Peter Greven, S. Zhaveri Pharmakem Pvt. Ltd., Mumbai, India) were used as raw materials for formulation development. All reagents and chemicals were of analytical grade and used as received.

Methods

Analytical methods for the determination of itraconazole

A validated Reversed-phase high-performance liquid chromatography (HPLC) (Shimadzu, Kyoto, Japan) method was used for determination of drug content as required throughout the study. The separation was achieved on Inertsil ODS 3-V (150 mm × 4.6 mm, 5 µm) at 1.5 mL/min flow rate with degassed mixture of buffer solution (27.2 g of tetra butyl ammonium hydrogen sulfate in 1000 mL) and acetonitrile in the ratio of 50:50% v/v as mobile phase with detection wavelength of 225 nm. Detail description of analytical method is mentioned in Supplementary 1.

Preformulation studies

Drug-excipient compatibility studies were performed on binary mixtures of itraconazole and selected excipients. The binary mixtures were exposed at 40°C/75% RH for 1 month and analyzed for related substances.

Preparation of itraconazole solid dispersion

The solid dispersion was prepared by spray drying technique employing Labultima LU 222 advanced spray dryer (Labultima, Mumbai, India). The operation was carried out using nozzle size of 0.8 mm, inlet air temperature of 60-80°C, feed rate of 6-8 g/min, atomization air pressure of 1.0-1.5 bar under negative air pressure of 100 mm Hg. Different trials with various hydrophilic excipients were taken as per below-mentioned procedure to formulate binary/ternary solid dispersions.

Drug followed by individual hydrophilic excipient (i.e., HPMC E3, HPMC E5, PVP K30, PVP K25, PEG 6000, PEG 20000, mannitol, MCC, lactose monohydrate, SSG, and crospovidone) were homogeneously dispersed or solubilized suitable solvent system as per the ratio shown in Table 1. The prepared solid dispersions were evaluated for physical property using differential scanning calorimeter (DSC) and drug release study.

Characterization of solid dispersion

The solid dispersions were analyzed for DSC, powder X-ray diffraction (PANalytical, Almelo, The Netherlands), Fourier transform infra-red (BrukerOptik, Mumbai, India), equilibrium solubility, and drug release studies. The release studies were carried out with USP apparatus II (paddle) (LabIndia, Mumbai, India) operated at 100 rpm agitation using 900 mL of pH 1.2 simulated gastric fluid (SGF) without enzyme as dissolution medium and 37 ± 0.5°C temperature. Initially, solid dispersion equivalent to 100 mg itraconazole was filled in size "00" hard gelatin capsule and evaluated for release study. The sampling volume was 5 mL which was replaced with equal amount of fresh medium each time. The equilibrium solubility was determined by adding excess amount of solid to 25 ml of aqueous medium placed in stoppered conical flasks pre-equilibrated to 37 ± 0.5°C using magnetic stirrer cum heater (Remi, Ahmedabad, India) with agitation of 300 rpm. The samples were withdrawn at predetermined time intervals which were filtered through 0.45 µ membrane filter and analyzed for drug content using HPLC.

Preparation and characterization of tablet

The solid dispersion of itraconazole was formulated into tablet dosage form using wet granulation approach. The solid dispersion was wet granulated with the help of binder, dried in fluid bed dryer, sized through multi-mill, mixed with extra-granular ingredients including super-disintegrant and lubricant and finally compressed into tablets using 12 mm round, standard concave punches employing rotary tablet press (Cadmach, Ahmedabad, India). Except hardness, all tablet compression parameters were kept similar for all batches. Experimental design was employed for optimization of tablet formulation. The prepared tablets were analyzed for drug release study using the same method as employed for evaluation of solid dispersion.

Stability studies

The stability studies were performed up to 6 months at accelerated (40 ± 2°C/75 ± 5% RH) conditions and up to 12 months at real-time (25 ± 2°C/60 ± 5% RH) conditions for optimized solid dispersion as well as prototype tablet formulation. The samples were withdrawn at predetermined time intervals and analyzed for assay, drug release, water content, and related substances.

RESULTS AND DISCUSSION

Drug-excipient compatibility study

Binary mixtures of drug and selected excipients were analyzed for related substances using HPLC. The results are shown in Table 2. Since no major difference in impurity levels were observed, compatibility of selected excipients with itraconazole was corroborated.

Evaluation of solid dispersion

The solid dispersion of itraconazole was attempted using different hydrophilic carriers. The carriers were selected with the aim to prepare a tablet formulation at the end of the development process. Hence, common excipients of tablet formulation, i.e., HPMC E3, HPMC E5, PVP K25, PVP K30, HPC EF, lactose, MCC, mannitol, PEG 6000, and PEG 20000 at different levels were explored to achieve the envisaged solid dispersion. Itraconazole as such was also subjected to spray drying to identify any physical or chemical change occurring during the process. Initial assessment for loss of crystalline form was determined using DSC. The DSC study revealed that spray drying of itraconazole alone did not convert it into the amorphous form; as spray dried and itraconazole (as such) displayed similar melting endotherm as shown in Figure 1a and b, respectively. However, spray drying of itraconazole with the carriers including HPMC E3, HPMC E5, PVP K30, PVP K25, Mannitol, PEG 6000 and PEG 20000 resulted in loss of crystalline form of itraconazole as suggested by the absence of DSC melting endotherm as shown in Figure 1c-h. Next, 100 mg itraconazole equivalent solid dispersions were filled in size "00" hard gelatin capsules and evaluated for drug release study; the results of which are shown in Table 3.

As shown in Table 3, spray dried binary systems of HPMC, PVP and PEG enhanced dissolution rate of itraconazole in comparison to pure form. At 60 min, HPMC E5 enhanced drug dissolution rate about 2-3 fold, PVP K25 and PVP K30 enhanced about 20-fold, while PEG 6000 and PEG 20000 enhanced about 10-fold.

For PVP K25, initially three levels, i.e., 1:0.5, 1:1 and 1:1.5% w/w, were tested for spray drying and subsequent drug release studies; however, similar results were obtained with all three trials and hence lower levels (i.e., <0.5% w/w) were further explored to evaluate their effects and to develop the solid dispersion with minimal amount of carrier. The binary systems with 1.0:0.4% w/w drug: PVP K25 exhibited about 20-fold increase in drug dissolution rate which was considered adequate for further development. This is a cut off level for PVP K25 above which the release rate remained largely same.

Thus, it was inferred from the trials that not all carriers are capable of converting crystalline form of itraconazole to the amorphous form and improve the dissolution rate.

Table 1: Preparation of binary solid dispersions using spray dryer

Excipient for binary solid dispersion	Drug: Excipient ratio
Drug	1:0
Drug: HPMC E5	1:0.5-1:2.5
Drug: HPMC E3	1:0.5-1:2.5
Drug: PVP K30	1:0.5-1:1.5
Drug: PVP K25	1:0.2-1:1.5
Drug: HPC LF	1:0.5-1:1.5
Drug: Lactose monohydrate	1:1-1:2
Drug: MCC Avicel PH 101	1:1-1:2
Drug: Mannitol	1:1-1:2
Drug: PEG 6000	1:0.4-1:1
Drug: PEG 20000	1:0.4-1:1
Drug: SSG	1:0.5-1:1
Drug: Crospovidone	1:0.5-1:1

PEG: Polyethylene glycol, SSG: Sodium starch glycolate, HPC: Hydroxypropyl cellulose, PVP: Polyvinylpyrrolidone, MCC: Microcrystalline cellulose, HPMC: Hydroxypropyl methylcellulose

Furthermore, loss of crystalline form did not always lead to improvement of drug dissolution rate, and dissolution improvement level is different with different carriers.

It was observed that above binary systems of drug and carriers did not provide desired rate of dissolution. Hence, attempts were made to develop the ternary solid dispersion employing combination of PVP K25 and PEG 6000 on account of their promising results with binary systems. Design of experimentation (DoE) was used as a tool for development, optimization, and evaluation of ternary solid dispersion.

Development and optimization of ternary solid dispersion using DoE

Factorial design is one of the basic designs which can be utilized for the experimental studies.[31] Three levels, two factors full factorial design was used for the optimization of ternary solid dispersion using Design Expert software. The experimental matrix along with their results is shown in Table 4.

Table 2: Results of drug-excipient compatibility study

Sample	Pack	Time	Impurity B	Any unspecified impurity (RRT)	Total impurities
Itraconazole API	-	Initial	ND	0.03 (0.16)	0.20
	Open glass vial	1 month	ND	0.04 (0.16)	0.34
	Sealed glass vial	1 month	ND	0.04 (0.16)	0.34
Itraconazole+povidone	-	Initial	ND	0.07 (0.14)	0.36
	Open glass vial	1 month	ND	0.04 (0.16)	0.34
	Sealed glass vial	1 month	ND	0.04 (0.16)	0.34
Itraconazole+lactose	-	Initial	ND	0.04 (0.16)	0.39
	Open glass vial	1 month	ND	0.05 (0.16)	0.34
	Sealed glass vial	1 month	ND	0.05 (0.16)	0.34
Itraconazole+PEG	-	Initial	ND	0.07 (0.14)	0.33
	Open glass vial	1 month	ND	0.06 (0.16)	0.38
	Sealed glass vial	1 month	ND	0.05 (0.16)	0.35
Itraconazole+MCC	-	Initial	ND	0.05 (0.16)	0.39
	Open glass vial	1 month	ND	0.04 (0.16)	0.34
	Sealed glass vial	1 month	ND	0.05 (0.16)	0.35
Itraconazole+crospovidone	-	Initial	ND	0.07 (0.14)	0.33
	Open glass vial	1 month	ND	0.05 (0.16)	0.33
	Sealed glass vial	1 month	ND	0.05 (0.16)	0.34
Itraconazole+aerosil	-	Initial	ND	0.05 (0.16)	0.39
	Open glass vial	1 month	ND	0.04 (0.16)	0.34
	Sealed glass vial	1 month	ND	0.05 (0.16)	0.35
Itraconazole+MgS	-	Initial	ND	0.07 (0.14)	0.33
	Open glass vial	1 month	ND	0.05 (0.16)	0.33
	Sealed glass vial	1 month	ND	0.05 (0.16)	0.34

ND: Not detected, MgS: Magnesium stearate, PVP: Polyvinylpyrrolidone, MCC: Microcrystalline cellulose

Table 3: Evaluation of spray dried binary system

Spray drying			Out come						
Excipient	Ratio against drug	Batch No.	Loss of crystal form	% Drug release					Dissolution improvement
				15 min	30 min	45 min	60 min	90 min	
-	0	F001	No	1.0±0.3	2.0±0.4	2.8±0.4	3.2±0.4	3.9±0.5	*
HPMC E5	0.5	F002	Partial	1.0±0.2	2.4±0.3	3.9±0.4	5.4±0.5	8.2±0.5	*
	1.5	F003	Yes	0.8±0.3	1.7±0.3	2.7±0.4	3.7±0.3	5.5±0.4	*
	2.5	F004	Yes	1.9±0.4	3.7±0.5	5.5±0.6	7.4±0.6	10.6±0.8	*
HPMC E3	0.5	F011	Yes	-	-	-	-	10.2±0.7	*
	1.5	F012	Yes	-	-	-	-	12.1±0.6	*
	2.5	F013	Yes	-	-	-	-	9.5±0.7	*
PVP K30	0.5	F005	Yes	18.5±2.0	44.3±2.3	58.2±2.4	62.7±3.1	64.6±3.2	++
	1	F006	Yes	15.3±2.1	40.8±2.8	55.6±3.0	63.1±3.1	65.8±3.0	++
	1.5	F007	Yes	11.8±1.9	38.9±2.3	56.1±2.6	61.7±2.6	64.9±2.9	++
PVP K25	0.5	F008	Yes	19.4±2.3	42.3±3.3	55.4±3.1	61.8±3.1	69.2±3.4	++
	1	F009	Yes	14.3±1.8	43.5±3.0	54.0±2.8	67.2±3.1	67.8±3.2	++
	1.5	F010	Yes	15.7±2.1	44.3±2.2	56.1±2.7	62.4±2.9	65.4±3.0	++
	0.2	F014	No	2.5±0.3	4.6±0.3	5.8±0.4	8.9±0.7	12.4±0.8	*
	0.3	F015	Yes	2.8±0.3	4.7±0.4	8.9±0.5	9.5±0.8	15.3±0.9	*
	0.4	F016	Yes	18.9±0.5	42.5±2.0	55.5±2.6	65.4±2.9	65.8±3.1	++
HPC LF	0.5	F017	No	-	-	-	-	-	Not done
	1	F018	No	-	-	-	-	-	Not done
	1.5	F019	No	-	-	-	-	-	Not done
Lactose	1	F020	No	-	-	-	-	-	Not done
	2	F021	No	-	-	-	-	-	Not done
MCC 101	1	F022	No	-	-	-	-	-	Not done
	2	F023	No	-	-	-	-	-	Not done
Mannitol	1	F024	Yes	-	-	-	-	5.8±0.7	*
	2	F025	Yes	-	-	-	-	6.7±0.6	*
SSG	0.5	F032	No	-	-	-	-	-	Not done
	1	F033	No	-	-	-	-	-	Not done
Crospovidone	0.5	F034	No	-	-	-	-	8.9±0.9	*
	1	F035	No	-	-	-	-	12.2±1.1	*
PEG 6000	0.4	F026	Yes	10.1±1.1	15.8±1.2	31.2±1.8	38.9±2.1	43.2±2.8	+
	0.7	F027	Yes	5.6±1.7	12.3±1.9	25.7±2.1	36.8±2.4	44.1±2.8	+
	1	F028	Yes	5.1±0.6	13.1±0.9	22.4±1.6	32.6±2.1	43.5±2.3	+
PEG 20000	0.4	F029	Yes	5.1±0.8	11.0±1.4	30.4±1.8	35.6±2.7	41.3±2.9	+
	0.7	F030	Yes	2.4±0.6	9.8±0.9	22.9±1.5	32.5±2.4	38.9±3.1	+
	1	F031	Yes	2.8±0.7	5.7±1.1	15.8±1.2	25.5±1.8	40.2±2.2	+

*: Almost no improvement in dissolution, +: Slight improvement – 30-50%, ++: Good improvement – 50-70%. PEG: Polyethylene glycol, SSG: Sodium starch glycolate, HPC: Hydroxypropyl cellulose, PVP: Polyvinylpyrrolidone, MCC: Microcrystalline cellulose, HPMC: Hydroxypropyl methylcellulose

Statistical analysis of Table 4 (using Design Expert) revealed that the model suggested quadratic fit and found to be significant (with $P = 0.0009$ and <0.0001 for 30 and 60 min dissolution, respectively). All ternary systems were evaluated for conversion of crystalline form to amorphous form using DSC. Conversion to amorphous form was observed in all ternary systems except one where both carriers are at lowest level (1:0.2:0.2). Figure 1f-h represents DSC thermogram showing the absence of peaks for ternary as well as binary system with PVP and PEG. All samples exhibited conversion of crystalline to amorphous form.

Figure 2 shows contour plot for effect of PVP K25 and PEG 6000 levels on drug release at 30 min and 60 min time points. It also shows that alone PVP K25 or PEG 6000 was not able to improve the drug release up to required level, whereas combinations of both imparted synergistic effect for drug release enhancement. Figure 3 represents response surface plots for effects of PVP K25 and PEG 6000 on drug release at 30 min and 60 min time points.

Optimization of level of PVP K25 and PEG 6000

Design Expert provides inbuilt options for optimization of independent variables based on observed responses.

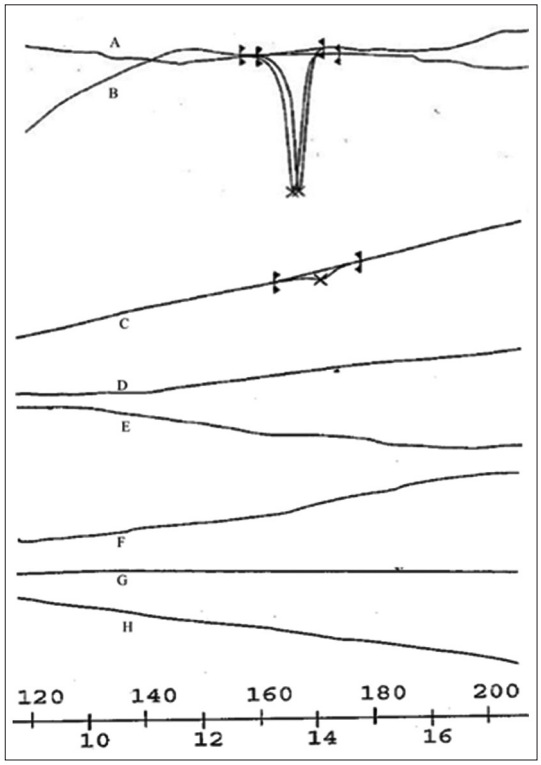

Figure 1: Differential scanning calorimeter thermogram (a) Itraconazole, (b) spray dried itraconazole, (c) solid dispersion itraconazole + hydroxypropyl methylcellulose (HPMC) (1:0.5), (d) solid dispersion itraconazole + HPMC (1:1.5), (e) solid dispersion itraconazole + HPMC (1:2.5), (f) solid dispersion itraconazole + polyvinylpyrrolidone (PVP), (g) solid dispersion itraconazole + PVP + polyethylene glycol (PEG), (h) solid dispersion Itraconazole + PEG

Contour plots can be used to identify optimum settings of independent variables to provide results in desired ranges. Individual contour plots can also be used to identify best settings for each response. Contour plots can be overlaid with the constraints for each response variable to define a subarea of settings that will meet the desired criteria. Constraints were defined for the current set of experiments. The goal was to limit the concentration of PVP K25 and PEG 6000 within the experimental range as well as to identify a range of these carriers where best and desirable results could be achieved. The desired results were defined as not <60% drug release at the end of 30 min and not <90% at the end of 60 min. Loss of crystalline form was also ranked numerically for the purpose of input of data. "0" was defined as absence of crystalline form and "1" was defined as presence of crystalline form.

Figure 4 displays overlay plot for all three response variables. The design space has been shown in yellow colored area where all responses were found to be within acceptable ranges. Within the defined design space, controlled working space (green colored rectangle) was further constrained (PVP K25: 0.55-0.60; PEG 6000: 0.45-0.50) to establish the working levels of selected carriers. Working space was established to minimize the operating risk at the edge of failure. The working space was further validated using confirmatory experiments.

Confirmatory batches of spray drying in working space

Two confirmatory batches of ternary solid dispersion were taken; one with 0.45% w/w PEG 6000 and 0.55% w/w PVP K25 (batch F049) and another with 0.45% w/w PEG 6000 and 0.60% w/w PVP K25 (batch F050). The drug release of both batches was performed in USP Apparatus II (Paddle) with 900 mL SGF without enzyme at 100 rpm agitation intensity. Both batches exhibited >60% drug release at 30 min time points and >90% at 60 min time points. Hence, optimized ternary solid dispersions were further employed for the formulation of tablet dosage form.

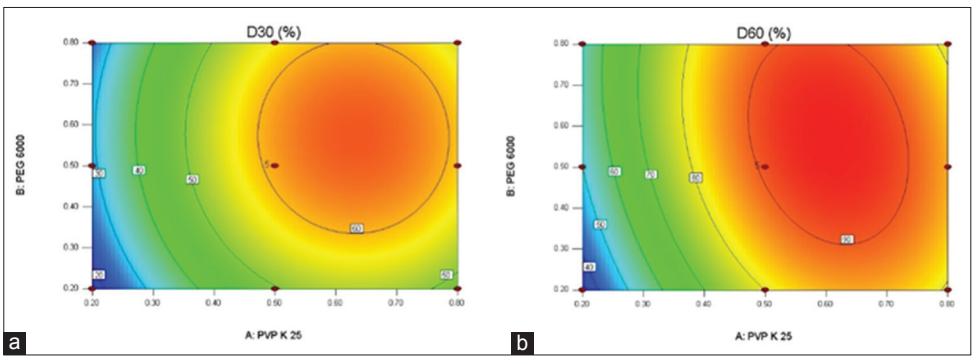

Figure 2: Contour plot for dissolution (a) at 30 and (b) at 60 min

Table 4: Experimental matrix and results of 3^2 full factorial design for optimization of ternary solid dispersion

Experiment No.	Itraconazole: PVP K25:PEG 6000 (%w/w/w)	*In-vitro* % drug dissolution at		Loss of crystal form
		30 min (D30)	60 min (D60)	
F036	1:0.2:0.2	19.2±2.0	35.6±2.3	No
F037	1:0.2:0.5	26.5±2.1	50.2±2.3	Yes
F038	1:0.2:0.8	24.8±2.0	52.1±2.2	Yes
F039	1:0.5:0.2	42.5±3.5	75.3±3.6	Yes
F040	1:0.5:0.5	60.1±5.3	90.2±6.1	Yes
F041	1:0.5:0.8	55.7±4.6	90.4±5.9	Yes
F042	1:0.8:0.2	52.1±3.1	82.5±4.2	Yes
F043	1:0.8:0.5	52.4±3.9	81.0±4.7	Yes
F044	1:0.8:0.8	56.2±4.3	78.4±4.6	Yes
F045	1:0.5:0.5	57.2±4.1	92.4±4.9	Yes
F046	1:0.5:0.5	67.5±4.2	90.2±5.1	Yes
F047	1:0.5:0.5	60.2±3.9	89.5±4.8	Yes
F048	1:0.5:0.5	68.9±4.6	95.2±5.4	Yes

PEG: Polyethylene glycol, PVP: Polyvinylpyrrolidone

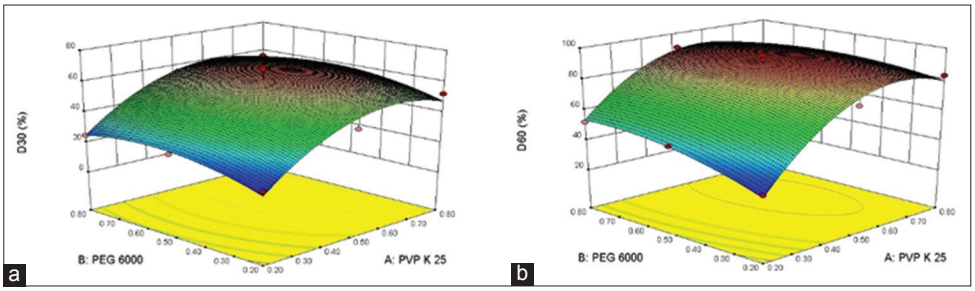

Figure 3: Three-dimensional view of effect of polyvinylpyrrolidone K25 and polyethylene glycol 6000 on dissolution (a) at 30 and (b) at 60 min

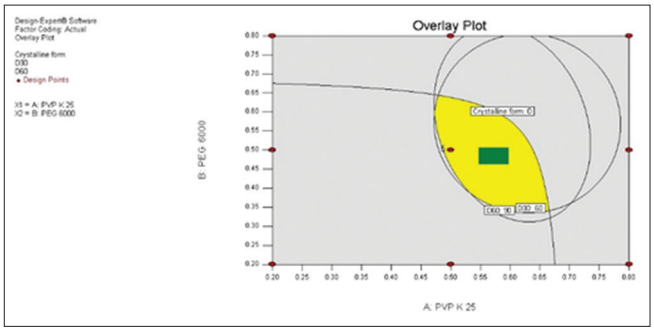

Figure 4: Overlay plot with design space for solid dispersion

Formulation of tablet

Development of tablet dosage form was carried out using quality by design approach as per International Conference on Harmonization Q8 guideline. Foremost, quality target product profile was identified and accordingly critical quality attributes (CQAs) were established. Disintegration time, drug release, assay, dosage uniformity as well as physical characteristics of tablet were identified as CQAs.

The critical formulation attributes include levels of ternary solid dispersion, disintegrant, binder, glidant, and lubricant. Risk assessment of all formulation variables against identified CQA was performed and high-risk variables were also identified. Preliminary experiment was taken up to identify a prototype formulation. Feasibility experiment was performed to have an insight of effect of levels of excipients to be selected for optimization, to evaluate physical parameters and to gain the experience of process parameters for the experiments.

Optimization of tablet formulation with DoE

Based on formulation risk assessment and identified CQAs, formulation design was established. Six independent variables as shown in Table 5 were selected for optimization of all CQAs except degradation products. Minimum run characterization design with resolution V, i.e., fractional factorial design with three center points was adopted for optimization. The study is powered above 99% based on signal to noise ratio for each parameter. The experimental matrix along with measured responses for the selected design is illustrated in Table 6. The studied responses were

disintegration time, drug release at 60 min, assay, content uniformity and tablet physical characteristic.

Based on the optimization experiments, it was inferred that disintegration time was mainly affected by concentration of crospovidone and hardness of tablet. Physical attributes were affected by the levels of MgS and Aerosil 200 in the formulation. Drug release at 60 min was mainly controlled by levels of crospovidone and MCC 101 along with tablet hardness to a lesser extent. None of the selected variables had any effect on assay value. All batches exhibited good content uniformity on account of MgS and Aerosil levels. Table 7 summaries the observed effect of independent factors on studied responses.

Table 5: Selected independent variables along with their studied levels

Factor	Name	Units	−1	+1	0
A	Crospovidone	%	5.00	15.00	10.00
B	Povidone	%	0.00	5.00	2.50
C	MCC PH 101	%	15.00	35.00	25.00
D	Colloidal SiO_2	%	0.00	1.00	0.50
E	MgS	%	0.00	1.00	0.50
F	Hardness	kp	8.00	20.00	14.00

MgS: Magnesium stearate, MCC: Microcrystalline cellulose

Further optimization was executed using graphical optimization tool of Design Expert. Overlay contour plots were studied to identify the design space for range of excipients and thereby formulation was optimized using graphical optimization tool. Figure 5 represents the derived overlay plot along with optimized design space with further constrained limit for disintegration time, viz., not <10 min instead of not <15 min.

Here, Aerosil 200 and MgS were fixed at a level of 0.5% w/w each as no significant advantage was observed at higher levels and levels lower than 0.4% w/w did not

Table 6: Tablet formulation experiments along with parameters and results

Experiment No.	A	B	C	D	E	F	G	H	I	J	K
F052	5	0.0	35	0.0	1.0	20	15	0	76.5±3.4	101.5	7.44
F053	15	5.0	35	0.0	1.0	8	9	1	82.5±3.8	97.1	4.08
F054	10	2.5	25	0.5	0.5	14	8	0	84.6±3.2	99.4	4.56
F055	5	5.0	15	1.0	1.0	8	11	0	79.2±3.1	100.2	1.2
F056	5	5.0	15	0.0	1.0	20	21	1	67.5±2.9	98.9	6.00
F057	5	5.0	15	1.0	0.0	20	19	2	65.2±3.1	99.2	4.56
F058	15	5.0	35	0.0	0.0	8	10	2	79.4±3.5	98.6	6.72
F059	10	2.5	25	0.5	0.5	14	9	0	88.1±4.1	97.9	3.36
F060	5	0.0	15	0.0	0.0	20	21	2	74.2±3.9	98.2	5.76
F061	5	0.0	35	1.0	1.0	8	12	0	79.5±4.5	97.5	2.88
F062	15	0.0	15	1.0	1.0	8	8	0	80.9±4.3	99.1	1.68
F063	10	2.5	25	0.5	0.5	14	8	0	82.6±4.7	101.2	4.32
F064	15	5.0	15	1.0	1.0	20	14	0	75.2±3.4	97.4	1.44
F065	5	5.0	35	0.0	0.0	8	10	2	82.6±4.8	101.4	7.68
F066	15	0.0	15	1.0	0.0	20	12	2	80.2±4.1	100.4	2.16
F067	15	0.0	15	0.0	1.0	20	10	1	82.5±3.9	100.5	5.76
F068	15	5.0	15	0.0	0.0	8	10	2	81.0±3.2	99.9	7.44
F069	15	0.0	35	1.0	1.0	20	10	0	79.5±3.8	103.4	2.40
F070	5	0.0	15	0.0	1.0	8	18	1	74.3±4.1	99.5	5.04
F071	15	5.0	35	1.0	0.0	8	8	1	84.1±3.9	99.8	2.64
F072	15	5.0	35	0.0	0.0	20	12	2	78.9±3.6	99.1	7.68
F073	5	0.0	35	1.0	0.0	20	16	1	72.4±3.2	103.0	4.56
F074	5	5.0	35	1.0	1.0	20	12	0	81.0±3.4	98.1	2.16
F075	15	0.0	35	0.0	0.0	8	7	2	86.5±3.7	102.8	6.96
F076	5	0.0	15	1.0	0.0	8	17	1	70.2±3.9	100.2	3.36

A - Crospovidone (% w/w), B - Povidone (% w/w), C - Microcrystalline cellulose (% w/w), D - Aerosil 200 (% w/w), E - Magnesium stearate (% w/w), F - Hardness (kp), G - Disintegration time (min), H - Physical characteristics*, I - Dissolution at 60 min (%), J - Assay (%), K - Uniformity of dosage unit (acceptance value). *Physical characteristics includes description and any physical defects of tablet like sticking, capping, etc., 0 is not acceptable, 1 is acceptable with precaution, 2 is excellent.

exhibit the responses in design space. Further, povidone demonstrated no effect on response variable, and hence it was eliminated from the formulation. MCC 101 at 20% w/w level was found to be optimum whereas higher levels offered no advantage. Two variables - i.e., tablet hardness and concentration of crospovidone - were found to be critical; the optimized levels of which are 8-14 kp and 12-15% w/w, respectively.

To validate the model, confirmatory experiments were performed at selected levels of crospovidone and tablet hardness. Tables 8 and 9, respectively, summarize composition of confirmatory batches and physical parameters of tablets. Out of the batches taken F078B was selected as the final composition and dissolution studies in different dissolution media have been performed.

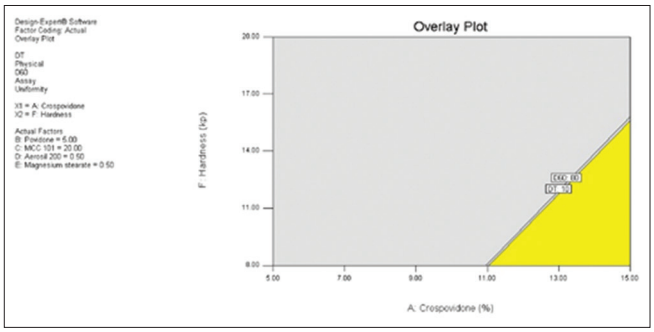

Figure 5: Overlay plot with design space for tablet formulation

Stability studies of developed itraconazole solid dispersion and optimized tablet formulation

Ternary solid dispersion of itraconazole as well as optimized tablet formulations were evaluated for stability as per ICH guidelines to identify any physical or chemical changes occurred during the testing period. The batches were charged in two different packs at accelerated (40 ± 2°C/75 ± 5% RH) as well as long term (25 ± 2°C/60 ± 5% RH) stability conditions. No significant difference in related substances, assay, water content or drug release profile was observed during the studied stability conditions for developed ternary system as well as optimized tablet formulation. Each CQA was well controlled and found to be within the acceptable range. Further, statistical analysis was also performed to identify any significant change in the chemical characteristics of the product and to estimate the shelf life. Based on the same, more than 60 months (5 years) of shelf life can be assigned to the developed tablet formulation. The results of stability study are mentioned in Supplementary 2.

CONCLUSION

Research emphasizes enhancement of solubility and dissolution rate of poorly soluble drug by development of amorphous solid dispersion using spray drying technique. Initially, trials were taken for development of binary solid

Table 7: Summary of effect of dependent variables against independent variables

Parameter	Crospovidone	Povidone	MCC 101	Aerosil	MgS	Hardness
DT	++	-	-	-	-	++
Physical	-	-	-	++	++	-
D60	++	-	++	-	-	+
Assay	-	-	-	-	-	-
Uniformity	-	-	-	+	+	-

-: No effect, +: Minor effect, ++: Major effect, MCC: Microcrystalline cellulose, MgS: Magnesium stearate

Table 8: Composition of confirmatory batches of itraconazole tablets

Ingredient	F077A and F077B		F078A and F078B	
	mg/tab	%w/w	mg/tab	%w/w
Itraconazole solid dispersion	200.00	33.33	200.00	33.33
Lactose	202.00	33.67	184.00	30.67
Avicel PH 101	120.00	20.00	120.00	20.00
Crospovidone	30.00	5.00	30.00	5.00
Water	qs	-	qs	-
Crospovidone	42.00	7.00	60.00	10.00
Aerosil 200	3.00	0.50	3.00	0.50
MgS	3.00	0.50	3.00	0.50
Total	600.00	100.00	600.00	100.00

MgS: Magnesium stearate

Table 9: Physical parameter and evaluation of itraconazole tablets

Parameter	F077A	F077B	F078A	F078B
Weight variation	590-610 mg	590-620 mg	592-610 mg	594-611 mg
Hardness	8.9-11.2 kp	12.5-14.1 kp	9.1-10.5 kp	12.4-13.8 kp
Disintegration time	7-8 min	10-11 min	7-8 min	8-9 min

dispersion with the help of various hydrophilic carriers; however, resulted binary systems were not capable enough of exhibiting desired dissolution rate. Hence, further attempt was made to develop the ternary solid dispersion with the help of PVP K25 and PEG 6000 based on the promising results obtained with study of binary systems. The ternary solid dispersion was optimized using full factorial design as a DoE tool. The optimized ternary solid dispersion substantially enhanced solubility and dissolution rate of itraconazole as compared to its crystalline form. The optimized ternary solid dispersion was further formulated into a tablet dosage form. The tablet formulation was optimized with the help of minimum run fractional factorial design as a DoE tool. The optimized tablet formulation exhibited significant enhancement of dissolution rate of itraconazole and found to be stable at accelerated (up to 6 months) and controlled (up to 12 months) storage conditions. In a nutshell, the developed tablet formulation is an IR formulation which has potential to enter into the market on account of its promising drug release and stability data; however human clinical trials are obligatory to prove its clinical efficacy. It is strongly expected that the present approach of dissolution enhancement can also be employed for other poorly soluble drugs to formulate their immediate release dosage forms.

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SUPPLEMENTARY 1

Dissolution

Dissolution parameters

Medium : 900 mL; SGF Without enzyme
Apparatus : USP-II (Paddle) without sinker
RPM : 100
Temperature : 37°C ± 0.5°C

Preparation of dissolution medium (SGF Without enzyme): Dissolve 2 g sodium chloride in 7.0 mL of Hydrochloric acid and sufficient water to make 1000 mL.

Standard preparation: Transfer an accurately weighed quantity of about 56 mg of Itraconazole working standard to a 50 mL volumetric flask. Add about 30 mL of diluent and sonicate to dissolve. Make volume up to the mark with diluent and mix. Dilute 5.0 mL of this solution to 50.0 mL with dissolution medium and mix.

Sample preparation: Set the dissolution parameters of the instrument as mentioned above. Place one capsule/tablet each into the vessel and operate the instruments exactly for specified time. At the end of specified time, withdraw about 10 mL of solution from a zone midway between the surface of the dissolution medium and top of the paddle, not less than 1 cm from the bowl wall. Filter the solution through 0.45 µm Millipore PVDF filter, collect the filtrate by discarding first few mL of filtrate.

The samples withdrawn above are to be analyzed on HPLC.

Buffer solution, mobile phase, diluent and chromatographic system follows as mentioned under assay.

System suitability: Chromatograph the standard preparation and record the peak responses as directed under procedure. The column efficiency is not less than 2000 theoretical plates and the tailing factor is not more than 2.0 for Itraconazole peak. The relative standard deviation for five replicate standard injections is not more than 2.0 %.

Procedure: Separately inject mobile phase, diluent, dissolution medium, standard preparation and sample preparation into the chromatograph. Record the chromatograms and measure the responses for analyte peak. Follow the injection sequence as mentioned below.

Sample	No. of injections
Mobile phase	1
Diluent	1
Dissolution medium	1
Standard preparation (system suitability)	5
Standard preparation	1
Sample preparation	1
Bracketing standard (standard preparation)	1

Calculate quantity as percentage of Itraconazole dissolved by using following formula.

$$\% \text{ of itraconazole} = \frac{AT}{AS} \times \frac{WS}{50} \times \frac{5}{50} \times \frac{900}{100} \times \frac{P}{100} \times 100$$

Where,
AT = Peak area of sample injection
AS = Peak area of standard injection
WS = Weight of working standard taken in mg
P = Percentage purity of working standard (on as is basis)

Uniformity of dosage units (By content uniformity)

Buffer solution, mobile phase, diluent, standard preparation, system suitability and chromatographic system follows as mentioned under assay.

Sample preparation: Transfer the content of one capsule/or whole tablet into 100 mL volumetric flask, add about 70 mL of diluent and sonicate with intermittent shaking for about 25 minutes, then add 10 mL of water and sonicate with intermittent shaking for about 10 minutes. Cool and make volume up to the mark with diluent and mix. Filter the solution through 0.45 µ Millipore PVDF filter, collect the filtrate by discarding first few mL of the filtrate. Dilute 5.0 mL of this solution to 50.0 mL with mobile phase and mix. Carry out the same procedure for further nine capsules/tablet.

Procedure: Separately inject mobile phase, diluent, standard preparation and sample preparation into the chromatograph, record the chromatograms and measure the responses for the analyte peak. Follow the injection sequence as mentioned below.

Sample	No. of injections
Mobile phase	1
Diluent	1
Standard preparation (system suitability)	5
Standard preparation	1
Sample preparation	1
Bracketing (standard preparation)	1

Calculate the quantity as percentage of Itraconazole per tablet by using following formula.

$$\% \text{ of itraconazole} = \frac{AT}{AS} \times \frac{WS}{50} \times \frac{5}{50} \times \frac{100}{100} \times \frac{50}{5} \times \frac{P}{100} \times 100$$

Where,
AT = Peak area of sample injection
AS = Peak area of standard injection
WS = Weight of working standard taken in mg
P = Percentage purity of working standard (on as is basis)

Assay

Buffer solution: Dissolve about 27.2 g of Tetra butyl ammonium hydrogen sulphate in 1000 mL of Milli Q water and mix. Filter through 0.45 µm filter.

Mobile phase: Prepare a degassed mixture of buffer solution and acetonitrile in the ratio of (50: 50).

Diluent: Prepare a mixture of Methanol and Tetrahydrofuran in the ratio of (1:1)

Standard preparation: Transfer an accurately weighed quantity of about 50 mg of Itraconazole working standard to a 50 mL volumetric flask. Add about 30 mL of diluent and sonicate to dissolve. Add 5 mL of water and mix well. Cool to room temperature and make volume up to the mark with diluent and mix. Dilute 5.0 mL of this solution to 50.0 mL with mobile phase and mix.

Prepare two independent sample preparations.

Sample preparation: Remove as completely as possible the content of not fewer than 20 capsules/tablet and crush, accurately counted and weighed and mix the content. Calculate the net content. Transfer an accurately weighed quantity of equivalent to about 100 mg of Itraconazole to a 100 mL volumetric flask, add about 70 mL of diluent and sonicate with intermittent shaking for about 25 minutes, then add 10 mL of water and sonicate with intermittent shaking for about 10 minutes. Cool and make volume up to the mark with diluent and mix. Filter the solution through 0.45 µ Millipore PVDF filter, collect the filtrate by discarding first few mL of the filtrate. Dilute 5.0 mL of this solution to 50.0 mL with mobile phase and mix.

Chromatographic system

Column	: Inertsil ODS 3-V (150 mm × 4.6 mm) 5 µm
Detector	: 225 nm
Flow rate	: 1.5 mL/min.
Injection volume	: 10 µL
Column temperature	: 30°C

System suitability: Chromatograph the standard preparation and record the peak responses as directed under procedure. The column efficiency for the analyte peak is not less than 2000 theoretical plates and tailing factor is not more than 2.0 for analyte peak. The relative standard deviation for five replicate standard injections is not more than 2.0 %.

Procedure: Separately inject mobile phase, diluent, standard preparation and sample preparation into the chromatograph. Record the chromatograms and measure the responses for analyte peak. Follow the injection sequence as mentioned below.

Sample	No. of injections
Mobile phase	1
Diluent	1
Standard preparation (system suitability)	5
Standard preparation	1
Sample preparation-1	1
Sample preparation-2	1
Bracketing standard (standard preparation)	1

Calculate the quantity in mg of Itraconazole per average net weight for both sample preparations using the following formula:

$$\text{Itraconazole (mg / dosage unit)} = \frac{ATi}{AS} \times \frac{WS}{50} \times \frac{5}{50} \times \frac{100}{WTi} \times \frac{50}{5} \times \frac{P}{100} \times \text{Avg.net cont}$$

Where,
ATi = Peak area of sample injection (i = 1 and 2)
AS = Peak area of standard injection
WS = Weight of working standard taken in mg
WTi = Weight of sample taken in mg (i = 1 and 2)
P = Percentage purity of working standard (on as is basis)

Related substances

Buffer solution: Dissolve about 27.2 g of Tetra butyl ammonium hydrogen sulphate in 1000 mL of Milli Q water and mix. Filter through 0.45 µm filter.

Mobile phase A: Use buffer solution as mobile phase A.

Mobile phase B: Prepare a degassed mixture of buffer solution and acetonitrile in the ratio of (10: 90).

Diluent: Prepare a mixture of Methanol and Tetrahydrofuran in the ratio of (1:1)

System suitability solution: Transfer an accurately weighed quantity of about 5 mg of Itraconazole working standard and 5 mg of Miconazole standard to a 100 mL volumetric flask. Add about 50 mL of diluent and sonicate to dissolve. Make volume up to the mark with diluent and mix.

Standard preparation: Transfer an accurately weighed quantity of about 40 mg of Itraconazole working standard to a 100 mL volumetric flask. Add about 50 mL of diluent and sonicate to dissolve. Make volume up to the mark with diluent and mix. Dilute 5.0 mL of this solution to 50.0 mL with diluent and mix. Further dilute 5.0 mL of this solution to 50.0 mL with diluent and mix.

Sensitivity solution: Dilute 1.0 mL of standard preparation to 10.0 mL with diluent and mix.

Placebo preparation: Transfer an accurately weighed quantity of placebo powder equivalent to about 200 mg of Itraconazole to a 100 mL volumetric flask. Add about 60 mL of diluent and sonicate for 30 minutes with intermittent shaking. Add about 10 mL of water and sonicate for 10 minutes with intermittent shaking. Cool to room temperature. Make volume up to the mark with diluent and mix. Filter the solution through 0.45 µm PVDF filter; collect the filtrate by discarding first few mL of the filtrate.

Sample preparation: Remove as completely as possible the content of not fewer than 20 capsules/tablet and crush, accurately counted and weighed and mix the content. Calculate the average net content. Transfer an accurately weighed quantity of crushed powder equivalent to about 200 mg of Itraconazole to a 100 mL volumetric flask. Add about 60 mL of diluent and sonicate for 30 minutes with intermittent shaking. Add about 10 mL of water and sonicate for 10 minutes with intermittent shaking. Cool to room temperature. Make volume up to the mark with diluent and mix. Filter the solution through 0.45 µm PVDF filter; collect the filtrate by discarding first few mL of the filtrate.

Chromatographic system

Column	: Waters, symmetry C18 (250 mm × 4.6 mm) 5µm
Detector	: 225 nm
Flow rate	: 1.0 mL/min.
Injection volume	: 20 µL
Column temperature	: 30°C

Gradient program

Time (minutes)	% Mobile phase A	% Mobile phase B
0	71	29
30	40	60
60	30	70
62	71	29
75	71	29

System suitability: Chromatograph the sensitivity solution and record the peak responses as directed under procedure. The signal to noise ratio for analyte peak is not less than 10.

Chromatograph the System suitability solution and record the peak responses as directed under procedure. The resolution between Miconazole and Itraconazole peak is not less than 2.0.

Chromatograph the standard preparation and record the peak responses as directed under procedure. The relative standard deviation for six replicate standard injections is not more than 10.0 %.

Procedure: Separately inject mobile phase, diluent, standard preparation and sample preparation into the chromatograph. Record the chromatograms and measure the responses for major peaks. Disregard any peaks due to diluent and placebo. Follow the injection sequence as mentioned below.

Sample	No. of injections
Mobile phase	1
Diluent	1
Sensitivity solution	1
System suitability solution	1
Standard preparation (system suitability)	6
Standard preparation	1
Placebo preparation	1
Sample preparation	1
Bracketing standard (standard preparation)	1
Bracketing (system suitability solution)	1

Calculate the percentage any individual unknown degradation product and total degradation products using the following formula:

$$\% \text{ of any individual unknown degradation product} = \frac{AT}{AS} \times \frac{WS}{50} \times \frac{5}{50} \times \frac{5}{50} \times \frac{100}{WT} \times \frac{P}{100} \times \frac{\text{Avg.net con}}{100} \times 100$$

Where,

AT = Peak area of any individual unknown degradation product in sample injection

AS = Peak area of Itraconazole in standard injection

WS = Weight of Itraconazole working standard taken in mg

WT = Weight of sample taken in mg

P = Percentage purity of working standard (on as is basis)

% of Total degradation products = Sum of % of all individual unknown degradation product

Water content

Add about 35 mL to 40 mL of methanol into the titration vessel and titrate to a electrometric end point with standardized

Karl-Fischer reagent. Crush content of at least 5 dosage unit and transfer an accurately weighed quantity of mixed contents (about 200 mg) into the titration vessel and titrate to a electrometric end point with standardized Karl-Fischer reagent. Calculate the water content using the following formula:

$$\%\ \text{of water} = \frac{Vs \times F \times 100}{W}$$

Where,
Vs = Volume of Karl Fischer reagent required for sample
F = Factor of Karl Fischer reagent used in mg/mL
W = weight of sample taken in mg

SUPPLEMENTARY S2

Supplementary Tables

Table S2-1: Accelerated stability study data of itraconazole ternary solid dispersion

Condition			40° C/75% RH					
Pack			Double polybag in alu pouch			Double polybag in HDPE		
Test	Specification	Initial	1 M	3 M	6 M	1 M	3 M	6 M
Impurity B	NMT 0.2	ND	ND	0.01	0.05	ND	BQL	0.03
Any unspecified impurity	NMT 0.2	0.05	0.04	0.04	0.08	0.05	0.04	0.06
Total impurities	NMT 1.2	0.39	0.34	0.24	0.42	0.35	0.22	0.36
Assay	90-110%	98.2	97.9	98.5	96.9	98.5	97.6	98.9
Water by KF	NMT 5%	2.3	2.6	2.1	2.2	2.8	2.9	3.2

Table S2-2: Long term stability study data of itraconazole ternary solid dispersion

Condition			25° C/60% RH					
Pack			Double polybag in alu pouch			Double polybag in HDPE		
Test	Specification	Initial	3 M	6 M	12 M	3 M	6 M	12 M
Impurity B	NMT 0.2	ND	ND	ND	0.03	ND	ND	ND
Any unspecified impurity	NMT 0.2	0.05	0.04	0.06	0.04	0.05	0.05	0.08
Total impurities	NMT 1.2	0.39	0.34	0.42	0.44	0.35	0.45	0.49
Assay	90-110%	98.2	98.4	97.9	98.6	99.1	98.1	98.5
Water by KF	NMT 5%	2.3	2.1	2.3	2.3	2.4	2.3	2.2

Table S2-3: Accelerated stability study data of optimized tablet formulation (F078B)

Condition			40°C/75% RH					
Pack			HDPE bottle			PVDC blister		
Test	Specification	Initial	1 M	3 M	6 M	1 M	3 M	6 M
Impurity B	NMT 0.2	ND	ND	ND	0.02	ND	ND	ND
Any unspecified impurity	NMT 0.2	0.04	0.04	0.07	0.08	0.06	0.09	0.12
Total impurities	NMT 1.2	0.23	0.23	0.35	0.41	0.32	0.45	0.68
Assay	90-110%	100.2	101.2	100.6	99.8	100.3	99.5	100.7
Water by KF	NMT 5%	2.9	3.1	3.1	3.7	3.6	3.9	4.2

Table S2-4: Long term stability study data of optimized tablet formulation (F078B)

Condition			25°C/60% RH					
Pack			HDPE Bottle			PVDC Blister		
Test	**Specification**	**Initial**	**3 M**	**6 M**	**12 M**	**3 M**	**6 M**	**12 M**
Impurity B	NMT 0.2	ND	ND	ND	ND	ND	ND	ND
Any unspecified impurity	NMT 0.2	0.04	0.05	0.05	0.06	0.06	0.08	0.09
Total impurities	NMT 1.2	0.23	0.28	0.32	0.35	0.32	0.38	0.41
Assay	90-110%	100.2	100.8	100.6	99.8	101.2	100.5	100.8
Water by KF	NMT 5%	2.9	3.0	2.9	3.1	2.9	3.1	3.3

Supplementary Figures

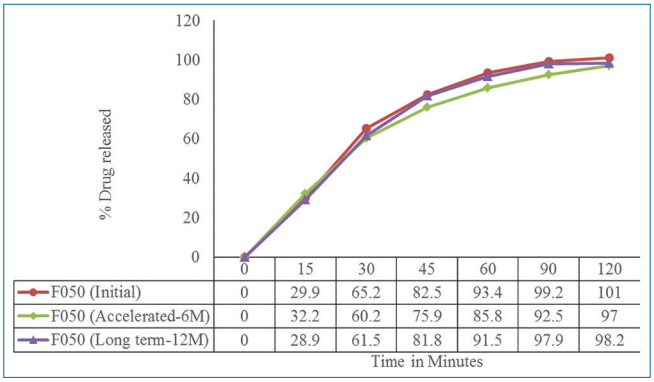

Figure S2-1: Effect of stability study on drug release profiles of itraconazole ternary solid dispersion

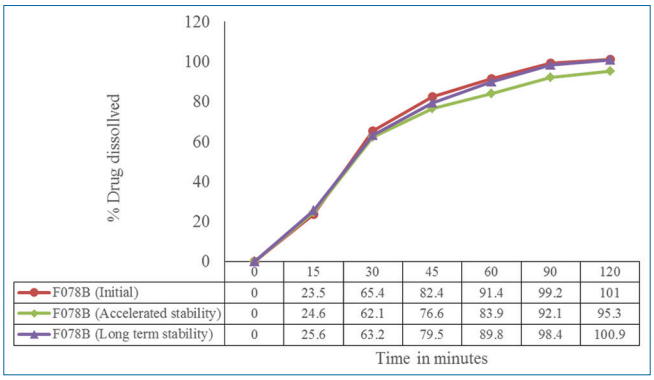

Figure S2-2: Effect of stability study on drug release profiles of optimized tablet formulation

Statistical analysis of stability data

Statistical analysis of real time stability data was carried out, to identify any trend, relationship and shelf life of the proposed formulation. Regression analysis approach was selected for statistical analysis. All stability indicting parameters including related substances, assay and water content were subjected to statistical analysis. Fitted line, Shelf life and residual plots were generated and studied.

Shelf life criteria selected as time period in which you can be 95% confident that at least 99.999% of response are within the specified limit. With 95 % confidence interval, the minimum shelf life of 67 months was predicted.