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DEVELOPMENT OF POSACONAZOLE DELAYED RELEASE FORMULATION FOR MUCORMYCOSIS BY HOT MELT EXTRUSION USING QBD APPROACH

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ABSTRACT

Amorphous solid dispersion (ASD) by hot-melt extrusion (HME) is an industrially feasible approach to overcome the solubility and bioavailability limitations of poorly soluble active pharmaceutical actives. The creation of HME-based ASDs was significantly impacted by the implementation of Quality by Design (QbD). The objective of the study was to develop an ASD of posaconazole for the effective management of mucormycosis. The impact of change in levels of extra granular materials were identified as critical quality attributes (CQA's) for the development of delayed release tablet. A 2^3 full factorial design was employed to study the impact of independent variables HPMCAS ($X1$), HPC($X2$) and CCS ($X3$) as CQA's on the dependent variables such as hardness ($Y1$) and Disintegration Time (Y2) and % Drug release ($Y3$). The design was analyzed by using ANOVA by using MINITAB software. The influence of the extra granular components on the dissolution of tablet was closely evaluated while finalizing the optimized batch. The extrudes were also evaluated by FTIR, XRD and DSC analysis which confirmed the purity and in-situ conversion from crystalline to amorphous form of the drug. Systematic development of a bioavailable and stable ASD of posaconazole was achieved by studying the CQA's at different levels by using the QbD and from the stability data, the optimized batch F4 was found to be stable up to 3 months at accelerated conditions40°C/75%Rh.

Keywords: Mucormycosis, Posaconazole, Quality by design, Full factorial design, Hot melt extrusion.

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19), pandemic is caused by severe acute respiratory syndrome virus 2 (SARS-CoV-2) has affected more than 160 million people worldwide accounting over 3.4 million deaths [1]. Besides, mucormycosis, an uncommon, serious angio-invasive fungal infection frequently referred to as "black fungus," is becoming a major concern caused by a group of fungi called mucormycetes in the recent pandemic situation. Spores of these ubiquitous fungi can be inhaled and then infect the lungs, sinuses and extend into the brain and eyes. More than 9K cases of mucormycosis have been reported so far [2]. The incidence of mucormycosis is challenging especially in immune-compromised, diabetic ketoacidosis, solid organ transplantation, neutropenia, long-term systemic corticosteroid uses and hemochromatosis patients. Further, the promising risk is noticed for people living with HIV and those using immunomodulating, steroids and the anti-fungal actives such as voriconazole in some high-risk groups [3]. The increased germinations of mucorales due to low oxygen saturation and high blood sugar level are found to be the main reason for mucormycosis [3-7].

Posaconazole, Isavuconazole and Amphotericin B are the most effective antifungal therapy which can be administered by IV and oral route. The delay in commencing therapy for mucormycosis is linked to an increased risk of death [7-11].

The chemical name of posaconazole is 4-[4-[4-[4-[[(3R,5R)-5- (2,4difluorophenyl) tetrahydro-5(1H-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-

piperazinyl]phenyl]-2-[(1S,2S)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one with an empirical formula of $C_{37}H_{42}F_2N_8O_4$ and a molecular weight of 700.8. Posaconazole is a white powder with low aqueous solubility. The melting point, boiling point, and pKa are 169°C, 170-172°C, and 5.49 respectively. Despite its strong protein binding of 98 percent, this lipophilic medication has a large volume of distribution. After 7-10 days, steady-state concentrations are reached, with a mean terminal elimination half-life of 35 hours [12].

It is commercially available as an oral suspension, delayed-release tablet, and an intravenous formulation. In the presence of concomitant illness conditions, medications, and dietary considerations that frequently change drug concentrations in the oral solution, the newly approved posaconazole delayed-release tablet and intravenous formulations show more consistent bioavailability [13, 14]. The posaconazole delayed-release oral tablet is not significantly affected by gastric acid suppression therapy. The new posaconazole delayed-release tablet and injectable formulations will improve dependability for usage as antifungal prophylaxis and treatment of oropharyngeal candidiasis in immune-compromised patients [12].

The new delayed-release tablet formulation of posaconazole was approved by FDA in November 2013. This new tablet formulation provides a consistent and dependable oral delivery of posaconazole than oral suspension. Though, the delayed-release tablets may lose their structural integrity when crushed or chewed which may limit their utility in patients who have difficulty in swallowing tablet. The FDA approved an intravenous formulation of posaconazole in March 2014 a few months after the oral tablet approval.

Posaconazole is an antifungal drug that shows broad activity against yeasts, molds, and dimorphic fungi [15, 16] an extended-spectrum triazole antifungal agent that has been approved for use in the United States since 2006. It is a BCS Class II compound thus exhibiting High permeability and low solubility. It works by inhibiting ergosterol synthesis, causing the structure and function of the fungal cell membrane to deteriorate. It works by preventing the conversion of lanosterol to ergosterol by inhibiting the cytochrome P450 (CYP)-dependent enzyme lanosterol 14a-demethylase (CYP51). Posaconazole also has a fungicidal activity that is dependent on the organism. It exhibits fungistatic activity against most Candida species and fungicidal activity against Aspergillus species and Mucormycetes [17]. Posaconazole appears to have the most useful in vitro activity among the triazole antifungal agents against Mucormycetes [18, 19]. Posaconazole currently holds U.S. Food and Drug Administration (FDA) indications for prophylaxis of invasive Aspergillus and Candida infections in immune-compromised populations and for treatment of oropharyngeal candidiasis [15, 16]. As compared with other triazole antifungals, Posaconazole most notably exhibits enhanced activity against Candida species (including fluconazole-resistant strains) [17], Aspergillus species, and the class of Mucormycetes [20, 21]. Posaconazole can be used in the treatment of invasive aspergillosis, as it shows fewer drug-drug interactions and lower hepatotoxicity as compared to other antifungal agents. Also, the new delayed-release tablet of posaconazole will enhance dependability for use as antifungal prophylaxis for immunocompromised patients and the treatment of oropharyngeal candidiasis. [12, 14].

In drug discovery pipelines two-third of the compounds show poor water solubility. According to the USP definition, they can be called practically insoluble. These compounds whose highest dose does not dissolve in 250mL or less of the buffer over pH range 1-7.5 at 37°C [22]. Most of these compounds fall into BCS II & IV class. Thus, these compounds show variable and erratic bioavailability depending on the dissolution rate in gastrointestinal fluids. Thus, different formulation strategies like prodrug formation [23], Micronization [24], Salt formation [25], self-emulsifying drug delivery systems [26], solubilization in concentrated aqueous solutions of a weak acid and base [27] and amorphous solid dispersion (ASD) [28, 29] are explored to improve the solubility.

Solid dispersions are a promising approach for overcoming the problem with poor aqueous solubility [30]. They can be obtained by techniques like Hot melt extrusion [31], Spray drying [32] and co-precipitation [33]. However, HME offers various advantages like no requirement of any solvent or water, thus avoiding the residual amount of solvent and stability risks associated during the shelf life of the solid dispersion dosage form [34]. HME involves the melting of material in a heated barrel with rotating screws. The polymer or drug substance melt is passed through a die opening to obtain extrudates which are then further processed into granules, tablets, or beads [35-37]. The process is continuous, simple, and efficient. Intense mixing and agitation by screws during the hot melt extrusion process disaggregates the particles, reduces the particle size of the

drug or allows the drug substance to dissolve in molten polymer to form a solid dispersion [38].

The objective of the current study was to identify suitable types and levels of extra granular excipients that are required to develop a posaconazole delayed release tablet prepared by HME process using a quality by design approach [39, 40]. Hydroxypropyl methylcellulose acetate succinate (HPMCAS), in recent years, has gained wide acceptance in ASD on account of its ability to keep a drug in the supersaturated state in aqueous media [41, 42].

Several products containing HPMCAS are manufactured by spray drying, HME, and co-precipitation. It is used as a solid dispersion polymer for bioavailability enhancement of poorly soluble active pharmaceutical ingredients. It appears as a white to off-white solid and offers Tg near 120°C, which helps to guide the lower end of HME processing temperature and it has a thermal decomposition range of 258-278°C, which helps in determining the higher end of the extrusion temperature range [43, 44]. It offers pH-dependent release by remaining insoluble in gastric pH and dissolving rapidly in the upper small intestine [43, 45].

The goal of the design of the experiment study was to understand the effect of different concentration levels of hydroxypropyl cellulose (binder), Cross carmellose sodium (disintegrant), and Hypromellose acetate succinate (release controlling polymer) on the dissolution profile of the drug product.

Quantities of hydroxypropyl cellulose (binder), Cross carmellose sodium (disintegrant), and Hypromellose acetate succinate (release controlling polymer) are three independent variables that may have an impact on dissolution profile. Two levels of each variable (low and high) have been identified to develop a full factorial design. A 2^3 factorial design was constructed with one center point to study the effect of dissolution release by controlling excipient level. Dissolution at different time points is the dependent variable which was monitored at the buffer stage 50mM pH 6.8 phosphate buffer containing polysorbate 80 at time points 130, 135, 140, 150, and 165 minutes. Analytical test method was used for the evaluation of the dissolution profile of these batches.

1.1. Design of Experiments for HME Tablet Formulations

To systematically evaluate the extra granular component requirements for manufacture of Posaconazole delayed-release tablets, a design of experiment (DOE) approach was employed. The design was analyzed by using MINITAB software with total 9 runs including one center point batch. The DOE consisted of three factors-release controlling polymer Hypromellose acetate succinate (HPMCAS), Binder Hydroxy propyl cellulose (HPC) and Disintegrant croscarmellose sodium (CCS). The design of experiment (DoE) comprising two levels, three factors (2^3) full factorial.

2. MATERIAL AND METHODS

2.1. Material

Posaconazole was purchased from Fisher Scientific International, Inc. HPMCAS was obtained from Shin-Etsu Chemical (Tokyo, Japan). Cellulose micro-crystalline, hydroxypropyl cellulose was purchased from Signet Chemical Corporation. Sodium starch glycolate (SSG) was purchased from Arihant Trading Company. The colloidal silica and magnesium stearate were purchased from SBF Pharma Pvt. Ltd. Opadry Yellow was purchased from Colorcon Asia Pvt. Ltd. All remaining solvents and reagents were of analytical grade.

2.2. Experimental design

The design of experiment (DoE) comprising two levels, three factors (2^3) full factorial design with one center point was applied to optimize the combined effect of HPMCAS ($X1$), HPC($X2$), and CCS ($X3$) as critical quality attributes (CQA's) on the dependent variables such as % drug release ($Y1$) at 30 minutes in buffer stage, hardness ($Y2$) and DT using the software MINITAB [46-48].

The selected factors, their levels and analyzed responses are summarized in Table 1, and the matrix of the full factorial design was represented as shown in Table 2, comprising all the excipients and their concentration range.

Table 1: DoE: variables in 2^3 full factorial design

Independent variables	Factors	Levels		
		-I	0	+I
X1	HPC	35	50	65
X2	CCS	35	50	65
X3	HPMCAS	150	200	250
Dependent variables		**Response**		
Y1		Hardness		
Y2		Disintegration Time		
Y3		% Drug release at 30 minutes in buffer stage		

Table 2: Posaconazole DR tablet 100mg Formulation

Ingredients	Role	Quantity (mg/tab)
Posaconazole	Active ingredient	100
Hypromellose acetate succinate	Release controlling polymer	150/200/250
Cellulose microcrystalline	Diluent	≤199
Hydroxy propyl cellulose	Binder	35/50/65
Cross carmellose sodium	Disintegrant	35/50/65
Colloidal silica	Glidant	15
Magnesium stearate	Lubricant	6
Opadry yellow	Coating material	18

2.3. Formulation of Delayed-release tablets

The final blend for each DOE run was prepared using the following procedure.

Initially Hypromellose acetate succinate and posaconazole were co-sifted through 20# and blending was performed for 15 mins. The process of hot-melt extrusion was carried out in a hot melt extruder equipped with a twin-screw configuration at speed rpm 75 and 150°C. Further, the extrudes were milled through #60 mesh using a mechanical sifter. The milled extrudates, binder, diluent, disintegrant & binder were weighed according to the DOE run formula and mixed in a double cone blender for 15 min at 25 rpm. The colloidal silicon dioxide and magnesium stearate were mixed by hand with a small amount of the blend from step 2. Further, the blend from initial step was added to the remaining blend and mixed in a double cone blender for 5 min at 25 rpm. Compression was carried out further with a blend from step no. 4 at an average weight of 588 mg using capsule-shaped biconvex punches and coated.

2.4. Characterization of delayed-release Tablets

2.4.1. FT-IR Spectroscopy

The Fourier-transform infrared spectra (FTIR) of pure posaconazole and posaconazole milled extrude solid dispersion were recorded over a range of 4000-400 cm^{-1} to study the principal peaks with Fourier transform infrared spectrophotometer model 4100 (Spectrum GX-FT-IR, Perkin Elmer, USA) using the potassium bromide (KBr) disc method [49].

2.4.2. Physicochemical characterization

2.4.2.1. Hardness

The hardness testing was performed on tablets using the Erweka hardness tester where a single tablet was placed between the moving metal plate and the diametrical force required to break the tablet was measured. The hardness measured is expressed in Newton [50].

2.4.2.2. In-vitro disintegration test

The disintegration times of six tablets from each batch were measured individually in purified water at 37° C±0.5°C using apparatus using the USP disintegration apparatus (Electrolab, India), and mean values were calculated.

2.4.2.3. In-vitro dissolution studies

The *in-vitro* dissolution test of tablets is carried out in USP apparatus II (paddle apparatus). The rotation speed of the paddle is adjusted to 75 rpm. A two-step non-sink dissolution method was developed to assess the performance of HME tablets. In the first step, the samples were suspended in 750 ml of 0.1N hydrochloric acid. The apparatus temperature was maintained at 37 ± 0.5°C. The sample was withdrawn at 120 minutes time point at the acid stage and in the second step the buffer stage 50mM pH 6.8 phosphate buffer containing polysorbate 80 was added to make a final 1000 ml volume at time points 130, 135, 140, 150, and 165 minutes. The amount of drug released was then monitored by the HPLC method. The Dissolution was also performed on innovator product Noxafil, and the results were compared with the formulation. Model Independent Approach Using Similarity Factor: Dissolution profiles were compared by using the following equation that defines a similarity factor (f_2) [51]:

$$f2 = 50\log\{[1+1/n\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} X\,100\}$$

Where, log = logarithm to base 10, n = number of sampling time points, R = dissolution at time point t of the reference, T_t = dissolution at time point t of the test.

2.4.2.4. X-Ray Powder Diffraction (XRPD)

XRPD analysis was performed at ambient temperature using a Bruker AXS X-Ray Powder Diffractometer

Model D8 Advance (Karlsruhe, Germany), at 40 mA and 40 kV with Cu Kα radiation (1.54 Å) in parallel beam mode utilizing a Xe filled detector. Samples were scanned over a range of 2θ values from 0° to 40° with a step size of 0.05° (2θ) and a counting time of 4 or 0.6 s. A 1-mm divergence slit was used with the incident beam along with 0.12-mm soller slits in the diffracted beam path [52].

2.4.2.5. Differential Scanning Calorimetry (DSC)

Thermal analysis was performed by using a PYRIS-1 Differential Scanning Calorimeter (DSC) (Perkin Elmer, USA) equipped with a liquid nitrogen attachment to study the drug and SD crystalline variability. Cooling was provided with a Perkin/Elmer refrigerated cooling device (FC-60-PED). Data were treated mathematically using the resident PYRIS Software. An empty aluminum pan was used as a reference. The samples were analyzed in 30 ml perforated and covered aluminum Perkin/Elmer pans under a nitrogen purge. Approximately 1.2 mg crystalline posaconazole was heated from 0 to 300° C with a heating rate of 10°C/min and afterward cooled with a cooling rate of 10°C/min to room temperature. A second heating cycle is then applied on the sample starting at room temperature up to 300°C with a heating rate of 10°C/min where 1 mg of the posaconazole milled extrudes were heated from room temperature up to 300°C with a heating rate of 10°C/min.

2.4.2.6. Accelerated stability studies

In the present study, stability studies were carried out on optimized formulation batch for six months period as prescribed by ICH guidelines. The accelerated stability study was carried out at 40 ± 2°C and RH 75% ± 5%. The tablets are withdrawn after 1, 2, and 3 months and analyzed for physical characterization, Assay, DT, and dissolution study.

2.5. Statistical analysis

The one-way ANOVA is used to statistically analyze with the least significant difference (LSD) by using MINITAB software. The statistical probability (*p*) value of < 0.05 is considered a significant difference.

3. RESULTS AND DISCUSSION

3.1. FTIR analysis

The interaction between drug and polymer in ASD were investigated by FTIR. FTIR spectra of pure posaconazole and the melt extrudes of posaconazole were investigated. The IR of pure posaconazole characteristic has sharp alkane stretching at 3654.69 cm^{-1}, CH2 at 2968.87 cm^{-1}, CH vibration at 2837.74 cm^{-1}. The saturated ketone stretch was observed at 1688 cm^{-1}. The stretching vibration of amide is seen at 1606.06 cm^{-1}. The functional group -C-F showed vibration at 1018 cm^{-1}cm. The IR spectra of posaconazole melt extrudes showed characteristic peaks at 3205 cm^{-1}, alkane stretching vibration CH_2 at 2979 cm^{-1}, CH at 2824.24 cm^{-1}. The C=O stretch was seen at 1736.58 cm^{-1}. Thus, it can be concluded that the presence of the drug is seen in the milled extrude of ASD which indicated no change in the functional properties of the drug. A slight shift in specific intensities was observed in comparison with pure Posaconazole which may be due to the presence of polymer during the HME process. Figure1.shows (a) FTIR spectra of pure Posaconazole API (b) FTIR spectra of Posaconazole extrude.

3.2. Effect on hardness (Y2)

The hardness of all the formulations was tested and it was found that F2 was having the lowest hardness (127 N) and F5 having the highest hardness (221 N).) The contour plots (Fig2 -a-c) displayed the effect of variables on hardness. The effect of change in concentration of HPC level was studied on table ability. Hardness increases as the concentration of hydroxypropyl cellulose increase above 50 mg (5.95%). As hydroxypropyl cellulose is acting as a binder, increasing its concentration leads to an increase in hardness. The contour plot in fig. 2 (a-c) displayed the effect on Hardness.

The regression equation is:

Hardness = 83.61 + 1.583 HPC

The Model F-value for hardness was found to be 92.62 and the p-value less than 0.05 which implies the model terms are significant. The ''Pred R2'' of 88.58 is in reasonable agreement with the ''Adj R2'' of 91.97.

3.3. Effect on disintegration time (Y3)

Disintegration time for all the formulations was tested and it was found that F8 was having the lowest DT and F4 having the highest DT. This can be explained by varying concentrations of HPMCAS, HPC, and CCS. F8 was having a high concentration of CCS disintegrant hence less Disintegration time. F4 is having a low concentration of CCS and thus higher disintegration time. From ANOVA, the p-value for all independent

factors is less than 0.05. The contour plots fig. 3 (a-c) displayed the effect on disintegration time.

The regression equation is DT = 769.39 - 0.7867 HPMCAS - 5.3000 HPC - 4.2500 CCS + 0.025333 HPMCAS*HPC - 0.013000 HPMCAS*CCS + 0.016667 HPC*CCS

The Model F-value for Disintegration time was found to be 32375.77 and the p-value less than 0.05 which implies the model terms are significant. The ''Pred R2'' of 99.96 is in reasonable agreement with the ''Adj R2'' of 100.00.

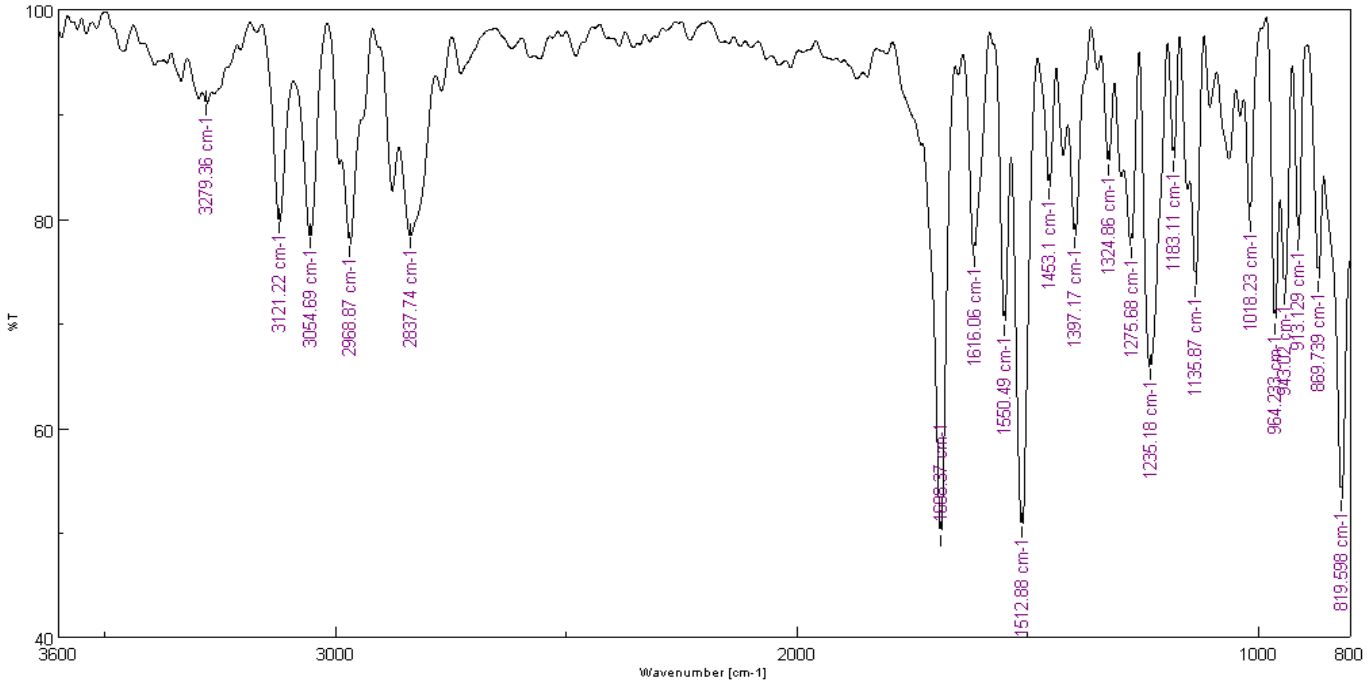

Fig. 1(a): FTIR spectra of pure Posaconazole API

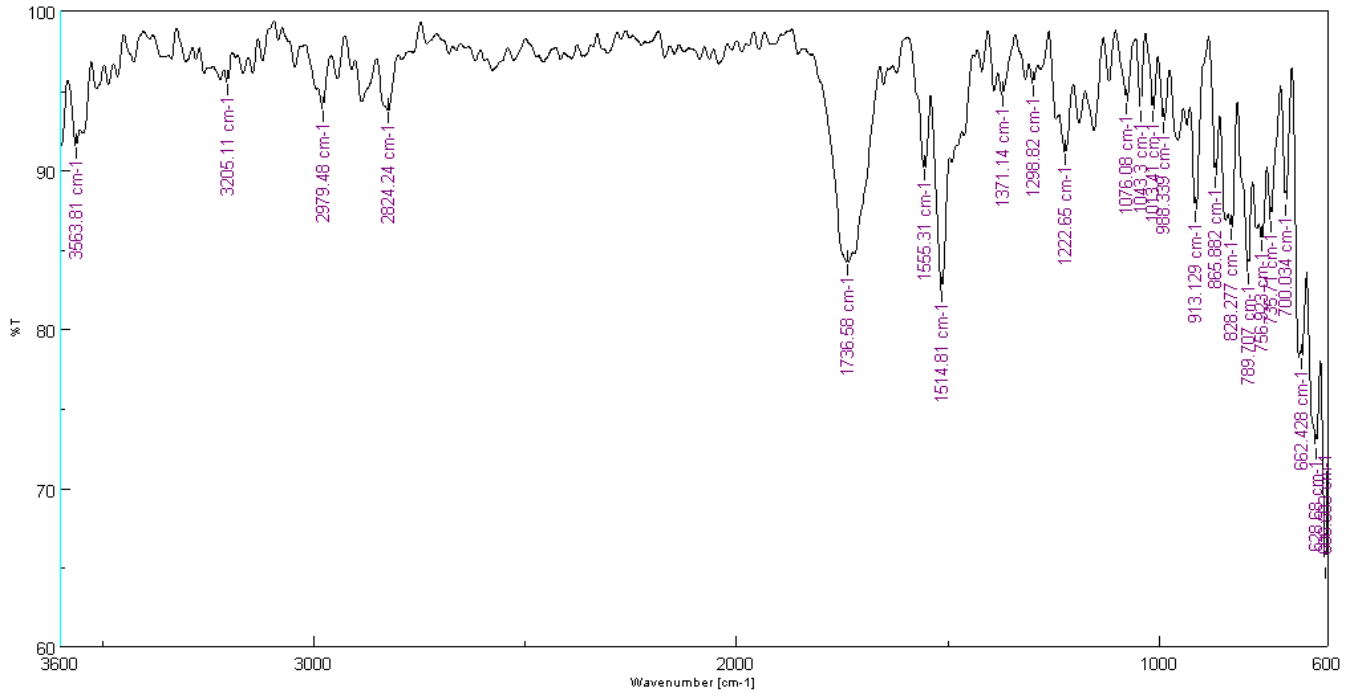

Fig. 1(b): FTIR spectra of Posaconazole extrudes

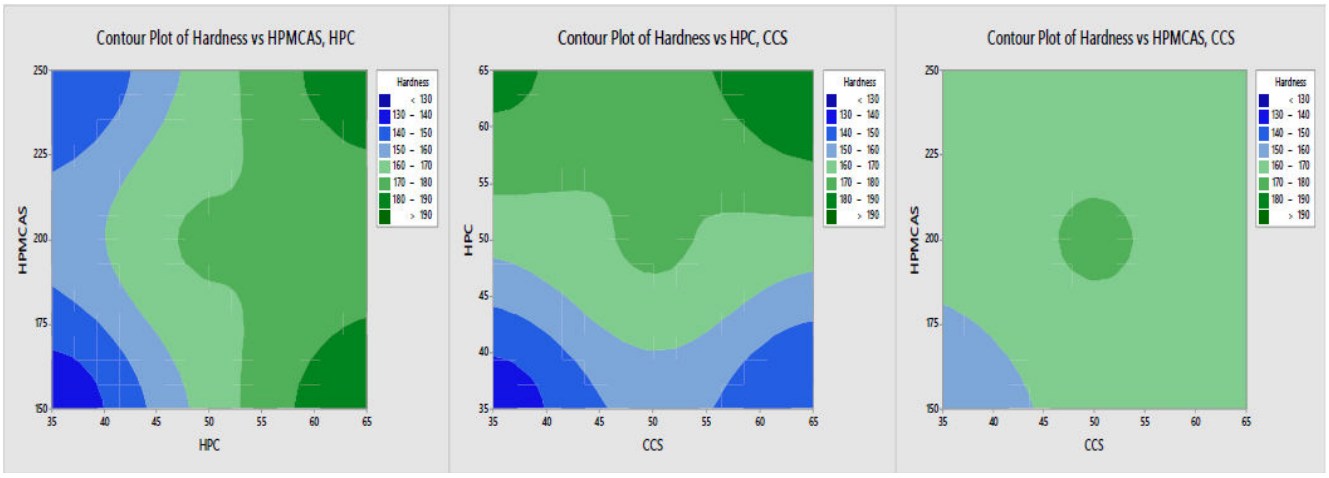

Fig. 2: (a-c): Contour Plot of Hardness

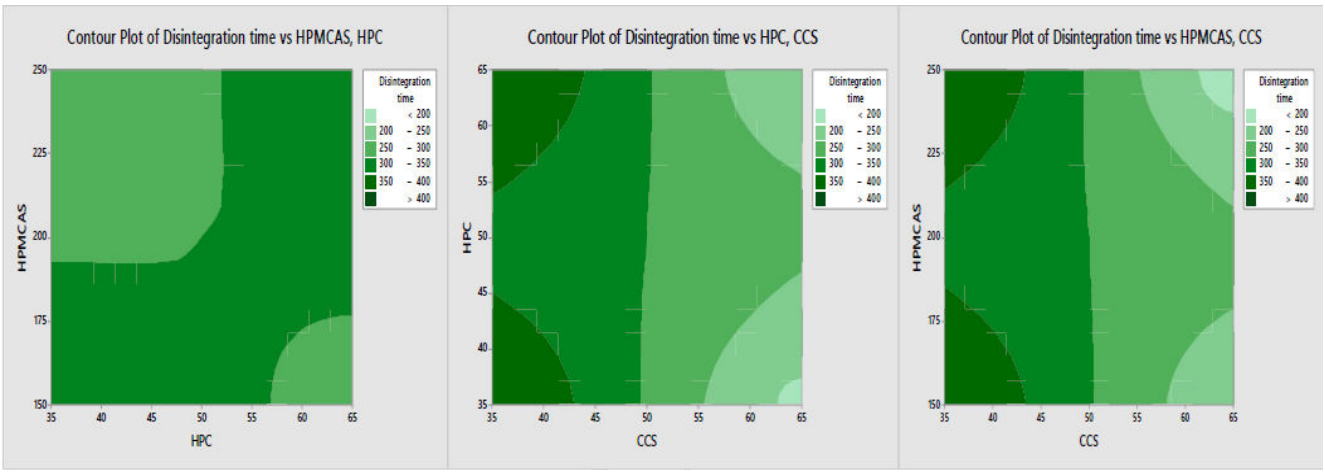

Fig. 3: (a-c): Contour Plot of Disintegration time

3.4. *In-Vitro* dissolution studies

Effect on % Release at 30 minutes in buffer stage (Y3)

Effect on % release at 30 minutes in buffer stage was tested and it was found that F1 was having the highest drug release and F5 was having the lowest release of 75%. This can be explained by varying concentrations of independent variables like HPMCAS, CCS, and HPC. F5 was having a low concentration of the release controlling polymer HPMCAS and a high concentration of binder hydroxypropyl cellulose and disintegrant cross carmellose sodium thus resulting in lower drug release, higher hardness, and disintegration time. F1 was having low concentration of HPMCAS and HPC binder and a high concentration of CCS, thus resulting in faster disintegration of the tablet and hence enhanced dissolution rate. ANOVA results indicate that factor HPMCAS is having a p-value less than 0.05 which indicates that it has a significant effect on % release in 30 minutes at the buffer stage.

The contour plots fig. 4 (a-c) displayed Contour Plot of % Drug release

The Model F-value for % Drug release was found to be 14.33 and the p-value was found to be less than 0.05 than which implies that Hypromellose acetate succinate has a significant effect on % drug release. The ''Pred R2'' of 84.85 is in reasonable agreement with the ''Adj R2'' of 69.70.

The regression equation is % DR = 30.7 + 0.2475 HPMCAS

3.5. Powder X-Ray Diffraction (P-XRD) analysis

The X-ray diffraction patterns of the posaconazole drug and physical mixture of posaconazole -HPMCAS polymer sample, and posaconazole -HPMCAS (extrudes) were recorded as shown in fig. 5. The XRD profile of posaconazole drug (a) depicted characteristic crystalline peaks at 2θ positions of 7.75°, 10.01°, 11.80°, 13.06°, 14.43°, 15.79°, 19.67°, 22.40°,

24.45°, 25.60°, 27.51° and 29.10°. XRD spectra of the physical mixture of PCZ-HPMCAS also depicted characteristic peaks at 7.75°, 10.01°, 11.80°, 14.43°, 19.67°, 22.40°, 24.45°, 25.60°. In the case of posaconazole-HPMCAS milled extrudes the powder X-ray diffractogram show a clear absence of crystalline peak which indicates the in-situ conversion of crystalline material to a fully amorphous material.

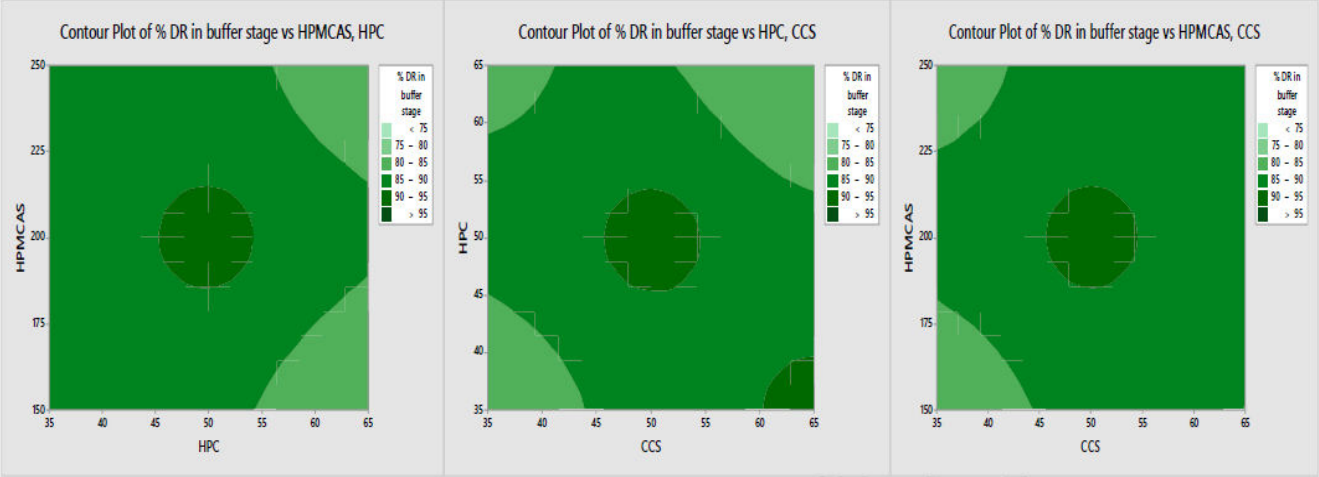

Fig. 4: (a-c): Contour Plot of % Drug release

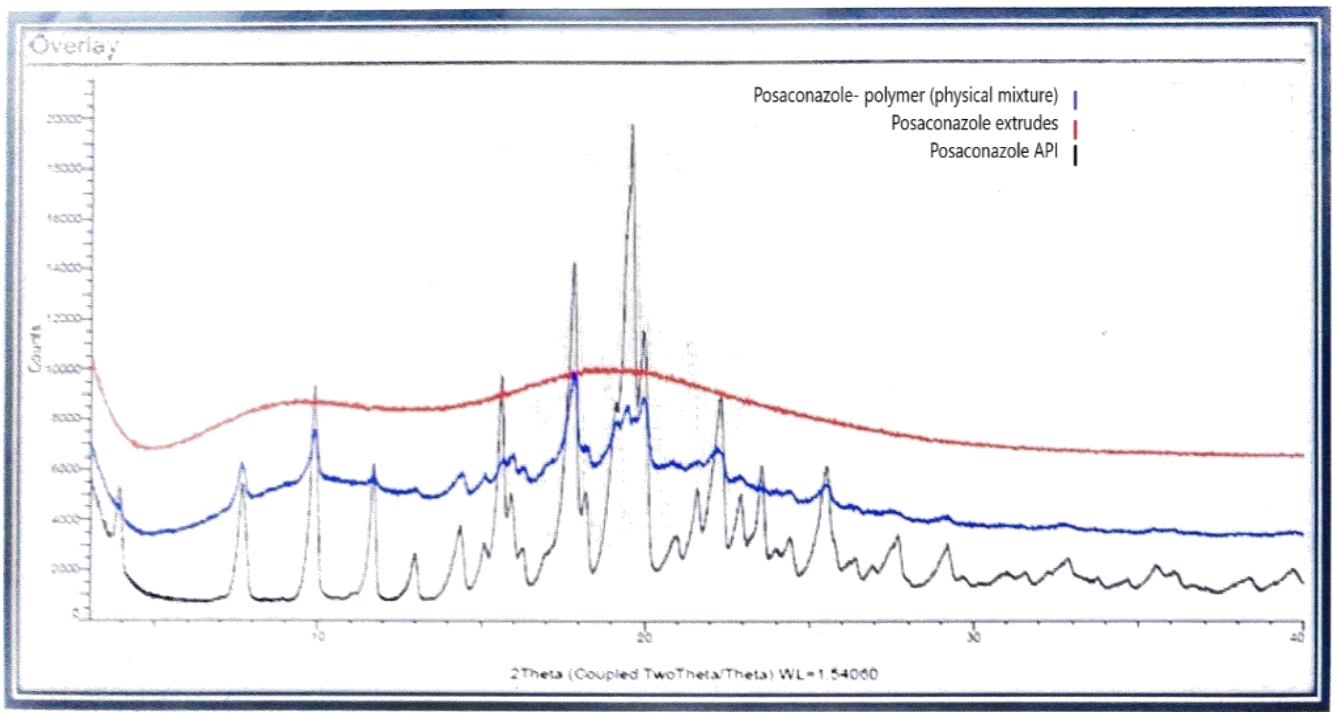

Fig. 5: XRD image of Posaconazole API, Posaconazole extrude, Posaconazole polymer (Physical mixture)

3.6. Differential scanning calorimetry (DSC)

The solid-state extruded amorphous solid dispersion was analyzed by DSC. It was used to identify the state of posaconazole in the extruded ASD and to study the drug-polymer interaction. In fig. 6 (a-b) The DSC thermogram of pure posaconazole showed a characteristic peak of crystalline Posaconazole at 169 °C which is closer to its melting point. This confirmed the purity of the API used in the delayed-release tablet formulation. In the case of the posaconazole -HPMCAS milled extrudes the presence of only Tg and the absence of melting endotherm of posaconazole indicate the formation of ASD during the HME process as represented in fig. 6(b).

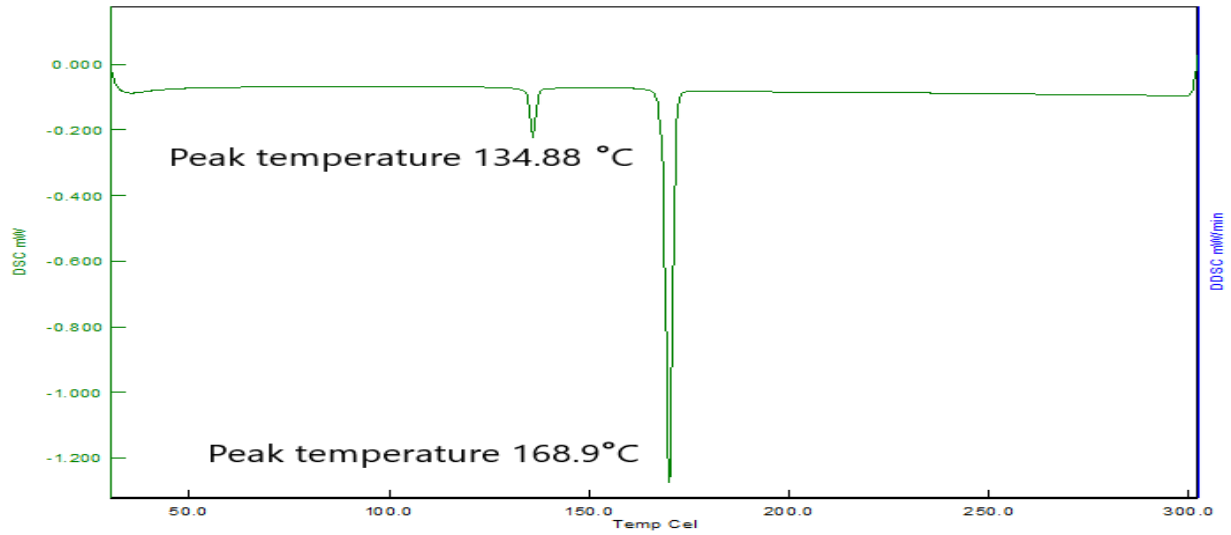

Fig. 6 (a): DSC of Posaconazole API

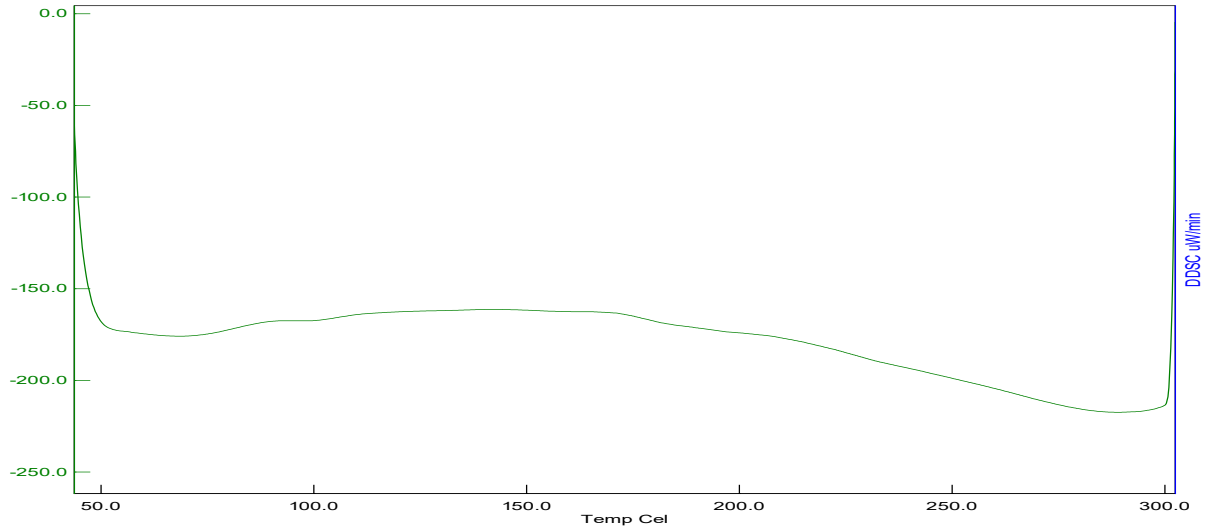

Fig. 6 (b): DSC of Posaconazole extrudes

Fig. 7: Dissolution Comparison of Noxafil and Posacoazole DR Tablet

3.7. Stability study

During the stability studies, the product was exposed to accelerated conditions as per the ICH Q1 (R2) guideline at 40°C/75% RH. These studies are designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions. The posaconazole DR tablet formulation was tested for three months and was found stable as no significant changes are observed in average weight, DT, hardness, and dissolution as depicted in Table 4. The assay and related substances were also found to be within limits thus indicating that the formulation was stable for up to 3 months. According to the design provided by Minitab, the concentration for X1 was 150 to 250mg and 35 to 65 mg for X2 and X3. The center point batch F4 is optimized as it is having a matching drug release profile with the innovator based upon F2 value by the model-independent method of analysis.

3.8. Statistical analysis

Table 3: ANOVA

Response	Source	DF	Adj SS	Adj MS	F-Value	P-Value
Y1	**Model**	1	4512.50	4512.50	92.62	0.000
	Linear	1	4512.50	4512.50	92.62	0.000
Y2	**Model**	6	70147.5	11691.3	32375.77	0.000
	Linear	3	66386.5	22128.8	61279.85	0.000
	HPMCAS	1	578.0	578.0	1600.62	0.001
	HPC	1	648.0	648.0	1794.46	0.001
	CCS	1	65160.5	65160.5	180444.46	0.000
	2-Way Interactions	3	3761.0	1253.7	3471.69	0.000
	HPMCAS*HPC	1	2888.0	2888.0	7997.54	0.000
	HPMCAS*CCS	1	760.5	760.5	2106.00	0.000
	HPC*CCS	1	112.5	112.5	311.54	0.003
Y3	**Model**	1	1225.1	1225.13	14.33	0.007
	Linear	1	1225.1	1225.13	14.33	0.007
	HPMCAS	1	1225.1	1225.13	14.33	0.007

Table 4: Parameters studied in accelerated stability study for optimized formulation

Test	Acceptance criteria	Results			
		Initial	**1 month**	**2 months**	**3 months**
Description	Yellow, coated capsule shaped tablet debossed with "F151" on one side and plain on other side	Complies	Complies	Complies	Complies
Average weight	588±3 mg	586±2.1mg	585±3.2 mg	586±2.7 mg	585 ±3.4 mg
Hardness	150- 190 N	168 ±2.2	171±1.2	173±2.4	172±1.0
DT	NMT 30 minutes	2 min 16 sec-2min 54 sec	2min 29sec-2min 43 sec	2min 38sec-2min 56sec	2min 54sec-3min 09sec
Dissolution	NMT 10% release in 120 mins at acid stage	5	4	4	4
	NLT 75% release in 30 mins at Buffer stage	91	93	92	90
Assay	95-105%	101.2	100.8	100.9	99.7
Impurities	Limits				
Impurity A	NMT 0.2%	ND	0.01	0.001	0.02
Unknown impurity	NMT 0.2%	0.04	0.07	0.07	0.09
Total impurity	NMT 1.0%	0.16	0.22	0.25	0.28

Table 5: Results of Optimization by DOE

Experimental number	X1-HPC (mg)	X2-CCS (mg)	X3-HPMCAS (mg)	Y1-Hardness	Y2- DT	Y3- % DR
F1	35	35	150	127	402	77
F2	35	35	250	145	367	88
F3	65	35	150	183	375	89
F4	35	35	200	171	300	91
F5	65	35	250	180	415	80
F6	35	65	150	143	234	95
F7	35	65	250	137	159	86
F8	65	65	150	190	221	75
F9	65	65	250	189	223	86

4. CONCLUSION

Systematic development of a bioavailable and stable ASD of posaconazole by HME process was achieved by studying the critical quality attributes at different levels by using the quality by design approach. Preliminary formulation development studies like FTIR analysis help in understanding the compatibility of the drug with the polymer HPMCAS. Thorough evaluation of physical stability of ASD was conducted by XRD studies also confirmed the in-situ conversion of crystalline Posaconazole into a fully amorphous state. The present study successfully vouches for the use of a rational QbD based approach for the development of optimized posaconazole DR tablet formulation by using Hot melt extrusion technology which helps in enhancing the bioavailability of the poorly water-soluble drug. The DSC studies indicated the conversion of posaconazole from crystalline form to amorphous form during hot melt extrusion with hypermellose acetate succinate (HPMCAS). From the stability data, the optimized batch F4 was found to be stable up to 3 months at accelerated conditions 40°C /75%RH.

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Disclosure of interest

There is no competing interest for publishing this article. There were no animals have been used in this experiment.

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