RESEARCH ARTICLE

Stability Indicating RP-HPLC Method for Posaconazole Assay Using QbD Approach

Vibhute Diksha[1], Deshpande Anant[2*], Komal Shinde[3], Priyanka Wankhede[4]

[1]*Department of Pharmaceutical Quality Assurance, Channabasweshwar Pharmacy College, Latur, Maharashtra, India.*
[2]*Department of Pharmaceutical Chemistry, Channabasweshwar Pharmacy College, Latur, Maharashtra, India.*
[3]*Department of Pharmacology, D. K. Patil Institute of Pharmacy, Loha, Nanded, Maharashtra, India.*
[4]*Department of Pharmaceutical Quality Assurance, D. K. Patil Institute of Pharmacy, Loha, Nanded, Maharashtra, India.*

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ABSTRACT

The development and optimization of analytical techniques utilizing the quality by design methodology is essential in the pharmaceutical industry. This approach helps in the direction of identifying and optimizing critical parameters during drug development and assesses their impact on key quality attributes. A stability-indicating RP-HPLC method was developed for quantifying posaconazole in bulk and tablet forms utilizing the quality-by-design approach. The Box-Behnken design optimized buffer flow rate, organic modifier percentage, and temperature, affecting retention time, theoretical plate count, and symmetry factor. Chromatography was performed on a Symmetry C18 column with a mobile phase of 0.01N potassium dihydrogen phosphate and acetonitrile (57.4:42.6% v/v), at a flow rate of 1.11 mL/min, detection at 220 nm, and column temperature of 30°C. Posaconazole's retention time was 3.663 minutes, with precise, accurate, and linear signals ($R^2 = 0.999$). The method is simple, fast, cost-effective, and ideal for routine quality control.

Keywords: Posaconazole, Quality by Design, RP-HPLC, Validation.

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INTRODUCTION

Quality by Design (QbD) is a methodology initially proposed by the well-known quality expert Josef M. Juran. QbD principles are used across industries for the improvement of product and process quality. In recent times, the FDA recognized QbD as a transformative approach for pharmaceutical discovery and manufacturing. Since its introduction, QbD has become essential for analytical method development in the industry.[1] This approach fosters a more thorough understanding of the interactions between various variables, leading to the creation of more efficient and adaptable systems. Unlike the traditional method of ensuring quality through testing, QbD emphasizes incorporating quality directly into the process design rather than relying solely on analytical techniques to assess the final product.[2] Critical parameters are identified and their interactions with the system response parameters are determined, which establishes an optimized design space for the technique.[3]

Posaconazole (Noxafil ®) is a systemic antifungal drug belonging to the triazole class, derived from itraconazole. It is primarily utilized in the direction of preventing invasive infections affected by *Aspergillus* and *Candida* in individuals with weakened immune systems. Posaconazole, like other azoles, inhibits lanosterol 14α-demethylase, disrupting ergosterol biosynthesis in fungal cell membranes. This disruption weakens the membrane structure, leading to its antifungal effects.[4] Posaconazole is a white to off-white crystalline powder with a molecular formula of $C_{37}H_{42}F_2N_8O$ and a molecular weight of 700.778 g/mol. It is soluble in dichloromethane as well as acetonitrile (ACN). The chemical structure is presented in Figure 1.[5,6]

A literature review found only a few analytical methods, including one QbD-based stability-indicating RP-HPLC technique, for estimating posaconazole in bulk and dosage forms.[7,8] However, the reported linearity ranges for these methods are quite narrow, limiting their overall effectiveness.[9-11] This study aimed in the direction of developing and validating a sensitive, precise, and robust stability-indicating RP-HPLC technique for posaconazole in bulk and tablet forms utilizing the QbD methodology.[12-15]

**Author for Correspondence: anantdeshpande1976@gmail.com*

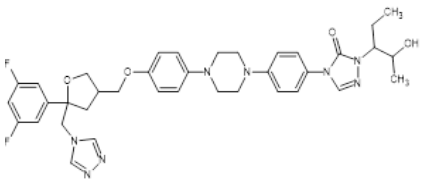

Figure 1: Structure of posaconazole

MATERIALS AND METHODS

Chemicals and Reagents

Posaconazole was obtained from Spectrum Pharma Lab (Hyderabad). HPLC-grade water was from Merck milli-Q, while acetonitrile and methanol were from Fisher Scientific. Analytical-grade HCl, NaOH, H_2O_2, and acetic acid were also from Fisher Scientific. Potassium dihydrogen phosphate and orthophosphoric acid were supplied by S.D. Fine.

Equipment

The investigation utilized a Waters Alliance HPLC 2965 system with a PDA detector at 220 nm. The columns Agilent C_{18} (150×4.6 mm, 5 µm), Discovery C_{18} (150*4.6 mm,5 µm), Zodiac (150*4.6 mm,5 µm), BDS (150*4.6 mm,5 µm) and Phenomenex (150*4.6 mm,5 µm) were utilized. Design Expert®11 software, a pH meter, a sonicator, an analytical balance, a vortex mixer, and hot air oven were also utilized.

Preparation of Solutions

Standard stock solutions

50mg of posaconazole was dissolved in a 50 mL volumetric flask with three-fourths of the diluent, sonicated for 10 minutes, and the volume was adjusted to 50 mL. This produced Solution A with 1000 µg/mL of posaconazole.

Standard working solutions

A 1 mL of solution A was diluted to 10 mL with the diluent to create solution B with 100 µg/mL of posaconazole.

Sample stock solutions

A 10 tablets were weighed, and the weight of one tablet was transferred to a 100 mL volumetric flask. After adding 50 mL of diluent and sonicating for 25 minutes, the volume was adjusted to 100 mL and filtered, producing Solution C with 1000 µg/mL of posaconazole.

Sample working solutions

A 1-mL of solution C was diluted to 10 mL with diluent to make solution D with 100 µg/mL of posaconazole.

Chromatographic Condition[16]

Wavelength selection

The UV spectrum of a 10 µg/mL posaconazole solution was recorded using dichloromethane as a blank that exhibited maximum absorbance at 220 nm.

Column selection

Several initial HPLC trials were conducted to determine the appropriate column. Based on these preliminary investigations, various C18 columns were evaluated, including Symmetry C18, Agilent C18, Discovery, and BDS (150×4.6 mm, 5 µm). The Symmetry C18 column was selected because of its lower tailing factor, higher theoretical plate count, and better peak shape for the drug compared to the Agilent, BDS, and Discovery columns.

Mobile phase selection

To achieve optimal separation of all analytes and improved selectivity, the selection of a suitable organic modifier is crucial. ACN and methanol are commonly used organic solvents for RP-HPLC. In this study, ACN was found to be a more effective and appropriate organic modifier than methanol because posaconazole dissolves more readily in ACN. Therefore, ACN was chosen as the organic modifier for supplementary optimization studies.

Method optimization

A QbD-based RP-HPLC technique was established for assessing posaconazole in both bulk and dosage forms. The technique development utilizing the QbD approach was carried out in two phases.[3]

Screening phase

The screening phase used Design Expert®11 software with a Box-Behnken design to identify key factors like buffer pH, flow rate, and organic modifier percentage affecting selectivity and peak shape. A design was utilized in the direction of optimizing critical parameters and assessing their interactions on quality attributes. This 3-factor, 3-level was chosen for its efficiency in optimizing parameters and assessing interactions. Different from the traditional OFAT (one factor at a time) methodology, this design allows all parameters to be varied simultaneously. 13 trials were conducted and analyzed utilizing DoE software.

Statistics and optimization

Statistical analysis was used to identify significant chromatographic factors and the impact of their interaction on three responses, i.e., retention time, NTP and symmetry factor of posaconazole. Statistical investigation identified key chromatographic factors influencing retention time (RT), NTP, and symmetry factor (SF). Figures 2-8 present 3D surface and actual vs. predicted plots. Parameters were evaluated utilizing a p-value ($p \geq 0.05$), and response variables met acceptable criteria. The optimized conditions are detailed in Table 2.

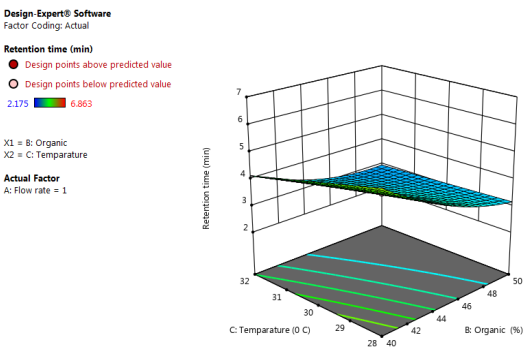

Figure 2: Impact of Temp. and %ACN on RT of Posaconazole

Table 1: Screening of factor by design

		Factors			*Responses*		
		1	*2*	*3*	*1*	*2*	*3*
Standard	*Run*	*A: Flow rate (FR)*	*B: Organic*	*C: Temp.*	*RT*	*NTP*	*SF*
		ml/min	*%*	*^0C*	*min*	*number*	*number*
11	1	1	36.591	30	5.872	8309	1.2
5	2	0.8	40	32	5.337	7229	1.24
13	3	1	45	26.6364	4.158	7561	1.22
1	4	0.8	40	28	6.863	8932	1.21
20	5	1	45	30	3.59	6682	1.27
7	6	0.8	50	32	3.994	6562	1.29
9	7	0.663641	45	30	5.573	7383	1.3
2	8	1.2	40	28	4.415	7326	1.21
6	9	1.2	40	32	3.457	7130	1.27
14	10	1	45	33.3636	2.943	6383	1.31
3	11	0.8	50	28	4.045	6671	1.3
18	12	1	45	30	3.543	6683	1.27
12	13	1	53.409	30	3.263	6365	1.27
10	14	1.33636	45	30	2.556	6019	1.27
19	15	1	45	30	3.535	7029	1.27
17	16	1	45	30	3.482	6862	1.27
4	17	1.2	50	28	2.553	5709	1.29
15	18	1	45	30	3.562	6650	1.29
8	19	1.2	50	32	2.175	5176	1.3
16	20	1	45	30	3.527	6663	1.27

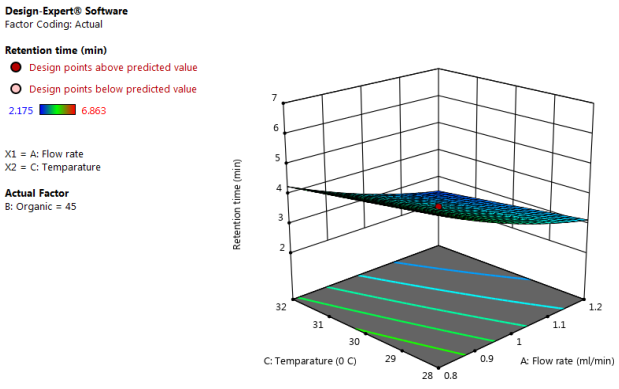

Figure 3: Impact of Temp. and FR on RT of posaconazole

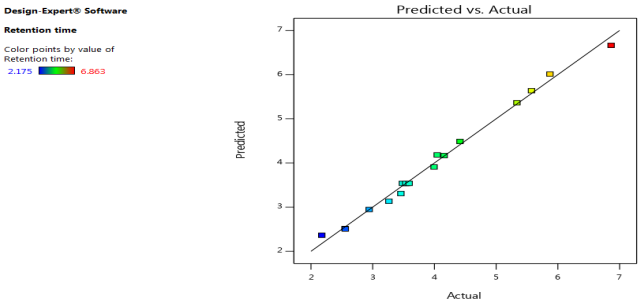

Figure 4: Actual vs predicted plot for RT of posaconazole

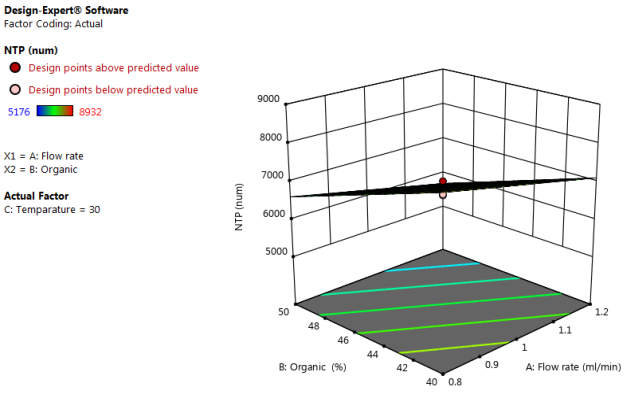

Figure 5: Impact of temperature and %ACN on NTP of posaconazole

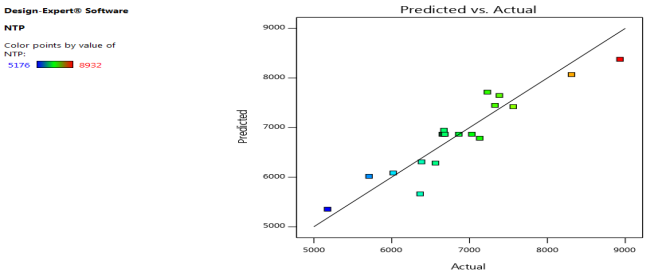

Figure 6: Actual vs predicted plot for NTP of posaconazole

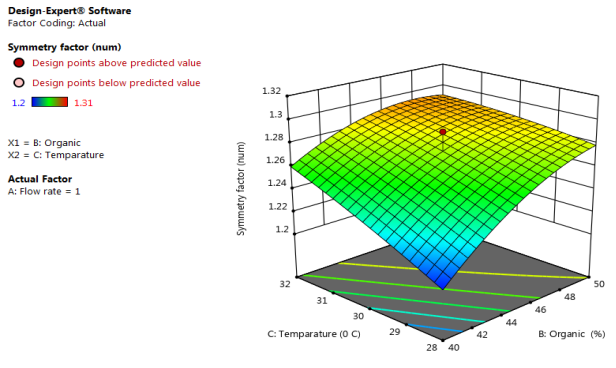

Figure 7: Impact of temperature and %ACN on SF of posaconazol

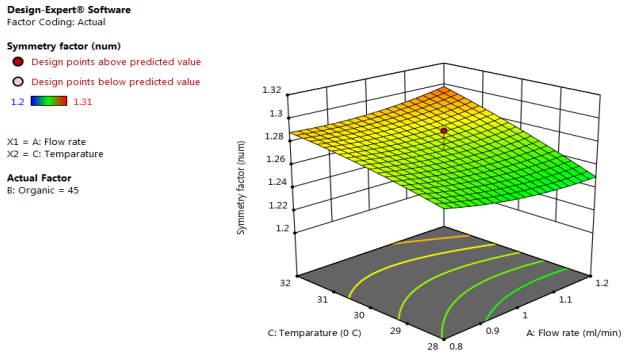

Figure 8: Impact of temperature and FR on SF of posaconazole

Table 2: Optimized chromatographic conditions

Parameters	*Specification*
Pump	Quaternary pump
Detector	PDA 220.0 nm
Integrator	Empower 2 software
Column	Symmetry C_{18} column
Wavelength	220 nm
Mobile phase	57.4% 0.0N KH_2PO_4: Acetonitrile 42.6%
Injection volume	10 µL
Flow rate	1.11 mL/min
Temperature	29.50

Force Degradation Studies

Force degradation studies were conducted in accordance with ICH guidelines Q1A (R2) and Q1B to demonstrate that the technique is stability-indicating.[17,18]

Acid Hydrolysis

A 1 ml stock solution was treated with 2N HCl and heated at 70ºC for 1 hour. After neutralization and dilution, HPLC analysis showed 5.41% degradation of posaconazole during acid hydrolysis. A stress test was also conducted on blank solutions under the same conditions as the drug solution. The HPLC system analyzed both the stressed sample and the blank solutions. Figures 9 and 10 show the chromatograms of the blank and the drug subjected to acid hydrolysis, correspondingly.

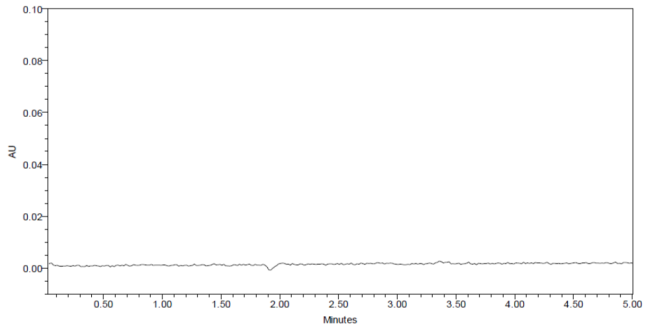

Figure 9: Blank chromatogram

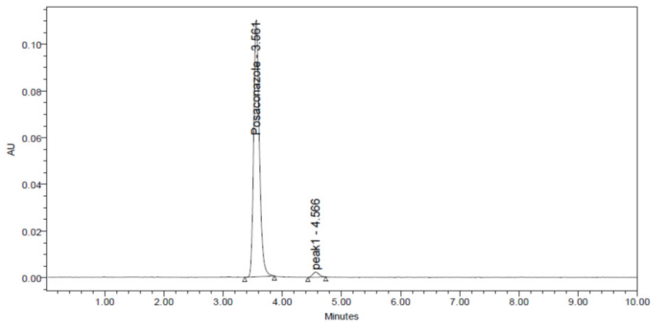

Figure 10: Chromatogram of drug in 2N HCL at 70°C temperature for 8 hours

Base Hydrolysis

A 1-mL stock solution was mixed with 1-mL of 2N NaOH and stirred at 70ºC for 1-hour. After neutralization and dilution, HPLC analysis showed 4.23% degradation of posaconazole with two degradation products formed. Further exposure to 2N NaOH and reflux at 70ºC for 8 hours was also conducted. A stress test was also conducted on blank solutions under the same conditions as the drug solution. The HPLC system was used to analyze both the stressed sample and the blank solutions. Figure 11 shows the chromatogram of the drug solution subjected to base hydrolysis.

Neutral Hydrolysis

A 50 mg posaconazole sample was liquefied in 50 mL of water as well as stirred at 70ºC for 24 hours. A stress test on blank solutions under the same conditions showed no degradation. Both stressed and HPLC investigated blank solutions.

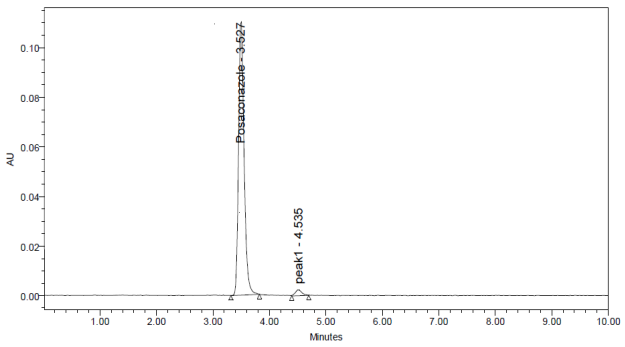

Figure 11: Chromatogram of drug in 2N NaOH at 70°C temperature for 8 hours

Oxidative Degradation

A 1-mL stock solution was mixed with 1-mL of 20% H_2O_2 and stored at room temperature in the dark for 24 hours. The stress investigation was conducted on the blank solutions in the same manner as the drug solution. No degradation was observed in both the stressed and blank solutions, as analyzed by HPLC.

Thermal Degradation

About 50 mg of posaconazole was kept in petri plate and heated at 70ºC in a hot air oven for one day. After dissolving in methanol and diluting, HPLC analysis showed no degradation.

Photo Degradation

A 50 mg of posaconazole was showing towards straight sunlight for 24 hours. Samples were taken at various times and analyzed by HPLC, showing no degradation.

Force degradation studies showed no products from UV exposure, heat, neutral, or peroxide hydrolysis. However, significant degradation products were identified from acid and base hydrolysis.

RESULT AND DISCUSSION

Method Validation

The ICH guidelines were monitored when doing the validation of the parameters for example, specificity, sensitivity, linearity, accuracy, and precision, robustness, and ruggedness.[20]

Specificity

Figure 12 represents the chromatogram for blank**.** No other interfering peaks around the posaconazole chromatogram with retention time (RT: 3.663 minutes) were observed. Thus, the method was found to be specific.[21]

Sensitivity

The LoD and LoQ for posaconazole centered on SD of slope and intercept were found to be 0.77 and 2.32 µg/mL correspondingly.[22]

Linearity

Linearity was confirmed in the range of 25 to 150 ppm with an R^2 of 0.999 and the equation y=7683.5x+1218.8, as presented in Figure 13.[23]

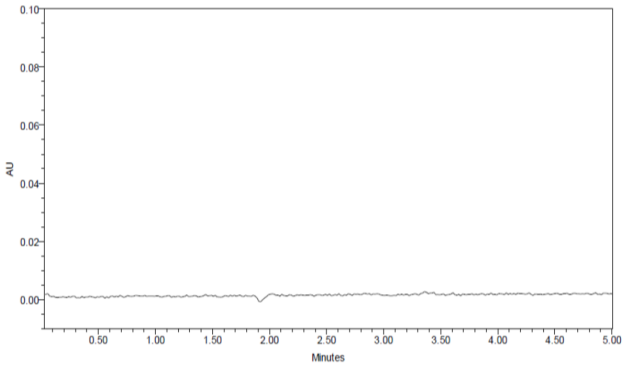

Figure 12: Chromatogram for blank solution

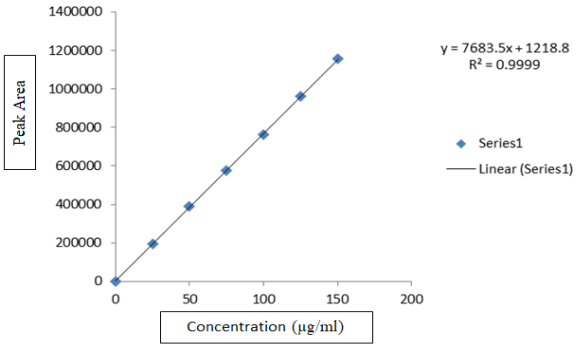

Figure 13: Linearity plot of posaconazole

Table 3: Intraday data of posaconazole

S. No.	*Peak area*
1	769847
2	770123
3	764964
4	776262
5	765486
6	768460
Average	769190
SD	4084.8
%RSD	0.5

Table 4: Interday data of posaconazole

S. No.	*Peak area*
1	769391
2	768187
3	774073
4	772560
5	768193
6	769969
Average	770396
SD	2413.6
%RSD	0.3

Table 5: Accuracy data of posaconazole

%Level	*Quantity spiked (µg/mL)*	*Quantity recovered (µg/mL)*	*%Recovery*	*Mean %Recovery*
50%	50	50.77	101.54	
	50	49.82	99.65	
	50	49.79	99.58	
	100	98.60	98.60	
100%	100	98.96	98.96	99.66%
	100	99.72	99.72	
	150	148.73	99.15	
150%	150	149.14	99.42	
	150	150.43	100.29	

Table 6: Robustness data of posaconazole

Parameter	*%RSD*
Flow (-)	0.2
Flow (+)	0.4
Mobile phase (-)	0.9
Mobile phase (+)	0.4
Temperature (-)	0.4
Temperature (+)	0.6

Table 7: Results of validation

Parameters		*Posaconazole*	*Limit*
Linearity Range(µg/ml)		25–150 µg/mL	
R^2		0.9999	
Slope(m)		7683.5	$R^2 < 1$
Intercept(c)		1218.8	
Regression equation		Y=7683.5x +1218.8	
Assay (%)		99.96%	90-110%
Specificity		Specific	No interference of any peak
System precision		0.5	NMT 2.0%
Accuracy		99.66%	98-102%
LOD		0.77	NMT 3
LOQ		2.32	NMT 10
Robustness	FM	0.2	%RSD NMT 2.0
	FP	0.4	
	MM	0.9	
	MP	0.4	
	TM	0.4	
	TP	0.6	
Degradation Study	Degradation condition	%Degraded	10%
	Acid	5.41	
	Base	4.23	
	Peroxide	4.88	
	Thermal	2.09	
	Photo	1.23	

Precision

Intraday precision for posaconazole was assessed with six injections of 100 ppm at different times, showing a %RSD of 0.5%. Interday precision was evaluated with six injections on two separate days, yielding a %RSD of 0.3%. Results are summarized in Tables 3 and 4.[24]

Accuracy

Accuracy was assessed utilizing the standard addition method with 50, 100, and 150% concentrations incorporated into pre-analyzed samples. The mean accuracy and relative standard deviation were calculated from triplicate samples. Results are summarized in Table 5.

Table 8: Assay of posaconazole marketed tablet

Sample No.	*%Assay*
1	99.83
2	99.67
3	100.43
4	100.24
5	99.67
6	99.90
Average	99.96
SD	0.31
%RSD	0.31

Robustness

Robustness was tested by altering mobile phase organic content, FR, and pH (±10%). Changes in these conditions, for example, FR, mobile phase composition, and temperature, were applied to assess the method's stability. The %RSD for these conditions was calculated. The results of the robustness testing and the validation of posaconazole are summarized in Tables 6 and 7, correspondingly.

Analysis Marketed Tablet

The average weight of ten noxafil tablets (100 mg posaconazole each) was determined. The tablets were powdered, and 100 mg of the powder was dissolved in 50 mL of diluent and sonicated. The volume was adjusted to 100 mL, creating Solution A. Solution A was diluted to 100 µg/mL (Solution B), which was then injected into the HPLC system. The assay results are in Table 8.

CONCLUSION

The developed and validated RP-HPLC technique proved to be precise, sensitive, robust, and stable. Employing the QbD approach for determining posaconazole resulted in fewer trials and reduced failure rates. The validation process adhered to current ICH recommendations. Degradation studies showed no products from peroxide, neutral, thermal, or UV hydrolysis. A significant product was found in 2N HCl and 2N base hydrolysis. The analytical technique, validated according to ICH guidelines, is appropriate for routine investigation of the drug in bulk and tablet forms.

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