**Drug Discovery**

**To Cite:**
Bharati SR, Nalawade MS, Pawar KR. Stability indicating high performance thin layer chromatography method development and validation of Trifluoperazine in bulk and tablet dosage form using a QbD apporach. *Drug Discovery* 2025; 19: e17dd2097
doi:

**Author Affiliation:**
[1]Abhinav Education Society's College of Pharmacy (B. Pharm), Narhe, Pune, 411041, India.

*Corresponding Author
Dr. Kumudini R Pawar,
Abhinav Education Society's College of Pharmacy (B. Pharm),
Narhe, Pune, 411041,
Maharashtra, India
E-mail: kumudiniphd30@gmail.com
ORCID: 0009-0001-6915-0424

**Peer-Review History**
Received: 05 June 2025
Reviewed & Revised: 18/June/2025 to 21/August/2025
Accepted: 25 August 2025
Published: 29 August 2025

**Peer-Review Model**
External peer-review was done through double-blind method.

Drug Discovery
pISSN 2278–540X; eISSN 2278–5396



# Stability indicating high performance thin layer chromatography method development and validation of Trifluoperazine in bulk and tablet dosage form using a QbD apporach

**Shweta R Bharati[1], Madhuri S Nalawade[1], Kumudini R Pawar[1]***

## ABSTRACT

This research emphasizes use of quality by design framework in conducting a qualitative assessment of Trifluoperazine in both its bulk and tablet forms, with the subsequent development and validation of a high-performance thin layer chromatography technique. Chromatographic separation was performed using thin-layer chromatography on aluminium silica gel 60 F254 plates, employing a mobile phase composed of methanol, ethyl acetate, and ammonia in a volumetric ratio of 9:1:0.2. Densitometric analysis is conducted at a wavelength of 303 nm, and the Rf value for trifluoperazine was determined to be 0.38. The method demonstrated a high degree of linearity ($r^2$= 0.9956). The process is optimized by evaluating the impact of critical method variables such as mobile phase composition and saturation time on chromatographic performance. Therefore, the previously mentioned parameters are subsequently refined utilizing the central composite design methodology, with the Rf value identified as the critical analytical attribute. The methodology is rigorously validated for parameters such as linearity, accuracy, precision, robustness, and sensitivity, with the limits of detection and quantitation showing favourable results. The validation process conformed to the standards established by the International Conference on Harmonization and met the required criteria. Consequently, this research illustrates the effective implementation of Quality by Design in formulation of superior high performance thin layer chromatography technique that integrates accuracy, reliability, and efficacy, along with system assurance and methodological robustness.

**Keywords:** Trifluoperazine, QbD, HPTLC, Analytical Method Development, Design of Experiments (DoE), Central Composite Design.

## 1. INTRODUCTION

Schizophrenia is a chronic and devastating mental illness that can cause abnormalities in perception, behaviour, emotion, and thought. Millions of people worldwide have schizophrenia, a severe mental illness that frequently results in significant social and professional impairments (Meyer et al., 2011). While the exact cause of schizophrenia is yet to be determined, it is believed that a combination of environmental, neurological, and genetic factors contributes to its development. Trifluoperazine is a commonly used antipsychotic medication from the phenothiazine class, prescribed for the treatment of schizophrenia and other psychotic disorders (Stepnicki et al., 2018). It works primarily by inhibiting the brain's dopamine D2 receptors, which stops the excessive dopaminergic activity that leads to symptoms of schizophrenia. By controlling neurotransmitter imbalance, Trifluoperazine reduces positive symptoms like delusions and hallucinations and enhances mental stability (Chong et al., 2016).

Its chemical structure is $C_{21}H_{24}F_3N_3S$ with a molecular weight of 480.4 g/mol. Its oral administration is typically dosed at 2–15 mg per day, depending on the severity of the condition and patient tolerability (Chatterjee et al., 2023). Stelazine is one of the brand names used to commercialize Trifluoperazine. Trifluoperazine frequently causes extrapyramidal symptoms, drowsiness, dry mouth, and hypotension, despite being typically well tolerated. Due to the risk of tardive dyskinesia and other movement disorders with long-term use, careful monitoring of patients is recommended (Zolotareva et al., 2025).

None of the published works explored the stability of the QbD-based HPTLC method. The ICH guidelines outline key Quality by Design (QbD) concepts, including Q8(R2), which addresses pharmaceutical development; Q9, which covers quality risk management; and Q10, which pertains to the pharmaceutical quality system (Yu LX et al., 2014, Pramod et al., 2016). ICH Q10 outlines a comprehensive approach to pharmaceutical analysis at every stage of manufacturing to ensure quality, aligning with the principles of Quality by Design (QbD). The use of QbD in the development of an analytical method is known as analytical quality by design. Regulatory bodies such as the FDA and ICH increasingly advocate for the use of scientifically robust procedures, guided by Design of Experiments (DoE), to enhance methodological standards in research and improve analytical precision. However, our literature review reveals that no method has yet incorporated the Design of Experiments (DoE) to determine Trifluoperazine in dosage forms for pharmaceuticals. Given this gap, the current research aims to develop and validate a Design of Experiments (DoE)-based, stability-indicating HPTLC method for the quantification of trifluoperazine, in accordance with the recommendations of ICH Q2(R1) (Kah Yung et al., 2019). Fig 1 shows chemical structure of Trifluoperazine.

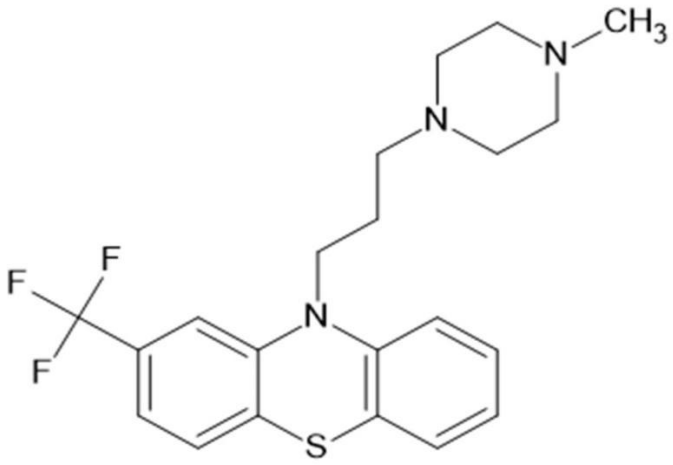


**Figure 1.** Chemical structure of trifluoperazine

## 2. MATERIALS AND METHODS

**Experimental**

***Materials***

A sample of Trifluoperazine API is procured from Syngenesis Chemscience Private Limited, Tathawade, Pune, India. Acetic acid, methanol, ethyl acetate, glacial acetic acid, acetonitrile, and ammonia were obtained from Loba Chemicals, Mumbai.

A marketed formulation of Trifluoperazine (GENCALM 5 mg) is purchased from the local market for analysis.

***Instrumentation***

The analysis is performed using a CAMAG TLC Scanner 3 (CAMAG, Muttenz, Switzerland) with WinCATS software. Sample application is performed using a Linomat 5 applicator (CAMAG, Muttenz, Switzerland), a 100 µL Hamilton microsyringe (CAMAG, Muttenz, Switzerland), and a twin-trough chamber (20 × 10 cm; CAMAG, Muttenz, Switzerland). The scanning process is performed using the CAMAG TLC Scanner 3, with analysis controlled by WinCATS software (version 1.4.3.6336). The stationary phase consisted of TLC Silica Gel 60 F254 aluminium sheets (20 x 20 cm, 0.1 mm thickness, Merck, Darmstadt, Germany).

***Chromatographic Conditions***

An appropriate volume of the standard and sample solutions is spotted onto the HPTLC plate in 6 mm-wide bands. The plates were kept at 100°C for 10 minutes before separation and prewashed with methanol. Methanol, ethyl acetate, and ammonia in a ratio of 9:1:0.2 (v/v/v) constituted the mobile phase The mobility stage achieved equilibrium in 10 minutes by using a straight upward development for 80 mm. After the development process was complete, the plates were allowed to air dry. Utilizing a CAMAG TLC Scanner 3, scanning was performed at 303 nm using a deuterium lamp as the radiation source. The scan data is treated with WinCATS software (VanDuyse et al., 2021, Calnan et al., 2013).

***Preparation of standard stock solution***

5 mg of Trifluoperazine dissolved in a 10 mL methanol to a concentration of 500 µg/mL

***Preparation of sample solution***

Twenty tablets of Trifluoperazine were accurately measured and finely ground to make powder. The mean weight of the tablets is assessed; an amount equivalent to 5 mg of trifluoperazine was weighed and transferred into a graduated flask containing 10 mL of methanol. The solution is then filtered using 0.45 µm Whatman filter paper (Ohage et al., 2016).

***Analytical quality by design-based HPTLC method development***

Determining the Analytical Target Profile (ATP), which involves selecting the drug sample and identifying the most suitable technique or tool for assessing the drug component, was the first step in developing a method for trifluoperazine. Essential elements in the process are identified as critical method parameters (CMPs), including mobile phase composition and saturation time. Particularly, the retardation factor is recognized as a crucial analytical attribute (CAA) necessary to guarantee the effectiveness of the devised approach and the dependability of the data produced (Prajapati et al., 2021, Muppayyanamath et al., 2025).

***Optimization of the method using design of experiments (DoE)***

A Central Composite Design with two factors at two levels is employed to optimize the analytical procedure. Stat-Ease software (version 23.1.8) is used to design the experiment. To evaluate significant method conditions and critical analytical characteristics that significantly affect the devised technique, preliminary mobile phase experiments are conducted. Critical Method Parameters (CMPs) and Critical Analytical Attributes (CAAs) were correlated using a response surface approach. The significance of the model is confirmed through Analysis of Variance (ANOVA), and the model's adequacy was evaluated using the lack-of-fit test, p-value, and F-value (Onyeogaziri et al., 2019, Maia et al., 2021).

***Establishment of method operable design region (MODR)***

Following the Central Composite Design-assisted experimental runs, the collected data is analyzed to construct regression models and understand the relationship between variables and responses. The objective of this investigation was to determine the Method Operable Design Region. Then, using overlay plats, optimal chromatographic conditions were identified from the MODR, taking into account the specific objective for every CMP. Within the design space, every specification included in the analytical target profile (ATP) is completed at a given degree of risk. The selected CMP criteria are used to identify the optimal runs (Simeoni et al., 2023, Chen et al., 2023).

**Analytical Method Validation**

A comprehensive HPTLC method validation for Trifluoperazine is performed, covering linearity, precision, accuracy, sensitivity, robustness, and specificity (Dai et al., 2015). Linearity was demonstrated across a concentration range of 200–1200 ng/band by transferring 0.2–1.2 µL of a stock solution into 10 mL volumetric flasks, followed by calibration using linear regression (with high $r^2$ values) from six repeated measurements. Both intraday and interday precision are confirmed by analysing three concentrations at multiple time points and on consecutive days, with low % RSD values (Cleary et al., 2025). Assay precision was evaluated through six replicate analyses of a 600 ng/band tablet solution, while accuracy was assessed at 80%, 100%, and 120% levels using the standard addition method, demonstrating acceptable recovery rates with minimal variation. The sensitivity parameters, LOD and LOQ, were calculated using the slope of the calibration curve and the standard deviation of the y-intercept. By adjusting the mobile phase components together with detection wavelengths, the method's robustness is established; meanwhile, specificity was validated by comparing Rf values and spectral profiles of the solvent and mobile phase, pure API, and tablet sample, verifying peak purity at multiple points along the band (Williams et al., 2019).

***Forced degradation studies***

In forced degradation investigations for Trifluoperazine, drug is exposed to different stress conditions: acidic conditions (0.01 N HCl for 1 hour), alkaline conditions (0.01 N NaOH for 1 hour), oxidative conditions (3% $H_2O_2$ for 1 hour), neutral conditions (distilled water for 1 hour), thermal conditions (50 °C for 1 hour), and photolytic conditions (UV exposure for 24 hours), (Tamiizi et al., 2016).

## 3. RESULTS AND DISCUSSION

**Selection and optimization of the mobile phase**

After a series of experiments, a mobile phase consisting of methanol, ethyl acetate, and ammonia (9:1:0.2 v/v/v) was selected, as it produced sharp peaks without fronting or tailing. In Fig. 2, the usual Trifluoperazine bands are displayed.

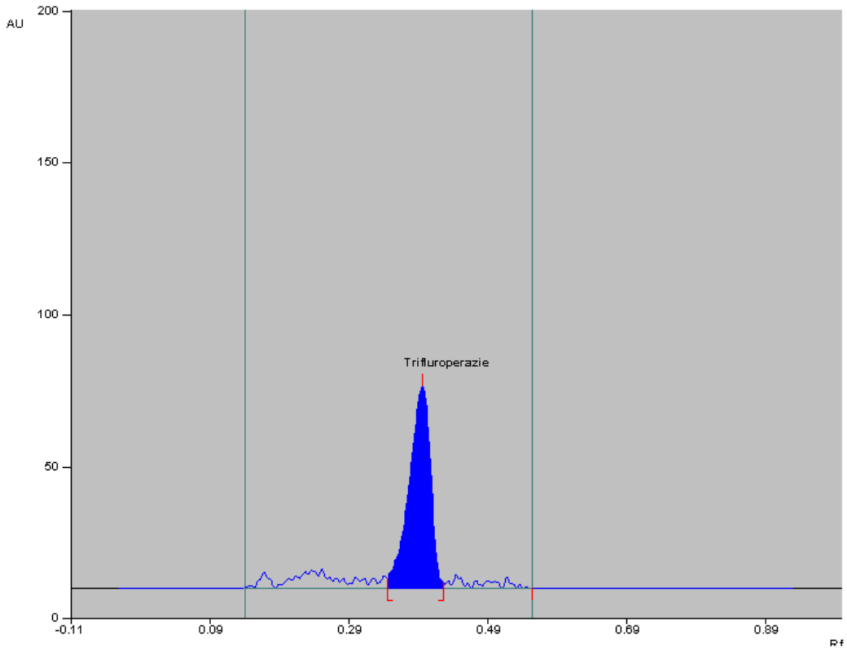


**Figure 2.** Densitogram of standard solution of Trifluoperazine (600 ng/band)

**Selection of the wavelength**

The effectiveness of HPTLC densitometry depends on the specific wavelengths used to detect the analytes. In this study, the developed HPTLC plate was scanned within the UV range of wavelength 200-400 nm using a TLC scanner III (CAMAG). The optimal estimation wavelength for Trifluoperazine is chosen as 303 nm, as depicted in Fig. 3.

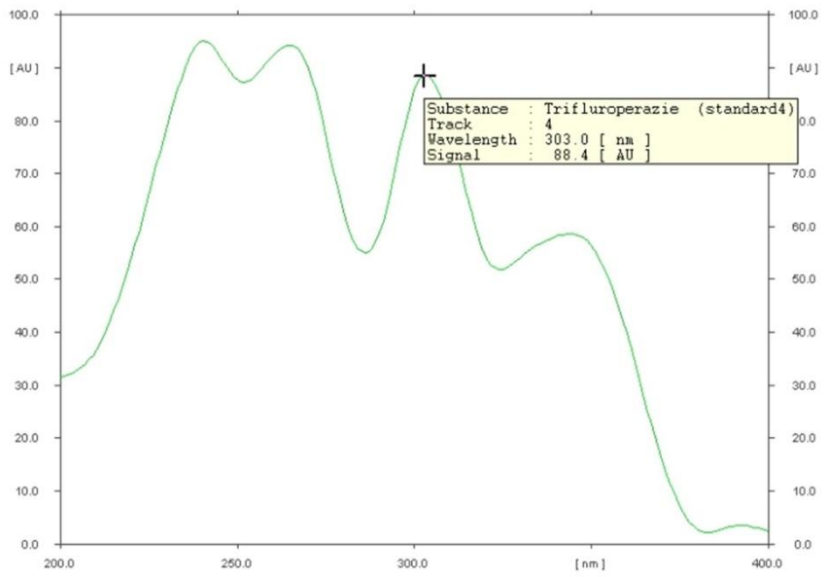


**Figure 3.** UV-Visible Spectra of Trifluoperazine

**Optimization of the method using design of experiments (DoE)**

Chromatographic parameters and their levels were selected based on previous experimental trials to determine Trifluoperazine using the HPTLC method. Toluene, methanol, ammonia, acetonitrile, formic acid, ethyl acetate, n-hexane, and glacial acetic acid are the solvents that are tested during the preliminary studies. Achieving an Rf value between 0.2 and 0.8 was the aim of the optimization process. Initial trials indicated that the mobile phase ratio and saturation time significantly affect the Rf value in HPTLC, leading to their selection for method optimization using Design of Experiments (DoE). As shown in Table 1, thirteen runs are conducted for chromatographic conditions under DoE. Once the HPTLC plates had completely dried, they are scanned at 303 nm. The final optimized chromatographic conditions included a mobile phase of methanol, ethyl acetate, and ammonia in a 9:1:0.2 (v/v/v) ratio, a saturation time of 15 minutes, a band length of 6 mm, and a solvent front of 80 mm. These conditions yielded an Rf value of 0.38 and the highest resolution. To reduce design bias, 13 experimental runs are conducted randomly. "The polynomial equation derived using Stat-Ease Design Expert software for the Rf value is presented as follows:

$$Y = -139.2237 + 31.2462A - 0.1692B - 1.7500A^2 - 0.0001B^2 + 0.0200AB,$$

where Y represents the Rf value, A denotes the mobile phase ratio, and B represents the saturation time. According to the above equation, the mobile phase (Factor A) and saturation time (Factor B) had a positive impact on the Rf value. The validation of the model was confirmed through analysis of variance (ANOVA), as shown in Table 2. The p-value was found to be 0.0012, indicating that a p-value less than 0.0500 signifies the significance of the model terms. An F-value of 14.10 indicated that the model was significant. The effects of parameters on the response are analyzed using response surface plots.

**Table 1.** Central composite design matrix for optimization of method parameters

| Std | Run | Factor A: Mobile Phase (mL) | Factor B: Saturation Time (minutes) | Response Rf value |
|---|---|---|---|---|
| 3 | 1 | 8.9 | 20 | 0.4 |
| 7 | 2 | 9 | 7.92893 | 0.34 |
| 12 | 3 | 9 | 15 | 0.38 |
| 6 | 4 | 9.14142 | 15 | 0.37 |

| | | | | |
|---|---|---|---|---|
| 1 | 5 | 8.9 | 10 | 0.32 |
| 11 | 6 | 9 | 15 | 0.38 |
| 10 | 7 | 9 | 15 | 0.38 |
| 5 | 8 | 8.85858 | 15 | 0.33 |
| 8 | 9 | 9 | 22.0711 | 0.42 |
| 2 | 10 | 9.1 | 10 | 0.29 |
| 9 | 11 | 9 | 15 | 0.38 |
| 13 | 12 | 9 | 15 | 0.38 |
| 4 | 13 | 9.1 | 20 | 0.41 |

**Table 2.** Response of ANOVA by Central composite design for Trifluoperazine

| Source | Sum of squares | df | Mean square | F-value | P-value | |
|---|---|---|---|---|---|---|
| **Model** | 0.0124 | 2 | 0.0062 | 14.10 | 0.0012 | **Significant** |
| A- Mobile Phase | 0.0002 | 1 | 0.0002 | 0.3793 | 0.5517 | |
| B-Saturation Time | 0.0123 | 1 | 0.0123 | 27.81 | 0.0004 | |
| **Residual** | 0.0044 | 10 | 0.0004 | | | |
| Lack of fit | 0.0044 | 6 | 0.0007 | | | |
| Pure Error | 0.0000 | 4 | 0.0000 | | | |
| **Cor Total** | 0.0168 | 12 | | | | |

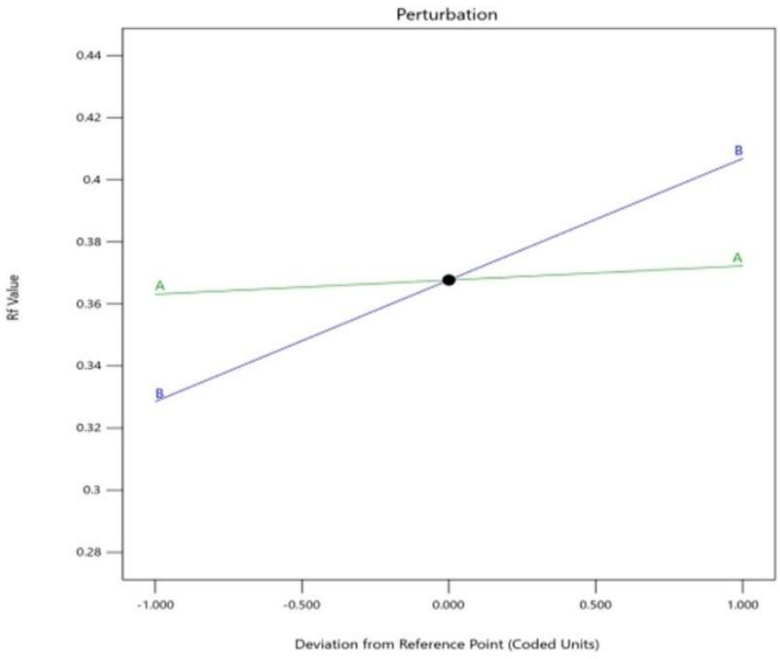


**Figure 4.** Trifluoperazine's Rf value is affected by this perturbation graph.

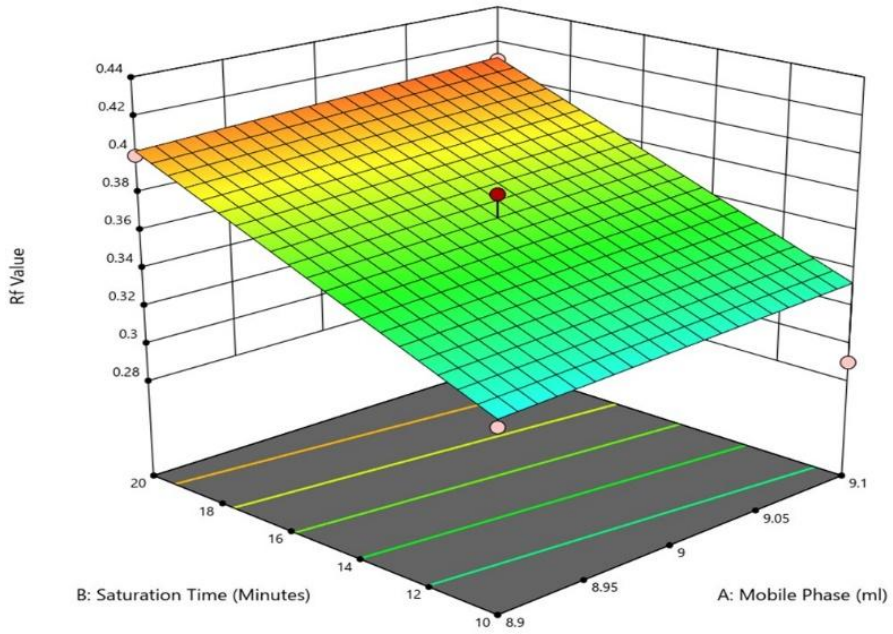


**Figure 5.** 3D surface plots showing interaction between saturation time (B) and mobile phase (A)

**Establishment of method operable design region (MODR)**

Method Operable Design Region (MODR) for analytical procedure is determined using an overlay contour plot, as shown in Fig. 6. This plot illustrates how the Rf value depends on the Mobile Phase composition (A) along the horizontal axis and Saturation Time (B) along the vertical axis. The plot reveals that variations in saturation time have a more substantial influence on the Rf value than minor adjustments to the mobile phase ratio.

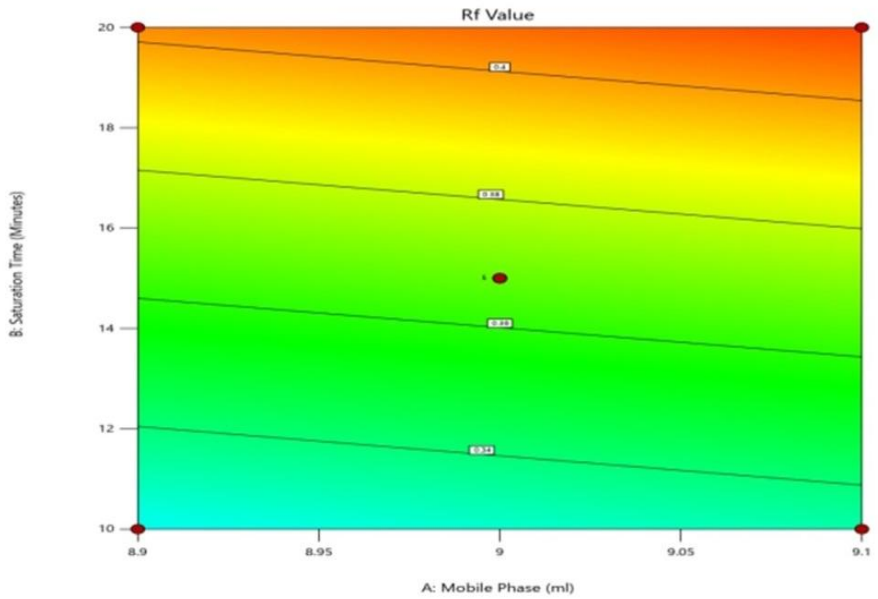


**Figure 6.** MODR plot for optimization of HPTLC method for Trifluoperazine

**Impact of saturation time and mobile phase ratio on Rf value is illustrated in the perturbation plots**

The perturbation plots in Fig. 7 illustrate the effect of mobile phase volume and saturation time on the Rf value of Trifluoperazine. 'B' plot shows a flat line and small confidence range, meaning changes in mobile phase volume have little impact. However, the plot for saturation time (Plot A) shows a rising trend and wider confidence band, indicating it strongly affects the Rf value. This highlights saturation time as a key factor for method optimization, supporting QbD principles for a reliable and consistent method.

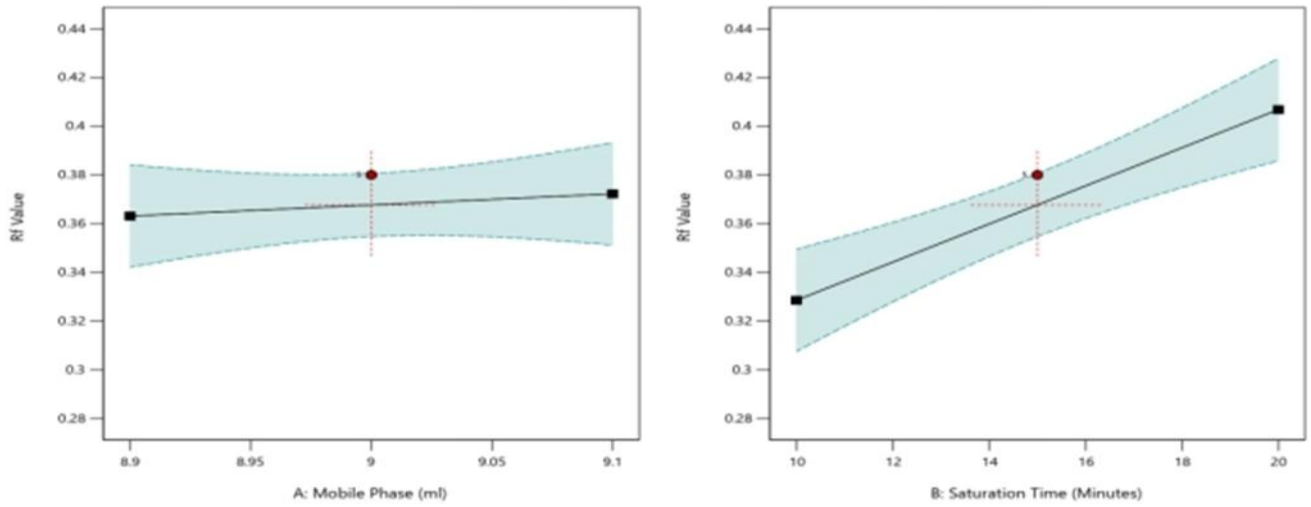


**Figure 7.** Relationship between mobile phase ratio, saturation time, and their response (Rf)

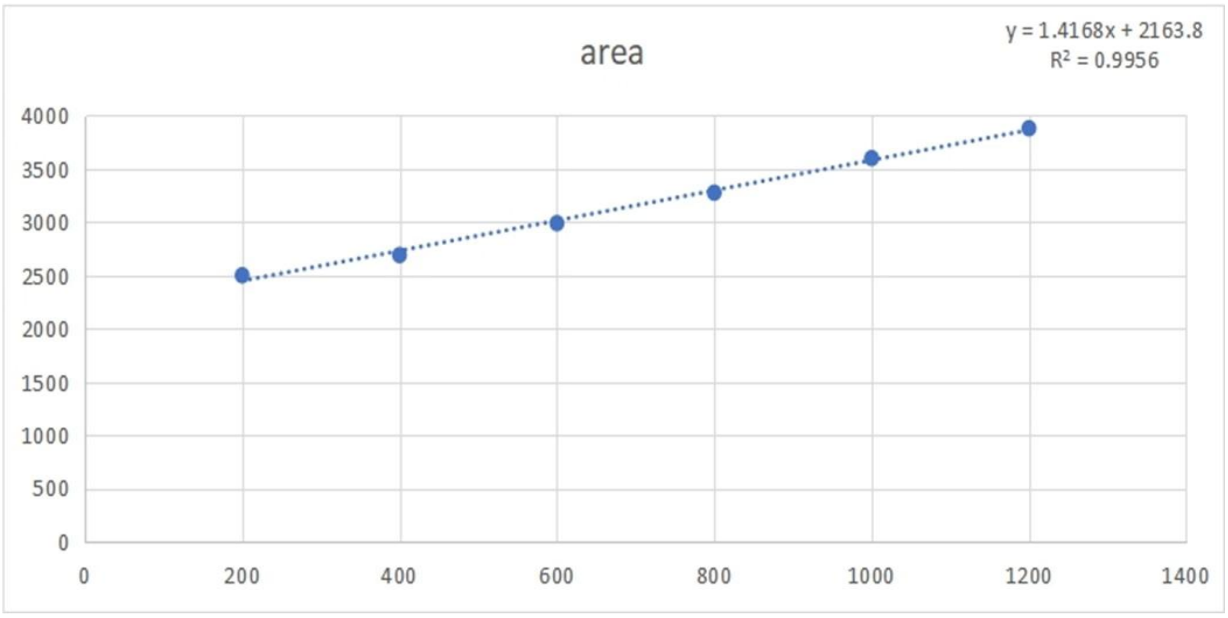


**Figure 8.** Calibration curve of Trifluoperazine

**Method validation**

Trifluoperazine concentration and peak area are found to be linearly related within the 200–1200 ng/band range. The regression coefficient ($R^2$) was found to be 0.9956, as shown in Fig. 8, indicating a strong linear relationship. The accuracy of the method was

assessed based on percentage recovery and standard deviation. Recovery values ranged from 100.30% to 101.90%, demonstrating that the method is accurate and reliable. Precision is considered acceptable when the percentage relative standard deviation (%RSD) is less than 2%. In this study, the %RSD for both intraday precision (0.94–1.42%) and interday precision (0.74–1.44%) fell within this limit, indicating good precision. Analysis confirmed that the IP content in the tablets, expressed as a percentage of the label claim, was consistent with the declared specifications. This suggests that no interference is caused by the excipients present in tablets. A drug content of 99.01 % ± 0.85 is found. The sensitivity of the method was confirmed by determining the limit of detection (LOD) and limit of quantification (LOQ), which corresponded to signal-to-noise ratios of 3:1 and 10:1, respectively. The LOD and LOQ were found to be 19.62 ng/band and 48.13 ng/band. Minor variations in wavelength and mobile phase composition are introduced to assess the robustness of the method. As the percentage relative standard deviation (%RSD) remained below 2%, the method is found to be robust. The method's specificity for Trifluoperazine is further demonstrated by spectral analysis, which verified the lack of interference from the solvent and mobile phase. Overview of the validation is presented in Table 3.

**Table 3.** Overview of Validation parameters

| Sr. No. | Validation parameters | Results |
|---|---|---|
| 1. | Linearity equation<br>$R^2$ | Y=1.4168x+ 2163.8<br>$R^2$= 0.9956 |
| 2. | Range | 200-1200 ng/band |
| 3. | Precision (% RSD) | |
| | Intra-day | 0.94 to 1.42 % |
| | Inter-day | 0.74 to 1.44 % |
| 4. | % Assay (Mean ± % RSD) | 99.01 ± 0.85 |
| 5. | Accuracy | Mean ± % RSD |
| | 80 % | 100.30 ± 0.23 |
| | 100 % | 100.34 ± 0.84 |
| | 120 % | 101.90 ± 0.50 |
| 6. | LOD | 19.62 ng/band |
| 7. | LOQ | 48.13 ng/band |
| 8. | Specificity | Specific |
| 9. | Robustness | Robust |

**Forced degradation study**

Trifluoperazine exhibited varying degrees of degradation under different stress conditions, as indicated by Densitogram showing additional peaks corresponding to degradation products. A summary of these findings is presented in Table 4. Acidic, alkaline, oxidative, neutral, thermal, and photolytic conditions resulted in degradation percentage 18.34 %, 11.61 %, 18.95 %, 13.96 %, 4.76 %, and 16.95 %, respectively, each showing distinct Rf values for the degradation products alongside the central peak of IP, as illustrated in Fig. 9,10,11,12,13 and 14 respectively.

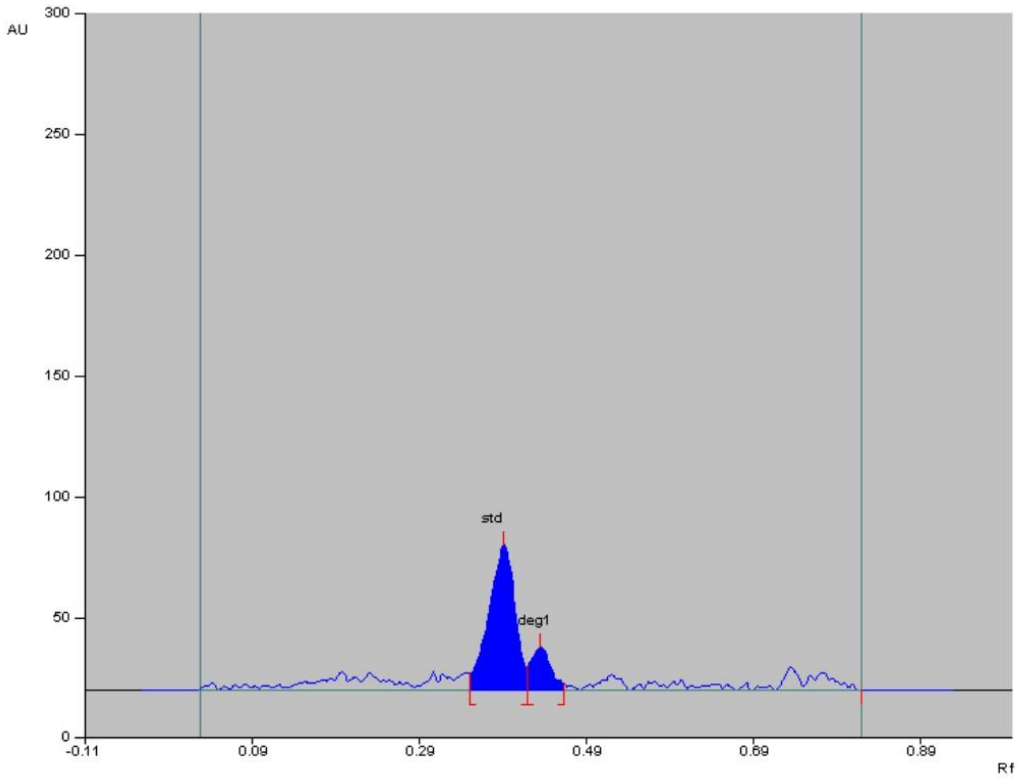


**Figure 9.** Densitogram of Acid degradation (Conc. HCl)

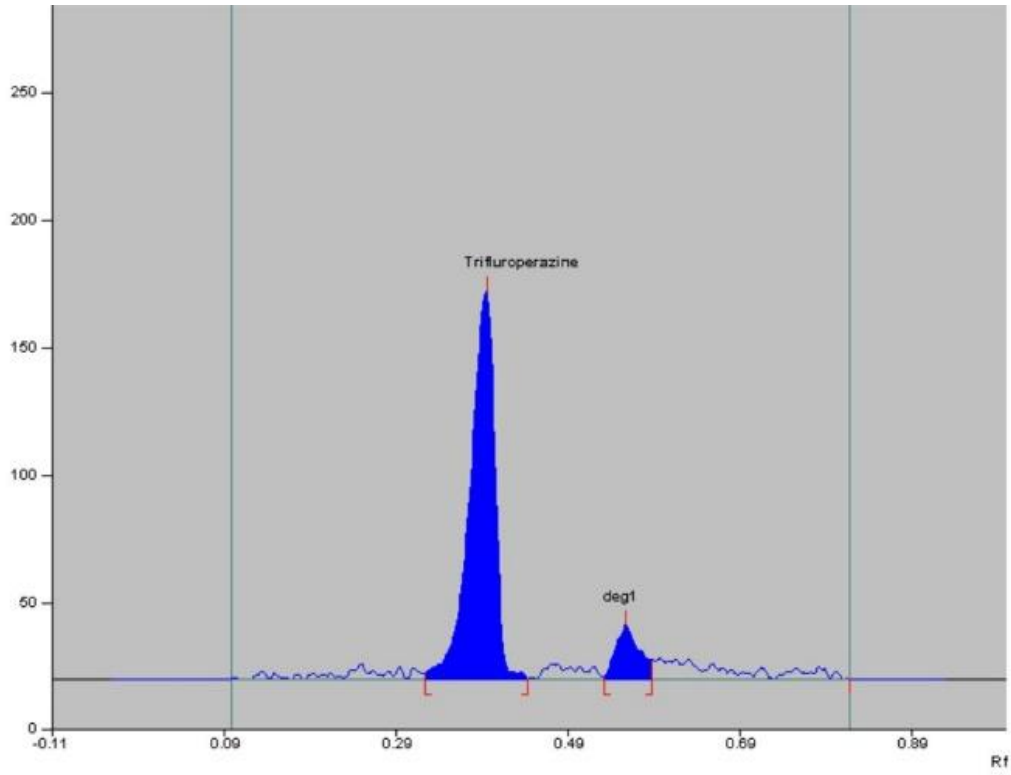


**Figure 10.** Densitogram of base degradation (NaOH)

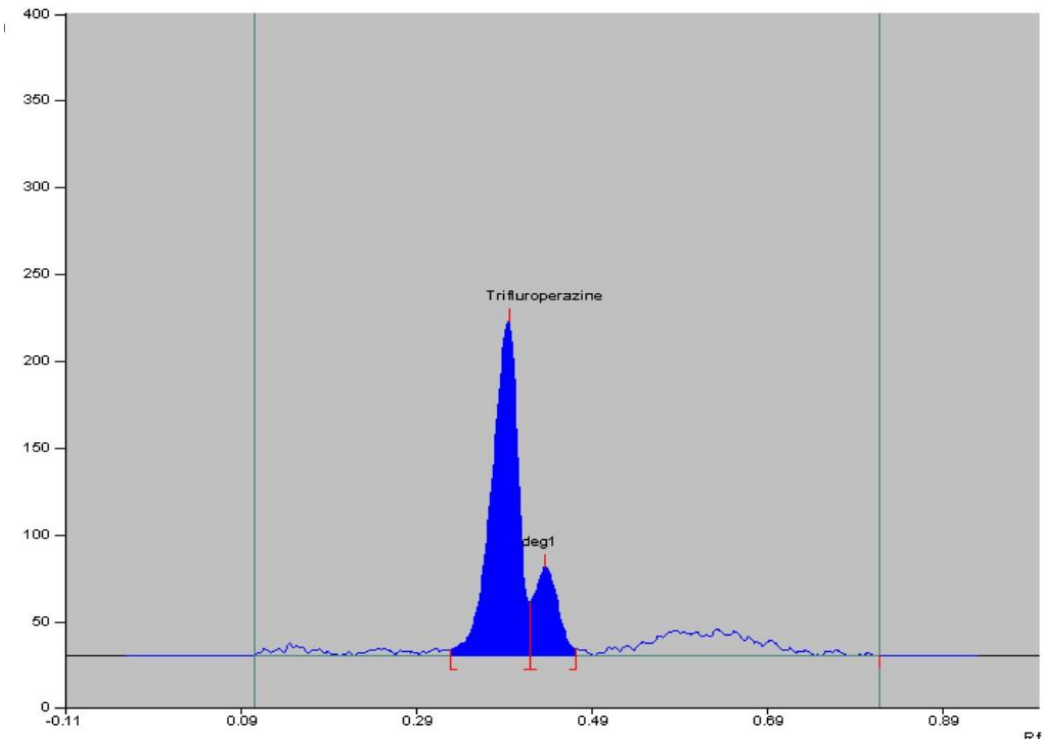


**Figure 11.** Densitogram of Oxidative degradation(H2O2)

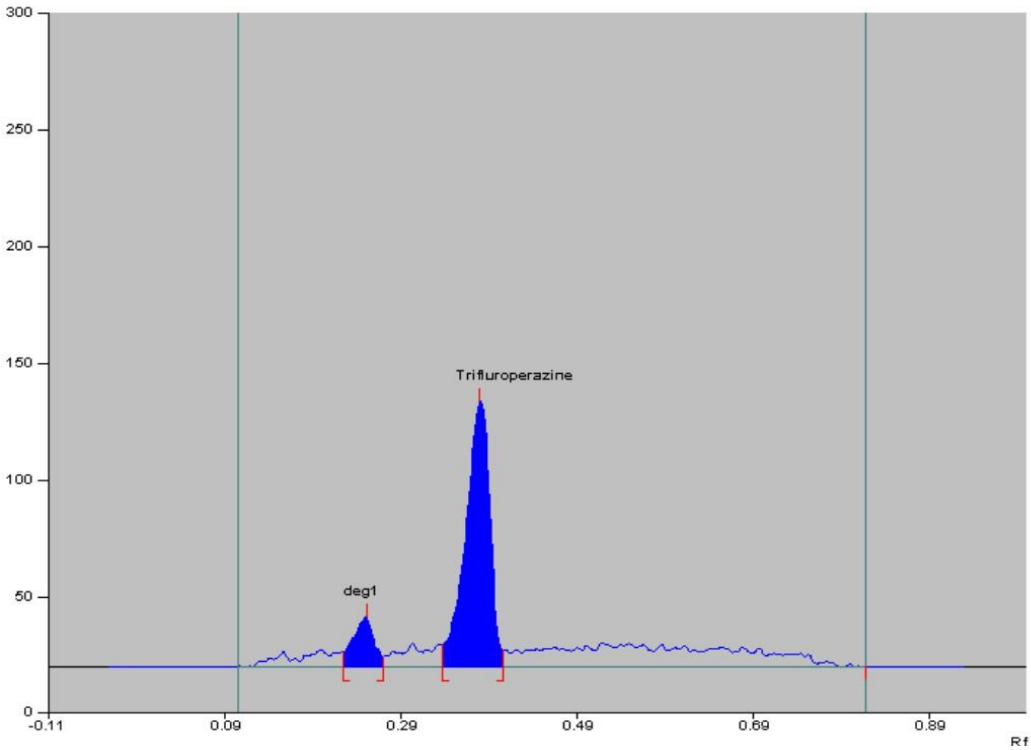


**Figure 12.** Densitogram of Neutral degradation (Dist. Water)

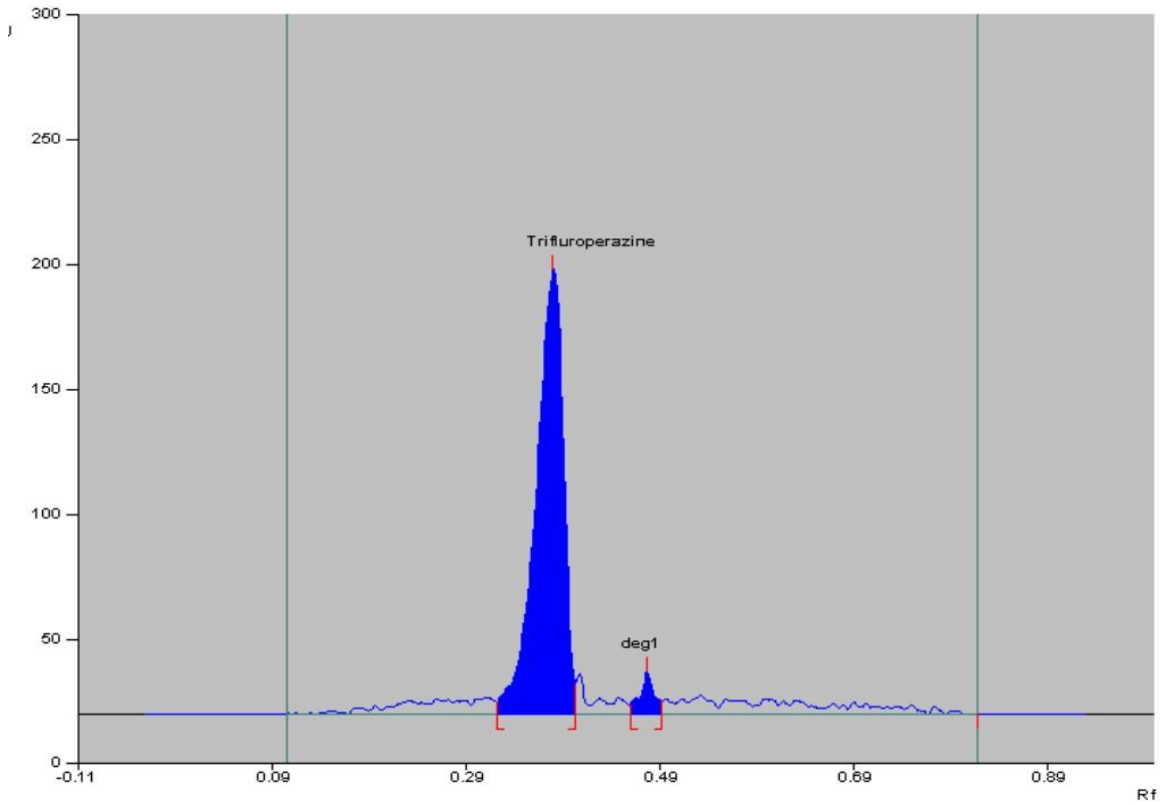


**Figure 13.** Densitogram of Thermal degradation (Oven)

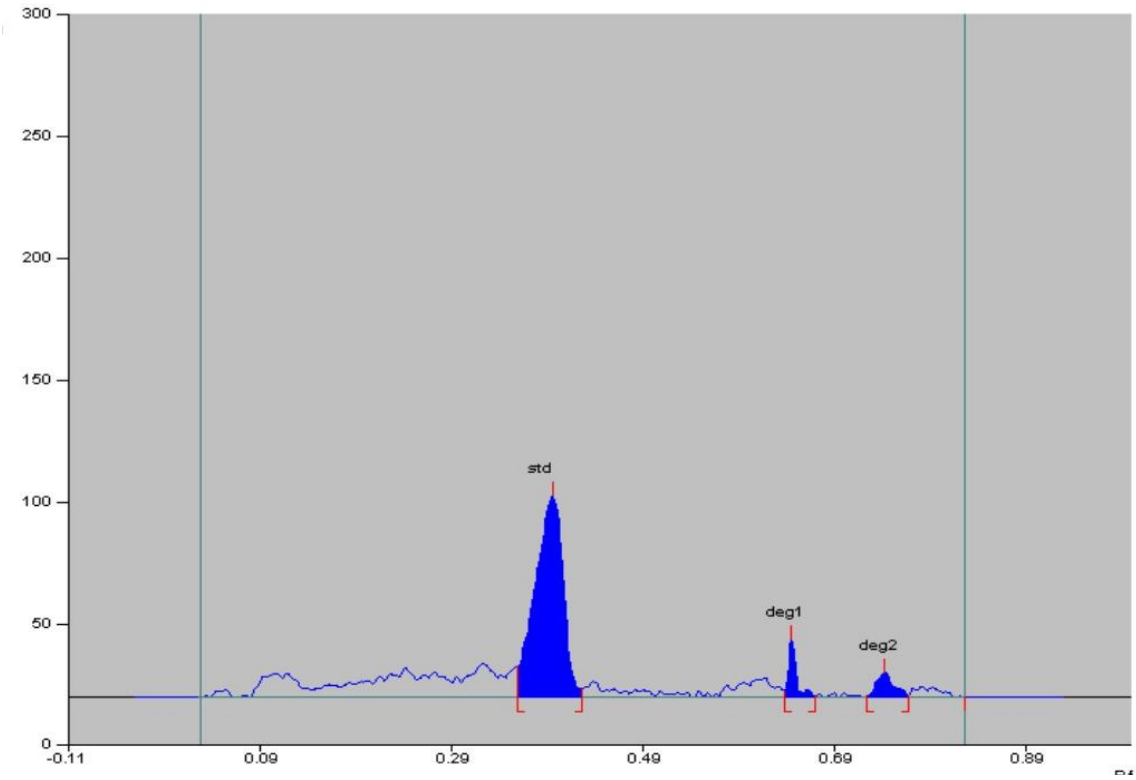


**Figure 14.** Densitogram of Photolytic degradation (UV Chamber)

**Table 4.** Summary of % degradation of standard Trifluoperazine

| Conditions | Temperature and time | Degradation % of Trifluoperazine |
|---|---|---|
| Acid (0.01N HCL) | At room temp. for 1 hr | 18.34 % |
| Base (0.01N NaOH) | At room temp. for 1hr | 11.61 % |
| Oxidative (3 % H2O2) | At room temp. for 1hr | 18.95 % |
| Neutral | At room temp. for 1 hr | 13.96 % |
| Thermal | 60°C for 1 hr | 4.76 % |
| Photolytic | UV Chamber for 24hr | 8.81 %, 16.95 % |

## 4. CONCLUSION

This research successfully demonstrates the application of the Quality by Design (QbD) framework in developing and validating a high-performance thin layer chromatography (HPTLC) method for the qualitative assessment of Trifluoperazine in both bulk and tablet forms. Optimization of critical method parameters (CMPs), such as saturation time and mobile phase composition, using a central composite design (CCD) approach, led to the development of a robust and reliable chromatographic method. The developed method exhibited excellent linearity ($r^2$ = 0.9956), precision, accuracy, and sensitivity, a well-defined retention factor (Rf = 0.38) and favorable detection and quantification limits. The validation adhered to ICH guidelines, ensuring the method's reliability for routine quality control analysis. Overall, the study underscores the effectiveness of the Quality by Design (QbD) approach in enhancing analytical method development, leading to a precise, accurate, and robust HPTLC method for the evaluation of Trifluoperazine.

**Acknowledgements**

The authors express their gratitude to the Principal of Abhinav Education Society's College of Pharmacy, Narhe, Pune, for their support. They also extend their appreciation to the Principal of Dr. D.Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune, for providing access to the HPTLC facility.

**Authors' Contributions**

*Shweta Bharti*: Conducted experimental work, data acquisition, and initial data analysis, manuscript drafting
*Madhuri S. Nalawade*: Contributed to data interpretation and literature review.
*Kumudini R. Pawar*: Conceived the study, designed the experimental setup, supervised the research and reviewed the final manuscript.
All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

**Ethical Approval**

Not applicable. This article does not contain any studies with human participants or animals performed by any of authors.

**Informed Consent**

Not applicable.

**Conflicts of interests**

The authors declare that there are no conflicts of interests.

**Funding**

This study has not received any external funding.

**Data and materials availability**

All data associated with this study are present in the paper.

## REFERENCES


1. Calnan N, O'Donnell K, Greene A. Enabling ICH Q10 Implementation--Part 1. Striving for Excellence by Embracing ICH Q8 and ICH Q9. PDA J Pharm Sci Technol. 2013 Nov-Dec;67(6):581-600. doi: 10.5731/pdajpst.2013.00940.
2. Chatterjee I, Chatterjee S. Investigating the symptomatic and morphological changes in the brain based on pre and post-treatment: A critical review from clinical to neuroimaging studies on schizophrenia. IBRO Neurosci Rep. 2023 Mar 24;14:366-374. doi: 10.1016/j.ibneur.2023.03.008.
3. Chen H, Wang R, McElderry JD. Discriminative Dissolution Method Development Through an aQbD Approach. AAPS PharmSciTech. 2023 Dec 8;24(8):255. doi: 10.1208/s12249-023-02692-8.
4. Chong HY, Teoh SL, Wu DB, Kotirum S, Chiou CF, Chaiyakunapruk N. Global economic burden of schizophrenia: a systematic review. Neuropsychiatr Dis Treat. 2016 Feb 16;12:357-73. doi: 10.2147/NDT.S96649
5. Cleary Y, Milani N, Ogungbenro K, Aarons L, Galetin A, Gertz M. Simultaneous Estimation of fm and FG Values Directly from Clinical Drug-Drug Interaction Study Data. AAPS J. 2025 Apr 29;27(4):83. doi: 10.1208/s12248-025-01064-3. Erratum in: AAPS J. 2025 May 16;27(4):92. doi: 10.1208/s12248-025-01081-2.
6. Dai W, Hu L, Ji L, Li J, Bi K, Li Q. A Comprehensive Method for Quality Evaluation of Houttuyniae Herba by a Single Standard to Determine Multi-components, Fingerprint and HPTLC Method. Anal Sci. 2015;31(6):535-41. doi: 10.2116/analsci.31.535.
7. Maia L. Experimental dataset from a central composite design with two qualitative independent variables to develop high strength mortars with self-compacting properties. Data Brief. 2021 Dec 21;40:107738. doi: 10.1016/j.dib.2021.107738.
8. Meyer U, Schwarz MJ, Muller N. Inflammatory processes in schizophrenia: a promising neuroimmunological target for the treatment of negative/cognitive symptoms and beyond. Pharmacol Ther. 2011 Oct;132(1):96-110. doi: 10.1016/j.pharmthera.2011.06.003.
9. Muppayyanamath A, Harish DR, Mastiholimath V, Patil PP, Patil VS, Hegde HV, Roy S. Quality by design-based optimization and HP-TLC densitometric standardization of Theobroma cacao L. extract as a nutraceutical supplement. Front Nutr. 2025 Apr 9;12:1537963. doi: 10.3389/fnut.2025.1537963.
10. Ohage E, Iverson R, Krummen L, Taticek R, Vega M. QbD implementation and Post Approval Lifecycle Management (PALM). Biologicals. 2016 Sep;44(5):332-40. doi: 10.1016/j.biologicals.2016.06.007.
11. Onyeogaziri FC, Papaneophytou C. A General Guide for the Optimization of Enzyme Assay Conditions Using the Design of Experiments Approach. SLAS Discov. 2019 Jun;24(5):587-596. doi: 10.1177/2472555219830084.
12. Prajapati PB, Jayswal K, Shah SA. Application of Quality Risk Assessment and DoE-Based Enhanced Analytical Quality by Design Approach to Development of Chromatography Method for Estimation of Combined Pharmaceutical Dosage Form of Five Drugs. J Chromatogr Sci. 2021 Aug 18;59(8):714-729. doi: 10.1093/chromsci/bmaa118.
13. Pramod K, Tahir MA, Charoo NA, Ansari SH, Ali J. Pharmaceutical product development: A quality by design approach. Int J Pharm Investig. 2016 Jul-Sep;6(3):129-38. doi: 10.4103/2230-973X.187350.
14. Simeoni P, Deissler M, Bienert R, Gritsch M, Nerkamp J, Kirsch S, Roesli C, Pohl T, Anderka O, Gellermann G. Using enhanced development tools offered by analytical Quality by Design to support switching of a quality control method. Biotechnol Bioeng. 2023 Nov;120(11):3299-3310. doi: 10.1002/bit.28517.
15. Stepnicki P, Kondej M, Kaczor AA. Current Concepts and Treatments of Schizophrenia. Molecules. 2018 Aug 20;23(8):2087. doi: 10.3390/molecules23082087
16. Tamizi E, Jouyban A. Forced degradation studies of biopharmaceuticals: Selection of stress conditions. Eur J Pharm Biopharm. 2016 Jan;98:26-46. doi: 10.1016/j.ejpb.2015.10.016.
17. VanDuyse SA, Fulford MJ, Bartlett MG. ICH Q10 Pharmaceutical Quality System Guidance: Understanding Its Impact on Pharmaceutical Quality. AAPS J. 2021 Nov 12;23(6):117. doi: 10.1208/s12248-021-00657-y.
18. Williams HE, Bright J, Roddy E, Poulton A, Cosgrove SD, Turner F, Harrison P, Brookes A, MacDougall E, Abbott A, Gordon C. A comparison of drug substance predicted chemical stability with ICH compliant stability studies. Drug Dev Ind Pharm. 2019 Mar;45(3):379-386. doi: 10.1080/03639045.2018.1542707.
19. Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, Woodcock J. Understanding pharmaceutical quality by design. AAPS J. 2014 Jul;16(4):771-83. doi: 10.1208/s12248-014-9598-3.7.
20. Zolotareva, D.; Zazybin, A.; Belyankova, Y.; Bayazit, S.; Dauletbakov, A.; Seilkhanov, T.; Kemelbekov, U.; Aydemir, M. Heterocyclic Antidepressants with Antimicrobial and Fungicide Activity. Molecules 2025, 30, 1102. doi:10.3390/molecules30051102