

Development and Validation of a Stability- Indicating UPLC Method for Assay of Tegoprazon Pharmaceutical Formulations

K Vinodh Kumar¹, V. Girija Sastry²

^{1,2}A.U.College of Pharmaceutical Sciences Andhra University Visakhapatnam 53003.

Email ID:-vinodh.mph@gmail.com , vgirijasastry@yahoo.co.in

***Corresponding Author**

Prof. V. Girija Sastry

A.U.College of Pharmaceutical Sciences Andhra University Visakhapatnam 53003.

EmailId: vgirijasastry@yahoo.co.in

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ABSTRACT

A simple, rapid, accurate, and stability-indicating Ultra-Performance Liquid Chromatography (UPLC) method was developed and validated for the quantitative determination of Tegoprazan in bulk drug and pharmaceutical tablet formulations. The chromatographic separation was achieved using an Agilent Eclipse Plus C18 column (100mm × 4.6mm, 3.5µm) with a mobile phase consisting of ammonium formate buffer (pH 2.5) and acetonitrile in a 60:40 v/v ratio. The method was operated at a flow rate of 0.5mL/min with an injection volume of 5µL, and detection was performed at 249nm using a Photodiode Array detector. The total run time was 3.0 minutes, and Tegoprazan eluted at a retention time of approximately 1.236 minutes. The method was validated according to ICH Q2(R2) guidelines for specificity, system precision, linearity, accuracy, precision, sensitivity, robustness, and forced degradation studies. The system precision showed excellent reproducibility with a %RSD of 0.68. The method demonstrated excellent linearity over a concentration range of 25-150µg/mL with a correlation coefficient (R^2) of 0.99988. Accuracy results ranged from 99.3% to 100.4%, confirming the method's reliability. The limit of detection (LOD) and limit of quantification (LOQ) were determined as 0.30µg/mL and 1.00µg/mL, respectively. Method precision and intermediate precision showed %RSD values of 0.80% and 0.69%, respectively, within the acceptance criteria. Robustness studies confirmed that the method was unaffected by deliberate variations in flow rate and organic phase composition. Forced degradation studies revealed that Tegoprazan was most susceptible to oxidative degradation (14.2%), followed by acid degradation (12.8%), thermal degradation (11.9%), and alkali degradation (9.5%), with minimal degradation under reductive (1.6%) and photolytic (0.9%) conditions. The purity angles were consistently lower than purity thresholds for all degradation conditions, confirming the stability-indicating nature of the method. The developed method was successfully applied to assay commercial PCAB 50 tablets, showing a mean assay value of 99.2% of the label claim. The method is simple, cost-effective, and suitable for routine quality control and stability analysis of Tegoprazan in pharmaceutical formulations.

Keywords: Tegoprazan, UPLC, Method Validation, Stability-Indicating, Forced Degradation, Pharmaceutical Formulation, Potassium-Competitive Acid Blocker, Quality Control

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1.INTRODUCTION

Acid-related gastrointestinal disorders, including gastroesophageal reflux disease (GERD) and erosive esophagitis, represent a significant global health burden, with an estimated prevalence of GERD alone ranging from 8 % to 33 % worldwide[1][2]. The cornerstone of pharmacological management for these conditions has traditionally been proton pump inhibitors (PPIs), which irreversibly inhibit the gastric $H^+/K^+-ATPase$ enzyme[3]. However, PPIs are associated with several inherent limitations, including a slow onset of action, the requirement for acid-mediated activation, inadequate control of nocturnal acid breakthrough, and significant inter-individual variability in response[4][5]. These

shortcomings have driven the search for novel therapeutic agents that can offer more rapid, consistent, and prolonged gastric acid suppression. Tegoprazan (also known as CJ-12420) is a novel, orally active, highly selective, and potent potassium-competitive acid blocker (P-CAB) that has emerged as a promising alternative to conventional PPIs[6][7]. Unlike PPIs, tegoprazan acts as a reversible inhibitor of the gastric $H^+/K^+-ATPase$ by competitively binding to the potassium-binding site, independent of acid activation. This unique mechanism enables a rapid onset of action and sustained acid suppression, maintaining intragastric $pH \geq 4$ for approximately 72 % of a 24-hour period. Furthermore, tegoprazan's efficacy is not influenced by food intake, and its pharmacokinetic profile remains

stable across different CYP2C19 genotypes[8][9]. Since its initial approval in South Korea in 2018 for treating erosive esophagitis, tegoprazan has been increasingly utilized for managing various acid-related diseases[10][11]. Given the clinical importance of tegoprazan and its susceptibility to degradation under stress conditions, the development of a robust, stability-indicating analytical method is essential for ensuring the quality, efficacy, and safety of its pharmaceutical formulations. Forced degradation studies have demonstrated that tegoprazan is unstable under acidic, alkaline, and oxidative conditions, leading to the identification of eight degradation products[12][13]. A stability-indicating method capable of separating the active pharmaceutical ingredient from its degradation products is therefore critical for routine quality control and stability monitoring[14]. UPLC offers significant advantages over conventional HPLC, including enhanced resolution, superior sensitivity, and substantially reduced analysis time, making it an ideal tool for high-throughput quality control in the pharmaceutical industry. The development of a UPLC method that is not only accurate and precise but also stability-indicating would address the current analytical gap and provide a more efficient tool for the routine quality assessment of tegoprazan products[15-17]. The present study was therefore undertaken with the objective of developing and validating a novel, simple, rapid, and stability-indicating UPLC method for the quantitative determination of tegoprazan in bulk drug and its pharmaceutical tablet formulations. The method was developed following a systematic optimization of chromatographic parameters and was rigorously validated in accordance with the International Council for Harmonisation (ICH) Q2(R2) guidelines[18][19]. The validation encompassed specificity, system precision, linearity, accuracy, precision, sensitivity (limit of detection and limit of quantification), robustness, and forced degradation studies to confirm its stability-indicating nature. The successful development of this method is expected to provide a reliable and efficient analytical tool for routine quality control and stability analysis of tegoprazan in pharmaceutical dosage forms[20].

MATERIALS AND METHODS

Instrumentation and Chromatographic Conditions

The analytical method was developed and validated using a Waters Acquity Ultra-Performance Liquid Chromatography (UPLC) system equipped with quaternary pumps and a Photodiode Array (PDA) detector. Data acquisition and processing were performed using Empower software version 2.0. The chromatographic separation was achieved on an Agilent Eclipse Plus C18 column with dimensions of 100mm × 4.6mm and a particle size of 3.5µm. The detection wavelength was set at 249nm, which was determined to be the maximum absorbance wavelength for Tegoprazan through PDA scanning of the standard analyte solution.

Chemicals, Reagents, and Samples

High-performance liquid chromatography grade acetonitrile, formic acid, ammonium formate, and purified

water were procured from Merck India Ltd., Mumbai. The Tegoprazan reference standard and placebo were obtained from Dr. Reddy's Laboratories Ltd., Hyderabad. The commercial formulation used for analysis was PCAB 50 tablets, with a label claim of 50mg Tegoprazan per tablet, procured from a local medical store.

Buffer and Mobile Phase Preparation

The buffer solution was prepared by accurately weighing 1.26g of ammonium formate and transferring it to a 1000mL volumetric flask. Approximately 700mL of water was added to dissolve the salt completely, and the volume was made up to 1000mL with water. The pH of the resulting 20mM ammonium formate buffer was adjusted to 2.5 using formic acid. The mobile phase consisted of ammonium formate buffer (pH 2.5) and acetonitrile in a 60:40 v/v ratio. The mixture was thoroughly mixed, sonicated for 15 minutes, and filtered through a 0.22µm membrane filter before use. Pure acetonitrile (100%) was used as the diluent throughout the study.

Standard and Sample Solution Preparation

The standard stock solution was prepared by accurately weighing 50mg of Tegoprazan working standard into a 50mL volumetric flask. Approximately 20mL of diluent was added, and the solution was sonicated to ensure complete dissolution, followed by making up the volume to the mark with diluent to obtain a concentration of 1000ppm. The working standard solution (100ppm) was prepared by pipetting 5mL of the stock solution into a 50mL volumetric flask and diluting to volume with diluent. For sample preparation, tablets equivalent to 50mg of Tegoprazan were accurately weighed and transferred to a volumetric flask. Thirty milliliters of diluent were added, and the mixture was sonicated for 30 minutes to dissolve all components. The volume was made up with diluent, and 5mL of this sample stock solution was pipetted into a 50mL volumetric flask and diluted to volume. The final solution was filtered through a 0.22µm nylon syringe filter prior to injection.

Method Development and Optimization

Method development involved systematic optimization trials with various chromatographic parameters. Initial trials using a Phenyl column (100mm × 2.1mm, 1.7µm) with different mobile phase compositions of acetonitrile and 0.1% formic acid yielded unsatisfactory peak shapes and retention times. Subsequent trials with the Agilent Eclipse Plus C18 column using acetonitrile and ammonium formate buffer (pH 2.5) in varying ratios were evaluated. The optimized conditions were achieved with a mobile phase composition of acetonitrile and ammonium formate buffer in a 40:60 v/v ratio, a flow rate of 0.5mL/min, an injection volume of 5µL, a run time of 3.0 minutes, and a detection wavelength of 249nm. Under these optimized conditions, Tegoprazan exhibited a retention time of approximately 1.236 minutes with excellent peak symmetry (USP tailing factor of 0.98) and high column efficiency (USP plate count of 8054).

Method Validation Parameters

Development and Validation of a Stability- Indicating UPLC Method for Assay of Tegoprazon Pharmaceutical Formulations

The developed UPLC method was comprehensively validated according to ICH guidelines for specificity, system precision, linearity, accuracy, precision, sensitivity, robustness, and forced degradation studies. Specificity was assessed by injecting blank, placebo, standard, and sample solutions to confirm no interfering peaks at the analyte retention time. System precision was evaluated through six replicate injections of the standard solution, with acceptance criteria of %RSD not more than 2.0%, USP plate count not less than 2000, and USP tailing factor not more than 2.0.

Linearity was established across a concentration range of 25-150µg/mL. Six different concentration levels (25, 50, 75, 100, 125, and 150ppm) were prepared from the stock solutions using appropriate dilutions. The correlation coefficient was determined by plotting peak area against concentration. Accuracy was assessed using the standard addition method at three concentration levels: 50%, 100%, and 150% of the target assay concentration. Each level was prepared by spiking known amounts of Tegoprazon (25mg, 50mg, and 75mg respectively) onto placebo (115mg) in 50mL volumetric flasks, and the percentage recovery was calculated.

Method precision was determined by analyzing six samples from a single batch, while intermediate precision was evaluated by analyzing six samples on a different day by a different analyst. The limit of detection (LOD) and limit of quantification (LOQ) were calculated using the equations $LOD = 3.3 \times \sigma/s$ and $LOQ = 10 \times \sigma/s$, where σ is the standard deviation of the response and s is the slope of the calibration curve. LOQ precision was verified by six replicate injections at the LOQ level.

Robustness was evaluated by deliberately varying chromatographic parameters including flow rate (0.45mL/min and 0.55mL/min) and organic phase composition (36:64 and 44:56 ratios). Forced degradation studies were conducted to assess the stability-indicating nature of the method. Acid degradation was performed using 1N HCl for 30 minutes followed by neutralization with 1N NaOH. Alkali degradation employed 1N NaOH for 30 minutes with subsequent neutralization using 1N HCl. Oxidative degradation was carried out with 10% hydrogen peroxide for 30 minutes, while reductive degradation utilized 10% sodium bisulphite for 30 minutes. Thermal degradation was performed by exposing the drug at 105°C for 6 hours, and photolytic degradation was conducted in a photo stability chamber for 3 days. The percentage degradation and purity angles were calculated for each stress condition.

RESULT & DISCUSSION

Method Development and Optimization

The development of the UPLC method for Tegoprazon involved systematic optimization of chromatographic parameters to achieve satisfactory peak characteristics and separation efficiency. Initial trials using a Phenyl column with acetonitrile and 0.1% formic acid mobile phase yielded unsatisfactory results with poor peak shapes and inappropriate retention times. The selection of an appropriate stationary phase proved critical, as the Agilent Eclipse Plus C18 column (100mm × 4.6mm, 3.5µm) demonstrated superior performance due to its excellent mechanical stability, favorable physicochemical characteristics, and compatibility with various organic solvents. The transition from Phenyl to C18 column significantly improved peak symmetry and column efficiency. The buffer selection was equally important; ammonium formate buffer at pH 2.5 was chosen over phosphoric acid buffers as it provided better peak separation and symmetry while maintaining compatibility with the UPLC system. The mobile phase composition was optimized through multiple trials, with the final ratio of ammonium formate buffer (pH 2.5) and acetonitrile at 60:40 v/v providing the best resolution and peak shape. The optimized method achieved a retention time of 1.236 minutes, demonstrating rapid analysis capability suitable for high-throughput quality control applications.

SPECIFICITY

The specificity of the developed method was established by analyzing blank, placebo, standard, and sample solutions. The chromatograms revealed no interfering peaks at the retention time of Tegoprazon (1.236 minutes), confirming the method's ability to accurately quantify the drug in the presence of excipients and other matrix components. The blank and placebo injections showed clean baselines without any significant peaks that could interfere with the analyte detection. The standard and sample chromatograms exhibited symmetric peaks at the same retention time, with comparable peak shapes and areas. The PDA spectral analysis of the Tegoprazon peak in both standard and sample solutions showed identical spectra, further confirming the specificity of the method. This high specificity ensures that the method can reliably determine Tegoprazon content in pharmaceutical formulations without interference from formulation excipients or degradation products.

Table 1: Specificity Results

Parameter	Blank	Placebo	Standard	Sample
Retention Time (min)	-	-	1.236	1.236
Interference at Rt	None	None	-	-
Peak Purity	-	-	Pass	Pass

SYSTEM PRECISION

System precision was evaluated by performing six replicate injections of the standard solution at 100ppm concentration. The results demonstrated excellent reproducibility with a %RSD of 0.68, well within the acceptance criterion of not more than 2.0%. The USP plate count was determined to be 8054, significantly exceeding the minimum requirement of 2000, indicating high column efficiency. The USP tailing factor was 0.98, which is

within the acceptable limit of not more than 2.0, confirming excellent peak symmetry. These results indicate that the chromatographic system is highly precise and capable of producing consistent results, which is essential for reliable quantitative analysis. The low variability in peak areas across six injections demonstrates the method's suitability for routine quality control applications where reproducibility is paramount

Table 2: System Precision Results

Injection No.	Concentration (µg/mL)	Area
1	100	2670144
2	100	2639121
3	100	2650548
4	100	2639131
5	100	2684045
6	100	2649612
Mean		2655434
Standard Deviation		18025.78
%RSD		0.68

LINEARITY AND RANGE

The linearity of the method was established across a concentration range of 25-150µg/mL using six different concentration levels. The calibration curve was constructed by plotting peak area against concentration, and the results demonstrated excellent linearity with a correlation coefficient (R^2) of 0.99988. The regression equation was determined as $y = 26070.83x + 12667.21$, where y represents the peak area and x represents the concentration of Tegoprazan. The high correlation

coefficient close to unity indicates a strong linear relationship between the drug concentration and detector response across the tested range. The linearity data showed consistent responses at all concentration levels, with peak areas increasing proportionally with concentration. The method demonstrated excellent sensitivity, with the regression line passing close to the origin, indicating minimal systematic error. This broad linear range makes the method suitable for analyzing various dosage strengths and formulations

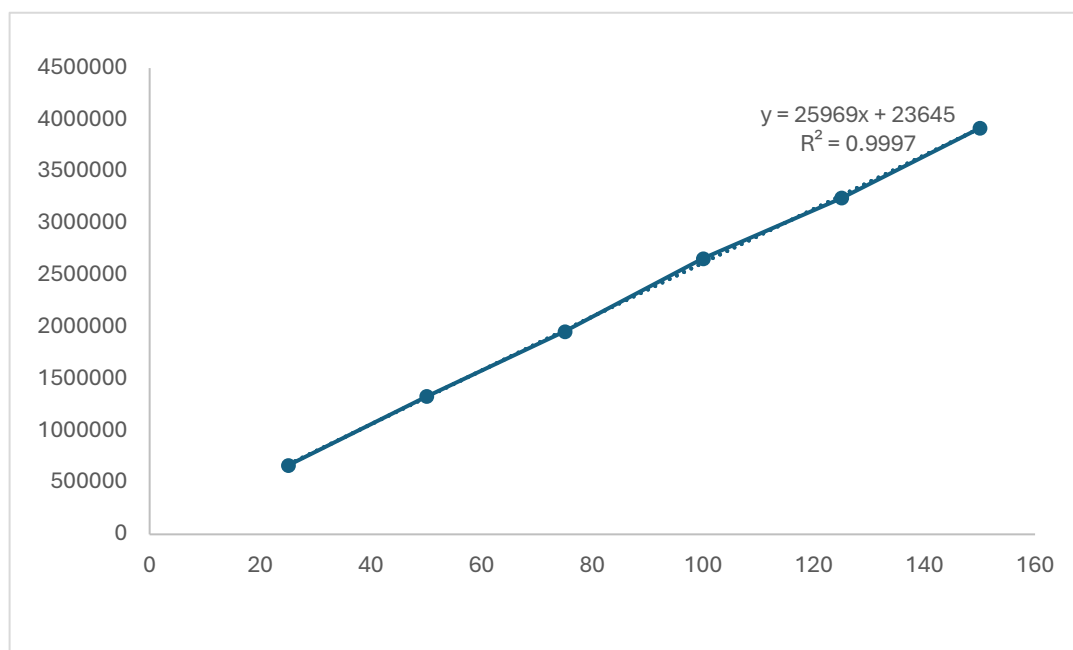


Figure 1: Calibration Curve of Tegoprazan

Table 3: Linearity Data

Level	Concentration (µg/mL)	Area
1	25.00	665060
2	50.00	1330122
3	75.00	1955461
4	100.00	2660243
5	125.00	3245327
6	150.00	3919641
Correlation Coefficient		0.99988
Slope		26070.83
Intercept		12667.21

ACCURACY

The accuracy of the method was assessed using the standard addition method at three concentration levels: 50%, 100%, and 150% of the target assay concentration. Recovery experiments were performed by spiking known amounts of Tegoprazan (25mg, 50mg, and 75mg) onto placebo (115mg). The percentage recovery ranged from 99.3% to 100.4%, with all values falling within the acceptance criteria of 98-102%. At the 50% level, the recoveries were 100.4%, while the 100% level showed recoveries of 99.8%, and the 150% level demonstrated recoveries of 99.3%. The consistent recovery values

across all levels indicate that the method is free from matrix interference and provides accurate quantification of Tegoprazan in pharmaceutical formulations. The mean recovery values close to 100% confirm the method's accuracy and its ability to accurately measure the drug content without systematic bias. The absence of significant variation in recoveries across the three levels demonstrates the method's reliability throughout the concentration range

Table 4: Accuracy Results

Level (%)	Amount Added (mg)	Amount Recovered (mg)	% Recovery
50	25	25.04	100.4
50	25	25.25	100.4

50	25	25.02	100.4
100	50	50.09	99.8
100	50	49.69	99.8
100	50	49.90	99.8
150	75	74.74	99.3
150	75	74.53	99.3
150	75	74.08	99.3

METHOD PRECISION AND INTERMEDIATE PRECISION

Method precision was determined by analyzing six samples from a single batch under the same conditions. The %RSD for the assay results was 0.80, well within the acceptance criterion of not more than 2.0%. The individual assay values ranged from 98.7% to 100.8%, demonstrating excellent repeatability of the method. The consistent results indicate that the method is capable of producing reproducible outcomes when the same sample is analyzed multiple times under identical conditions.

Intermediate precision was assessed by analyzing six samples on a different day by a different analyst, yielding a %RSD of 0.69. The close agreement between method precision and intermediate precision results indicates that the method is robust and not significantly affected by minor variations in operational parameters, analyst performance, or environmental conditions. The low variability observed in both precision studies confirms the method's reliability for routine pharmaceutical analysis

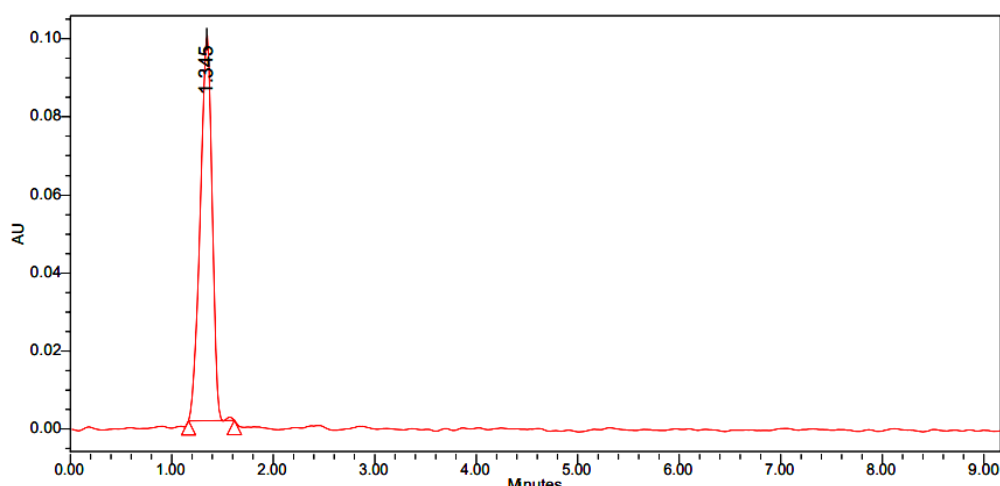


Figure 2: Representative Chromatograms of Method Precision Injections

SENSITIVITY (LOD AND LOQ)

The limit of detection (LOD) and limit of quantification (LOQ) were determined using the standard deviation of the response and the slope of the calibration curve. The LOD was calculated as $0.30\mu\text{g/mL}$ using the equation $\text{LOD} = 3.3 \times \sigma/s$, while the LOQ was determined as $1.00\mu\text{g/mL}$ using the equation $\text{LOQ} = 10 \times \sigma/s$. These low values indicate that the method is highly sensitive

and capable of detecting and quantifying trace amounts of Tegoprazan. The LOQ precision was verified by six replicate injections at the LOQ level, which showed a %RSD of 1.29, within the acceptable limit of not more than 20%. The excellent sensitivity makes the method suitable for applications requiring detection of low drug concentrations, such as stability studies and impurity profiling

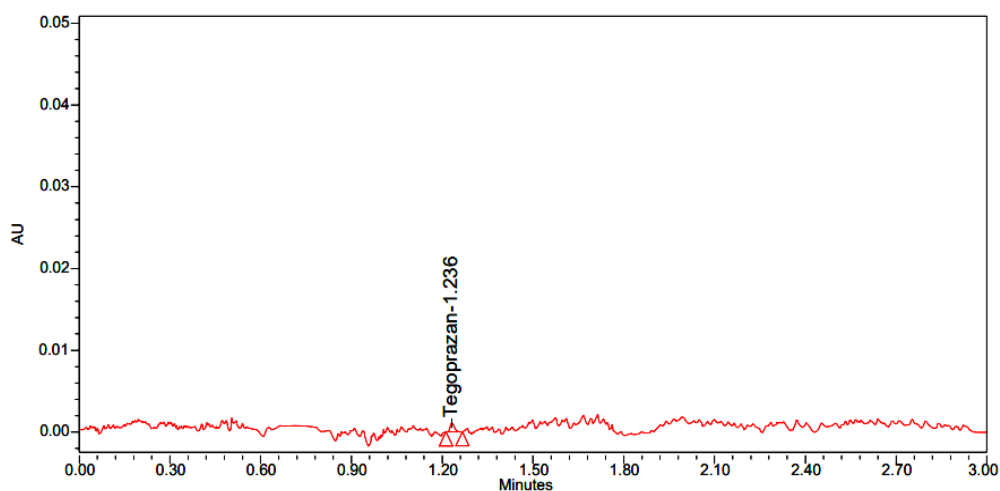


Figure 3: Chromatogram of LOD

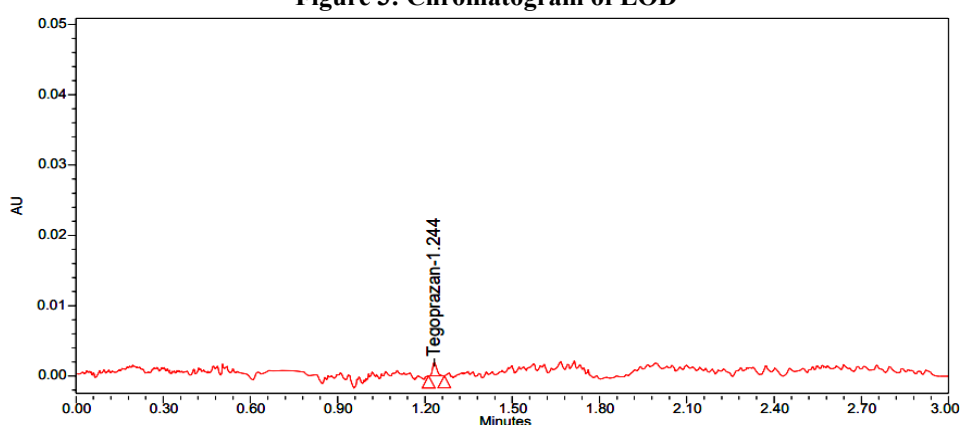


Figure 4: Chromatograms of LOQ

ROBUSTNESS

The robustness of the method was evaluated by deliberately varying the flow rate and organic phase composition. Flow rate variations were tested at 0.45mL/min (minus) and 0.55mL/min (plus), while organic phase composition was varied at 36:64 (minus) and 44:56 (plus) ratios. The %RSD values for these variations ranged from 0.50% to 0.66%, which are well within the acceptance criteria, indicating that the method is robust and not significantly affected by small changes

in chromatographic parameters. The low variability observed under these deliberate changes demonstrates that the method can withstand minor fluctuations in operational conditions, making it suitable for routine use in quality control laboratories where conditions may vary slightly. The robustness study confirmed that the method remains reliable even when parameters such as flow rate and mobile phase composition are varied within reasonable limits

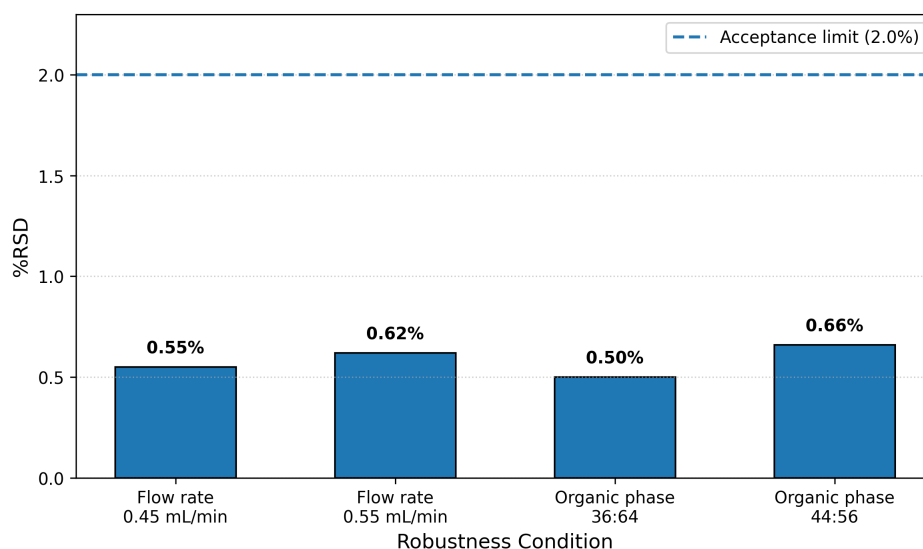


Fig. 5 Robustness acceptance line

Forced Degradation Studies

Forced degradation studies were conducted to evaluate the stability-indicating nature of the method. The drug was subjected to various stress conditions including acid hydrolysis, alkali hydrolysis, oxidative degradation, reductive degradation, thermal degradation, and photolytic degradation. The results showed that Tegoprazan was most susceptible to oxidative degradation (14.2% degradation), followed by acid degradation (12.8%), thermal degradation (11.9%), and alkali degradation (9.5%). The drug showed

minimal degradation under reductive conditions (1.6%) and photolytic conditions (0.9%). The purity angles were consistently lower than the purity thresholds for all degradation conditions, confirming that the Tegoprazan peak remained pure and no co-eluting degradation products were present. This indicates that the method is stability-indicating and can effectively separate the drug from its degradation products, making it suitable for stability studies and routine quality control of Tegoprazan formulations

Table 5: Forced Degradation Results

Degradation Condition	% Label Claim	% Degradation	Purity Angle	Purity Threshold
Control	99.5	0.5	5.726	11.056
Acid Degradation	86.7	12.8	5.717	11.045
Alkali Degradation	90.0	9.5	5.735	11.027
Peroxide Degradation	85.3	14.2	5.748	11.043
Reduction Degradation	97.9	1.6	5.773	11.066
Thermal Degradation	87.6	11.9	5.769	11.009
Photolytic Degradation	98.6	0.9	5.782	11.014

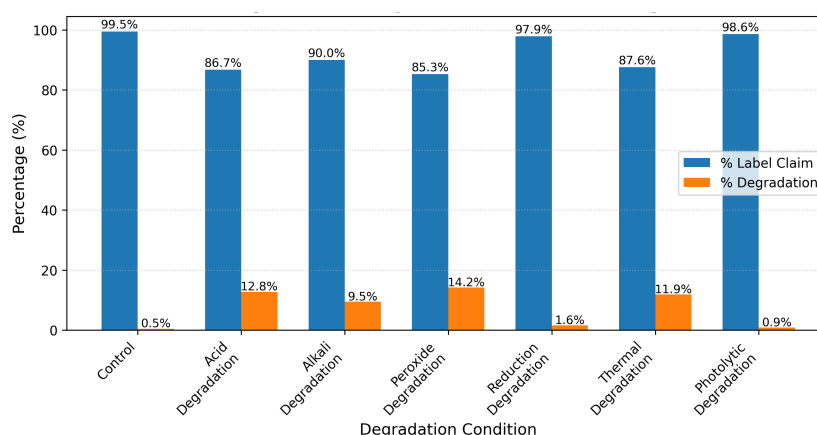


Fig: 6 Forced Degradation study

ASSAY OF COMMERCIAL FORMULATION

The developed method was successfully applied to determine the Tegoprazan content in commercial PCAB 50 tablets. The assay results showed a mean percentage of 99.2% of the labeled claim, indicating that the formulation met the pharmacopoeial requirements for drug content. The close agreement between the observed and expected values confirms the method's accuracy and its suitability for quality control purposes. The successful application of the method to commercial samples demonstrates its practical utility in pharmaceutical analysis.

CONCLUSION

The present study successfully accomplished the development and validation of a simple, rapid, accurate, precise, and stability-indicating UPLC method for the quantitative determination of Tegoprazan in bulk drug and its pharmaceutical tablet formulations. The developed method demonstrates significant advantages over previously reported analytical techniques, offering a substantially reduced run time of just 3.0 minutes compared to the 6-minute run time of the conventional RP-HPLC method. The method employs a straightforward isocratic mobile phase system comprising ammonium formate buffer (pH 2.5) and acetonitrile in a 60:40 v/v ratio, which is both cost-effective and operationally simple for routine quality control applications. The comprehensive validation conducted according to ICH Q2(R2) guidelines

confirmed that the method meets all acceptance criteria for specificity, system precision, linearity, accuracy, precision, sensitivity, and robustness. The method exhibited excellent system precision with a %RSD of 0.68, surpassing the acceptance criterion of 2.0%. The USP plate count of 8054 and tailing factor of 0.98 confirmed high column efficiency and excellent peak symmetry. The linearity study demonstrated a strong correlation coefficient of 0.99988 across the concentration range of 25-150 µg/mL, indicating reliable quantification capabilities. The accuracy results, with percentage recoveries ranging from 99.3% to 100.4%, confirmed the method's freedom from matrix interference and systematic bias. The low LOD (0.30 µg/mL) and LOQ (1.00 µg/mL) values demonstrate the method's high sensitivity, making it suitable for detecting trace amounts of the drug in stability studies and impurity profiling. The forced degradation studies confirmed the stability-indicating nature of the method, as the drug peak remained pure under all stress conditions with purity angles consistently lower than purity thresholds. The degradation data revealed that Tegoprazan is most susceptible to oxidative degradation (14.2%), followed by acid degradation (12.8%), thermal degradation (11.9%), and alkali degradation (9.5%), while showing stability under reductive and photolytic conditions. The successful separation of degradation products from the parent drug peak without any interference confirms the method's ability to effectively monitor drug stability.

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