RESEARCH PAPER

A Robust Stability-Indicating RP-HPLC Method for Imeglimin Hydrochloride in Bulk and Tablet Dosage Forms: From Method Development to Degradation Profiling

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Abstract

Aim: The objective of the present study was to develop a novel, robust, and stability-indicating RP-HPLC method for the estimation of Imeglimin Hydrochloride in bulk and tablet dosage forms. The method was further validated to ensure simplicity, precision, accuracy, and rapid analysis, followed by forced degradation studies to evaluate its stability-indicating capability. **Methodology:** Chromatographic separation was carried out on a Shimadzu C_{18} column (4.6 × 250 mm, 5 µm particle size). The mobile phase consisted of water, acetonitrile, and formic acid in the ratio of 70:30:0.1 (% v/v/v) under isocratic conditions. The flow rate was maintained at 1.5 mL/min, and detection was performed at 250 nm using a UV detector.The retention time of Imeglimin Hydrochloride was found to be 2.391 mins.The method was validated according to ICH guidelines, and forced degradation studies were conducted under acidic, basic, oxidative, thermal, UV- light and photolytic conditions. **Results:** The method showed good linearity over 1–5 µg/mL (R^2 = 0.9997), with satisfactory system suitability and precision (% RSD <2.0%). Imeglimin Hydrochloride remained stable under acidic, basic, oxidative, and photolytic conditions, while degradation was observed under UV-light and thermal stress. The method effectively separated the drug from degradation products, confirming its stability-indicating capability.

Keywords: Imeglimin Hydrochloride, RP-HPLC, Method Development, Method Validation, Stability-Indicating Method, Pharmaceutical Analysis.

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Introduction:

Imeglimin is the first member of a novel class of oral antidiabetic agents known as glimins, characterized by a tetrahydrotriazine heterocyclic structure.1 Its IUPAC name is (6R)-N^2,N^4-dimethyl-6-(2-methylpropyl)-1,4,5,6-tetrahydro-1,3,5-triazine-2,4-diamine. It was discovered through phenotypic screening in rodent models and chemically optimized to enhance antihyperglycaemic activity. It is a first-in-class drug, approved in 2021 by the PMDA (Japan), and has also received approval from the Central Drugs Standard Control Organization (CDSCO), India, for the management of type 2 diabetes mellitus.2

Type 2 diabetes is a chronic metabolic disorder affecting over 500 million people worldwide, characterized by persistent hyperglycaemia, insulin resistance, and β-cell dysfunction, representing a major global health

burden.3Imeglimin exhibits a unique mechanism of action targeting mitochondrial dysfunction, insulin secretion, and insulin sensitivity. It enhances mitochondrial bioenergetics by modulating respiratory chain activity and reducing reactive oxygen species (ROS) production.4,5 It also improves glucose-stimulated insulin secretion and peripheral insulin sensitivity, contributing to improved glycaemic control. Additionally, it inhibits mitochondrial permeability transition pore opening, suggesting potential organ-protective effects.6

From a pharmaceutical analysis perspective, accurate quantification of imeglimin is essential for quality control and stability assessment. RP-HPLC is widely used due to its precision, sensitivity, and ability to separate drug from degradation products.7–10 Stability-indicating methods ensure reliable evaluation of purity, safety, and shelf life in bulk and tablet dosage forms.[11]

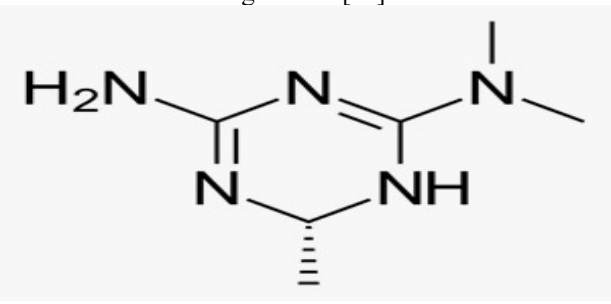


FIGURE 1: Chemical structure of for Imeglimin Hydrochloride

Accurate and reliable analytical methods are essential for the quality control and stability assessment of pharmaceutical compounds. RP-HPLC is a preferred technique due to its simplicity, precision, and efficiency in separating complex mixtures. It provides rapid analysis with short run times, making it suitable for routine pharmaceutical testing. RP-HPLC is also effective in detecting drug and its degradation products, supporting stability-indicating studies.12,13 Hence, it is widely used for the development and validation of analytical methods for Imeglimin Hydrochloride, ensuring its purity, stability, and quality in bulk and tablet dosage forms.7–10

The present study is useful as it provides a robust, rapid, and stability-indicating RP-HPLC method that can be applied for routine quality control, regulatory compliance, and stability testing of Imeglimin Hydrochloride in pharmaceutical formulations.

Drug Profile:

Chemical Name: Imeglimin Hydrochloride
Molecular Formula: $C_6H_{14}ClN_5$
Molecular Weight: 191.66 g/mol7,10
Class: Oral antidiabetic agent (Glimes)1
Appearance: white crystalline powder
Melting Point: 223–272°C

Pharmacological Profile Of Imeglimin Hydrochloride

Mechanism of Action: Imeglimin hydrochloride is a novel oral antidiabetic agent that exerts its glucose-lowering effect through a unique mechanism targeting mitochondrial bioenergetics. Unlike conventional antidiabetic drugs that primarily act on insulin secretion or insulin sensitivity alone, imeglimin acts at the cellular energy level. It improves mitochondrial function by restoring the balance of the electron transport chain and reducing excessive production of reactive oxygen species (ROS). This mitochondrial modulation enhances the efficiency of glucose metabolism in insulin-sensitive tissues.4,5

In pancreatic β-cells, imeglimin restores glucose-stimulated insulin secretion by improving ATP production, which is essential for insulin release. In peripheral tissues such as skeletal muscle and adipose tissue, it enhances insulin sensitivity, thereby improving glucose uptake. Additionally, in the liver, it suppresses excessive gluconeogenesis, leading to reduced hepatic glucose output. The combined effect of these actions results in better glycemic control without causing significant hypoglycemia.5

Pharmacokinetics: After oral administration, imeglimin hydrochloride is rapidly and well absorbed from the gastrointestinal tract. Its bioavailability is moderate to high, and food does not significantly affect its absorption profile. The drug shows minimal plasma protein binding, which allows it to remain largely in the free, active form in systemic circulation.14

Imeglimin undergoes very limited metabolic transformation in the body, indicating that it is largely excreted unchanged. The primary route of elimination is renal excretion through glomerular filtration and tubular secretion. The elimination half-life is approximately 10 to 12 hours, supporting its twice-daily dosing regimen. Because it is not extensively metabolized by hepatic enzymes such as CYP450, the risk of drug–drug interactions is relatively low.14

Pharmacodynamics: Pharmacodynamically, imeglimin exhibits a glucose-dependent action, meaning its insulin-enhancing effects are more pronounced under hyperglycemic conditions. This property significantly reduces the risk of hypoglycemia compared to traditional insulin secretagogues.4,5 Its primary pharmacological action involves improvement of mitochondrial oxidative phosphorylation efficiency, leading to enhanced cellular energy production.

By restoring mitochondrial function, imeglimin simultaneously improves both insulin secretion and insulin sensitivity. In pancreatic β-cells, increased ATP levels facilitate closure of ATP-sensitive potassium channels, leading to calcium influx and insulin release. In insulin-resistant tissues, improved mitochondrial efficiency enhances glucose uptake and utilization. Furthermore, its effect on hepatic metabolism reduces excessive glucose production, contributing to overall glycemic control.5

Materials And Method

Instrumentation:

Shimadzu HPLC system (Shimadzu C18 4.5 × 250mm ×5 µm column, UV- Visible detector, Lab solution software), Shimadzu HPLC system LC-20AD,all weighing was done on electronic balance (Model Shimadzu AUX- 220), Sonicator was used for sonication of the sample solution, Hot air oven InfraDIGI-250°C.

Materials and chemicals:

A Pure Imeglimin hydrochloride was received from pharmaceutical company in New Delhi, India. A pharmaceutical preparation was purchased from the local pharmacy, HPLC grade water, HPLC grade Acetonitrile,

Formic acid (analytical grade). All solvents and solutions were filtered through a millipore 0.45µm filter and sonicated

Method Optimization:

The objective of the present study was to develop and validate a sensitive, precise, and accurate reverse-phase high-performance liquid chromatography (RP-HPLC) method using a Shimadzu HPLC system equipped with a UV detector for the quantitative estimation of Imeglimin Hydrochloride in pharmaceutical dosage forms. Method optimization was carried out under isocratic elution conditions by evaluating different mobile phase compositions and various C18 columns with different dimensions to achieve efficient separation and acceptable chromatographic performance.[7–10]

Among the columns tested, the C18 column (250 mm × 4.6 mm, 5 µm particle size) was found to provide optimal resolution, peak symmetry, and satisfactory run time for the analysis of Imeglimin Hydrochloride. Several aqueous mobile phase systems consisting of water and acetonitrile with 0.1% Formic acid in different proportions were investigated, and a composition of water and acetonitrile with 0.1% Formic acid(70:30 % v/v) was selected as the optimized mobile phase.

The chromatographic analysis was performed at different detection wavelengths, namely 224, 228, 245, and 253 nm. Based on the overlay UV absorption spectra of the drug, 250 nm was identified as the optimum analytical wavelength for the estimation of Imeglimin Hydrochloride. Following optimization of the chromatographic conditions, the flow rate was maintained at 1.5 mL/min, and the drug exhibited a retention time of approximately 2.391 minutes, indicating efficient separation with a short analysis time.

Preparation Of Mobile Phase

The mobile phase was prepared using water, acetonitrile, and 0.1% formic acid in the optimized ratio. The required quantities of solvents were accurately measured and mixed thoroughly to obtain a homogeneous solution. The prepared mobile phase was then filtered, if necessary, and degassed by sonication for 15 minutes prior to chromatographic analysis to remove dissolved gases and ensure stable baseline performance during RP-HPLC analysis.

Preparation Of 0,1% Formic Acid:

Accurately measure 1 ml of formic acid and transfer it into a 1000 ml volumetric flask containing a small quantity of HPLC-grade water. Mix thoroughly and make up the volume to 1000 mL with HPLC-grade water to obtain a 0.1% v/v formic acid solution. The prepared solution was sonicated and filtered before use in RP-HPLC analysis.

Preparation Of Standard Stock Solution

The standard stock solution of Imeglimin Hydrochloride was prepared by accurately weighing 100 mg of the drug and transferring it into a 25 ml volumetric flask. About 10 ml of diluent was added, and the mixture was shaken vigorously to ensure complete dissolution of the drug. The volume was then made up to the mark with the same diluent to obtain a standard stock solution having a concentration of 4000 µg/ml

Preparationof Working Standard Solution

An aliquot of 2.5 ml from the previously prepared standard stock solution containing 4000 µg/mL of Imeglimin Hydrochloride was accurately transferred into a 100 ml volumetric flask. The volume was then made up to the mark with diluent and mixed well to obtain a final concentration of 100 µg/ml

Quantitative estimation of Marketed Formulation

Preparation of sample solution for assay

Twenty tablets of Imeglimin Hydrochloride were accurately weighed, powdered, and mixed uniformly. A quantity of powder equivalent to 500 mg of the drug was transferred into a 100 ml volumetric flask, dissolved in diluent with sonication for 15 minutes, and diluted to volume with the same diluent. The solution was filtered through Whatman filter paper to remove insoluble materials.From the filtrate, 2 ml was transferred into a 100 mL volumetric flask and diluted up to the mark with diluent to obtain a concentration of 100 µg/ml. Further, 0.2 ml of this solution was diluted to 10 ml with diluent to obtain a final concentration of 2 µg/ml, which was used for routine HPLC analysis.

Method Validation

Method validation in Reverse-Phase High-Performance Liquid Chromatography (RP-HPLC) is performed to ensure that the analytical method is accurate, precise, specific, and reliable for its intended application. The method development and validation were carried out according to International Council for Harmonisation guidelines15 by optimizing chromatographic conditions such as mobile phase, column, and detection wavelength. Validation parameters including accuracy, precision, specificity, linearity, limit of detection (LOD), and limit of quantification (LOQ) were evaluated. RP-HPLC is widely used in pharmaceutical analysis for the separation and quantification of drug compounds, thereby ensuring the quality, safety, and efficacy of pharmaceutical products.

System Suitability

System suitability was evaluated by injecting a standard solution of Imeglimin Hydrochloride. The peak asymmetry was found to be less than 1, and the theoretical plate count was greater than 2000. The %RSD for Imeglimin Hydrochloride was below 2%, indicating that all system suitability parameters were within acceptable limits.

Linearity

Linearity for Imeglimin Hydrochloride was evaluated over the concentration range of 1–5 µg/ml. Aliquots (0.1–0.5 ml) of a 100 µg/ml working standard were diluted to 10 ml with diluent to obtain concentrations of 1, 2, 3, 4, and 5 µg/ml Similarly, linearity for Imeglimin Hydrochloride was studied in the same range (1–5 µg/mL), and the calibration curve showed excellent linearity with a correlation coefficient (r^2) of 0.9997.

Precision

The precision of the developed method was evaluated by analyzing a standard solution of Imeglimin Hydrochloride (2 µg/ml) six times within the same day. The %RSD was calculated to assess repeatability of the method.

Accuracy

A 2 µg/mL solution of Imeglimin Hydrochloride was prepared and divided into three labeled volumetric flasks (A, B, and C). Each flask was spiked with 50%, 100%,

and 150% of the working standard solution, respectively, and diluted to 10 ml with diluent. The peak areas were recorded at 250 nm, and the amount of drug recovered at each level was calculated to determine the percentage recovery.

LOD and LOQ:

The limit of detection (LOD) and limit of quantification (LOQ) were determined using the equations LOD = 3.3 × (SD/S) and LOQ = 10 × (SD/S).15 Here, SD represents the average standard deviation of absorbance, and S denotes the slope of the calibration curve.

Ruggedness

Ruggedness of the proposed method was evaluated by analysing a 2 µg/ml solution of Imeglimin Hydrochloride under the same experimental conditions using two different analysts and two different instruments

Robustness.

Robustness of the method was evaluated by introducing small deliberate variations in the chromatographic conditions. A 2 µg/mL solution of Imeglimin Hydrochloride was analyzed by slightly changing parameters such as flow rate, mobile phase composition, and wavelength. The results showed no significant variation in peak area or retention time, indicating that the method is robust.

Acid degradation:

From a 100 µg/ml working standard solution of Imeglimin Hydrochloride, 0.2 ml was transferred into a 10 ml volumetric flask. To this, 1 ml of 0.1 N H_2SO_4 was added and kept for 24 hours for acid degradation. The solution was then neutralized with 1 ml of 0.1 N KOH, diluted to volume with mobile phase, and injected into the HPLC system. Chromatograms were recorded to observe degradation peaks and changes during the stress study.

Base degradation

From a 100 µg/ml working standard solution of Imeglimin Hydrochloride, 0.2 ml was transferred into a 10 ml volumetric flask and treated with 1 mL of 0.1 N KOH for 24 hours for alkaline degradation. The solution was then neutralized with 1 ml of 0.1 N H_2SO_4, diluted to volume with mobile phase, and injected into the HPLC system. Chromatograms were recorded to evaluate degradation and formation of degradation peaks.

Oxidative degradation

From a 100 µg/mL working standard solution ofImeglimin Hydrochloride, 0.2 ml was transferred into a 10 ml volumetric flask and treated with 1 mL of 0.3% hydrogen peroxide for 24 hours. The volume was then made up with mobile phase and injected into the HPLC system. Chromatograms were recorded to evaluate oxidative degradation and formation of degradation peak

Thermal degradation

Standard Imeglimin Hydrochloride was subjected to thermal degradation at 70°C for 24 hours. A 100 µg/ml solution was prepared, diluted appropriately with mobile phase, and injected into the HPLC system to evaluate thermal degradation

Photolytic degradation

The standard drug was exposed to sunlight for 4 hours. A 100 µg/mL solution was prepared, diluted with mobile phase, and analyzed by HPLC to study photolytic degradation.

UV degradation

The standard drug was exposed to UV light for 24 hours. A 100 µg/mL solution was prepared, diluted with diluent, and injected into the HPLC system to assess degradation under UV exposure.

Results And Discussion

Selection of Analytical Wavelength

The UV spectrum ofImeglimin Hydrochloride (10 µg/ml) was scanned in the selected mobile phase over the range of 200–400 nm against a diluent blank. A sharp absorption maximum was observed at 250 nm without any interference from the diluent; hence, 250 nm was selected as the analytical wavelength.

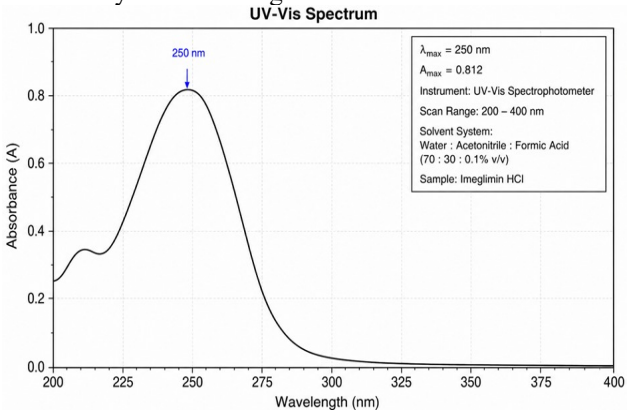


Figure 2: UV-Spectrum of Imeglimin HCl

Linearity

Linearity of Imeglimin Hydrochloride was evaluated over the concentration range of 1–5 µg/ml in duplicate. The calibration curve showed excellent linearity with the regression equation y = 27395x + 174198 and a correlation coefficient (r^2) of 0.9997, indicating a strong correlation between concentration and peak area.

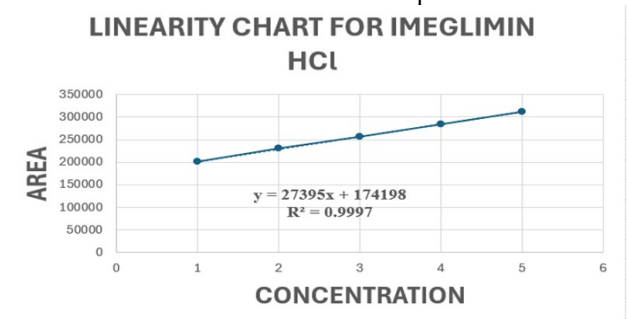
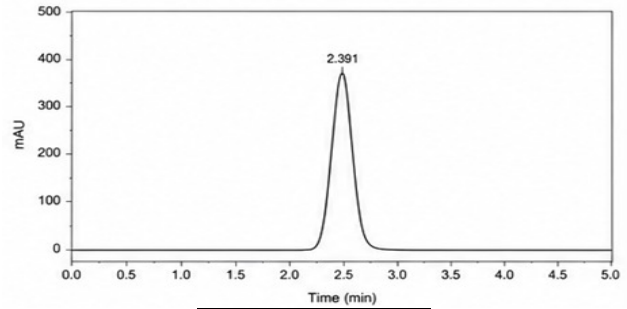


Figure 3: UV- Calibration curve of Imeglimin HCl

Table 1: Linearity



CONCENTRATION	AREA
1	200890
2	230187
3	255916
4	283915
5	310999

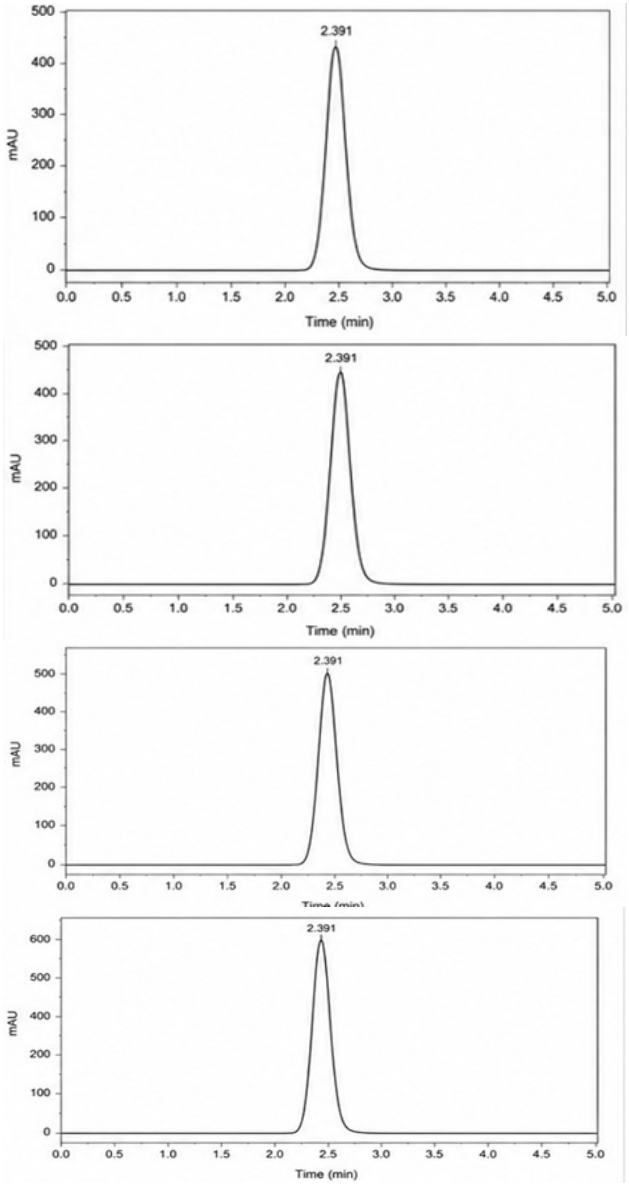


Figure 4: Linearity peak of Imeglimin HCl

PRECISION:

System precision was assessed by six replicate injections of a 2 µg/mL sample solution. The mean purity, standard deviation, and % RSD were calculated. The obtained % RSD of 0.55% was within the acceptable limit, confirming satisfactory system precision. The results are presented in Table 2, and the chromatogram is shown in **Figure 5.**

Table 2: Precision

Sl. No	AREA	AMOUNT FOUND (mg/tab)	% PURITY	S.D	% RSD
1	228180	492.50	98.50	0.546284	0.550708
2	228881	497.50	99.50		
3	228490	493.45	98.84		
4	228776	495.00	99.65		
5	228776	499.22	99.00		
6	228660	498.27	99.19		
AVERAGE % PURITY = 99.19					

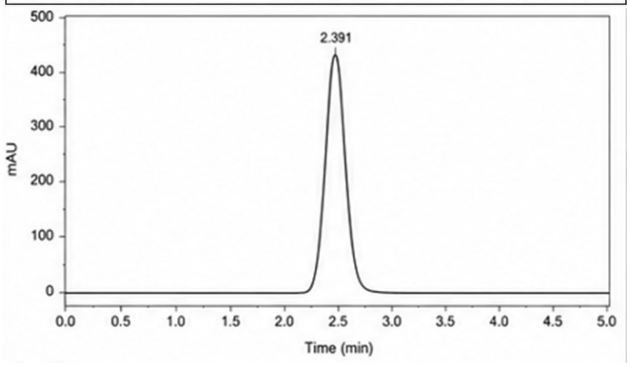


Figure 5: Precision Peak of Imeglimin HCl

Accuracy

Accuracy was assessed at three concentration levels using the standard addition method. Three replicate samples were prepared at each concentration level, and the mean percentage recovery was determined. The results indicated that the percentage recovery of drug was within the acceptable limits, confirming the accuracy of the proposed method.

Table 3: Accuracy

CONC %	AMOUNT PRESENT	AMOUNT ADDED	AMOUNT ESTIMATED	AMOUNT RECOVERY	AVERAGE % RECOVERY	S.D	% RSD
50 %	2	1	2.98	0.98	98.00	0.577 3	0.589 13
100	2	2	4.00	2.00	100	0.577	0.583
%						3	18
150 %	2	3	4.99	2.99	99.66	0.508 46	0.513 59

n – mean of 3 observations

LOD AND LOQ:

To calculate the average of standard deviation of absorbance, and "S" is the slope of the corresponding calibration curve. The data were provided in **Table 4.**

Table 4: Optical Characteristics

Sl. No	AREA	AMOUNT FOUND (mg/tab)	% PURITY	S.D	% RSD
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4	228776	495.00	99.65		
5	228776	499.22	99.00		
6	228660	498.27	99.19		
AVERAGE % PURITY = 99.19					

Ruggedness:

The ruggedness of the method was confirmed by performing the analysis under different conditions, and the % RSD was found to be within acceptable limits, indicating good reproducibility. The result was shown in **Table 5.**

Table 5: Ruggedness Data

PARAMETER	AVERAGE% PURITY	S. D	% RSD
ANALYST-1	100.30	0.1456	0.1466
ANALYST-2	99.78	0.1345	0.1308
INSTRUMENT-1	100.16	0.1409	0.1453
INSTRUMENT-2	99.83	0.1398	0.1314

n – mean of 3 observations

Robustness

Robustness was evaluated by making deliberate variations in wavelength (249 and 251 nm), flow rate (1.4 and 1.6 mL/min), and mobile phase composition (71:29 and 69:31% v/v). The % RSD values remained within acceptable limits, with no significant effect on system suitability parameters, confirming the robustness of the method. The results are presented in Table 6.

Table 6: Robustness Data

PARAMETER	%PURITY	SD	% RSD
1.4 ml/min	99.60	0.1801	0.1808
1.5 ml/min	99.76	0.1750	0.1760
1.6 ml/min	99.69	0.0551	0.0553
249 nm	99.77	0.0409	0.0416
250 nm	99.67	0.0404	0.0409
251 nm	99.65	0.3415	0.3115
(71:29 %v/v)	99.81	0.1596	0.1894
(70:30 %v/v)	99.74	0.2115	0.2116
(69:31 %v/v)	99.77	0.1724	0.1732

n= mean of 3 observations

Stability studies

The forced degradation study of Imeglimin Hcl was carried out under acidic, basic, oxidative, thermal, and UV stress conditions to evaluate its stability.11,16 The drug remained stable under acidic, basic, and oxidative conditions, with no significant degradation observed. However, noticeable degradation was observed under thermal and UV stress conditions. The degradation behavior under different stress conditions demonstrated the ability of the proposed method to effectively assess the stability of Imeglimin Hcl. Therefore, the developed method can be considered suitable as a stability-indicating analytical method for the estimation of Imeglimin Hcl

Table 7: Stability Studies

SI.NO	CONDITIONS	%UNDEGRADED	%DEGRADATED
1	ACID	100	-
2	BASE	100	-
3	OXIDATIVE	100	-
4	THERMAL	88.96	11.04
5	PHOTOLYTIC	100	-
6	UVDEGRADATION	77.65	22.35

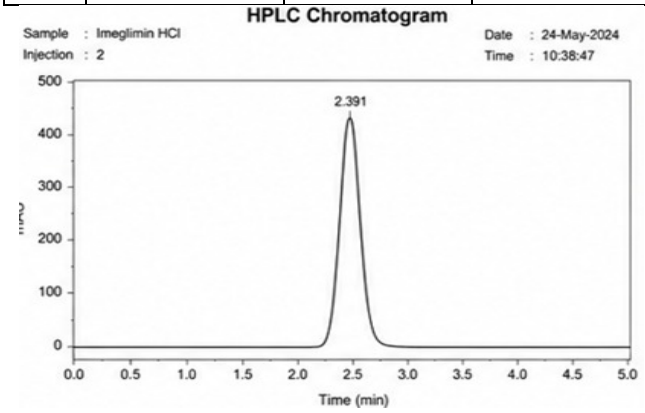


Figure 6: Acid Degradation

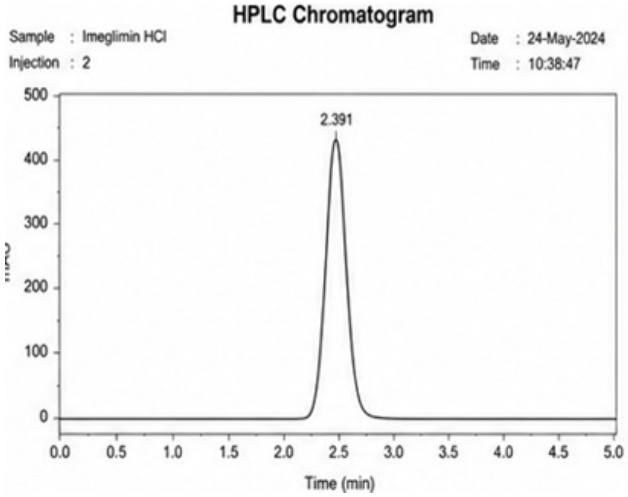


Figure 7: Base Degradation

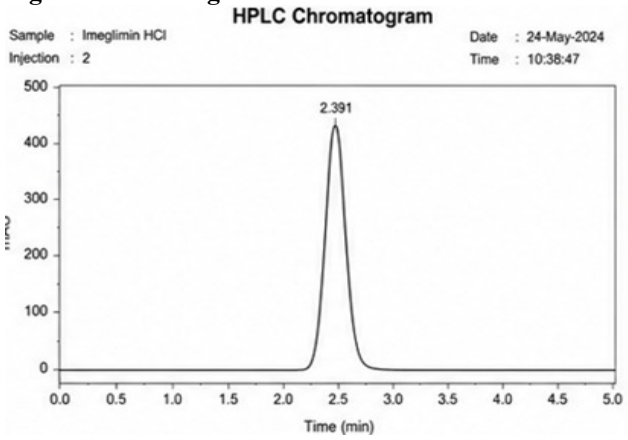


Figure 8: Oxidative Degradation

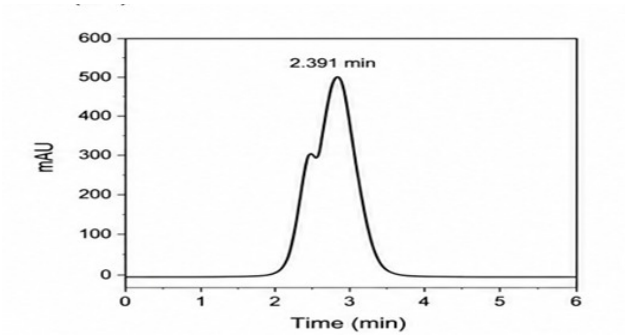


Figure 9: Thermal Degradation

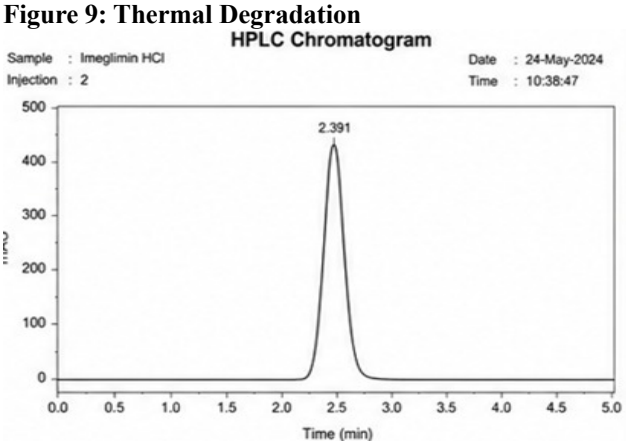


Figure 10: Photolytic Degradation

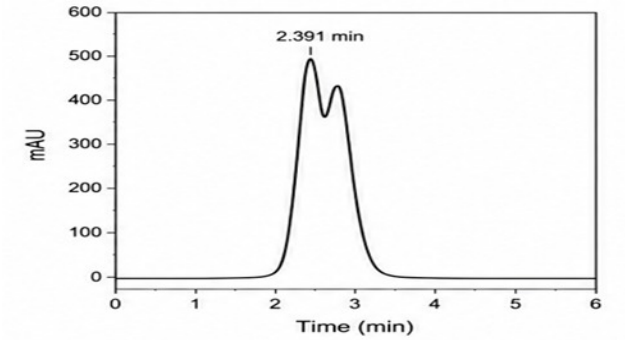


Figure 11: UV Degradation

Conclusion

The present study successfully developed and validated a simple, rapid, precise, accurate, and stability-indicating RP-HPLC method for the estimation of Imeglimin Hydrochloride in bulk and tablet dosage forms. The optimized chromatographic conditions provided satisfactory separation with a short retention time of 2.391 min, making the method suitable for routine pharmaceutical analysis. The method demonstrated good linearity, precision, and system suitability, with validation parameters complying with ICH guidelines.[15] The forced degradation studies revealed that Imeglimin Hydrochloride remained stable under acidic, basic, oxidative, and photolytic conditions, whereas degradation was observed under UV-light and thermal stress conditions. The degradation observed under UV-light and thermal conditions, along with the satisfactory separation of the analyte from degradation products, demonstrated the stability-indicating capability of the proposed RP-HPLC method. Hence, the developed method can be effectively applied for routine quality control, stability assessment, and quantitative determination of Imeglimin Hydrochloride in bulk drug and tablet dosage forms.

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