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A NEW SIMPLE ANALYTICAL REVERSE PHASE RP-HPLC METHOD DEVELOPMENT AND VALIDATION FOR ESTIMATION OF DORAVIRINE IN BULK AND PHARMACEUTICAL DOSAGE FORMS

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Abstract:

An efficient and simple RP-HPLC method has been developed and validated for the estimation of Doravirine in bulk and marketed pharmaceutical dosage forms. The mobile phase used for the chromatographic runs consisted of Methanol and Phosphate buffer (0.02M, pH-3.6) in the ratio of 40:60% v/v. The separation was achieved on an Inertsil C18 ODS (4.6mm × 250mm) 5µm particle size column using isocratic mode. Drug peak were well separated and were detected by a UV detector at 246 nm. The retention time of Doravirine was found to be 5.493minutes. The method was linear at the concentration range 6–14 µg/ml for Doravirine. The method has been validated according to ICH guidelines with respect to system suitability, specificity, precision, accuracy and robustness. Doravirine limit of detection (LOD) and limit of quantification (LOQ) were 0.487µg/ml and 1.477µg/ml respectively.

Keywords: *Doravirine, RP-HPLC, Accuracy, Precision, Robustness, ICH Guidelines.*

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INTRODUCTION:

Doravirine is a non-nucleoside reverse transcriptase inhibitor used in combination with other antiretrovirals to treat HIV-1 infections. Doravirine is an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) intended to be administered in combination with other antiretroviral medicines[1]. Doravirine is available by itself or as a combination product of Doravirine (100 mg), lamivudine (300 mg), and tenofovir disoproxil fumarate (300 mg). Doravirine is a prescription medication used exclusively in combination with other antiretroviral agents to treat Human Immunodeficiency Virus type 1 (HIV-1) infections[2]. Classified as a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI), it works by blocking the enzyme HIV needs to multiply, which helps lower the amount of virus in the body. The IUPAC Name of Doravirine is 3-chloro-5-[[1-[(4-methyl-5-oxo-1H-1, 2, 4-triazol-3-yl) methyl]-2-oxo-4-(trifluoro methyl)-3-pyridinyl] oxy] benzonitrile[3]. The Chemical Structure of Doravirine is as follows

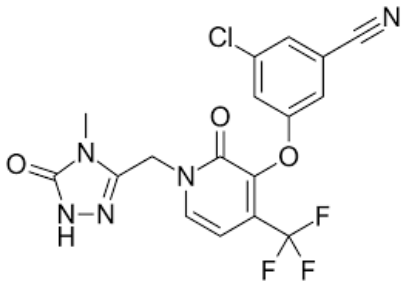


Fig-1: Chemical Structure of Doravirine

MATERIALS AND METHODS:

Table-1: List of Equipments

S.No.	Instruments/Equipments/Apparatus
1.	HPLC WATERS with Empower2 Software with Isocratic with UV-Visible Detector.
2.	T60-LABINDIA UV – Vis spectrophotometer
3.	High Precision Electronic Balance
4.	Ultra Sonicator (Wensar wuc-2L)
5.	Thermal Oven
6.	Symmetry C_{18} Column, 250 mm x 4.6 mm and 5µm particle size
7.	P^H Analyser (ELICO)
8.	Vaccum Filtration Kit (Labindia)

Chemicals and Reagents:

Table-2: List of Chemicals used

S.No.	Name	Grade	Manufacturer/Supplier
1.	HPLC grade water	HPLC	Sd fine-Chem ltd; Mumbai
2.	Methanol	HPLC	Loba Chem; Mumbai.
3.	Ethanol	A.R.	Sd fine-Chem ltd; Mumbai
4.	Acetonitrile	HPLC	Loba Chem; Mumbai.
5.	DMSO	A.R.	Sd fine-Chem ltd; Mumbai
6.	DMF	A.R.	Sd fine-Chem ltd; Mumbai

Method Development:

HPLC Instrumentation & Conditions: The HPLC system[4] employed was HPLC WATERS with Empower2 Software with Isocratic with UV-Visible Detector.

Standard Preparation for UV-Spectrophotometer Analysis:

The Standard Stock Solutions – 10 mg of Doravirine standard was transferred into 10 ml volumetric flask, dissolved & make up to volume with Methanol. Further dilutions[5] were done by transferring 1 ml of the above solution into a 10ml volumetric flask and make up to volume with methanol to get 10ppm concentration.

It scanned in the UV spectrum[10-17] in the range of 200 to 400nm. This has been performed to know the maxima of Doravirine, so that the same wave number can be utilized in HPLC UV detector for estimating the Doravirine.

Selection of Wavelength:

The detection wavelength was selected by dissolving the drug in mobile phase to get a concentration of 10µg/ml for individual and mixed standards. The resulting solution was scanned in U.V range from 200-400nm.

Selection of Chromatographic Methods:

The proper selection depends upon the nature of the sample, (ionic or ion stable or neutral molecule) its molecular weight and stability. The drugs selected are polar, ionic and hence reversed phase chromatography was selected.

Optimization of Column:

The method was performed with various columns like Hypersil C_{18} column, X- bridge column and X-terra (4.6 ×150mm, 5µm particle size), Inertsil C18 ODS (4.6mm×250mm) 5µm particle size Column was found to be ideal as it gave good peak shape and resolution at 1ml/min flow.

Mobile Phase Optimization:

Initially the mobile phase tried was Water: Methanol and Water: Acetonitrile and Methanol with TEA Buffer with varying proportions. Finally, the mobile phase was optimized to Methanol: Phosphate Buffer (0.02M, pH-3.6) (40:60%v/v) respectively.

Preparation of Mobile Phase:

Accurately measured 400 ml (40%) of HPLC Grade Methanol and 600 ml of Phosphate buffer (60%) were mixed and degassed in a digital ultra sonicater for 15 minutes and then filtered through 0.45 µ filter under vacuum filter.

Preparation of 0.01M Potassium dihydrogen orthophosphate Buffer Solution:

About 2.7217grams of Potassium dihydrogen orthophosphate was weighed and transferred into a 1000ml beaker, dissolved and diluted to 1000ml with HPLC Grade water. The pH was adjusted to 3.6 with diluted orthophosphoric acid.

Diluent Preparation:

Accurately measured 400 ml (40%) of HPLC Grade Methanol and 600 ml of Phosphate buffer (60%) were mixed and degassed in a digital ultra sonicater for 15 minutes and then filtered through 0.45 µ filter under vacuum filter.

Assay of Marketed Pharmaceutical Dosage Forms

Preparation of the Doravirine standard solution:

Preparation of standard solution: (Doravirine)

Accurately weigh and transfer 10 mg of Doravirine, working standard into a 10ml of clean dry volumetric flasks add about 7ml of diluent and sonicate to dissolve and removal of air completely and make volume up to the mark with the diluent.
Further pipette 0.1ml of Doravirine from stock solution in to a 10ml volumetric flask and dilute up to the mark with diluent.

Procedure:
Inject the samples by changing the chromatographic conditions and record the chromatograms, note the conditions of proper peak elution for performing validation parameters as per ICH guidelines.

Preparation of Sample Solution:
Take average weight of Tablet and crush in a mortar by using pestle and taken weight 10 mg equivalent weight of Doravirine sample into a 10ml clean dry volumetric flask and add about 7ml of Diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent.

Procedure:
Further pipette 0.1ml of Doravirine from above stock solution into a 10ml volumetric flask and dilute up to the mark with diluent.
Inject the three replicate injections of standard and sample solutions and calculate the assay by using formula:

$$\%ASSAY = \frac{\text{Sample area}}{\text{Standard area}} \times \frac{\text{Weight of standard}}{\text{Dilution of standard}} \times \frac{\text{Dilution of sample}}{\text{Weight of sample}} \times \frac{\text{Purity}}{100} \times \frac{\text{Weight of tablet}}{\text{Label claim}} \times 100$$

Analytical Method Validation
Validation is a process of establishing documented evidence which provide a high degree of assurance that specific activity will consistently produce a desired result or product meeting its predetermined specification and quality characteristics.

System Suitability
System suitability[6] is the evaluation of the components of an analytical system to show that the performance of a system meets the standards required by a method. A system suitability evaluation usually contains its own set of parameters. For chromatographic assays, these may include tailing factor, resolution, precision, capacity factor time and theoretical plates.

Accuracy:
For preparation of 50% Standard stock solution:
Further pipette 0.05ml of Doravirine from stock solutions in to a 10ml volumetric flask and dilute up to the mark with diluent.

For preparation of 100% Standard stock solution:
Further pipette 0.1ml of Doravirine from stock solutions in to a 10ml volumetric flask and dilute up to the mark with diluent.

For preparation of 150% Standard stock solution:
Further pipette 0.15 ml of Doravirine from stock solutions in to a 10ml volumetric flask and dilute up to the mark with diluent.

Procedure:
Inject the Three replicate injections of individual concentrations (50%, 100%, 150%) were made under the optimized conditions. Recorded the chromatograms and measured the peak responses. Calculate the Amount found and Amount added for Doravirine and calculate the individual recovery[7] and mean recovery values.

Acceptance criteria:
The %RSD for each level should not be more than 2
.

Precision:
Repeatability
Preparation of Doravirine for Precision:
Further pipette 0.1 ml of Doravirine from stock solutions in to a 10ml volumetric flask and dilute up to the mark with diluent
The standard solution was injected for five times and measured the area for all five injections in HPLC. The %RSD for the area of five replicate injections was found to be within the specified limits.

Ruggedness
To evaluate the intermediate precision[8] of the method, Precision was performed on different days by maintaining same conditions.

Procedure:
DAY 1:
The standard solution was injected for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.

DAY 2:
The standard solution was injected for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.
The % RSD for the area of five standard injections results should be not more than 2%.

Linearity:
Preparation of Level – I (6µg/ml of Doravirine):
Further pipette 0.06 ml of Doravirine from stock solutions in to a 10ml volumetric flask and dilute up to the mark with diluent.

Preparation of Level – II (8µg/ml of Doravirine):
Further pipette 0.08 ml of Doravirine from stock solutions in to a 10ml volumetric flask and dilute up to the mark with diluent.

Preparation of Level – III (10µg/ml of Doravirine):
Further pipette 0.1ml of Doravirine from stock solutions in to a 10ml volumetric flask and dilute up to the mark with diluent.

Preparation of Level – IV (12µg/ml of Doravirine):
Further pipette 0.12ml of Doravirine from stock solutions in to a 10ml volumetric flask and dilute up to the mark with diluent.

Preparation of Level – V (14µg/ml of Doravirine):
Further pipette 0.14ml of Doravirine from stock solutions in to a 10ml volumetric flask and dilute up to the mark with diluent.

Procedure:
Inject each level into the chromatographic system[9] and measure the peak area. Plot a graph of peak area versus concentration (on X-axis concentration and on Y-axis Peak area) and calculate the correlation coefficient.

Acceptance Criteria: Correlation coefficient[18] should be not less than 0.999.
Limit of Detection:
The detection limit[19] is determined by the analysis of samples with known concentration of analyte and by establishing that minimum level at which the analyte can reliably detected.

Limit of Quantitation
The quantification limit[20] is generally determined by the analysis of sample with known concentrations of analyte and by establishing the minimum level at which the analyte can be quantified with acceptable accuracy and precision.

Robustness:
The analysis was performed in different conditions to find the variability of test results. The following conditions are checked for variation of results. .

Effect of Variation of flow Rate:
The sample was analyzed at 0.9 ml/min and 1.1 ml/min instead of 1ml/min, remaining conditions are same. 20µl of the above sample was injected and chromatograms were recorded.

Effect of Variation of Mobile Phase Organic Composition:
The sample was analyzed by variation of mobile phase i.e. Methanol: Phosphate Buffer was taken in the ratio and 45:55, 35:65 instead of 40:60, remaining conditions are same. 20µl of the above sample was injected and chromatograms were recorded[21-22].

RESULTS AND DISCUSSION:
Method Development:
Selection of Wavelength:
The UV spectrum of Doravirine was obtained and the Doravirine showed absorbance's maxima at 246nm. The UV spectra of drug are follows:

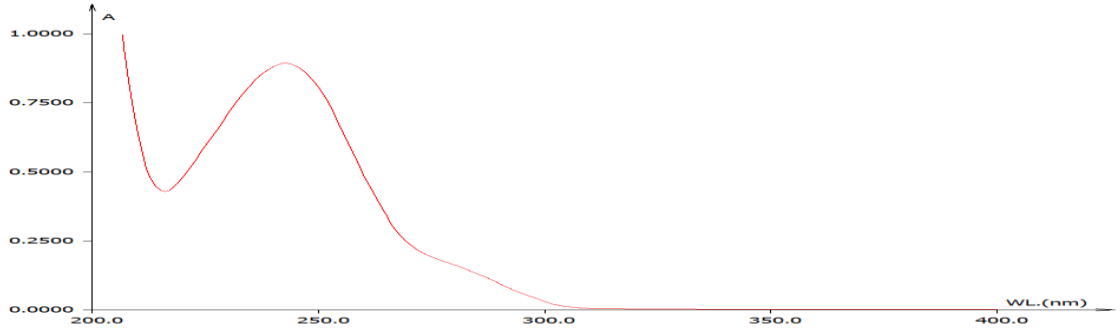


Fig-2: UV Spectrum of Doravirine (246nm)

Observation: While scanning the Doravirine solution we observed the maxima at 246nm. The UV spectrum has been recorded on T60-LAB INDIA make UV – Vis spectrophotometer model UV-2450.

Optimization of Analytical Method:
The chromatographic conditions were optimized to achieve efficient separation, satisfactory peak resolution, and reproducible results during the quantitative estimation of the drug using the RP-HPLC method. The analysis was performed using an Inertsil C18 ODS column (250 mm × 4.6 mm i.d., 5 µm particle size) as the stationary phase. The mobile phase consisted of methanol and 0.02 M phosphate buffer adjusted to pH 3.6 in the ratio of 40:60% v/v. The mobile phase was pumped through the column at a constant flow rate of 1.0 mL/min to ensure consistent and efficient elution of the analyte. Detection was carried out at a wavelength of 246 nm using a UV detector to obtain a suitable analytical response. An injection volume of 20 µL was maintained throughout the analysis to ensure reproducible sample introduction. The column temperature was maintained at ambient conditions, and the total chromatographic run time was fixed at 10 minutes. These optimized chromatographic conditions were selected to obtain satisfactory chromatographic performance and ensure reliable quantitative estimation of the drug in bulk and marketed pharmaceutical dosage forms.

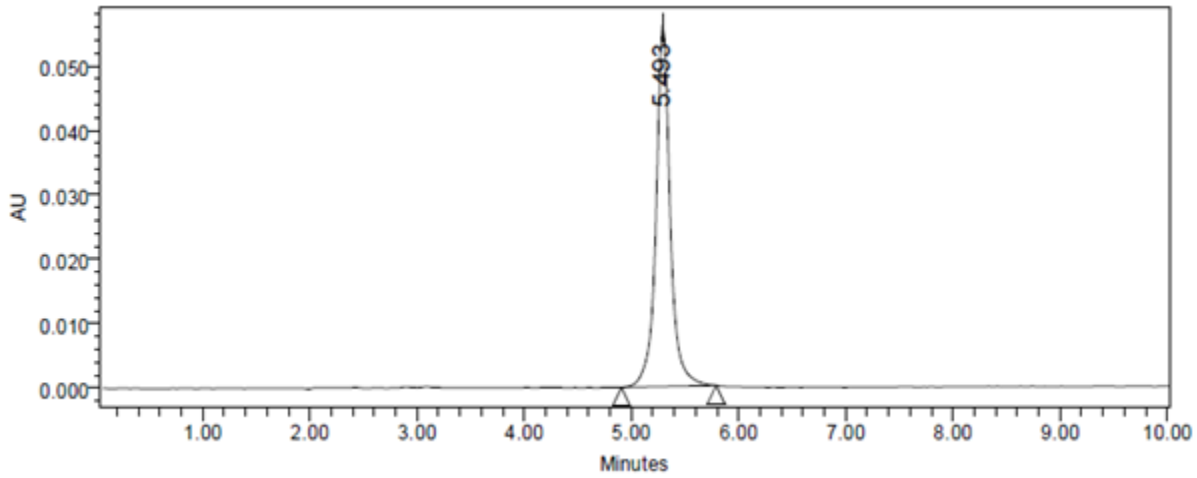


Fig-3: Optimized Chromatographic Condition

Method Validation:
According to the FDA, "Analytical method validation is the process of demonstrating that an analytical procedure is suitable for its intended purpose. The methodology and objective of the analytical procedures should be clearly defined and understood before initiating validation studies.

System suitability is the checking of a system to ensure system performance before or during the analysis of unknowns. System suitability tests are an integral part of chromatographic methods, and are used to verify that the resolution and reproducibility[24] of the system are adequate for the analysis to be performed.

System Suitability:

Table-3: Observation of System Suitability Parameters

S.No.	Parameter	Doravirine
1.	Retention Time (min)	5.453
2.	Theoretical Plates	6967
3.	Tailing factor	1.12
4.	Peak Area (AUC)	647856

The system suitability parameters were found to be within the specified limits for the proposed method.

Specificity

The ICH documents define specificity as the ability to assess unequivocally the analyte in the presence of components that may be expected to be present, such

as impurities, degradation products, and matrix components.

Analytical method was tested for specificity to measure accurately quantitates Doravirine in drug product.

$$\%ASSAY = \frac{\text{Sample area}}{\text{Standard area}} \times \frac{\text{Weight of standard}}{\text{Dilution of standard}} \times \frac{\text{Dilution of sample}}{\text{Weight of sample}} \times \frac{\text{Purity}}{100} \times \frac{\text{Weight of tablet}}{\text{Label claim}} \times 100$$

The % purity of Doravirine in present in the marketed pharmaceutical dosage form was found to be 99.85%.

Linearity:

Linearity[25] should be evaluated by visual inspection of a plot of signals as a function of analyte concentration or content. If there is a linear relationship, test results should be evaluated by appropriate statistical methods, for example, by calculation of a regression line by the method of least squares

Table-4: Chromatographic Data for Linearity Study of Doravirine

Concentration µg/ml	Average Peak Area
6	468784
8	615798
10	768759
12	925748
14	1078765

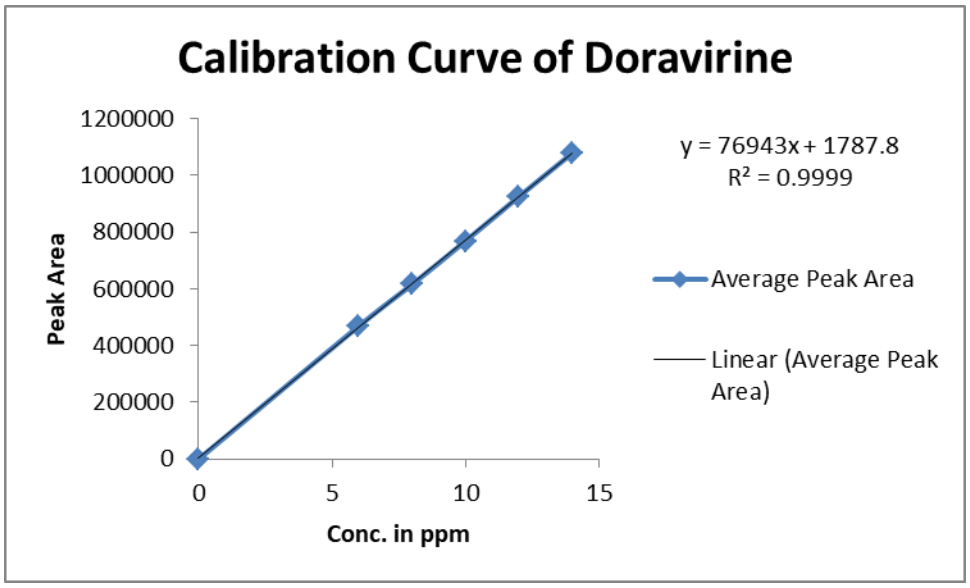


Fig-4: Calibration Curve of Doravirine

Linearity Plot: The plot of Concentration (x) versus the Average Peak Area (y) data of Doravirine is a straight line.

Y = mx + c

Slope (m) = 76943

Intercept (c) = 1787

Correlation Coefficient (r) = 0.99

Validation Criteria: The response linearity is verified if the Correlation Coefficient is 0.99 or greater.

Conclusion: Correlation Coefficient (r) is 0.99, and the intercept is 76943. These values meet the validation criteria.

Precision:

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions.

Repeatability:

Obtained Six (6) replicates of 100% accuracy solution as per experimental conditions. Recorded the peak areas and calculated % RSD.

Table-5: Results of Repeatability for Doravirine:

S. No.	Peak Name	Retention time	Area (µV*sec)	Height (µV)	USP Plate Count	USP Tailing
1	Doravirine	5.419	645784	83685	6825	1.05
2	Doravirine	5.405	642589	84932	6849	1.09
3	Doravirine	5.478	643658	85847	6845	1.08
4	Doravirine	5.466	648759	86295	6839	1.09
5	Doravirine	5.493	649657	86587	6895	1.07
6	Doravirine	5.466	647854	87853	6874	1.10
Mean			**646383.5**			
Std. Dev			**2853.319**			
%RSD			**0.441428**			

Intermediate Precision/Ruggedness:
Analyst 1:

Table-6: Results of Intermediate precision for Doravirine

S.No.	Peak Name	RT	Area (µV*sec)	Height (µV)	USP Plate Count	USP Tailing
1	Doravirine	5.484	636854	84863	6758	1.09
2	Doravirine	5.493	637489	84759	6726	1.08
3	Doravirine	5.406	635762	84685	6749	1.09
4	Doravirine	5.419	636984	84697	6698	1.07
5	Doravirine	5.446	634856	84258	6728	1.08
6	Doravirine	5.452	639689	84753	6699	1.08
Mean			**636939**			
Std. Dev.			**1649.149**			
% RSD			**0.258918**			

Analyst 2:

Table-7: Results of Intermediate Precision Analyst 2 for Doravirine

S.No.	Peak Name	RT	Area (µV*sec)	Height (µV)	USP Plate Count	USP Tailing
1	Doravirine	5.491	628985	85698	6985	1.09
2	Doravirine	5.482	624879	85479	6899	1.07
3	Doravirine	5.416	625846	85748	6928	1.06
4	Doravirine	5.482	623568	85647	6874	1.09
5	Doravirine	5.495	628985	85246	6984	1.07
6	Doravirine	5.427	628473	85924	6872	1.08
Mean			**626789.3**			
Std. Dev.			**2340.636**			
% RSD			**0.373433**			

Accuracy:

Accuracy at different concentrations (50%, 100%, and 150%) was prepared and the % recovery was calculated.

Table-8: The Accuracy Results for Doravirine

%Concentration (at specification Level)	Area	Amount Added (ppm)	Amount Found (ppm)	% Recovery	Mean Recovery
50%	386559	5	5.00	100.000%	100.130%
100%	768536	10	9.965	99.650%	
150%	1164522	15	15.111	100.740%	

Limit of Detection

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

$$LOD = 3.3 \times \sigma / s$$

Where,

σ = Standard deviation of the response

S = Slope of the calibration curve

Result: 0.487µg/ml

Quantitation Limit

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined.

$$LOQ=10\times\sigma/S$$

Where,

σ = Standard deviation of the response
S = Slope of the calibration curve
Result: 1.477µg/ml
Robustness:

The robustness was performed for the flow rate variations from 0.9 ml/min to 1.1ml/min and mobile phase ratio variation from more organic phase to less organic phase ratio for Doravirine. The method is robust only in less flow condition. The standard of Doravirine was injected by changing the conditions of chromatography. There was no significant change in the parameters like resolution, tailing factor, asymmetric factor, and plate count.

Table-9: Results for Robustness of Doravirine

Parameter used for sample analysis	Peak Area	Retention Time	Theoretical plates	Tailing factor
Actual Flow rate of 1.0 mL/min	648759	5.484	6845	1.08
Less Flow rate of 0.9 mL/min	635248	5.599	6786	1.09
More Flow rate of 1.1 mL/min	659865	4.576	6528	1.05
Less organic phase	625986	7.415	6689	1.03
More organic phase	615869	3.827	6354	1.01

SUMMARY AND CONCLUSION:

In the present study, a simple, accurate, precise, and reproducible RP-HPLC method was successfully developed and validated for the quantitative estimation of the drug in bulk and marketed pharmaceutical dosage forms. The chromatographic separation was achieved using an Inertsil C18 ODS column (250 mm × 4.6 mm, 5 µm) with methanol and 0.02 M phosphate buffer (pH 3.6) in the ratio of 40:60% v/v as the mobile phase. The flow rate was maintained at 1.0 mL/min, with detection at 246 nm and a run time of 10 minutes. The method was validated for system suitability, specificity, linearity, accuracy, precision, intermediate precision, robustness, and solution stability according to ICH guidelines. All validation parameters were found to be within the acceptable limits, confirming the reliability and reproducibility of the method. Hence, the proposed RP-HPLC method is suitable for routine quantitative estimation and quality control analysis of the drug in bulk and marketed pharmaceutical dosage forms.

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