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DEVELOPMENT AND VALIDATION OF AN ANALYTICAL RP-HPLC METHOD OF QUANTITATIVE DETERMINATION OF EDOXABAN IN BULK FORM & MARKETED PHARMACEUTICAL DOSAGE FORMS

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Abstract:

A new analytical simple, rapid, precise, accurate and reproducible RP-HPLC method for estimation of Edoxaban in bulk form and marketed pharmaceutical formulations. Separation of Edoxaban was successfully achieved on a Phenomenex Gemini ODS C18 (4.6mm x 250mm, 5µm) column in an isocratic mode of separation utilizing Methanol: Phosphate Buffer in the ratio of (25:75% v/v) at a flow rate of 1.0 mL/min and the detection was carried out at 272nm. The method was validated according to ICH guidelines for linearity, sensitivity, accuracy, precision, specificity and robustness. The response was found to be linear in the drug concentration range of 10-50mcg/mL for Edoxaban. The correlation coefficient was found to be 0.999 for Edoxaban. The LOD and LOQ for Edoxaban were found to be 1.1µg/mL and 3.2µg/mL respectively. The proposed method was found to be good percentage recovery for Edoxaban, which indicates that the proposed method is highly accurate. The specificity of the method shows good correlation between retention times of standard solution with the sample solution. Therefore, the proposed method specifically determines the analyte in the sample without interference from excipients of pharmaceutical dosage forms.

Keywords: *Edoxaban, RP-HPLC, Method Development, Accuracy, ICH Guidelines.*

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INTRODUCTION:

Edoxaban is a novel oral anticoagulant used for reducing the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF). Edoxaban is indicated for reducing the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF)[1]. However, it should not be used in patients with creatinine clearance (CrCL) > 95 mL/min because of increased risk of ischemic stroke compared to warfarin at the highest dose studied (60 mg). It is also indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5-10 days of initial therapy with a parenteral anticoagulant[2]. Edoxaban (brand name Savaysa) is a direct oral anticoagulant (DOAC) used to prevent blood clots and stroke. It is primarily indicated to reduce the risk of stroke in nonvalvular atrial fibrillation (NVAF) and to treat deep vein thrombosis (DVT) and pulmonary embolism (PE), often following initial injectable anticoagulant therapy[3]. Chemically Edoxaban[3] is 2-[1-ethyl sulfonyl-3-[4-(7H-pyrrolo [2, 3-d] pyrimidin-4-yl) pyrazol-1-yl] azetidin-3-yl] acetonitrile. The Chemical Structure of Edoxaban is follows

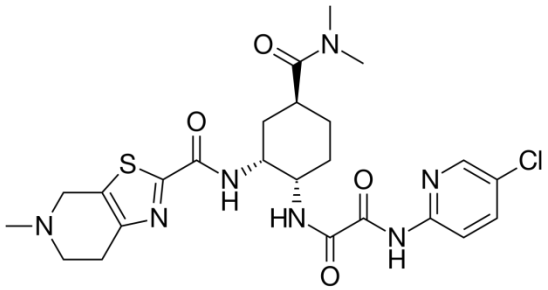


Fig-1: Chemical Structure of Edoxaban

EXPERIMENTAL METHODS

Table-1: Instruments Used

S.No.	Instruments and Glass wares	Model
1	HPLC	WATERS Alliance 2695 separation module, Software: Empower 2, 996 PDA Detector.
2	pH meter	Labindia
3	Weighing machine	Sartorius
4	Volumetric flasks	Borosil
5	Pipettes and Burettes	Borosil
6	Beakers	Borosil
7	Digital ultra sonicator	Labman

Table-2: Chemicals Used

S.No	Chemical	Brand Names
1	Edoxaban (Pure)	Synpharma Research Lab, Hyderabad
2	Water and Methanol for HPLC	LICHROSOLV (MERCK)
3	Acetonitrile for HPLC	Merck

HPLC METHOD DEVELOPMENT:

Preparation of Standard Solution:

Accurately weigh and transfer 10 mg of Edoxaban working standard into a 10ml of clean dry volumetric flasks add about 7ml of Methanol and

sonicate to dissolve and removal of air completely and make volume up to the mark with the same Methanol.
Further pipette 0.3ml of the above Edoxaban stock solutions into a 10ml volumetric flask and dilute up to the mark with Methanol.

Preparation of Sample Solution:
Take average weight of the Powder and weight 10 mg equivalent weight of Edoxaban 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.
Further pipette 0.3ml of the above Edoxaban stock solutions into a 10ml volumetric flask and dilute up to the mark with Methanol.

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[32-33].

Mobile Phase Optimization:
Initially the mobile phase tried was methanol: Water and ACN: Water with varying proportions. Finally, the mobile phase was optimized to Methanol: Phosphate Buffer 25:75% v/v) respectively[4].

Optimization of Column:
The method was performed with various C_{18} columns like Symmetry, Zodiac and Xterra. Phenomenex Gemini ODS C18 (4.6mm x 250mm, 5µm) Column was found to be ideal as it gave good peak shape and resolution[5] at 1.0ml/min flow.

Preparation of Mobile Phase:
Accurately measured 250 ml (25%) of HPLC Methanol and 750 ml of Phosphate Buffer (75%) were mixed and degassed in a digital ultra sonicater for 15 minutes and then filtered through 0.45 µ filter under vacuum filtration.

Diluent Preparation:
The Mobile phase was used as the diluent.

Method Validation Parameters
System Suitability
Accurately weigh and transfer 10 mg of Edoxaban working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Further pipette 0.3ml of the above Edoxaban stock solutions into a 10ml volumetric flask and dilute up to the mark with Methanol.

Procedure:
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[5].

Specificity:
Preparation of Standard Solution:
Accurately weigh and transfer 10 mg of Edoxaban working standard into a 10ml of clean dry volumetric flasks add about 7ml of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Further pipette 0.3ml of the above Edoxaban stock solutions into a 10ml volumetric flask and dilute up to the mark with Methanol.

Preparation of Sample Solution:
Take average weight of the Powder and weight 10 mg equivalent weight of Edoxaban 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.
Further pipette 0.3ml of the above Edoxaban stock solutions into a 10ml volumetric flask and dilute up to the mark with Methanol.
Procedure:
Inject the five replicate injections of standard and inject the three replicate injections sample solutions and calculate the assay by using formula[6]:

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

Linearity:
Accurately weigh and transfer 10 mg of Edoxaban working standard into a 10ml of clean dry volumetric flasks add about 7ml of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Preparation of Level – I (10ppm of Edoxaban):
Take 0.1ml of stock solution in to 10ml of volumetric flask and make up the volume up to mark with diluent[7].

Preparation of Level – II (20ppm of Edoxaban):

Take 0.2ml of stock solution in to 10ml of volumetric flask and make up the volume up to mark with diluent.

Preparation of Level – III (30ppm of Edoxaban):
Take 0.3ml of stock solution in to 10ml of volumetric flask and make up the volume up to mark with diluent.

Preparation of Level – IV (40ppm of Edoxaban):
Take 0.4ml of stock solution in to 10ml of volumetric flask and make up the volume up to mark with diluent.

Preparation of Level – V (50ppm of Edoxaban):
Take 0.5ml of stock solution in to 10ml of volumetric flask and make up the volume up to mark with diluent.

Procedure:
Inject each level into the chromatographic system 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[8].

Precision
Repeatability
Preparation of Edoxaban Product Solution for Precision:
Accurately weigh and transfer 10 mg of Edoxaban working standard into a 10ml of clean dry volumetric flasks add about 7ml of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Take 0.3ml of stock solution in to 10ml of volumetric flask and make up the volume up to mark with diluent.
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.

Intermediate Precision:
To evaluate the intermediate precision (also known as Ruggedness) of the method, Precision was performed on different days by maintaining same conditions[9-10].

Procedure:
Analyst 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.

Analyst 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.

Accuracy:
For Preparation of 50% Standard Stock Solution:
Accurately weigh and transfer 10 mg of Edoxaban working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Take 0.15ml of stock solution in to 10ml of volumetric flask and make up the volume up to mark with diluent.

For Preparation of 100% Standard Stock Solution:
Accurately weigh and transfer 10 mg of Edoxaban working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Take 0.3ml of stock solution in to 10ml of volumetric flask and make up the volume up to mark with diluent.

For Preparation of 150% Standard Stock Solution:
Accurately weigh and transfer 10 mg of Edoxaban working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Take 0.45ml of stock solution in to 10ml of volumetric flask and make up the volume up to mark with diluent.

Procedure:
Inject the Three replicate injections of individual concentrations (50%, 100%, 150%) were made under the optimized conditions[11]. Recorded the chromatograms and measured the peak responses. Calculate the Amount found and Amount added for Edoxaban and calculate the individual recovery and mean recovery values[12].

Limit of Detection (LOD) and Limit of Quantification (LOQ):
Preparation of 0.597µg/ml solution (LOD):
Accurately weigh and transfer 10 mg of Edoxaban working standard into a 10ml of clean dry volumetric flasks add about 7ml of Methanol and sonicate to dissolve and removal of air completely and make volume up to the mark with the same Methanol.

Further pipette 0.00597ml of the above Edoxaban stock solutions into a 10ml volumetric flask and dilute up to the mark with Methanol.

Preparation of 1.811µg/ml solution (LOQ):
Accurately weigh and transfer 10 mg of Edoxaban working standard into a 10ml of clean dry volumetric flasks add about 7ml of Methanol and sonicate to dissolve and removal of air completely and make volume up to the mark with the same Methanol.
Further pipette 0.01811ml of the above Edoxaban stock solutions into a 10ml volumetric flask and dilute up to the mark with Methanol.

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

For preparation of Standard Solution:
Accurately weigh and transfer 10 mg of Edoxaban working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Take 0.3ml of stock solution in to 10ml of volumetric flask and make up the volume up to mark with diluent.

Effect of Variation of Flow Conditions:
The sample was analyzed at 0.9ml/min and 1.1ml/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. ACN: Methanol was taken in the ratio and 75:25, 85:15 instead of 80:20, remaining conditions are same. 20µl of the above sample was injected and chromatograms were recorded.

RESULTS AND DISCUSSION:

Optimization of Analytical Method:
Several trials were performed to develop and optimize the proposed RP-HPLC method for the estimation of Edoxaban. Different chromatographic conditions were evaluated to achieve efficient separation, good peak symmetry, and reproducible results[13]. The mobile phase consisting of methanol and phosphate buffer in the ratio of 25:75 (v/v) was optimized using a Phenomenex Gemini ODS C18 column (4.6 × 250 mm, 5 µm). The analysis was carried out at a flow rate of 1.0 mL/min with UV detection at 272 nm and an injection volume of 20 µL. The optimized chromatographic conditions produced a sharp and symmetrical peak with satisfactory chromatographic performance within a short analysis time. The total run time was 8 minutes, and the optimized conditions were considered suitable for the subsequent validation of the developed RP-HPLC method[14].

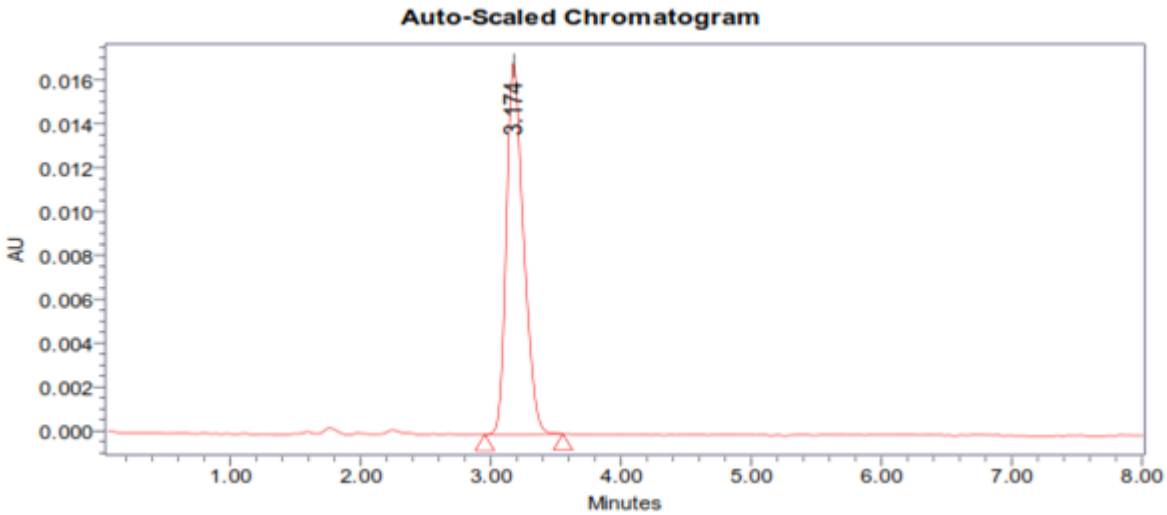


Fig-2: Optimized Chromatographic Condition of Edoxaban

Validation of Analytical Method
Validation of the developed HPLC method was carried out according to the International Council on Harmonization (ICH) guidelines Q2 (R1) for linearity and range, accuracy, precision, LOD and LOQ, specificity and robustness by the following procedure[15-16].

System Suitability
Standard solutions were prepared as per the test method and injected into the chromatographic system. The system suitability parameters like theoretical plates, resolution and asymmetric factor

were evaluated. The results were presented in Table 3.

Table-3: Results of System Suitability for Edoxaban

S.No.	Peak Name	RT	Area (µV*sec)	Height (µV)	USP Plate Count	USP Tailing
1	Edoxaban	3.192	225645	20584	6286	1.38
2	Edoxaban	3.146	225847	20965	6358	1.39
3	Edoxaban	3.123	228656	20758	6285	1.41
4	Edoxaban	3.167	228547	20859	6278	1.40
5	Edoxaban	3.158	229658	20968	6395	1.42
Mean			227670.6			
Std. Dev.			1810.899			
% RSD			0.795403			

Specificity

The specificity was studied to examine the presence of interfering components, while in the comparison of Chromatograms; there was no interference from blank and standard Chromatogram[17].

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

= 99.24%

The % purity[18] of Edoxaban in marketed pharmaceutical dosage form was found to be 99.24%.

Linearity

Linearity was performed by preparing a standard solution of Edoxaban at different concentration levels, i.e., 10–50 µg/mL. The absorbance was measured at 272 nm. Linearity was proven by regression analysis by the least square method[19-20]. The correlation coefficient and linearity results were presented in Table 4, and the linearity curve was represented in Figure 3.

Table-4: Data for Linearity of Edoxaban

Concentration µg/ml	Average Peak Area
10	78683
20	146545
30	213584
40	279895
50	346568

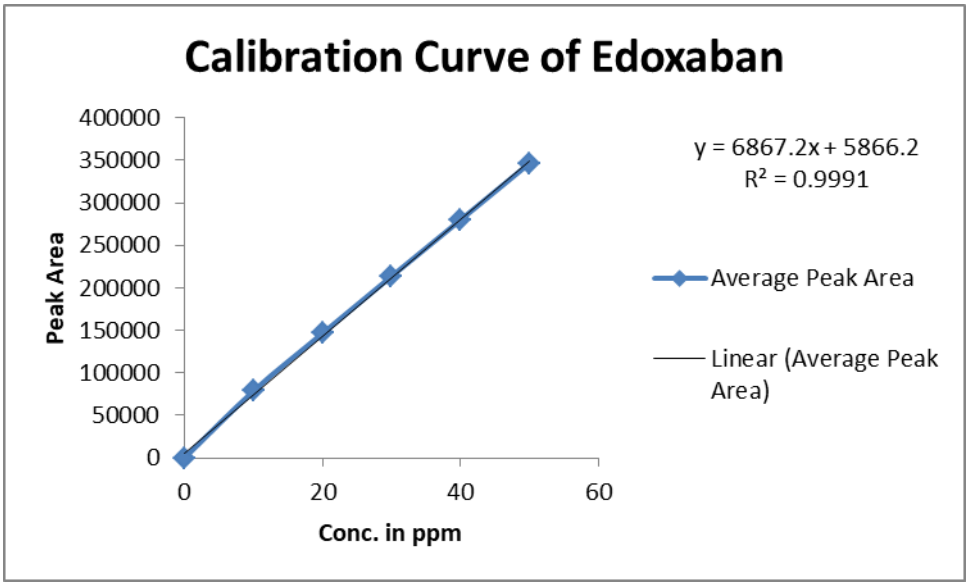


Fig-3: Calibration Curve of Edoxaban

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

Y = mx + c
Slope (m) =6867
Intercept (c) = 5866
Correlation Coefficient (r) = 0.99

Validation Criteria: The response linearity is verified if the Correlation Coefficient is 0.99 or greater[21].

Conclusion: Correlation Coefficient (r) is 0.99, and the intercept is 5866. These values meet the validation criteria.

Precision

Precision was studied to find out intra-day and inter-day variation in the test methods of Edoxaban for 6 times on the same day and different day[22-26]. The intra-day and inter-day precision obtained was %RSD (<2.0) indicates that the proposed method is quite precise and reproducible, and results are shown in Table 5 and 6 & 7.

Table-5: Results of Method Precision for Edoxaban:

S. No	Peak name	Retention time	Area (µV*sec)	Height (µV)	USP Plate Count	USP Tailing
1	Edoxaban	3.165	225645	20562	6125	1.36
2	Edoxaban	3.163	225847	20645	6129	1.36
3	Edoxaban	3.158	226542	20534	6135	1.35
4	Edoxaban	3.167	226598	20564	6189	1.36
5	Edoxaban	3.171	226584	20549	6138	1.35
6	Edoxaban	3.181	226859	20685	6179	1.37
Mean			226345.8			
Std. Dev			482.1068			
%RSD			0.212996			

Intermediate Precision:

Analyst 1:

Table-6: Results of Ruggedness for Analyst 1 for Edoxaban

S.No	Peak Name	RT	Area (µV*sec)	Height (µV)	USP Plate Count	USP Tailing
1	Edoxaban	3.165	226534	20653	6235	1.35
2	Edoxaban	3.163	226542	20598	6198	1.36
3	Edoxaban	30158	225989	20653	6254	1.36

4	Edoxaban	3.167	226512	20548	6281	1.35
5	Edoxaban	3.171	226531	20653	6199	1.36
6	Edoxaban	3.171	225898	20658	6253	1.35
Mean			226334.3			
Std. Dev.			304.2622			
% RSD			0.13443			

Analyst 2:

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

S.No.	Peak Name	RT	Area (µV*sec)	Height (µV)	USP Plate count	USP Tailing
1	Edoxaban	3.173	225487	20542	6253	1.35
2	Edoxaban	3.134	225484	20532	6098	1.36
3	Edoxaban	3.161	225364	20541	6254	1.35
4	Edoxaban	3.174	226513	20534	6235	1.36
5	Edoxaban	3.199	225487	20549	6199	1.36
6	Edoxaban	3.199	226532	20451	6235	1.35
Mean			225811.2			
Std. Dev.			553.0524			
% RSD			0.244918			

Accuracy

The accuracy of the method was determined by the standard addition method. A known standard drug was added to the fixed amount of pre-analyzed drug sample solution. The standard addition method was performed at three concentration levels in triplicate at 50%, 100%, and 150%. Percent recovery (Table 8) was calculated by comparing the peak area before and after adding the standard drug. Accuracy at different concentrations (50%, 100%, and 150%) was prepared and the % recovery was calculated[27].

Table-8: The Accuracy Results for Edoxaban

%Concentration (at specification Level)	Area	Amount Added (ppm)	Amount Found (ppm)	% Recovery	Mean Recovery
50%	109283.3	15	15.060	100.40%	100.42%
100%	212732	30	30.124	100.413%	
150%	316263.3	45	45.201	100.446%	

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[28].

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

Where

σ = Standard deviation of the response

S = Slope of the calibration curve

Result:

= 0.597µg/ml

Limit of Quantitation

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined[29].

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

Where

σ = Standard deviation of the response

S = Slope of the calibration curve

Result:

= 1.811µg/ml

Robustness

To demonstrate the method's robustness, prepared solution as per test method and injected at different variable conditions like using different conditions like flow rate and organic content in the mobile phase[30-37]. The results for robustness are represented in Table 9.

Table-9: Results for Robustness of Edoxaban

Parameter Used for Sample Analysis	Peak Area	Retention Time	Theoretical Plates	Tailing Factor
Actual Flow rate of 1.0 mL/min	225645	3.155	6125	1.36
Less Flow rate of 0.9 mL/min	236586	3.488	6452	1.38
More Flow rate of 1.1 mL/min	219865	2.877	6098	1.42
Less organic phase	235848	4.705	6126	1.43
More organic phase	241245	2.090	6324	1.39

SUMMARY AND CONCLUSION:

The RP-HPLC method was successfully developed and optimized for the estimation of Edoxaban by selecting suitable chromatographic conditions. The optimized method employed a Phenomenex Gemini ODS C18 column with methanol and phosphate buffer (25:75% v/v) as the mobile phase, at a flow rate of 1.0 mL/min and a detection wavelength of 272 nm. The injection volume was maintained at 20 µL, with an ambient column temperature and a total run time of 8 minutes. The drug showed a satisfactory retention time of 3.174 minutes with good peak symmetry and chromatographic performance. The method exhibited good linearity over the concentration range of 10–50 µg/mL, with percentage recovery ranging from 98–102%. The validation results demonstrated satisfactory accuracy, precision, robustness, and ruggedness in accordance with ICH guidelines. Overall, the developed RP-HPLC method was found to be simple, rapid, accurate, precise, and reproducible, making it suitable for routine quantitative estimation and quality control analysis of Edoxaban in bulk and marketed pharmaceutical dosage forms.

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