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Analytical Method Development and Validation RP-HPLC Method for the Quantitative Determination of Rivaroxaban in Bulk and Pharmaceutical Formulation

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Abstract
In the present study, a new, sensitive, suitable, simple, precise, and robust reversed-phase high-performance liquid chromatography (RP-HPLC) method was developed and validated for the Rivaroxaban. Optimization was done by response surface methodology, applying Central Composite Design. Two factors selected were mobile phase composition, flow rate. The separation was carried on an HPLC system containing LC Solution software and HPLC Column C18 (250 x 4.6 mm),5µm. The detection was carried out at wavelength 250 nm. In the developed RP-HPLC method, 0.01M Sodium dihydrogen orthophosphate Buffer and Acetonitrile in the ratio of 40:60 v/v was used as mobile phase, at a flow rate of 1.0 mL/min and the retention time was found to be 4.4 min for Rivaroxaban. The results of the analysis in the method were validated in terms of linearity, accuracy, precision and specificity. The linearity of the developed method with a coefficient of correlation for the standard curve is 0.9991. The RSD for the precision of the method were found less than 2.0 %. The percentage recoveries of Rivaroxaban were found to be 100.19%. The developed and validated RP-HPLC method is robust, reproducible can be used for routine quality control in bulk and pharmaceutical dosage form in pharmaceutical industry.

Keywords
RP-HPLC, Rivaroxaban Method Development, Validation.

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INTRODUCTION:
Analytical method validation is the process of establishing documented evidence that an analytical procedure is suitable for its intended purpose. Validation confirms that the developed method consistently produces accurate, precise, and reliable results within specified limits.

Method validation is an essential regulatory requirement in pharmaceutical industries and is performed according to International Council for Harmonisation (ICH) guideline Q2 (R1): "Validation of Analytical Procedures: Text and Methodology."
Validation provides confidence that the analytical method is capable of producing scientifically sound results during routine quality control testing.

DRUG PROFILE:
Rivaroxaban

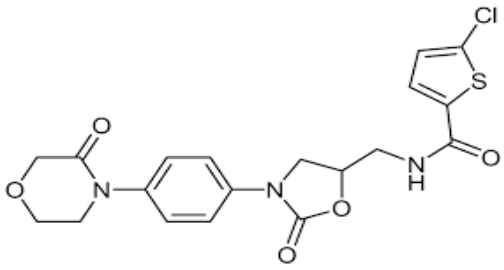

Figure 1: Structure of Rivaroxaban

Parameter	Description
Drug Name	Rivaroxaban
IUPAC Name	5-Chloro-N-{[(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl) phenyl]-1,3-oxazolidin-5-yl] methyl} thiophene-2-carboxamide
Molecular Formula	$C_{19}H_{18}ClN_3O_5S$
Molecular Weight (g/mol)	435.88 g/mol
CAS Registry No.	366789-02-8
pKa	Approximately 13.6
Log P	Approximately 1.5–1.7
Melting Point	228–229°C
Half life	5–9 hours
Storage	Store at 20–25 °C
Category	Direct Oral Anticoagulant (DOAC); selective direct Factor Xa inhibitor

MATERIAL AND INSTRUMENTS
Material:

1. **Drug samples**

Table 1: Procurement of Drug Samples

Sr. No.	Name of the Drug	Quantity	Supplied by
1	Rivaroxaban	5 gm	Arni Analytical Lab, Nashik

2. **Reagents and chemicals**

Table 2: List of Reagents Used

Chemicals/ Reagents/ Solvents	Supplier	Grade
Potassium dihydrogen Orthophosphate	Fisher scientific	AR grade
Acetonitrile	Fisher scientific	HPLC grade
Water	Fisher scientific	HPLC grade

INSTRUMENTS:

Table 3: List of Instruments used

Instruments / Equipment's	Instruments / Equipment's Make
HPLC System	Shimadzu, LC-2010C$_{HT}$
Software	LC Solution
pH Meter	Lab India
Sonicator	Life Care Instruments Pvt. Ltd.
Analytical Balance	Web-Man
HPLC Column: C18, (4.6 mm x 15-cm), 5µm	Agilent

Validation of RP-HPLC Method:

The developed method for simultaneous estimation of Rivaroxaban was validated as per ICH Q2 (R1) guidelines for the following parameters.

Specificity

The specificity of the method was ascertained by analyzing standard drugs and sample. The retention time (RT) of Rivaroxaban was confirmed by comparing the RT with that of the standard. Rivaroxaban and interference were observed in the chromatogram of blank.

Preparation of Solutions:

1. Standard Solution:

Weigh accurately 20 mg of Rivaroxaban standard in 100ml volumetric flask add 60ml of Mobile phase and sonicate for 5 minutes and make up volume with Mobile phase further dilute 5ml to 50 ml with Mobile phase.

2. Sample Solution:

Weigh accurately 10 tablets and determine average weight. Crush the tablets to fine powder. Weigh accurately powder weight equal to average weight (Tablet weight) in 100 ml volumetric flask. Add 60ml of Mobile phase and sonicate for 10 minutes and make up volume with Mobile phase. Filter
the above solution through what-man filter paper 41. Collect the filtrate. Further dilute 5ml of above solution to 50ml and dilute with Mobile phase.

Acceptance criteria:

The relative standard deviation for Rivaroxaban should not be more than 2.0%

There is no interference of blank with the principal peaks i.e. Rivaroxaban.

3. Precision

Precision is a measurement of degree of Reproducibility of analytical method and it will be expressed in terms of % relative standard for the area and retention time of Solution prepared. 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.

Preparation of Solutions:

1. Standard Solution:

Weigh accurately 20 mg of Rivaroxaban standard in 100ml volumetric flask add 60ml of Mobile phase and sonicate for 5 minutes and make up volume with Mobile phase further dilute 5ml to 50 ml with Mobile phase.

2. Sample Solution:

Weigh accurately 10 tablets and determine average weight. Crush the tablets to fine powder. Weigh accurately powder weight equal to average weight (Tablet weight) in 100 ml volumetric flask. Add 60ml of Mobile phase and sonicate for 10 minutes and make up volume with Mobile phase filter the above solution through what-man filter paper 41. Collect the filterate. Further dilute 5ml of above solution to 50ml and dilute with Mobile phase.

Acceptance criteria:

The relative standard deviation for Rivaroxaban should not be more than 2.0 %

4. Accuracy:

The accuracy of an analytical method is defined as the closeness between the observed values with actual or true value for a specific concentration. Accuracy - closeness to the true value, measured by % recovery

- 80 % of the standard concentration.
- 100 % of the standard concentration.
- 120 % of the standard concentration.
- Calculate % Recovery for every solution at each level.

Preparation of Solutions:

1. Standard Solution:

Weigh accurately 20 mg of Rivaroxaban standard in 25ml volumetric flask add 15ml of Mobile phase and sonicate for 5 minutes and make up volume with Mobile phase further dilute 5ml to 50 ml with Mobile phase.

2. Sample Solution:

1) 80% Solution: Weigh accurately 20 mg of Rivaroxaban standard in 25ml volumetric flask add 30ml of Mobile phase and sonicate for 5 minutes and make up volume with Mobile phase further dilute 4ml to 50 ml with Mobile phase.

2) 100% Solution: Weigh accurately 20 mg of Rivaroxaban standard in 25ml volumetric flask add 30ml of Mobile phase and sonicate for 5 minutes and make up volume with Mobile phase further dilute 5ml to 50 ml with Mobile phase.

3) 120% Solution: Weigh accurately 20 mg of Rivaroxaban standard in 25ml volumetric flask add 30ml of Mobile phase and sonicate for 5 minutes and make up volume with Mobile phase further dilute 6ml to 50 ml with Mobile phase.

Acceptance criteria:

Mean recovery should be in range of 98-102 %

RSD should NMT 2.0 %

5. Linearity and Range

Linearity of analytical procedure is its ability to produce results which are directly proportional to analyte concentration in sample.

Linearity Sample Stock Solution:

Weigh accurately 20 mg of Rivaroxaban standard in 25ml volumetric flask add 15ml of Mobile phase and sonicate for 5 minutes and make up volume with Mobile phase.

6. Stability of Solution:
The solution stability of Rivaroxaban in the assay method was carried out by leaving the working standard in tightly capped volumetric flasks at room temperature for 32 hrs. The assay sample is also prepared and kept for stability up to 24 hours.

Preparation of Solutions:

1. Standard Solution:
Weigh accurately 20 mg of Rivaroxaban standard in 100ml volumetric flask add 60ml of Mobile phase and sonicate for 5 minutes and make up volume with Mobile phase further dilute 5ml to 50 ml with Mobile phase.

2. Sample Solution:
Weigh accurately 10 tablets and determine average weight. Crush the tablets to fine powder. Weigh accurately powder weight equal to average weight (Tablet weight) in 100 ml volumetric flask. Add 60ml of Mobile phase and sonicate for 10 minutes and make up volume with Mobile phase. Filter the above solution through what-man filter paper 41. Collect the filtrate. Further dilute 5ml of above solution to 50ml and dilute with Mobile phase

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RESULT AND DISCUSSION:

Rivaroxaban

Table 4: Result of Preliminary characterization and identification of Drug

Parameter	Rivaroxaban
Colour	White
Odour	Odourless
Appearance	Crystaline powder

Scouting step:
This is preliminary study step include some trials to find out a mobile phase that gives an acceptable separation of analyte and selection of other chromatographic factor.

TRIAL-1

Chromatographic Condition:
Column: C18, 250mm × 4.6mm, 5µ Agilent Zorbax
Wavelength:250 nm
Flow :1.0ml/min
Temperature :30°C
Injection Volume :20µL
Mobile Phase: Mixture of Water and Acetonitrile in the ratio of (50:50) v/v

Standard Preparation:
Weigh accurately 20 mg of Rivaroxaban standard in 100ml volumetric flask add 60ml Methanol and sonicate for 5 minutes and make up volume with Methanol further dilute 5ml to 50 ml with Methanol.

Observation:
No peak is observed.

Action:
Needs to add buffer in Mobile phase.

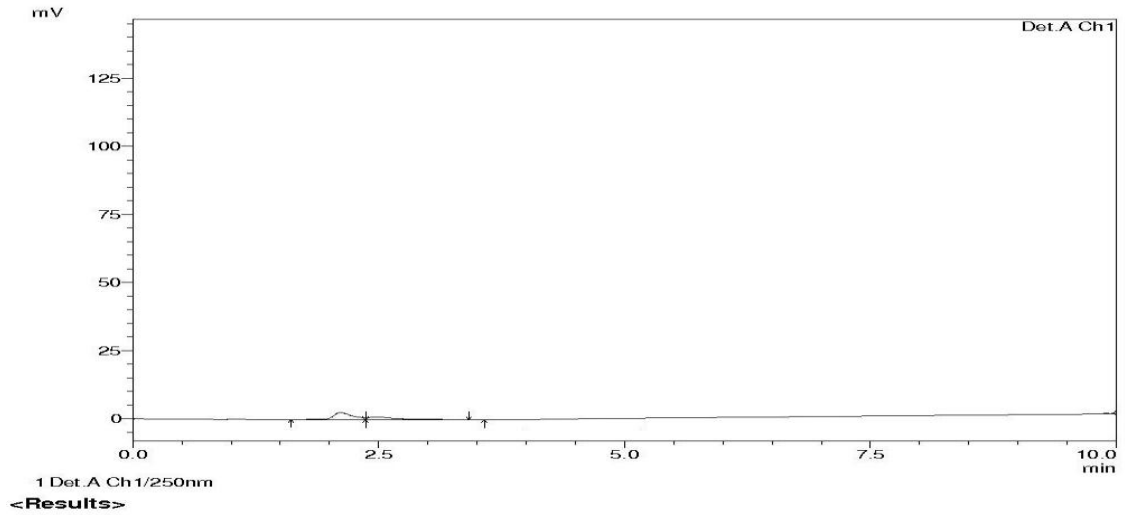


Figure 2: Chromatogram of Trial-1

Statistical data analysis (DOE)
The layout of actual design of DOE with subsequent response result are show in table as given below:

Table 5: Layout of actual design of DOE

Std	Run	Factor 1 A: Mobile Phase ACN	Factor 2 B: Flow Rate	Response 1 Retention Time
5	1	52	1	4.913
11	2	60	1.2	4.236
4	3	60	1	4.492
2	4	55	1.2	4.693
7	5	60	1	4.489
1	6	67	1	2.732
13	7	65	0.8	4.489
10	8	60	1	4.517
12	9	60	0.7	4.667
3	10	60	1	4.528
6	11	55	0.8	4.913
8	12	60	1	4.539
9	13	65	1.2	3.194

Response: Retention Time of Rivaroxaban

Fit Summary:

After entering the data in Design-Expert software, fit summary applied the data after which the "Quadratic model" was suggested by the software.

Table 6: Fit summary table of retention time of Rivaroxaban

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	**0.0013**	**< 0.0001**	**0.6839**	**0.4641**	**Suggested**
2FI	0.1450	< 0.0001	0.7262	0.5323	
Quadratic	**0.0262**	**< 0.0001**	**0.8757**	**0.4080**	**Suggested**
Cubic	< 0.0001		0.9988		**Aliased**

ANOVA of Rivaroxaban

The analysis of variance (ANOVA) was performed to identify significant and insignificant factors. The results of ANOVA for the resolution are as following Table 7.

Table 7: ANOVA table for Retention time of Rivaroxaban

Source	Sum of Squares	d f	Mean Square	F-value	p-value	
Model	4.61	5	0.9223	17.91	0.0007	significant
A-Mobile Phase	3.39	1	3.39	65.89	< 0.0001	
B-Flow Rate	0.5397	1	0.5397	10.48	0.0143	
AB	0.2889	1	0.2889	5.61	0.0497	
A^2	0.6603	1	0.6603	12.82	0.0090	
B^2	0.0043	1	0.0043	0.0841	0.7803	
Residual	0.3604	7	0.0515			
Lack of Fit	0.3585	3	0.1195	247.15	< 0.0001	significant
Pure Error	0.0019	4	0.0005			
Cor Total	4.97	12				

The **Model F-value** of 17.91 implies the model is significant. There is only a 0.07% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, B, AB, A^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

The **Lack of Fit F-value** of 247.15 implies the Lack of Fit is significant. There is only a 0.01% chance that a Lack of Fit F-value this large could occur due to noise.

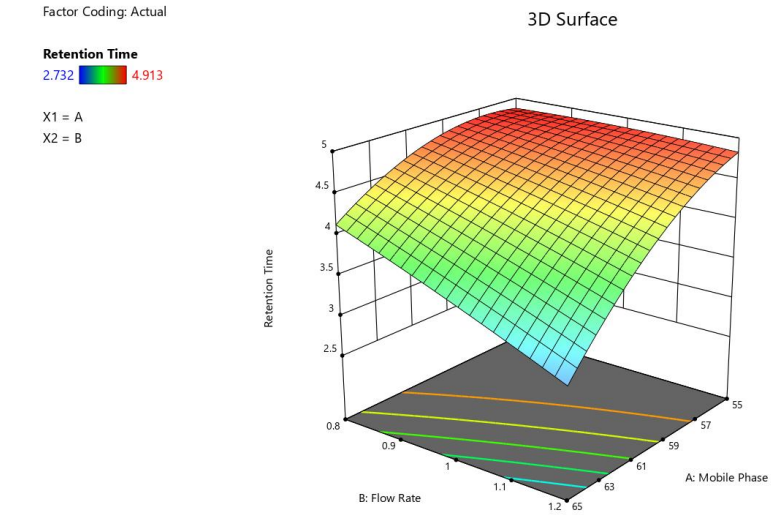
Model assessment for resolution response as dependent variable

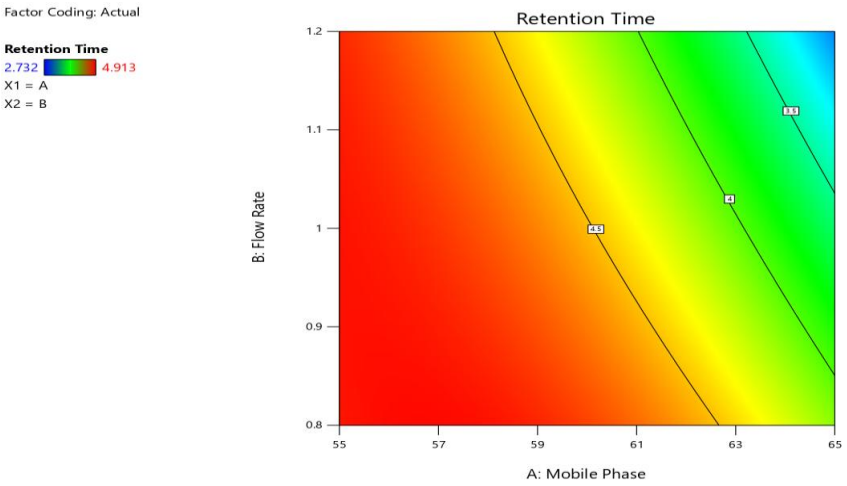
After entering the data in design expert software, fit summary applied to data after which "linear model" was suggested by the software. According to this model following polynomial equation was obtained, polynomial equation in coded terms.

Retention Time = +4.52-0.6375A-0.2882B-0.2687AB-0.2780A^2-0.0284B^2

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

Graphical Presentation: Retention time of Rivaroxaban





Desirability:

Desirability function range from 0 (undesired response) to 1 (fully desired response). D value close to 1 means combination of different criteria globally optimal.

Table 8. Desirability optimized method selected by software1 out of 73 solutions.

Number	Mobile Phase	Flow Rate	Retention Time	Desirability	
1	**60.000**	***1.000***	**4.516**	**1.000**	**Selected**
2	60.000	*1.200*	4.199	1.000	
3	60.000	*1.014*	4.495	1.000	
4	60.000	*0.993*	4.526	1.000	

Number	Mobile Phase	Flow Rate	Retention Time	Desirability
5	60.000	*0.892*	4.663	1.000
6	60.000	*0.960*	4.572	1.000
7	60.000	*1.034*	4.467	1.000
8	60.000	*0.976*	4.550	1.000
9	60.000	*0.825*	4.746	1.000
10	60.000	*1.005*	4.509	1.000
11	60.000	*0.990*	4.531	1.000
12	60.000	*1.037*	4.461	1.000
Up to 73	60.000	*1.168*	4.254	1.000

Figure 3: Desirability optimized method suggested

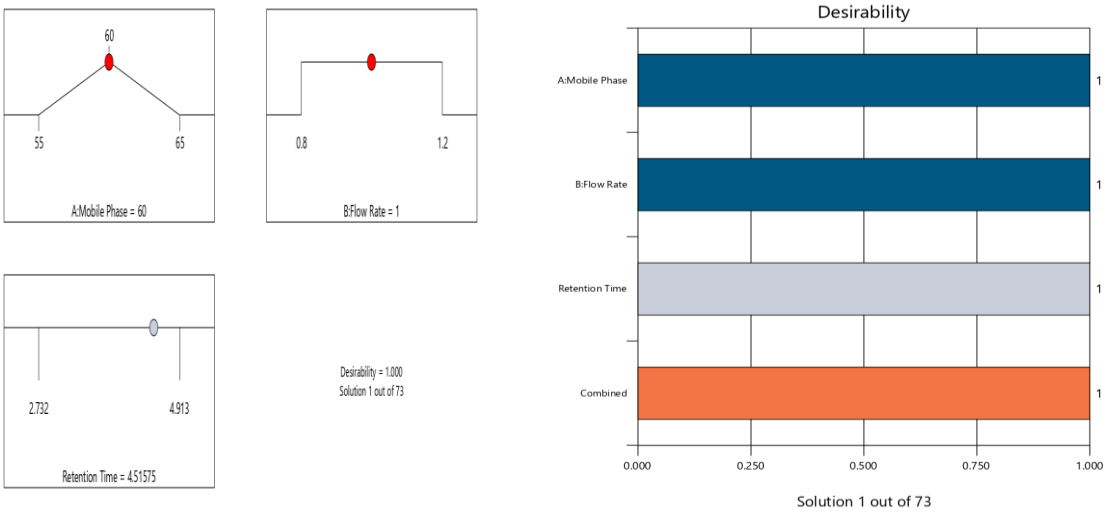
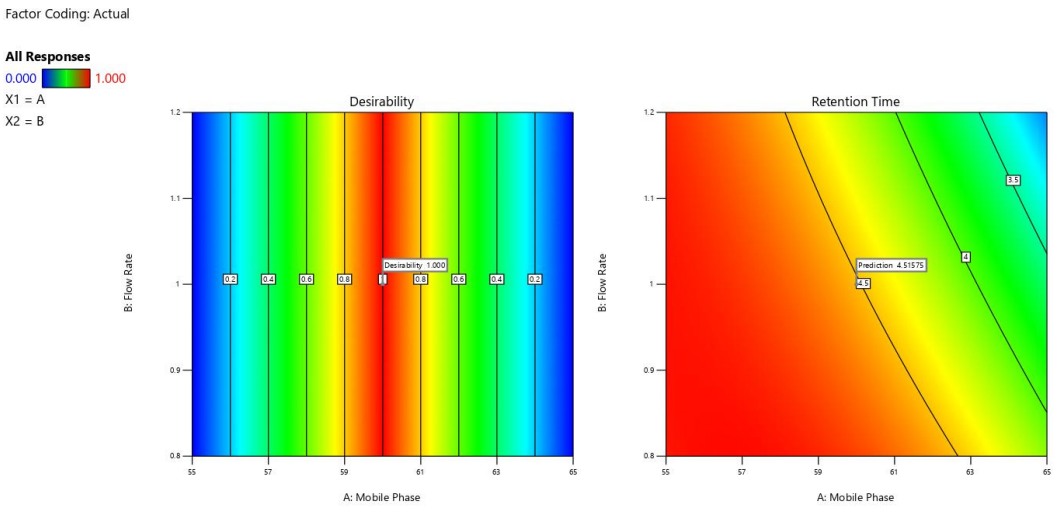


Table 9: Final optimized condition for method

Mobile Phase	Flow rate
Buffer: ACN (40:60 v/v)	**1 ml /min**



Validation of Method

Specificity:

Table 10: Observation table for specificity

Rivaroxaban	Retention Time
Blank	0.000
Standard Solution	4.492
Sample Solution	4.489

Acceptance criteria:

The relative standard deviation for Rivaroxaban should not be more than 2.0%

There is no interference of blank with the principal peaks i.e. Rivaroxaban

Conclusion:

There was no interference observed in Standard & Sample due to Blank.

Precision:

A. System Suitability observed during Precision

Table 11: Analytical data of System Suitability observed during Precision

Number of Injection	Standard Solution Area of Rivaroxaban
1	770998
2	764718
3	766009
Average	**767242**
STDEV	3316.504
RSD	**0.43**

Acceptance criteria:

The relative standard deviation for Rivaroxaban should not be more than 2.0%

B. % Assay

Table 12: Analytical data of Percentage Assay

Number of Injection	Sample Solution Area of Rivaroxaban Area	% Assay
1	760253	99.09
2	762263	99.35
3	761938	99.31
Average	**761485**	**99.25**

% Assay = Average of sample area/Average of standard area x 100=761485/ 767241 x 100 = 99.25 %

Acceptance criteria:

% Assay of Rivaroxaban is NLT 90.0% And NMT 110.0%.

Conclusion:

The assay values of three preparation of Rivaroxaban are having % Assay is NLT 90.0% and NMT 110.0% so the method for assay of Rivaroxaban tablet is precise.

Intermediate Precision:

A. System Suitability observed during Precision

Table 13: Analytical data of System Suitability observed during intermediate Precision

Number of Injection	Standard Solution Area of Rivaroxaban
1	786728
2	796013
3	797980
Average	**793574**
STDEV	6009.545
RSD	**0.76**

B. % Assay

Table 14: Analytical data of Percentage Assay

Number of Injection	Sample Solution Area of Rivaroxaban Area	% Assay
1	786028	99.05
2	797364	100.48
3	787199	99.20
Average	**790197**	**99.57**

% Assay = Average of sample area/ Average of standard area x 100=790197/ 793573 x 100=99.57 %

Difference between Precision %Assay & Intermediate Precision %Assay

Parameter	% Assay Rivaroxaban
Precision %Assay	99.25
Intermediate Precision %Assay	99.57
Difference	0.32

(Difference = Intermediate Precision % Assay – Precision %Assay)

Acceptance criteria:
% Assay of Rivaroxaban is NLT 90.0% And NMT 110.0%

Conclusion: The assay values of three preparation of Rivaroxaban is having % Assay is NLT 90.0% and NMT 110.0%, so the method for assay of Rivaroxaban and tablet precise.

Accuracy:

Table 15: Analytical data of Accuracy

Sr. No.	Level	mg of drug spiked	Rivaroxaban Area	mg of drug Recovered	% Recovery
1	80%	707822	0.032197	100.62	100.62
2	100%	880831	0.040067	100.17	100.17
3	120%	1052942	0.047896	99.78	99.78
			Average		**100.19**
			Std. Dev		0.42
			% RSD		0.42

Acceptance Criteria:
The % recovery of the Rivaroxaban for each injection of each concentration must be between 98 % and 102%

Conclusion:
The % recovery of the Rivaroxaban for each injection of each concentration is 100.62 %, 100.17 %, 99.78 % and mean recovery is 100.19 % which is within the acceptance criteria, hence the method for % assay determination of Rivaroxaban is accurate.

Linearity & range:

Table 16: Analytical data of Linearity & Range

Sr. No.	Concentration in ppm	Concentration of Solution	Diluted to	Area
1	32.0	80	50	562108
2	36.0	90	50	621972
3	40.0	100	50	682934
4	44.0	110	50	753958
5	48.0	120	50	816929

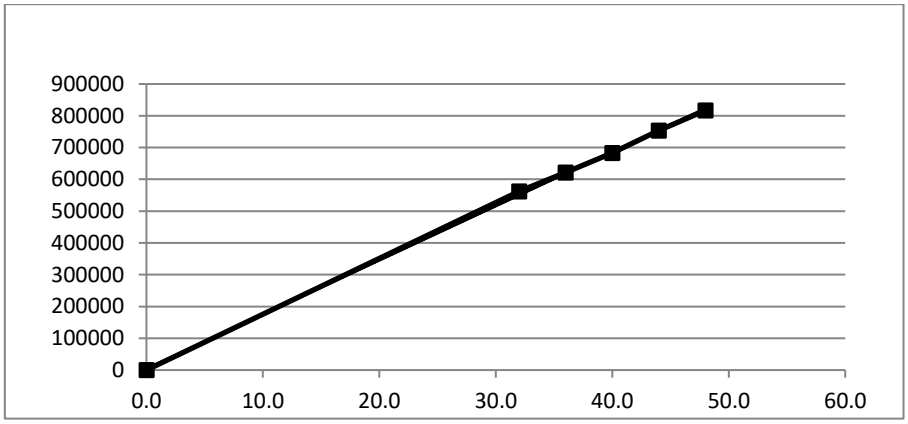


Figure 1.4 Linearity of Rivaroxaban

Rivaroxaban	
Y intercept	**45952.2000**
Slope	**16040.7000**
Correlation coefficient	**0.9991**

Y = mx + c
Where, Y – Dependent variable
X – Independent variable
M – Slope
C – y-intercept

Acceptance Criteria:
The limit for coefficient of correlation for the standard curve must not be less than 0.99

Conclusion:
The obtained results are within the range and coefficient of correlation for the standard curve is 0.9991 which is within acceptance criteria of 0.9990, hence the method is linear within given range.

Stability of Solution:

Table 17: Analytical data of Stability of Solution

Number of Injection	**Standard Solution Area of Rivaroxaban**
1	730664
2	724397
3	735531
Average	**730197**
STDEV	5581.651
RSD	**0.76**

Table 18: Observation data of solutions stability after specific time

Sr. No.	**Hours**	**Area Rivaroxaban**	**% Assay Rivaroxaban**	**%Assay Difference Rivaroxaban**
1	Initial	730197	99.25	-
2	4 Hour	720790	98.71	0.54
3	24 Hour	713980	97.78	1.47

Acceptance Criteria:
Stability of solution: % Difference between Initial solution & different Interval is NMT 2.0 %.

Conclusion:
The sample solutions of Rivaroxaban are stable up to 24 hours at room temperature.

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.

Calculated by following formula

$$= \frac{3.3 \times Std.Deviation}{Slope}$$

$$= \frac{3.3 \times 3548.3}{16040.700}$$

LOD = 0.7 ppm

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 with suitable precision.

Calculated by following formula

$$= \frac{10 \times Std.Deviation}{Slope}$$

$$= \frac{10 \times 3548.3}{16040.700}$$

LOQ = 2.6 ppm

CONCLUSION:

The analytical method was successfully validated and met all predefined acceptance criteria. The method demonstrated satisfactory specificity, precision, accuracy, linearity, solution stability, and stability-indicating capability. All validation results were within acceptable limits, confirming that the method is reliable, accurate, and suitable for routine quality control analysis and stability studies of the pharmaceutical product. Estimation of Rivaroxaban by using different chromatographic conditions was done. The method displayed excellent linearity across the validated concentration range with correlation coefficient, 0.9991. The method's Limit of Detection was established at 0.7 ppm and Limit of Quantitation was at 2.6 ppm. Validation was conducted as per ICH Q2 (R1) guidelines. The method demonstrated high accuracy with recovery values within the acceptable range of 98% - 102%.

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