第 49 卷 第 6 期
2022 年 6 月

湖南大学学报（自然科学版）
Journal of Hunan University (Natural Sciences)

Vol. 49 No. 6
June 2022

Open Access Article https://doi.org/10.55463/issn.1674-2974.49.6.11

Comparison of Chemical Parameters of Different Brands of Rivaroxaban Tablets Available in Pakistan

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Abstract: A major issue is that the dissolution and assay methods are not discussed in any pharmacopeia, so the assay method was developed following the guidelines of the Food and Drug Administration. The analytical and dissolution methods were developed and validated in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use's (ICH) guidelines. This study aims to discover the presence of counterfeit or substandard drugs in the market, to classify the most compliant brands, and to ascertain the appropriateness of interchangeability. Four different brands of rivaroxaban were selected in order to perform different quality control tests, which included the analytical, dissolution, and assay methods in accordance with the guidelines of the United States Pharmacopeia. The four chosen brands were tested and the results were found to be compliant with chemical parameters such as dissolution, content uniformity, and assay. Hence, it can be concluded that rivaroxaban 10 mg tablets, manufactured in Pakistan by leading pharmaceutical companies, are consistent in quality and can be easily interchangeable.

Keywords: rivaroxaban, anticoagulant, quality control parameters.

巴基斯坦不同品牌利伐沙班片化学参数比较

摘要：一个主要问题是任何药典都没有讨论溶出度和测定方法，因此该测定方法是按照食品和药物管理局的指导方针开发的。分析和溶出方法是根据国际人用药品技术要求协调委员会(非物质文化遗产)指南开发和验证的。本研究旨在发现市场上假冒或劣质药品的存在，对最合规的品牌进行分类，并确定互换性的适当性。选择了四种不同品牌的利伐沙班，以进行不同的质量控制测试，包括符合美国药典指南的分析、溶出和测定方法。对四个选定的品牌进行了测试，发现结果符合化学参数，例如溶出度、含量均匀度和含量。因此，可以得出结论，由领先的制药公司在巴基斯坦生产的利伐沙班10毫克片剂质量一致，并且可以轻松互换。

关键词：利伐沙班，抗凝剂，质量控制参数。

Received: March 17, 2022 / Revised: April 12, 2022 / Accepted: May 24, 2022 / Published: June 30, 2022

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1. Introduction

Rivaroxaban is used as an anticoagulant to inhibit the clotting of blood. Clotting can block the blood supply to the brain or to the heart, causing strokes or heart attacks. Rivaroxaban is derived from oxazolidinone [1–4].

Rivaroxaban was developed by Bayer and is marketed by Janssen Pharmaceuticals in the United States under the brand name Xarelto. The European Commission approved the use of rivaroxaban for two additional conditions, that is, for strokes and systemic embolism in adult patients [5]. Rivaroxaban was also accepted in North America for the prevention and treatment of recurring pulmonary embolism and deep vein thrombosis (DVT) in adult patients, and it has now been approved by the European Commission as an antiplatelet agent for the treatment of venous thromboembolism (VTE) and for patients having coronary syndromes and raised cardiac biomarkers [6]. Rivaroxaban has no antidotes; therefore, it is necessary to quickly measure the risk of bleeding and anticoagulation through prothrombin time [7]. The drug is available in dosages that can be taken orally as tablets for anticoagulation and as a mechanism for direct action Factor Xa (FXa) inhibitor. Rivaroxaban has been approved by the Food and Drug Administration (FDA) to be used as a DVT deterrent [8].

Rivaroxaban is prescribed for VTE in patients undergoing major orthopedic medical procedures for lower appendages, the treatment of DVT, pneumonic embolism, stroke anticipation with nonvalvular fibrillation, and secondary anticipation in patients with coronary disorder. Rivaroxaban was approved by the FDA, the European Commission, and Health Canada in September 2008 [5, 6, 7, 9]. It is a specific inhibitor of FXa, and there is no need for a cofactor (e.g., antithrombin III) for activity. It also inhibits platelet stimulation by selecting the active site of FXa by activating Factor X to FXa through an intrinsic–extrinsic pathway, which plays a significant role in the blood clotting cascade. Rivaroxaban inhibits platelet aggregation indirectly after tempting thrombin but it has no effect on direct platelet aggregation [10, 11]. Anti-FXa activity is also affected by rivaroxaban [12].

Bioavailability of rivaroxaban is based on doses; for example, a 10 mg pill (80–100%) can be taken with or without sustenance and is not affected by nourishment. The peak plasma time is 2–4 h after oral administration. AUC: 29–56% falling when discharged in proximal small digestive system contrasted with gastric ingestion [10]. Protein bound: 92–95% (albumin) volume of circulation at a consistent state. Vd: 50 L [11]. Rivaroxaban is metabolized by hydrolysis and further by oxidative degeneration and catalyzed by CYP3A4/5 and CYP2J2. Rivaroxaban dose mixing in human plasma is unchanged, with no main or dynamic metabolite [11]. Approximately 36% of unchanged rivaroxaban is eliminated through urine and 7% through feces. Rivaroxaban exhibits a half-life of approximately 11–13 h in the elderly and 5–9 h in young adults [10]. Use of rivaroxaban with non-steroidal anti-inflammatory drugs (e.g., aspirin) can increase the risk of bleeding; therefore, avoid the use of other anticoagulants to reduce the risk of hemorrhage [11, 12]. The quality control test conducted on the tablets includes chemical parameters such as dissolution, content uniformity, and assay.

2. Materials and Methods

2.1. Materials

The materials used throughout are working standard rivaroxaban, measuring cylinder, volumetric flask, filter paper, filter funnel, mortar and pestle, syringe, and beaker.

2.2. Reagents

The reagents used throughout are phosphoric acid, potassium dihydrogen phosphate, methanol, sodium hydroxide, acetonitrile, acetic acid, sodium acetate, and sodium lauryl sulphate (all purchased from Merck).

2.3. Equipment

The equipment used during the study are listed in Table 1.

Table 1 Equipment list

S. No.	Equipment Name	Model	Manufacturer	Country Origin
1	HPLC	LC20	Shimadzu	Japan
2	Dissolution tester	PT-DT70+ DT7	Pharma Test	Germany
5	Analytical Balance	ME20T	Mettler Toledo	Germany
6	pH meter	PH0731 P	Mettler Toledo	Germany

2.4. Sample Collection

Rivaroxaban tablets, manufactured and marketed by a reputed pharmaceutical company in Pakistan, were procured from the local market.

2.5. Analytical Method Development

High performance liquid chromatography (HPLC) method with an isocratic reverse phase was developed to determine the rivaroxaban in a solid dosage form as a tablet. For this objective, a wide literature survey was conducted, and a method was developed using different

HPLC columns/systems and different compositions of buffers and solvent systems. To obtain the wavelength at which maximum absorbance was attained, an ultraviolet (UV) spectrophotometer was beneficial for scanning the rivaroxaban standards. After successful scanning, different samples were also run through HPLC at different wavelengths. Following this, a 308 nm wavelength was found satisfactory for rivaroxaban, as the peak symmetry for the drug was excellent and reliable for testing rivaroxaban from tablets. The separation was done by using the C18 column (4.6 × 250 mm, 5 µm) as the stationary phase. The mobile phase included a buffer and acetonitrile in the ratio of 60:40 (v/v), adjusted at a flow rate of 1.0 ml/minute with the injection volume set at 10 µl. The method was developed, and the parameters were adjusted as per FDA guidelines.

2.6. Analytical Method Validation

After the development of a method for rivaroxaban analysis, the analytical procedure was validated to demonstrate that the developed method is suitable for its intended purpose. These procedures were developed and performed to prove that the drug meets the recommended standards and criteria of quality, safety, identity, purity, and potency, as per the guidelines of different regulatory authorities such as the FDA, USP, ICH, and BP.

The method was validated as per FDA and ICH guidelines for the following parameters/steps:

2.6.1. System Suitability

System suitability of 10 mg rivaroxaban tablets was performed by running six standards on HPLC and statistically analyzed. System suitability testing is an integral part of many analytical procedures.

2.6.2. Accuracy

The accuracy of an analytical procedure expresses the closeness of agreement between the values, which is either a true conventional value or an accepted reference value and the value found. For accuracy, three different concentrations were prepared in the 80-120% range by mixing placebo and rivaroxaban active material and running on HPLC in triplicate.

2.6.3. Repeatability

The repeatability of the method for the assay was demonstrated by preparing six samples. The samples were analyzed according to the analytical method, and each sample's percentage of rivaroxaban was determined.

2.6.4. Intermediate Precision

The intermediate precision of the method for the assay was demonstrated by preparing six samples for each step. Two different analysts carried out the test, six samples each, to compensate for individual handling. The samples were analyzed, and the percent label claim for rivaroxaban was determined for each sample. All acceptance criteria were met.

2.6.5. Linearity

Assay linearity was demonstrated by preparing five standard solutions within the range of ~80-120%. Each solution was prepared by serial dilution from single stock and injected in duplicate. Linear regression analysis was performed, excluding the origin as a point. Statistical analysis was performed to evaluate the test results, and a data plot was presented.

2.6.6. Range

The range for the assay method was demonstrated by analyzing five final samples in a range between ~80% and 120% of the nominal method. Each solution was analyzed in duplicate. Linear regression analysis was performed, excluding the origin as a point.

2.6.7. HPLC Chromatographic System

HPLC: LC-20.
Column: C18, 4.6 x 250 mm 5 um.
Flow rate: 1.0 ml/minute.
Wavelength: 250 nm.
Inject volume: 10.0 µl.

2.6.8. Preparation of Buffer

3.4 gm of potassium dihydrogen phosphate was added to 1000 mL of water, and we adjusted the pH to 3.4 with orthophosphoric acid (OPA).

Mobile Phase: Buffer:Acetonitrile 400:600.
Diluent: Water:Acetonitrile 40:60.

2.7. Procedure

Independently inject an equivalent volume of the standard and sample and record the chromatograms.

2.7.1. Calculations

Assay of FG calculated by the given formula below:

$$\frac{Mg}{tablet} = Peak\ area\ Spl/area\ Std \times Wt\ of Std/100 \times \frac{5}{100} \times \frac{100}{1} \times 25/5 \times \%Potency$$

$$\%\ of\ label\ claim = \frac{mg}{tablet}/LC \times 100$$

2.7.2. Acceptance Criteria

Assay of the finished product should be 90-110%.

2.7.3. Preparation of Rivaroxaban Reference Standard Working Solution

20 mg of rivaroxaban were transferred to a 100 mL volumetric flask. Dissolve and make up the volume with

diluent. Dilute 5 ml of this solution in a 50 ml volumetric flask and make up the volume with diluent.

2.7.4. Preparation of a Rivaroxaban Sample in a Working Solution

A rivaroxaban sample was prepared by crushing 20 tablets (accurately weighed, crushed powder is approximately 210 mg, which is equivalent to 20 mg of rivaroxaban) and transferring them to a 100 ml volumetric flask. 25 ml of a diluent was added to dissolve and was sonicated for 25 minutes. It was then mixed magnetically for 30 minutes. 5 ml of this solution was diluted in a 50 ml volumetric flask.

2.8. HPLC Analysis Procedure and Calculation

We separately injected equal volumes of the standard and sample solutions and recorded the chromatograms. After verifying system suitability, the sample solution was injected to the HPLC system and the chromatogram was recorded. The rivaroxaban content was assessed in comparison with the concentration of the reference standard solution.

The assay of rivaroxaban in each tablet was calculated by using the formula mentioned below:

Rivaroxaban:

$$\frac{mg}{tablet} = Peak\ area \frac{spl}{Peak} area\ std \times wt\ of \frac{std}{100} \times \frac{5}{50} \times \frac{100}{spl} wt \times \frac{50}{5} \times Av\ Wt \times \%\ potency$$

$$\%\ of\ label\ claim = \frac{mg}{tab} / LC\ \times 100$$

2.8.1. Acceptance Criteria

As per USP recommendation, the assay of the finished product should be 90–110%.

2.8.2. Dissolution Assessment

This test is performed to evaluate the quantity of the drug release from a unit dosage form into a dissolution medium. The dissolution method of rivaroxaban is not available in any pharmacopeia. So, the dissolution assessment test was performed using a method as described by US FDA.

2.8.3. Dissolution Conditions

Method: Paddle.
Speed: 75 rpm.
Dissolution medium: acetate buffer + 0.4% SLS.
Dissolution medium volume: 900 ml.
Time: 45 minutes.
Temperature: 37.0 ± 0.5°C.

2.8.4. HPLC Chromatographic Conditions

Column: C18, 4.6 x 250 mm, 5 µm.
Flow rate: 1.0 ml/minute.
Wavelength: 250 nm.
Injected volume: 10.0 µl.

2.8.5. Preparation of Acetate Buffer + 0.4 SLS

Dissolved: 17.94 gm.
Sodium acetate: 9.96 ml. Acetic acid and 30 gm sodium lauryl sulfate in 6 l of water.

2.8.6. Preparation of the Buffer

Weighing 3.4 gm of potassium dihydrogen phosphate was done and added in 1,000 ml water and adjusted the pH to 3.4 with orthophosphoric acid (OPA).
Mobile Phase: Buffer:Acetonitrile 400:600.
Diluent: Water:Acetonitrile 40:60.

2.9. Preparation of Reference Standard Solution

20 mg of rivaroxaban was accurately weighed and transferred to a 100 mL volumetric flask. We dissolved and made up the volume with diluent. 5 ml of this solution was diluted to a 100 ml volumetric flask with diluent.

2.9.1. Working Sample Solution

We transferred 900 ml of dissolution medium to each vessel and set the parameters mentioned above. When the system was thermostatic at 37.0 ± 0.5°C, we transferred one tablet in each of the six dissolution vessels. We started the dissolution apparatus, then, after 30 minutes, withdrew the sample from each vessel and filtered it.

2.9.2. HPLC Analysis Procedure and Calculation

Analysis was performed to evaluate the quantity of drug release from the unit dosage form into the dissolution medium.

2.9.3. Calculation

The percentage of Rivaroxaban in each tablet was calculated using the following equation:

$$\%\ of\ Rivaroxaban = Peak\ area\ Spl \times Wt\ of \frac{Std}{Peak} area\ Std\ \times \frac{5}{100} \times \frac{900}{100} \times \frac{Potency}{LC} \times \frac{100}{100}$$

2.9.4. Content Uniformity of Rivaroxaban

Content uniformity of rivaroxaban in the finished product measured the individual content of the active substance in a single dosage form.

2.9.5. Chromatographic Conditions

HPLC techniques were as follows: column - C18, 4.6 x 250 mm 5 um, flow rate - 1.0 ml/minute, wavelength - 250 nm, inject volume - 10 µl.

2.9.6. Preparation of Buffer

3.4 gm of Potassium dihydrogen phosphate were

added to 1000 mL of water, and we adjusted the pH to 3.4 with orthophosphoric acid (OPA).

Mobile Phase: Buffer:Acetonitrile 400:600.

Diluent: Water:Acetonitrile 40:60.

2.9.7. Standard Solution

20 mg of rivaroxaban were transferred to a 100 mL volumetric flask. Dissolve and make up the volume with diluent. Dilute 5 ml of this solution in a 50 ml volumetric flask and make up the volume with diluent.

2.9.8. Sample Preparation

Add one tablet into a 100 ml volumetric flask separately. Add 5 ml of water to disintegrate the tablet and 25 ml of diluent to dissolve and sonicate for 10 minutes. Then shake magnetically for 30 minutes. And then make up the volume with diluent to 100 ml. Filter through filter paper. Discard the first 10 ml of filtrate and dilute 5 ml in a 25 ml volumetric flask with diluent.

2.9.9. Calculation

Content uniformity is calculated by using the formula below:

$$\frac{mg}{tablet} = Peak\ area \frac{Spl}{Peak} area\ Std\ \times Wt\ of \frac{Std}{100} \times \frac{5}{50} \times \frac{100}{1} \times \frac{25}{5} \times \%\ Potency$$

$$\%\ of\ label\ claim = \frac{mg}{tab}/LC\ \times 100$$

2.9.10. Acceptance Criteria

Content of all tablets should be 85-115%.

3. Results

The present research compared the chemical parameters of different brands of rivaroxaban tablets in Pakistan. One of the major issues is that dissolution and assay methods do not exist in any pharmacopeia, so the assay method is developed according to FDA guidelines.

After several efforts, the new method was developed and validated successfully as per FDA guidelines for evaluating different brands. The spectrum of the standard material was performed to check the wavelength at which maximum absorbance was achieved by a UV spectrophotometer. Then, 250 nm wavelength was found to be satisfactory as the peak's symmetry of rivaroxaban was excellent and reliable at this wavelength.

The new method was validated according to ICH guidelines. Then, testing of different brands was performed by using the new method. The critical parameters evaluated are dissolution, content uniformity, and assay.

3.1. Assay Method Development and Validation

After the successful method development, the method was validated for different parameters as per US FDA and ICH guidelines. The first step of the method validation was the system suitability, which was performed by preparing a standard solution, and the results are presented in Table 2.

Table 2 System suitability

	Peak Area of Rivaroxaban
Run 1	628141
Run 2	627937
Run 3	628533
Run 4	627963
Run 5	628093
Run 6	628404
Average	628178.5
RSD	0.038 %

The linearity of rivaroxaban was determined in concentrations ranging from 80% (16.50 mcg/ml) to 120% (23.856 mcg/ml) by preparing different standard solutions, and the results are presented in Table 3 and Fig. 1.

Table 3 Linearity of rivaroxaban

Target Level	**Concentration (mcg/ml)**	**Area Response**	**Average**	**% RSD**
80%	16.500	503909 504444	504176.5	0.0750
90%	17.693	545935 546367	546151	0.0559
100%	20.178	629198 629656	629427	0.0515
110%	21.073	653237 654164	653700.5	0.1003
120%	23.856	758981 759649	759315	0.0622
Correlation Coefficient (r^2) = 0.9985				

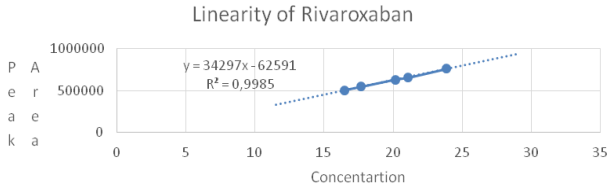

Fig. 1 Linearity of rivaroxaban

The range of the rivaroxaban method validation was determined by preparing different samples of concentrations ranging from 16.500 mcg/mL (80%) to 23.856 mcg/mL (120%), and the results are mentioned in Table 4 and Fig. 2.

Table 4 Range of rivaroxaban for Assay

Target Level	**Concentration (mcg/ml)**	**Area Response**	**Average**	**% RSD**
80%	16.567	504192 503993	504092.5	0.0279

Continuation of Table 4				
90%	17.696	545176 545565	545370.5	0.0504
100%	20.008	627289 627711	627500	0.0476
110%	21.107	654724 654556	654640	0.0181
120%	23.856	760077 759973	760025	0.0097
Correlation Coefficient 0.9981				

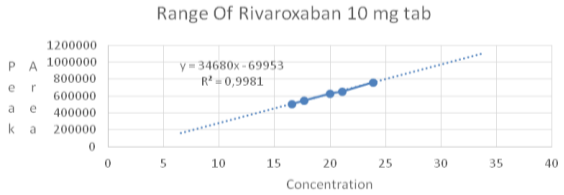

Fig. 2 Range of rivaroxaban

The precision is one of the most important steps for method validation, for which a repeatability test was performed by preparing six different sample solutions; the results are shown in Table 5.

Table 5 Repeatability precision

Sample #	Weight of sample (mg)	Peak area of the sample	Theoretical percentage (%)	Practical result (%) of the label claim
1	210.2	629376	100	97.88
2	209.3	629559	100	98.33
3	209.5	627117	100	97.85
4	210.3	627533	100	97.55
5	210.5	629087	100	97.69
6	210.9	627425	100	97.25
Mean			97.76 %	
Standard Deviation (SD)			0.36	
Relative standard deviation (RSD)			0.37%	
Limit: NMT 2.0%				

Analysts A and B tested six different sample solutions; the results are shown in Tables 6 and 7.

Table 6 Intermediate Precision Analyst 1

Sample #	Weight of Sample (mg)	Peak Area	Theoretical Percentage (%)	Assay (% of Label Claim)
1	210.1	627530	100	99.25
2	210.2	628124	100	99.30
3	210.5	627165	100	99.00
4	210.4	629515	100	99.42
5	210.9	628142	100	98.97
6	210.8	627435	100	98.91
Mean			99.14 %	
Standard Deviation (SD)			0.21	
Relative standard deviation (RSD)			0.21%	
Limit: NMT 2.0%				

Table 7 Intermediate Precision Analyst 2

Sample #	Weight of sample (mg)	Peak area	Theoretical Percentage (%)	Assay (% of label claim)
1	210.9	627983	100	98.47
2	210.00	626940	100	98.72
3	210.4	652817	100	102.60
4	211	625957	100	98.10
5	209.5	628802	100	99.25
6	210.4	627124	100	98.57
Mean			99.29 %	
Standard Deviation (SD)			1.67	
Relative standard deviation (RSD)			1.67%	
Limit: NMT 2.0%				

The percentage recovery for accuracy and specificity of the method was also determined by preparing three samples of different concentrations (80%, 100%, and 120%) of tablet brand, and the results of percentage

recovery for accuracy of rivaroxaban are illustrated in Table 8.

Table 8 Recovery percentage for accuracy of rivaroxaban

Sample #	Quantity of the Active Substance	Peak Area Run A	Peak Area Run B	Peak Area Run C	Mean Area	% Rivaroxaban	% Quantity Recovered
1	80 % concentration	504128	504697	504399	504408	81.23	101.533
2	100 % concentration	629699	629428	629886	629671	101.01	101.013
3	110 % concentration	760717	760891	761053	760887	122.35	101.961
Mean					101.503%		
Standard Deviation (SD)					0.475		
Relative standard deviation (RSD)					0.468%		
Limit: NMT 2.0%							

3.2. Evaluation of Dissolution, Uniformity of Contents, and Assay of Rivaroxaban Tablets

For the verification of rivaroxaban tablet dissolution, uniformity of contents and the complete assay procedure performed after successful HPLC analysis results were calculated.

Comparative results of dissolution are shown in Table 14. Comparative results of uniformity of contents are shown in Table 15. Comparative results of the assay are shown in Table 16.

3.3. Assay Method Validation

System suitability peak area of rivaroxaban.

Table 9 Validation of dissolution method: system suitability

Run No.	Rivaroxaban Peak Area
1	415158
2	412964
3	414011
4	409610
5	409055
6	412251
Mean	412174.833
RSD	0.586%

Table 10 Linearity of rivaroxaban for dissolution

Target Level	Concentration (mcg/ml)	Area Response	Average	% RSD
120%	12.027	502261 498096	500178.5	0.5888
110%	10.686	446702 444763	445732.5	0.3076
100%	9.940	412677 412606	412641.5	.0122
90%	8.747	363250 358800	361025	0.8716
80%	8.201	335732 332730	334231	0.6351
Correlation Coefficient 0.9993				

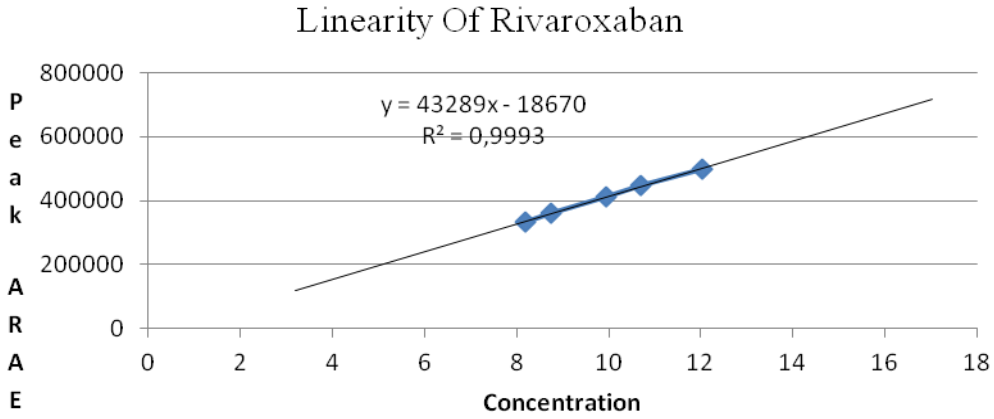

Fig. 3 Linearity of rivaroxaban

Table 11 Repeatability

Sample #	Peak Area of Sample	Q-Value (%)	% Dissolved
1	451367	80	98.01
2	451712	80	98.08
3	450234	80	97.76

Continuation of Table 11			
4	447211	80	97.10
5	408243	80	88.64
6	407708	80	88.53
Mean		99.69 %	
Standard Deviation (SD)		4.74	
Relative standard deviation (RSD)		5.01%	
Limit: NMT 2.0%			

Table 12 Intermediate Precision Analyst 1

Sample #	Peak Area of Sample	Q-Value (%)	% Dissolved
1	411321	80	88.92
2	452670	80	97.86
3	454328	80	98.22
4	409641	80	88.56
5	459020	80	99.24
6	453890	80	98.13
Mean		95.15 %	
Standard Deviation (SD)		4.99	
Relative standard deviation (RSD)		5.24%	
Limit: NMT 2.0%			

Table 13 Intermediate Precision Analyst 2

Sample #	Peak Area of Sample	Q-Value (%)	% Dissolved
1	448460	80	96.58
2	441760	80	95.13
3	449184	80	96.73
4	451722	80	97.28
5	463041	80	99.72
6	465011	80	100.14
Mean		97.60%	
Standard Deviation (SD)		1.95	
Relative standard deviation (RSD)		1.99%	
Limit: NMT 2.0%			

Table 14 In-vitro dissolution of tablets: comparative results

Sample #	MNC01 % active amount	LPC02 % active amount	LPC03 % active amount	LPC04 % active amount
1	9.62	10.21	10.35	9.10
2	9.61	8.50	10.10	8.95
3	9.40	9.80	10.46	9.09
4	10.77	9.49	10.16	9.2
5	9.19	9.80	10.34	9.2
6	9.41	9.34	10.58	9.02
Average	9.66	9.52	10.33	9.09

Table 15 Comparative results of content uniformity

Sample #	MNCO1	LPC02	LPC03	LPC04
1	99.89	100.47	97.24	99.92
2	98.39	101.30	97.60	100.02
3	99.82	108.73	97.83	104.23
4	96.49	92.53	99.31	104.11
5	102.33	102.95	99.91	105.24
6	101.13	100.31	97.90	105.58
7	100.72	101.38	98.78	101.30
8	101.63	109.16	99.16	101.29
9	97.52	92.09	99.50	101.03
10	103.09	103.39	99.71	101.16
Average	100.101	101.231	98.694	102.388

Table 16 Comparative results of chemical assay

S. No.	MNC01	LPC02	LPC03	LPC04
1	98.30	103.93	97.29	94.12
2	98.13	104.97	98.28	95.28
Average	98.215	104.45	97.78	94.7

4. Discussion

In 2004, World Health Organization declared that 30% of the population had no access to life-saving drugs, approximately 50% in a few Asian countries and South Africa. Some generic manufacturers were not following current good manufacturing practices due to poor regulation. Poorly manufactured medicine directly impacts upon patient health as well as life itself because of the ultimately poor quality of said medicine. Thus, the objective of this research is to evaluate the chemical parameters of different brands of rivaroxaban tablets available in Pakistan. Current research was designed to evaluate the chemical parameters against the ilk of United States Pharmacopeia, British Pharmacopeia, or the Food Drug Authority (FDA). Chosen brands are

registered with the local Drug Regulatory Authority except the MNC01 brand.

4.1. Chemical Parameters

The study was designed for quality parameters evaluation in terms of chemical parameters, dissolution, content uniformity, and assay. There were no significant variations found in order to meet quality parameters. The uniformity of dosage units through the content uniformity method was calculated by performing one tablet sample; 10 different numbers of tablets were used for each brand. The HPLC analysis was then performed, and subsequently the quantitative determination of rivaroxaban in tablet dosage form was performed successfully. According to the analytical developed method, the four different brands' products were tested, and the percentage release of drug calculated. The percent of label claim for each sample of brand was deemed to be satisfactory. For the verification of rivaroxaban tablet assay, the complete assay procedure was performed after successful HPLC analysis results were calculated; the results were determined and found satisfactory.

5. Conclusion

After several efforts, the new method was developed and validated successfully as per FDA guidelines for the evaluation of different brands. A spectrum of the standard material was performed to check the wavelength at which maximum absorbance could be achieved by UV spectrophotometer; the 250 nm wavelength was then found to be satisfactory. The peak's symmetry of rivaroxaban was excellent and reliable at this wavelength. The new method validated according to ICH guidelines was then tested on different brands; the critical parameters evaluated were dissolution, content uniformity, and assay. The dissolution testing method and assay testing method were developed and validated in accordance with ICH guidelines. The QC parameters of four various brands of rivaroxaban 10 mg pills obtainable in Pakistan were evaluated (physical and chemical parameters) and compared to assess the efficacy of the subjected drug. For example, QC tests, weight variety, friability, hardness, and DT tests, as well as a thickness test, were performed. The weight variation test results demonstrated hardly any variation among the leading pharmaceutical companies except LPC04, where a difference of weight was found. A hardness average was found to be more than 4kg, while disintegration, thickness, friability, dissolution, and content uniformity, as well as assay test results, were found to be as per the given specification in USP.

Therefore, this detailed study has concluded that rivaroxaban tablets produced by the leading pharmaceutical companies in Pakistan are complying consistently with the physical and chemical parameters of the USP specifications. All selected local pharmaceutical manufacturers are thus maintaining the standard of their products much like multinational or innovators are maintaining the quality of their products. More importantly, the study has also indicated that consistency of quality parameters is not only being maintained but also regulatory compliance is being ensured.

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