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Formulation and Evaluation of Mouth Dissolving Tablet Rivaroxaban and its Validation

Laxmikant B. Borse[1]*, Atul R. Bendale[1], Sandhya L. Borse[2], Vaishali D. Naphade[2] and Anil G. Jadhav[1]

[1]Sandip Institute of Pharmaceutical Sciences, Nasik, Maharashtra, 422213, India.
[2]School of Pharmaceutical Sciences, Sandip University, Nasik, Maharashtra, 422213, India.

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The foremost intention of present research was the preparation and assessment of mouth dissolving formulation Rivaroxaban and its validation. During present work, this tablet was formulated by straight compression technique by means of Cros-carmellose sodium and Sodium starch glycolate as super-disintegrants (concentration of 2, 4, 6%) and Avicel 102 as a binder. The formulated preparations were exposed to different consideration parameters like hardness test, friability test, disintegration test, release of drug and content of drug. The calibration curve of API using solvent phosphate buffer pH 6.8 was carried out. All prepared formulations exposed to different assessment parameters have shown the findings within prescribed limit. Due to the large concentration of super disintegrants in F8, disintegration time can reach 29±0.06 seconds. In used buffer, drug release was calculated at intervals of 0, 2, 4, 6, 8, 10, and 12 minutes. The F8 demonstrates 96.5±0.567 percent medication release. UV spectrophotometric validation was performed for the quantification of Rivaroxaban in bulk. Rivaroxaban was estimated at 247nm in phosphate buffer 6.8. The linearity range was observed 2–12μg/ml.

Keywords: Croscarmellose Sodium; Mouth Dissolving Tablet; Rivaroxaban; Sodium Starch Glycolate; Validation.

Oral medication conveyance remains the favored course for consumption of a variety of medicaments. Solid dosage forms are accepted due to accurate dosage, effortlessness administration, self-medication and most significantly the compliance of patients[1-3]. Despite of this, the important disadvantage is dysphagia or complexity for swallowing. To address the aforementioned issue, scientists have made concerted efforts to develop a fast-dissolving delivery system. Such preparations allow for product expansion in the many elderly persons who have difficulty administering traditional oral dose forms (tablets, solutions and capsules) due to hand tremors and dysphagia. [4-6]. The advancements used for manufacture of mouth dissolving formulation incorporate molding, lyophilization, straight compression, sublimation, cotton-candy method, spray drying, and fast liquify film formation[7-9]. Dysphasia is a concern in both elderly and pediatric individuals. The oral bioavailability of Rivaroxaban was 50%. As a result, the medicine's bioavailability is enhanced by developing a fast-dissolving drug delivery (Mouth dissolving) approach. The boost in absorption from mouth to throat and pharynx to esophagus increases bioavailability[10-11]. Likewise,

*Corresponding author E-mail: laxmikant.borse@gmail.com

the current study intended to develop and evaluate a mouth dissolving tablet of Rivaroxaban.

MATERIALS AND METHODS

Materials

Rivaroxaban was provided from Mehta API Pvt. Ltd., Andheri-Kurla Road, Mumbai 400 093 India. All additional chemicals utilized were of analytical rating.

Determination of ë $_{max}$

UV 3000 is an UV-visible spectrometer was used to obtain the UV spectra of Rivaroxaban. A precisely weighed 0.01gm of the medication introduced to a volumetric flask of 100 ml. Water (100 g/ml) was used to fill the volume to 100 ml. This solution was employed as a backup. 1 ml of the stock solution was withdrawn and the quantity was raised to 10 ml with water to achieve a solution of 10 g/ml. The spectra of the resultant solution was determined and by scanning it from 400 to 200 nm to identify the maximum wavelength frequency in solvents. [12].

Formulation of Rivaroxaban inclusion complex

The preparation technique consists of the dispersion of Rivaroxaban in the Hydroxyl propyl beta cyclodextrin at 1:1 proportion. The subsequent inclusion complex was formulated by utilizing additional ingredient and dissolution was carried out. The inclusion complex was prepared by using kneading and physical mixer.

Drug excipients compatibility study by FTRI spectrophotometer

Rivaroxaban's infrared (IR) spectra was acquired with excipients in the range of 4000 to 400 cm-1 using a FTIR[13].

Preparation of mouth dissolving formulation

Rivaroxaban tablets were made using the straight compression technique, the content publicized in table 2. Croscarmellose sod. and sod. starch glycolate were employed in several amounts as super disintegrants.[16-19] The dose of Rivaroxaban was 10mg in 36.9mg of drug inclusion complex. All of the components were sieved #40 and dried to eliminate moisture content at temperatures ranging from 40 to 45 degrees Celsius.

Except for magnesium stearate and talc, weighed amounts of medication and excipients were physically mixed for 20 minutes using a geometric expansion technique. Magnesium stearate and talc and were then put via sieve no. 80 and thoroughly assorted with first mixture. The medication and excipient mixture were squeezed using a fluid pack tablet punching machine with 8 mm diameter round punches.[20-22]

Preparation optimization

Factorial design of 3^2 found to be suitable for the preparation which exhibit the acceptable outcomes to observe outcome of changeable number of self-regulating variables Cross-carmellose sod. (X1), sod. starch glycolate (X2) on dependent variables like disintegration time, hardness and cumulative drug release[14] and shown in Table 1. The master formula of mouth dissolving tablet of Rivaroxaban is shown in Table 2.

Validation

Validation of the tablet was performed according to ICH guidelines[25-27].

Selection of solvent

Solvent was selected based on solubility of the drug in different solvents such as water, methanol, DMF, DMSO,6.8 pH phosphate buffer.

Preparation of standard stack solution of Rivaroxaban (100µg/ml)

0.01 gm of the drug shifted to volumetric flask and dissolved in about 10 ml of phosphate buffer 6.8. The volume was then made sufficient with phosphate buffer 6.8 up to 100ml. This solution contained 100µg of drug per ml of the solution.

Test preparation

Powdered tablets corresponding to 0.01 gm of Rivaroxaban transferred into 100ml volumetric flask, then 15ml of buffer was introduced with swirling to dissolve it. Then volume was adjusted up to 100ml by phosphate buffer 6.8. This solution contained 100µg of drug per ml of the solution.

Linearity

Solutions for linearity 2, 4,5,6,7,8,10 and 12 ppm were arranged by diluting 0.2, 0.4, 0.6, 0.8,1 and 1.2 ml of standard stock solution and volume was made up to 10ml by phosphate buffer 6.8. Approval standard for linearity is correlation coefficient (R_2) is 0.99

Limit of Detection and Limit of Quantitation

Linearity solution of 2, 4, 6, 8, 10 and 12 ppm were prepared from standard stock solution for calculation of LOD and LOQ.[29]

Precision

Pipette out 1ml of the test solution and

dilute it with phosphate buffer 6.8 to a volume of 10ml. Repeat the technique six times more. Consider the UV absorbance of six test samples and one reference sample at 247 nm of 10 ppm. Determine the percentage of assay, standard deviation, and percent relative standard deviation.[30]

Acceptance criteria

A. Percent assay in between 98 to 102%,

B. % Relative Standard Deviation (RSD) not more than2%

Accuracy

For accuracy the solution of mixture of standard and test solution of concentration 18,20 and 22 ppm were prepared. 0.8,1, 1.2 ml stock standard solution was mixed with 1ml of 100 ppm test solution. The above mixture was diluted up to 10ml with phosphate buffer 6.8.

Acceptance criteria of percent recovery =98 to 102% and %RSDd"2%.

Robustness

It is a degree of the ability to stay unpretentious by tiny but purposeful modifications in procedural limitations verified in procedure documentation, and it indicates its usefulness during routine use[31]. Acceptance criteria: % RSD d" 2%

Table 1. Independent variables

Variables which are Independent	Level		
	Lower (-1)	Middle (0)	Upper (+1)
Cross carmellose sodium	3.0	6.0	9.0
Sod. starch glycolate	4.0	8.0	12.0

Table 2. Master formula of mouth dissolving tablet of Rivaroxaban

Excipients in mg.	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-.09
Rivaroxaban	36.9	36.9	36.9	36.9	36.9	36.9	36.9	36.9	36.9
Cross-carmellose sodium	3.0	3.0	3.0	6.0	6.0	6.0	9.0	9.0	9.0
Sodium starch glycolate	4	8	12	4	8	12	4	8	12
Avicel 102	50	50	50	50	50	50	50	50	50
Aspartame	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Magnesium stearate	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Talc	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Aerosil	1	1	1	1	1	1	1	1	1
Mannitol	47.1	43.1	39.1	44.1	40.1	36.1	41.1	37.1	33.1
Total (mg)	150	150	150	150	150	150	150	150	150

Table 3. Result of drug solubility in water

Concentration (µg/ml)	Absorbance [water as solvent]	Solubility of drug inclusion complex [water as solvent] (mg/ml)	Absorbance [Phosphate buffer 6.8]	Solubility of drug inclusion complex [Phosphate buffer 6.8] (mg/ml)
0	0	0	0	0
2	0.1228	0.0213	0.1394	0.0222
4	0.2296	0.0401	0.2495	0.0398
6	0.3495	0.0608	0.3895	0.0622
8	0.4596	0.0800	0.5138	0.0820
10	0.5772	0.100	0.6234	0.0995

RESULTS AND DISCUSSION

Design of calibration curve and λ $_{max}$ of Rivaroxaban

Calibration curve and λ max of Rivaroxaban was resolute in phosphate buffer[28]. The linearity calibration curve at 248nm represented (as per Beers - Lambert's law) in Fig. 1.

Solubility study

The solubility of Rivaroxaban inclusion complex was increased as compared to drug solubility. The solubility of Rivaroxaban pure drug in water was 0.025mg/ml. Result were specified in table 3. Calibration curve and ë $_{max}$ of Rivaroxaban inclusion complex in water and phosphate buffer 6.8 represented in Fig. 2, and 3.

Drug excipients compatibility study by FTIR spectrometer

Figure 4 and 5 depict the IR spectrum of Rivaroxaban, additives and a physical combination. The fact that the IR absorption bands detected in the IR spectra of drug and additives mimic those observed in physical mixtures demonstrates the drug's compliance with polymers, Pre and post compression parameters of F1 to F9 are shown in Table 4 and 5.

Precompression evaluation parameters of powder

% Cumulative drug release

The percent drug release of the varied prepared preparations to be in the range of 68.34 to 96.85 percent. The drug release in this formulation increases when the quantity of cros carmellose sodium and sod. starch glycolate increases. The drug's in vitro release was calculated by evaluating the dissolution profile. The US device included two paddles that could revolve at 50 rpm, and the dissolution media was buffer pH 6.8. Percent (%) cumulative drug release for mouth dissolving tablets of F1 to F9 is shown in Table 6 and zero order graph is shown in fig 6.

Optimization

The goal of the 32 factorial design was to plot the response values. A comprehensive analysis of influence of progression factors such as cros-carmellose sod. (X1) and sod. starch glycolate (X2), as well as their connections, was conducted via Design expert software version 9.0.2.0 and

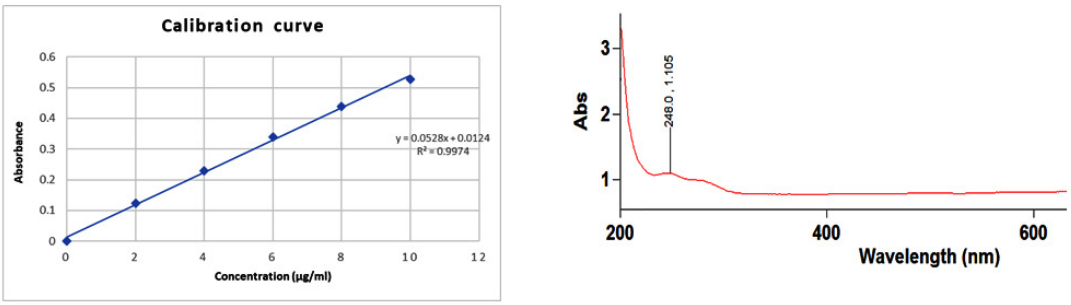

Fig. 1. a- Calibration curve and b- λ max of Rivaroxaban in phosphate buffer 6.8

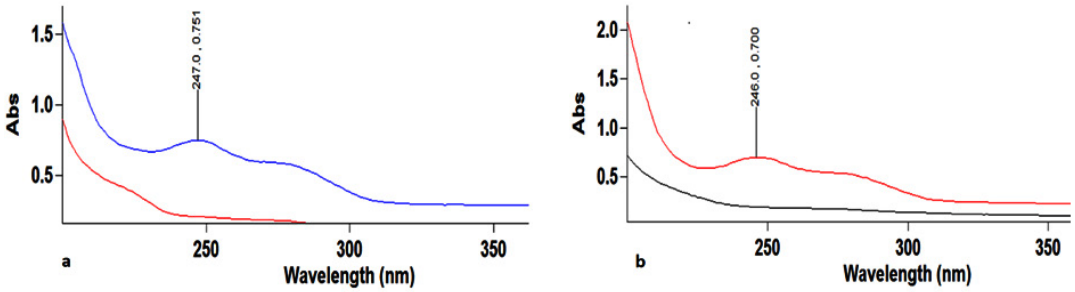

Fig. 2. Calibration curve- a. in water, b. in phosphate buffer 6.8

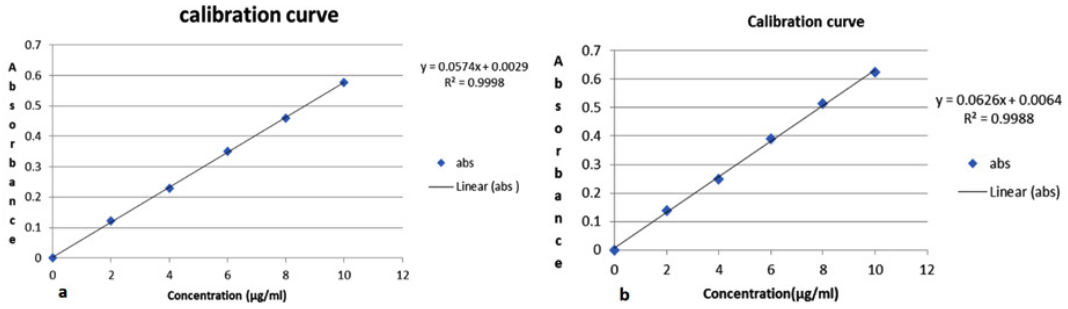

Fig. 3. λ max of Rivaroxaban inclusion complex- a. in water, b. in phosphate buffer 6.8

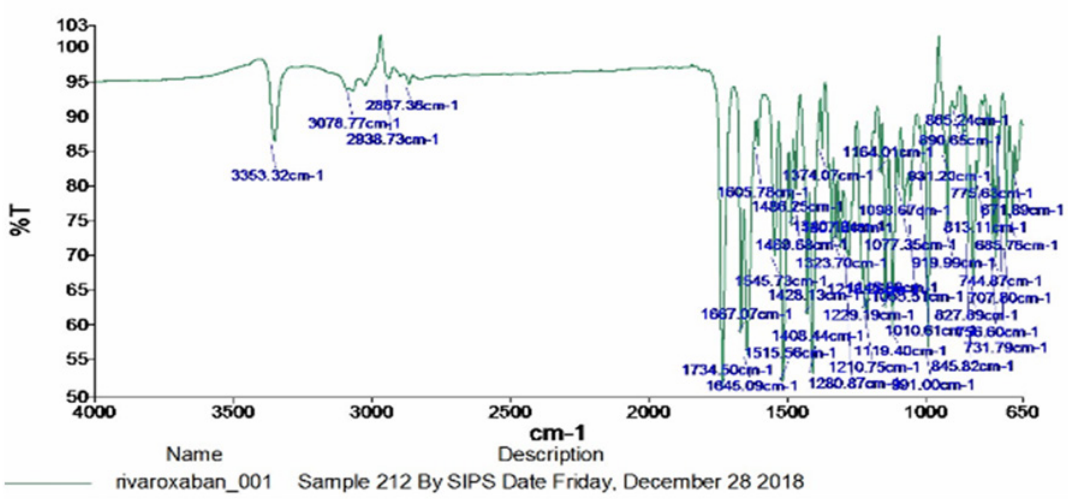

Fig. 4. FTIR spectra of Rivaroxaban

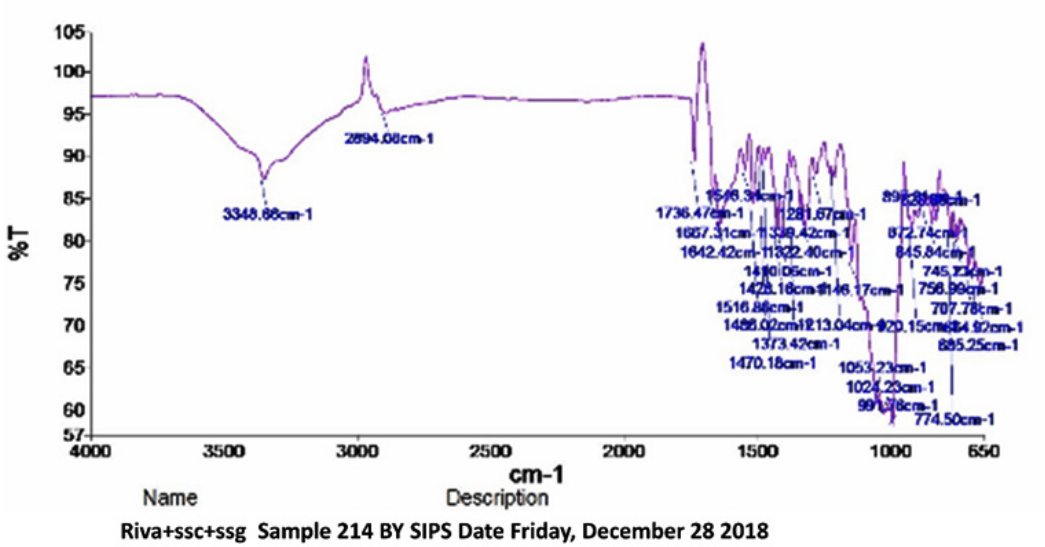

Fig. 5. FTIR spectra of Rivaroxaban + Cross carmellose sodium +Sod. starchglycolate

1-way ANOVA at 0.05 levels. Statistical modelling was used, and the polynomial equation was derived based on the major influence of two parameters on their experimental design. Response surface approach was used to highlight the impact of the primary effect on responses. The nonlinear two-dimensional contour design coupling X1 and X2 indicated a two-variable interaction, shown in fig. 7, 8 and 9.

Linearity

Six-point calibration curves were obtained in a concentration range from 2-12 ppm for Rivaroxaban. The answer of the drug observed linear in the study concentration range and the linear regression equation was y= 0.0556x+0.0098 with correlation coefficient $R^2 = 0.99$ as shown in fig. 10

Table 4. Precompression parameters of F1 to F9

Formulation Encryption	Angle of Repose(θ) (degree)	Bulk Density (gm/cm^3)	Tapped Bulk Density (gm/cm^3)	Compressibility Index (%)	Hausner's ratio
F1	30.20	0.520	0.625	15.76	1.216
F2	25.70	0.518	0.621	16.35	1.205
F3	28.60	0.512	0.628	16.18	1.210
F4	31.12	0.510	0.621	15.04	1.214
F5	26.11	0.508	0.625	16.66	1.212
F6	30.16	0.500	0.619	16.20	1.220
F7	31.60	0.510	0.618	15.16	1.220
F8	25.10	0.516	0.624	15.04	1.214
F9	31.09	0.512	0.620	16.18	1.210

Table 5. Post compression parameters of F1 to F9

Formulation Code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%)	Wetting time (sec)	Dis Integration time(sec)
F1	2.94	3.2	0.715	155.20	97.59	26	36
F2	2.90	3.1	0.620	148.20	97.71	22	33
F3	2.93	3.1	0.718	149.60	94.75	25	32
F4	2.92	3.3	0.705	150.56	94.77	20	33
F5	2.80	3.1	0.625	150.48	94.77	22	33
F6	2.74	3.3	0.610	150.11	92.00	26	32
F7	2.84	2.9	0.705	152.12	93.51	20	29
F8	2.87	2.8	0.612	150.10	96.16	20	29
F9	2.90	2.9	0.618	150.12	91.85	22	30

Table 6. Percent (%) cumulative drug release for mouth dissolving tablets of F1 to F9

Time(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	11.16	12.07	13.79	13.79	14.71	14.31	15.87	16.59	16.03
4	23.33	25.07	27.01	28.83	28.76	30.82	32.70	36.05	38.42
6	32.78	39.77	40.78	46.41	47.88	45.46	46.96	46.39	48.34
8	43.88	48.60	55.24	59.97	59.78	59.89	61.19	64.89	68.50
10	58.62	62.19	65.49	65.59	70.72	72.62	73.25	80.49	81.84
12	68.34	73.92	78.27	80.43	82.33	90.59	91.54	96.85	94.91

Limit of Quantitation (LOQ) and limit of detection (LOD)

The results show LOD-0.4328and LOQ-1.3117values within specified limits, whereas SD is 0.0072. It proves sensitivity of the method.

Precision

The method was observed precise, as it was having %RSD value less than 2. It also gives % assay value within the acceptance limits, as shown in table 7 and 8.

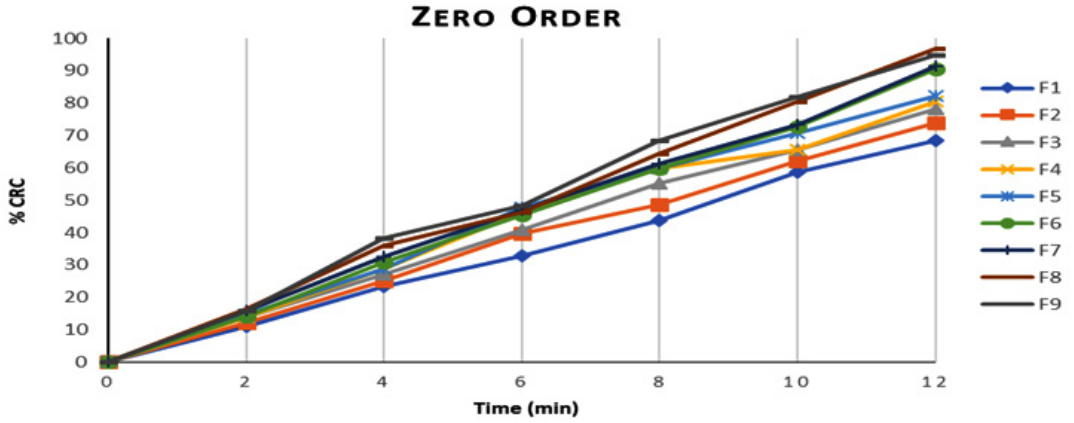

Fig. 6. Zero order graph of percent (%) cumulative drug release for mouth dissolving tablets of F1 to F9

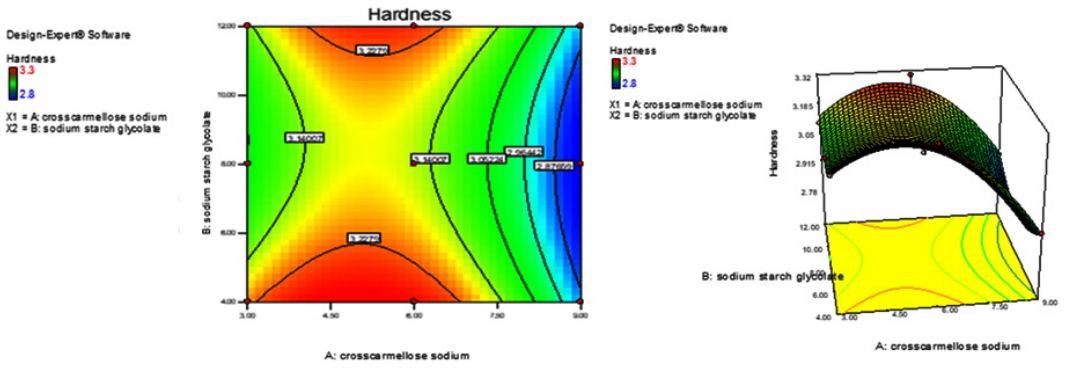

Fig. 7. The contour design & Surface response design show the effect of additives on Hardness

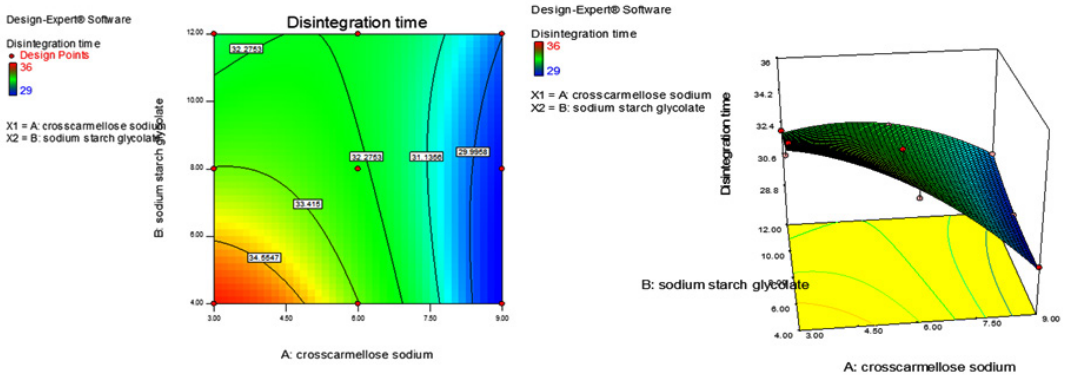

Fig. 8. The contour design & Surface response design showthe effect of additives on disintegration time

Accuracy

The result has shown that best % recovery102.84% of the drug was obtained at each added concentration, representing that the method was accurate. Absorbance of Standard =0.00987. It is shown in figure 11.

Robustness

The results are expressed as SD and RSD. The results are offered in Table 9. The low values of the SD and RSD indicates the robustness of the method.

Table 7. Intraday and Interday Precision result

Concentration (µg/ml)	Intraday Precision result		Interday Precision Result	
	Absorbance	% Assay	Absorbance	% Assay
10	0.5736	100.50%	0.5520	100.05
10	0.5626	100.77%	0.5689	100.09
10	0.5539	100.00%	0.5693	100.06
10	0.5627	100.0%	0.5744	100..00
10	0.5527	101.00%	0.5569	100.02
10	0.5628	100.87%	0.5678	100.00

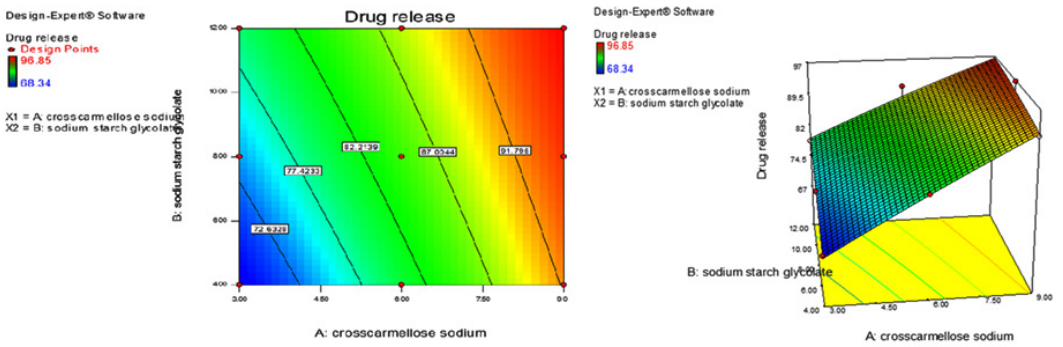

Fig. 9. The contour design & Surface response design show the effect of additives on % cumulative drug release

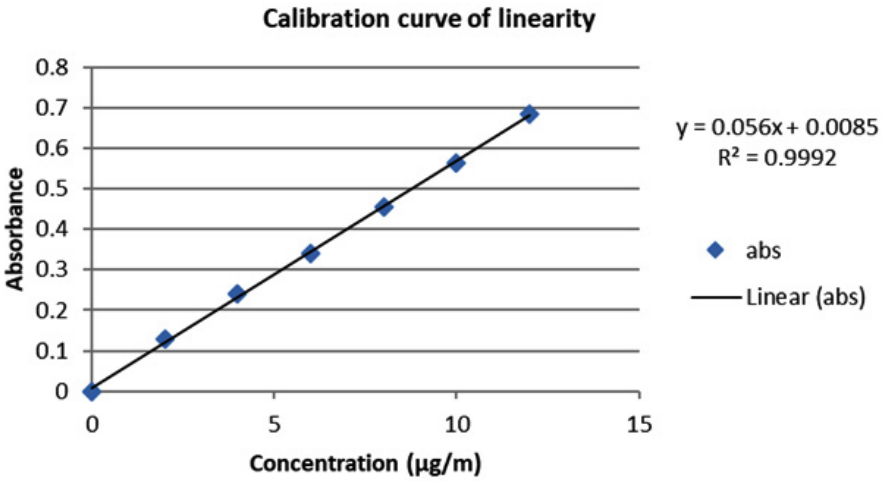

Fig. 10. Calibration curve of linearity

Table 8. Intraday and Interday Observation

Validation Parameter	Observation - Intraday Precision		Observation -Interday Precision	
	Acceptance criteria	Observation	Acceptance criteria	Observation
Precision	% Assay (98-102%) % RSD	100.00% 1.069%	% Assay (98-102%) %RSD	100.19% 1.076%

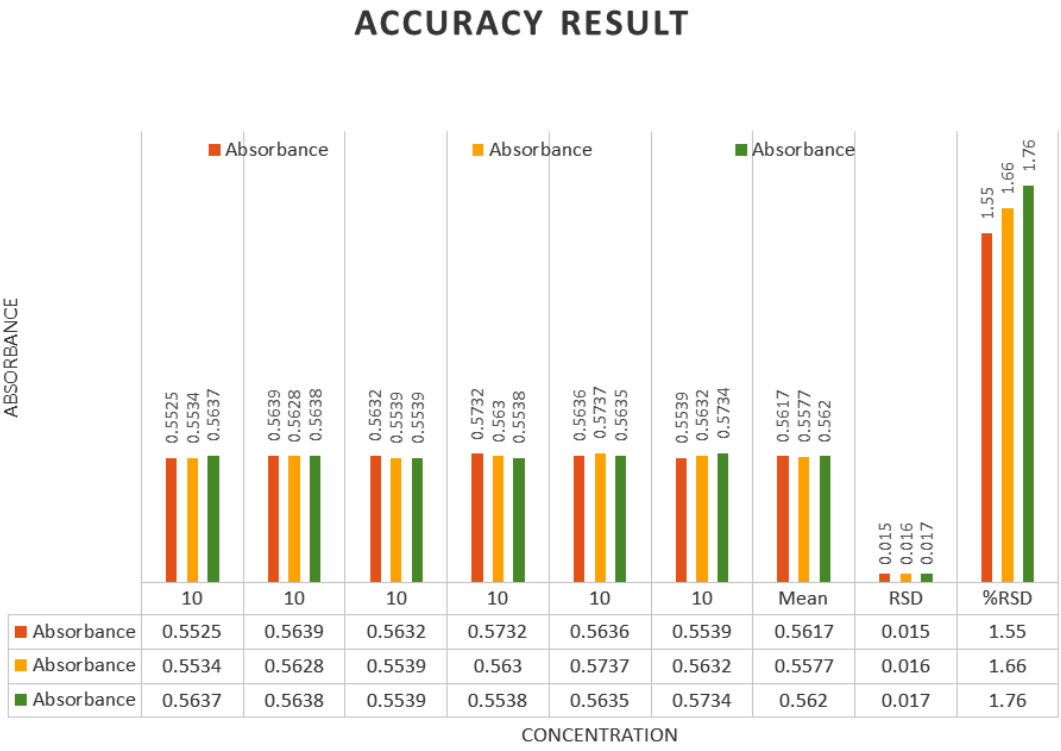

Fig. 11. Accuracy result

DISCUSSION

The optimized formulation was imperiled to multiple evaluation constraints, and the outcomes attained were inside the limitations shown in the tables. The hardness of all formulations indicates strong binding and tablet strength to resist shocks during transit, as well as the possibility of good disintegration. The thickness and the drug content of all formulations was found to be uniform. All manufactured formulations pass the (Indian Pharmacopoeia) IP disintegration and weight variation tests. Based on the results of the in vitro dissolving test, the formulation F8 comprising croscarmellose sod. and sod. starch glycolate in the proportion of (9.0:6.0) was chosen as the optimal preparation.

It is shown that higher amount of super-disintegrants increase in vitro medication release and disintegration. The validation of the mouth dissolving pill yielded the greatest results. The drug's linearity response was confirmed to be linear in the research concentration range. The output shows LOD and LOQ values that are within the given limitations. The approach was deemed to be exact because it's percent RSD value was less

Table 9. Observation table for Robustness

% Recovery level	Standard (ml)	Test (ml)	Absorbance	Amount added	Amount found	% Recovery
80	0.8	1	0.7245	18	17.2602	95.89
	0.8	1	0.7314	18	17.4246	96.80
	0.8	1	0.7456	18	17.7629	98.68
100	1	1	0.8366	20	19.9309	99.65
	1	1	0.8351	20	19.8951	99.47
	1	1	0.8392	20	19.9928	99.96
120	1.2	1	0.9472	22	22.5658	102.57
	1.2	1	0.9497	22	22.6253	102.84
	1.2	1	0.9228	22	21.9845	99.92

than 2. It also provides a percentage test value that is within the acceptable limits. The results showed that the best drug recovery (95-102 percent) was attained at each additional concentration, indicating that the method was accurate. The method's robustness is shown by the less values of the SD and RSD.

CONCLUSION

The present research seeks to successfully design and optimize the mouth dissolving tablet of Rivaroxaban, as well as to increase the drug's bioavailability by enhancing solubility.

F8 outperforms other formulations in case of friability, hardness, homogeneity of drug content, disintegration, and in vitro drug release assays when compared to the set batches of tablets.

Thus, by adding a higher amount of super-disintegrants to aid in rapid disintegration in the oral cavity, medication release from the mouth dissolving tablet was boosted.

Because the medicine disintegrates quickly, there is more drug available for dissolving, leading in quicker absorption and perhaps higher bioavailability, which leads to a rapid commencement of act in systemic circulation.

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Conflict of Interest

The authors declared that there is no conflict of interest.

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