World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

FORMULATION DEVELOPMENT AND INVITRO EVALUATION OF RIVAROXABAN SUSTAIN RELEASE MATRIX TABLETS

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Article Received on 27/05/2020 **Article Revised on 17/06/2020** **Article Accepted on 07/07/2020**

ABSTRACT

The main aim of proposed work was to develop Rivaroxaban matrix tablets, sustained release dosage form. Sustained release formulation is the drug delivery system that is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. The sustained release tablets were prepared by direct compression method using Hydroxylpropylmethyl cellulose (HPMC K4M,K15M), and Guar gum in varying ratios. Tablets blends were evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. The compressed tablets were then evaluated for various physical tests like diameter, thickness, uniformity of weight, hardness, friability, and drug content. The granules exhibited satisfactory rheological demeanor. The results of all these tests were found to be satisfactory. The in vitro dissolution study was carried out for 12 hours using paddle method in phosphate buffer (pH 6.8) as dissolution media. Among all the formulations, F6 formulation shows maximum drug release at the end of 12hrs and it follows first order with non fickian diffusion.

KEYWORDS: Rivaroxaban, HPMC K4M, K-15M, Guar gum.

INTRODUCTION

Increased complications and expense involved in marketing of new drug entities has focused greater attention on development of sustained release (SR) or controlled release (CR) drug delivery systems[1] Sustained or controlled release delivery systems can achieve predictable and reproducible release rates, extended duration of activity for short half - life drugs, decreased toxicity, and reduction of required dose, optimized therapy and better patient compliance.[2,3] Matrix type sustained delivery systems are popular because of their ease of manufactures. It excludes complex production procedure such as coating and pellitization during manufacturing and drug release from the dosage form. It is controlled mainly by the type and proportion of the polymers used in the preparation. Hydrophilic polymer matrix is widely used for formulating a sustained release dosage form.[4,5] The hydrophilic polymer selected for the present study was hydroxylpropyl methylcellulose K (HPMC-K). Hydrophilic polymer matrix system are widely used for designing oral sustained release delivery systems because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. HPMC K 100 forms transparent tough and flexible films from aqueous solution. The films dissolve completely in the gastrointestinal tract at any biological pH and provide good bioavailability of the active ingredient. However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic matrix.

Rivaroxaban is an anticoagulant and the first orally active direct factor Xa inhibitor. Unlike warfarin, routine lab monitoring of INR is not necessary. However there is no antidote available in the event of a major bleed. Only the 10 mg tablet can be taken without regard to food. The 15 mg and 20 mg tablet should be taken with food. FDA approved on July 1, 2011. Rivaroxaban has been shown more effective than the standard prescription of warfarin in reducing the like hood of ischemic strokes in patients with atrial fibrillation or abnormal heart rhythms. Rivaroxaban has poor water solubility and belongs to BCS Class II drugs.[6]

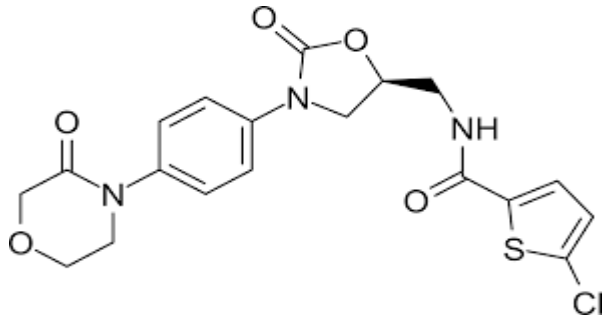


Figure 1: Chemical structure of Rivaroxaban.

Materials and Methods

Materials

Rivaroxaban purchased from the B.M.R Chemicals, Hyderabad HPMC K4M, HPMC K15M gifted from Strides arcolab, Bangalore, Guar gum purchased from Himedia laboratory. Mumbai, Talc, PVP K 30, Magnesium Stearate, Micro Crystalline cellulose were purchased Lobachemiepvt.ltd, Mumbai.

Experimental work

Preformulation studies[7-8]

Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with pharmaceutical excipients. It is the first step in the ratio development of dosage form.

a. Solubility

Solubility of Rivaroxaban was determined in pH 1.2, pH 7.4, and 6.8 phosphate buffers. Solubility studies were performed by taking excess amount of Rivaroxaban in beakers containing the solvents. The mixtures were shaken for 24hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no.41. The filtered solutions are analyzed by spectrophotometrically.

b. Compatibility Studies

Compatibility study with excipients was carried out by FTIR. The pure drug and its formulations along with excipients were subjected to FTIR studies. In the present study, the potassium bromide disc (pellet) method was employed.

c. Identification of Rivaroxaban

Identification of Rivaroxaban and polymers were identified by FTIR method.

Preparation Of Reagents

Potassium Dihyrogen Phosphate (0.2M)

27.22gm of potassium di-hyrogen phosphate is dissolved in distilled water and makeup to 1000 ml with the same.

Sodium Hydroxide Solution (0.2M)

8 gm of sodium hydroxide was dissolved in 1000mlof distilled water.

Phosphatebuffer pH 6.8

50 ml 0.2M of potassium dihydrogen phosphate solution and 22.4 ml of 0.2M Sodium hydroxide solution were mixed and made up to 200 ml with distilled water.

Determination of UV spectrum of Rivaroxaban

10mg of Rivaroxaban was dissolved in 2ml of methanol and volume was made up to 10ml with buffers so as to get a stock solution of 1000 µg/ml concentration. From the above stock solution pipette out 1ml of the solution and makeup the volume to 10ml using buffer to get the concentration of 100µg/ml concentration. From this stock solution pipette out 1ml of the solution and makeup the volume to 10ml using buffer to get the concentration of 10µg/ml concentration, this solution was scanned under UV Spectroscopy using 200-400nm.

Standard calibration curve for Rivaroxaban

Rivaroxaban standard calibration curve was plotted in pH 1.2 buffers.

Accurately weighed amount of 10 mg of drug was transferred into a 10 ml volumetric flask and the primary stock solution was prepared by making up volume to 10 ml with pH 1.2 buffer. This gives a solution having concentration of 1000 µg/mL of Rivaroxaban in stock solution. From this primary stock solution 1 ml was transferred into another 10 ml volumetric flask and made up to 10 ml with pH 1.2, from this secondary stock 0.5, 1, 1.5, 2, 2.5, and 3ml was taken separately and made up to 10 ml with pH 1.2 buffer, to produce 5, 10, 15, 20, 25 and 30µg/ml solution respectively. The absorbance was measured at 246 nm using UV spectrophotometer. Similarly Rivaroxaban standard graphs were plotted in pH 6.8 phosphate buffer and pH 6.8 phosphate buffer by following the above procedure.

Preparation Of Rivaroxaban Controlled Release Matrix Tablets[9-13]

Controlled release tablets of Rivaroxaban were prepared by direct compression method using variable concentrations of different polymers like HPMC K4M, HPMC K15M and Guar gum. Direct compression method is widely employed method for production of compressed tablets.

Direct compression

In this process the tablets are compressed directly from powder blends of active ingredient and suitable excipients, which will flow uniformly in to the die cavity and forms a firm compact.

Brief manufacturing procedure for the preparation of tablets

Step 1- Weighed all the ingredients separately.

Step 2- The drug and the other excipients were passed through 40# sieve together and blended for 10 minutes.

Step 3- The magnesium stearate was passed through 60# sieve and added to the blend of step2 and blended for 5 minutes.

Step 4- Compressed the blend of step 3 in to tablets by using 8mm, round punches.

Table 1: Tablet composition of different formulations of Rivaroxaban matrix tablets.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rivaroxaban	10	10	10	10	10	10	10	10	10
HPMC K4M	10	20	30	--	--	--	--	--	--
HPMC K15M	--	--	--	10	20	30	--	--	--
Guar gum	--	--	--	--	--	--	10	20	30
MCC	115	105	95	115	105	95	115	105	95
PVP K30	10	10	10	10	10	10	10	10	10
Mg.st	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3
Total	150	150	150	150	150	150	150	150	150

Evaluation Parameters[14-24]

Pre Compression Parameters

A. Bulk density (D_b)

It is the ratio of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/cc and is given by,

$D_b = M / V_o$

Where, D_b=Bulk density (gm/cc) M is the mass of powder (g)

$V_o$is the bulk volume of powder (cc)

B. Tapped density (D_t)

Ten grams of powder was introduced into a clean, dry 100ml measuring cylinder. The cylinder was then tapped 100times from a constant height and tapped volume was read. It is expressed in gm/cc and is given by,

$D_t = M / V_t$

Where, D_t=Tapped density (gm/cc) M is the mass ofpowder (g)

$V_t$isthe tapped volumeof powder (cc)

C. **Compressibility index:** The compressibility of the powder was determined by the
Carr's compressibility index.

$$CI = \frac{\rho_{tap} - \rho_{bulk}}{\rho_{tap}} \times 100$$

where ρ_{tap} is the tap density and ρ_{bulk} is the bulk density.

Table 2: Relation between the Carr's index of powder and its flow characteristics.

Sr.No.	Carr's index	Type of flow
1.	5-15	Excellent
2.	12-15	Good
3.	18-21	Fair
4.	23-30	Poor
5.	33-38	Very poor
6.	>40	Extremely poor

D. Hausner ratio

Hausner ratio =tapped density/ bulk density
Values of Hausner ratio; <1.25: good flow
>1.25: poor flow
If Hausner ratio is between 1.25-1.5, flow can be improved by addition of glidants.

E. Angle of repose (θ)

It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height(h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of funnel. The angle of repose was then calculated using the formula,

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Where, θ= angle of repose
h =height of pile, r=radius of the base of the pile.

Table 3: Comparison between angles of reposes and flow property.

Angle of Repose	Flow
<25	Excellent
25 – 30	Good
30 – 40	Moderate (addition of 0.2% glidant required)
>40	Poor

Post Compression Parameters

A. Thickness and diameter

Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm.

B. Hardness

The Mansanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm^2.

C. Friability (F)

Tablet strength was tested by Friabilator USPEF-2. Pre-weighed tablets were allowed for 100 revolutions (4min), taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets. The % friability was then calculated by,

$$F = \frac{(W_{initial}) - (W_{final})}{(W_{intial})} \times 100$$

D. Weight variation test

The weight of the tablet being made in routinely measured to ensure that a tablet contains the proper amount of drug. The USP weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablet meet the USP test if not more than 2 tablets are outside the percentage limits and if no tablets differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in the following table.

Table 4: Weight variation limits.

Sr. No.	Average weight of tablet (mg)	Maximum % difference allowed
1	130 or less	10
2	130-324	7.5
3	324 or more	5

$$PD = \frac{(W_{avg}) - (W_{initial})}{(W_{avg})} \times 100$$

Where, PD=Percentage deviation, W_{avg}=Average weight of tablet, $W_{initial}$ = individual weight of tablet.

E. Uniformity of drug content.

Five tablets of various formulations were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in different buffers, the drug content was determined using a UV/Visible Spectrophotometer (PG Instruments).

In-vitro release study.

Apparatus	USP XXIV dissolution testing apparatus II (paddle method)
Dissolutionmedium	0.1N HCL, 6.8pH phosphate buffer
Temperature	37 ± 0.5^0 C
RPM	50
Vol. withdrawn and replaced	5ml every 1 hour
λ max	246
Blank solution	Buffers used
Duration of study	12hours
Volume of dissolution media	900ml

Procedure

The release rate of Rivaroxaban from tablets was determined using The United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle type). The dissolution test was performed using 900 ml of pH 1.2, for first 2 hours hours and followed by phosphate buffer (pH 6.8; 900 mL) for remaining hours at 37.5 ± 0.5^0C and 50 RPM. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hours, and the samples were replaced with fresh dissolution medium. The samples diluted to a suitable concentration with respected dissolution medium. Absorbance of these solutions was measured at 246nm using a UV-Visible Spectrophotometer (PG Instruments). Cumulative percentage of drug release was calculated.

Kinetic Analysis of In-Vitro Release Rates of Sustained Release Tablets[54-55]

The results of in-vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero – order kinetic model– Cumulative% drug released versus time.
2. First–order kinetic model–Log cumulative percent drug remaining versus time.
3. Higuchi's model–Cumulative percent drug released versus square root of time.
4. Korsmeyer equation/ Peppa's model – Log cumulative percent drug released versus logtime.

Zero Order Kinetic
It describes the system in which the drug release rate is independent of its concentration.
Qt = Qo + Ko t

Where
Qt=Amount of drugdissolved in time t
Qo =Initial amount of drugin thesolution, which is often zero and
Ko =zero order release constant.

If the zero order drug release kinetic is obeyed, then a plot of Qt versus t will give a straight line with a slope of Ko and an intercept at zero.

First Order Kinetic
It describes the drug release from the systems in which the release rate is concentration dependent.
Log Qt = log Qo + kt/ 2.303

Where

Qt = amount of drug released in time t.
Qo =initial amount of drug in the solution
k = first order release constant

If the first order drug release kinetic is obeyed, then a plot of log (Qo-Qt) versus t will be straight line with a slope of kt/ 2.303 and an intercept at t=0 of log Qo

Higuchi Model
It describes the fraction of drug release from a matrix is proportional to square root of time.
$Mt / M\infty = kHt^{1/2}$

Mt and M∞ are cumulative amounts of drug release at time t and infinite time,

kH=Higuchi dissolution constant reflection formulation characteristics.

If the Higuchi model of drug release (i.e. Fickian diffusion) is obeyed, then a plot

Of Mt / M∞ versus $\mathbf{t^{1/2}}$ will be straight line with slope of kH.

Korsmeyer - Peppasmodel (PowerLaw)
The power law describes the drug release from the polymeric system in which release deviates
From Fickian diffusion, as expressed in following equation.
$Mt / M\infty = ktn$
$\log [Mt / M\infty] = \log k + n \log t$

Where
Mt and M∞ are cumulative amounts of drug release at time t and infinite time (i.e. fraction of drug release at time t), device, **k=**constant incorporating structural and geometrical characteristics of CR **n=** diffusional release exponent indicative of the mechanism of drug release for drug dissolution.

To characterize the release mechanism, the dissolution data {Mt / M∞ <0.6} are evaluated.

A plot of log {Mt / M∞}versus log t will be linear with slope of n and intercept gives the value of log k.
Antilog of logk gives the value of k.

Peepas used the n value in order to characterize different release mechanisms as shown in the table below

Table 5: Mechanism of Drug Releaseas per Korsmeyer Equation/Peppa's.

S. No.	N Value	Drug release
1.	0.5	Fickian release
2.	0.5 <n <1	Non – Fickian release
3.	1	Case II transport

RESULTS AND DISCUSSION

Solubility studies
Table 6: Solubility studies of Rivaroxaban.

Solvent	Solubility (µg/mL)
0.1 N HCL	0.321
6.8pH buffer	0.568
7.4pH buffer	0.705

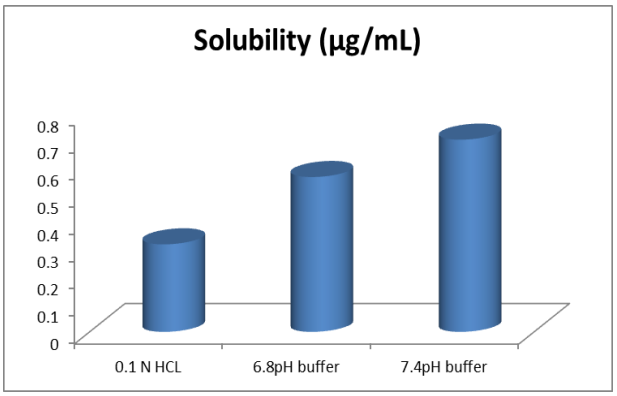


Figure 2: Solubility studies of Rivaroxaban

From the solubility studies it was observed that pH1.2 acidic buffer has more solubility than the other buffers.

Determination of UV Spectrum

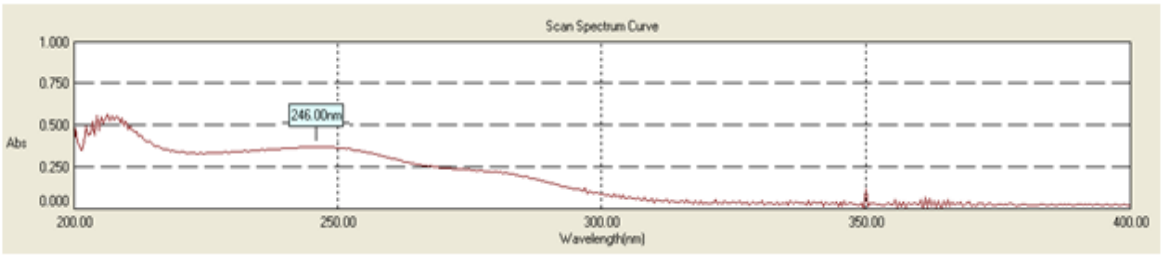


Figure: UV Spectrum of Rivaroxaban.

From the UV spectral analysis of Rivaroxaban in 10µg/ml it was observed that the Rivaroxaban has 246nm.

Standard Calibration Curve of Rivaroxabanin pH1.2

Table 7: Standard Calibration Curve of Rivaroxabanin pH 1.2.

Concentration (µg/ml)	Absorbance
0	0
5	0.112
10	0.241
15	0.355
20	0.491
25	0.607
30	0.732

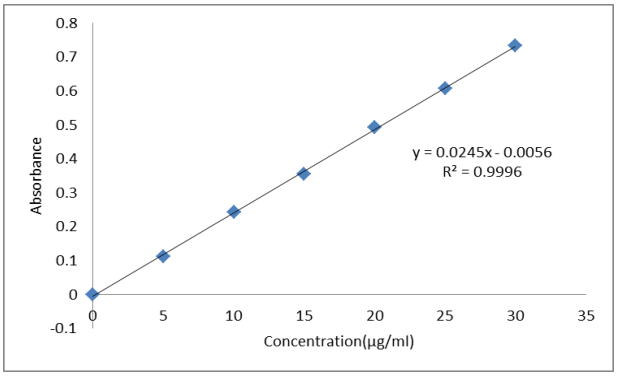


Figure 3: Standard calibration curve of Rivaroxabanin pH1.2.

Standard Calibration Curve of Rivaroxaban pH6.8

Table 8: Standard Calibration Curve of Rivaroxaban in pH 6.8.

Concentration(µg/ml)	Absorbance
0	0
5	0.161
10	0.315
15	0.492
20	0.637
25	0.786
30	0.974

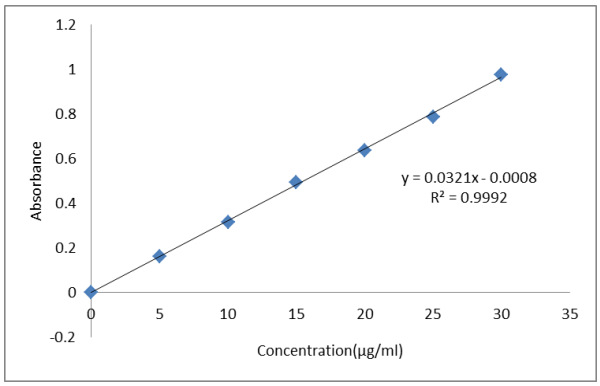


Figure 4: standard calibration curve Rivaroxabanin pH6.8

FTIR studies

Spectrum of pure Rivaroxaban

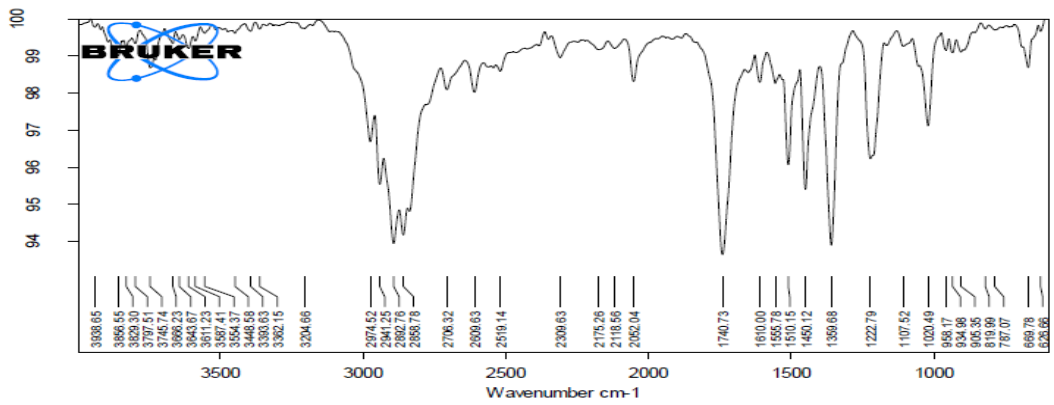


Figure 5: FTIR spectrum of pureRivaroxaban.

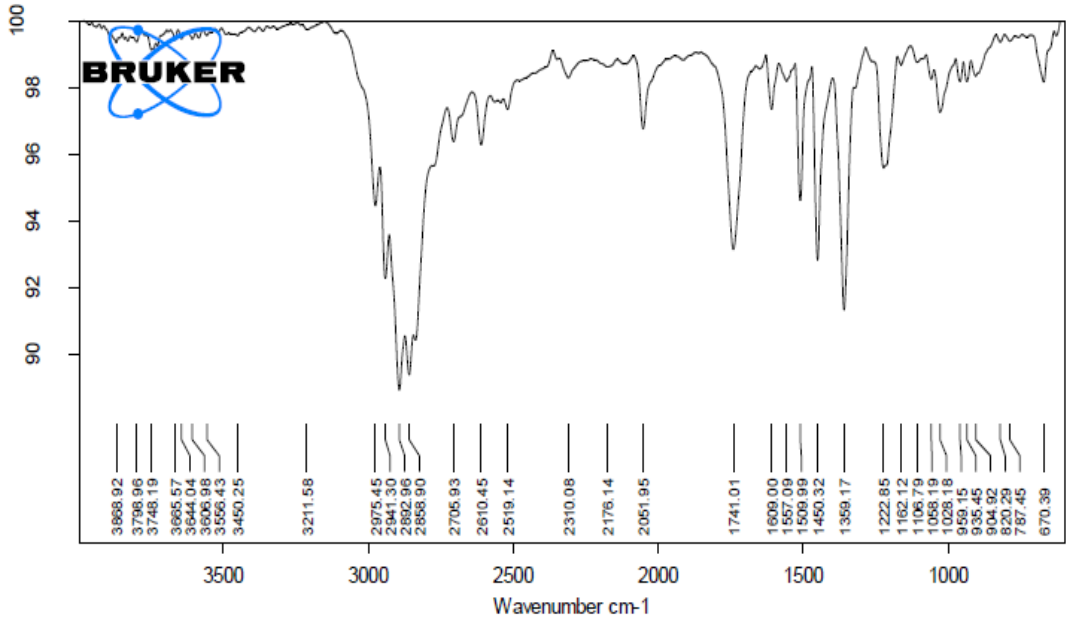


Figure 6: FTIR spectrumofRivaroxaban and Excipients.

Evaluation of Rivaroxaban sustained release matrix Tablets

Table 9: PreCompression Parameters of Rivaroxaban sustained release matrix Tablets.

FC	Angle of Repose	Bulk density	Tapped density	Hausners ratio	Carrs index
F1	25.26	0.331	0.412	1.24	19.66
F2	26.43	0.326	0.401	1.23	18.70
F3	25.15	0.364	0.421	1.16	13.54
F4	29.68	0.352	0.412	1.17	14.56
F5	30.42	0.321	0.395	1.23	18.73
F6	25.76	0.324	0.387	1.19	16.28
F7	31.09	0.345	0.398	1.15	13.32
F8	26.42	0.328	0.385	1.17	14.81
F9	29.38	0.314	0.354	1.13	11.30

PostCompression Parameters of Rivaroxaban controlled release matrix Tablets

Table10: Physical properties of tablet formulation (F-1 toF-9).

FC	Avg.Wt (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)
F1	146.32	3.02	6.8	0.23	96.43
F2	149.52	3.01	7.1	0.41	96.24
F3	148.73	3.24	6.9	0.53	99.32
F4	146.32	3.05	6.2	0.21	97.61
F5	151.05	3.01	6.1	0.21	99.32
F6	150.43	3.10	6.5	0.63	101.25
F7	149.32	3.06	7.2	0.41	100.64
F8	148.36	3.24	7.3	0.25	98.73
F9	147.32	3.04	6.9	0.20	99.36

The average weight of the Rivaroxaban tablets was found to be in the range of 146.32to 151.05mg. Thickness of the Rivaroxaban tablets was found to be in the range of 3.01 to 3.24mm. Hardness of the Rivaroxaban tablets was found to be in the range of 6.1 to 7.3kg/cm^2. Friabilityof the Rivaroxaban tablets were found to be in the range of 0.20 to 0.63%. Drug content of the Rivaroxaban tablets were found to be in the range of 96.24 to 101.25%.

In-vitro drug release studies

In-vitro drug release studies were carried out using USPXXII dissolution apparatus type II (Lab India DS 8000) at 50rpm.The dissolution medium consisted of 900 ml of buffer, maintained at 37±0.5C .The drug release at different time intervals was measured using an ultraviolet-visible spectrophotometer (PG Instruments). The study was performed in triplicate.

Table 11: In vitro dissolution studies.

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	29.31	26.94	22.05	25.48	23.16	20.34	26.05	13.62	10.26
1	36.05	32.05	29.64	36.15	32.45	29.64	31.86	22.86	19.34
2	52.31	46.32	42.06	49.72	43.61	38.14	46.92	36.86	31.05
3	70.31	59.34	55.74	58.16	51.29	46.31	58.31	49.21	43.26
4	81.52	71.26	66.98	71.23	62.98	53.16	69.37	62.31	53.95
6	98.43	86.32	78.43	83.62	73.46	66.31	81.05	76.32	60.75
8		96.32	89.32	95.01	86.92	75.49	98.42	87.42	66.15
10			96.38		98.36	86.32		96.35	72.34
12						95.45			79.23

In Vitro Drug Release Studies

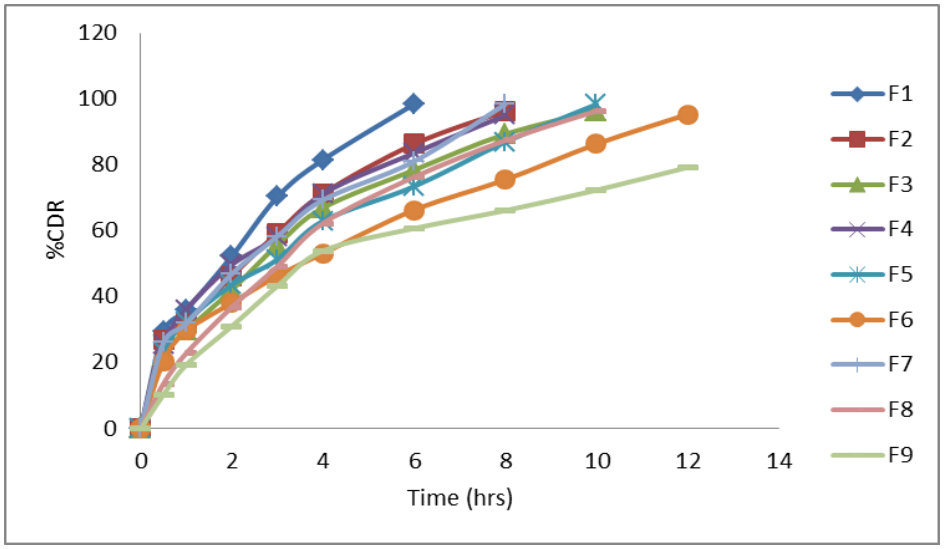


Figure 7: In Vitro Drug Release Studies Of F1-F9 Formulations.

From the in vitro drug release studies of Rivaroxaban controlled release tablets using HPMC K4M, HPMC K15M, and guar gum in four different polymer ratios using MCC as a filler and PVP K30 as binder.

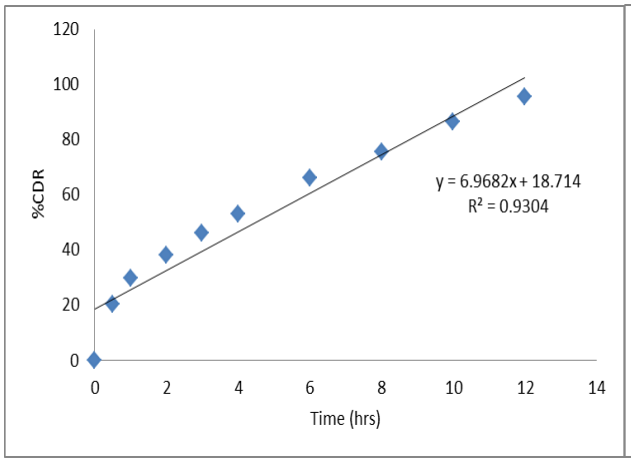
Among the all 9 trails F1-F3 trails were formulated using HPMC K4M in three different ratios the drug release was decreased with increase in the polymer concentration. F1 formulation containing 10mg of HPMC K4M shows 98.43% of drug release at the end of 6hours, while F2 formulation containing 20mg of HPMC K4Mshows 96.32% of drug release at the end of 8hours, whereas F3 formulation containing 30mg of HPMC K4M shows 96.38% of drug release at the end of 10hours, Among all the four formulations cant sustained the drug release for 12hours. So further formulations were prepared using HPMC K15M.

Then F4-F6 trails were formulated using HPMC K15M in three different ratios like 10, 20, 30mg the drug release was decreased with increase in the polymer concentration. F4 formulation shows 95.01% of drug release at the end of 8hours, while F5 formulation shows 98.36% of drug release at the end of 10hours, whereas F6 formulation shows 95.45% of drug release at the end of 12hours.

Then F7-F9 trails were formulated using Guar gum in three different ratios like 10, 20, 30mg. F7 formulation shows 98.42% of drug release at the end of 8hours, while F8 formulation shows 96.35% of drug release at the end of 10hours, whereas F9 formulation shows 79.23% of drug release at the end of 12hours.

Among the all 9 formulations, based upon the *invitro* studies F6 formulation containing 30mg of HPMC K15Mchoosen as optimized formulation. So the drug release kinetics were performed for the F6 formulation.

Drug Release Kinetics
Zero order first order



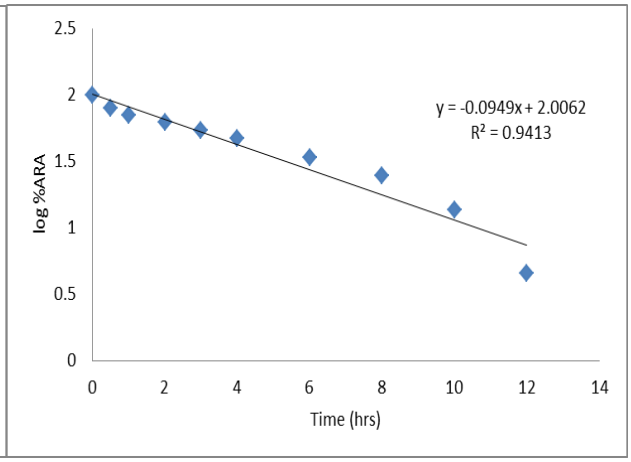
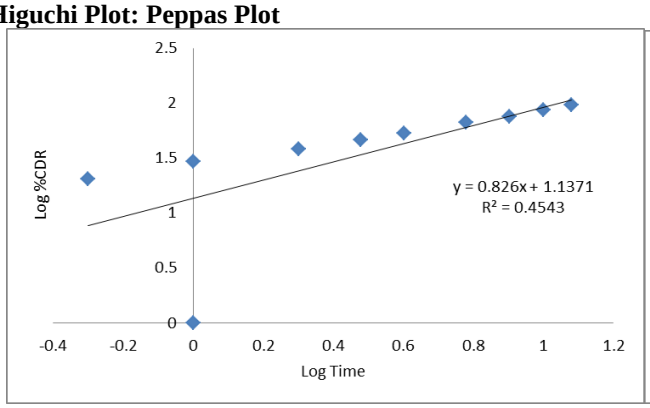


Figure 8: Zero order graph of optimized formulation. Figure 9: First order graph of optimized formulation.

Higuchi Plot: Peppas Plot



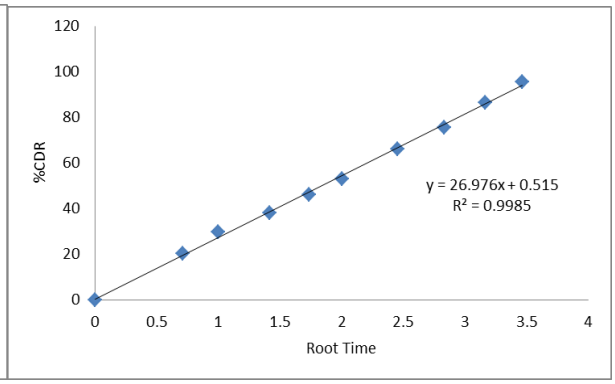


Figure 10: Higuchi graph of optimized formulation. Figure 11: Peppas graph of optimized formulation

Table 12 Drug release kinetics.

R^2 values					n values
Formulation	**Zero order**	**First order**	**Higuchi**	**Korsmeyer - Peppas**	**Korsmeyer- Peppas (n)**
F6	**0.930**	**0.941**	**0.998**	**0.454**	**0.826**

The invitro dissolution data for best formulation F6were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F6 shows R^2 value 0.941. As its value nearer to the '1' it is conformed as it follows the First order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot, if n = 0.45 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non-Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport.

The 'n' value is 0.826 for the optimized formulation (F6) i.e., n value was 0.45 < n < 0.89this indicates anomalous behavior or non-Fickian transport. The release kinetics for the optimized formula are shown in table 12.

CONCLUSION

The aim of this investigation was to develop and evaluate sustained release drug delivery system for Rivaroxaban and comparing with marketed product. Hydrophilic matrix based tablets formulated using different concentrations of different grades of HPMC i.e. K4M, K15M, and guar gum, were used to develop twenty four formulations (F1 – F9) using direct compression technique and were subjected to physicochemical and *in vitro* dissolution studies by comparing with marketed product. The net content of Rivaroxaban was 10mg and the total tablet weight was 100mg.

Excipients used in the formulation reduce the cost, which are available at lower price in market. As the excipients used are mostly available and cheaper at cost. The study includes development of the robust and stable product, which complies with the marketed product.

REFERENCES

1. Gwen MJ, Joseph RR. In: Banker GS and Rhodes, CT, (editors). Modern pharmaceutics. 3rd ed. Vol 72. New York: Marcel Dekker Inc., 1996; 575.

2. Chein YW. Novel drug delivery systems. 2nd ed. New York: Marcel Dekker Inc., 1997; 1-42.
3. Ritchel WA. Biopharmaceutic and pharmacokinetic apects in the design of controlled release per-oral drug deliver system. Drug Dev Ind Pharm, 1989; 15: 1073-103.
4. Reddy KR, Mutalik S, Reddy S. Once daily sustained release matrix tablets of nicorandinal formulation in vitro evaluation. AAPS Pharm Sci Tech, 2003; 4: 1-9.
5. Mohammed AD, James LF, Michael HR, John EH, Rajabi-Siahboomi AR. Release of propranolol hydrochloride from matrix tablets containing sodium carboxymethylcellulose and hydroxypropylmethylcellulose. Pharm Dev Tech, 1999; 4: 313-24.
6. Anwer MK, Mohammad M, Iqbal M, Ansari MN, etal., Sustained release and enhanced oral bioavailability of rivaroxaban by PLGA nanoparticles with no food effect. Journal of Thrombosis and Thrombolysis, 2020: 2: 1-9.
7. Girishchandra R. Mandake, Indrajit S. Patil, Omkar A Patil, Dr. Manoj M. Nitalikar, Dr. Shriniwas K MohiteUV Spectroscopy Analysis and Degradation Study of Rivaroxaban. Asian J. Res. Pharm. Sci., 2018; 8(2): 57-60.
8. Çelebier, Mustafa & Kaynak, Mustafa & altinoz, sacide & Sahin, Selma. (2014). UV Spectrophotometric Method for Determination of the Dissolution Profile of Rivaroxaban. Dissolution Technologies. 21. 56-59. 10.14227/DT210414P56.
9. Bhalekar MR, Avari J, Umalkar RA. Preparation and in vitro evaluation of sustained release drug delivery system for verapamil HCl. Ind J Pharm Sci., 2007; 69(3): 418-22.
10. Huang Y, Hung Y, Yang WC, Chang J, Pao CW, Takayama K. Once-daily propranolol extended release tablet dosage form: formulation design and in vitro in vivo investigation Eur J Pharm and Biopharm, 2004; 58: 607-14.
11. Raghuram R, Mutalik S, Srinivas R. Once daily sustained release matrix tablets of Nicorandil: formulation and in vitro evaluation AAPS Pharm Sci Tech, 2003; 4(4): 61.
12. Cox P, Khan K, Munday D, Jomjai S. Development and evaluation of a multiple unit oral sustained release dosage form for ibuprofen: preparation and release kinetics. Int J Pharm, 1999; 193: 73-84.
13. Gohel MC, Parikh RK, Padshala MN, Sarvaiya KG, Jena G. Formulation and optimization of directly compressible isoniazid modifiedrelease matrix tablet. Ind J Pharm Sci., 2007; 69(5): 640-5.
14. Indiran P, Russell I, Syce A, Neau H. Sustained release theophylline tablets by direct compression Part 1: formulation and in vitro testing. Int J Pharm, 1998; 164: 1-10.
15. Grassi M, Voinovich D, Moneghini M, Franceschinis E, Perissutti B, Filipovic JG. Preparation and evaluation of a melt pelletized paracetamol/ stearic acid sustained release delivery system. J Control Release, 2003; 88: 381-91.
16. Mutalik S, Hiremath D. Formulation and evaluation of chitosan matrix tablets of nifedipine. The Eastern Pharmacist, 2000; 2: 109-111.
17. CH.M.M.Prasada Rao et.al., Chitosan Based Sustained Release Mucoadhesive Buccal Patches Containing Amlodipine Besylate (AMB) , Asian J. Res. Pharm. Sci., 2017; 2(7): 1-8.
18. Shah NH, Lazarus JH, Jarwoski CL. Carboxy methylcellulose: Effect of degree of polymerization and substitution on tablet disintegration and dissolution. J Pharm Sci., 1981; 70(6): 611-613.
19. Hogan JE. Hydroxypropyl methylcellulose sustained release technology. Drug Dev Ind Pharm, 1989; 15(27): 975-999.
20. Chien, Y. W. In Novel drug delivery systems. Marcel Decker, Inc. New York, 2nd edition, 1992; 6-15.
21. CH.M.M.Prasada Rao et.al., Formulation and evaluation of mouth dissolving Tablets of carbamazepine, Asian J. Pharm. Tech, 2017; 7(3): 1-5.
22. Lee, T. W.; Robinson, J. R. In Remington: The science and practice of pharmacy. Gennaro, Ed.; Lippincott Williams and Wilkins: Baltimore, 2nd edition, 2000; 903-929.
23. Khan GM, Zhu JB. Studies on drug release kinetics from ibuprofen-carbomer hydrophilic matrix tablets: Influence of co-excipients on release rate of the drug. J Control Release, 1999; 57: 197–203.
24. Korsemeyer RW, PeppasNA. Macromolecular and modeling aspects of swelling – controlled Systems. In: Mansdrofsz, Roseman TJ, ad, Controlled Release Delivery systems. New – York, NY: Marcel Dekker, 1983; 77.