Development and Invitro Evaluation of Rivaroxaban Controlled Release Tablets

Chinnadevi G, Gangaram Santhosh*
Department of Pharmaceutics, University College of Pharmaceutical Sciences,
Palamuru University, Mahabubnagar, Telangana, India,509001.
e-mail ID: gchinnadevi@gmail.com

ABSTRACT:
The aim of the present work is to develop and characterize controlled release of Rivaroxaban matrix tablets used for treatment of vein thrombosis. Development of CR Rivaroxaban is proposed considering the adverse event profile and high fluctuation index of Rivaroxaban observed with CR dosage forms.Rivaroxaban was subjected to Preformulation studies, based on the results obtained Rivaroxaban controlled release tablets were successfully formulated.Formulations prepared by direct compression technique. Set of trials were formulated for which Rivaroxaban evaluated parameters (bulk density, tapped density, compressibility index, Hauser's ratio, weight, thickness, hardness) were found to lie within the specifications. Dissolution study was performed in USP type II apparatus at 100 RPM in pH 6.8 phosphate buffer. From the results of the invitro study it appears that the release of the Rivaroxaban was significantly influenced by the characteristics of the polymer used.
Keywords: Rivaroxaban, polymers, FTIR studies, direct compression technique, in vitro drug release studies, zero order kinetics

I. INTRODUCTION

The controlled release formulations have many advantages over theconventional dosage form. Among all thecontrolled release dosage form matrix technologieshave got wide acceptance due to many reasons.The matrix drug delivery devices are prepared fromhydrophobic or hydrophilic polymer where thedrugs are homogeneously dispersed.[1] Matrix Systems are the earliest and most frequently used method to modify release profiles of drugs. Here, the drug is homogeneously dissolved or dispersed in the polymeric matrix.[2] In particular, slowly dissolving or erodible matrices provide a simple way of retarding the release rate of drugs with rapid dissolution.Natural polymers can be used as matrix materials.[3] The matrix may be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a direct compression containing the drug and hydrophilic matrix material.The bioavailability of rivaroxaban at the higher doses is considerably reduced when the drug is administered on an empty stomach.[4] This can lead to inadequate anticoagulant effect, and therefore, it is recommended to use the higher doses at fed state.[5]Therefore, the aim of this study was to evaluate innovative rivaroxaban containing formulations designed to eliminate the food effect to ensure reliable absorption and thus to improve patient adherence with the treatment.

II. EXPERIMENTAL WORK

MATERIALS

Rivaroxaban procured from Synpharma Research Labs, HYD. Sodium alginate and Guargumwas obtained from Synpharma Research Labs, Hyderabad. Other chemicalsandthe reagents used were of analytical grade.

METHODOLOGY

Fourier Transform Infrared Spectroscopy (FTIR)[6]

FTIR spectroscopy Rivaroxaban discs were created by compressing the Rivaroxaban with KBr and the spectra was scanned in the range between4000 to 400 cm^{-1}. Perfect operational conditions were maintained. The absorption maxima which is denoted as max in spectrum obtained with the drug substance is compared with the intensity to those of reference spectrum.

Table-1: Formulation table of Rivaroxaban controlled release tablets

S.No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1	Rivaroxaban	10	10	10	10	10	10	10	10
2	Sodium alginate	10	20	30	40	-	-	-	-
3	Guargum	-	-	-	-	10	20	30	40
4	Microcrystalline Cellulose	75	65	55	45	75	65	55	45
5	Magnesium stearate	3	3	3	3	3	3	3	3

6	Talc	2	2	2	2	2	2	2	2
7	Total weight	100	100	100	100	100	100	100	100

Preparation method:[7]
Tablets of Rivaroxaban were prepared by direct compression method as per the formulae given in Table. All the materials required as per the formulae were blended in a closed polyethylene bag. The blends were compressed into tablets on a tablet punching machine to a hardness of 6 kg/cm ^{2} using 8 mm concave punches.

Evaluation of tablet[8]
Weight Variation
Weight variation is one of the official quality control tests for tablets. This is important because it directly relates with drug content. To do this test, minimum 20 tablets were weighed separately and average weight was calculated and compared with individual weight. The deviation gives the report of the weight variation. Usually it is expressed in percentage. Weight variation should be done in process checking and for finished products.

Thickness
The dimensions like thickness and diameter of the tablets may have important effect in the drug content and other parameters. Hence it is required to maintain the thickness and diameter in the optimum acceptable range. This can be done by means of Vernier caliper. 10 tablets prepared from each trial were used. The average values were noted.[9]

Tablet Hardness
Monsanto hardness tester was utilized to find the tablet hardness. In each formulation, 10 tablets were taken and the hardness was measured. The tablet was kept in the perfect position in the axis in the two jaws of instrument. The measurement should be zero kg/cm^2 at this stage. The knob is rotated to apply force to the tablet, the force is continued until there is fracture in the tablet. The point at which tablet breaks is break point and it was noted in kg/cm^2.[10]

Friability
Tablet strength can be measured by using friabilator. This is performed to know the impact of shock abrasion on tablets when on travelling and handling. The test involves keeping the tablets in a plastic chamber and allowing it to revolve at 25rpm for 4 minutes that is equivalent to 100 rotations. In this test the tablets are subjected to drop at heights of 6 inches in each revolution. The initial weight and final weight of the tablets after dedusting were noted.[11] The limit acceptable is less than 1% weight variation. It was calculated as follows. The percentage friability was measured using the formula,
% F = {1-(Wo/W)} ×100
Where,
% F = friability in percentage
W o = Initial weight of tablet
W = weight of tablets after revolution

Drug Content
The drug content directly relates to the pharmacological efficacy, so it is mandatory to do the drug content test. It is an official quality control test. The drug content in all formulations were analyzed by triturating 20 tablets in mortar and pestle, then from the powder 75 mg equivalent of Rivaroxaban was taken and transferred to 100ml standard volumetric flask. Then the volume was prepared to 50ml with pH 6.8 phosphate buffer. This was shaken for 15 min to mix. Then the volume was prepared to 100ml with phosphate buffer. The solution was strained by using whatmann filter paper and then it is diluted and absorbance was determined by using UV-Visible spectrophotometer at 285 nm using pH 6.8 phosphate buffer as blank.[12]

In vitro release studies
This in vitro release can be done by using USP dissolution apparatus I. The test is performed at 50 rpm. The media used were pH 1.2 buffer for initial 2 h, followed by 8 h in pH 6.8 phosphate buffer. The temperature was maintained at 37 ± 0.5°C. The samples were taken at predetermined time and the dissolution basket is replenished with the buffer. The taken samples were filtered through filtered through a 0.45 membrane filter. The absorbance was measured at 270 nm. For every trials, the experiments were done in triplicate. The release data of all the trials were analyzed to observe the release kinetics using zero order, first order and matrix, korsmeyer-peppas equations.[13]

Release kinetics [14]
The release kinetics can be understand basically by applying the obtained data to the release kinetics models.

Zero order

C = K0t

K0 - rate constant for Zero-order (concentration/time) t - Time (h).

First order

LogC = LogC0 – Kt / 2.303

Where C0 - Initial concentration of drug K = constant first order and t = Time (h)

Higuchi

Qt = Kt1/2

Where Qt - Amount of the drug release drug in time t K- Kinetic constant and t- is time in hrs Korsmeyer Pappas

Mt / M = Kt n

Where, Mt - amount of the released drug at time t, M- Overall drug amount released after 8 hrs. K- Diffusion constant n- Diffusion exponent mechanism of release of drug.

Stability studies:

The stability studies are performed to analyze the quality of drug and drug product with exposure to different temperature and humidity conditions on estimated time. General conditions like light, environment and other general parameters are maintained and the general evaluation tests were performed at different time interval periods. It is undesirable and time consuming to do full shelf life period study. To avoid this accelerated stability studies has been adopted.[15]

III. RESULTS AND DISCUSSION

DRUG - EXCIPIENT COMPATIBILITY STUDIES (FT-IR):

Thecompatibilitybetweenthedrug and the selected excipientswas evaluated using FTIR peak matching method.There was no appearance or disappearance of peaks in the drug-polymer mixture, which confirmed the absence of any chemical interaction between the drug, polymer and other chemicals.

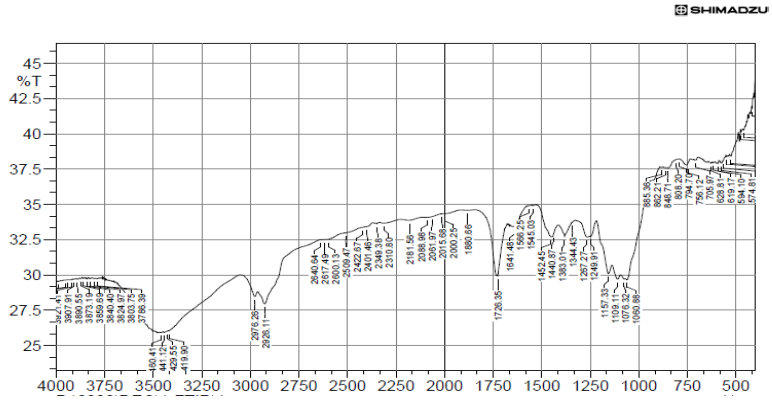
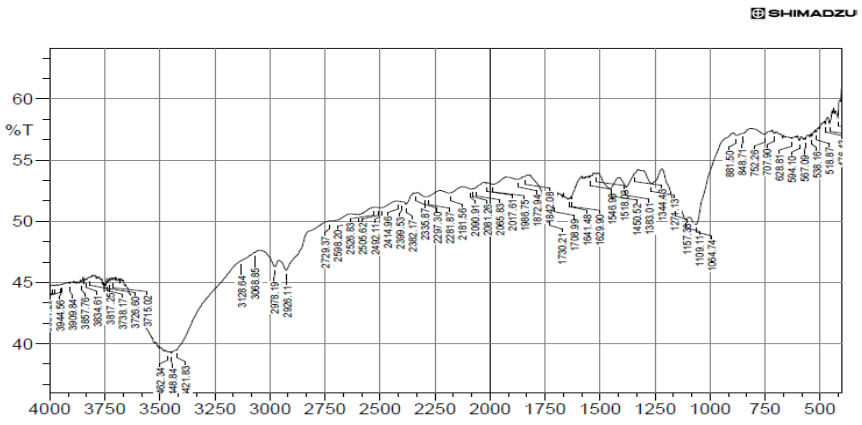


Fig-1: FTIR spectra of Rivaroxaban



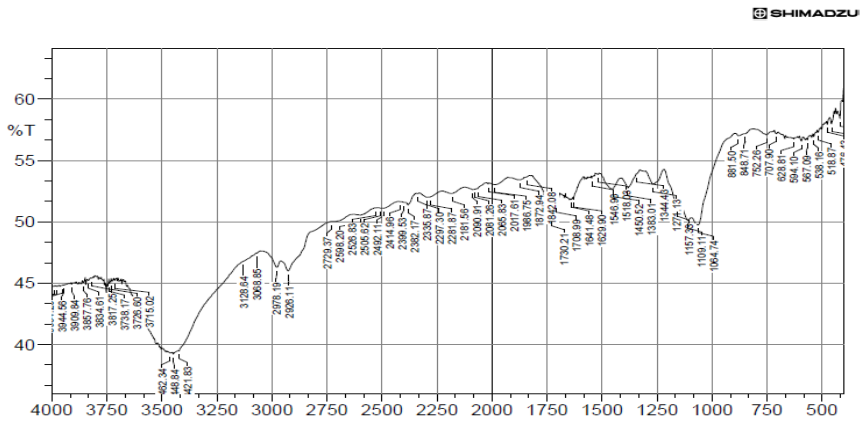


Fig-2: FTIR Spectra of physical mixture of drug and excipient

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks was obtained as above and as they were in official limits (±100 cm^{-1}) the drug is compatible with excipients.

Evaluation parameters

Weight variation:

All the formulated (F1 to F8) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness:

Tablets mean thickness were uniform in F1 to F8 formulations and were found to be in the range of 4.06 mm to 4.23 mm.

Hardness:

The measured hardness of tablets of each batch ranged between 5.27 to 5.63 kg/cm^2. This ensures good handling characteristics of all batches.

Friability:

The % Friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity:

The percentage of drug content for F1 to F8 was found to be between 79.52 % and 83.65 % of Rivaroxaban it complies with official specifications.

Table-2: Results of Evaluation parameters of tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	100	4.20	5.63	0.39	79.68
F2	99	4.18	5.27	0.41	80.21
F3	101	4.23	5.40	0.53	78.62
F4	98	4.19	5.29	0.45	81.26
F5	100	4.16	5.30	0.47	79.52
F6	100	4.20	5.31	0.50	83.65
F7	101	4.06	5.29	0.38	82.32

F8	99	4.21	5.48	0.62	80.25

In-vitro Dissolution Study

Table-3: *In vitro* release data of tablet F_1 to F_8

Time(hrs)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
0	0	0	0	0	0	0	0	0
1	14.86	15.98	15.69	16.93	15.98	16.89	16.30	13.20
2	27.59	25.67	27.82	25.76	27.15	28.46	26.58	27.52
3	35.60	36.85	37.15	34.25	35.60	37.82	35.10	34.39
4	43.98	45.35	46.21	47.82	48.92	49.68	45.71	46.35
5	55.19	56.91	57.80	58.10	59.81	55.82	54.19	57.16
6	68.72	67.89	69.86	71.26	73.64	75.98	76.90	75.12
7	83.67	82.36	83.69	86.97	87.56	86.35	82.31	80.20
8	94.65	93.22	95.58	94.86	95.82	96.82	95.10	93.98

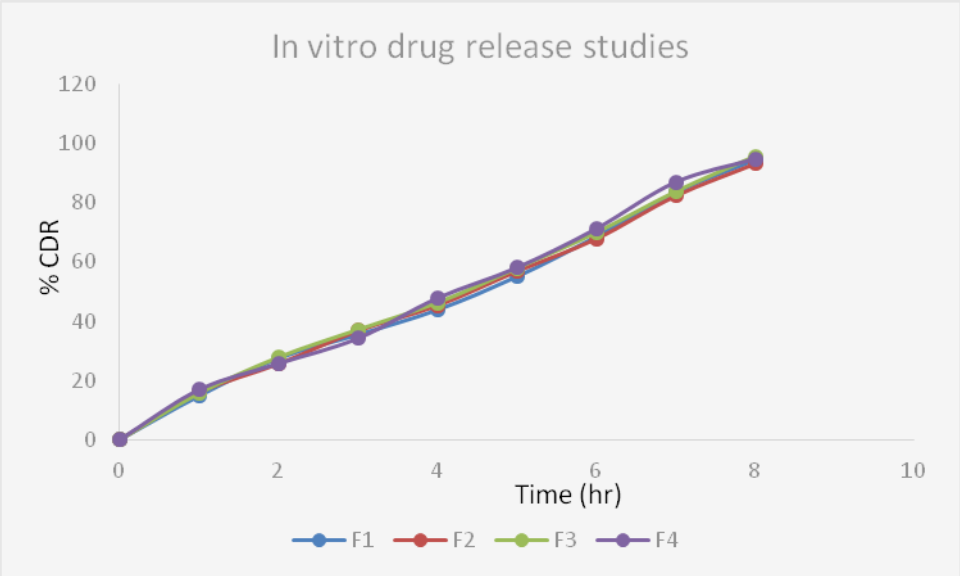


Fig-3: In vitro drug release studies of F1-F4 formulations

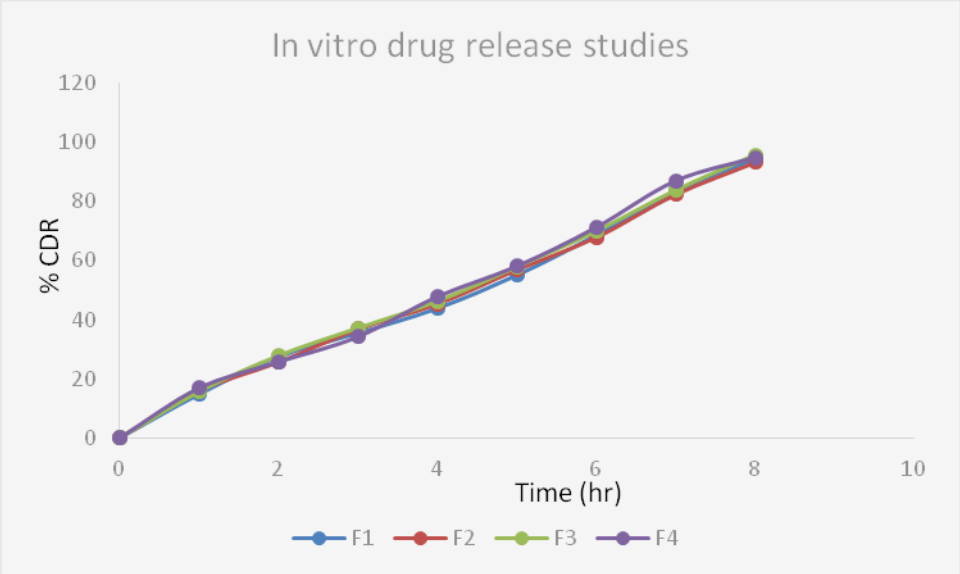


Fig-4: In vitro drug release studies of F4-F8 formulations

Kinetic modelling of drug release

All the 8 formulation of prepared matrix tablets of Rivaroxaban were subjected to invitro release studies these studies were carried out using dissolution apparatus.

The dissolution medium consisted of 900 ml of Standard buffer pH 1.2 for the first 2 hrs, followed by pH 6.8 for remaining period of time.

The results obtaining in vitro release studies were plotted in different model of data treatment as follows:

1. Cumulative percent drug released vs. time (zero order rate kinetics)
2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)
3. Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
4. Log of cumulative % release Vs log time (Pappas Exponential Equation)

Zero order kinetics

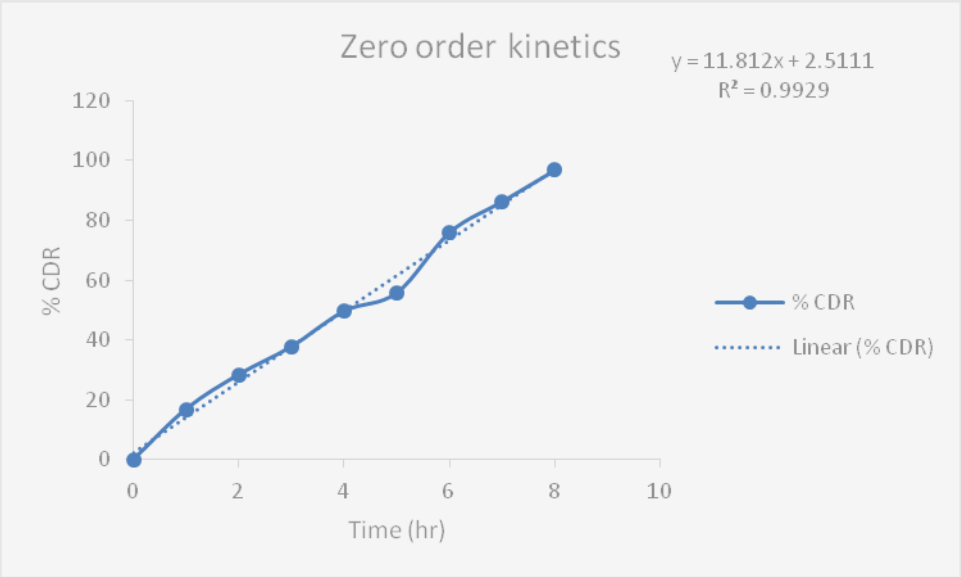


Fig-5: Zero order kinetics of optimized formulation

First order kinetics

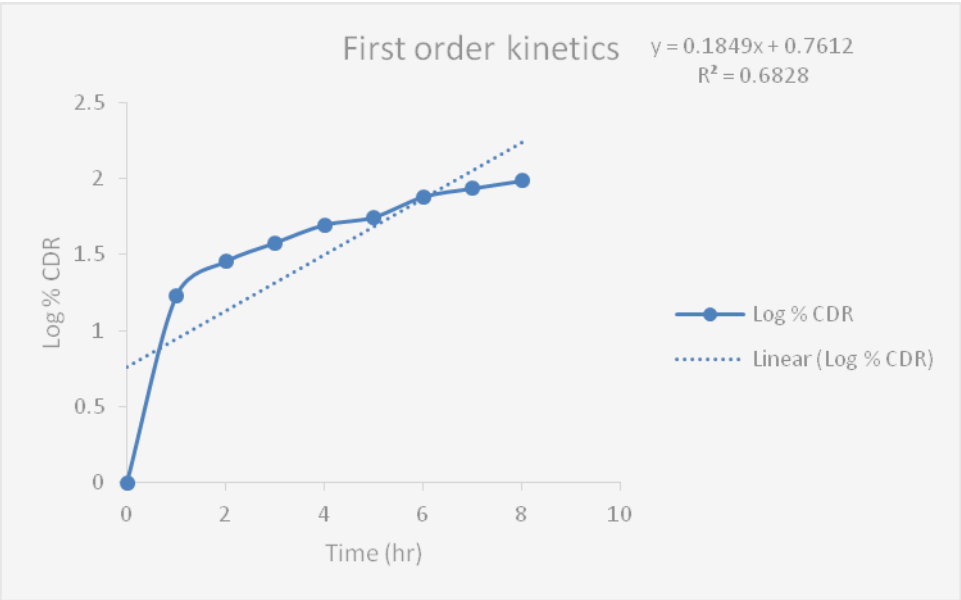


Fig-6: First order kinetics of optimized formulation

Higuchi model

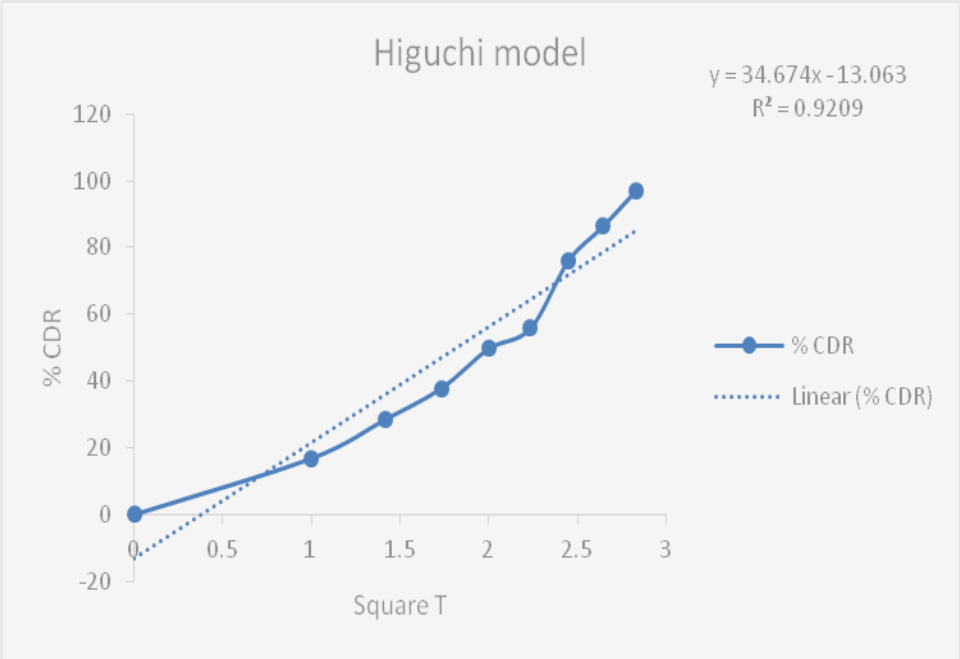


Fig-7: Higuchi modelof optimized formulation

Korsmeyer peppas

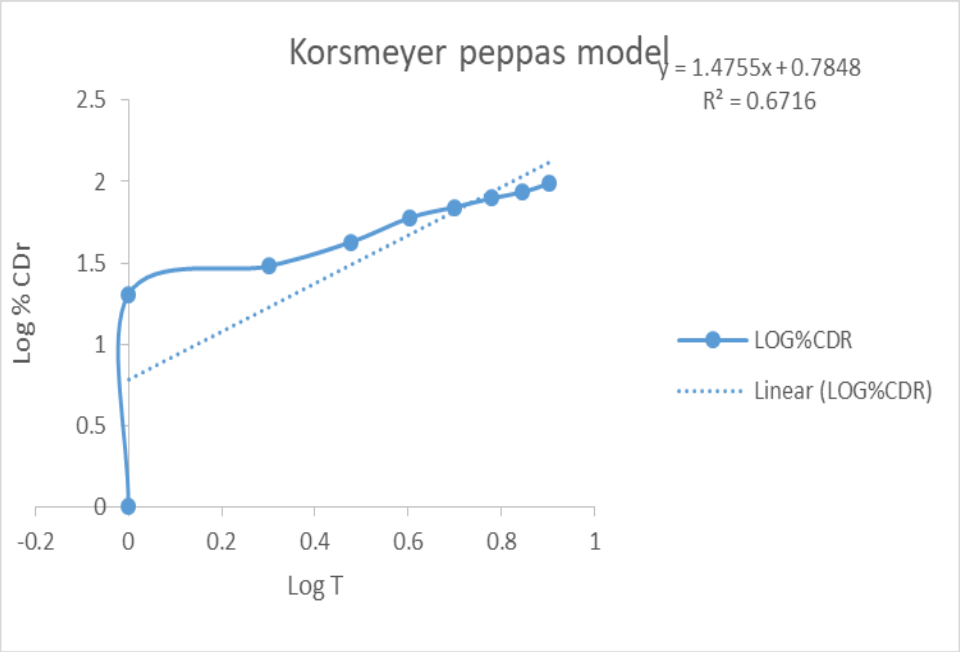


Fig-8: Korsmeyer peppasof optimized formulation

The kinetic values obtained for formulation F6 were shown. The values of invitro release were attempted to fit into various mathematical models.

Regression values are higher with Zero order release kinetics. Therefore, all the Rivaroxaban tablets Zero order release kinetics. Therefore, all the Rivaroxaban tablets follow first order release kinetics.

Stability studies

There was no significant change in physical and chemical properties of the tablets of formulation F-6 after 3 months. Parameters quantified at various time intervals were shown;

Table-4: Results of stability studies of optimized formulation F6

Formulation Code	Parameters	Initial	1st Month	2nd	3rd	Limits as per Specifications
F-6	**25^{0}C/60%RH**	96.82	95.64	94.76	93.67	**Not less than**
F-6	**30^{0}C/75% RH**	96.82	95.6	94.58	93.42	**Not less than**
F-6	**40^{0}C/75% RH**	96.82	95.47	94.35	93.28	**Not less than**

CONCLUSION

All the prepared tablet trials showed acceptable pharmaco technical properties and passes the official pharmacopoeia standards. The in vitro release profiles were applied on various kinetic models. The release studies revealed that the release rate was decreased with increase in polymer proportion. From the results of present study, it appears that the release of Rivaroxaban was significantly influenced by the characteristics of polymer and excipients used. In-vitro release from the formulation F6 with the hardness of 5.31 kg/cm^2. Higher hardness tablets contain a compact mass of polymer with relatively less pore, resulting in slower release. All other tested parameters of F6 formulation were in the acceptable limits. So formulation F6 was found to be better than other batch of formulations.In the current research work, matrix formulation F6 containing Guar gum were perhaps show maximum delay of drug release and it shows super case-II transport, for these causes, it was reflected that the formulation F8 as optimum formulation among all formulationsStability study was carried out with F6 formulation and the marketed sample as per ICH guidelines and found to be stable both in accelerated and long term stability conditions

REFERENCES

1. Dinda SC, Durga P, Pattanayak, Narayan UL, Design and evaluation of a fixed Dose combination formulation of Valsartan and Metformin Hcl for biphasic drug release: A novel approach to increase therapeutic efficacy, International Journal of Pharmaceutical Science and Technology, 6, 2011, 44-63.
2. ShivakalyaniAdepu, Controlled Drug Delivery Systems: Current Status and Future Directions,Molecules. 2021 Oct; 26(19): 5905
3. Ali, The Role of Oral Controlled Release Matrix Tablets in Drug Delivery Systems, Bioimpacts. 2012; 2(4): 175–187
4. Shailesh, Formulation and Evaluation of Controlled-Release Tablet of Zolpidem Tartrate by Melt Granulation Technique, International Scholarly Research Notices,2012
5. Pradeep kumar, preparation and evaluation of saquinavir mesylate oral suspension, international journal of drug formulation & research, VOL. 1; 2;2012.
6. Vishwakarma Swati, Formulation and Evaluation of Controlled Release Tablet of Lamotrigine, International Journal of Pharmaceutical & Biological Archives 2018; 9(3):151-156
7. Jain V, Prasad V, Jadhav P, Mishra PR. Preparation and performance evaluation of saquinavir laden cationic submicron emulsions. Drug Deliv. 2009 Jan;16(1):37-44.
8. Fukuda M, Peppas NA, McGinity JW, Properties of sustained release hot-melt extruded tablets containing chitosan and xanthum gum, International Journal of Pharmaceutics, 310, 2006, 90-100.
9. Mahajan P, Mahajan SC, Mishra DK, Valsartan release from sustained release matrix tablet and effect of cellulose derivatives, International Journal of Pharmacy and Life Science, 2, 2011, 521
10. Lachman L, Liberman HA and Kanig JL. The Theory and Practice of Industries Pharmacy, 3rd edition. Varghese publishing house, 2008;296-303,430-456.
11. Venkatesh DN, Jawahar N, Ganesh GNK, Kumar RS, Senthil V, Samanta MK, Sankar S and Elango K. Development and In Vitro evaluation of sustained release matrix tablet of theophylline using hydrophilic polymer as release retardant. Int J Pharm Sci Nano. 2009;2(1):34-38.
12. Mridanga RR, Bose SK and Sengupta K. Design, Development and in vitro evaluation of directly compressed sustained release matrix tablet of famotidine Research J Pharm and Tech. 2008;1(3):175-178.
13. Hingmire LP, Deshmukh VN and Sakarkar DM. Development and evaluation of sustained release matrix tablet using natural polymer as release modifier. Research J Pharm Tech. 2008; 1(3):123.
14. Kralovicova J, Bartunek A, Hofmann J, et al. Pharmacokinetic variability in pre- clinical studies: sample study with abiraterone in rats and implications for short- term comparative pharmacokinetic study designs. Pharmaceutics. 2022; 14:643.
15. US Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry, Bioanalytical Method Validation. Accessed June 23, 2023.