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Formulation and Evaluation of Immediate Release Tablet of Rivaroxaban

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HUMAN

[1]Manjari N. Bobde, [2]*Sadhana R. Shahi, [3]Anil Battase, [4]Priyanka Kale

[3]Department of Pharmaceutics, Govindrao Nikam College of Pharmacy, Sawarde, Ratnagiri, Maharashtra-415606 India.

[1, 2,4]Government College of Pharmacy, Aurangabad, Maharashtra-431005 India.

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ABSTRACT

Rivaroxaban is an anticoagulant and the first orally active direct factor Xa inhibitor. The purpose of this research work was to formulate an immediate-release tablet of Rivaroxaban for the treatment of deep vein thrombosis and pulmonary emboli and prevent blood clots in atrial fibrillation and following hip or knee surgery, by using superdisintgrant such as Croscarmellose sodium and microcrystalline cellulose. Immediate release tablets of Rivaroxaban were prepared by wet granulation method using different concentrations of binder HPMC E-5 and surfactant SLS. Tablets were subjected to physicochemical characterization such as thickness, hardness, friability, weight uniformity, drug content, disintegration time, *in vitro* drug release, and stability study. Tablets were found to be satisfactory when evaluated for thickness, hardness, friability, weight uniformity, drug content, disintegration time and *in vitro* drug release. The tablet disintegration time was less than two minutes for all the tablet formulations. The *in vitro* drug release in optimized formulation F6 was found to be 95.02 % in 45 min. Theoptimized formulation F6 also showed satisfactory hardness (5.0±0.026 kg/cm2), friability (0.47%±0.03), drug content (95.02%±0.32), weight variation (170.1±0.65 mg), and disintegration time (88-94 seconds).

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1. INTRODUCTION

Immediate-release dosage forms allow manufacturers to extend market exclusivity while providing convenient dosing to patients forms or dosing regimens. Immediate-release tablets are tablets designed to fast disintegrate, dissolve and release the drug. Special rate control features such as special coatings and other technologies[iii] Recently, immediate-release tablets have gained popularity and acceptance as a drug delivery system. The main reasons are ease of administration, rapid onset of action, economy and improved patient compliance. They are also tools for expanding markets, extending product lifecycles and creating opportunities.

Immediate-release systems typically release the drug in less than one hour and act in a first-order kinetic configuration. The duration of action of the drug is limited to when the drug concentration is higher than MEC.

Rivaroxaban is an anticoagulant medication (blood thinner) taken by oral route, it is also used to treat and prevent deep vein thrombosis (DVT), which can cause blood clots to form in the lungs (pulmonary embolism). Rivaroxaban is a direct factor Xa inhibitor. It works by preventing the formation of blood clots. The first time it was developed by Bayer and marketed by Janssen Pharmaceuticals in the United States. Rivaroxaban was approved for medical use in 2011 and patented in the United States in 2007. Patent rivaroxaban is expired in 2020. This is the first active direct factor Xa inhibitor available to be administered orally. Rivaroxaban exhibits dose-dependent bioavailability. For a 10 mg dose, bioavailability is about 80-100% and is not affected by feed. The bioavailability of the 20 mg dose is 66%. Fasted state, although exposure is increased when taken with food. It is recommended that Doses of 15 mg and 20 mg should be taken with the evening meal. The absorption of rivaroxaban is depending on the site of drug release in the gastrointestinal tract.

In the present study an attempt has been made to prepare immediate-release tablets of Rivaroxaban. It is the generic type of tablet using different modification of API other than the marketed tablet. The comparison of modifications 1 and 2 is clearly distinguishable by X-ray diffractogram, IR spectrum, NIR spectrum, FIR spectrum and Raman spectrum.

Using different Super disintegrant and different concentrations of excipients. Concentration of SLS and HPMC E-5 concentration was varied for all batches. Best batches were optimized using dissolution of their tablets and % cumulative drug release was calculated from tablet. Depending on pre, post compression parameters and % cumulative release of drug

formulation batches was optimized using ANOVA and Grid analysis. In nine batches of immediate release tablet SLS and HPMC E-5 concentration was used in different concentrations and F6 were found as an optimized batch of the formulation.

2. MATERIALS

Rivaroxaban was obtained as a gift sample from Lupin pharmaceutical limited Mumbai. HPMC E5, Sodium lauryl sulphate obtained from Hi media chem Mumbai. magnesium stearate, MCC, and lactose were obtained from S.D. fine chemicals Mumbai.

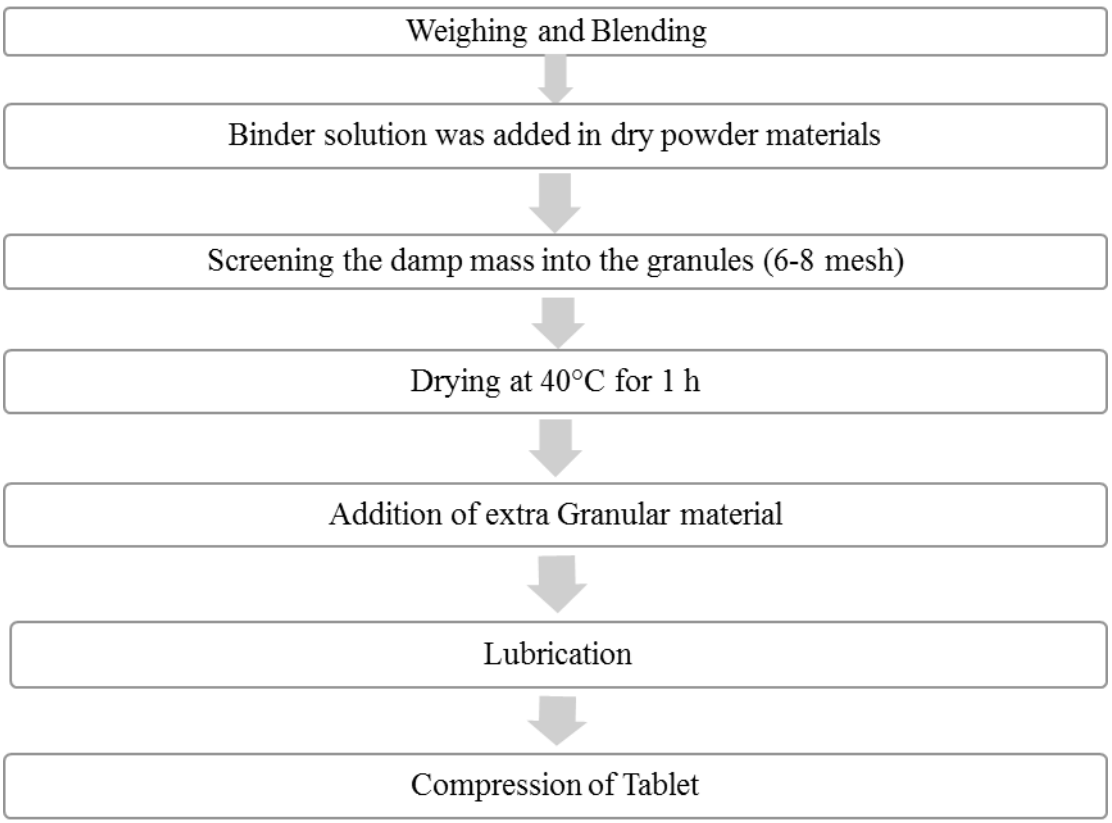
3. METHODS

3.1. Manufacture of Rivaroxaban Tablet

3.1.1. Wet Granulation

In the wet granulation process, granules were produced by using HPMC as a binder in water. Subsequent drying and milling to produce granules. The steps used in wet granulation are mentioned as follows.

3.1.2. Procedure[iii]



According to the formulation table, immediate release tablets of rivaroxaban were effectively prepared by wet granulation method using super disintegrants such croscarmellose sodium and surfactant sodium lauryl sulphate. Table no. [1].

Table [1]: Formulation of Immediate Release Tablet of Rivaroxaban

INGREDIENTS (mg)	**Formulation Batches**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Rivaroxaban	20	20	20	20	20	20	20	20	20
MCC Ph 101	88.6	87.4	86.2	87.6	88.4	87.2	86.6	86.4	88.2
Lactose Monohydrate	48	48	48	48	48	48	48	48	48
Cross Carmellose Sod	8	8	8	8	8	8	8	8	8
Hypromellose E5	3.8	4.8	5.8	4.8	3.8	4.8	5.8	5.8	3.8
Sodium Lauryl Sulphate	0.4	0.6	0.8	0.4	0.6	0.8	0.4	0.6	0.8
Magnesium Stearate	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
TOTAL WT	**170**	**170**	**170**	**170**	**170**	**170**	**170**	**170**	**170**

4. EVALUATION OF POWDER BLEND

Particle size distribution

Particle size distribution was measured by the sieving method with vibrating sieve device. Sieve stack with 6 sieves in the opening progression loaded with powder in the roughest conditions constructed stacks and nests are sifted mechanical vibration, after 10 min, the particles are considered to be retained on the sieve mesh; then weighed the powder retained in the sieves and the respective parameters were calculated.

Drug–Excipient Interaction Study

The drug, polymer and other formulation ingredients were characterized by IR spectroscopy using a FTIR 8400S (Shimadzu, Japan). The spectra were taken by KBr discs method in the range of 4700–400 cm^{-1}.

Bulk density

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. An 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. It is expressed in **gm/ml** and is given by the formula

Bulk Density=M/Vo

Where, M = Mass of the powder

Vo = Bulk Volume of the powder

Tapped density

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

Tapped density=M/Vt

Where, M = mass of the powder

Vt = final tapping volume of the powder

Angle of repose (θ)

It is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. A fixed funnel method was used. A funnel was fixed with its tip at a given height ‘h, above a flat horizontal surface to 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 the funnel.

The angle of repose was then calculated using the following equation,

Angle of repose Ø = tan-1(h/r)

Where, h= Height of the pile

r= Radius of the pile

Compressibility index (Carr's index)

The compressibility index is used as an important parameter to determine the flow behaviour of the powder. It is indirectly related to the relative flow property rate, cohesiveness and particle size. It is simple, fast and popular method for predicting flow characteristics. Carr's index can be represented by an equation,

CI=DT-DB/DTX100

Where, DT=Tapped density of powder,

DB=Bulk density of powder.

Hausner's ratio

Hausner's ratio is used to predict the flowability of the powders. This method is similar to the compressibility index. Hausner's ratio can be represented by Equation[iv,v,vi.vii.]

Hausner's ratio= DT/DB

Where DT= Tapped Density,

DB=Bulk density

5. EVALUATION OF TABLETS[viii]

All of the tablets were analysed for various parameters such as thickness, hardness, friability, and uniformity, weight, disintegration time, drug content, and an *in-vitro* dissolution test.

Dimensional Analysis

The thickness and diameter of the tablets were measured with a vernier calliper. The average value was determined using twenty tablets from each batch.

Hardness

The Monsanto hardness tester was used to determine the hardness of the tablet. The tablet was held firmly between the fixed and movable jaws. The scale was reset to zero, and the load was steadily raised until the tablet fractured. The value of the load at that location indicates the [ix]tablet's hardness. It is measured in **kg/cm^2**. The hardness of six tablets was evaluated for each formulation, and an average value was calculated.

Weight variation

Twenty tablets were weighed individually and collectively in a single pan balance at random. The average weight was noted and the standard deviation was calculated. If no more than two tablets go outside the % limit and no tablet differs by more than double the percentage limit, the tablets pass the test. The USP limit for weight fluctuation in tablets up to 130 mg is 10%, 130 mg to 324 mg is 7.5%, and more than 324 mg is 5%.

$PD = [(W_{avg} – W_{initial}) / (W_{avg})] \times 100$

Where,

PD = Percentage deviation,

W_{avg} = Average weight of the tablet,

$W_{initial}$ = Individual weight of the tablet.

Drug Content

Tablets were crushed, and the powder equivalent to 100mg of drug was precisely weighed and transferred. To 50ml volumetric flask. A sufficient amount of distilled water was poured to this flask to thoroughly dissolve the tablets. The flask capacity was then increased using the same solvent. 1 ml of the sample was pipetted out of this solution and transferred to a 10 ml volumetric flask. Distilled water was used to make up the volume in the second flask. To keep the concentration within the beer's range, 0.6ml, 0.8ml, and 1ml samples were collected and volume was adjusted to 10ml. This final diluted solution was UV spectrophotometrically estimated at 248 nm.

Friability

Twenty tablets samples were weighed accurately and placed in friability (Roche friabilator). After the given specification (4 min at 25 rpm), loose dust was removed from the tablets. Finally, the tablets were weighed. The loss in weight indicates the ability of the tablets to withstand this type of wear.

The % friability was then calculated by,

$[(W_{avg} – W_{initial}) / (W_{avg})] \times 100$

Disintegration test

Each batch's tablets disintegrate immediately. The disintegration time ranged from 25 to 30 seconds. Its rapid disintegration is caused by Croscarmellose Sodium's rapid water uptake from the medium, and burst action[x,xi].

***In-vitro* Drug Release**

Dissolution testing was performed using a USP apparatus 2 (paddle). The paddle was set at 75 rpm, and 900 ml of dissolution media was used to test all samples. Prior to testing, the dissolution media was preheated and degassed to prevent air bubble formation during the transfer of buffers into the vessels. Dissolution testing was started after the temperature of 37°C (±0.5°C) was confirmed in all vessels. At pre-set time points of 10, 15, 20, 30, 45, and 60 min, samples were withdrawn[xii].

Kinetics of Drug Release

The dissolution profiles of all formulations were fit to first-order kinetics, Higuchi, Hixson-Crowell, Korsmeyer, and Peppas to determine the kinetic modelling of drug release using DD solver and the model with the highest correlation coefficient was considered the best model. The data was further analysed by Korsmeyer Peppas equation to determine the drug release mechanism, and the value of n, i.e., release exponent, was derived[xiii].

Stability Studies

The stability studies were carried out by keeping the optimised formulation of tablets in a stability chamber at 40±2° C/75±5% RH for 45 days. The samples were withdrawn after 45 days, and analysed for several physical tests and drug release studies.

Analysis of Data by Design Expert Software and Grid Analysis

The observed data was analysed by State Ease Design Expert 13 and Grid analysis was performed to get the optimized formulation.

Comparison of release profile with marketed product

The *in-vitro* release studies were carried out for the marketed product (Xarelto, Bayer pharma Rivaroxaban 20 mg) in order to compare its release profile with optimized formulation of immediate-release tablets of rivaroxaban. The observations are noted in Table[6].

6. RESULTS AND DISCUSSION

Organoleptic Properties

The physical identification test like color, odour, taste and appearance of prepared tablets were observed.

Melting Point

Determination of melting point The observed melting points in a range of 227-232ºC

Compatibility study

The FTIR spectrum analysis revealed that there was no change in any of the pure drug's particular peaks. Excipients, confirming the absence of chemical interaction between the drug and the excipients. Figures [1] and [2] show the FTIR spectra of pure drug and drug with excipients, respectively.

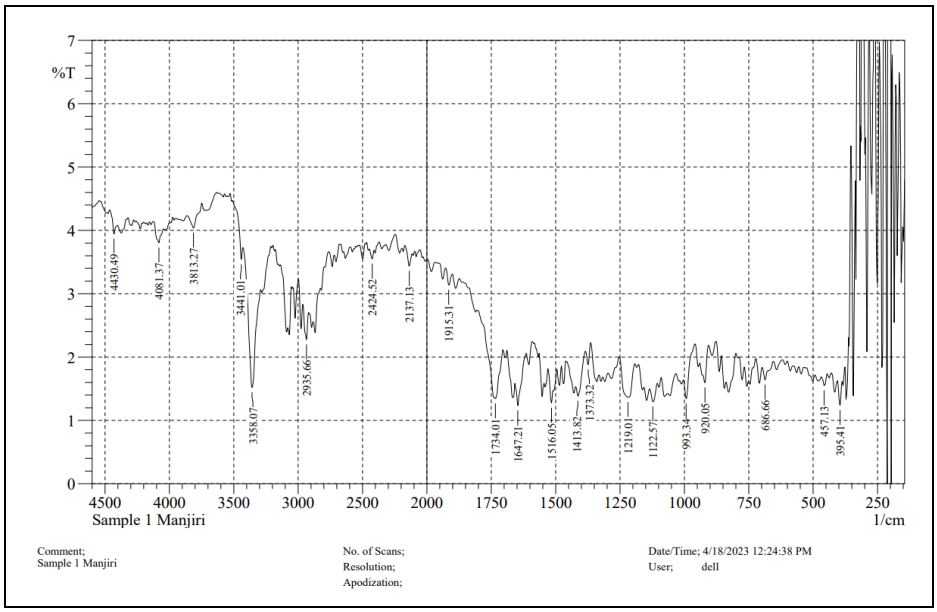


Figure [1]: IR of API Rivaroxaban

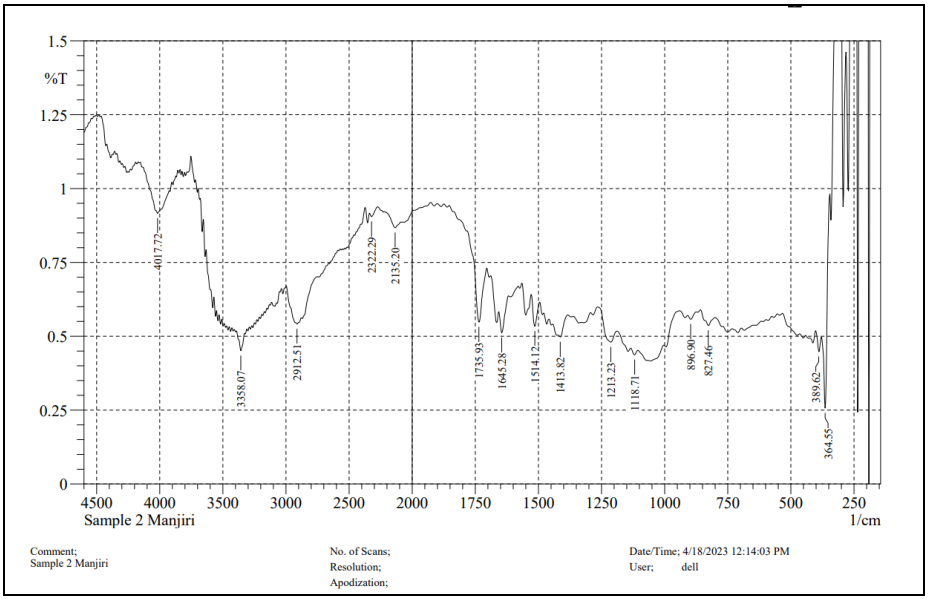


Figure [2]: IR of Drug+ Excipients

Mass -Volume relationship

The characterizations of different formulations were done for the determination of mass-volume relationship parameters. The assessed variables are the bulk density, the tapped density, the compressibility index, the angle of repose, and Carr's index, which is noted in Table[2].

Table [2]: Evaluation of Precompressed Powder Blend

Formulation Code	**Bulk Density (gm/ml)**	**Tapped Density (gm/ml)**	**Carr's Compressibility Index**	**Hausner's Ratio**	**Angle of Repose** (θ)
F1	0.523±0.30	0.66±0.42	16.80±0.98	1.30±0.32	23.24±0.23
F2	0.491±0.92	0.657±0.60	15.84±0.76	1.26±0.72	27.20±0.75
F3	0.478±0.34	0.549±0.20	18.25±0.54	1.23±0.06	30.45±0.42
F4	0.481±0.64	0.652±0.60	17.87±0.84	1.25±0.45	26.07±0.60
F5	0.494±0.30	0.697±0.35	14.72±0.46	1.29±0.42	30.62±0.78
F6	0.485±0.74	0.712±0.26	15.15±0.34	1.22±0.37	23.96±0.88
F7	0.502±0.23	0.674±0.42	15.06±0.75	1.21±0.23	29.17±0.56
F8	0.515±0.24	0.680±0.23	18.34±0.23	1.24±0.44	26.76±0.42
F9	0.479±0.06	0.658±0.54	17.29±0.36	1.22±0.35	28.56±0.27

All values expressed as mean ± SD

Flow Characteristics

The powder had a bulk density of 0.47 to 0.52gm/ml and a tapped density of 0.54 to 0.71gm/ml. The powder had a density of 0.47 to 0.67gm/ml, indicating that it was not bulky. The angle of repose of the formulations was in the range of 26^{o} to 30^{o}, indicating excellent powder flow. Carr's index was found to be in the 14 to 19 range. The observations are noted in Table[3].

Table [3]: Evaluation of Immediate Release Tablets of Rivaroxaban

Formulation code	**Hardness (Kg/cm^2)**	**Thickness (mm)**	**Average weight(mg)**	**Friability (%)**	**Drug Content (%)**	**Disintegration Time (sec)**
F1	4.8±0.02	2.80±0.04	171.3±0.72	0.79±0.01	91.89±0.61	70-81
F2	4.2±0.06	2.83±0.06	170.7±0.46	0.67±0.01	93.11±0.42	118-140
F3	4.30.06	2.87±0.06	170.3±0.32	0.56±0.01	91.12± 0.71	120-134
F4	5.7±0.08	2.86±0.07	172.1±0.54	0.75±0.00	91.45±0.63	90-100
F5	5.4±0.03	2.87±0.06	171.6±0.32	0.71±0.01	92.57±0.42	60-72
F6	5.0±0.02	2.90±0.05	170.1±0.65	0.47±0.03	95.02±0.32	88-94
F7	5.9±0.04	2.97±0.06	169.7±0.24	0.52±0.87	92.83±0.43	125-131
F8	5.7±0.06	2.97±0.02	170.1±0.45	0.56±0.67	93.36±0.61	132-140
F9	5.4±0.03	3.00±0.06	172.8±0.64	0.60±0.04	93.24±0.44	97-104

All values expressed as mean ± SD.

Tablet Thickness

The thickness of the formulations varied from 2.80±0.04 to 3.00±0.06 mm.

Hardness

The hardness was uniformly maintained and it was found to be within 4.2±0.06 to 5.9±0.04 kg/cm2.

Friability

The values of friability were within the acceptable range noted.

Disintegration Test

Each batch's tablets immediately start to disintegrate. The duration of disintegration ranged from 25 to 30 seconds. The quick absorption of water from the medium, swelling, and burst effects of croscarmellose sodium are the causes of this rapid disintegration**.**

Weight Variation

Weight variation was non-significant. It ranged from 169 mg to 172 mg, with extremely high standard deviation values. The weight fluctuation was greatly minimised as microcrystalline cellulose was increased. Table [3] summarises the findings. The weight variation test is passed by all formulations.

Percentage Drug Release

Comparative cumulative percentage drug release data for all formulations is provided in table. In Figures 3 and 4, the dissolution profiles of the formulations F1 to F9 are presented. The drug release ranged from 91.12 to 95.02 % within 45 minutes for various batches. In 45 minutes, F6 had the highest drug release of any formulation. All the observations of % drug release are mentioned in Table 4.

Table 4: Comparative % Drug Release Profiles of Formulation

TIME (min)	**% Drug Release**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
5	47.19±0.3	46.64±0.7	47.03±0.52	45.9±0.41	44.89±0.53	49.41±0.42	46.94±0.55	43.84±0.51	48.01±0.54
10	68.82±0.41	72.17±0.51	70.98±0.55	71.62±0.36	69.92±0.47	72.94±0.33	70.95±0.61	71.53±0.46	69.98±0.52
15	82.12±0.6	84.78±0.45	83.32±0.61	85.12±0.43	84.67±0.61	86.04±0.51	84.76±0.7	85.23±0.62	85.12±0.55
20	86.68±0.32	88.38±0.71	87.32±0.48	87.67±0.74	88.04±0.56	90.13±0.64	86.78±0.46	89.06±0.43	88.34±0.36
30	90.22±0.53	91.02±0.63	89.74±0.36	89.99±0.44	90.97±0.6	93.21±0.46	91.88±0.53	92.19±0.48	91.23±0.61
45	91.89±0.61	93.11±0.42	91.12±0.71	91.45±0.63	92.57±0.42	95.02±0.32	92.83±0.43	93.36±0.61	93.24±0.44

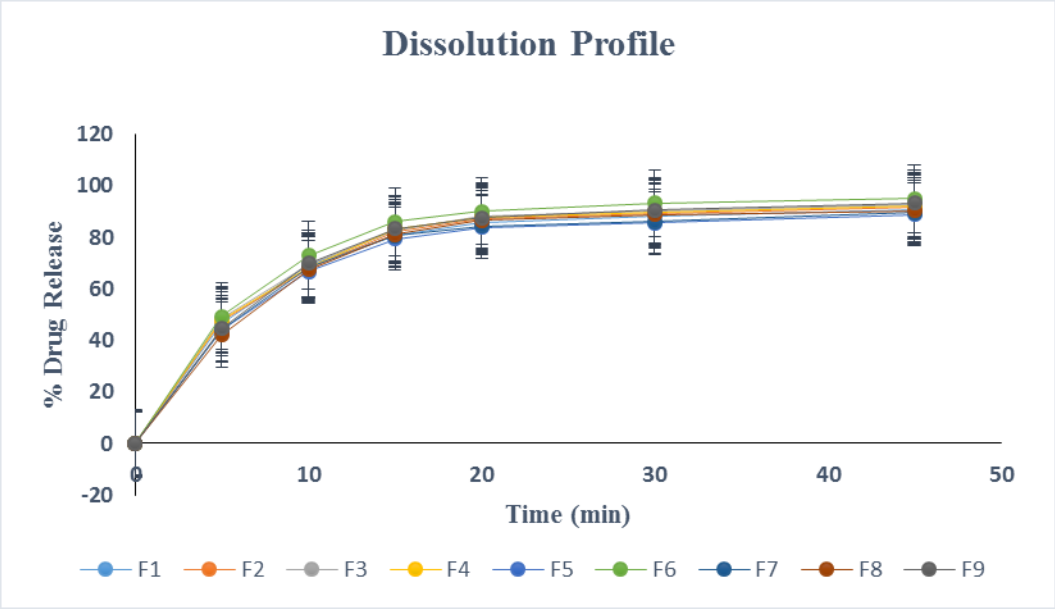


Fig 3: *In vitro* % Drug Release

Kinetics of Drug Release

Various mathematical models for predicting the drug release by dissolution profile of all the formulated batches i.e., Korsmeyer-Peppas, zero order, first order, Hixon crowell, Higuchi release model to ascertain the kinetic modelling of drug release by using DD Solver software. The coefficient of determination (R) and release constant (k) for each dissolution model were evaluated. A large value of R indicates that profile fits best to the model.

Table 5: Kinetics of Drug Release

Formulation Batch	Kinetic Models							
	First Order	Hixson-Crowell	Weibull	Peppas-Sahlin	Korsmeyer-Peppas	Higuchi	n	k
F1	0.9815	0.9459	0.9972	0.9964	0.9651	0.8218	0.254	37.65
F2	0.9862	0.9513	0.9978	0.9924	0.9561	0.8068	0.249	38.88
F3	0.9785	0.9395	0.9970	0.9940	0.9580	0.7988	0.242	39.12
F4	0.9802	0.9436	0.9962	0.9909	0.9504	0.7949	0.245	39.00
F5	0.9864	0.9572	0.9962	0.9922	0.9519	0.8190	0.261	37.16
F6	0.9926	0.9559	0.9981	0.9952	0.9629	0.8064	0.244	40.31
F7	0.9859	0.9511	0.9973	0.9940	0.9596	0.8140	0.252	38.40
F8	0.9896	0.9636	0.9973	0.9908	0.9466	0.8197	0.266	37.00
F9	0.9864	0.9518	0.9960	0.9944	0.9609	0.8120	0.250	38.83

Analysis of Data by Design Expert Software and Grid Analysis

ANOVA for the dependent variable % drug release Q_{30} respectively. The coefficients of X1 and X2 were found to be significant at $P < 0.05$, hence confirming the significant effect of both variables on the selected responses. Increasing the concentration of the SLS resulted in the increase in the release of Rivaroxaban. Overall, both the variables caused significant change in the responses. ANOVA and Multiple regression analysis were done using Stat Ease Design Expert 13 software. However, both variables favour the preparation of immediate-release tablets of rivaroxaban[xiv].

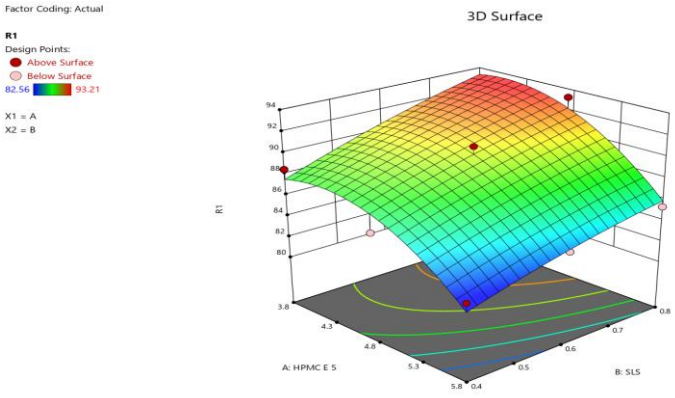


Fig 4: Response Surface Plot for % Drug Release

Comparison of Release Profile with Marketed Preparation

The release profile of the F6 was compared with that of the marketed preparation (Xarelto). The observed F2 (Differential Factor) value is 74.457.

Table 6: Comparison of Release Profile with Marketed Preparation

Time (min)	**Drug Release (%)**	
	Xarelto 20 mg	**F6**
5	45.21	49.41
10	68.41	72.94
15	85.49	86.04
20	88.52	90.13
30	90.34	93.21
45	92.23	95.02

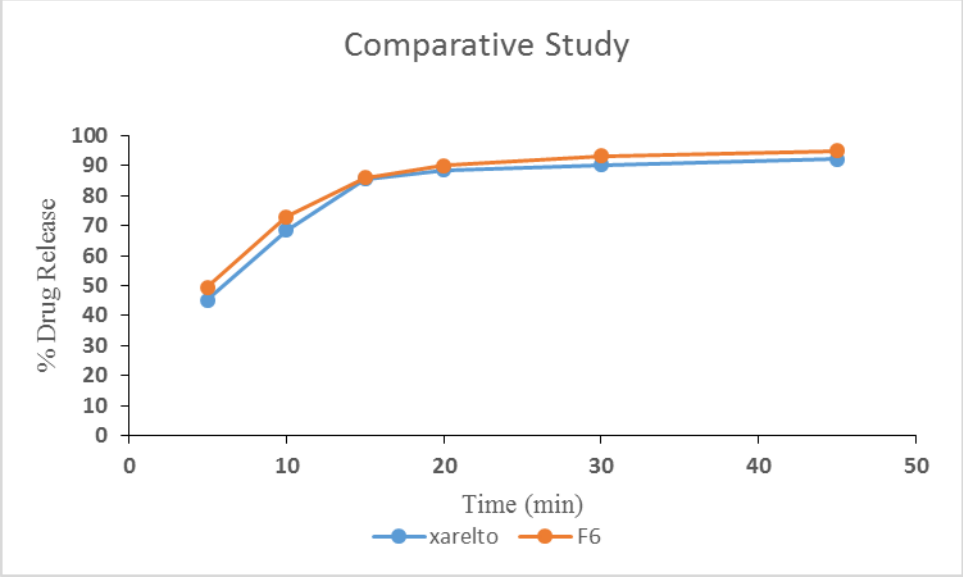


Fig 5: Comparison of Release Profile with Marketed Preparations

Conclusion:

All formulations were found to be satisfactory when evaluated for thickness, weight uniformity, hardness, friability, drug content uniformity, and disintegration time and *in-vitro* drug release. The tablet disintegration time was less than one minute for all the tablet formulations. The *in vitro* drug release in optimized formulation F6 was found to be 95.02 % in 45 min. The optimized formulation F6 also showed satisfactory hardness (5.0±0.02 kg/cm2), friability (0.47±0.03 %), drug content (95.02±0.32%), weight variation (170.1±0.65mg), and disintegration time (88-94 seconds).

Reference:

[i] Fu Y, Yang S, Jeong SH, Kimura S, Park K. Orally fast disintegrating tablets: developments, technologies, taste-masking and clinical studies. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2004;21(6).

[ii] Bhatti A. Fast disintegrating tablets of diazepam. INDIAN DRUGS-BOMBAY-. 2006;43(8):643.

[iii] Hiremath P, Nuguru K, Agrahari V. Material attributes and their impact on wet granulation process performance. In Handbook of pharmaceutical wet granulation 2019 Jan 1 (pp. 263-315). Academic Press.

[iv] Adelakun TA, Ohwoavworhua FO. Phosphoric Acid-Mediated Depolymerization and Decrystallization of a-Cellulose obtained from Corn Cob: preparation of Low Crystallinity Cellulose and Some Physicochemical Properties. Trop. j. pharm. res.(Online). 2005:509-16.

[v] Bultmann JM. Multiple compactions of microcrystalline cellulose in a roller compactor. European journal of pharmaceutics and biopharmaceutics. 2002 Jul 1;54(1):59-64.

[vi] Hancock BC, Clas SD, Christensen K. Micro-scale measurement of the mechanical properties of compressed pharmaceutical powders. 1: the elasticity and fracture behaviour of microcrystalline cellulose. International journal of pharmaceutics. 2000 Nov 19;209(1-2):27-35.

[vii] Mashadi AB, Newton JM. Assessment of the mechanical strength properties of compacted sorbital instant. InJournal of Pharmacy and Pharmacology 1987 (Vol. 39, p. 67P). Pharmaceutical Press.

[viii] Das P, Das D, Das P. Formulation, development and evaluation of buffer esomeprazole tablet in tablet preparation. Int. J. Pharm. Sci. Drug Res. 2014;1:7-35.

[ix] Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrial pharmacy. Philadelphia: Lea & Febiger; 1976.

[x] Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrial pharmacy. Philadelphia: Lea & Febiger; 1976.

[xi] Adeyeye CM, Barabas E. Povidone. In Analytical Profiles of Drug Substances and Excipients 1993 Jan 1 (Vol. 22, pp. 555-685). Academic Press.

[xii] Reddy NH, Patnala S, Löbenberg R, Kanfer I. In vitro dissolution of generic immediate-release solid oral dosage forms containing BCS class I drugs: comparative assessment of metronidazole, zidovudine, and amoxicillin versus relevant comparator pharmaceutical products in South Africa and India. AAPS PharmSciTech. 2014 Oct;15:1076-86.

[xiii] Ekenna IC, Abali SO. Comparison of the Use of Kinetic Model Plots and DD Solver Software to Evaluate the Drug Release from Griseofulvin Tablets. Journal of Drug Delivery and Therapeutics. 2022 Apr 15;12(2-S):5-13.

[xiv] Shahi SR, Shinde SB, Zadbuke NS, Padalkar AN. Formulation developement and evaluation of floating matrix tablet of Verapamil HCl. Asian Journal of Pharmaceutics (AJP). 2013;7(1).