International Journal of Pharmacy and Biological Sciences
ISSN: 2321-3272 (Print), ISSN: 2230-7605 (Online)
IJPBS™ | Volume 8 | Issue 4 | OCT-DEC | 2018 | 369-378
Research Article | Pharmaceutical Sciences | Open Access | MCI Approved| ज्ञान-विज्ञान विमुक्तये
|UGC Approved Journal |

FORMULATION DEVELOPMENT AND EVALUATION OF IMMEDIATE RELEASE ANTI-COAGULANT DRUG RIVAROXABAN FILM COATED TABLETS

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ABSTRACT

The aim of the present study is to develop immediate release tablets of Rivaroxaban, to enhance solubility and dissolution for increasing its oral bioavailability. Rivaroxaban is widely prescribed as anti-coagulant drug which belongs to BCS class II.In present study, DOE trails was applied in the study by using solubilizing agent (SLS), Binding agent (HPMC), super disintegrant (CCS). Pre-compression studies were performed in formulation suggested by software and results were found to be within limits. The formulation were compressed by wet granulation method & evaluation tests were weight variation, hardness, friability, drug content, in-vitro drug release studies were performed. The cumulative drug release from all the formulations were compared with that of the Innovator. The enhanced Rivaroxaban release was by using 0.4 % SLS solution in dissolution media. Formulation trail F8 containing, Croscarmellose sodium(5.6mg), Hydroxy propyl methyl cellulose(4.0mg), Sodium Lauryl Sulphate(0.4mg) was selected as an optimized formulation as it showed same dissolution profile as innovator. It also matched the multimedia dissolution profile with the innovator.

KEY WORDS

Rivaroxaban, Croscarmellose sodium, Hydroxy Propyl methyl cellulose, Sodium Lauryl Sulphate, Immediate release tablets, In-vitro dissolution.

INTRODUCTION

Oral drug delivery is the most widely used route of administration than all other routes that have been explored for systemic delivery of drugs from pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptability and cost-effective manufacturing process. Oral drug delivery is the most desirable and preferred method of administering the drugs for their systemic effects. This is reflected by the fact that well over 80% of the drugs in the United States that are formulated to produce systemic effects are marketed as oral dosage forms[1].

TABLETS:

Tablets are unit solid pharmaceutical dosage forms. They contain active pharmaceutical ingredients with or without suitable excipients and prepared either by compression or molding methods. Tablets are mostly in different shapes like discoid and round, oval, oblong, cylindrical or triangular.

Properties of Tablets:

- It should have sufficient strength and resistance to shock, abrasion, withstand during handling, manufacturing, packing, shipping and use.
- The individual tablet must be uniform in weight and drug content.
- Tablets must retain its drug stability and efficacy.
- The drug content of the tablet should be bio-available.

Immediate release drug delivery system

Immediate release tablets are whose which disintegrate rapidly and get dissolved to release the medications with no special rate controlling features, such as special coatings and other techniques.

Ideal properties:

- It should dissolve or disintegrate within a short period of time
- Rapid onset of action
- It should leave any residue in the mouth after oral administration
- Exhibit low sensitivity to humidity and temperature

Advantages of Immediate Release Drug Delivery System:

- Improved compliance/added convenience
- Improved stability
- Allows high drug loading
- Cost – effective
- Accurate dosing as compared to liquids
- Ease of swallowing is possible

Disadvantages of Immediate Release Drug Delivery System:

- Frequent dosing is necessary for drug having short half-life
- Drug release at a time may produce high plasma concentration which may lead to toxicity

Criteria for Drug Selection

- Drugs having poor solubility, and which require immediate action
- The immediate release composition desired daily dosage of about 20 mg to 400 mg
- Immediate release composition shows 80% of *in-vitro* drug release within 30 min and 50% of *in-vitro* drug release in 15 minutes

Unsuitable drug characteristic for immediate release tablets

Drugs having following characteristics are unsuitable for immediate release

- Low biological half life
- Low bioavailability drugs
- Higher clearance and elimination half life

METHODOLOGY

Chemicals: Rivaroxaban, Microcrystalline cellulose, Lactose monohydrate, Croscarmellose sodium, Hydroxy Propyl methyl cellulose, Sodium Lauryl Sulphate, Magnesium stearate, Opadry red.

Instruments: Electronic balance, Electromagnetic sieve shaker, Tap density tester, Rapid Mixer Granulator, Multiattachment Blender, Mobile cone mill, Peristaltic pump, Friabilator, Rapid mixer, UV Spectrophotometer, Instrumented Smart press, Moisture Analyzer, Digital Vernier caliper, Monsanto Type tablet Hardness tester, Disintegration tester, Laboratory stirrer, Automatic Coating system, Dissolution test apparatus (USP II).

PREFORMULATION STUDIES:

- Physical characterization of API
- Solubility studies of API
- Flow properties of API
- Drug and excipient compatibility studies

METHOD:

Dissolution:

Drug release studies were carried out by using USP type II (paddle) apparatus. 900 ml of pH 4.5 acetate buffer+0.4% SLS was used as dissolution medium and the basket was rotated at 75 rpm at temperature (37ºC ± 0.5ºC). Sampling was done at regular intervals of time and was replaced by media after each sampling interval. The samples are then analyzed using HPLC.

FORMULATION DEVELOPMENT:

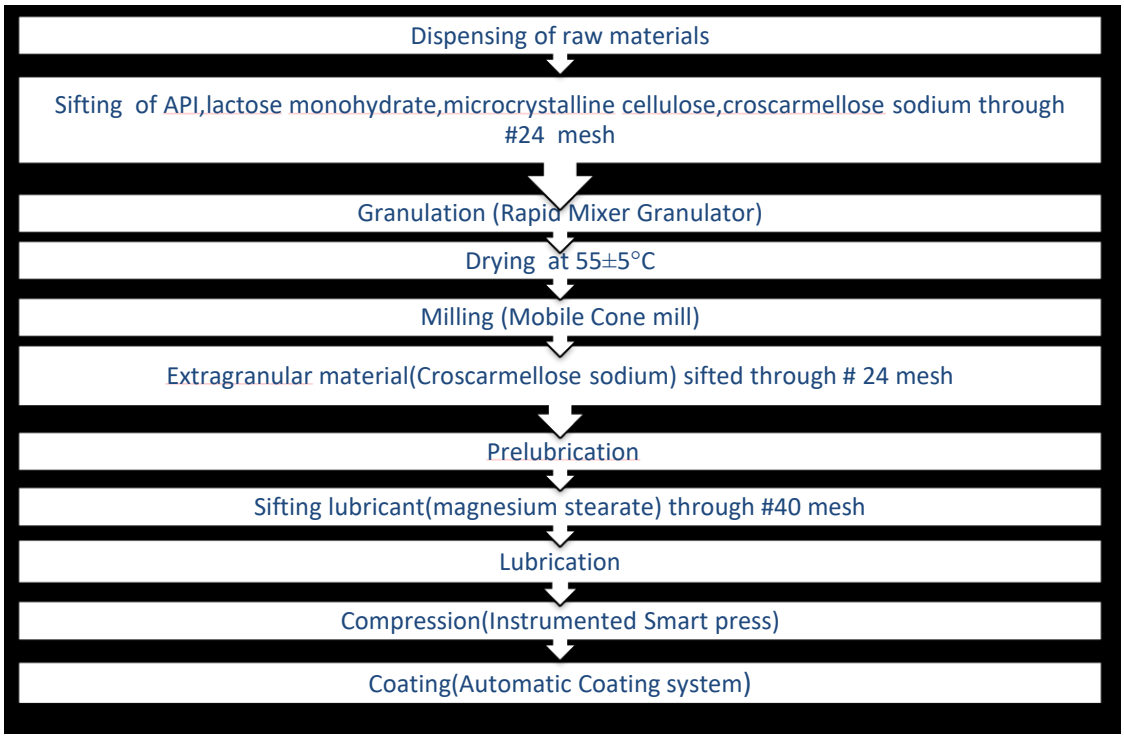
Physical characterization of tablets:

- Weight variation
- Thickness
- Hardness
- Friability
- Dissolution test

Table No: 01 Formulation Trials

Ingredients	F01 (mg)	F02 (mg)	F03 (mg)	F04 (mg)	F05 (mg)	F06 (mg)	F07 (mg)	F08 (mg)	F09 (mg)
Intra granular part									
Rivaroxaban	20	20	20	20	20	20	20	20	20
Microcrystalline cellulose	35	35	35	35	35	35	35	35	35
Lactose monohydrate	33.8	33.8	33.8	33.8	33.8	33.8	33.8	33.8	33.8
Croscarmellose Sodium	5.4	5.5	6.7	6.5	4.5	5.1	4.7	5.6	6.05
Binder solution									
Hydroxy Propyl Methyl Cellulose	4.3	4.0	3.0	3.0	5.0	4.5	5.0	4.0	3.5
Sodium Lauryl Sulphate	0.2	0.4	0.2	0.35	0.3	0.3	0.2	0.4	0.25
Purified water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Extra granular part									
Croscarmellose Sodium	3	3	3	3	3	3	3	3	3
Magnesium Stearate	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Total core tablet weight	102	102	102	102	102	102	102	102	102
Film coating									
Opadry red	3	3	3	3	3	3	3	3	3
Total coated tablet weight	105	105	105	105	105	105	105	105	105

The following steps are involved in the formulation:



RESULTS AND DISCUSSION

PREFORMULATION STUDIES

Table no: 02 physical characterization of Rivaroxaban

S.NO	Description	Result
1	Color	White
2	Odor	Odorless
3	Taste	Bitter
4	LOD	0.5% L

SOLUBILITY STUDIES OF API:

Table no: 03 Solubility studies of API

S. No	Solubility studies	Solubility (mg/ml)
1	Water	0.01
2	Water + 0.2% SLS	0.04
3	0.1 N HCl	0.01
4	0.1 N HCl + 0.2% SLS	0.03
5	pH 4.5 acetate buffer	0.01
6	pH 4.5 acetate buffer + 0.2% SLS	0.04
7	pH 4.5 acetate buffer + 0.4% SLS	0.08
8	pH 5.5 acetate buffer	0.01
9	pH 5.5 acetate buffer + 0.2% SLS	0.04
10	pH 5.5 acetate buffer + 0.4% SLS	0.07
11	pH 6.8 phosphate buffer (KH_2PO_4)	0.01
12	pH 6.8 phosphate buffer ($NaH_2PO_4.H_20$) + 0.2% SLS	0.04

Solubility of Rivaroxaban was found more in pH 4.5 acetate buffer + 0.4% SLS. Solubility found to be increased as concentration of SLS in above medium increased. Solubility was found similar in pH 4.5 acetate buffer & pH 5.5 acetate buffer with and without SLS.

Drug-Excipient Compatibility studies:

Table No: 04 Drug- Excipient compatibility studies

Name of the ingredient	Ratio	Condition					
		Initial	40°C/75% RH			60°C	
		Closed vials	Dry conditions			Wet condition closed vials	Dry condition closed vials
			15 days (open vials)	1 month (open vials)	1 month (closed vials)	15 days	1 month	1 month
		Physical description					
Rivaroxaban	N/A	Off white powder	No change	No change	No change	No change	No change	No change
Microcrystalline cellulose	1	White powder	No change	No change	No change	No change	No change	No change
Lactose monohydrate	1	White powder	No change	No change	No change	No change	No change	No change
Hydroxy propyl methyl cellulose	1	White powder	No change	No change	No change	No change	No change	No change
Croscarmellose sodium	1	White powder	No change	No change	No change	No change	No change	No change
Sodium Lauryl Sulphate	1	White powder	No change	No change	No change	No change	No change	No change
Magnesium stearate	1	White powder	No change	No change	No change	No change	No change	No changes
Opadry Red	1	Dark red color powder	No change	No change	No change	No change	No change	No change
Rivaroxaban +Microcrystalline cellulose	1:10	White powder	No change	No change	No change	No change	No change	No change

Rivaroxaban +Lactose monohydrate	1:10	White powder	No change	No change	No change	No change	No change	No change
Rivaroxaban +Hydroxy propylmethyl cellulose	1:1	Off white powder	No change	No change	No change	No change	No change	No change
Rivaroxaban +Croscarmellose sodium	1:1	Off white powder	No change	No change	No change	No change	No change	No change
Rivaroxaban +Sodium Lauryl Sulphate	1:0.4	Off white powder	No change	No change	No change	No change	No change	No change
Rivaroxaban +Magnesium stearate	1:0.25	Off white powder	No change	No change	No change	No change	No change	No change
Rivaroxaban +Opadry Red	1:1	Light red color powder	No change	No change	No change	No change	No change	No change
Rivaroxaban +All excipients	1:1	Light red color powder	No change	No change	No change	No change	No change	No change

FLOW PROPERTIES OF LUBRICATED BLEND:

Table No: 05 Pre-compression parameters of lubricated blend

Formulation Trials	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index (%)	Hausner's ratio	Angle of repose
	Mean ± SD	Mean ± SD			
1	0.416±0.04	0.588±0.02	29.167±0.04	1.41±0.03	28º58±0.03
2	0.434±0.06	0.588±0.03	26.087±0.02	1.35±0.02	28º48±0.01
3	0.454±0.01	0.666±0.01	31.818±0.04	1.46±0.05	27º51±0.02
4	0.434±0.02	0.625±0.02	30.435±0.03	1.43±0.04	29º29±0.03
5	0.454±0.02	0.625±0.03	27.273±0.05	1.37±0.01	30º38±0.05
6	0.434±0.03	0.625±0.05	30.435±0.01	1.43±0.05	27º49±0.02
7	0.416±0.05	0.625±0.03	33.333±0.06	1.50±0.01	25º98±0.04
8	0.434±0.01	0.625±0.02	30.435±0.03	1.43±0.03	26º58±0.02
9	0.454±0.06	0.666±0.01	31.818±0.07	1.46±0.04	30º32±0.02

(n=3)

Particle size distribution of Lubricated blend:

Table No: 06 Results of Particle size distribution of Lubricated blend

Sieve no.	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)
#30	0.1	0.3	0.1	0.2	0.1	0.1	0.1	0.1	0.1
#40	3.1	2.4	5.5	7	2.3	2.4	0.2	3.2	1.6
#60	12.3	11.1	17.6	20.8	11.8	11.5	5.1	13.8	10.7
#100	21.9	22	32.2	39.2	21.7	22.1	15.6	26.7	22
#200	26	26.3	35.7	46.5	23.7	23.9	17.8	30.7	24.1
COLLECTOR	100	100	100	100	100	100	100	100	100

POST COMPRESSION PARAMETERS:

Table No: 07 Results of Post Compression Parameters of Rivaroxaban film coated tablets

Trials	Avg weight (mg)	Thickness (mm)	Hardness (kP)	Disintegration time
	AM ± SD	AM ± SD		
F1	106±2	3.21±0.3	7.6 ±4	1 min 58 sec – 2 min 20 sec
F2	104±3	3.27±0.2	7.1±2	1 min 10 sec – 1min 15 sec
F3	105±1	3.30±0.1	6.9±1	1 min 2 sec – 1 min 8sec
F4	105±1	3.24±0.2	8.2±1	1 min 5 sec- 1 min 15 sec
F5	106±0.5	3.23±0.4	7.4±3	1 min 48sec- 1min 58 sec
F6	104±2	3.23±0.5	7.5±1	1 min 52 sec- 2 min 2 sec
F7	105±1	3.25±0.2	8.4±2	2 min 30 sec- 2 min 38 sec
F8	106±0.5	3.24±0.2	7.3±3	1 min 28 sec- 1min 34 sec
F9	105±2	3.26±0.2	9.2±2	59 sec- 1 min 5 sec
RLD	89±5	2.79±0.5	7.9±2	1 min 30 sec- 1 min 35 sec

(n=3)

Assay:

Assay percentage of the Innovator product was 100.31±1.02 & Assay percentage of optimized formulation F8 showed assay percentage of 100.26±0.85 which is in limit and matches the marketed Rivaroxaban product.

Table no: 08 Drug Content data for formulation trails

Test	Assay (95 – 105 % USP)
RLD	100.31±1.02
F1	98.67±0.45
F2	99.04±0.36
F3	100.78±1.54
F4	99.89±0.67
F5	100.4±1.43
F6	99.35±1.54
F7	100.5±0.76
F8	100.26±0.85
F9	101.57±1.56

(n=3)

Dissolution:

Table No: 09 % Cumulative drug release of formulation trails

	Cumulative drug release (%) (A. M±S.D)									
Time (min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**RLD**
0	0	0	0	0	0	0	0	0	0	0
10	87±3.20	74±2.32	89±1.10	75±1.74	82±5.92	89±2.56	72±8.45	84±1.06	70±7.16	76±2.79
15	90±1.03	87±1.76	93±1.38	86±1.17	88±1.64	91±0.89	84±3.40	91±1.01	81±3.87	90±1.72
20	92±0.63	89±2.00	94±0.98	88±0.89	92±1.17	91±0.98	87±2.67	93±0.86	85±2.73	94±1.94
30	94±0.84	91±2.04	96±0.91	90±0.82	95±1.79	92±0.97	90±1.29	96±0.67	87±1.20	96±1.37
45	97±1.01	95±2.17	97±0.76	92±0.55	96±1.51	95±0.75	93±1.13	98±0.75	89±1.95	99±0.52

(n=3)

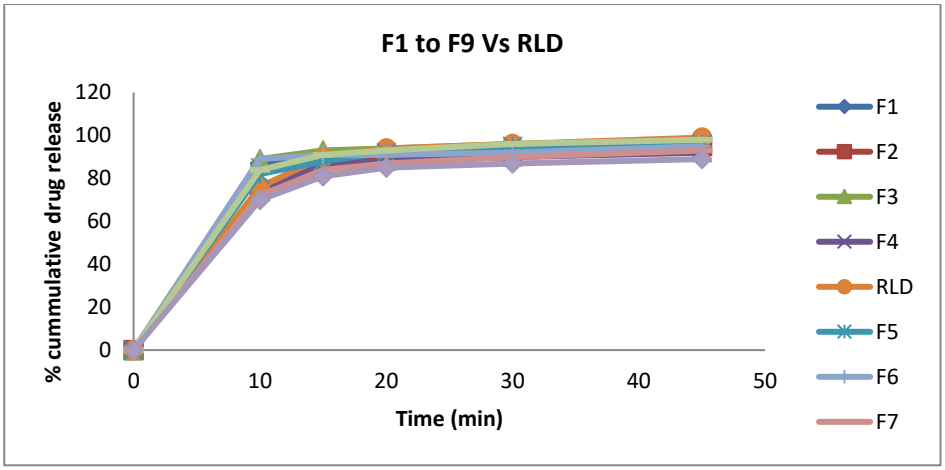


Figure 01: *In-vitro* dissolution profiles of all formulations

Dissolution studies were performed for the formulation trails of Rivaroxaban immediate release tablets in pH 4.5 acetate buffer + 0.4 % SLS and results were compared with the innovator. From the results it was concluded that in comparison to formulations with increase in the concentration of the SLS and CCS showed more drug release.

Among all the formulations held, the formulation trail F8, F3 showed maximum % drug release and matched with that of the innovator dissolution profile.

Table No: 10 Comparison of cumulative drug release of optimized formulation with RLD

	Cumulative drug release (%) (A. M±S.D)	
Time (min)	**F8**	**RLD**
0	0	0
10	84±1.06	76±2.79
15	91±1.01	90±1.72
20	93±0.86	94±1.94
30	96±0.67	96±1.37
45	98±0.75	99±0.52

(n=3)

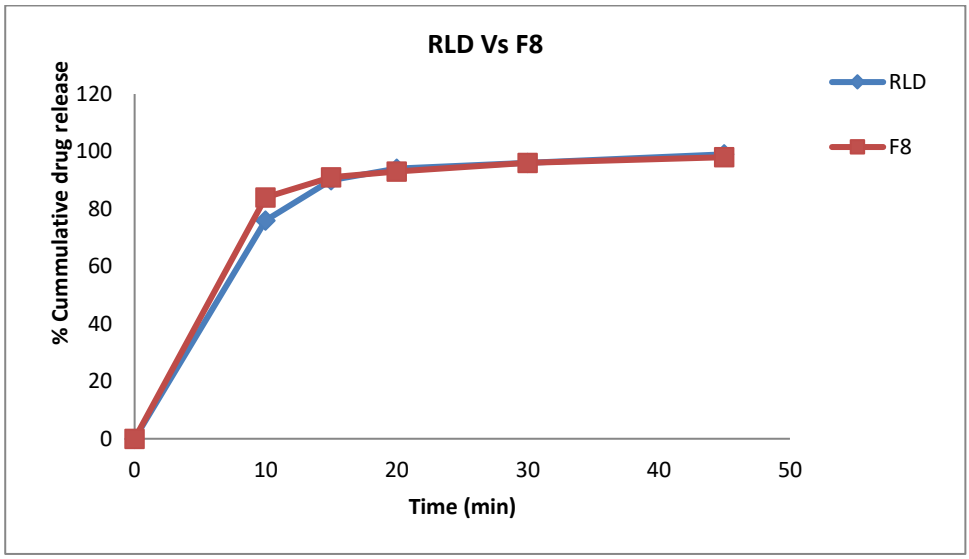


Figure 02: *In-vitro* dissolution graph of formulation F8 Vs RLD

MULTI-MEDIA DISSOLUTION:

Table No: 11 Multimedia *In-vitro* release data of RLD & F8

Time points (min)	RLD		F8	
	0.1N HCl +0.4% SLS	6.8 PB + 0.4% SLS	0.1N HCl + 0.4% SLS	6.8 PB + 0.4% SLS
	% Cumulative drug release			
0	0	0	0	0
10	67±2.01	84±1.76	69±2.11	85±1.87
15	74±1.87	88±1.65	73±1.75	90±1.50
20	76±1.45	90±1.30	75±1.62	93±1.49
30	80±1.09	95±0.76	78±1.37	96±1.24
45	82±0.43	98±0.11	80±0.94	98±0.37

(n=3)

Further in the multimedia dissolution also the trail F8 matched with the innovator multimedia drug release data, so it is considered as the optimized formulation in this work.

This trail is further used to carry out the evaluation parameters and they also undergo stability studies under certain conditions. A graph was plotted by taking time on x-axis and the cumulative % drug release on y-axis and the drug release was plotted along with time.

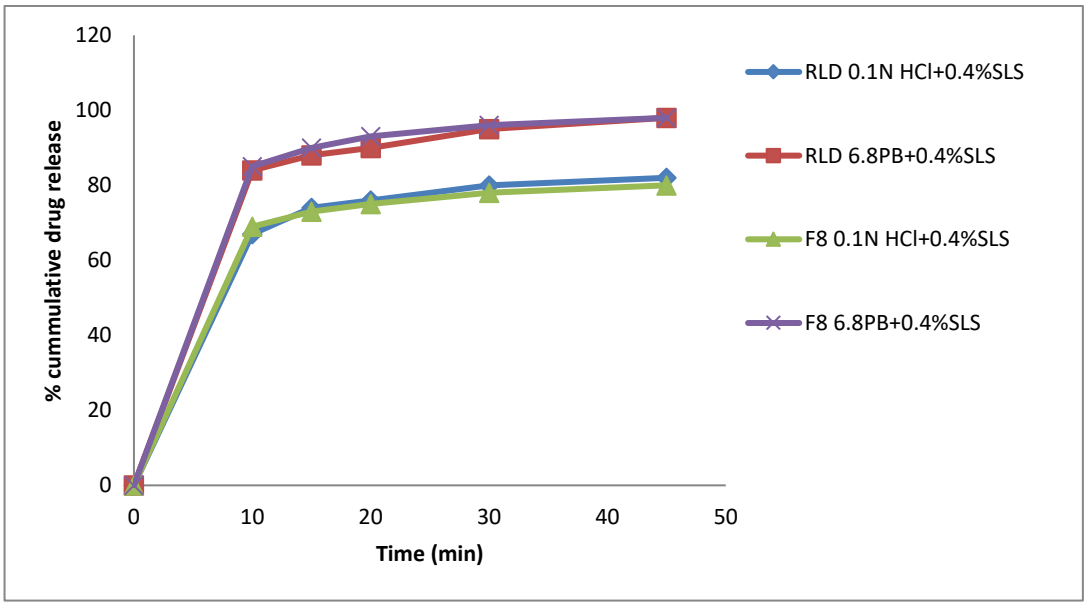


Figure 03: Multimedia *In-vitro* release graph RLD & F8

Further in the multimedia dissolution also the trail F8 matched with the innovator multimedia drug release data. So, it is considered as the optimized formulation in this work.

This trail is further used to carry out the evaluation parameters and they also undergo stability studies under certain conditions. A graph was plotted by taking time on x-axis and the cumulative % drug release on y-axis and the drug release was plotted along with time.

- **Stability study data (accelerated) of trail F8:**

Table No 12: Stability study results of optimized formulation

S. No	Parameter	Specification	Initial	1 Month	Results
1	Description	Deep red color, round film coated tablets debossed "20" on one side & plain on other side	Comply	Comply	Comply
2	Uniformity of Weight (mg)	105±5% m/m (100.8 mg to 109.20 mg)	106±0.5	106±0.7	Complies
3	Thickness (mm)	3.30 ± 0,5 mm (2.80mm-3.80mm)	3.24±0.2	3.24±0.1	Complies
4	Hardness (kp)	7±3 (4kp-10kp)	7.3±3	7.1±2	Complies
5	Disintegration	NMT 15 minutes	1 min 28sec-1min 34sec	1 min 26sec-1min 30sec	Complies
6	Assay	100±5% (95% - 105%)	100.26±0.85	100.21±0.78	Complies
7	Dissolution	NLT 80% labeled amount of API dissolved in 30min	98±0.75	97±0.8	Complies

(n=3)

Table No 13: Accelerated stability studies dissolution data

Time points (min)	Initial (% drug release)	40°C/75%RH
		1 Month (% drug release)
0	0	0
10	84±1.06	82±1.02
15	91±1.01	90±0.58
20	93±0.86	93±0.83
30	96±0.67	95±0.66
45	98±0.75	97±0.72

(n=3)

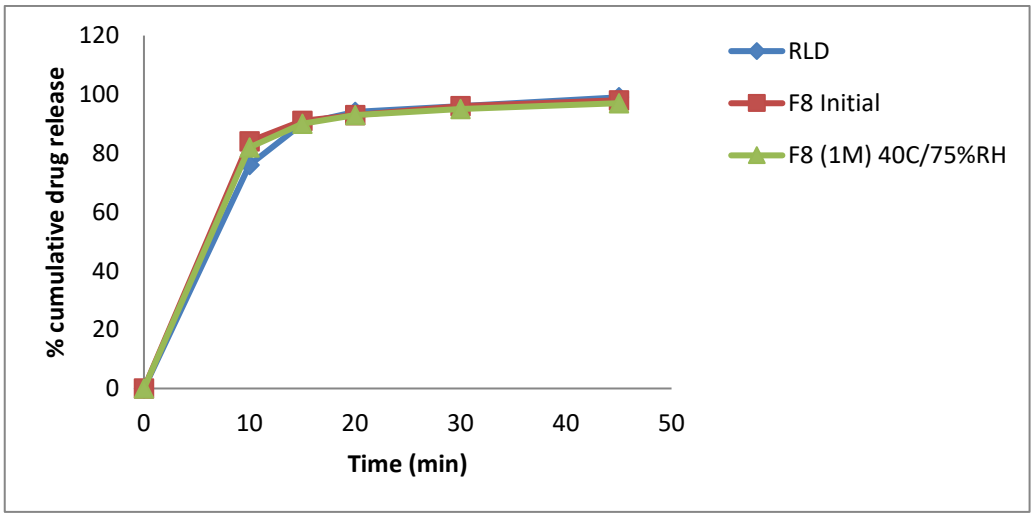


Figure 04: Comparison of 1month stability data of optimized trial with Initial data & RLD

Samples kept under stability studies i.e., accelerated conditions were evaluated for every time interval for 1 month. In which description, uniformity of weight, hardness, thickness, disintegration and dissolution studies were done. All the parameters were evaluated, and the dissolution data is 98% indicating the developed formula was stable at extreme storage conditions and the values were within the limits.

ACKNOWLEDGEMENT

It is with great pleasure and profound sense of gratitude that I express my most cordial and humble thanks whole heartedly to my esteemed guide, **Dr. M. Sunitha Reddy, Assistant professor, CPS IST, JNTUH,** for the moral support, guidance, keen interest, unflinching inspiration and encouragement, which were fruitful for shaping my ideas in this research. I owe my sincere thanks to my teacher Dr. M. Sunitha Reddy for her generous affection towards me. I would also like to express my sincere thanks for having provided excellent infrastructure facilities.

REFERENCES

1. Ansel. " *Pharmaceutical dosage forms & drug delivery systems* ", 8th Edition, ed.: 2006. pg: 227-260.
2. Lachman L, liberman HA, Kanig JL.," *The theory and practice of industrial pharmacy* ", 3rd Edition. ed.: 2006. pg:293-335.
3. Abdalwahab, M., Mansour, Y. and El-Dib, A. (2015). A study on the role of rivaroxaban in management of venous thromboembolism. *Egyptian Journal of Chest Diseases and Tuberculosis*, 64(4), pp.893-896.
4. Chandra shekar K., Sathyavani P.(2012)., A new method development and validation for analysis of rivaroxaban in formulation by RP HPLC.
5. Celebier, Mustafa & Reçber, Tuba & Kocak, Engin & Altinöz, Sacide. (2013). RP-HPLC method development and validation for estimation of rivaroxaban in pharmaceutical dosage forms. *Brazilian Journal of Pharmaceutical Sciences*. 49(2) pp 21-26.
6. Hitesh, P. (2011). Formulation and evaluation of immediate release tablets of zolpidem tartrate by direct compression. *International Journal of Pharmaceutical Sciences Review and Research*, 7(41), pp.81-84.
7. Mayank, B. (2013). Formulation and Evaluation of Immediate Release Tablets of Zaltoprofen Mayank Bansal. *Scholars Academic Journal of Pharmacy,* 2(5), pp.398-405.
8. Reddy, P. and Giugliano, R. (2014). The Role of Rivaroxaban in Atrial Fibrillation and Acute Coronary Syndromes. *Journal of Cardiovascular Pharmacology and Therapeutics*, 19(6), pp.526-532.
9. Rohit, S. (2015). Formulation and evaluation of immediate release tablet of valsartan. *International Journal of Pharmaceutical Sciences and Research*, 6(2) (0975-8232), pp.808-815.
10. Sahoo, Suraj & Kumar Mekap, Suman. (2017). Assay comparison of rivaroxaban by new HPLC method with an existing method in tablet dosage form. *Pharmaceutical and Biological Evaluations.* 4(2), pp 20-32.
11. Santosh B. (2014). Formulation and evaluation of immediate release tablets of Imipramine hydrochloride. *International Journal of Biomedical and Advance Research*, 5(22), pp.560-565.
12. Sahu, S. (2013). Formulation, development and evalution of an immediate release tablet of methotrexate. *International Journal of Research and Development in Pharmacy and Life Sciences*, 2(78), pp.589-595.
13. Syed, a. (2012). Design & Evaluation of Immediate Release Tablet of Rupatadine Fumrate. *International Journal of Pharma Professional's Research*, 3(09), pp.660-668.
14. Raymond C Rowe, Paul J Sheskey, Sian C Owen, editor, "*Hand book of Pharmaceutical Excipients",* 5th ed., London: American Pharmaceutical Association, Pharmaceutical Press; 2006. CROSCARMELLOSE SODIUM: p. 206-208.
15. Raymond C Rowe, Paul J Sheskey, Sian C Owen, editor, "*Hand book of Pharmaceutical Excipients",* 5th ed., London: American Pharmaceutical Association, Pharmaceutical Press; 2006. CROSPOVIDONE: p. 208-210.
16. Raymond C Rowe, Paul J Sheskey, Sian C Owen, editor, "*Hand book of Pharmaceutical Excipients",* 5th ed., London: American Pharmaceutical Association, Pharmaceutical Press; 2006. MANNITOL: p.424-427.

Received:04.08.18, Accepted: 07.09.18, Published:01.10.2018

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