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Formulation and Evaluation of Controlled Release Matrix Tablets of Ranolazine

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ABSTRACT

In the present research work an attempt was made to formulate and evaluate CR tablets of Ranolazine by using different polymers, polymers namely HPMC Phthalate and Eudragit S 100. Drug polymer interaction studies were carried out by using FTIR analysis which confirmed that there were no interactions between the drug and excipients. All the physical parameters of Drug & Drug – excipients (wet granules) carried out. The results indicate that all formulations were within the pharmacopoeial specifications. The various formulations of CR tablets of Ranolazine were formulated by using various concentration different polymers HPMC Phthalate and Eudragit S 100. The tablets were evaluated for pre compression and post compression parameters and *In-vitro* dissolution. The results indicated that the, physical parameters of formulated tablets were within the Pharmacopeial specifications. The controlled release tablets of Ranolazine formulations was optimized on the basis of different physical parameters and mainly with the comparison of formulations on the basis of *in-vitro* dissolution study and the optimized formulation F4 were found to be 97.0 % drug release within 24 hours. The kinetic studies To know the kinetic drug release, the data was treated according to different model. The drug release data of F1-F5 fitted to Higuchi plots were best fit into Higuchi equation and diffusion mechanism. The zero order plots for all formulation were found linear. The result shows that, drug release rate for the F4 formulation follow the zero order mechanism. The accelerated stability studies of selected formulation (F4) showed that there were no significant changes.

Keywords: Ranolazine, HPMC Phthalate and Eudragit S 100.

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INTRODUCTION

The basic rational for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamics of pharmacological active moieties by using novel drug delivery system or by modifying the molecular structure and physiological parameters inherent in the selected route of administration. It is desirable that the duration of drug action becomes more a design property of a rate controlled dosage form and less or not at all a property of the drug molecules properties, inherent kinetics. Thus optional design of controlled release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drugs[1-2].

The mechanism of action of ranolazine's antianginal effects has not been determined. Ranolazine has anti-ischemic and antianginal effects that do not depend upon reductions in heart rate or blood pressure. It does not affect the rate-pressure product, a measure of myocardial work, at maximal exercise. Ranolazine at therapeutic levels can inhibit the cardiac late sodium current.[2]

The main aim of the present study is to formulate and evaluate controlled release matrix tablets of Ranolazine. Ranolazine Elimination half-life is 7 hours and has low bioavailability only 13%. Controlled release dosage form maintains the plasma concentration for longer period of time and avoids initial higher plasma concentrations, so that dose related side effects can be avoided[3-4]. The rationale for development of a once daily controlled release formulation of a drug is to enhance its therapeutic benefits. Minimizing its side effects while improving the management of the diseased condition[5].

MATERIAL AND METHOD

Ranolazine was gifted by Max wel Pharmaceuticals, Mumbai, Microcrystalline cellulose, Crospovidone HPMC Phthalate, Eudragit S 100 and Magnesium stearate was gifted by Merck Limited, Bangalore.

Preparation of Standard Calibration Curve

Preparation of 0.1 N Hydrochloric acid

0.1 N Hydrochloric acid prepared by diluting 8.5ml of concentrated hydrochloric acid to 1000ml with distilled water.

Preparation of standard stock solution

100mg of Ranolazine transferred into 100ml volumetric flask. It was dissolved in methanol and volume was made up to the mark with methanol. This gives stock solution of concentration (1000mg/ml), from this 10ml was withdrawn and diluted to 100ml to get a concentration of (100mg/ml).

Standard curve preparation of Ranolazine

From this standard solution stock solution, aliquots 1 to 10ml were withdrawn and made up to 10ml methanol to give a concentration of 1 to 10mg/ml. Absorbance of these solution was measured 271nm.

Preparation of standard stock solution

100mg of Ranolazine transferred into 100ml volumetric flask. It was dissolved in methanol and volume was made up to the mark with 0.1 N Hydrochloric acid. This gives stock solution of concentration (1000mg/ml), from this 10ml was withdrawn and diluted to 100ml to get a concentration of (100mg/ml).

Standard curve preparation of Ranolazine

From this standard solution stock solution, aliquots 1 to 10ml were withdrawn and made up to 10ml 0.1 N Hydrochloric acid to give a concentration of 1 to 10mg/ml. Absorbance of these solution was measured 271nm.

The results were mentioned in the table. : 1 – 3.

Infra-Red Spectrophotometric Analysis[6]

The pellets were made with mixing 1gm of drug and 100gm of dried potassium bromide powder. Mixer was then compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The thin pallet was put on pellet disc to get IR Spectra.

The results were mentioned in the Figure: 1 – 4.

Preformulation[7-8]

Preformulation is a branch of pharmaceutical sciences that utilizes biopharmaceutical principles in the determination of physiochemical properties of a drug substance. The goal of pre-formulation studies is to choose the correct form of the substance, evaluate its physical properties and understanding of the material's stability under various conditions, leading to the optimal drug delivery system. The preformulation study focuses on the physiochemical parameters that could effect the development of efficacious dosage form. These properties may ultimately provide a rationale for formulation design. Also it will help in minimizing the problems in later stages of drug development, reducing drug development costs decreasing products time to market. It gives the information needed to define the nature of the drug substance and provide framework for the drug combination with pharmaceutical excipients in the dosage form.

Evaluation of Granules[7-8]

Angle of repose, Determination of tap density and bulk density, Compressibility index, Hausner Ratio & Sieve analysis

The results were mentioned in the table. No: 4 – 5.

Formulation of Matrix Tablet

Matrix tablets containing Ranolazine were prepared by wet granulation technique using variable concentrations of HPMC Phthalate & Eudragit S 100.

All the ingredients except magnesium stearate were blended in glass mortar uniformly. All the ingredients were mixed and passed through sieve no 60. Granulation was done with sufficient binding solution of Crospovidone and water. Wet mass was passed through sieve no 12 and dried at 45-55^{o}C for 2 hrs. Dried granules were sized by sieve no. 18 and mixed with magnesium stearate. Granules obtained were compressed with 9mm punch. The weight of the tablets was kept constant for formulations F1 to F5.

Table 7: Formulations of the CR Matrix Tablets of Ranolazine

S.No	Ingredients	F1	F2	F3	F4	F5
1	Ranolazine	500	500	500	500	500
2	Microcrystaline Cellulose PH 101	137	62	137	62	62
3	Crospovidone	30	30	30	30	30
4	Water	q.s	q.s	q.s	q.s	q.S
5	HPMC Phthalate	75	150	-	-	75
6	Eudragit S 100	-	-	75	150	75
7	Magnesium Stearate	8	8	8	8	8
Total		750 mg for each tablet				

Evaluation of Tablet

In process parameters evaluation[7-8]

Appearance

Tablet from each formulation were randomly selected and organoleptic properties such as color, odour, taste, and shape were evaluated.

Weight variation test

20 tablets were selected randomly from the lot and weighted individually to check for weight variation.

The results were mentioned in the table. No: 6

Hardness test

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm2.

The results were mentioned in the table. No: 6

Thickness

The thickness of tablets was determined suing a Digimatic veriner caliper (Mitutoya, Japan). Three tablets from each batch were used, and average values were calculated.

The results were mentioned in the table. No: 6

Friability (F)

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Pre-weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F=W_{initial}-W_{final}x100/W_{initial}$$

Acceptance criteria for % friability, %weight loss should be less than 1%

The results were mentioned in the table. No: 6

Finished product parameter[7-8]

***In vitro* drug release study (Ranolazine):**

The release rate of drug from CR was determined using USP Dissolution testing apparatus II (paddle method). The dissolution medium was 0.1 N Hydrochloric acid, the volume being 900ml. The temperature was maintained at 37±0.5ºc. The rotation speed was 50rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus at 1, 4, 12 and 24 Hours. And the samples were replaced with fresh dissolution medium. The samples were filtered through a membrane filter and absorbance of these solutions was measured at 271nm using a UV/V is double-beam spectrophotometer of Cumulative percentage drug release was calculated using linear equation obtained from a standard curve.

The results were mentioned in the Table. No: 7.

Assay (Ranolazine)

Twenty tablets from each batch were weighed accurately and powdered powder equivalent to 100mg Ranolazine was shaken with 100ml of 0.1 N Hydrochloric acid in 100ml amber colored volumetric flask and from this 10ml pipette out and dilute upto 100ml.from standard solution again 10ml pipette out and diluted upto 100ml in 100ml amber colored volumetric flask. resulting solution was filtered and assayed at 272nm and content of Ranolazine was calculated.

The results were mentioned in the Table. No: 8

Kinetic Modeling[7-8]

Kinetic modeling of drug release

All the eight formulation of prepared matrix tablets of Ranolazine were subjected to in-vitro release studies except batch B1 and B4 these studies were carried out using Electrolab TDT 08L dissolution apparatus (USP). The dissolution medium consisted of 900 ml of purified water for 12 hrs.

The results obtained in 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. Log Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
4. Log of cumulative % release Vs. log time (Peppas Exponential Equation)
5. (Percentage retained)$^{1/3}$ Vs. time (Hixson –Crowell Erosion Equation)

The results were mentioned in the Table. No: 9.

Stability Studies[9-10]

Sustained release matrix tablets of Ranolazine formulated in the present study were subjected to accelerated stability studies. Stability studies of the prepared formulations were performed at ambient temperature and humidity conditions at i.e. 25°C/60%RH, 30°C/65%RH, 40°C/75%RH for 3 months and analyzed after one month and three months for its appearance, hardness, friability, drug content and in-vitro release.

The results were mentioned in the Table 10.

RESULT AND DISCUSSION

Determination of λ_{max}:

The standard stock solution was prepared as per the method described in experimental section 6.1 and scanned by UV spectrophotometer. The λ_{max} was found to be 271 nm.

Calibration curve:

The different concentration(1 to 10 µg/ml) of Ranolazine were prepared with methanol & 0.1 N Hydrochloric acid and analyzed through UV at 271 nm using corresponding media as a blank. The absorbance obeys the Beers-Lamberts law at the range 1 to 10 µg/ml. the data are shown in Table 1 – 3.

Table 1 : Standard calibration curve of Ranolazine (Methanol)

S.No.	Concentration (mcg/ml)	Absorbance
1	1	0.0089
2	2	0.031

3	3	0.0544
4	4	0.0841
5	5	0.1051
6	6	0.1233
7	7	0.1496
8	8	0.1655
9	9	0.1833
10	10	0.1996

*Mean±SD (n=6)

Table 2 : Standard calibration curve of Ranolazine (0.1 N Hydrochloric acid)

S.No.	Concentration (mcg/ml)	Absorbance
1	1	0.068
2	2	0.1012
3	3	0.1418
4	4	0.1826
5	5	0.2415
6	6	0.2734
7	7	0.3142
8	8	0.3689
9	9	0.4203
10	10	0.4535

*Mean±SD (n=6)

Table 3: Regression Analysis

Parameters	Value in Methanol	Value in 0.1 N Hydrochloric acid
R^2	0.994	0.997
Slope	0.021	0.044
Intercept	0.005	0.009

DISCUSSION

On the basis of preliminary identification test it was concluded that the drug complied the preliminary identification. From scanning of drug in methanol dissolution media, it was also concluded that the drug had maximum wavelength of 271nm.

From standard calibration curve of Ranolazine in methanol dissolution media, it was observed that the drug obeys Beer-Lamberts law in concentration range of 1-10 µg/ml in the media.

Identification of drug (Ranolazine) sample

The drug was identified and confirmed by FTIR spectrum. Figure 3 – 6 shows the FT-IR spectrum of Ranolazine. The characteristic absorption peaks of Ranolazine are within the Pharmacopeial limits.

Drug Excipients Compatibility study:

Compatibility of the drug with recipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after combined it with the recipients. The samples were taken for FT-IR study.

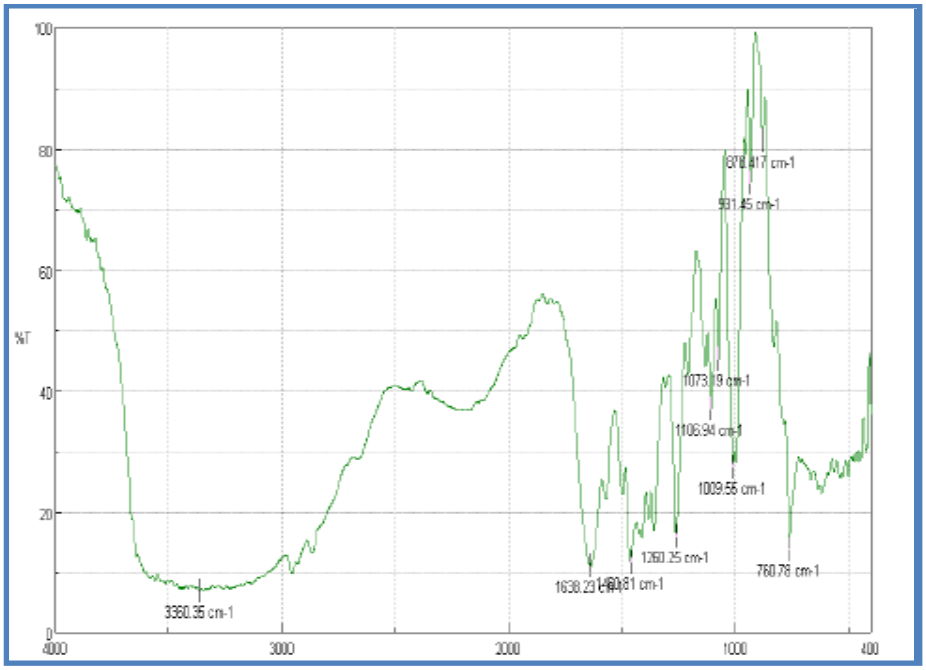

Figure: 1 FT-IR Spectrum of Pure Drug (Ranolazine)

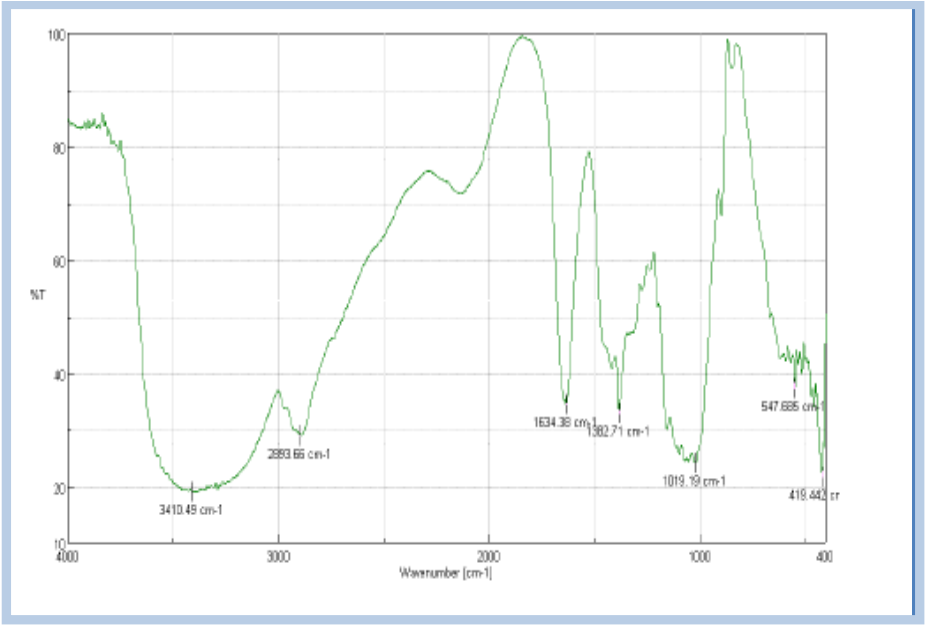

Figure: 2 FT-IR Spectrum of Ranolazine + HPMC Phthalate

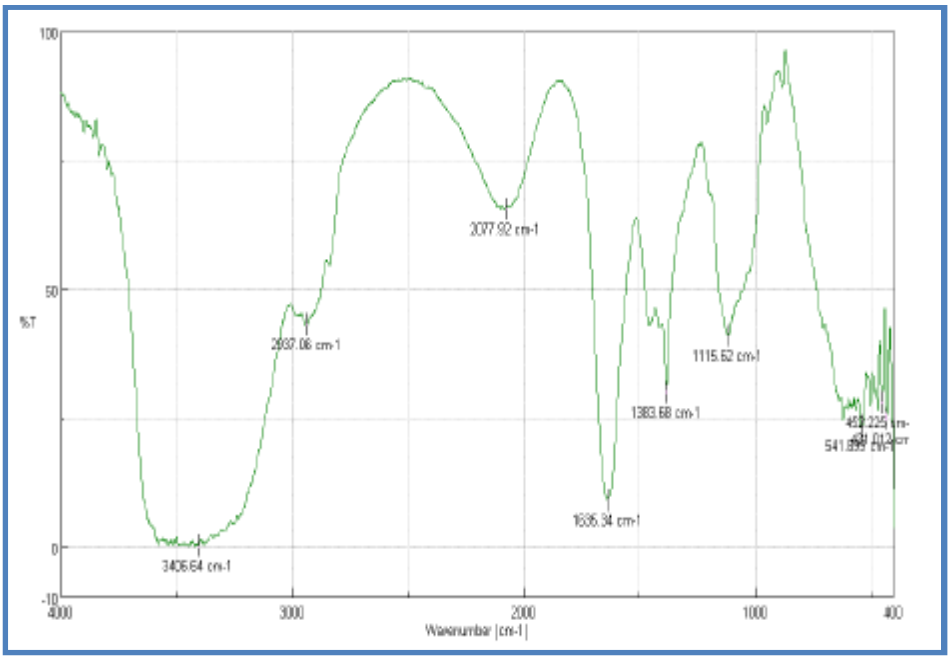

Figure: 3 FT-IR Spectrums of Ranolazine + Eduragit S 100

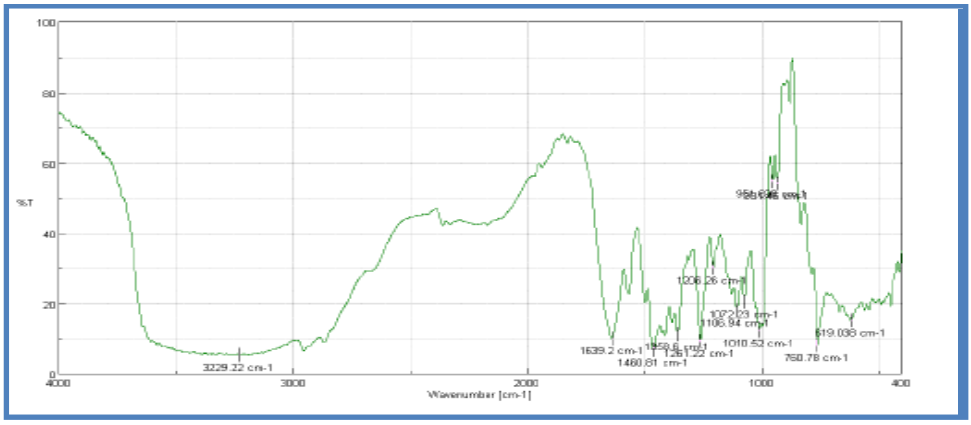

Figure: 4 FT-IR Spectrum of Ranolazine Microspheres (Optimized formulation)

Discussion

Drug polymer interaction studies were carried outby using FTIR analysis which confirmed that there were no interactions between the drug and selected excipients.

Preformulation studies

Table: 4 Flow properties of pure drug

S.No.	Drug	Bulk density (gm/ml) *	Tapped density (gm/ml) *	Compressibility index (%) *	Hausners ratio *	Angle of repose *
1	Ranolazine	0.434	0.491	13.5	1.13	27

*Mean±SD (n=6)

Table: 5 Physical characteristics of Ranolazine granules

Batch Code	F1	F2	F3	F4	F5
Bulk Density *	0.582+ 0.002	0.605+ 0.015	0.612+ 0.012	0.595+ 0.002	0.581+ 0.002
Tapped Density*	0.658+ 0.011	0.671+ 0.001	0.667+ 0.007	0.667+ 0.006	0.650+ 0.002
Carr's Index	11.49%	13.14%	8.25%	10.70%	10.71%
Hausner Ratio	1.13	1.11	1.09	1.12	1.12
Angle of Repose	25.53 0	24.86 0	23.92 0	25.06 0	25.26 0
Seive Analysis	65% Coarse 35%fine	38% Coarse 62%fine	35% coarse 65%fine	39% coarse 61%fine	40%coarse 60%fine

*Mean±SD (n=6)

Discussion

The physical parameters of drug as well as excipients concluded that these were considerably good to formulate the CR tablets using wet granulation technique.

Evaluation of Matrix Tablets of Ranolazine

Table: 6 Physical Characteristics of Controlled Release Ranolazine Tablets

S.N	Specification	F1	F2	F3	F4	F5
1.	Weight of tablets (mg) **	762±0.08	752±1.25	752±1.18	751±1.17	750±1.25
2.	Hardness (kg/cm2) *	9.0±0.13	9.0±0.15	10.0±0.12	10.0±0.15	9.0±0.15
3.	Thickness(mm) *	6.4±.02	6.3±0.02	6.2±0.03	6.4±0.02	6.3±0.03
4.	Friability (%) *	0.05%	0.04%	0.1%	0.1%	0.1%

*Mean±SD (n=6) **Mean±SD (n=20)

Table: 7 *In vitro* Dissolution profile of Controlled Release Ranolazine Tablets F1-F5

Time in hours	Limits	F1	F2	F3	F4	F5
1st	NMT3%	6.1 + 0.74%	10.8 +0.17%	66.2 + 0.03%	11.9 + 25%	51.9 + 0.05%
4th	20-30%	24.4+0.09%	25.0 +0.03%	89.9+0.024%	34.9+ 0.07%	68.1+0.035%
12th	NLT60%	40.6+0.46%	44.9+0.041%	96.0 + 0.03%	71.4+0.041%	75.3+ 0.03%
24th	NLT80%	46.9+0.04%	50.1+0.037%	98.0 + 0.40%	97.0+0.043%	88.9 +0.04%

*Mean±SD (n=6)

Discussion

From this table it can be seen that amount of CR Ranolazine dissolved in 24 Hours is NLT 80% respectively. So, the above criteria as acceptance limit.

Table: 8 Assay of different formulations

Formulations	% Assay of Ranolazine**
F1	100.542
F2	98.019
F3	100.22
F4	102.378
F5	98.759

**Mean±SD (n=20)

Kinetic Studies

Table 9: Kinetic Data of Formulations F4

Code	Zero-order		First order		Higuchi		Hixson Crowell		Peppas	
	R^2	Slope	R^2	Slope	R^2	slope	R^2	slope	R^2	N
F4	0.982	6.194	0.943	2.086	0.970	-7.269	0.985	4.705	0.981	1.034

Discussion

As per the results shown in table 19, the batch F4 had appreciable correlation with zero order plot (R^2=0.982) and simultaneously apparent to Higuchi drug release profile (R^2=0.970) presented a controlled drug release tablets. As per data fitting with Korsmeyer Peppas model, value of n for each batch was calculated and for batch F4, then value was 1.034 describing non-Fickian drug release mechanism.

All the formulations exhibited anomalous (Non - Fickian transport) diffusion mechanism and followed zero order kinetics. Based on the found data of *in vitro* drug release and kinetic data modeling, formulation F4 was selected for the stability studies.

Stability studies

The Stability studies were undertaken in the investigation of stability of solid oral dosage forms to support post formulation strategies as per ICH guidelines. The accelerated stability studies data of selected formulation (F4) shown in Table 10. The drug content, weight variation, thickness, friability, hardness and *in vitro* drug release were closely monitored and analyzed at regular intervals (3month). There were no significant changes observed in the drug content thickness, weight variation, hardness, friability and *in vitro* drug release during and period of stability studies

Table: 10 Stability Parameters of Optimized Formulation F4

Parameters	1st Month		3rd Month	
	RT	40°C/75%RH	RT	40°C/75%RH
Uniformity of weight	150.57±2.12	150.57±1.84	150.07±2.10	150.01±1.40
Thickness	2.54±0.07	2.54±0.04	2.24±0.04	2.51±0.01
Hardness	6.18±0.58	6.18±0.42	6.08±0.51	6.12±0.32
Friability	0.17±0.03	0.17±0.08	0.12±0.02	0.14±0.03
Percentage Drug Content	100.31±0.07	100.27±0.11	100.01±0.05	100.07±0.10
Percentage Drug Release	98.435±0.48	98.548±0.82	98.015±0.43	98.48±0.65

*Mean ± SD, (n=3)

SUMMARY AND CONCLUSION

In the present research work an attempt was made to formulate and evaluate CR tablets of Ranolazine by using different polymers, which are having release rate controlling ability, permeable, non-toxicity, non-irritancy, stable in stomach pH, polymers namely HPMC Phthalate and Eudragit S 100, have been chosen as carriers for the preparation of controlled release.

Drug polymer interaction studies were carried outby using FTIR analysis which confirmed that there were no interactions between the drug and excipients.

The Bulk Density, Tapped Density, Carr's Index, Hausner Ratio, Angle of Repose were carried out. The results indicate that all formulations were within the pharmacopoeial specifications. The physical parameters of drug as well as excipients concluded that these were considerably significant to formulate the CR tablets using wet granulation technique

The various formulations of CR tablets of Ranolazine were formulated by using various concentration different polymers HPMC Phthalate and Eudragit S 100.

The tablets were evaluated for pre compression and post compression parameters (Weight of tablet, Thickness, Hardness, Friability) and In-vitro dissolution. The results indicated that the, physical parameters of formulated tablets were within the Pharmacopeial specifications.

The controlled release tablets of Ranolazine formulations was optimized on the basis of different physical parameters and mainly with the comparison of formulations on the basis of in-vitro dissolution study and the optimized formulation F4 were found to be 97.0 % drug release within 24 hours.

Results of all the physical and in-vitro dissolution data concluded that formulation F-4 was the most promising formulation.

The accelerated stability studies of selected formulation (F4) showed that there were no significant changes observed in the drug content, thickness, weight variation, hardness, friability and *in vitro* drug release during the period of study.

From, these it was concluded that the Controlled release tablets of Ranolazine (F4) showed improved dissolution, minimizes the dose and improves the patient compliance and effective CR tablets in oral route of administration.

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