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ORIGINAL ARTICLE

Design, Development, Optimization and Evaluation of Ranolazine Extended Release Tablets

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ABSTRACT

Objectives: The objective of the current study was to develop an extended release (XR) tablet formulation for ranolazine using Eudragit L 100-55 and hydroxypropylmethylcellulose (HPMC) K100M in an appropriate composition. Ranolazine, an anti-anginal agent, is mainly used for treating chronic stable angina pectoris. The main advantage of this drug that it exhibits anti-ischemic effect, which was not influenced by either blood pressure or heart rate.

Materials and Methods: XR tablets of ranolazine were prepared using variable amounts of Eudragit L 100-55 and HPMC K100M in various proportions as *per* 3^2 factorial design by direct compression technique. The amount of polymers with desired sustained drug release was labeled as factors. On other hand, time taken for drug dissolution was labeled as responses ($t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$).

Results: Nine formulations were obtained as *per* design, developed, and evaluated for quality control parameters. The obtained results clear that all formulations pass the compendial limits. Data obtained from the dissolution study fitted well to kinetic modeling and kinetic parameters were determined. Polynomial equations were derived for responses and checked for validity.

Conclusion: RF_5 composed of 31.25 mg of Eudragit L 100-55 and 31.25 mg of HPMC K100M, is the best formulation showing similarity f_2: 85.78, f_1: 2.32 with the marketed product (RANEXA). Formulation RF_5 follows zero order, whereas the release mechanism was found to be non-fickian type (n= 0.65).

Key words: Ranolazine, extended release, Eudragit L 100-55, HPMC K100M, 3^2 factorial design, non-fickian diffusion

INTRODUCTION

Extended release (XR) formulations deliver effective plasma concentrations of the drug for desired prolonged period. They improve patient compliance by reducing the repeated administration of dosage regime. They also offer improved *in vivo* clinical performance (good clinical outcome).[1,2]

The popularly used symbols for extended release are extra long/extra large; long acting; XR. They show a 2-fold reduction in the dosing frequency and maintains steady state plasma profile.[3] There are many challenges for formulation of prolonged release dosage forms in a controlled manner for obtaining absorption and improved bioavailability.[4,5]

Ranolazine is an anti-anginal agent, which is a piperazine acetamide derivative. It acts by partial inhibition of fatty acid oxidase that increases the adenosine triphosphate production from glucose, thereby improves the functionality of the myocardium. Hence, it exhibits anti-ischemic action, independent of hemodynamics such as blood pressure and heart rate. There will be no significant effect of its effectiveness by the above-mentioned factors and other co-morbidities. Due to this advantage, it is employed as effective anti-ischemic or antiangina agents for treating unstable chronic angina pectoris (exercise induced variant), myocardial infarction, and cardiac arrhythmias.[6-8]

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Ranolazine belongs to biopharmaceutical classification system class-II agent. It shows an erratic (variant) and extensive first pass effect. Solubility was found to be relatively high at acidic pH (stomach). The half-life is around 2.5 h (2.5 ± 0.5). Hence, selection of release rate modifiers is a challenging task for researchers.[9-14]

The current study focuses on, development of XR tablets for ranolazine with the help of polymers Eudragit L 100-55 (partially neutralized pH dependent polymer) along with hydroxypropylmethylcellulose (HPMC) K100M (pH independent polymer).

The application of polynomial based response surface morphology (RSM) occupies a major volume in case of pharmaceutical product development. The most widely used methods in the above-mentioned category as follows factorial design (2^3, 3^2, 3^3), central composite design, Box-Behnken design.[15,16]

The manufacture of tablets processed using direct compression technique is a frequent method, observed in many pharmaceutical industries.[17]

A two factors, 3-levels study (3^2 factorial design) was used to observe the combination effect of both polymers (Eudragit L 100-55; HPMC K100M) on the drug release from the formulation (to see the effect of factors on the responses),[18] which may improve patient compliance by using enhanced clinical efficiency.

MATERIALS AND METHODS

Materials

A gift sample of ranolazine was procured from Mahys Pharma, Solan, India. Eudragit L 100-55 was obtained from KU Pharma Pvt Ltd., while bartoli HPMC K100M was gifted from QIM Chemicals, Guntur. All other excipients were obtained from S.D. Fine Chem., Ltd. Mumbai, India.

Design and development of extended release tablets for ranolazine

Quantities required for the Eudragit L 100-55 and HPMC K100M for developing ranolazine XR tablets were chosen as factors (X_1, X_2 respectively). Time to obtain dissolution was chosen as responses ($t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$). RSM prediction equations (polynomial) were derived for responses according to linear stepwise backward regression technique.[19]

The 3 levels of X_1 (Eudragit L 100-55) were 3.75%, 6.25%, 8.75%. Three levels of X_2 (HPMC K100M) were 3.75%, 6.25%, 8.75% (% with respect to weight of active ingredient). Nine ranolazine XR tablet formulations were designed using selected combinations of X_1, X_2 and checked for selecting optimum composition required to meet the primary objective of the study.

Preparation of ranolazine extended release tablets

A 3 level, 2-factor design was used for this research work. The amount of Eudragit L 100-55 chosen as X_1 and amount of HPMC K100M chosen as X_2 shown in Table 1. Three levels of both factors chosen indicated as -1=3.75%; 0=6.25%; +1=8.75%. XR tablets for ranolazine were obtained using the direct compression method. Each tablet contained 500 mg of ranolazine. The formulae for the preparation of tablets are presented in Table 2. All ingredients were collected and weighed accurately as *per* the formula. All were subjected to sifting to achieve good compression properties. After sifting, they were mixed in polya for obtaining uniform blend. The obtained blend was subjected to lubrication and processed for applying force to get desired tablet press. Resultant tablets were subjected to pharmaceutical product performance tests.

Evaluation of ranolazine extended release tablets

Crushing strength

It was determined using tablet hardness tester on the basis of diametric breakage of tablets.

Friability

This test was performed using a friability test apparatus (Roche). The selected number of tablets (20) were weighed accurately weight was noted (W_0), tablets were subjected to rotations (25 rpm for 4 min) again weight was noted (W). % weight loss was determined using the following formula.

Weight loss (%) = $[W_0 - W / W_0] \times 100$

Drug content

It was carried out as *per* the standard procedure, take 20 tablets and triturated to obtain fine powder, a quantity equivalent to 100 mg of ranolazine was calculated and was dissolved in 0.1 N HCl. The sample was subjected to sonication and clarified by passing the solution *via* 0.45 µ filter press. After preparing the aliquots, their absorbances were measured at 272 nm using ultraviolet-visible (UV) spectrophotometer.

Thickness

It was obtained using vernier calipers on the principal longitudinal basis.

Drug dissolution

This test was performed using USP tablet dissolution test apparatus (type 2) as per the standard conditions, such as 900 mL of pH 1.2 buffer as the dissolution medium for the first 2 h followed by phosphate buffer pH 6.8. The temperature was maintained at 37 ± 0.5°C and paddle was rotated at a rate of 50 revolutions per minute. The samples were collected as *per* the protocol and analyzed for drug release using spectrometry at 272 nm. Analysis is done in triplicate manner.[14]

Statistical analysis

The data obtained were fit to kinetic modeling to ascertain the mechanism of drug release. The statistical parameters (a, b, r) were determined as kinetic parameters.[20,21] The dissolution parameters were also determined using polynomial equations.

RESULTS AND DISCUSSION

XR tablets of ranolazine were developed as *per* 3-level, 2-factor design for optimizing the combination of drug release modifiers (Eudragit L 100-55, HPMC K100M). The formulation design is

presented in Table 1. The quantity of Eudragit L 100-55 (X_1) and HPMC K100M (X_2) chosen as factors and time for obtaining dissolution chosen as responses ($t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$). Nine trials were developed as *per* the formula given in Table 2.

All trials have ranolazine (500 mg) as an XR formulation, obtained as tablet using direct compression technique. The developed formulations were evaluated for pharmaceutical product performance tests. The data are presented in Table 3. All formulations have sufficient mechanical strength. All formulations found to be less friable, as within the limits. All batches passed the drug content uniformity test. All formulation batches passed the weight variation test. Dissolution rate test was carried as *per* standard procedure, the dissolution specifications such as 900 mL of simulated gastric fluid for the first 2 h followed by simulated intestinal fluid; paddle was rotated at a speed of 50 rpm, the temperature maintained as 37 ± 0.5°C throughout the test period. The dissolution profile was well fit to kinetic modeling, results are presented in Table 4 and the same was presented as plots from Figure 1-4. From the results, observed that there was a clear relation existed between the quantities of polymers in combination with the drug release rate (both were inversely proportional to each other). Predicted sustained release of drug was obtained by appropriate composition of factors (X_1, X_2).

Based on the desirability factor, RF_5 is considered the best formulation among all batches. RF_5 composed of both Eudragit L 100-55 and HPMC K100M in equal quantity *i.e.* 31.25 mg each, produced promising dissolution characteristics, which help in meeting the purpose of research by extended period of drug release (optimum delivery of drug) from dosage form.

Table 1. Experimental design layout

Formulation code	X_1	X_2
RF_1	1	1
RF_2	1	0
RF_3	1	-1
RF_4	0	1
RF_5	0	0
RF_6	0	-1
RF_7	-1	1
RF_8	-1	0
RF_9	-1	-1
CR_1	-0.5	-0.5
CR_2	+0.5	+0.5

Table 2. Formulae for ranolazine extended release tablets

Name of ingredients	Quantity of ingredients *per* each tablet (mg)								
	RF_1	RF_2	RF_3	RF_4	RF_5	RF_6	RF_7	RF_8	RF_9
Ranolazine	500	500	500	500	500	500	500	500	500
Avicel pH 101	36.5	49	61.5	49	61.5	74	61.5	74	86.5
Eudragit L 100-55	43.75	43.75	43.75	31.25	31.25	31.25	18.75	18.75	18.75
HPMC K100M	43.75	31.25	18.75	43.75	31.25	18.75	43.75	31.25	18.75
Magnesium stearate	8	8	8	8	8	8	8	8	8
Talc	8	8	8	8	8	8	8	8	8
Total weight	640	640	640	640	640	640	640	640	640

HPMC: Hydroxypropylmethylcellulose

Table 3. Post-compression parameters for the formulations (n= 3)

Batch code	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Average weight (mg)	Drug content (%)
RF_1	8.47 ± 0.27	4.06 ± 0.08	0.10 ± 0.001	641.09 ± 0.01	99.94 ± 0.49
RF_2	8.2 ± 0.28	3.98 ± 0.085	0.11 ± 0.001	641.11 ± 0.01	99.45 ± 0.50
RF_3	7.93 ± 0.27	3.9 ± 0.08	0.09 ± 0.001	641.10 ± 0.01	99.11 ± 0.51
RF_4	8.52 ± 0.42	4.1 ± 0.06	0.06 ± 0.001	641.14 ± 0.02	99.74 ± 0.32
RF_5	8.10 ± 0.41	4.05 ± 0.06	0.07 ± 0.001	642.2 ± 0.02	99.43 ± 0.33
RF_6	7.7 ± 0.41	3.99 ± 0.05	0.07 ± 0.001	641.31 ± 0.02	99.11 ± 0.34
RF_7	8.35 ± 0.42	4.18 ± 0.05	0.05 ± 0.001	640.66 ± 0.02	99.70 ± 0.43
RF_8	7.91 ± 0.42	4.05 ± 0.06	0.04 ± 0.001	641.2 ± 0.01	99.23 ± 0.47
RF_9	7.49 ± 0.41	4.02 ± 0.06	0.05 ± 0.001	640.65 ± 0.01	98.77 ± 0.35

Table 4. Regression analysis for factorial trials

Formulation code	Kinetic parameters											
	Zero order			First order			Higuchi			Korsmeyer-Peppas		
	a	b	r	a	b	r	a	b	r	a	b	r
RF_1	14.410	3.284	0.982	1.988	0.034	0.986	1.685	17.614	0.995	1.089	0.629	0.962
RF_2	14.857	3.285	0.981	1.986	0.034	0.986	1.308	17.641	0.995	1.098	0.625	0.959
RF_3	15.304	3.285	0.979	1.985	0.034	0.986	0.930	17.667	0.995	1.107	0.621	0.957
RF_4	15.946	3.819	0.982	2.110	0.065	0.931	2.738	20.473	0.995	1.125	0.651	0.960
RF_5	16.302	3.834	0.982	2.171	0.077	0.877	2.481	20.560	0.995	1.132	0.649	0.958
RF_6	16.657	3.848	0.981	2.117	0.068	0.931	2.224	20.646	0.995	1.138	0.647	0.956
RF_7	23.404	3.915	0.948	2.112	0.093	0.964	2.240	21.685	0.992	1.199	0.641	0.950
RF_8	23.778	3.923	0.948	2.185	0.110	0.949	2.539	21.742	0.993	1.204	0.638	0.948
RF_9	24.304	3.883	0.946	2.286	0.124	0.915	3.157	21.565	0.993	1.210	0.634	0.945
Marketed product	17.313	3.884	0.979	2.201	0.086	0.897	1.910	20.897	0.995	1.148	0.644	0.955

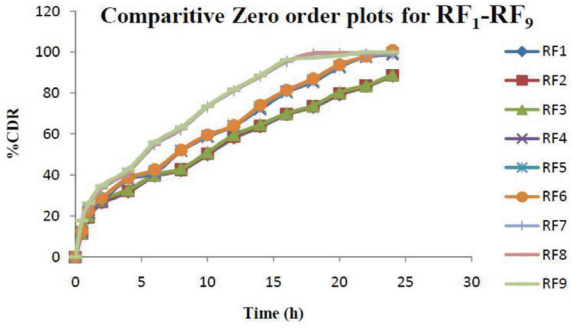

Figure 1. Comparative zero order plots

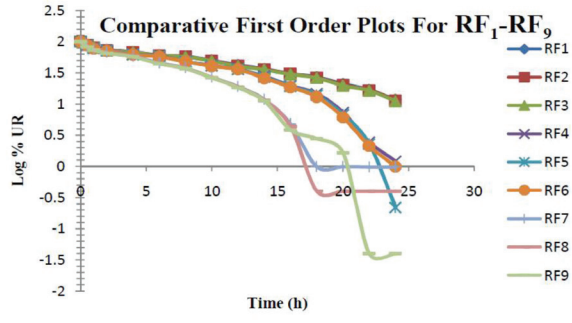

Figure 2. Comparative first order plots

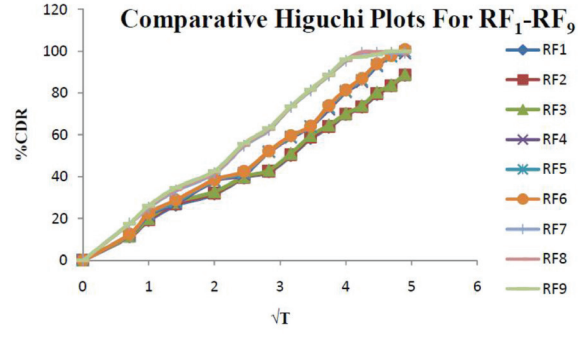

Figure 3. Comparative Higuchi plots

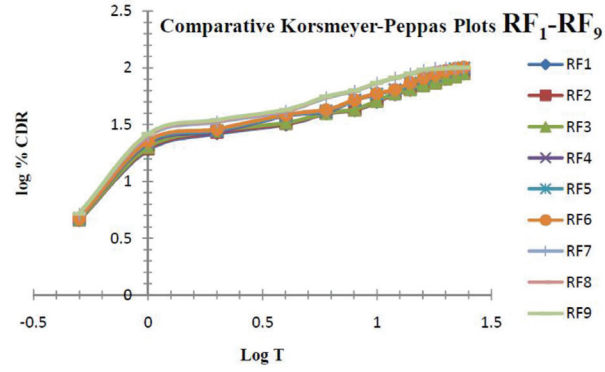

Figure 4. Comparative Korsmeyer-Peppas plots

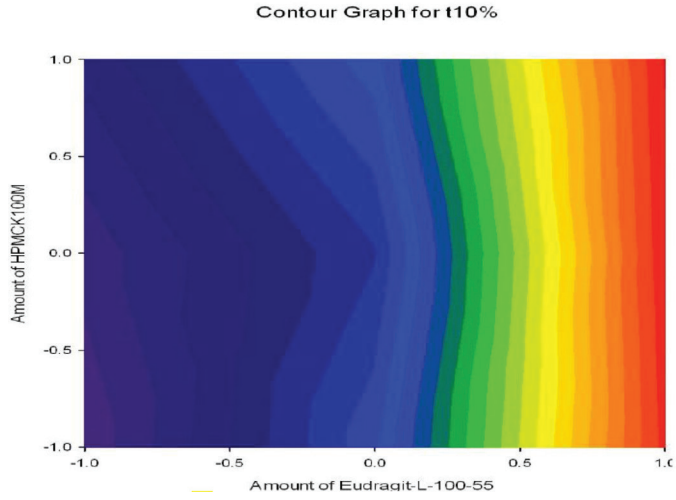

Figure 5. Contour plots for $t_{10\%}$

RSM equations (polynomial) were derived for all responses using PCP Disso and RSM plots were obtained with the help of Design-Expert 7.0. The response morphological plots were presented as Figure 5-9. The dissolution parameters for RF_1-RF_9 were summarized as Table 5.

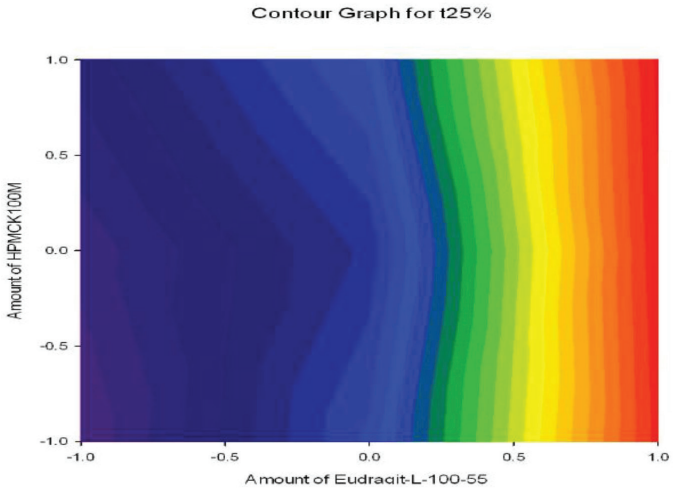

Figure 6. Contour plots for $t_{25\%}$

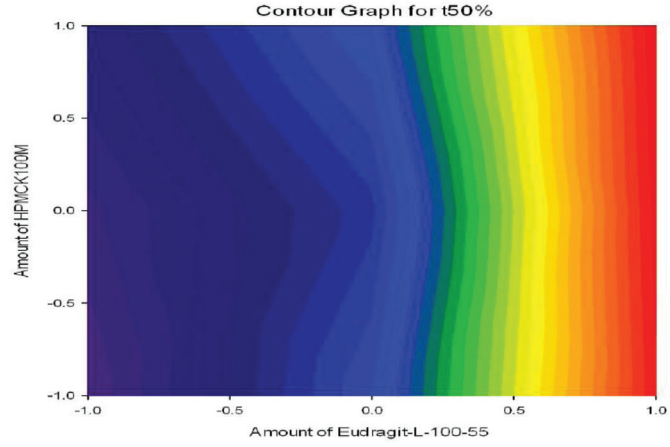

Figure 7. Contour plots for $t_{50\%}$

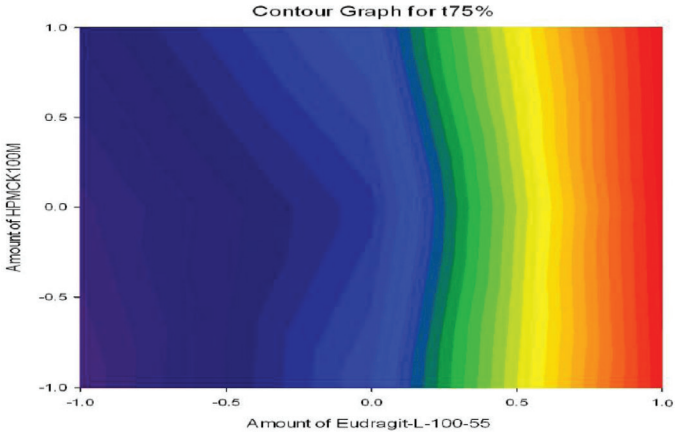

Figure 8. Contour plots for $t_{75\%}$

RSM equations for the determination of predicted kinetic parameters as follows;

$Y_1=0.810+0.461X_1+0.038X_2-0.024X_1X_2+0.232\ X_1^2+0.035X_2^2\ (t_{10\%})$

$Y_2=2.210+1.23X_1+0.084X_2-0.065\ X_1X_2+0.632\ X_1^2+0.096\ X_2^2\ (t_{25\%})$

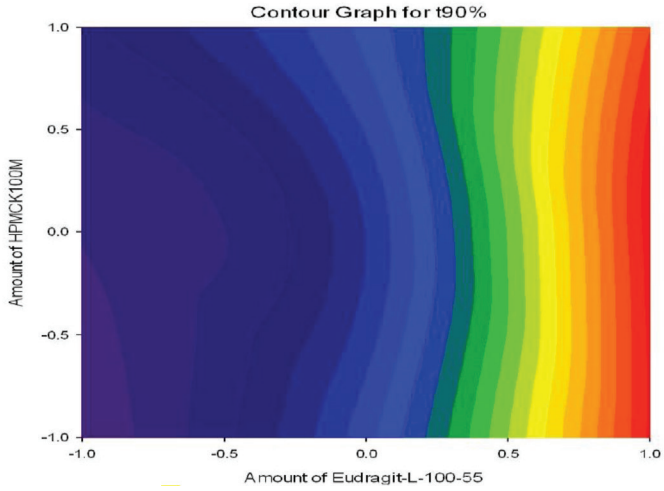

Figure 9. Contour plots for $t_{90\%}$

Table 5. Dissolution parameters for factorial formulations

Formulation code	Dissolution parameters				
	$t_{10\%}$ (h)	$t_{25\%}$ (h)	$t_{1/2}$ (h)	$t_{75\%}$ (h)	$t_{90\%}$ (h)
RF_1	1.362	3.719	8.962	17.923	29.779
RF_2	1.348	3.679	8.865	17.731	29.460
RF_3	1.333	3.639	8.769	17.537	29.139
RF_4	0.701	1.913	4.611	9.221	15.321
RF_5	0.596	1.627	3.921	7.843	13.030
RF_6	0.669	1.827	4.401	8.803	14.626
RF_7	0.493	1.345	3.242	6.484	10.773
RF_8	0.415	1.132	2.728	5.456	9.065
RF_9	0.369	1.007	2.426	4.852	8.061
Marketed product	1.362	1.447	3.487	17.923	11.589

$Y_3=5.33+3.04X_1+0.21X_2-0.156\ X_1X_2+1.52\ X_1^2+0.23\ X_2^2\ (t_{50\%})$

$Y_4=10.65+6.07X_1+0.41X_2-0.31\ X_1X_2+3.04\ X_1^2+0.46\ X_2^2\ (t_{75\%})$

$Y_5=17.695+10.08X_1+0.675\ X_2-0.518\ X_1X_2 5.05\ X_1^2+0.765\ X_2^2\ (t_{90\%})$

Results for the predicted responses *vs* actual responses are presented in Table 6. Not much deviation was observed in the predicted *vs* actual responses. It indicates the validity of the developed equation. RF_5 was considered as ideal, it shows similarity factor (f2) 85.78, difference factor (f1) tcl, t_{cal} ⟨0.05 compared with the marketed product (RANEXA). Comparative dissolution plots for best formulation (RF_5) and marketed product are shown in Figure 10.

CONCLUSION

On the basis of the current study, the use of macromolecules (polymers) in combination had its own advantages of maintaining integrity and extended drug release form of the formulation. The combination of a partially neutralized pH-dependent polymer and pH-independent polymer at an appropriate proportion will yield desired extended drug release,

Table 6. Dissolution parameters for check point formulations

Formulation code	Predicted value					Actual observed value				
	$t_{10\%}$ (h)	$t_{25\%}$ (h)	$t_{50\%}$ (h)	$t_{75\%}$ (h)	$t_{90\%}$ (h)	$t_{10\%}$ (h)	$t_{25\%}$ (h)	$t_{50\%}$ (h)	$t_{75\%}$ (h)	$t_{90\%}$ (h)
CR_1	0.624	1.704	4.106	8.22	13.643	0.62	1.69	4.31	8.19	13.71
CR_2	1.116	3.047	7.342	14.684	24.397	1.12	3.11	7.54	14.55	23.99

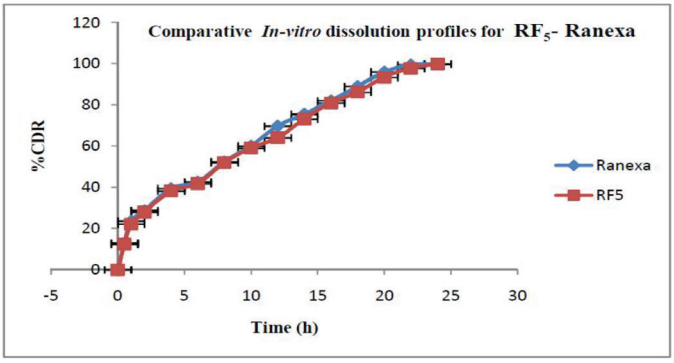

Figure 10. Comparative dissolution plots for RF5-Ranexa

which ultimately 2-fold reduction in the dosing frequency of ranolazine. This is achieved by preparing the ranolazine with combination polymers like Eudragit L 100-55 and HPMC K100M employing along with other excipients using 3^2 factorial design approaches. Among the various ER formulations studied, the formulation (RF_5) showed the best result in all aspects of objective, which was considered as the ideal formulation. The best formulation RF_5 follows zero order release, non-fickian diffusion, it may improve patient compliance by reducing the dosing frequency to 2 fold or more, which will ultimately improve the clinical response.

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Ethics

Ethics Committee Approval: There is no requirement for ethical approval.

Informed Consent: Not applicable.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: R.K.G., D.D., Design: K.R.G., Data Collection or Processing: R.K.G., Analysis or Interpretation: P.R.M., D.D., Literature Search: R.K.G., Writing: R.K.G., K.R.G.

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