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Effect of pH dependent and pH independent polymers on the drug release of anti-ischemic agent

Raghavendra Kumar Gunda[a*], Prasada Rao Manchineni[b] , K. Anil Kumar[c], D. Dhachinamoorthi[d], GSN Koteswara Rao[e]

a. Department of Pharmaceutics, M.A.M College of Pharmacy, Kesanupalli (V), Narasaraopet, Guntur, Andhra Pradesh, India - 522601.
b. Department of Pharmaceutical Analysis, M.A.M College of Pharmacy, Kesanupalli (V), Narasaraopet, Guntur, Andhra Pradesh, India - 522601.
c. Department of Pharmaceutics, Sarada College of Pharmaceutical Sciences, Kondakavuru (V), Narasaraopet, Guntur, Andhra Pradesh, India - 522602.
d. Department of Pharmaceutics, QIS College of Pharmacy, Vengamukapalem (V), Ongole, Prakasam, Andhra Pradesh, India - 523272.
e. Department of Pharmaceutics, KL College of Pharmacy, KLEF deemed to be university, Vaddeswaram (V), Guntur, Andhra Pradesh, India – 522502.

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*** Corresponding Author:**
Raghavendra Kumar Gunda
Email: raghav.gunda@gmail.com

Abstract:

The objective of current study is to study the effects of the combination of pH independent (HPMCK100M) and dependent (partially neutralized; Eudragit L 100-55) polymers on the drug release of Ranolazine form extended release tablet formulation. Ranolazine, an anti-ischemic or anginal agent. It is Mainly used for treating exercise induced, variant, and stable chronic angina pectoris along with myocardial infarction. Anti-ischemic effect exhibited by Ranolazine is independent of hemodynamic effects, due to this benefit, it was useful for treating patients, who did not respond to other anti-anginals. Extended release tablets of Ranolazine were prepared using various proportions of Eudragit L 100-55,HPMCK100M in by direct compression technique. 9 formulations were developed and characterized for pharmacopoeia limits. Data obtained from the dissolution study fitted well to kinetic modeling and kinetic parameters were determined. EHR_5 containing 31.25 mg of Eudragit L 100-55& 31.25 mg of HPMCK100M, is the best formulation showing similarity f_2=85.77, f_1= 2.31 with the marketed product (RANOLAZ). Formulation EHR_5 follow zero order, whereas release mechanism found to be nonfickian type (n= 0.653).

Keywords: Ranolazine; extended release; Angina; ischemic; Eudragit L 100-55; HPMCK100M; Non-Fickian Diffusion.

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1. Introduction

Extended release formulations reduce the dosing frequency in a 2-fold decline manner and they also maintain effective plasma concentrations for longer time periods. They improve patient compliance. They also offer improved *in-vivo* clinical outcome [1-2].

XL, LA (Long acting) ,and XR are popularly used symbols for Extended release dosage forms [3]. Several difficulties were presented to researchers for designing controlled release systems for better absorption and improved bioavailability [4-5].

Ranolazine, as an anti-ischemic and antianginal agent, is a piperazine acetamide derivative. It increases the ATP production from glucose thereby improving the functionality of myocardium. Hence it exhibits antieschemic actions independent of hemodynamics such as blood pressure and heart rate. (There will no significant effect of its effectiveness by the above mentioned factors and other co-morbidities.) Due to its advantages, it is employed as effective anti-ischemic or anti angina agent in the treatment of unstable chronic angina pectoris (exercise induced variant), myocardial infarction, and cardiac arrhythmias. [6-8]

Ranolazine belongs to BCS class- II agent. It shows erratic (variant) and extensive first pass effect. The solubility was found to be relatively high in acidic pH (stomach). The half-life was in and around 2.5 h (2.5±0.5). Hence selection of release rate modifiers is a challenging task for researchers. [9-14]
in the current study, An attempt is made to develop an extended release drug delivery system for Ranolazine with the help of polymers Eudragit L 100-55 (partially neutralized pH dependent polymer) along with HPMCK100M (pH independent polymer) [15-16].
Manufacture of tablets by Direct Compression technique is a method frequently used in Pharmaceutical Industry [17-18].

2. Materials *&* Methods

2.1 Materials

A gift sample of Ranolazine was procured from Mahys Pharma, solan, India. Eudragit L 100-55 was obtained from KU Pharma Pvt Ltd, baroli. HPMCK100M was gifted from QIM Chemicals, Guntur. All other excipients were obtained from S.D. Fine Chem. Ltd, Mumbai, India.

2.2 Development of Extended release tablets for

Ranolazine

Direct compression technique was utilised for the preparation of tablets, each containing 500 mg Ranolazine. Formulae for the preparation of tablets were presented in **Table 1.** Accurately weighed ingredients (except Ranolazine) were screened for obtaining uniform size to ensure proper mixing, and to obtain polymer mixture. The drug was then mixed with the polymer mixture for 10 minutes for uniform mixing of powder blend. Blend was lubricated with magnesium stearate. Powder blend was subjected to compression with the help of rotary tablet compression machine (Tablet Minipress). Compressed tablets were processed for Quality Control measures as per Pharmacopoeia. Final formulations were transferred to airtight and light resistance packaging bottles [19].

2.3 Evaluation of Ranolazine Extended Release Tablets

2.3.1 Hardness

The breaking/ crushing strength for the dosage forms were obtained by the diametric break of tablets with the help of Pfizer tablet hardness tester.

2.3.2 Friability

This test is performed by using Friability test apparatus (Roche). Selected number of tablets (20) were weighed accurately (W_0),then tablets were subjected to rotation (25 rpm for 4 minutes) and again the weight was noted (W). % weight loss was determined using following formula.

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

2.3.3 Assay

Assay was performed by triturating stated number of tablets in Indian pharmacopoeia (20) converted to powder, powder equivalent to 100mg of drug was added in 100 ml of 0.1 N HCl, followed by sonication. The solution was filtered through a 0.45 µ membrane filter, suitable aliquots were prepared, and the absorbance of the resultant solution was measured by spectrophotometry at 272 nm using 0.1 N HCl as blank.

2.3.4 Thickness

Thickness of formulations were determined by using vernier calipers, by placing tablet between its two arms.

2.3.5 In-Vitro drug release study

The *In-vitro* dissolution rate study for formulation trails were performed using USP XXIII type-II dissolution test apparatus containing 900 ml of 0.1 N HCl for initial 2 h followed by phosphate buffer up to end of the study, the apparatus run under conditions like temperature 37 ± 0.5°C and rotated at a speed of 50 rpm. At predetermined time intervals, 5 ml of the samples were withdrawn as per the pharmacopoeia procedure. The resultant samples were analyzed for estimation of drug release by measuring the absorbance at 272 nm using UV-Visible spectrophotometer after suitable aliquots. The samplings were performed in triplicate manner (n = 3) [14].
The dissolution profile of all the formulations was subjected to kinetic modeling such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to know the drug release mechanisms.

3. Results and Discussion

Extended release tablets of Ranolazine were developed using combination of partially neutralized pH dependent polymer (Eudragit L 100-55) and pH independent polymer (HPMCK100M); to know the relative effect on the drug release form formulation. 9 trials were developed as per the formulae given in Table 1.
All trials have Ranolazine (500 mg) as an extended release formulation, obtained as tablet by direct compression technique. Developed formulations were evaluated for pharmaceutical product performance tests. Data was presented in Table 2.

Table 1. Formulae for Ranolazine Extended Release Tablets

Name of Ingredients	Quantity of Ingredients per each Tablet (mg)								
	EHR_1	EHR_2	EHR_3	EHR_4	EHR_5	EHR_6	EHR_7	EHR_8	EHR_9
Ranolazine	500	500	500	500	500	500	500	500	500
Microcrystalline cellulose	18.25	24.5	30.75	24.5	30.75	37	30.75	37	43.25
Lactose	18.25	24.5	30.75	24.5	30.75	37	30.75	37	43.25
Eudragit L 100-55	43.75	43.75	43.75	31.25	31.25	31.25	18.75	18.75	18.75
HPMCK100M	43.75	31.25	18.75	43.75	31.25	18.75	43.75	31.25	18.75
Aerosil	16	16	16	16	16	16	16	16	16
Total Weight	640	640	640	640	640	640	640	640	640

Table 2. Post-Compression Parameters for the Formulations (n= 3)

Batch Code	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Average Weight (mg)	Drug Content (%)
EHR_1	8.5±0.3	4.05±0.09	0.10±0.001	640.09±0.01	99.94±0.49
EHR_2	8.2±0.3	3.97±0.09	0.11±0.001	642.11±0.01	99.45±0.50
EHR_3	7.98±0.22	3.91±0.08	0.09±0.001	640.10±0.01	99.11±0.51
EHR_4	8.53±0.47	4.05±0.06	0.06±0.001	641.14±0.02	99.74±0.32
EHR_5	8.10±0.41	4.06±0.06	0.07±0.001	642.2±0.02	99.98±0.33
EHR_6	7.71±0.41	3.98±0.05	0.07±0.001	640.31±0.02	99.11±0.34
EHR_7	8.38±0.42	4.2±0.05	0.05±0.001	640.66±0.02	99.70±0.43
EHR_8	7.93±0.42	4.1±0.06	0.04±0.001	640.2±0.01	99.23±0.47
EHR_9	7.5±0.40	4.03±0.06	0.05±0.001	640.7±0.01	98.77±0.35

Table 3. Regression analysis data

Formulation Code	Kinetic Parameters											
	Zero order			First order			Higuchi			Korsmeyer-peppas		
	a	b	r	a	b	r	a	b	r	a	b	r
EHR_1	14.411	3.29	0.982	1.991	0.034	0.986	1.685	17.614	0.995	1.089	0.629	0.962
EHR_2	14.86	3.29	0.981	1.986	0.034	0.986	1.308	17.641	0.995	1.098	0.625	0.959
EHR_3	15.31	3.28	0.979	1.985	0.034	0.986	0.930	17.667	0.995	1.107	0.621	0.957
EHR_4	15.95	3.82	0.982	2.110	0.065	0.931	2.738	20.473	0.995	1.125	0.651	0.960
EHR_5	16.31	3.84	0.982	2.171	0.077	0.877	2.481	20.560	0.995	1.132	0.653	0.958
EHR_6	16.66	3.85	0.981	2.117	0.068	0.931	2.224	20.646	0.995	1.138	0.647	0.956
EHR_7	23.41	3.92	0.948	2.112	0.093	0.964	2.240	21.685	0.992	1.199	0.641	0.950
EHR_8	23.78	3.93	0.948	2.185	0.110	0.949	2.539	21.742	0.993	1.204	0.638	0.948
EHR_9	24.31	3.89	0.946	2.286	0.124	0.915	3.157	21.565	0.993	1.210	0.634	0.945

All formulations have sufficient mechanical strength. All formulations found to be less friable, as within the limits. All batches pass the drug content uniformity test. All formulation batches passed the Weight variation test. Dissolution rate test was carried as per standard procedures, the dissolution specifications such as 900 mL of simulated gastric fluid for first 2 h followed by simulated intestinal fluid; paddle was rotated at a speed of 50 rpm, temperature maintained as 37±0.5ºC throughout the test period. Dissolution profile was well fit to kinetic modeling, results were presented in Table 3 and the same was presented as plots from Figure 1-4.

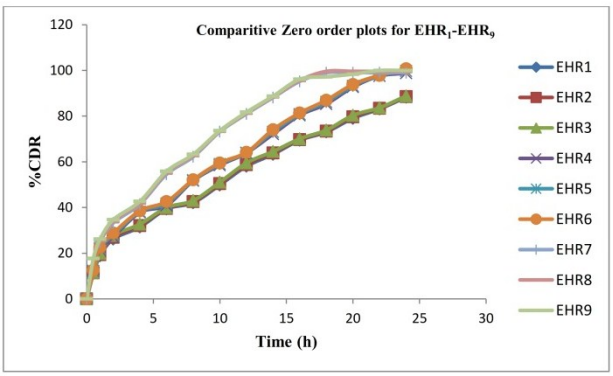

Figure 1. Comparative zero order plots

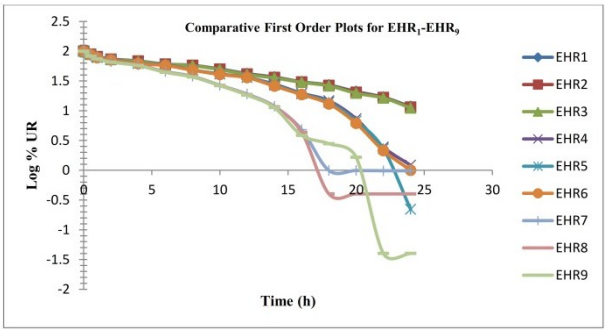

Figure 2. Comparative first order plots

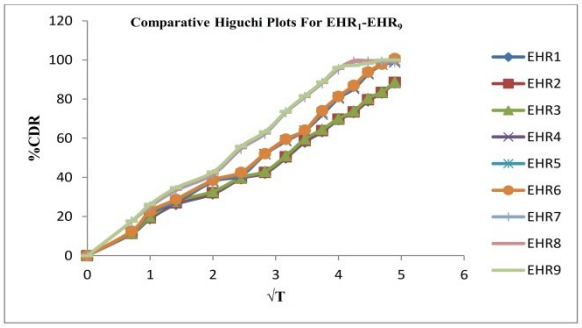

Figure 3. Comparative higuchi plots

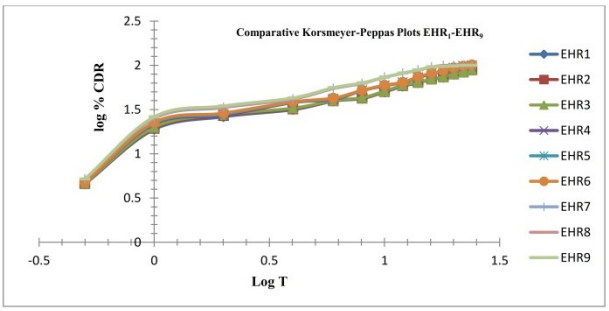

Figure 4. Comparative korsmeyer-peppas plots

From the results, observed that there was a clear relation existed between quantities of polymers in combination to the drug release rate (both were inversely proportional to each other). Predicted sustained release of drug was obtained by appropriate proportions of Eudragit L 100-55 and HPMCK100M. Dissolution parameters were summarized in Table 4. The combined effects of various proportions of polymers on the drug delivery of Ranolazine were studied with the help Response Surface Morphology plots presented as Figure 5-9. RSM plots were constructed using Sigmaplot V13.

EHR_5 is considered as best formulation among all batches. 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.

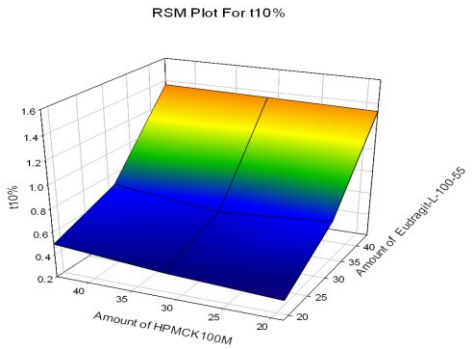

Figure 5. Response surface morphological plot for $t_{10\%}$

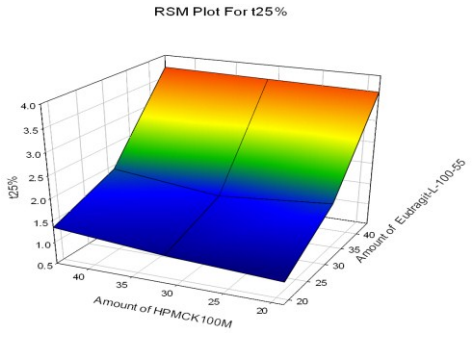

Figure 6. Response surface morphological plot for $t_{25\%}$

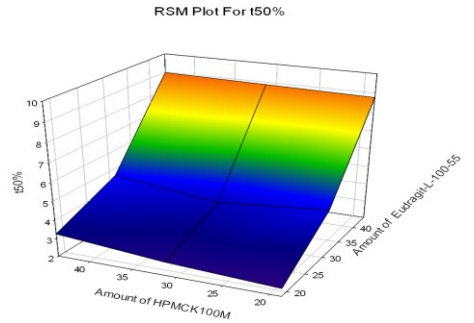

Figure 7. Response surface morphological plot for $t_{50\%}$

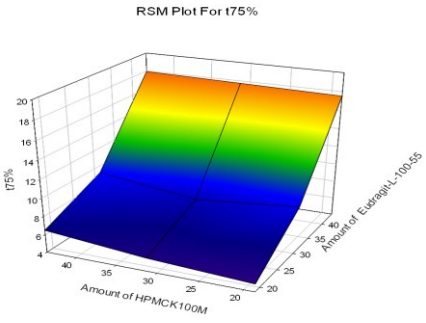

Figure 8. Response surface morphological plot for $t_{75\%}$

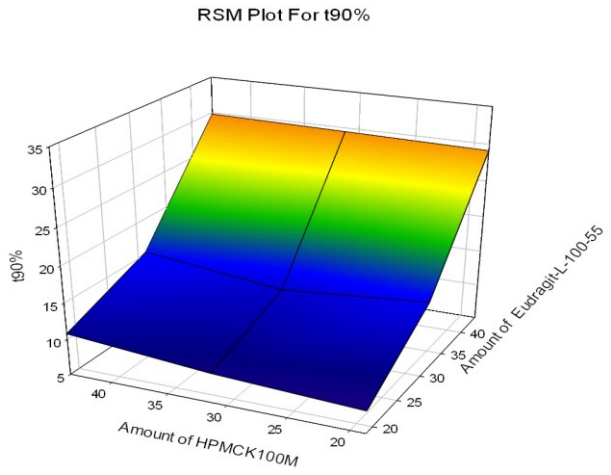

Figure 9. Response surface morphological plot for $t_{90\%}$

EHR_5 composed of both Eudragit L 100-55and HPMCK100M in equal quantity i.e. 31.25 mg each, produced promising dissolution characteristics, which helps meeting the purpose of research by extending the period of drug release (optimum delivery of drug) from dosageform.EHR_5 was considered to be ideal, It shows similarity factor (f2) 85.77, difference factor (f1) 2.31, t_{cal} <0.05 when compared with marketed product (RANOLAZ). Comparative dissolution plots for best formulation (EHR_5) and marketed product shown in Figure 10.

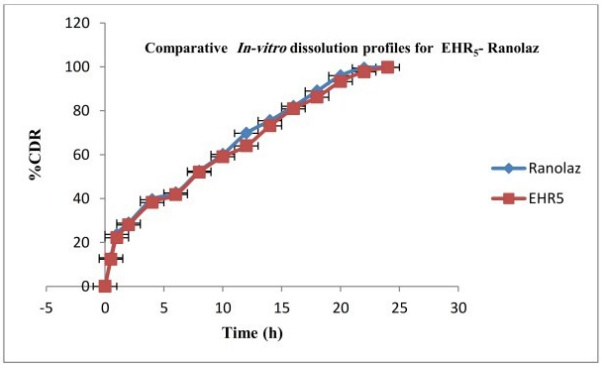

Figure 10. Comparative dissolution profiles for EHR_5-Ranolaz

4. Conclusion

On the basis of the current research study, the use of macro molecules (polymers) in combination had its own advantages for example maintaining integrity and extended drug release form the formulation. The combination of partially neutralised pH dependent polymer with pH independent polymer at an appropriate proportion will yield desired extended drug release which ultimately results in 2-fold reduction in the dosing frequency of Ranolazine. It is achieved by preparing the Ranolazine with combination polymers like Eudragit L 100-55, HPMCK100M employing along with other excipients. Among the various ER formulations studied, the formulation (EHR_5) showed the best result in all aspects of objective and it was considered as the ideal formulation**.** Best formulation EHR_5 follows Zero order release, Non-Fickian Diffusion, and it may improve patient compliance by reducing the dosing frequency by 2 fold or more, which will ultimately improve the clinical response.

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Conflict of interest

None.

Ethics

No ethical clearance required for the current study.

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Authors' ORCIDs

Dr. Raghavendra Kumar Gunda:
https://orcid.org/0000-0002-4271-814

Dr. Prasada Rao Manchineni:
https://orcid.org/0000-0003-2975-4538

Dr. K. Anil Kumar:
https://orcid.org/0000-0003-2975-4538

Dr. Dhachinamoorthi D:
https://orcid.org/0000-0002-9922-2636

Dr. GSN Koteswara Rao:
https://orcid.org/0000-0003-1257-7133

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