Int. J. Pharm. Investigation, 2022; 12(1) : 87-92

Original Article

Optimization and Analysis of Xanthan Gum and Hypromellose Combined Matrices for Extended Release of Ranolazine Using Quality by Design

C Sowmya[1,*], V Lava Kumar[2], Bishnu Adhikari[3]

[1]Department of Pharmaceutics, Sri Ramachandra College of Pharmacy , Sri Ramachandra Institute of Higher Education and Research (DU), Porur, Chennai, Tamil Nadu, INDIA.

[2]Department of Pharmacology, Arulmigu Kalasalingam College of Pharmacy, Srivilliputtur, Tamil Nadu, INDIA.

[3]Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research, Anantapur, Andhra Pradesh, INDIA.

ABSTRACT

Background: Xanthan gum (XG) is a natural polymer with numerous uses. But its poor tableting and release charact1eristics reduce its usage as a tablet matrix former. Hence, the aim of the study is to improve the quality of XG by blending it with a successful semisynthetic polymer, hypromellose (HPMC). **Methods:** Extended release (ER) tablets were made using wet granulation technique using XG and HPMC blend. The blend was optimised using Central composite design. Prepared tablets were evaluated for *in vitro* tableting characteristics and drug release. *In vivo* absorption studies are carried out in New Zealand white rabbits. **Results:** Under optimal conditions, the ideal combination of factors was observed in the range of X_1: 2.75-4.25 %w/w and X_2: 10-20% w/w. At these finest concentrations, the predictable responses, the drug release at 4th hr was 36.31-40.34%, 20th hr was 82.21-91.43% and the hardness of the tablet was 6.6-8.5 kg/Cm^2. The drug release of the optimized batch (RANERT 14) showed 90.9% similarity with the standard commercial ER tablets. Further, *in vivo* pharmacokinetic testing of the same batch showed, bioavailability (88.0 ±2.5%), mean residence time (16.1± 2.85 h) and biological half-life (11.47 ±0.42 h) against pure drug (BA: 65.0 4%; MRT: 5.1± 2.85 h; t1/2: 2.6151 ± 0.54 h). **Conclusion:** Comparable drug release profiles with the commercial tablets and enhanced pharmacokinetic profile made this combination as successful in achieving extended-release for a period of 24 hr by overcoming the drawbacks associated with XG.

Key words: Central composite design, Drug release kinetics, Mean dissolution time, Non-aqueous granulation, Similarity factor

Correspondence

C Sowmya

Department of Pharmaceutics, Sri Ramachandra College of Pharmacy, Sri Ramachandra Institute of Higher Education and Research (DU), Porur, Chennai, Tamil Nadu, INDIA.

Email id: drcsowmya@sriramachandra.edu.in

DOI: 10.5530/ijpi.2022.1.16

INTRODUCTION

Xanthan gum (XG) is a high molecular weight bacterial polymer made by fermenting *Xanthomonas campestris*.[1] The US FDA declared it GRAS in 1968. XG has been examined as a thickening, suspending, and emulsifying agent.[2,3] Although it has acceptable compatibility and inertness, but poor tableting and releasing properties, limiting its usage as a matrix forming material. Many studies have shown that issues related to single polymer usage can be solved by combining compatible polymers. Hypromellose (HPMC) is a semi-synthetic cellulose-based polymer commonly utilised in controlled release dosage forms, due to its good tablet compaction and release characteristics.[4]

The objective of the study was to prepare extended-release matrix tablets with XG and HPMC and optimise matrix compositions to achieve desired drug release using RSM. In RSM, optimisation was done by central composite design (CCD) as it can handle multiple independent variables at a time.[5] The tablet matrix's sustained release capabilities were then evaluated *in vitro* and *in vivo*. Ranolazine (RAN) is a synthetic angina medication that works by suppressing the late sodium current in cardiac cells. Due to its moderate high solubility at lower pH, it has a shorter time of action.[6] So, to challenge the above difficulties, RAN was chosen as model drug in this study.

MATERIALS AND METHODS

Materials

Finoso Pharma Ltd., Hyderabad provided RAN and HPMC K 100 M, while Sigma Aldrich, India provided XG. I bought acetonitrile and formic acid from Merck, Bombay. All other chemicals and reagents used were analytical grade and used as received.

Statistical Analysis and Formulation Optimization

Design-Expert software version 10.0.6.0 (Stat-Ease Inc., Minneapolis, MN, USA) was used in this study. Optimizing a two-factor, five-level CCD with positive and negative axial points (+α/-α), positive and negative factorial points (+1/-1) and a centre point (0). Here, HPMC and XG used in the manufacturing of RAN matrix tablets were taken as independent variables (factors) and labelled as X_1 and X_2, respectively, while drug release at 4 hr (%), 20 hr (%), and tablet hardness (Kg/cm^2) were designated as dependent variables (responses) and represented as Y_1, Y_2 and Y_3. Preliminary experiments and literature identified effective component ranges (HPMC = 2.75-4.25 % w/w; XG =10-20 %w/w) for developing controlled release matrices. This data was placed in *stat ease* software and analysed using CCD to obtain several design batches.

Preparation of RANER tablets with XG and HPMC matrix

RANER tablets, 1-13 experimental batches and 14-15 checkpoint optimised batches were manufactured by non-aqueous wet granulation

method. Each tablet contains 500 mg of RAN and totally weighs 720 mg. For each formula, a batch of 30 tablets was prepared. The medication was fully mixed with the polymer mixture (Table 1) and diluent, microcrystalline cellulose. Granulation was done manually using 70% of isopropyl alcohol. These were then compressed using 9 mm round punches in a 12-station rotating tablet compression machine (Rimek mini press, Ahmadabad, India). The tablet formulations contained 1% w/w citric acid as a stabiliser. Until testing, the tablets were stored in HDPE bottles. The granules' flowability and compressibility were evaluated prior to compression.

Study of Drug Excipient Interactions

Studies were carried out utilising a Differential scanning calorimeter (Mettler Toledo 822E with E star software) operated between 30 and 300°C temperature. FT-IR spectroscopy was used to capture IR spectra from 4000 to 400 cm^{-1} (Shimadzu 8400S, Shimadzu, Japan). The study was performed using the highest concentrations of polymers blended with medication in tablet manufacturing.

Characterization of Tablets

RAN matrix tablets were assessed for thickness, hardness, friability and weight variation (USP). The drug content was evaluated using a Shimadzu 1601, Kyoto, Japan UV Visible spectrophotometer by measuring the absorbance at 272 nm.

In vitro Drug Release Studies

In vitro drug release was examined using the USP-XXIII dissolution apparatus-II, rotating paddle type with sinker (TDT-08L; Electrolab, Mumbai, India) operated with 50 rpm paddle speed at 37 ± 0.5°C. The dissolution medium employed was 900 ml of 0.1 M HCl for a period of 24 h.[7] The sink condition was preserved during the entire study. Samples of 5 ml were withdrawn and filtered through 0.45µ PTFE filters and analysed spectrophotometrically by measuring the absorbance at 272 nm. The dissolution studies were conducted in triplicate. Drug release profiles were constructed by plotting the cumulative percent of drug release (%) against time (h).

Table 1: Observed responses of RANER tablets 1-13 formulations by central composite design (data are mean values, *n*=3).

Std	Run	Factor 1 (X1) A:HPMCK100M (% W/W)	Factor 2 (X2) B:XANTHAN GUM (% W/W)	Response 1 (Y1) Drug release at 4th hr (%)	Response 2 (Y2) Drug release at 20th hr (%)	Response 3 (Y3) Tab. Hardness (kg/cm^2)
7	1	3.5	7.92893	40.34	86.43	6.6
10	2	3.5	15	39.41	84.9	7.6
13	3	3.5	15	40.12	84.45	7.8
8	4	3.5	22.0711	36.37	82.21	8.5
5	5	2.43934	15	36.31	83.07	7.2
3	6	2.75	20	37.01	82.34	8
12	7	3.5	15	39.89	85.01	7.6
6	8	4.56066	15	40.13	86.39	7.9
2	9	4.25	10	38.53	91.43	7
9	10	3.5	15	39.93	85.56	7.7
4	11	4.25	20	38.17	83.01	8.2
1	12	2.75	10	40.32	86.06	6.8
11	13	3.5	15	40.12	86.02	7.7

Analysis of Drug Releases Kinetics

The obtained drug release data was substituted in several kinetic equations, viz., zero-order ($Q_t = Q_0 + K_0 t$), first-order ($\log C = \log C_0 - k t/2.203$). Higuchi ($Q = K h t_{1/2}$),[8] Korsmeyer-Peppas ($Mt/M = Kt^n$) and Hixson–Crowell ($(UR)^{1/3} = k_s t$)[9] were used to find the best fit equation and to predict the drug release mechanism.(10) The best fit model was considered the one that had the maximum r^2 value.

The MDT was determined using following equation[10]

$$MDT = \frac{n}{n+1} k^{-1/n} \quad (1)$$

'n' denotes the release exponent, and k denotes the release rate constant.

Comparison of RANERT Dissolution Patterns with Commercial Tablets

Dissolution profiles were compared to the commercially available ranolazine extended release (ER) formulation (Ranozine 500 SR tablets, Ambica Pharma, Bombay) using the similarity factor f_2.[11] The factor f_2 is a logarithmic transformation of the sum of squared discrepancies between the test (Tt) and reference products (Rt) over all time points. f_2 is calculated by using following equation.

$$f_2 = 50 \times \log\left\{\left[(1+1/n)\sum_{t=1}^{n}(R_t - T_t)^2\right]\right\}^{-0.5} \times 100 \quad (2)$$

Where, R_t and T_t are the percent dissolved of the reference (commercial ER tab) and test (RANERT 14 and 15) products at each time point 't', 'n' is the number of time points at which the average dissolution points are compared.

In vivo Pharmacokinetic Studies

The Institutional Animal Ethics Committee (IAEC) of Arulmigu Kalasalingam College of Pharmacy (AKCP), No. AKCP/IAEC/03/18-19, approved an *in vivo* pharmacokinetic study. All procedures were carried out in conformity with institutional animal usage rules. The study included 18 New Zealand white rabbits, each weighing around 2.00 ± 0.12 kg. Group 1 was kept as a normal control and groups 2 and 3 were used in *in vivo* testing. Group 2 was administered with a RAN pure drug sample, while group 3 was given optimised batch tablets, RANERT 14. Tablets were administered to the rabbits by the gastric intubation method. Blood samples were withdrawn from the ear veins at the preselected time intervals of 0.5, 1, 2, 4, 8, 12 and 24 h post dosing into heparinized tubes.[12] Plasma was separated by centrifugation of blood at 3500 g for 5 min at 4°C and kept frozen at -70°C until analysis. Doses for rabbits were calculated by adopting the formula of Ghosh.[13]

$$\text{Rabbit dose} = 0.07 \times \text{human dose} \quad (3)$$

Estimation of Plasma RAN Concentration using HPLC

The RAN in rabbit plasma was estimated using a sensitive HPLC (HPLC-LC-2010C HT, Shimadzu, Japan) technique.[14] The mobile phase, acetonitrile:0.1% formic acid (90:20), was supplied at 1.0 ml/min using a C_{18} column (3.9 mm 150 mm) silica at 272 nm. In all cases, the plasma drug concentration (PDC) time profile was produced at room temperature.

Data analysis: The PDC time profile was used to calculate C_{max} (maximum drug concentration in the blood) and T_{max} (time taken to reach maximum concentration). The trapezoidal method was used to estimate AUC. The elimination rate constant, Ke, and terminal half-life

(t1/2 = 0.693/ke) were obtained using unweighted linear regression of the last 4 data points. The MRT was calculated using non-compartmental analysis. The absorption rate constant (Ka) was also computed.

RESULTS

The DSC thermogram of pure RAN showed a pronounced endothermic peak at 121°C, started at 118°C and finished at 123°C. DSC thermograms were shown in Figure 2a, b, c. The FTIR spectrum of RAN showed that the N=H stretch is 3326 cm^{-1}, the C-H stretch is 2910 cm^{-1}, the OH stretch is 3500 cm^{-1} and the C=O stretch is 1638 cm^{-1} (Figure 3a, b, c). Weight variation of tablets is in the range of -2.5 to +1.2 % and friability was form 0.2 – 0.4 % loss. Hardness of the tablet was from 6.6-8.5 kg/cm^2. Table 2 summarised ANOVA test findings. Figure 4a and b show the *in vitro* drug release characteristics of RANER tablets**.** Correlation coefficient values of first, zero order kinetics are r^2= 0.9218 to 0.9587, 0.8528 – 0.9282 and Higuchi kinetics from 0.948 to 0.9716. The r^2 and n value of korsemeyer peppas are 0.9249 - 0.9587 and 0.5 to 0.64. RANER tablets showed MRT, relative bioavailability, biological half-life and t_{max} as 16.1 hr, 88.04%, 11.4697 h and 6.2 h respectively.

DISCUSSION

Natural polymers have been widely employed as matrix materials in sustained release tablets for decades. XG was explored as a matrix former in the preparation of theophylline[15] and indomethacin sustained release tablets. Earlier research used a range of polymers to prepare RANER matrix tablets, including Natrosol Type 250 HHX, Eudragit and HPMC combination.[16] The present work undertakes the problem of anomalous drug release in acidic pH by applying optimal concentrations of XG and HPMC polymer blends in tablet formulation.

To obtain the best combination of polymers, the best fitting model was chosen for optimization of selected variables after CCD analysis. On considering ANOVA test findings, the response polynomial equations are obtained as follows

Response 1 $(Y1) = +39.89 +0.6(X_1) -1.16 (X_2) +0.74 (X_1X_2) -0.78 (X_1^{2})- 0.72 (X_2^{2})$ (4)

Where Y_1 *i*s the 4-hr drug release, X_1 is the HPMC concentration, and X_2 is the XG concentration. Model (Quadratic) F = 5.83, and Prob > F (0.0194) implies model terms are important (X_2). The expected Y_1 response ranges from 35.9% to 40%. The 4th hr drug release increases with decreasing XG levels and vice versa. The effects of X_1 and X_2 on Y_1 were represented on 3D response surface plot (Figure 1a).

Response 2 $(Y_2) = +85.14 +1.34 (X_1) -2.26 (X_2) -0.17 (X_1 X_2)$ (5)

Y_2 is the 20th hr of medication release. This is supported by the model (2-factor interaction) F value of 19.30. (X_1, X_2 *and* $X_1 X_2$). The Y_2 response values range from 81.94 to 89.93% HPMC's higher swelling and viscosity boosted the gelling nature of the polymer blend, allowing for longer controlled release.[17] 3D response surface plot revealed that X_1, X_2, and $X_1 X_2$ were shown to affect Y_2 (Figure 1b).

Response 3 $(Y_3)= +7.58 + 0.17 (X_1) +0.64 (X_2)$ (6)

Y_3 is tablet hardness. The model F value of 108.14 indicates significance and Prob>F (0.0001) indicates model (linear) terms are important (X_1&X_2). A range of 6.69 to 8.48 kg/cm^2 is expected for Y_3. The independent variables X_1 & X_2 directly affect the response Y_3. The tablet's hardness rises with both polymer concentrations.[18] Thus, altering the XG and HPMC concentrations in the formula controls tablet hardness. The 3D response surface plots show the impacts of X_1 & X_2 on Y_3 (Figure 1c). Table 2 summarises the ANOVA results and errors.

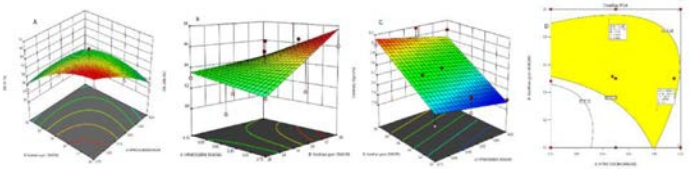

Figure 1: Response surface plots of A) Drug release after 4 hr; B) Drug release after 20 hr; C) hardness; D) overlay plot.

Table 2: Summary of ANOVA results in analysing lack of fit (LOF) and pure error for the responses of RANERT 1-13 formulations.

Parameter	Sum of squares	d_f	Mean square	*F* value	*P* value Prob>F	Remarks
Drug release at 4th hr (Quadratic Model)						
Model	22.71	5	4.54	5.83	0.0194	Significant
Residual	5.46	7	0.78	-	-	-
Lack of fit	5.12	3	1.71	20.21	0.007	Significant
Pure error	0.34	4	0.084	-	-	-
Drug release at 20th hr (2FI Model)						
Model	60.92	3	20.31	19.30	0.0003	Significant
Residual	9.47	9	1.05	-	-	-
Lack of fit	7.98	5.0	1.6	4.28	0.0918	not Significant
Pure error	1.49	4	0.37	-	-	-
Tablet hardness (Linear Model)						
Model	3.48	2	1.74	108.14	< 0.0001	Significant
Residual	0.16	10	0.016	-	-	-
Lack of fit	0.13	6	0.022	3.16	0.1426	not Significant
Pure error	0.028	4	7.000E-003	-	-	-

d_f = degrees of freedom

The graphical optimization was utilised to validate the experimental design. The overlay plot was created using response targets (commercial tablet features) such as 40% drug release at 4 hr, 80% at 20 hr, and 7.5 kg/cm^2 tablet hardness. The overlay map demonstrated the optimised design space for tablets (Figure 1d) and placing of flags displayed all responses and factors at that point of space. Using the design space, two checkpoint batches (RANERT 14 and 15) were made and analysed for responses. This was in close agreement with the model predictions (drug release at 4th h is 38.9 and 39.9%, 20th h is 83.9 and 85.2% and hardness is 7.7 and 7.3 kg/cm^2) and so confirmed the design (Table 3).

From Figure 2a, the endothermic peak at 121°C is attributed to its melting point and Figure 2c, (thermogram of RAN with excipients) preserved the peak at 121°C and hence confirmed the absence of drug-excipient interactions.[19] All of the functional groups present in RAN were shown in the drug-placebo mix at 3327 cm^{-1}, 2909 cm^{-1}, 3568 cm^{-1}, 1725 cm^{-1}, 1436 cm^{-1} and 1221 cm^{-1} respectively (Figure 3 a, b, c). Hence, the FTIR spectra further confirmed the absence of drug excipient interactions.[20]

All prepared tablets had a weight fluctuation of less than 5% (w/w), which is acceptable for uncoated tablets per USP-2004. Due to the tablet's integrity and mechanical strength, friability losses were low and hardness was satisfactory. The results indicated satisfactory granule flow

Table 3: Results of optimised batches (RANERT 14-15) selected from design space proposed by an overlay plot of design expert software.

Optimized batch	Independent variable		Dependent variables					
			Actual values			Predicted values		
	X1	*X2*	*Y1*	*Y2*	*Y3*	*Y1*	*Y2*	*Y3*
RANERT 14	3.24176	16.9972	39.52	83.2	8.0	38.9175	83.9406	7.7786
RANERT 15	3.28841	13.8506	40.5	85.4	7.5	39.9403	85.2102	7.3892

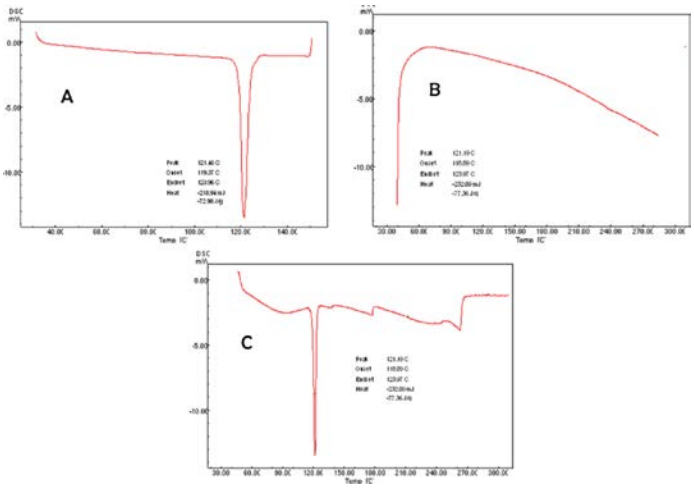

Figure 2: DSC thermograms of A) Pure Ranolazine B) Placebo mixture C) Ranolazine with excipients.

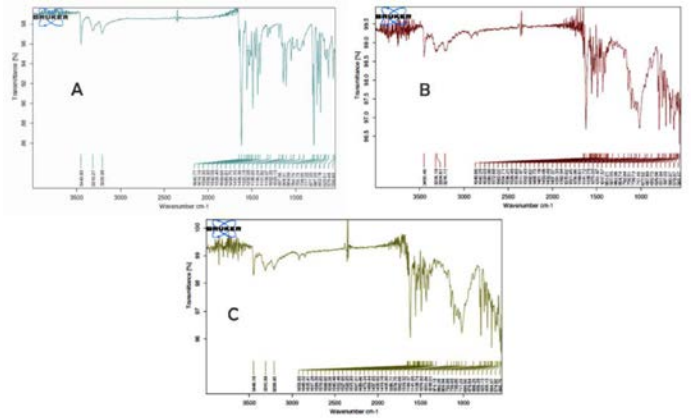

Figure 3: FTIR spectra of A) pure ranolazine, B) placebo mixture, and C) ranolazine containing excipients.

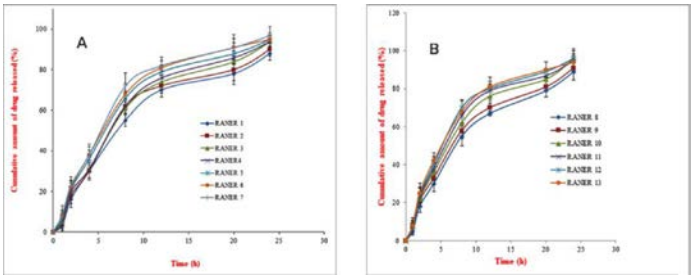

Figure 4: Drug release profiles of Ranolazine extended-release tablets A) RANER 1–7; B) RANER 8–13; C) RANER 14–17; D) RANER 18–23; E).

and compaction and hence the examined tablet physical qualities were acceptable.

Absence of burst release in drug release plots overcomes the undesirable aspects of RAN release using XG and HPMC combination. This may be attributed to early surface dissolution of polymer matrix blends forming a high viscosity surface layer that effectively controls medication release. All graphs indicated similar drug release patterns and shown >80% drug release after 20 hr (Figure 4).

Table 4 demonstrates that RANER tablets use a diffusion-controlled release mechanism (r^2= 0.948 to 0.9716) with a high linearity between the log cumulative amount of drug released and log time. 'n' value of Peppas suggested non-fickian diffusion (0.5 < n < 1) and confirms that the drug release was controlled by more than one process. The extremely viscous mixed polymer matrix generated a rubbery hydrated layer on the surface.[21] In contrast, a non-hydrated core forms in the tablet's centre, as time passes, water molecules penetrate the tablet's core, forming solvated polymer chains, hence the matrix swells. As more water enters the matrix, the polymer concentration on the tablet's surface falls, causing erosion. As a result, the rate of drug release from this combination matrix depends on drug diffusion from the viscous gel matrix and polymer erosion.[22] MDT values rise with polymer concentration (6.5 to 7.7 hr: Table 4). Hence, MDT validated polymer concentration-dependent release retarding efficacy of RANER tablets.[23]

The drug release pattern of commercially available tablets is used as a benchmark. Hence, the dissolution data of optimized RANERT14 and 15 were compared with commercial data using model independent similarity (f_2) factor calculation and exhibited as 90.9 and 88.6%. Hence, the drug release characteristics of RANERT 14 and 15 comparable with commercial RANER tablets in this investigation.

In vivo PK investigations demonstrated that RANERT 14 had lower plasma concentrations than RAN pure drug, indicating sluggish absorption of RAN from extended-release tablets. RANERT 14 plasma concentrations were steady and narrow for prolonged periods of time. The MRT increased from 3.1 to 16.1 hr with ER tablets, indicating a longer drug presence of drug in the body. The relative bioavailability of RAN from ER tablets was 88.04% compared to pure RAN (65.04%). The biological half-life and T_{max} were increased from 2.6151 to 11.4697 and 4.1 to 6.2 hr. Thus, *in vivo* testing revealed the chosen polymer combination could control drug release over 24 hr.

CONCLUSION

The present work demonstrated the utilisation of XG + HPMC as a matrix material for ER formulations containing ranolazine, a BCS-II medication. The polymer combination releases the drug in sustained release fashion by combining diffusion of the drug with erosion polymer mechanisms. *In vivo* pharmacokinetic studies showed that using this polymer combination enhanced ranolazine's biological half-life, bioavailability, and MRT. XG and HPMC combination matrices were used to achieve continuous uninterrupted medication release through increased tableting capabilities. Hence, the drawbacks associated with XG

Table 4: Correlation coefficient values and kinetics of drug release based on the dissolution profiles of RANER 1-13 tablets.

Formulation code	Zero order		First order		Hixon crowell	Higuchi	Korsemeyer peppas		$t_{50\%\ (h)}$	MDT(h)
	r^2	K_0 (mg/h)	r^2	K_1 (h^{-1})	r^2	r^2	r^2	'n' value		
RANER 1	0.9066	7.3322	0.9932	0.1771	0.6609	0.9713	0.9472	0.6449	6.2	8.24
RANER 2	0.8849	7.4484	0.9901	0.1980	0.6339	0.9653	0.9473	0.579	5.7	7.58
RANER 3	0.8682	7.3132	0.9785	0.1835	0.6292	0.956	0.9333	0.5844	5.6	7.44
RANER 4	0.871	7.2405	0.9775	0.1830	0.6248	0.9575	0.9351	0.5665	5.5	7.31
RANER 5	0.8528	7.3129	0.9685	0.1860	0.6192	0.948	0.9249	0.5688	5.4	7.18
RANER 6	0.8743	7.5431	0.962	0.2146	0.6327	0.9567	0.9336	0.5864	5.3	7.0
RANER 7	0.9282	7.3581	0.984	0.1630	0.6729	0.9771	0.9587	0.6414	6.5	8.64
RANER 8	0.8552	7.3234	0.9704	0.1870	0.6217	0.9484	0.9249	0.5726	5.4	7.18
RANER 9	0.8879	8.0711	0.979	0.2731	0.6544	0.9606	0.9388	0.6399	5.2	6.9
RANER 10	0.8658	7.4709	0.9762	0.2019	0.6285	0.9528	0.9292	0.5826	5.3	7.0
RANER 11	0.866	7.3825	0.9794	0.1925	0.6228	0.9568	0.935	0.5738	5.5	7.31
RANER 12	0.9005	7.1939	0.987	0.1711	0.6415	0.9716	0.9454	0.5977	6.2	8.24
RANER 13	0.8743	7.2138	0.969	0.1759	0.6391	0.9542	0.9218	0.623	6.0	7.98

k0: Zero order rate constant; k1: First order rate constant; r: Correlation coefficient; n: Diffusion exponent indicative of the release mechanism; c t50: Time for 50% of the drug release (mean of six tablets with SD ± 0.25); MDT: Mean dissolution time (mean of six tablets with SD within ± 0.18 h)

and RAN was successfully overcome by this combination drug delivery. However, additional *in vivo* research in human volunteers is required to demonstrate the matrix combination's sustained release capacity.

ACKNOWLEDGEMENT

The authors thank Sri Ramachandra Institute of Higher Education and Research for providing the essential facilities. The SEM pictures and FTIR spectra were provided by the International Research Centre, Kalasalingam Academy of Research and Education, Krishnankoil.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

US FDA: United States Food and Drug administration; **GRAS:** Generally recognised as safe; **MN:** Minnesota; **USA:** United States of America; **HDPE:** High density polyethylene; **PTFE:** Poly tetra fluoro ethylene; **MDT:** Mean Dissolution Time; **ANOVA:** Analysis of variance; **PDC:** Plasma drug concentration.

REFERENCES

1. Bueno VB, Bentini R, Catalani LH, Petri DFS. Synthesis and swelling behavior of xanthan-based hydrogels. Carbohydr Polym. 2013;92(2):1091-99. doi: 10.1016/j.carbpol.2012.10.062, PMID 23399133.
2. Kar R, Mohapatra S, Bhanja S, Das D, Barik B. Formulation and *in vitro* characterization of xanthan gum-based sustained release matrix tables of isosorbide-5- mononitrate. Iran J Pharm Res. 2010;9(1):13-9. PMID 24363701.
3. Andreopoulos AG, Tarantili PA. Xanthan gum as a carrier for controlled release of drugs. J Biomater Appl. 2001;16(1):34-46. doi: 10.1106/XBFG-FYFX-9TW9-M83U, PMID 11475358.
4. Salsa T, Veiga F, Pina ME. Oral controlled-release dosage forms. I. Cellulose ether polymers in hydrophilic matrices. Drug Dev Ind Pharm. 1997;23(9):929-38. doi: 10.3109/03639049709148697.
5. Vuppalapati L, Cherukuri S, Neeli V, Yeragamreddy PR, Kesavan BR. Application of central composite design in optimization of valsartan nanosuspension to enhance its solubility and stability. Curr Drug Deliv. 2016;13(1):143-57. doi: 10.2174/1567201812666150724094358, PMID 26205900.
6. Rayner-Hartley E, Sedlak T. Ranolazine: A contemporary review. J Am Heart Assoc. 2016;5(3):e003196. doi: 10.1161/JAHA.116.003196, PMID 26979079.
7. Pani NR, Nath LK. Development of controlled release tablet by optimizing HPMC: Consideration of theoretical release and RSM. Carbohydr Polym. 2014;104:238-45. doi: 10.1016/j.carbpol.2014.01.037, PMID 24607183.
8. Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963;52(12):1145-9. doi: 10.1002/jps.2600521210, PMID 14088963.
9. Kumar P, Ganure AL, Subudhi BB, Shukla S. Design and Comparative Evaluation of *in-vitro* Drug Release, Pharmacokinetics and gamma Scintigraphic Analysis of Controlled Release Tablets Using Novel pH Sensitive Starch and Modified Starch- acrylate Graft Copolymer Matrices. Iran J Pharm Res. 2015;14(3):677-91. PMID 26330856.
10. Möckel JE, Lippold BC. Zero-order drug release from hydrocolloid matrices. Pharm Res. 1993;10(7):1066-70. doi: 10.1023/a:1018931210396, PMID 8378249.
11. Kuksal A, Tiwary AK, Jain NK, Jain S. Formulation and *in vitro, in vivo* evaluation of extended-release matrix tablet of zidovudine: Influence of combination of hydrophilic and hydrophobic matrix formers. AAPS PharmSciTech. 2006;7(1):E1. doi: 10.1208/pt070101, PMID 16584139.
12. Parasuraman S, Raveendran R, Kesavan R. Blood sample collection in small laboratory animals. J Pharmacol Pharmacother. 2010;1(2):87-93. doi: 10.4103/0976-500X.72350, PMID 21350616.
13. Ghosh M. Fundamentals of experimental pharmacology. Indian J Pharmacol. 2007;39(4):216.
14. Zhao L, Li H, Jiang Y, Piao R, Li P, Gu J. Determination of ranolazine in human plasma by liquid chromatographic-tandem mass spectrometric assay. J Chromatogr Sci. 2008;46(8):697-700. doi: 10.1093/chromsci/46.8.697, PMID 18796225.
15. Lu MF, Woodward L, Borodkin S. Xanthan gum and alginate based controlled release theophylline formulations. Drug Dev Ind Pharm. 1991;17(14):1987-2004. doi: 10.3109/03639049109048063.
16. Murthy T, Babu V, Mukkala BV. Formulation and evaluation of ranolazine extended release tablets: Influence of polymers. Asian J Pharm. 2011;5(3). doi: 10.4103/0973-8398.91992.
17. Ahmed SI, Zaheer Z, Khan FN, Hasan M. The formulation and evaluation of gastro-bilayer floating tablets of losartan potassium as immediate release layer and ramipril hydrochloride as sustained release floating layer. Int J Pharm Investig. 2020;10(3):294-9. doi: 10.5530/ijpi.2020.3.53.
18. Dhopeshwarkar V, Zatz JL. Evaluation of xanthan gum in the preparation of sustained release matrix tablets. Drug Dev Ind Pharm. 1993;19(9):999-1017. doi: 10.3109/03639049309062997.
19. Chiu MH, Prenner EJ. Differential scanning calorimetry: An invaluable tool for a detailed thermodynamic characterization of macromolecules and their interactions. J Pharm Bioallied Sci. 2011;3(1):39-59. doi: 10.4103/0975-7406.76463, PMID 21430954.

20. Lavakumar V, Sowmya C, Venkateshan N, Ravichandiran V, Leela KV, Harikrishanan N, *et al.* Microcapsule-based chronomodulated drug delivery systems of montelukast sodium in the treatment of nocturnal asthma. Int J Pharma Investig. 2018;8(1):24-32. doi: 10.4103/jphi.JPHI_101_17.
21. Wang L, Chen K, Wen H, Ouyang D, Li X, Gao Y, *et al.* Design and evaluation of hydrophilic matrix system containing polyethylene oxides for the zero-order controlled delivery of water-insoluble drugs. AAPS Pharm Sci Tech. 2017;18(1):82-92. doi: 10.1208/s12249-016-0498-y, PMID 26883263.
22. Ghori MU, Conway BR. Hydrophilic matrices for oral control drug delivery. Am J Pharmacol Sci. 2015;3(5):103-9.
23. Wadher KJ, Kakde RB, Umekar MJ. Study on sustained-release metformin hydrochloride from matrix tablet: Influence of hydrophilic polymers and *in vitro* evaluation. Int J Pharm Investig. 2011;1(3):157-63. doi: 10.4103/2230-973X.85966, PMID 23071938.

Article History: Submission Date : 11-10-2021; Revised Date : 02-11-2021; Acceptance Date : 24-11-2021.
Cite this article: C Sowmya, V Lavakumar, Adhikari B. Optimization and Analysis of Xanthan Gum and Hypromellose Combined Matrices for Extended Release of Ranolazine using Quality by design. Int. J. Pharm. Investigation. 2022;12(1):87-92.