WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 7, Issue 8, 529-544 Research Article ISSN 2278 – 4357

FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF RANOLAZINE USING NATURAL GUMS AND SYNTHETIC POLYMERS

Palli Bhagyasri[1] and Srinivasa Rao Baratam[1]*

Department of Pharmaceutical Technology, St. Ann's College of Pharmacy, Cantonment, Viziangaram, Andhra Pradesh- 535003.

Article Received on
27 May 2018,

Revised on 17 June 2018,
Accepted on 07 July 2018

DOI: 10.20959/wjpps20188-12044

***Corresponding Author**
Srinivasa Rao Baratam
Department of Pharmaceutical Technology, St. Ann's College of Pharmacy, Cantonment, Viziangaram, Andhra Pradesh- 535003.

ABSTRACT

The aim of this work is to formulate a sustained release matrix tablets using natural gums and synthetic polymers as a matrix forming materials. Ranolazine was selected as a model drug. Due to the low biological half-life it requires frequent administration. Hence sustained or prolonged release dosage forms are formulated to reduce the dosing frequency thereby improving patient compliance. Main objective of the work is to formulate sustained or prolonged dosage form by adopting direct granulation method using Carbopol 974P, guar gum and Eudragit RS 100 as a retarding material at different concentrations. All the formulations are evaluated for hardness, friability, thickness, weight uniformity, content uniformity and *in vitro* dissolution studies and followed by stability and kinetics study for the best formulation among them.

KEYWORDS: Ranolazine, Carbopol 974P, guar gum, Eudragit RS 100, *in vitro* dissolution and sustained release tablets.

INTRODUCTION

Oral route of drug administration is most appealing route for delivery of drugs of various dosage forms. The tablets is one of the most preferred dosage form because of its ease of administration, accurate dosing and stability as compared to oral liquid dosage forms and when compared to capsules, tablets are more temper evident. Tablets may be defined as solid unit pharmaceutical dosage forms containing drug substance with or without suitable

excipients and prepared by either compression or molding methods. The first step in the development of dosage form is pre-formulation, which can be defined as investigation of physicochemical properties of drug substance alone and when combined with excipients. The main objective of pre-formulation studies, is to develop stable dosage form and study of factors affecting such stability, bioavailability and to optimize so as to formulate the best dosage form, here optimization of formulation means finding the best possible composition. Compressed tablets are formed by applying pressure, for which compression machines (tablet presses) are used and they are made from powdered crystalline or granular material, alone or in combination with binder, disintegrants, release polymers, lubricants and diluents and in some cases colorant.[1]

After oral administration, a peak plasma concentration of ranolazine is reached between 2 and 5 hours. After oral administration of ^{14}C-ranolazine as a solution, 73% of the dose is systemically available as ranolazine or metabolites. The bioavailability of ranolazine from the extended dosage form relative to that from a solution of ranolazine is 76%. Because ranolazine is a substrate of P-glycoprotein (P-gp), inhibitors of P-gp may increase the absorption of ranolazine. Food especially high fat breakfast has no important effect on the C_{max} and AUC of ranolazine. Therefore, ranolazine may be taken without regard to meals. Over the concentration range of 0.25 to 10 µg/mL, ranolazine is approximately 62% bound to human plasma proteins.

In the present study ranolazine sustained release matrix tablets using natural gums and synthetic polymers as a matrix forming materials were prepared. Due to the low biological half-life it requires frequent administration. Hence sustained or prolonged release[2,4] dosage forms are formulated to reduce the dosing frequency thereby improving patient compliance. Main objective of the work is to formulate sustained or prolonged dosage form by adopting direct granulation method using Carbopol 974P and natural gum (guar gum) and Eudragit RS 100 as a retarding material at different concentrations. All the formulations are evaluated[5] for hardness, friability, thickness, weight uniformity, content uniformity and *in vitro* dissolution studies and followed by stability and kinetics study for the best formulation among them.

MATERIALS AND METHODS

Materials

Ranolazine was obtained as a gift sample from Zydus Cadila Healthcare Ltd. Guar Gum purchased from Shree Scientific Chemical, Hyderabad. Eudragit RS100 was kindly gifted by Evonic India Pvt. Ltd. Mumbai, India. Carbopol 974P was procured from Lupin Research Park, Pune, India. Magnesium stearate and talcum powder were manufactured by Loba Chemicals. All chemicals used for analysis were analytical grade.

Pre formulation studies

Pre formulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

Preparation of standard stock solution

100 mg pure drug was taken in 100 ml volumetric flask and the volume is made up with buffer solution. From this 1ml is taken and diluted to 10 ml in a 10 ml volumetric flask. From this 1 ml is taken and diluted to 10 ml in a 10 ml volumetric flask to get10 µg/ml concentration of solution. From the standard stock solution 0.5 ml was transferred into 100 ml volumetric flask. The volume was diluted to 100 ml with buffer solution (0.1N HCl) to obtain a solution of strength 5 µg/ml was scanned between 200 to 400 nm. Finally samples were analyzed at a λ max of 262 nm.

Drug excipient compatibility studies

Fourier transform infrared (FTIR) analysis

FT-IR analysis[6,21] of pure drug, individual polymer and combination of drug and polymers in higher concentration were taken for the study. Samples were compressed with potassium bromide and transformed into disk and scanned between 4000-400 cm^{-1} in a SHIMADZU FT-IR (IR Affinity-1) spectrophotometer 12.

Preparation of sustained release of ranolazine

In the present work sustained-release (SR) matrix tablets of ranolazine were prepared by using different polymers like guar gum, Eudragit RS 100, Carbopol 974P. Out of different granulation technologies[7,11] direct compression[12,14] technique was used to prepare the SR tablets. All the ingredients including drug were weighed accurately and passed through 60 mesh sieve separately. The drug and polymer was mixed by small portion of both each time

and blend it to get a uniform mixture and kept aside. Then all the ingredients weighed and kept aside. Then all the ingredients weighed are mixed in geometrical order excluding magnesium stearate and talc to get a uniform blend. Finally mixture is blended with magnesium stearate and tablets were compressed of 13 mm sized concave round punch to get tablet using Cadmach compression machine. Compositions of all batches are represented in Table 1. The compressed tablets were evaluated to study the effect of nature of the polymer and also the drug to polymer ratio on the rate of drug release profile from the tablet formulations including relevant kinetic profiles.

Evaluation of Ranolazine Sustained Release Tablets[22]

Thickness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using Vernier caliper. Average thickness and standard deviation values were calculated.

Hardness

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

Friability test

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, deducted and reweighed. The friability was calculated as the percentage weight loss.

% Friability = $(W_1 - W_2) \times 100/W_1$

Where, W_1= Initial weight of the 20 tablets; W_2 = Final weight of the 20 tablets after testing.

Weight variation test

To study weight variation individual weights (W_I) of 20 tablets from each formulation were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

% weight variation = $(W_A - W_I) \times 100/ W_A$

As the total tablet weight was 100 mg, according to IP 1996, out of twenty tablets ±10% variation can be allowed for not more than two tablets. According to USP 2004, ±10% weight variation can be allowed for not more than two tablets out of twenty tablets.

Disintegration test

For most tablets the first important step toward solution is break down of tablet into smaller particles or granules, a process known as disintegration. This is one of the important quality control tests for disintegrating type tablets. Six tablets are tested for disintegration time using USP XXII apparatus. Disintegration type conventional release tablets are tested for disintegrating time.

Drug content (Assay)

The drug content in each formulation was determined by triturating 10 tablets and powder equivalent to 10 mg was added in 100 ml of pH 6.8 phosphate buffer followed by stirring for 10 minutes. The solution was filtered through a 0.45 µ membrane filter, diluted suitably and the absorbance of resultant solution was measured by using Elico UV-Visible spectrophotometer at 262 nm using pH 6.8 phosphate buffers.

***In vitro* drug release characteristics**

Drug release was assessed by using dissolution test apparatus USP type II (paddle method). The *in vitro* release of ranolazine tablets was studied in 900 ml of 0.1N HCl for 2 h at 37±0.5°C at 50 rpm, and then release studies were conducted in pH 6.8 phosphate buffer for 16 h. Aliquot (5 ml) was withdrawn at specific time intervals and replaced with the same volume of pre warmed (37°C ± 0.5°C) fresh dissolution medium. The absorbance values were analyzed by UV-visible spectrophotometer at 262 nm. All the experiments were conducted in triplicates (n=3).

Kinetic analysis of dissolution data

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate equation (Eq. 1) describes the systems where the drug release rate is independent of its concentration.[15] The first order equation (Eq. 2) describes the release from system where release rate is concentration dependent. Higuchi described[16] the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion equation (Eq. 3). The Hixson-Crowell cube root law[17] equation (Eq. 4)

describes the release from systems where there is a change in surface area and diameter of particles or tablets.

$C = K_0 t$ (1)

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$\text{Log } C = \text{Log } C_0 - K_1 t / 2.303$ (2)

Where, C_0 is the initial concentration of drug and K_1 is first order constant.

$Q = K_H t^{1/2}$ (3)

Where, K_H is the constant reflecting the design variables of the system.

$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t$ (4)

Where, Q_t is the amount of drug remained in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

Mechanism of drug release

Korsmeyer *et.al* derived a simple relationship which described drug release from a polymeric system equation (Eq. 5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer Peppasmodel.[18,23]

$M_t / M_\infty = Kt^n$ (5)

Where M_t / M∞ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent. The n value is used to characterize different release mechanisms. A plot of log cumulative % drug release vs. log time was made. Slope of the line was 'n'. The 'n' value is used to characterize different release mechanisms for the cylindrical shaped matrices. Case-II generally refers to the erosion of the polymeric chain and anomalous transport (Non- Fickian) refers to a combination of both diffusion and erosion controlled-drug release (Peppas, 1985).

Stability studies and sample preparation method for stability studies

Excipients that are likely to be used in the formulation will be identified. Appropriate quantities of the drug and excipients were weighed in different ratios as mentioned in table. The weighed drug and the excipients will be blended physically and will be transferred to glass vials and sealed. The sealed vials are placed inside stability chambers at 25°C/60%RH,

30°C/75%RH, 40°C/75%RH & 60°C. Samples were analyzed for physical appearance, assay and the solid state property of the drug in the blended mixture ratios.

RESULTS AND DISCUSSION

Calibration curve of the pure ranolazine drug was prepared in the concentration range of 20-100 µg/ml at the wavelength of 262 nm. The calibration curve showed good linearity and regression coefficient was 0.999 (r^2). Calibration curve was given in Fig. 1.

Physical characteristics

Characterization of powder formulations

The formulation powders before compression were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and drug content. Angle of repose was less than 35° and Carr's index values were less than 12 for the raw material of all the batches indicating good to fair flow ability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties. The drug content was more than 90% for all the granules of different formulations. All the parameters were postulated in the Table 2.

Physical evaluation of sustained release tablets

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in Table 3. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between ±5mg. The hardness of the tablets ranged from 5.5 to 10 Kg/cm^2 and the friability values were less than 1% indicating that the matrix tablets were compact and hard. The thickness the tablets ranged from 6.35 to 6.75 mm. All the formulations satisfied the content of the drug as they contained 90 to 101% of ranolazine and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practice within control.

Drug-polymer interaction/ compatibility study using FTIR

Physical mixture of drug and polymer was characterized by FTIR spectral analysisfor any physical as well as chemical alteration of drug characteristics. The functional groups like CN- (1400.37), CH- (934.54), NH- (3370.72), NH- (635.57) and NH_2 (3173.97) were unaltered. From results, it was concluded that there was no interference in the functional group as the principle peaks of ranolazine were found to be unaltered in the drug polymer physical mixture. FTIR spectra's were given in Fig. 2-5.

In vitro dissolution[19,20] and release kinetics

The results of release studies of formulations F1 to F9 are shown in Fig. 6-8. Here the press coated tablets were formulated using Eudragit RS 100, Carbopol 974P, guar gum. The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. As the percentage of polymer decreased, the kinetics of release increased. Formulations F1, F2 and F3 had shown 85.81, 83.29 and 80.17% of drug release in 16 h respectively. Formulations F4, F5, F6, F7, F8 and F9 had shown a drug release of 94.28, 90.16, 89.25, 98.20, 95.12 and 93.7% respectively in 20 h. Sustained release was found with F7 product, where the formulation consists of guar gum polymer. Guar gum is having high viscous nature when compared to Eudragit RS 100, Carbopol 974P. Overall F7 was considered as optimized formulation with respect to sustained release properties.

Kinetic analysis of dissolution data

The release rate kinetic data for the F7 is shown in Table4 and Fig. 9- 12drug release data was best explained by first order equation, as the plots showed the highest linearity (r^2= 0.9873), followed by Higuchi's equation (r^2= 0.9295). As the drug release was best fitted in first order kinetics, indicating that the rate of drug release is concentration dependent. Higuchi's kinetics explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases. As shown in Fig.12 the corresponding plot (log cumulative percent drug release Vs log time) for the Korsmeyer Peppas equation indicated a good linearity (r^2= 0.9477). The diffusion exponent "n" was between 0.45-0.89, which appears to indicating the diffusion mechanism is non-fickian diffusion and indicates that the drug release was controlled by more than one process (both diffusion and dissolution).

Stability Studies

The selected formulation F7 was evaluated for stability studies. The tablets were stored at $40^{o}c\pm2^{o}c/75\%\pm5\%$ RH for 1 month and analyzed for their physical parameters and drug content after one month interval. Based on the results indicated that, there was no interaction between the drug substances and the chosen excipients and hence these excipients were considered for the use in the development of the formulation. The stability results were given in Table 5.

Table 1: Composition of ranolazine sustained release tablets.

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ranolazine	500	500	500	500	500	500	500	500	500
MCC	190	165	140	190	165	140	190	165	140
Lactose	190	165	140	190	165	140	190	165	140
Edragit RS100	100	150	200	-	-	-	-	-	-
Carbopol 974P	-	-	-	100	150	200	-	-	-
Guargum	-	-	-	-	-	-	100	150	200
Talc	10	10	10	10	10	10	10	10	10
Mg. stearate	10	10	10	10	10	10	10	10	10
Total weight (mg)	1000	1000	1000	1000	1000	1000	1000	1000	1000

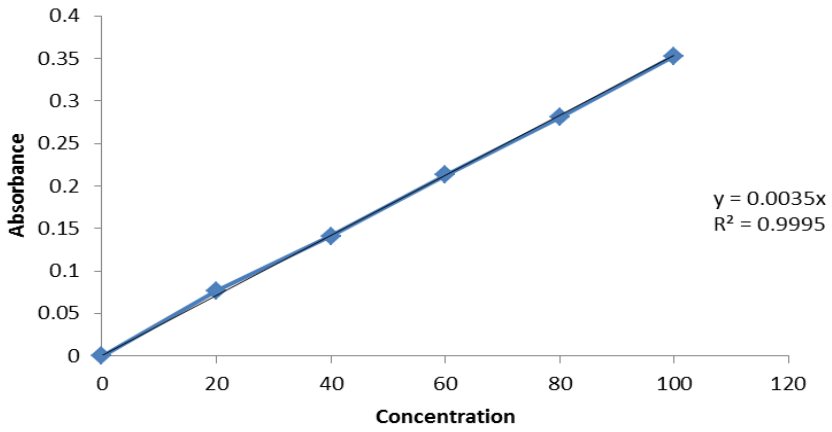

Figure 1: Standard graph of ranolazine in 6.8 pH phosphate buffer.

Table 2: Physical properties of ranolazine(API) and formulations.

Formula code	Angle of repose(°)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio
API	30	0.44	0.49	11.60	1.13
F1	22.5	0.607	0.647	6.18	1.066
F2	21.6	0.566	0.626	9.58	1.106
F3	28.4	0.556	0.612	9.15	1.10
F4	27.2	0.55	0.62	11.29	1.127
F5	24.96	0.611	0.639	4.38	1.046
F6	26.06	0.614	0.646	4.95	1.052
F7	25.03	0.596	0.652	9.39	1.09
F8	23.5	0.599	0.631	5.34	1.05
F9	24.61	0.28	0.28	14.28	1.1

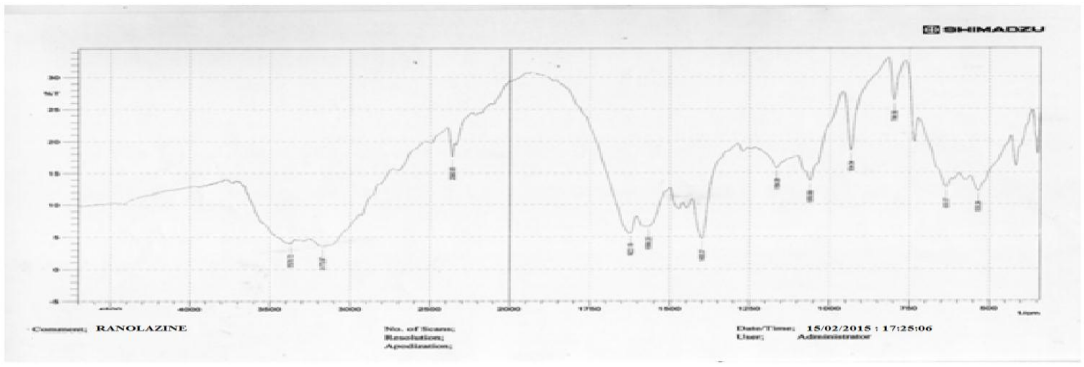

Figure 2: FTIR spectral analysis of ranolazine.

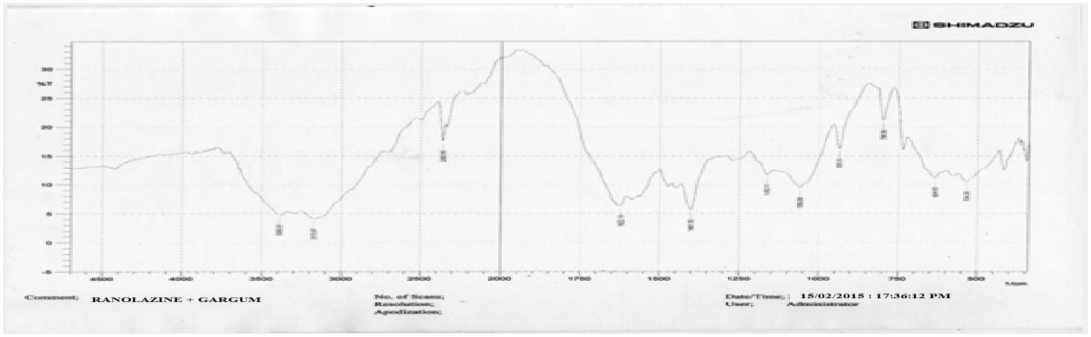

Figure 3: FTIR spectral analysis of physical mixture of drug and polymer (ranolazine + Guar gum).

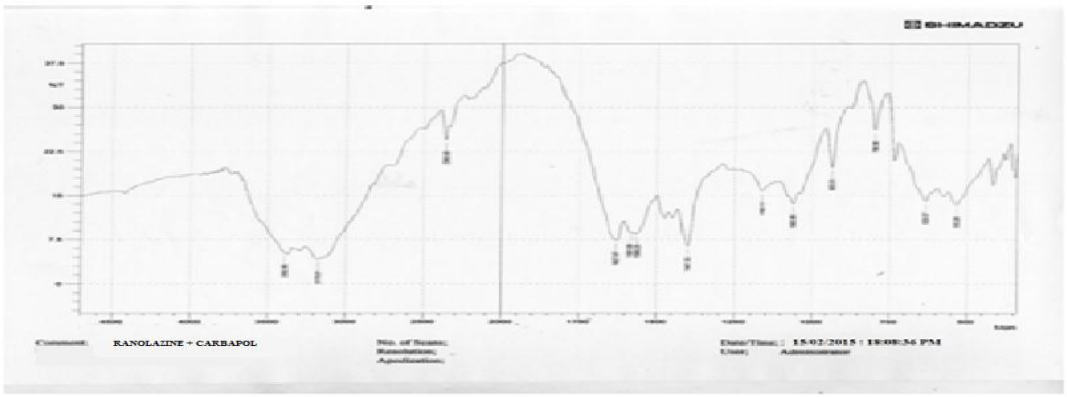

Figure 4: FTIR spectral analysis of physical mixture of drug and polymer (ranolazine + Carbopol 974P).

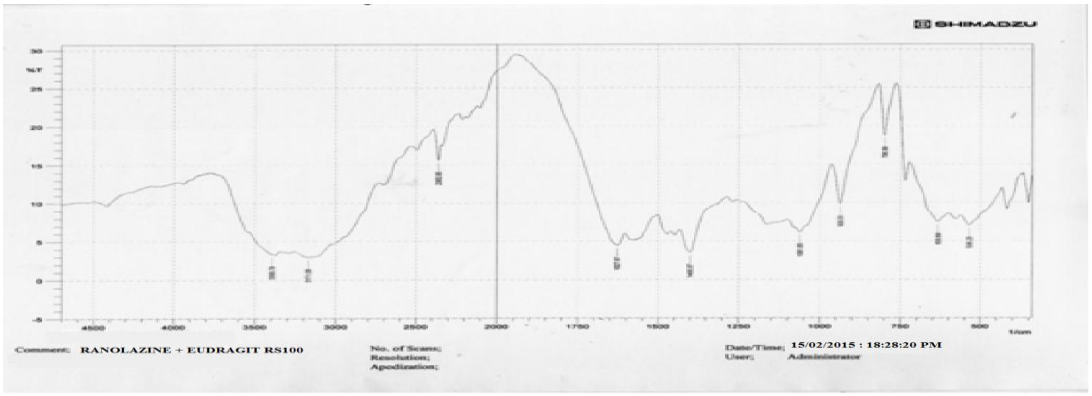

Figure 5: FTIR spectral analysis of physical mixture of drug and polymer (ranolazine + Eudragit RS100).

Table 3: Physical evaluation of press coated tablets.

Formula code	Hardness (kg/cm^2)	Thickness (mm)	Weight (mg)	Friability (%)	Drug content (%)
F1	7.75±0.15	6.45±0.07	999.15±4.16	0.75	100±1.14
F2	7.90±0.14	6.24±0.07	1001.2±5.17	0.48	98±0.80
F3	7.12±0.07	6.44±0.05	1000.4±3.21	0.55	99±2.47
F4	7.30±0.11	6.27±0.04	998.3±6.24	0.72	98±1.87
F5	7.25±0.15	6.44±0.07	1003.9±5.23	0.30	97±1.22
F6	7.05±0.14	6.69±0.09	1002.6±4.78	0.21	99±1.37
F7	7.23±0.04	6.05±0.06	1000.5±1.24	0.42	99±1.17
F8	7.74±0.12	6.24±0.23	1001.2±2.35	0.30	99±1.20
F9	7.4±0.033	6.05±0.022	999.5±1.24	0.42	99±1.17

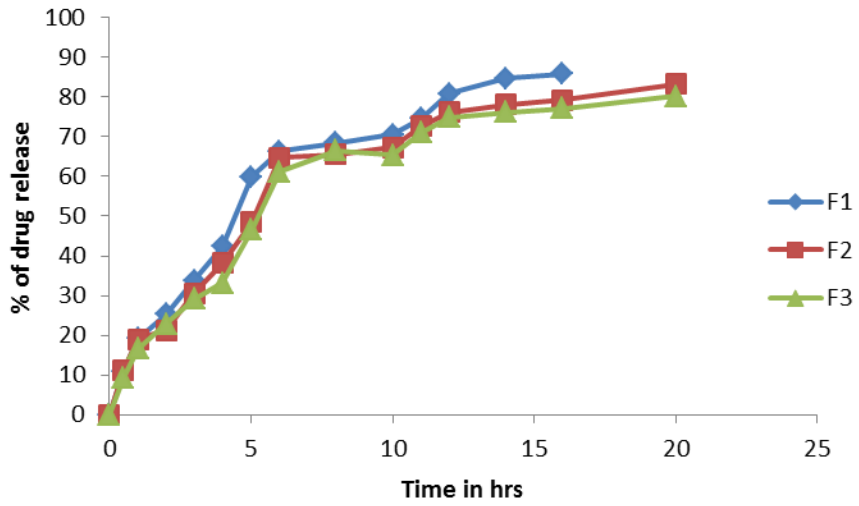

Figure 6: Percentage cumulative drug release *in-vitro*release data of sustained release tablet sranolazine from F1- F3 formulations.

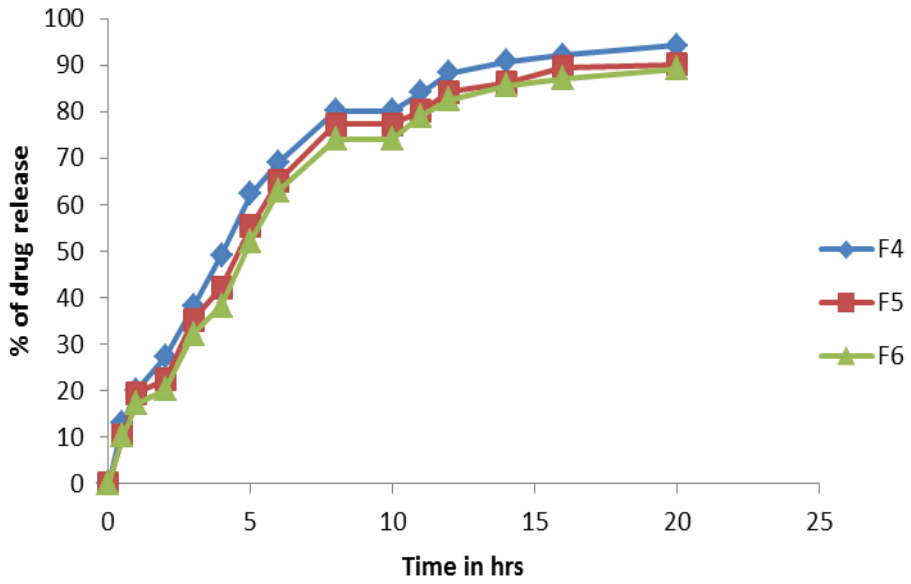

Figure 7: Percentage cumulative drug release *in-vitro* release data of sustained release tabletsranolazine from F4- F6 formulations.

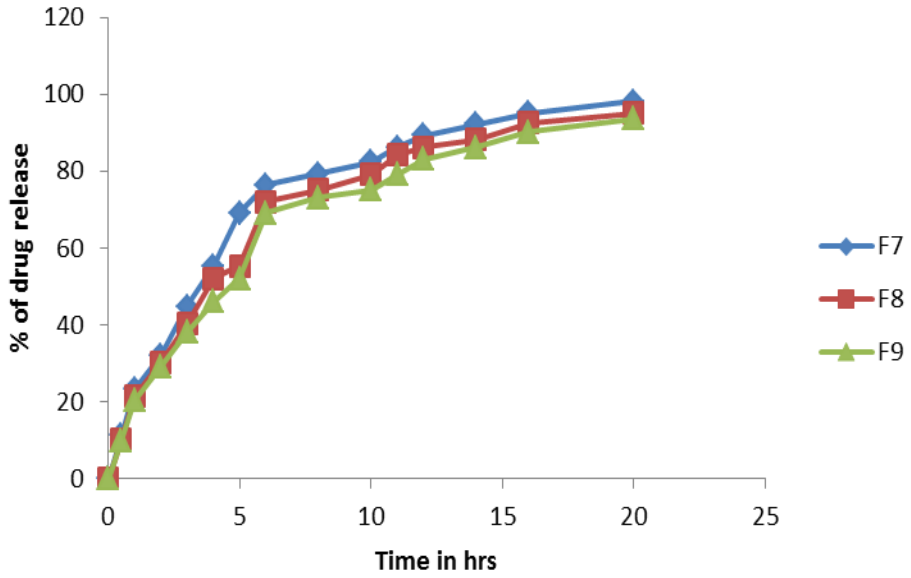

Figure 8: Percentage cumulative drug release *in-vitro*release data of sustained release tabletsranolazine from F7- F9 formulations.

Table 4: Drug release kineticsof F7 optimized formulationsustained release tablets.

Time	Log time	Square root of time	Cumulative % drug released	Log cumulative % drug released	Cumulative % drug remained	Log cumulative % drug remained
0	0	1.000	-	-	100	2.0000
0.5	0.7071	-0.3010	11.15	1.04727	88.85	1.948657
1	1.000	0.000	23.22	1.36586	76.78	1.885248
2	1.4142	0.3010	32.14	1.50704	67.86	1.831613
3	1.7320	0.4771	44.72	1.65050	55.28	1.742568
4	2.000	0.6020	55.28	1.74256	44.72	1.650501
5	2.2360	0.6989	69.14	1.83972	30.86	1.489395
6	2.4494	0.7781	76.30	1.88252	23.70	1.374748
8	2.8284	0.9030	79.21	1.89878	20.79	1.317854
10	3.1622	1.000	82.30	1.91539	17.70	1.247973
11	3.3166	1.0413	86.10	1.93500	13.9	1.14301
12	3.4641	1.0791	89.24	1.95055	10.76	1.031812
14	3.7416	1.1461	92.12	1.96435	7.88	0.896526
16	4.000	1.2041	95.10	1.97818	4.90	0.690196
20	4.4721	1.3010	98.20	1.99211	1.80	0.255272

*r^2 = Correlation coefficient; K = Kinetic constant; n= Diffusion exponent.

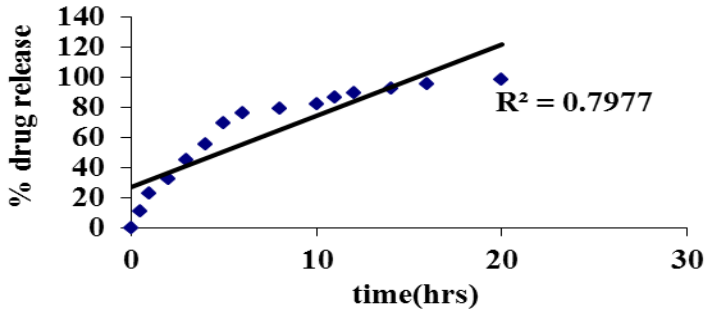

Figure 9: Zero order graph of optimized formulation (F7).

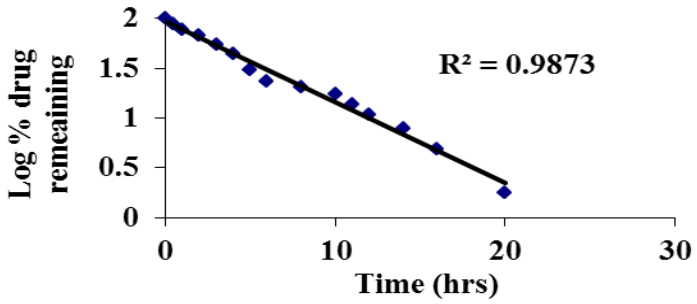

Figure 10: First order graph of optimized formulation (F7).

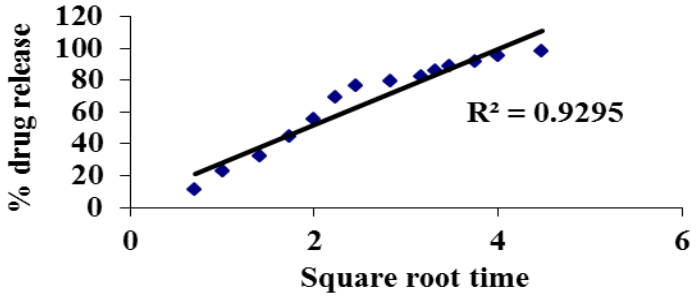

Figure 11: Higuchi plot of optimized formulation (F7).

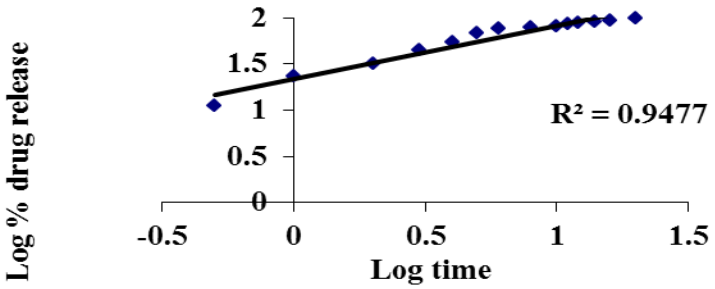

Figure 12: Korsmeyer-Peppas plot for optimized formulation (F7).

Table 5: One month stability data of ranolazine tablets.

S. No.	Test	Test conditions			
		25°C/60%RH	30°C/65%RH	40°C/75%RH	60°C
1	Description	White coloured	White coloured	White coloured	White coloured
2	Assay (%)	98.8	98.8	98.7	98.7
3	Hardness	7.23	7.04	7.04	7.04
4	Friability	0.21	0.29	0.29	0.30
5	Thickness	6.69	6.69	6.68	6.68

CONCLUSION

The present study was undertaken with an aim to design oral sustained release tablet of ranolazine. Results indicated that release of the drug from the tablet 10% guar gum, as polymers for sustained release layer showed desired drug release. So, sustained release tablets could be a potential dosage form for delivering ranolazine. Success of the *in-vitro* drug release studies recommends the product for further *in vivo* studies.

ACKNOWLEDGEMENTS

Authors are thankful to the St. Ann's College of Pharmacy to carry out this project.

REFERENCES

1. Lachman L, Liberman HA, King JL. The theory and practice of I.P" 3rd edition (a) chapter 14 in S.R dosage form, 430-456.
2. Kovvasu SP, Kunamaneni P, Janjanam KC. Formulation and optimization of controlled release paroxetine hydrochloride tablets using response surface methodology. J Global Trends Pharm Sci, 2016; 7: 3520-3534.
3. Colombo P, Bettini R, Massimo G. Drug diffusion front movement is important in drug release control from swellable matrix tablets. J Pharm Sci, 1995; 84(8): 99-997.
4. Colombo P, Bettini R, Santi P, Peppas NA. Swellable matrices for controlled drug delivery: gel-layer behavior, mechanisms and optimal performance. Pharm Sci Technol Today., 2000; 3: 198-204.
5. USP 27/NF 22, Asian edition, General test procedures, U.S. Pharmacopoeial convention, Rockville MD, 2004; 1.
6. Kovvasu SPR, Chowdary KPR. Formulation development and *in vivo* evaluation of pioglitazone inclusion complexes: A factorial study. Int J Applied Pharmaceu, 2018; 10(3): 49-55.
7. Chowdary KPR, Prakasarao KS. Formulation development of etoricoxib tablets employing HP β cyclodextrin- Poloxamer 407- PVP K30: A factorial study. Asian J Pharmaceu Clin Res, 2012; 5(1): 161-164.
8. Chowdary KPR, Prakasarao KS. Formulation development of pioglitazone tablets employing β cyclodextrin-Poloxamer 407-PVP K30: A factorial study, Der Pharmacia Lettre, 2011; 3(6): 24-30.
9. Shanmugam S. Granulation techniques and technologies: recent progresses. Bioimpacts, 2015; 5(1): 55-63.
10. Chowdary KPR, Prakasarao KS, Madhuri D. Formulation and evaluation of etoricoxib tablets employing cyclodextrin- Poloxamer 407- PVP K30 inclusion complexes. Int J Applied Bio Pharmaceu Tech, 2011; 2(4): 43-48.
11. Parikh DM. Anonymous. Handbook of pharmaceutical granulation technology. 3rd ed. editor. Marcel Dekker, INC.; 2009.
12. Chowdary KPR, Sundari PT, Prakasarao KS. Formulation and evaluation of piroxicam and aceclofenac tablets employing Prosolve by direct compression method. Asian J Chem, 2009; 21(8): 5847-5850.
13. Anonymous. Pharmaceutics: The Science of Dosage Form Design. 2nd ed. Churchill Livingstone, 2001.

14. Chowdary KPR, Sundari PT, Prakasarao KS.Formulation and evaluation of piroxicam and celecoxib tablets employing Prosolve bydirect compression method. Int J Chem Sci, 2008; 6(3): 1270-1275.
15. Hadjiioannou TP, Christian GD, Koupparis MA. Quantitative calculations in pharmaceutical practice and research. VCH Publishers Inc, New York, NY, 1993; 345-348.
16. 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: 1145-1149.
17. Hixson AW, Crowell JH. Dependence of reaction velocity upon surface and agitation, I-theoretical consideration. Ind Eng Chem., 1931; 23: 923-931.
18. Korsmeyer RW, Gurny R, Doelker E, Buri P. Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm, 1983.
19. Chowdary KPR, Prakasarao KS.Individual and combined effects of cyclodextrins, Poloxamer and PVP on the solubility and dissolution rate of BCS class II drugs. Asian J Chem, 2011; 23(10): 4520-4524.
20. Chowdary KPR, Prakasarao KS, Sunkavalli V. A factorial study on the effects of hydroxypropylβ cyclodextrin and Poloxamer on the solubility and dissolution rate of nimesulide. Int J Pharmaceu Sci Res, 2012; 3(2): 460-464.
21. Mulagada S, Baratam SR. Design and evaluation of ondansetron fast disintegrating tablets using natural polymers and modified starches as super disintegrants for the enhancement of dissolution. J Young Pharm., 2017; 9(4): 519-24.
22. S Rao, Ratnam BV. Formulation and Optimization of Sustained Release Tablets of Rosuvastatin Using HPMC K4M, HPMC K100M and Carrageenan. Int J Chem Tech Res., 2018; 11(5): 376-386.
23. Baratam SR, V Ratna J. Formulation and evaluation of floating matrix tablets of levofloxacin hemihydrate using hydroxypropyl methylcellulose k4m to treat helicobacter pylori infection. Asian J Pharm Clin Res., 2018; 11(6): 1-4.