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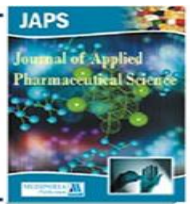

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Development of Sustain Release Matrix Tablet of Ranolazine Based on Methocel K4M CR: In Vitro Drug Release and Kinetic Approach

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ABSTRACT

In this study an attempt was made to design and evaluate oral sustained release matrix tablets of ranolazine using Methocel K4M CR as the retardant polymer. Tablets were prepared by conventional wet granulation technique. Tablets were evaluated for parameters such as weight variation, hardness, friability and drug content. All the formulations showed compliance with pharmacopieal standards. *In vitro* release studies were performed using USP type II apparatus (paddle method) in 900 mL of 0.1N HCl at 50 rpm for 8 hours. The release kinetics was analyzed using the zero-order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas equations to explore and explain the mechanism of drug release from the matrix tablets. *In vitro* release studies revealed that percent drug release decreased with increase of polymer loading. Based on the dissolution data comparison with innovator brand F-5 formulation (16% Methocel K4M CR w/w of drug) was elected as the best formulation. The drug release profile of the best formulation was well controlled and uniform throughout the dissolution studies. The drug release of optimized formulation follows the Higuchi kinetic model (R^2 = 0.99) and the mechanism is found to be non-Fickian/anomalous according to Korsmeyer–Peppas equation. All the formulations were checked for stability as per ICH guidelines and formulations were found stable during the study.

Keywords: Ranolazine, sustained release, Methocel K4M CR, kinetic approach.

INTRODUCTION

Conventional tablets are the most popular and available oral solid formulations that are preferred by physicians and patients. But conventional tablet formulations are not ideally suited to some drugs having high solubility in low pH and short plasma half-life. Ranolazine is such a novel drug that is freely soluble in aqueous buffered solutions at pH 4.4 or lower and its plasma half-life is 2.5±0.5 hours. Conventional tablet formulations of ranolazine result in rapid drug absorption and clearance causing large and undesirable fluctuation in plasma concentration that necessitates frequent oral administration for adequate treatment. On the other hand ranolazine is extensively metabolized in gut and liver and its absorption is highly variable. Sustain release (SR) tablet formulations are preferred for ranolazine because they maintain uniform drug levels, reduce dose and side effects, increase the safety margin for high-potency drugs and thus offer better patient compliance (Priya *et al*., 2011). Ranolazine was approved by the US FDA in January 2006 for the treatment of chronic stable angina in patients who have an inadequate response to traditional anti-anginals. It acts by pFOX (partial fatty acid oxidation) inhibition which is followed by increase in

the efficacy of myocardial oxygen use and consequently prevents or reduces ischemia. It is a reserved drug for the treatment of symptomatic chronic angina in patient with severe coronary artery. Following administration of an oral solution or IR capsule, peak plasma concentrations (C_{max}) are observed within 1 hour. The mean absolute bioavailability of ranolazine after oral administration of immediate rerelease ranolazine tablets ranged from 35−50%, with large inter-individual variability. Ranolazine is extensively metabolized by cytochrome P450 (CYP) 3A enzymes and, to a lesser extent, by CYP2D6. Approximately 5% unchanged drug excreted by renal route. Elimination half-life of ranolazine is only 1.4-1.9 hours that is not suitable for prolong action.

Sustained release oral delivery systems of ranolazine can help to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects (Vergnaud, 1993). Among the different approaches studied with this aim, matrix systems still appear as one of the most attractive from both the economic as well as the process development and scale-up points of view (Lordi, 1986). Due to above reasons several researchers reported various matrix tablet formulations for control release of ranolazine. Uddin *et al.,* 2009 and Rahman *et al.,* 2011 used different viscosity grades of HPMC as release retarding polymer. They used same but high polymer loading (up to 60%), but percent drug release were quiet different. Bidada *et al.,* 2011 used combination of Carbopol 971P, Ethyl cellulose N20 and Ethyl cellulose N50 for matrix formulation. Priya *et al.,* 2011 used Eudragit L100-55 as release retardant for 24 hour ranolazine release. Combination of polymer is some time better to control drug release but the efficacy depends on many factors such as proper selection of polymer, uniform mixing and absence of polymer-polymer interaction. The average time required for a dosage unit to pass the GIT is 5-7 hr and therefore 24 hour drug release matrix system may not be useful for reproducible uniform plasma drug level. So development of simple formulation for control release (CR) of ranolazine is still required.

In this study an initiative was taken to design oral sustained release matrix tablet formulations of ranolazine using Methocel K4M CR as the release retarding polymer and mannitol as channeling agent for delivery of ranolazine as twice daily regimen. Methocel K4M CR, a semi synthetic derivative of cellulose, is a swellable and hydrophilic polymer. It is very suitable to use as a retardant material in SR matrix tablets, as it is nontoxic and easy to handle (Cameron *et al.,* 1987). Matrix tablets prepared using Methocel K4M CR on contact with aqueous fluids gets hydrated to form a viscous gel layer through which drug will be released by diffusion and/or by erosion of the matrix (Perez-Marcos *et al.,* 1994). The tablets were prepared by conventional wet granulation technique and their physical parameters and *in vitro* release characteristics were evaluated. Stability of tablets (potency and drug release) was also studied to find out any excipients-drug interaction in the formulation.

MATERIALS AND METHODS

Materials

Chemicals: Ranolazine (Divis Laboratories Ltd., India), Methocel K4M CR (Colorcon Asia Pvt. Ltd.), Mannitol (Tuhin Chemicals, India), Microcrystalline Cellulose (Avicel PH 101) (Veer Pharma Chem, Ahmedabad, India), Magnesium Stearate (Chemical Management Co. Germany)

Reagents: Hydrochloric acid (Merck, Germany).

Equipments: Simadzu UV Spectophometer (Shimadzu, Model UV-160A, Kyoto, Japan)**;** Electro lab Tablet Dissolution Test machine (XXII)**;** Sartorius electronic balance, Thickness gauge (Campbell Electronics, India), Monsanto hardness tester (Campbell Electronics, India), Roche Friabilator (Campbell Electronics, India).

Preparation of matrix tablet

Matrix tablets of ranolazine were prepared using wet granulation technique. The composition of tablet is summarized in Table 1. Calculated amount (required to prepare a 50 tablet batch) of the drug (ranolazine), polymer (Methocel K4M CR), filler (Avicel PH 101) and channeling agent (Mannitol) were mixed thoroughly. Sufficient volume of the specified granulating agent (purified water) was added slowly and mixed. When enough cohesiveness was obtained, the granules were dried at 60°C for 2 hours in a tray dryer and there after kept in desiccators for 24 hours at room temperature. The LOD of the granules was kept between 2.5 to 3.0%. The dried granules were collected and screened through a #20 mesh sieve. Prior to compression, all prepared granules were evaluated for several tests such as Bulk Density, Compressibility Index and Angle of Repose. Magnesium Stearate was added as lubricant. Appropriate amount of the mixture was weighed (660 mg) and then compressed using a Shimadzu laboratory hydraulic press equipped with 18.1 x 8.1 mm, caplet shaped punch and die set. All compressed tablets were stored in an airtight container at room temperature for further study.

Table 1: Composition of ranolazine matrix tablets (mg/tablet).

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7
Ranolazine	500	500	500	500	500	500	500
Methocel K4M CR	52	59	66	73	80	87	94
Mannitol	60	60	60	60	60	60	60
Microcrystalline Cellulose (Avicel PH 101)	47	40	33	26	19	12	5
Mg-Stearate	1	1	1	1	1	1	1

Evaluation of Granules

Bulk Density

LBD (Loose Bulk Density) and TBD (Tapped Bulk Density) were determined by pacing 2 g of powder from each formula (previously lightly shaken to break any agglomerates formed) into a 10-ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals.

The reading of tapping was continued until no further change in volume was noted. Using the following equation LBD and TBD was calculated:

LBD = Weight of the powder / volume of the packing.
TBD = Weight of the powder / Tapping volume of the packing.

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index:

$$\text{Carr's index (\%)} = \{(TBD - LBD) \text{ X } 100\}/TBD$$

Angle of Repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$$\text{Angle of Repose } \theta = tan^{-1}\, h/r$$

Where, h = Height of the powder cone.
r = Radius of the powder cone

Evaluation of Tablets

Hardness and Friability

For each formulation, the hardness of 6 tablets and friability of 20 tablets were determined using the Monsanto hardness tester (Campbell Electronics, India) and the Electrolab friabilator (Electrolab, India) respectively.

Thickness

The thicknesses of the tablets were determined by using a thickness gauge (Campbell Electronics, India). Five tablets from each batch were used and average values were calculated.

Weight Variation Test

To study weight variation, 20 tablets of each formulation were weighed using a Sartorius electronic balance and the test was performed according to the official method of British Pharmacopoeia.

Drug Content

Five tablets were weighed individually and the drug was extracted in 0.1N hydrochloric acid. The solution was filtered through 0.45-µ membrane filter paper. The absorbance was measured at 272 nm after suitable dilution by using a Simadzu UV Spectophometer (Shimadzu, Model UV-160A, Kyoto, Japan).

In Vitro Release Studies

For dissolution simulated gastric medium (pH 1.2) prepared by mixing 8.6 ml of hydrochloric acid (37% w/v) with sufficient water to produce 1000 ml was used. The release rates of ranolazine sustain release tablet was determined using US FDA Dissolution Guide line. Dissolution Testing Apparatus was apparatus 2 (paddle method). The dissolution test was performed using 900 ml medium at 37 ±0.5°C and 50 rpm. The medium was preheated to 37°C, added to the vessels and was allowed to equilibrate for 15 min. Six tablets from each formulation were weighed and placed in the baskets. The operation was carried out for 8 hours. After every 2 hours 10 ml of sample solution was withdrawn and filtered. The released drug was assayed by using UV spectrophotometer (Shimadzu, Model UV-160A, Kyoto, Japan) at 272 nm after suitable dilution. The amount of drug present in the samples were calculated from calibration curves constructed from the standard solution of reference standard.

Drug release kinetics

To study the release kinetics, data obtained form in vitro drug release study were tested with the following mathematical model.

Zero order equation

The equation assumes that the cumulative amount of drug release is directly related to time. The equation may be as follows:

$$C = K_0\, t \text{---------- (1)}$$

Where, K_0 is the zero order rate constant expressed in unit concentration/time and t is the time in hour. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

First order equation

The release behavior of first order equation is expressed as log cumulative percentage of drug remaining vs time. The equation may be as follows (Wagner, 1969):

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

Where,

C = The amount of drug un-dissolved at t time,
C_0 = Drug concentration at $t = 0$,
k = Corresponding release rate constant.

Higuchi square root law

The Higuchi release model describes the cumulative percentage of drug release vs square root of time. The equation may be as follows (Higuchi, 1961):

$$Q = K\sqrt{t} \text{ ---------- (3)}$$

Where, Q = the amount of drug dissolved at time t. K is the constant reflecting the design variables of the system. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Hixson-Crowell cube root law

It is the law that represents idea about the evaluation of drug release pattern changes with the surface area and the diameter of the particles/tablets (Hixon *et al.,* 1931). It is mentioned as the

cube root of the percentage of drug remaining in the matrix vs time. The equation may be as follows

$$Q_0^{1/3} - Q_t^{1/3} = k_{HC} \times t \text{ ---------- (4)}$$

Where,

Q_0 = Initial amount of the drug in the tablets.

Q_t = The amount of drug release in time 't'.

k_{HC} = The rate constant for the Hixson-Crowell cube root law.

Korsmeyer–Peppas equation

Korsmeyer *et al* developed a simple, semi-empirical model relating exponentially the drug release to the elapsed time . The equation may be as follows:

$$Q/Q_0 = Kt^n \text{ ---------- (5)}$$

Where,

Q/Q_0 = The fraction of drug released at time '*t*'.

k = Constant comprising the structural geometric characteristics.

n = The diffusion exponent that depends on the release mechanism.

If $n \leq 0.5$, the release mechanism follows a Fickian diffusion, and if $0.5 < n < 1$, the release follows a non-Fickian diffusion or anomalous transport (Peppas, 1985). The drug release follows zero order drug release and case II transport if n=1. But when n>1, then the release mechanism is super case II transport. This model is used in the polymeric dosage form when the release mechanism is unknown or more than one release phenomena is present in the preparation.

Stability studies

Stability studies were done according to ICH guidelines to assess the drug and formulation stability (Cartensen, 1995). All the formulations were subjected to stability study at 40 ± 2ºC and 75 ± 5% RH for 90 days. The samples were evaluated for physical changes, hardness, friability, drug content and percentage drug release during the stability studies.

RESULTS AND DISCUSSION

Characterization of granules

The granules of different proposed formulations (F-1 to F-7) were evaluated for LBD, TBD, compressibility index and angle of repose (Table 2). The results of LBD and TBD ranged from 0.421 to 0.516 g/cm^3 respectively. The bulk densities of granules of the proposed formulation F-4 to F-7 were quite higher than those of other granules. This may be due to the presence of more fine granules. The results of compressibility index (%) ranged from 11.43 to 21.43. Generally, compressibility index values up to 15% result in good to excellent flow properties. So the granules of F-3 to F-7 showed good flow properties than other granules. The results of angle of repose ranged from 24 to 32. The results of angle of repose (<30°) indicate good flow properties of granules which was supported the results found from compressibility index. All these results indicate that the granules possessed satisfactory flow properties and compressibility.

Physicochemical evaluation of matrix tablets

The results of physical parameters (weight, hardness, thickness and friability) and drug content of the prepared matrix tablets are shown in Table 3. The thickness of the tablets were found between 5.21 ± 0.01 mm to 5.31 ± 0.09 mm, hardness of the tablets ranged from 8.69 ± 0.52 kg/cm^2 to 9.29 ± 0.14 kg/cm^2 and friability ranged from 0.10% to 0.17%.The weight variations of prepared tablets complied with the pharmacopoeial specifications. The drug content of every formulation was found about to 100% of labeled content. So it can be said that physical properties and drug content of the compressed matrix tablets were satisfactory.

Table 2: Physical properties of the prepared granules of different formulations.

Parameters	F-1	F-2	F-3	F-4	F-5	F-6	F-7
LBD (g/cm^3)	0.421	0.432	0.461	0.493	0.501	0.512	0.516
TBD (g/cm^3)	0.51	0.503	0.522	0.557	0.563	0.57	0.575
Compressibility Index (%)	21.43	16.44	12.8	12.98	12.38	11.33	11.43
Angle of Repose	32	30	29	28	26	25	24

Table 3: Physical properties of the prepared tablets of different formulations.

Formulations	Thickness (mm) ± SD (n = 5)	Hardness (N) ± SD (n = 6)	Friability (%) (n = 20)	Weight (mg) ± SD (n = 20)	Drug Content (%) ± SD (n = 5)
F-1	5.21 ± 0.01	8.90 ± 0.60	0.17%	659.44 ± 2.34	100.60 ± 0.59
F-2	5.25 ± 0.07	9.13 ± 0.37	0.15%	662.10 ± 1.11	99.53 ± 0.37
F-3	5.29 ± 0.10	8.82 ± 0.08	0.15%	658.73 ± 3.20	97.80 ± 0.42
F-4	5.30 ± 0.03	8.73 ± 0.24	0.14%	660.05 ± 1.62	100.67 ± 0.71
F-5	5.24 ± 0.06	9.29 ± 0.14	0.10%	661.27 ± 2.45	98.27 ± 0.47
F-6	5.22 ± 0.11	9.01 ± 0.33	0.10%	657.34 ± 1.74	99.00 ± 0.89
F-7	5.31 ± 0.09	8.69 ± 0.52	0.14%	658.45 ± 2.21	99.37 ± 0.19

SD- Standard deviation; n- Number of replicates.

***In vitro* release study**

The release profiles of different formulations (F-1 to F-7) of ranolazine matrix tablets are shown in Fig. 1. All dissolution data are based on the actual drug content of the test tablets as calculated from the assay results. As per the results of dissolution study formulations F1, F2, F3, F4, F5, F6, F7 showed 97.25%, 97.01%, 96.89%, 95.62%, 91.54%, 63.22% and 59.4% drug release in 8 hours respectively. This showed that the drug release from the tablet was sustained for 8 hr. Drug release decreased with increase of polymer loading as HPMC polymers form viscous gelatinous layer (gel layer) upon exposure to aqueous medium by undergoing rapid hydration and chain relaxation and this gel layer acts as the barrier to release of drug and as a result drug release is prolonged.

Drug release kinetics

The data from Table 4 shows that most of the formulations all the formulations were found to follow 1st order, Higuchi and Hixon Crowell release model. F-5 was best fitted in terms of 1st order release kinetics (R^2= 0.98), Higuchi model (R^2 = 0.99), Hixon-Crowell model (R^2= 0.99).

Table 4: Y-equation (Y = aX+b) and correlation co-efficient (R^2) from different plots of formulation F-1 to F-7.

Formula	Zero Order		1st Order		Higuchi Model		Hixson-Crowell Model	
	Y equation	R^2	Y equation	R^2	Y equation	R^2	Y equation	R^2
F-1	y = 10.32x + 27.11	0.784	y = -0.181x + 1.964	0.985	y = 33.98x + 8.247	0.964	y = -0.372x + 4.285	0.966
F-2	y = 10.60x + 23.68	0.828	y = -0.177x + 1.993	0.978	y = 34.24x + 5.369	0.981	y = -0.371x + 4.372	0.978
F-3	y = 10.91x + 18.23	0.895	y = -0.171x + 2.041	0.946	y = 34.19x + 1.101	0.996	y = -0.367x + 4.509	0.984
F-4	y = 11.10x + 13.92	0.937	y = -0.157x + 2.054	0.947	y = 33.97x - 2.205	0.996	y = -0.353x + 4.587	0.987
F-5	y = 10.94x + 11.03	0.954	y = -0.128x + 2.031	0.98	y = 33.10x - 4.237	0.99	y = -0.314x + 4.596	0.997
F-6	y = 7.557x + 11.14	0.892	y = -0.057x + 1.958	0.925	y = 24.40x - 1.022	0.973	y = -0.162x + 4.479	0.938
F-7	y = 7.486x + 6.707	0.924	y = -0.049x + 1.974	0.97	y = 22.37x - 2.803	0.979	y = -0.152x + 4.538	0.959

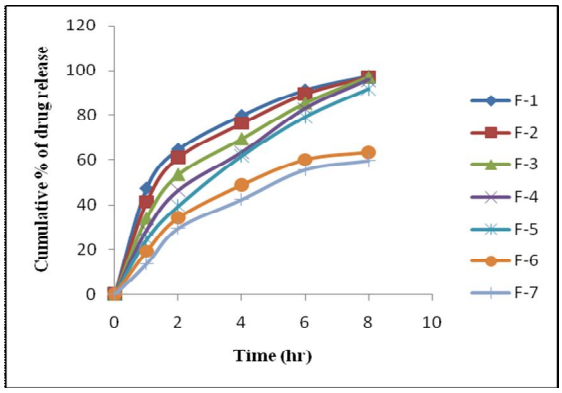

Fig: 1 Drug release from different formulations (F-1 to F-7)

Release Mechanism

To confirm the drug mechanism, the data were fitted into Korsmeyer–Peppas equation (table 5). Formulation F-1 to F-7 showed exponent (n) values ranging from 0.35 to 0.7, indicating that both Fickian diffusion (F-1 to F-3) and non-Fickian diffusion or anomalous transport non-Fickian/anomalous diffusion (F-4 to F-7) as if $n \leq 0.5$, the release mechanism follows a Fickian diffusion, and if $0.5 < n < 1$, the release follows a non-Fickian diffusion or anomalous transport (Peppas, 1985).

Table 5: Drug release rate parameters.

Formulation	K	n	R2	T80%	MDT
F-1	1.687	0.345	0.990	4.202	2.058
F-2	1.635	0.403	0.985	4.600	2.299
F-3	1.550	0.489	0.991	5.248	2.720
F-4	1.470	0.568	0.994	5.764	3.093
F-5	1.397	0.638	0.998	6.212	3.433
F-6	1.321	0.572	0.972	10.373	5.575
F-7	1.191	0.694	0.961	10.583	5.980

[Rate constant (K), release exponent (n), correlation co-efficient (R^2), time for 80% drug release (T80%) and release exponent (n)]

Comparison of dissolution data

Difference factor (f1), similarity factor (f2) and dissolution efficiency (%DE) were calculated to compare the dissolution profile with innovator brand. Difference factor f1 is the percentage difference between two curves at each point and is a measurement of the relative error between the two curves.

The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. The following equations were used to calculate difference factor f1 and similarity factor f2.

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} X100$$

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum_{i=1}^{n} (R_t - T_t)^2 \right)^{-0.5} X100 \right\}$$

where n is the number of time points, Rt is the dissolution value of reference product at time t and Tt is the dissolution value for the test product at time t.

Table 6: Comparison of dissolution (f1, f2 and %DE) data with innovator brand (IB).

Pair Comparison	f2	f1	%DE
IB			64.68
F-1	40.34	23.40	78.39
F-2	45.57	18.73	75.88
F-3	57.93	10.88	71.02
F-4	75.93	4.33	67.06
F-5	76.16	3.86	62.19
F-6	36.52	27.26	47.46
F-7	32.24	34.95	42.86

Dissolution efficiency is the area under the dissolution curve within a time range (t1 - t2). DE was calculated by using the following equation:

$$AUC = \sum_{i=1}^{i=n} \frac{(t_i - t_{i-1})(y_{i-1} + y_i)}{2}$$

Where *y* is the percentage dissolved at time '*t*'.

Table 6 shows the f1, f2 and % DE values of different brands in respect of innovator brand. Similarity factor f2 has been

adopted by FDA (1997) and the European Agency for the valuation of Medicinal Products (EMEA, 2001) by the Committee for Proprietary Medicinal Products (CPMP) to compare dissolution profile. Two dissolution profiles are considered similar and bioequivalent, if f1 is between 0 and 15 and f2 is between 50 and 100 (FDA, 1997). F-5 seems to be best similar to the innovator brand for higher f2 (76.16) and lower f1 value (3.86).

Stability study

Drug release and potency of different formulations (F-1 to F-7) after 90 days are summarized in table 7. Potency and drug release were almost similar with the initial values (Table 3 and Fig 1) which indicates that the there is no interaction between drug and polymer.

Table 7: Drug release and potency from different formulations (F-1 to F-7) after 90 days.

Time (Hour)	Cumulative % drug release						
	F-1	F-2	F-3	F-4	F-5	F-6	F-7
0	0	0	0	0	0	0	0
1	47.2	41.3	34.1	28.7	24.5	19.29	13.7
2	64.4	60.9	53.2	46.4	39.5	34.33	29.6
4	79.7	76.2	69.2	63.2	61.5	48.78	42.4
6	91	89.4	85.2	82.8	79	59.92	55.3
8	97.3	97	96.9	95.6	91.5	63.22	59.4
After 90 days	**Potency**						
	F-1	F-2	F-3	F-4	F-5	F-6	F-7
	101	99.2	97.4	99.5	98.2	99.02	99.1

CONCLUSION

The present study was undertaken with an aim to design oral sustained-release tablets of ranolazine for twice daily administration for the therapy of chronic angina. It can be concluded that the present study indicates that the oral sustained release tablets of ranolazine provides a better option for development of a twice daily formulation of the drug. Success of the *In vitro* drug release studies recommends the product for further in vivo studies.

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