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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF RANOLAZINE

M Vanaja kumari[1]*, P Venkateswar reddy[1] and M Sudhakar[2]

[1]Hetero drugs limited, Jeedimetla, Hyderabad-500055, India
[2]Department of Pharmaceutics, Malla Reddy College of Pharmacy, Dulapally, Secunderabad, India

***Corresponding author e-mail:** tappireddy@yahoo.co.in

ABSTRACT
The aim of the present study was to prepare and characterize the Sustained release matrix tablets of Ranolazine using Kollidon® SR. Kollidon® SR is a polyvinyl acetate based excipient. Three different strengths i.e 375mg, 500mg and 750mg of ranolazine SR tablets were prepared by direct compression method and by using common blend. The influence of compression force was studied on the dissolution release profile of Ranolazine SR tablets. In vitro release studies were performed for all the formulations using USP type II apparatus (paddle method) in 900 ml of 0.1N hydrochloric acid at 50 rpm for 24 hours and analyzed by UV spectrophotometer at 272nm. Further, in-vitro release pattern of drug from the optimized formulation was compared with innovator formulation and it was found to be super imposable with the Innovator product RANEXA based on dissimilarity and similarity factors.

Keywords: Ranolazine, Kollidon® SR and Sustained release

INTRODUCTION

A polyvinyl acetate based excipient for directly compressible matrix tablets by direct compression has attracted much attention due to its technological simplicity in comparison with other controlled release systems. It required fewer unit operations, less machinery, reduced number of personnel and processing time. Kollidon SR is derived from a polyvinyl acetate-dispersion and appears as a spray dried, non hygroscopic powder consisting of polyvinyl acetate (8 parts w/w) and polyvinyl pyrrolidone (2 parts w/w). Ranolazine is soluble[6] in dichloromethane and methanol; sparingly soluble in tetrahydrofuran, ethanol, acetonitrile, and acetone; slightly soluble in ethyl acetate, isopropanol, toluene, and ethyl ether; and very slightly soluble in water.
Ranolazine is indicated for the treatment of chronic angina, Ranolazine may be used with beta-blockers, nitrates, calcium channel blockers, anti-platelet therapy, lipid-lowering therapy and angiotensin receptor blockers. The recommended initial dose of Ranolazine is 375 mg twice daily. After 2–4 weeks, the dose should be titrated to 500 mg twice daily and, according to the patient's response, further titrated to a recommended maximum dose of 750 mg twice a daily. Ranolazine plasma half life[1] is 2.5±0.5hours. After oral administration of Ranolazine, peak plasma concentrations (C_{max}) are typically observed between 2 and 6 hours. Steady state is generally achieved within 3 days of twice-daily dosing. The terminal half-life at steady state after oral administration of ranolazine is about 7 hours, due to the absorption rate-limited elimination.

MATERIALS AND METHODS

Materials: Ranolazine (Hetero Drugs limited), Kollidon® SR (BASF AG), microcrystalline cellulose (FM**C** BioPolymer), Magnesium stearate (Ferro) and opadry yellow (colorcon).
Reagents: Hydrochloric acid.

Preformulation studies (compatibility studies): Preformulation study was conducted to determine the interaction of the ranolazine with kollidon SR,

microcrystalline cellulose and magnesium stearate. Ranolazine with the excipients in suitable proportions were filled in glass vials closed with rubber stoppers and kept at Accelerated and stress condition for 30days that is 40^0C/75%RH and 60^0C respectively.

Method of Preparation of Film Coated Tablets:

Matrix tablets of Ranolazine were prepared by using direct compression technique. The composition of tablets for different strengths was summarized in Table 1. Initially studies were performed on higher strength (750mg, F1-F3) due to common blend for all strengths; later studies were extended for strengths (500, 375mg i.e F4-F5). All the ingredients were weighed accurately as per the formula. Ranolazine, Kollidon® SR and Microcrystalline cellulose were passed through #20 mesh & collected in a polybag. Above sifted materials was loaded in a blender and mixed for 10minutes and Magnesium Stearate was passed through #40 mesh and loaded in a double cone blender and mixed for 5minutes. Prior to compression, all prepared granules were evaluated for several tests such as Bulk Density and Compressibility Index. Blended material was loaded in a hopper and compresses the powder into tablets by using compression machine with standard concave punches. Tablet evaluation tests like weight variation, hardness (Hardness tester), friability (Friabilator), and thickness were performed to meet the parameters. All compressed tablets were coated using opadry yellow.

Evaluation of Granules Bulk Density: LBD (Loose Bulk Density) and TBD (Tapped Bulk Density) was determined by placing 3 g of powder from each formula (previously lightly shaken to break any agglomerates) 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 were used for determining LBD and TBD
LBD = Weight of the powder / volume of the powder.

TBD = Weight of the powder / Tapping volume of the powder

Compressibility Index[4]: The compressibility index of the granules was determined by using following formula

Compressibility index (%) = {(*TBD* – *LBD*) X 100}/*TBD*.

Evaluation of Tablet Parameters: For each formulation, the hardness, thickness and friability were determined. To study weight variation, 20 tablets of each formulation were weighed using a Sartorius electronic balance.

In Vitro Release Studies: Based on office of generic drugs recommendation 0.1N Hcl was used as dissolution medium and conditions were selected for development purpose. The release rates of Ranolazine sustain release tablets were determined by 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. Six tablets from each formulation were weighed and placed in the baskets. The dissolution was carried out for 24 hours (time intervals 0.5,2,4,8,12,20, and 24hr). The released drug was assayed by using UV spectrophotometer[3] at 272 nm after suitable dilution.

RESULTS AND DISCUSSIONS

Compatibility studies at accelerated conditions and stress conditions that is 40^0C/75%RH and 60^0C for 30days respectively showed that, there was no significant change in description of the physical mixtures and Ranolazine. Based on these results, excipients were selected for formulation development.

Evaluation of Granules: The granules of different proposed formulations (F-1 to F-5) were evaluated for LBD, TBD, and compressibility index. The results of LBD and TBD ranged from 0.415 to 0.555 g/ml respectively. The bulk densities of granules of the proposed formulation F-3 to F-5 were quite higher than those of other granules. The results of compressibility index (%) ranged from 11.53 to 15.65. Generally, compressibility index values up to 15% result in good to excellent flow properties. So the granules of F-3 to F-5 showed good flow properties than other granules. All these results indicate that the granules possessed satisfactory flow properties and compressibility.
The results are as shown in table 2

Physicochemical evaluation of matrix tablets: The results of physical parameters (weight, hardness, thickness and friability[2]) and drug content of the prepared matrix tablets are shown in Table 3. The thickness, hardness and friability of the tablets were found satisfactory. From the results physical

properties of the compressed matrix tablets were satisfactory. *The results are as shown in table 3*

***IN VITRO* RELEASE PROFILE**

The release profiles of different formulations (F-1 to F-5) of Ranolazine matrix tablets are shown in table4 & Fig. 1.
From the results all formulations were sustained for 24hours. Based on the dissimilarity factor (f1) and similarity factor (f2)[5] the results of formulations F1and F2 were not satisfactory, but formulation F3 F4 and F5 were satisfactory. The formulae of dissimilarity factor (f1) and similarity factor (f2) as follows.

$$f1 = \{[\Sigma_{t=1}^{n} |R_t - T_t|] / [\Sigma_{t=1}^{n} R_t]\} \times 100$$
$$f2 = 50 \times \log \{[1 + (1/n) \Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\}$$

Where, n is the number of dissolution sample times,
R_t and T_t are the individual or mean percent dissolved at each time point, t, for the reference and test dissolution profiles, respectively.
Dissimilarity factor (f1) and similarity factor (f2) values are as shown in table 5
The influence of compression force on release of Ranolazine matrix tablets 750mg, 500mg and 375mg are shown in Fig. 2.

The release profiles of Low, optimum and high hardness tablets 750mg, 500mg and 375mg in Table.6

Comparative *In vitro* release study with Innovator product: The release profiles of formulations (optimum hardness F-3 to optimum hardness F-5) of Ranolazine matrix tablets with market sample are shown in Fig. 3 and Table 4. Sustained release matrix optimum hardness tablets of Ranolazine 750mg, 500mg and 375mg strengths (F3-F5) were super imposable with the innovator product. So the results were satisfactory.

CONCLUSION

Ranolazine SR tablets, developed by Kollidon SR, microcrystalline cellulose and magnesium stearate. In which kollidon SR is a polyvinyl acetate based excipient for directly compressible matrix tablets. It required fewer unit operations, less machinery, reduced number of personnel and processing time. In present study five formulations were developed and compared with innovator (reference sample). All formulations were sustained for 24hrs but based on dissimilarity factor (f1) and similarity factor (f2) values F3, F4 and F5 were satisfactory.

Table 1: The composition of Ranolazine tablets (mg/tablet)

S.no	Ingredients	Strengths 750mg/500mg/375mg				
		F-1	F-2	F-3	F-4	F-5
1.	Ranolazine	750	750	750	500	375
2.	Kollidon® SR	50	100	150	100	75
3.	Microcrystalline Cellulose	194	188	90	60	45
4.	Magnesium Stearate	6	12	12	8	6
Core tablet weight		975	975	975	650	487.5
6.	Opadry yellow	19.5	19.5	19.5	13	9.75
Total tablet weight (mg)		**994.5**	**994.5**	**994.5**	**663**	**497.25**

Table 2 Evaluation of granules of different formulations

Parameters	F-1	F-2	F-3	F-4	F-5
LBD (g/ml)	0.415	0.426	0.442	0.480	0.491
TBD (g/ml)	0.492	0.499	0.501	0.545	0.555
Compressibility Index (%)	15.65	14.6	11.78	11.9	11.53

Table 3: Evaluation of matrix tables parameters

Formulations	F-1	F-2	F-3	F-4	F-5
Description	Yellow color capsule shaped film coated tablets				
Punches	19.45x9.25mm	19.45x9.25mm	19.45x9.25mm	17.5x8mm	14x7mm
Thickness (mm)	5.8 to 6.5	5.8 to 6.5	5.8 to 6.5	5.6 to 6.1	4.6 to 5.0
Hardness (kp)	12 to 18	12 to 18	12 to 18	8 to 13	5 to 10
Friability (%)	0.18%	0.17%	0.10%	0.10%	0.10%
Weight (mg)	994.5± 2%	994.5± 2%	994.5± 2%	663± 2%	497.25± 2%

Table 4: Comparative *In vitro* release study with marketed product

Hours	% Drug release					
	F-1	F-2	F-3	F-4	F-5	Market sample (INNOVATOR)
0.5	35	30	20	19	21	16
2	50	45	35	34	36	34
4	70	60	50	53	51	48
8	80	72	66	60	64	63
12	90	83	75	78	77	75
20	99	95	85	87	85	86
24	99	100	97	99	98	98

Table 5: Dissimilarity & Similarity factors of all formulations

FORMULATION	Dissimilarity factor (f1)	similarity factor (f2)
F1	31.62	38.82
F2	21.08	47.39
F3	6.51	66.09
F4	6.51	62.13
F5	7.75	63.88

Table.6: Invitro drug release in Different Hardness of optimized formulation.

Hours	% Drug release in Different Hardness of 750mg,500mg and 375mg								
	F-3 (750mg)			F-4 (500mg)			F-5 (375mg)		
	Low	Optimum	High	Low	Optimum	High	Low	Optimum	High
0.5	21	20	18	20	19	22	23	21	21
2	36	35	33	36	34	33	37	36	32
4	53	50	49	55	53	52	53	51	52
8	67	66	65	62	60	62	66	64	64
12	78	75	74	75	78	79	79	77	75
20	87	85	86	89	87	88	87	85	88
24	99	97	99	98	99	100	100	98	99

There is no influence of compression force on release of Ranolazine from ablets (750mg, 500mg and 375mg strenrths).

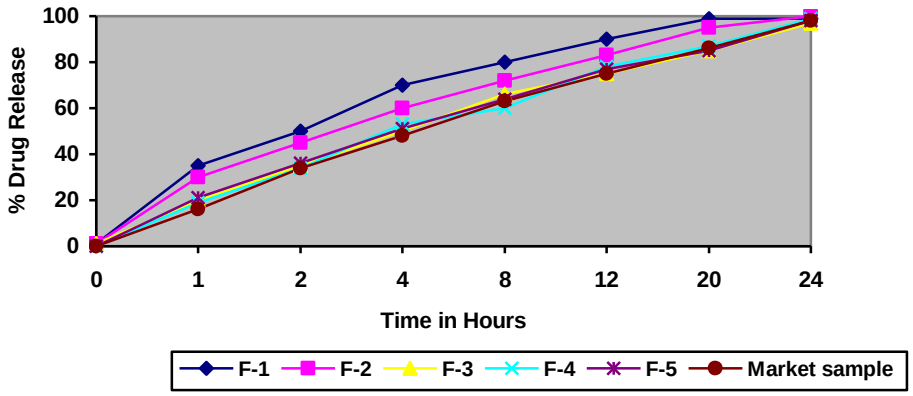

Fig1: The release profiles of different formulations (F-1 to F-5) of Ranolazine matrix tablets

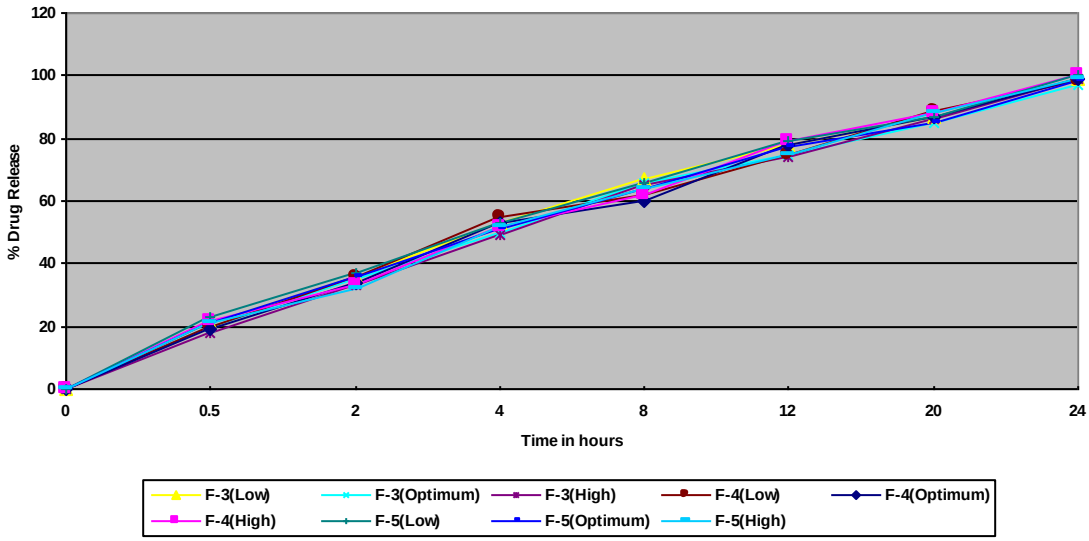

Fig 2: The influence of compression force on release of Ranolazine matrix tablets

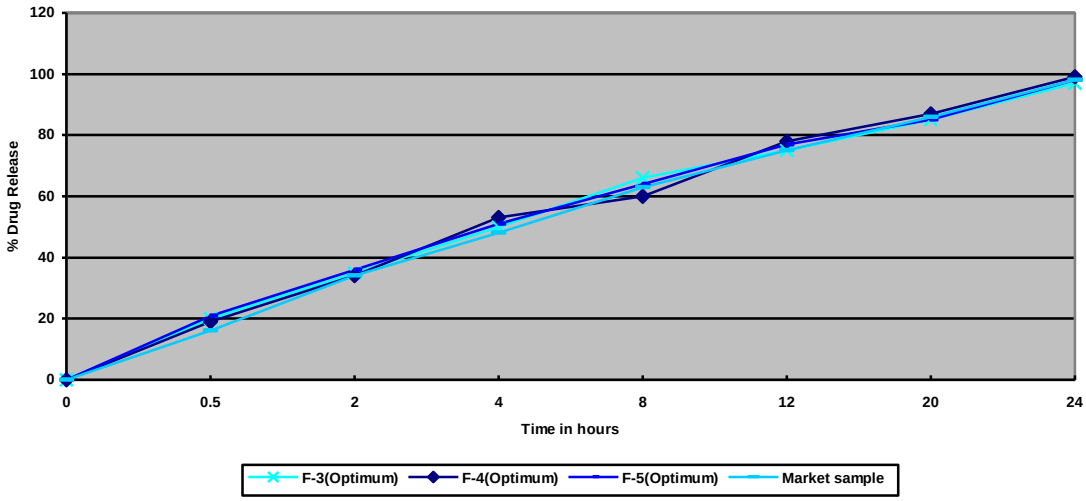

Fig3: Comparative *In vitro* release study with Innovator product

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