JPR INFO
Journal of Pharma Research

Journal of Pharma Research
Available online through
www.jprinfo.com

Research Article
ISSN: 2319-5622

Optimization and Evaluation of Ranolazine Extended release Matrix Tablets

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Received on: 17-03-2014; Revised and Accepted on: 28-03-2014

ABSTRACT

The optimization of extended release formulation of Ranolazine was undertaken due to the short biological half-life of the active substance and consequently the difficulties in maintaining the desired concentrations in the blood, by developing a matrix tablets. The tablets were made by aqueous wet granulation technique with release retarding agent incorporated both intra-granularly and as a granulation agent. The specific polymorphic From I of API was required for development. The systematic approach of using combination of release retarding agents helped in achieving a stable, optimized extended release formulation, which could be industrially viable.

Keywords: *Ranolazine, matrix tablet, polymorphic form, photo-stability, extended release formulation.*

INTRODUCTION

Ranolazine [1-2] extended release tablets are registered in US and Europe market and also available in Indian market. The mechanism of action [3-4] of Ranolazine is largely unknown. Ranolazine may have some anti-anginal effects by inhibition of the late sodium current in cardiac cells. This reduces intra-cellular sodium accumulation and consequently decreases intracellular calcium overload. Ranolazine, via its action to decrease the late sodium current, is considered to reduce these intra-cellular ionic imbalances during ischemia. This reduction in cellular calcium overload is expected to improve myocardial relaxation and thereby decrease left ventricular diastolic stiffness. The short biological half-life of Ranolazine and consequently the difficulties in maintaining the desired concentrations in the blood, determined the need for the development of an extended release formulation. The desired extended-release characteristics are achieved by developing a matrix tablet, where a pH-dependent polymer (methacrylic acid-ethyl acrylate copolymer 1:1) is used that is insoluble in low pH and begins to dissolve at about pH >5. In this way, the polymer restricts the high solubility of Ranolazine in acidic mediums (e.g. gastric environment) and achieves an extended release by dissolving in a basic environment, where drug is less soluble and thus more time is needed for its release [5].

MATERIALS AND METHODS

Materials:

Ranolazine was obtained as gift sample from Unichem Laboratories, Mumbai, India. Eudragit L100, Eudragit NE 30D and Colloidal silicon dioxide was obtained from Evonik Industries. Povidone K-30 was procured from BASF and magnesium stearate from Sunshine Organics Pvt Ltd. Instacoat universal was procured from Ideal cures Pvt Ltd.

Pre-formulation studies:

Pre-formulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. Bulk density, compressibility index, Hausner's ratio were determined by using tapped density tester (Electrolab, ETD-1020). Flow properties was determined by angle of repose method, and compatibility studies was done by only physical appearance as the excipients used in the formulation were similar to reference product.

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Polymorphism study:

Ranolazine exhibits three different crystalline forms named as Form I, Form II, Form III [5] and one amorphous form. Form I is the only one that was thermodynamically stable, Form II and Form III are kinetically unstable. For generic development it is necessary that the polymorphic form being used must be similar to reference product. Hence, X-ray Powder Diffraction was conducted between Reference product and API used and two theta values were determined as a comparative study.

Methods: [5-9]

Ranolazine, Microcrystalline cellulose (Avicel PH 101), Eudragit L 100 -55, Povidone (K-30) were sifted through #40 sieve and dry mixed at 100 rpm in Rapid Mixer granulator. The blend was granulated with Eudragit NE30D dispersion. Additional purified water was added to form desired granules. Wet mass formed towards the end of granulation.

The wet mass was dried in fluid bed processor at inlet temperature of 65°C until LOD was not more than 2.5%w/w (at 70°C). Dried granules were sifted through # 20sieve. The sifted granules was blended with colloidal silicon dioxide (#40sieve) for 5mins and finally lubricated with magnesium stearate (#60sieve) for 5 minutes in blender. The lubricated blend was tested for blend parameters.

The tablets were compressed on 16 station compression machine. The tablets were further film coated with Instacoat universal orange till 2.5% to tablet weight.

Physical evaluation of lubricated blend and tablets:

The blend was tested for bulk density, tapped density, compressibility, Hausner's ratio and particle size distribution using electronic density tester and sieve shakers.

The core tablets were evaluated for individual weight variation, hardness, thickness and friability. Film coated tablets were evaluated only for average weight, thickness and hardness.

Hygro-scopicity Study:

To determine hygro-scopicity of the study samples, the coated tablets were exposed to 75 % ± 5% humidity at 25°C for 7 days. Initial LOD and after exposure was determined using moisture balance (Make: Mettlor Toledo)

Photo-stability Study:

Study was conducted on tablets packed in Alu- PVC/PVDC Clear blister pack. The tablets were exposed to UV and visible light as per requirement of ICH Q1 B [23]. The following two exposure criteria for confirmatory photo-stability studies are:

- Not less than 1.2 million Lux hours of visible (400 to 800 nm) exposure.

- Not less than 200 Watt hours/square meter of UV (320 to 400 nm) exposure. The duration of exposure was based on the below given criterion.

Stability studies:

Stability studies were carried out as per ICH Q_1A [21] stability testing guidelines. The optimized formulations were stored in Alu- PVC/PVDC. Clear blister pack and were subjected to a storage condition of 40°C ± 2/75% RH ± 5%RH for 3 months. The samples were withdrawn at time intervals of 0, 1, 2, and 3 months and evaluated for percentage drug content using UV spectrophotometer and absorbance of the solution at about 272nm.

Table No. 1: Composition of Feasibility trials

Ingredients	FT1	FT2	FT3	FT4	FT05(SB1)
	(%w/w)				
Intra-granular excipients					
Ranolazine	71.42	71.42	71.42	69.93	66.66
Microcrystalline cellulose (Avicel PH 101)	15.00	12.57	11.57	11.32	11.53
Eudragit L 100 -55	8.57	9.28	9.28	9.09	10.00
Eudragit NE 30D(solid content)	**2.00**	**3.00**	**4.00**	**6.01**	**8.00**
Povidone (K-30)	2.00	2.00	2.00	1.95	2.00
Colloidal silicon dioxide (Aerosil 200)	--	--	--	--	0.50
Binder					
Water	Q.s.	Q.s	Q.s	Q.s	Q.s
Lubricants					
Colloidal silicon dioxide (Aerosil 200)	1.00	0.71	0.71	0.699	0.50
Magnesium stearate	1.00	1.00	1.00	0.98	1.00

Table 2: Granulation parameters for Rapid mixer granulator

Steps	Mixing Time	Impellor speed		Chopper speed		Amperes
		Slow	Fast	Slow	Fast	
Dry mixing (Drug + MCC +Eudragit L100-55+PVP K-30)	15 min	75 rpm	--	--	--	1.9
Binder addition						
Eudragit NE30 D	5min	75 rpm	--	--	--	2.1
Water (100 ml)	3min	75 rpm	--	--	--	2.1
Water (100 ml)	3min	75 rpm	--	1450 rpm	--	2.1
Water (50 ml)	2min	--	150 rpm	--	--	2.1
Water (50 ml)	2min	75 rpm	--	1450 rpm	--	2.1

RESULTS AND DISCUSSION

Pre-formulation studies:

Through pre-formulation studies it was concluded that drug has solubility below pH 5 beyond that the solubility drops drastically, observed through results given in **Table No. 3**.

The drug has poor flow and compressibility as per the results given in **Table No. 4**. Micronized API was used as the drug was practically in soluble in water. Particle size D (0.5) NLT 40 µm& D (90)125 µm was selected to inform the wettability of the drug.

Table No. 3: Result of solubility

Solution pH	Solubility (mg/mL)	USP [10] Solubility Class
4.81	161	Freely soluble
4.89	73.8	Soluble
4.90	76.4	Soluble
5.04	49.4	Soluble
5.35	16.7	Sparingly soluble
5.82	5.48	Slightly soluble
6.46	1.63	Slightly soluble
6.73	0.83	Very slightly soluble
7.59 (unbuffered water)	0.24	Very slightly soluble
7.73	0.17	Very slightly soluble
12.66	0.18	Very slightly soluble

Discussion: Solubility of the drug plays a crucial role for release of the drug in the particular pH. Through patent search it was revealed that Ranolazine is relatively insoluble in aqueous solutions having a pH above, about 6.5, while the solubility begins to increase dramatically below about pH 6. The results for solubility in different pH range are given in Table 3.0.

Table No. 4: Result of Flow properties of Ranolazine

Flow Properties[10]	Results
Bulk Density (g/ml)	0.238
Tapped Density (g/ml)	0.50
Compressibility index (%)	52.381
Hausner's Ratio	2.10
Angle of repose (θ)	No flow through funnel

Result	Poor flow

Discussion: From the above observation it is known that drug was having very low bulk density and poor flow properties which would need to be monitored critically during formulation development.

Table No. 5: Result of Particle size distribution of Ranolazine

Particle size	Results
D(0.5)	NLT 40 µm
D(90)	125 µm

Discussion: From the above given results it was known that the API used is having particle size within the range of 40 – 125 µm.

Polymorphism:

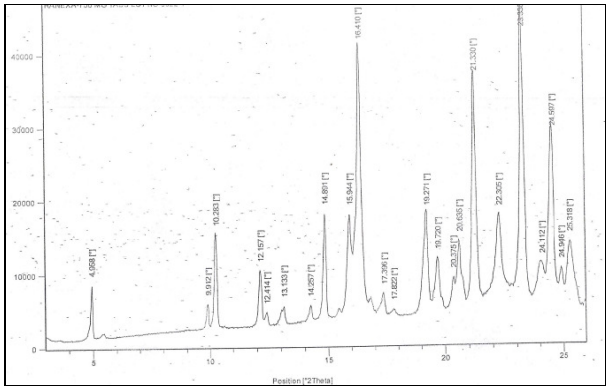

Fig. 1: Polymorphic form I (XRPD) of Reference Product

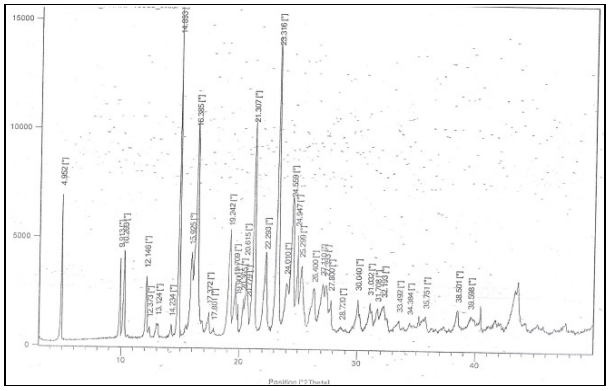

Fig. 2: Polymorphic form I (XRPD) Of Unichem API

Table No. 6: XRPD comparison table

API(Deg 2 theta)	Reference product (Deg 2 theta)
5.0	5.0
9.9	9.9
10.3	10.3
12.1	12.2
12.3	12.4
13.1	13.1
14.2	14.3
14.9	14.9
15.9	15.9
16.4	16.4
17.4	17.4
17.8	17.8
19.2	19.3
19.7	19.7
20.4	20.4
20.6	20.6
21.3	21.3
22.3	22.3
23.3	23.3
24.0	24.1
24.6	24.6
24.9	24.9
25.3	25.3

Discussion: Ranolazine exists as FORM- I. Drug substance sample shows polymorphic FORM- I. Also, it is clear from the above comparative study of 2theta values that Marketed formulation also exhibits drug in FORM I.

Feasibility Trials Based on Experimental work:
Physical evaluation:

Table No.7: Physical evaluation of blend parameters and core tablets

Sr. No.	Parameters	Results			
		F1	F2	F3	F4
1	**LOD of Unlubricated blend (% w/w)**	2.45	2.40	2.18	**2.18**
2	**LOD of Lubricated blend (%w/w)**	2.60	2.58	2.40	**2.40**
3	**Tapped density (g/ml)**	0.588	0.60	0.60	**0.60**

4	**Bulk density (g/ml)**	0.526		0.52		0.50		**0.50**
5	**Compressibility index (%)**	10.53		13.33		16.66		**16.66**
6	**Hausner's ratio**	1.12		1.15		1.2		**1.2**
7	**Tablet weight (mg)**	691 -712		690 -710 mg		710-725mg		**710-725mg**
8	**Thickness (mm)**	6.40		6.40 -6.80		6.6– 6.7 mm		**5.9 -6.1mm**
9	**Hardness (N)**	150-200N		150-200N		180-220N		**180-220N**
10	**Friability (%), 100 revolutions at 25 rpm**	0.125 %		0.125 %		0.17 %		**0.17 %**
11	**Weight variation (mg)**	698	710	713	700	713	718	713 **718**
		700	712	710	702	710	720	710 **720**
		702	705	712	695	712	716	712 **716**
		695	705	715	710	715	720	715 **720**
		700	**700**	**718**	**691**	**718**	**715**	**718** **715**

Dissolution [11] profile:

Table No. 8: Comparative dissolution profile of feasibility trails with Marketed product

Time (hr)	Dissolution Media: 0.1 N HCl , Method : USP-II (Paddle), RPM-50,Volume: 900ml					
	% Released					
	Marketed product	FT1	FT2	FT3	FT4	FT05(SB1)
0.5	17	20	20	21	22	21
2.0	35	47	42	53	45	41
4.0	49	58	59	76	65	58
8.0	64	65	79	98	87	75
12.0	75	87	92	103	98	86
20.0	88	99	104	104	103	98
24.0	92	100	105	104	104	100
F2 factor	--	**52**	**45.0**	**32.88**	**39.65**	**53**

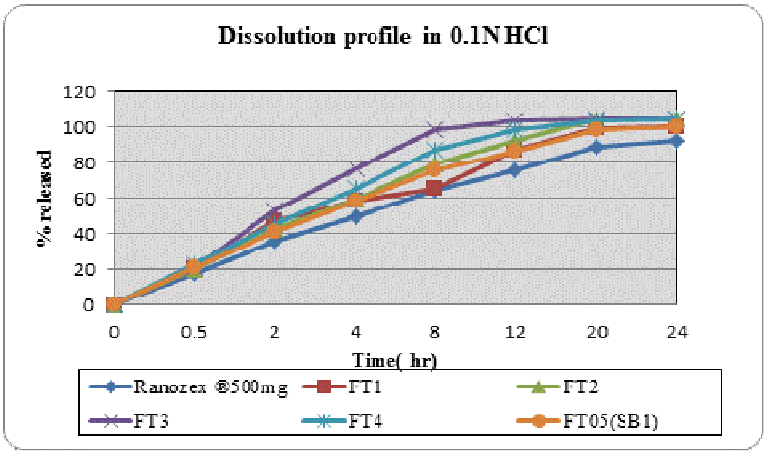

Fig. 3: Comparative dissolution profile of Feasibility trials with marketed product

Discussion: All the physical parameters were satisfactory for feasibility trials F1 to F4. LOD of lubricated blend was within the limit of 2.18% -2.45% w/w. Bulk density was within the range of 0.50- 0.526 g/ml & tapped density 0.58-0.60 g/ml. Compressibility index 10.53 -16.66% and Hausner's ratio 1.12 -1.2.

The dissolution profile was comparable with reference product for F1 and F5 trial with similarity factor more than 50. Hence, 2 reproducible batches were conducted and the tablets were packed in Alu- PVC/PVDC clear blister pack and charged on photo-stability and for 3Months at 40°C/75% RH.

Photo-stability [12-13] study results of Ranolazine ER tablet 500mg:

Table No. 9: Photo-stability results

Sr. No.	Test Parameters	Initial Sample	Exposed Sample in Primary Pack (Alu- PVC/PVDC clear Blister)	
			UV light	Tube light
1	**Description**	Light orange colored capsule shaped tablets plain on one side and break-line on other side.	No change	No change
2	**Assay (NLT 90% & NMT 110%)**	102.2	98.8	101.0
3	**Related Substance**			
	Single max unknown impurity (%)			
	At RRT 0.66	0.19	ND	ND
	At RRT 0.71	ND	ND	ND
	At RRT 1.23	ND	ND	ND
	Total impurity (%)	0.38 %	ND	ND

Discussion: The samples studied in the primary pack i.e. Alu- PVC/PVDC clear Blister do not show any color change or chemical degradation. Based on the above data it can be concluded that the formulation of photo stable.

Stability [14-15] study results of Ranolazine ER tablet 500mg:

Table No.10: Results of 3 M stability at 40°/75% RH

Test	Marketed product				SB1				SB2				SB3			
	Initial	1M	2M	3M	Initial	1M	2M	3M	Initial	1M	2M	3M	Initial	1M	2M	3M
Dissolution % released																
30mins	17	17	19	19	21	19	21	21	19	20	20	19	23	22	21	20
2hr	35	34	-	-	41	39	40	42	35	38	40	39	43	--	-	-
4 Hr	49	48	50	50	58	53	55	59	57	53	56	54	60	54	52	48
8 Hr	64	63	-	-	75	70	72	75	69	71	76	73	80	--	-	-
12 Hr	75	74	79	77	86	81	83	87	92	83	89	85	91	85	80	74
18 Hr	85	86	-	-	96	92	93	98	99	95	100	98	100	--	-	-
20 Hr	88	87	90	90	98	94	95	101	104	97	100	100	101	98	93	88
24 Hr	92	92	-	-	100	97	104	98	106	100	105	106	103	--	--	--
Assay (%)	102.2	101.7	99.3	101	100.9	97.9	99.1	100.8	102.3	97.4	100.5	102.8	100.7	103.4	101.4	99.7

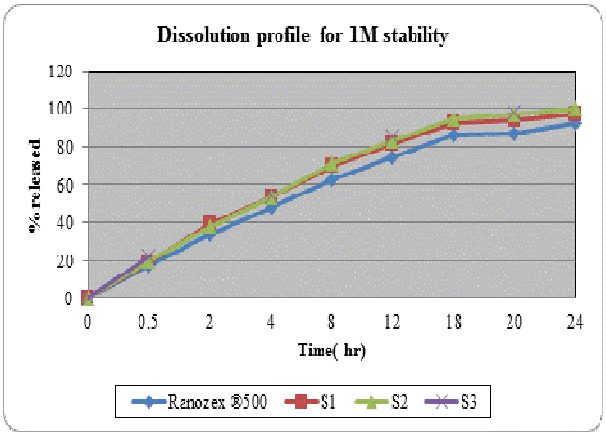

Fig. 4: 1M stability data of three reproducible batches on stability

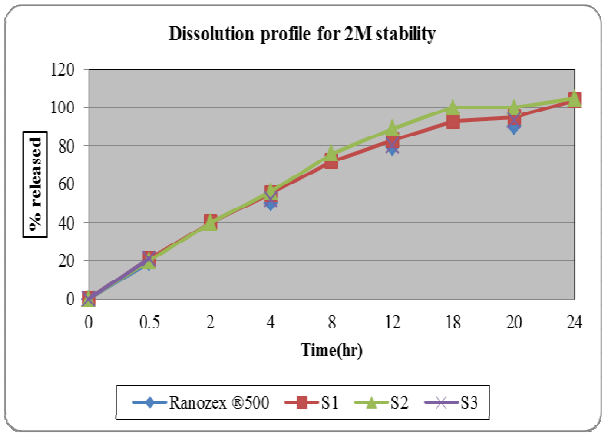

Fig. 5: 2M stability data of three reproducible batches on stability

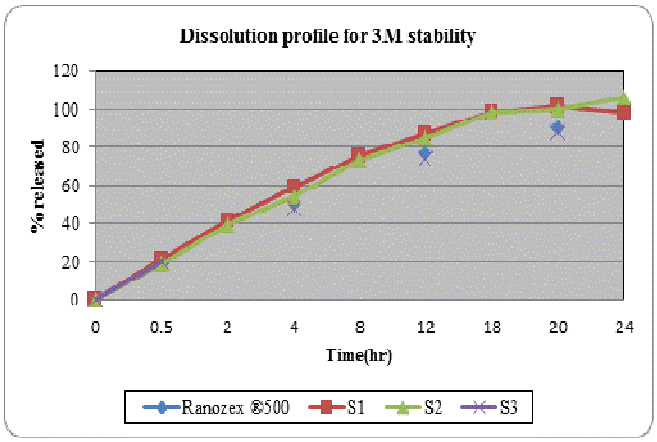

Fig. 6: 3M stability data of three reproducible batches on stability

CONCLUSIONS

From the study, it is possible to conclude that the proposed tablet formulations were suitable for wet granulation process. According to the release studies, the decrease in the release rate was observed with an increase in the concentration of the polymeric system. Polymer with higher viscosity and higher proportion of Eudragit L100-55 and Eudragit NE 30 D was shown to be beneficial in controlling drug release. The results of in-vitro release studies indicated achieving sustained release matrix tablets for Ranolazine by the use of Eudragit L 100-55 and Eudragit NE 30 D combinations. 3M stability study was conducted and it was confirmed that the product was stable for 3M.

ACKNOWLEDGEMENT

The authors are thankful to Unichem laboratories Ltd., India for their generous donation of API Ranolazine, excipients and equipment's. The authors are also thankful to Dr. L.H. Hiranandani college of Pharmacy, Ulhasnagar for their supports and co-operations for the successful completion of this project.

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Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil