RESEARCH ARTICLE

Formulation and evaluation of ranolazine extended release tablets: Influence of polymers

Murthy TEGK, Bala Vishnu Priya Mukkala, Suresh Babu VV[1]

Department of Pharmaceutics, Bapatla College of Pharmacy, Bapatla, Guntur, Andhra Pradesh, [1]Natco Pharma Limited, Kothur, Hyderabad, Andhra Pradesh, India

An extended release tablet provides prolonged periods of drug in plasma levels thereby reduce dosing frequency, improve patient compliance and reduce the dose-related side effects. Ranolazine is indicated for the chronic treatment of angina in patients who have not achieved an adequate response with other anti-anginal agents. The present investigation was undertaken to design extended release tablets of Ranolazine employing hypromellose phthalate grade HP-55, ethocel standard 7FP premium ethyl cellulose, Surelease E-7-19040, Klucel HF pharm and Natrosol Type 250 HHX as matrix forming agents using wet granulation method. Formulated tablets were evaluated for uniformity of weight, assay, water content, *in vitro* drug release studies and stability studies. The drug release followed first order kinetics with both erosion and diffusion as the release mechanism. It is concluded that the desired drug release pattern can be obtained by using natrosol type 250 HHX compared to other polymers. The similarity factor (f2) was calculated to select best formulation by comparing *in vitro* dissolution data of the commercial formulation Ranexa®. The formulated tablets fulfilled the compendia requirements. The formulated Ranolazine Extended release tablets were found to be stable.

Key words: *Ehocel, extended release tablets, hypromellose phthalate, klucel HF pharm and natrosol, ranolazine, surelease*

INTRODUCTION

Extended release drug delivery technology can provide smooth plasma levels of drug over longer periods of time, reduce dosing frequency and improve the patient compliance.[1] Ranolazine is indicated for the treatment of chronic angina. Unlike other anti-anginal medications such as nitrates and beta blockers, ranolazine does not significantly alter either the heart rate or blood pressure. Hence, it is of particular use in individuals with angina that is nonresponsive to maximal tolerated doses of other anti-anginal medications.[2] Cellulose ethers (hydroxypropylcellulose HPC and hydroxyethylcellulose HEC) are commonly employed as the hydrophilic, swellable and must erodible matrix polymers for orally administered types of controlled release systems.[3,4] Ethyl cellulose and Surelease were used as release retardant binder for the manufacturing of inert matrices for controlled release formulations.[5-7] In this study, attempts were made to study the influence of polymers on release profiles of extended release tablets of Ranolazine.

Address for correspondence:
Dr. TEGK Murthy,
Department of Pharmaceutics, Bapatla College of Pharmacy,
Bapatla, Guntur, Andhra Pradesh – 522 101, India.
E-mail: gopalakrishnatalasila@yahoo.com

MATERIALS AND METHODS

Ranolazine was procured from the Natco Pharma Ltd, Hyderabad. Microcrystalline cellulose (FMC biopolymer, New York), Hypromellose phthalate grade HP-55 (Shin-Etsu chemical.co.ltd, Japan), Klucel HF pharm Hydroxy Propyl cellulose and Natrosol type 250 HHX Hydroxy Ethyl cellulose (Hercules incorporated, Wilmington, U.S.A.), Ethocel standard 7FP premium ethyl cellulose and Surelease E-7-19040 aqueous ethyl cellulose dispersion (Colorcon Asia Private limited, Goa), Magnesium Stearate (Signet Chemical Corporation, Mumbai) were used in this investigation.

Preparation of ranolazine extended release tablets

The ranolazine extended release tablets were prepared by wet granulation technique. Drug and other excipients were accurately weighed, mixed and sifted through ASTM (American society of Testing and Materials) 40 mesh. Isopropyl alcohol and water were used as the

Access this article online

Quick Response Code:

Website: www.asiapharmaceutics.info

DOI: 10.4103/0973-8398.91992

granulation fluid [Table 1]. The wet mass was passed through ASTM 12 mesh and granules were dried at 50°C. Dried granules were further passed through ASTM 18 mesh. The granules were lubricated and compressed into oblong shaped (16.5 X 8.0 mm) tablets using 12-station rotary compression machine (Rimek minipress –II MT). Composition of the ranolazine extended release tablets was showed in Table1.

Evaluation of tablets

Uniformity of weight

All prepared tablets were evaluated for its uniformity of weight according to the United States pharmacopoeia.[8]

Water content (By KF method)

Approximately 35 to 40 ml of a mixture of methanol was transferred to the titration vessel and titrated with Karl Fischer reagent to the electrometric end point. Five tablets of ranolazine extended release were ground to a fine powder in an atmosphere of temperature and relative humidity known not to influence the results. Total of 300 mg of the powder was accurately weighed and transferred into the titration vessel, mixed and titrated with the Karl Fischer reagent to the electrometric endpoint.[9] Calculated the water content of the specimen in mg taken using the following formula

$$\frac{SXF \times 100}{W}$$

Where,

S is the volume (ml) of reagent consumed in the second titration

F is the water equivalence factor of the Karl Fischer reagent,

W is the weight of sample taken in grams.

In vitro drug release studies

In vitro drug release studies were conducted in 900 ml of 0.1 N HCL using USP apparatus type II (paddle) at a stirrer speed of 50 rpm and temperature was maintained at 37±0.5°C. Five milliliter of the sample was withdrawn at regular intervals of time (30 min, 1st, 2nd, 4th, 6th, 8th, 12th, 20th, and 24th hour) and filtered through 0.45 μm membrane filter. The same volume was replenished with fresh dissolution medium to maintain the sink conditions.[10] The samples were analyzed at a λ_{max} of 272 nm using UV-Visible spectrophotometer.

Assay

Drug content was determined with the HPLC technique. Twenty tablets was accurately weighed and powdered to fine powder. Equivalent to 500 mg of ranolazine was accurately weighed and transferred in to 100 ml of volumetric flask. About 50 mL of mobile phase (phosphate buffer (pH 7.0): methanol (35: 65)) was added, and sonicated for 30 minutes with occasional shaking. Cooled to room temperature and made the volume up to the mark with mobile phase. It was mixed well and filtered though a 0.45-μm membrane filter. The resulting solution was suitably diluted and injected into the Supelcosil C18, (250 x 4.6 mm), 5 μm column maintained at ambient temperature. The flow rate of mobile phase was maintained at 1.0 ml/min for 15 min runtime. The sample was detected at a λ_{max} of 220 nm.

$$\% \text{ Content of Ranolazine} = \frac{TA}{SA} \times \frac{SW}{50} \times \frac{5}{50} \times \frac{100}{TW} \times \frac{100}{2} \times \frac{P}{100} \times \frac{Avg.\ wt}{LA} \times 100$$

TA : Peak area response due to Ranolazine from sample preparation

SA : Peak area response due to Ranolazine from sample preparation

SW : Weight of Ranolazine working standard, taken in mg

TW : Weight of sample taken, in mg

P : Purity of Ranolazine working standard taken on as is basis

Avg.wt : Average weight of tablet

LA : Label Amount

Table 1: Composition of the ranolazine extended release tablets 500 mg

Ingredients	S_1	S_2	S_3	S_4	S_5	S_6	S_7	S_8	S_9
	mg/tablet	mg/tablet	mg/tablet	mg/tablet	mg/tablet	mg/tablet	mg/tablet	mg/tablet	mg/tablet
Ranolazine	500	500	500	500	500	500	500	500	500
Hypromellose phthalate grade HP-55	100	–	50	–	–	–	–	–	–
Ethocel Standard 7 FP premium	–	100	50	–	–	–	–	–	–
Surelease E-7-19040	–	–	–	50	–	–	–	–	–
Natrosol type 250 HHX	–	–	–	–	100	–	120	–	60
Klucel HF pharm	–	–	–	–	–	100	–	120	60
Avicel PH 101	50	50	50	100	50	50	30	30	30
Purified water	–	–	–	–	0.35ml	0.25ml	0.4ml	0.3ml	0.3ml
IPA	0.35ml	0.35ml	0.3ml	–	–	–	–	–	–
Magnesium stearate	15	15	15	15	15	15	15	15	15
Total	665	665	665	665	665	665	665	665	665

Related substances

Related substances were determined using by HPLC method. 20 tablets was accurately weighed and powdered to fine powder. Equivalent to 500 mg of ranolazine was accurately weighed and transferred in to 100ml of volumetric flask. 50 ml of mobile phase (phosphate buffer (pH 7.0): methanol (35: 65)) was added, and sonicated for 20 minutes with occasional shaking. Cooled to room temperature and made the volume up to the mark with mobile phase. Mixed well and filtered though a 0.45 μm membrane filter. The resulting solution was suitably diluted and injected into the supelcosil C18, (250 × 4.6 mm), 5 μm column maintained at ambient temperature. The flow rate of mobile phase was maintained at 1.0 ml/min for 60 min runtime. The sample was detected at 220 nm. Related substances were calculated by area normalization method.

Stability studies

The Ranolazine extended release tablets were packed in unit-of-use high density polyethylene bottle (60 tablets per 150 cc bottle) with child resistant closure and stored at temperature of 40±2°C/75±5.0% RH (accelerated). Samples were analyzed for description, identification, water content, dissolution, assay, and related substances at regular intervals of time as per ICH guidelines.[11]

RESULTS AND DISCUSSION

The tablets formulated with Hypromellose phthalate grade HP-55, exhibited the burst release at the end of half an hour and hence this was undesirable. The tablets formulated with Ethocel Standard 7 FP premium, with combination of Ethocel Standard 7 FP premium and Hypromellose phthalate grade HP-55 and with Surelease E-7-19040 as the rate controlling polymers, the drug was found to be completely released at the end of 12 hours, whereas the formulation is intended to be a once-a- day formulation with an anticipated 90% release at the end of 20 hour. The rate of drug release was controlled with the inclusion of Natrosol Type 250 HHX and Klucel HF pharm as the release controlling polymer with the active core. As the amount of Natrosol Type 250 HHX and Klucel HF pharm increased then the % drug release was decreased. The tablets were formulated with combination of Natrosol Type 250 HHX and Klucel HF pharm as rate controlling polymer exhibited release profile similar to that of tablets containing Natrosol type 250 HHX and Klucel HF pharm.

Based on the results obtained from the preliminary investigations, Natrosol type 250 HHX was concluded as good rate controlling polymer compared to klucel HF pharm, ethocel Standard 7 FP premium, surelease E-7-19040 and hypromellose phthalate grade HP-55 [Table 2 and Figure 1].

The *in vitro* drug release profiles of formulations were compared with the reference product (Ranexa® Ranolazine ER tablet 500 mg) as per Office of Generic Drugs (OGD) recommendations. The similarity factor (f2) was calculated and ranolazine tablets formulated with Natrosol type 250 HHX as matrix forming agent was exhibited good similarity (69.92) compared to others.

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models:

Zero order: $C = K_0 t$

K_0 - zero order release rate constant
t- Time in hours
First order: Log C = log C_0 - Kt/2.303
C_0-initial concentration of drug
k- First order release rate constant

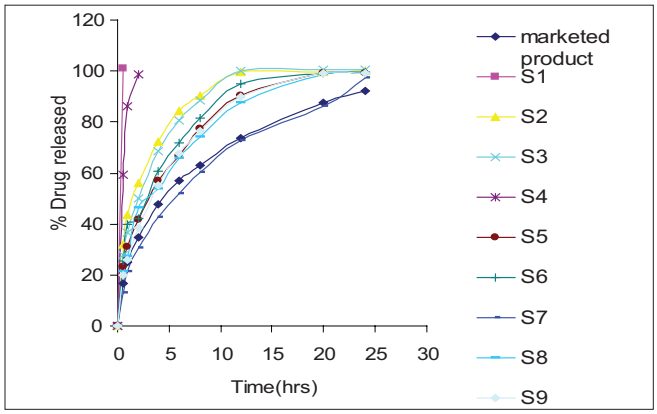

Figure 1: Comparative *in vitro* dissolution profiles of ranolazine tablets formulated with various polymers and marketed formulation

Table 2: *In vitro* drug release data of Ranolazine extended release tablets 500 mg

Time (hours)	Innovator	S_1	S_2	S_3	S_4	S_5	S_6	S_7	S_8	S_9
0.5	16.8	100.8	31.9	27.9	59.3	23.1	25.7	12.9	21.2	20
1	24.8	–	43.4	36.5	86.4	31	39.9	21.3	27.4	25.9
2	34.8	–	56	50.2	98.8	41.7	42.2	30.7	46.3	38.3
4	47.5	–	72.1	68.6	–	57	60.5	42.4	53.7	55.2
6	56.8	–	84.1	80.6	–	66.9	71.9	51.7	65.8	67.6
8	63.2	–	90.2	88.6	–	77.2	81.6	60.1	74.1	76.6
12	73.5	–	99.8	100.2	–	90.4	94.8	72.8	87.7	90
20	87.7	–	99.8	100.6	–	99.2	99.3	86.2	98.6	99.1
24	92.2	–	100.1	100.4	–	99.3	99.4	97.3	99.1	99.2
	f2	–	33.77	36.53	8.59	48.95	42.8	69.92	51.64	50.75

To evaluate the mechanism of drug release from Ranolazine extended release tablets, data of drug release were plotted in Korsmeyer *et al's* equation:

$Mt/ M8 = kt^n$

Where
Mt/ M8- the fractional solute release,
t - Release time in hrs,
k- Kinetic constant characteristics of the drug/polymer system, and
n- An exponent that characterizes the mechanism of release of tracers.

For cylindrical matrix tablets, if the exponent $n=0.45$, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion. An exponent's value of 0.89 is indicative of case-II Transport or typical Zero-order release.[12]

The drug release kinetics followed first order [Table 3] and mechanism of drug release was found to be combination of diffusion and erosion as the *n* value found to be 1.3095.

Results from stability studies [Table 4] indicated that there was no appreciable change observed in physical properties, assay, and dissolution during the testing period.

Table 3: *In vitro* drug release kinetics of Ranolazine extended release tablets 500 mg

Formulation	Correlation coefficient				Exponential coefficient (*n*)
	Zero order	First order	Higuchi	Peppas	
Innovator	0.8413	0.9919	0.9826	0.9923	1.3922
F_1	–	–	–	–	–
F_2	0.614	0.7668	0.8535	0.9492	1.6435
F_3	0.6598	0.8822	0.8843	0.9558	1.587
F_4	–	–	–	–	–
F_5	0.7781	0.9825	0.9538	0.9869	1.5014
F_6	0.7298	0.9867	0.9253	0.9679	1.5557
F_7	0.8921	0.9335	0.9951	0.9926	1.5914
F_8	0.7899	0.987	0.9583	0.977	1.4776
F_9	0.7864	0.9844	0.956	0.9804	1.4482

CONCLUSION

In the present investigation, an attempt was made to formulate ranolazine extended release tablets to provide effective drug release for 24 hours. Natrosol type 250 HHX was found to be more effective as rate controlling polymer compared to other polymers. Tablets containing Natrosol type 250 HHX (120 mg) as matrix forming agent was considered to be the optimized formulation with the desired drug release profile. The formulated Ranolazine extended release tablets were found to be stable as per ICH guidelines.

Table 4: Stability studies of optimized formulation of Ranolazine extended release tablets 500 mg

Product name: Ranolazine ER tablets (500 mg)	Optimized formulation		Storage condition: 40±2°C/75±5.0%RH			
Test	**Acceptance criteria**		**Initial**	**1st month**	**2nd month**	**3rd month**
Description	Pale yellow colored biconvex shaped tablets embossed with "500" on one side and plain on another side		Compiles	Compiles	Compiles	Compiles
Identification (by HPLC)	The retention time of the major peak in the chromatogram of the sample preparation corresponds to that chromatogram of the standard preparation, as obtained in the assay.		Compiles	Compiles	Compiles	Compiles
Water content (by KF)	Not more than 5.0%		2.53	2.65	3.05	3.33
Assay % (by HPLC)	90.0 to 110.0%		99.3	99.7	99.8	99.6
Dissolution profile in 900 ml of 0.1 N HCL, 50 RPM, Paddle as stirrer		Time (hr)	% release	% release	% release	% release
	Not more than 20%	0.5	12.9	13.8	14.1	14.8
	Not more than 60%	1	21.3	24.1	22.9	24.2
		2	30.7	32.4	34.2	35.9
		4	42.4	46.6	46.8	46.2
		6	51.7	54.7	54.2	54.2
	Not Less than 80%	8	60.1	63.5	63.9	64.3
		12	72.8	77.2	77.9	75.9
		20	86.2	89.4	89.1	90.4
		24	97.3	101.6	99.3	101.2
		f2	69.92	70.63	73.45	72.03
Related substances (by HPLC)						
Single unknown impurity maximum	Not more than 0.1%		0.02	0.02	0.02	0.03
Total impurities	Not more than 2.0%		0.04	0.03	0.04	0.06

HPLC: High-performance liquid chromatography, ER: Enhancement ratio

ACKNOWLEDGEMENTS

The authors are grateful for the Natco Pharma Ltd, Hyderabad and Management of Bapatla College of Pharmacy, Bapatla for providing appropriate facilities.

REFERENCES

1. Remington. The science and practice of pharmacy. 21st ed. USA: Lippincott, Williams and Wilkins Publications; 2005. p. 939-64.
2. Thomson. Physician Desk Reference. 61st ed. Montvale, New Jersey: Thomson PDR; 2007, p. 1035-37.
3. Ferrero Rodriguez C, Bruneau N, Barra J, Alfonso D, Doelker E. Hydrophilic Cellulose derivatives as drug delivery carriers: influence of substitution type on the properties of compressed matrix tablets, In: Wise DL, editor Handbook of Pharmaceutical Controlled Release Technology. New York: Marcel Dekker; 2000. p. 1-30.
4. Lee PI, Diffusional release of a solute from polymeric matrix-approximate analytical solutions. Journal of Membrane Science 1980:7:255-75.
5. Tiwari S, Rajabi-Siahboomi AR, Extended-release oral drug delivery technologies: monolithic matrix systems. Drug delivery systems. Totowa NJ, Jain KK, editors. New York: Humana Press; 2008. p. 217-43.
6. Vass S, Deng H, Rajabi-Siahboomi AR, Investigation of ethylcellulose in the preparation of theophylline extended release inert matrix tablets, AAPS annual meeting and exposition; 2008.
7. Ruiz NR, Ghaly ES. Mechanism of drug release from matrices prepared with aqueous dispersion of ethylcellulose. Drug Dev Ind Pharm 1997:23:113-7.
8. The United States Pharmacopeia, 34th revision and the National formulary. 29th ed., vol. 1. The United States Pharmacopeial Convention, 12601 Twinbrook Parkway, MD 20852; 2011. p. 403-6.
9. The United States Pharmacopeia, 34th revision and the National formulary. 29th ed., vol. 1. The United States Pharmacopeial Convention, 12601 Twinbrook Parkway, MD 20852; 2011. p. 407-10.
10. Available from: http://www.accessdatadata.fda.gov/scripts/cder/dissolution/dsp_searchresults_dissolution. Cfm. [Last accessed on 2011 Jul 19].
11. Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ ucm201217.pdf. [Last accessed on 2011 Jul 19].
12. Kulkarni SV, Kumar PR, Rao BS, Kumar PA, Ramesh B, Pranitha Y, *et al*. Preparation and *in vitro* evaluation of controlled release matrix tablets of stavudine using natural and synthetic polymers. J Pharm Res 2010:3:1463-66.

How to cite this article: Murthy T, Mukkala BP, Babu VS. Formulation and evaluation of ranolazine extended release tablets: Influence of polymers. Asian J Pharm 2011;5:162-6.

Source of Support: Nil. **Conflict of Interest:** None declared.