ISSN 0976 – 3333

Available Online at www.ijpba.info

International Journal of Pharmaceutical & Biological Archives 2013; 4(6): 1164 - 1171

ORIGINAL RESEARCH ARTICLE

Formulation and Evaluation of Ranolazine Extended Release Tablets by using pH Dependent and Independent polymers

Bhargavi Pittala[*1], Naveen Kumar bommagani[1], Anitha Kakkerla[1], Dr. S.Vasudeva Murthy[2], Mounika.Basani[1], Preethi Nagavalli[1]

[1]*Department of pharmaceutics, Jayamukhi College of Pharmacy, Narsampet-506332, Warangal, (A P), India*
[2]*Department of Pharmacology, Jayamukhi College of Pharmacy, Narsampet-506332, Warangal, (A P), India*

Received 22 Aug 2013; Revised 04 Dec 2013; Accepted 15 Dec 2013

ABSTRACT

Ranolazine is an anti-anginal drug used to treat chronic stable angina in adults The main drawback with normal conventional dosage form is that the solubility of Ranolazine is relatively high at the lower pH(4.5 and below) and also having short plasma half- life of 7hrs. In this study an attempt was made to design Ranolazine 500 mg extended release tablet by wet granulation method, using an intimate mixture of Ranolazine and a partially neutralized pH-dependent polymer Eudragit L-100-55 and HPMC K15M is a pH-independent polymer. By using different concentrations of both Eudragit L-100-55 and HPMC K15M, will better control the dissolution rate. The physicochemical compatibility of the drug and polymers were found to be compatible. The *in-vitro* release of Ranolazine extended release tablets was studied in 900 ml of 0.1N HCl as dissolution medium using a USP dissolution paddle assembly at 50 rpm and 37±0.5°C for 2hrs, then release studies were conducted in pH 6.8 phosphate buffer for 24 hrs. Optimized formulation released 99.4% of drug for 24 hrs. The optimized formulation was compared with the marketed product RANEXA. It was found to be stable during accelerated stability studies conducted at 40 °C / 75% RH for three months as per ICH guidelines.

Key words: Ranolazine, Eudragit L 100-55, HPMC K15M, Extended release.

INTRODUCTION

In Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects, when compared to other routes of administration. In general, the oral medication is considered as the first avenue investigated in the discovery and development of new pharmaceutical active ingredients and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration, and cost- effective manufacturing process.[1] A dosage form that allows at least a two –fold reduction in dosage frequency as compared to that drug presented as an immediate release(conventional) dosage form are considered as extended-release formulations.[2]

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier, which is usually a water- insoluble polymer. Diffusion of the drug molecule through a polymeric membrane describes the basis of diffusion controlled matrix systems. The membrane can be either formed from encapsulating the drug particle in a polymer membrane (reservoir systems) or incorporating the drug into a polymer matrix (matrix devices). The drug is available only after partitioning through the polymer layer.[2,3]

Ranolazine is novel drug used in treatment of chronic heart disease such as angina. It has anti-anginal effect that does not depend upon reduction in rate or blood pressure. The exact mechanism of action is un known, but it was believed to reduce angina/ischemia by selectively inhibiting the late sodium current that results in reduced intracellular sodium and calcium overload during ischemia. The QT prolongation effect of ranolazine on the surface electrocardiogram is the result of inhibition of IKr, which prolongs the ventricular action potential.[4,5,6]

***Corresponding Author:** Bhargavi Pittala, **Email:** bhargavipittala@gmail.com

Ranolazine and its pharmaceutical salt is having relatively high solubility at the low pH that occurs in the stomach. Ranolazine shows high pH dependent solubility, it is freely soluble in aqueous solutions having pH below 4.5 and then, as the pH increases solubility of the drug decreases dramatically, furthermore Ranolazine has a short half life 7 hrs, the acid solubility property of Ranolazine results in rapid drug absorption and clearance, causing large and undesirable fluctuation in plasma concentration and short duration of action, thus necessitating frequent oral administration for adequate treatment. In order to maintain plasma drug concentration in the body twice daily formulation of Ranolazine is needed for better control of drug release and therapeutic activity up to 24 hrs. [7,8]

In the present work an attempt was made to design Ranolazine extended release tablets by using one pH dependent polymer (Eudragit L 100-55) and one pH independent polymer (HPMC K15M)in different concentrations, such that the formulation can closely control the drug release and extend the release upto 24 hrs. By this the frequency of dose to be administered is reduced by twofold so side effects of the drug may be reduced and in turn the patient compliance may also increase.

MATERIALS AND METHODS

Materials:

Ranolazine is an antianginal drug gifted by (MSN Pharma.Chem), Microcrystaline cellulose (Avicel pH101) is used as a diluent supplied by (signet chemical corporation),Methacrylicacid co-polymer EudragitL-100-55 is used as a pH dependent polymer supplied by (S.Zhavei and co), HPMC K15M (Methocel) used as pH independent polymer supplied by (Colorcon Asia Pvt Ltd) Meglumine is used as an organic base which adjust the pH, is supplied by (Sunshine organics Pvt. Ltd), magnesium stearate used as lubricant supplied by (Signet chemical corporation).

Instruments:

Electronic weighing balance (Sartorious precision balance), Electronic LOD measurement apparatus (Sartorious), Digital Vernier calipers (Fischers scientific), Tablet hardness tester (Pharmatest), Friability tester (Electro lab EF-2), Analytical Sieve Shaker (Retsec), Tap density tester (Electro lab), Mechanical stirrer (Remi motors, Mumbai), pH meter (Digisum Electronics),Mesh #20,40,60 (Retsec), Dissolution test apparatus(Electrolab USP XXII TDT-08L),Rapid Mixer Granulator (Saral,India), Tablet Compression machine (cadmesh), UV-spectrometer (shimadzu), Stability chambers (Thermolab).

Preformulation studies:

Pre-formulation studies on active pharmaceutical ingredients (API), inactive ingredients (Excipients), and their combinations were carried out to finalize specifications of active pharmaceutical ingredients, to study the chemical compatibility between active and inactive ingredient, FTIR studies for Ranolazine, methocel,Eudragit L-100 55 were carried out by weighing approximately 1-3 mg of the sample and 0.1g of previously dried potassium bromide. Carefully grind the mixture and place the homogeneous mixture in an IR pellet die. The KBr disks were prepared by compressing the powder. The scanning range was kept from 4000–450 $cm.^{-1}$ in perkin-Elmer Spectrum-one FTIR spectrometer (Shelton, CT, USA).[9]The flow properties like bulk density, tapped density, compressibility index and hausners ratio were determined by using tapped density tester and flow characteristics were determined by using angle of repose method to evaluate the flowability of the drug and excipients blend.[10]

Preparation of standard calibration curve:

Ranolazine were spectrophotometrically measured at 272 nm by using 0.1N pH 1.2 acid buffer. Weigh accurately 100mg of Ranolazine and transfer into a 100ml volumetric flask. Volume was made with 0.1N Hydrochloric acid. It was mixed well to get a concentration of 1000 µg/ml. From the stock solution, 10 ml was withdrawn & dilute to 100ml with respective Medias to get 100µg/ml. From this secondary stock 0.5 to 5 ml, was taken separately and made up to 10ml with buffer,to produce a concentration range of 5-50 µg/ml. The absorbance was measured at 272 nm in UV- spectrophotometer using 0.1N HCl as blank .plot the graph between the concentration on x-axis and absorbance on y –axis get the calibration curve of drug.[11]

Preparation of matrix tablets:

In the present study various formulations with different concentrations of polymers were prepared by both dry granulation and wet granulation method.

Table 1: Formulae for preparation of Ranolazine ER tablets

Ingredients	F1 * (mg/tab)	F2 (mg/tab)	F3 (mg/tab)	F4 (mg/tab)	F5 (mg/tab)	F6 (mg/tab)	F7 (mg/tab)	F8 (mg/tab)	F9 (mg/tab)
Ranolazine	500	500	500	500	500	500	500	500	500
Microcrystalline cellulose pH101	108.25	96.55	81.6	68.35	55.05	75.05	61.7	46.2	48.4
Eudragit L-100 55	33.25 (5%)	33.25(5%)	33.25(5%)	33.25(5%)	33.25(5%)	39.9(6%)	53.2(8%)	59.9(9%)	66.5(10%)
HPMCK15M	13.5(2%)	27(4%)	39.9(6%)	53.2(8%)	66.5(10%)	39.9(6%)	39.9(6%)	39.9(6%)	39.9(6%)
Meglumine	-	7	7	7	7	7	7	7	7
Purified Water	-	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium stearate	10	10	12	12	12	12	12	12	12
Total weight(mg)	665	665	665	665	665	665	665	665	665

F1* Indicates formulation batch was prepared by dry granulation method.
F2-F9 Indicates formulation batch was prepared by wet granulation method

Dry granulation method

F1 Formulation batch were prepared by dry granulation method. Weigh the required quantities of Ranolazine, Eudragit and Sift the drug, Eudragit, hydroxy propyl methyl cellulose, Micro crystalline cellulose materials through #40 mesh and the blend is mixed in a poly bag for uniform distribution of API. Then dry blend was made in to slugs. The resulting slugs were passed through #20 in order to get uniform sized granules. Required amount of magnesium stearate is weighed and passed through #60 mesh and blended with previously sieved dry granules. The preformulation studies of granules are carried out by determining Bulk density, Tapped density, Compressibility index (carr's index), Angle of repose, Hansner's ratio. Then granules were compressed by using 17x8mm caplet shape standard concave punches using compression machine.[12]

Wet granulation method:

F2-F9 Formulation batches were prepared by wet granulation method.Weigh the required quantities of ranolazine, Eudragit and Sift the drug, Eudragit, hydroxy propyl methyl cellulose, Micro crystalline cellulose materials are passed through #40 mesh and the blend is mixed for uniform distribution of API. For granulation process all the ingredients are placed in RMG mixer and dry mixing is carried for 5mins. Required amount of meglumine is weighed and is dissolved in sufficient quantity of water. Then this solution is slowly added to the granulator. After formation of granules they are allowed to dry by placing them in tray dryer. The dried granules are sifted by passing through #20 mesh to achieve uniform sized granules. Required amount of magnesium stearate is weighed and passed through #60 mesh and blended with previously sieved dry granules. Then preformulation studies of granules are carried out by determining, Bulk density, Tapped density, Compressibility index, Angle of repose, Hansner's ratio. Then the granules were compressed by using 17x8mm caplet shape standard concave punches using compression machine.[12]

Evaluation of prepared matrix tablets:

The compressed extended release tablets from different formulations were evaluated for different compression parameters like hardness, weight variation, thickness, friability and *In-vitro* dissolution testing is carried out for drug release.[13,14,15]

Appearance

The general appearance of a tablet, its visual identity and over elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and general tablet to tablet and for monitoring troubled free manufacturing.

2. Weight Variation Test

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

Hardness:

Tablets must be able to withstand the rigors of handling and transportation experienced in the manufacturing plant, in the drug distribution system, and in the field at the hands of the end users. Hardness of tablets was determined by using hardness tester.

Thickness:

Thickness of tablets was determined by using Vernier calipers.

Friability

(ElectrolabEF-2) Friability test apparatus is used to determine the friability of the tablets. About 10

tablets were selected, de-dusted and weighed. Then they are placed in a friabilator and rotated for 100 rpm. Then the tablets are reweighed. The % friability is calculated by

% F = {1- (Wt / W)} × 100

Where,

% F = friability in percentage,
W = Initial weight of tablet,
Wt = weight of tablets after revolution

Drug content uniformity:

The average drug content of 10 tablets of each formulation was weighed individually and the drug was extracted in buffer and allowed to sonicate for 10 mins. The solution was filtered. The absorbance is measured at 272 nm by using a Simadzu UV Spectrophotometer

In-vitro Dissolution Study of Tablets:

In vitro Drug release study for prepared extended release tablets of Ranolazine were conducted for 24hrs using (ELETRO lab USP XXIITDT- 08L) apparatus by using dissolution medium pH 1.2 acid buffer & 6.8 pH Phosphate buffer of 900ml, bath temperature maintained at 37 ± 0.5 ºC and Speed of 50 rpm and the samples are withdrawn at a time interval of 0.5 ,2, 4,8,12,20,24 hrs, and replaced with the fresh sample, and the absorbance were measured at 272 nm using Simadzu UV Spectrophotometer.[8,16,17,]

Stability studies

Stability studies, carried out according to ICH guidelines by storing the tablets at 40°c/75±5%RH for a period of three months. [18]

RESULTS AND DISCUSSION

Precompression studies:

Flow properties of granules, prepared from all the formulations are good except for F1 formulation as obtained from the Bulk density, Tapped density, Hausner's ratio, Compressibility index and angle of repose values indicated, in the (**Table 2**).

Table 2: Flow properties of prepared Granules from formulations F1-F9

Formulation	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose
F-1	0.68 ± 1.08	0.93 ± 0.41	27.5 ± 0.27	1.37 ± 0.25	44
F-2	0.46 ± 0.09	0.59 ± 0.04	22.1 ± 0.11	1.28 ± 0.27	30
F-3	0.47 ± 0.17	0.59 ± 0.18	20.3 ± 0.22	1.25 ± 0.21	26
F-4	0.46 ± 0.28	0.58 ± 0.01	20.6 ± 0.01	1.26 ± 0.16	24
F-5	0.46 ± 0.20	0.57 ± 0.25	19.7 ± 0.14	1.23 ± 0.15	25
F-6	0.47 ± 0.05	0.59 ± 0.13	20.4 ± 0.04	1.25 ± 0.24	23
F-7	0.46± 0.02	0.57 ± 0.17	19.5 ± 0.15	1.24 ± 0.14	24
F-8	0.46 ± 0.24	0.57 ± 0.05	18.8 ± 0.14	1.23 ± 0.21	23
F-9	0.46 ± 0.04	0.57 ± 0.07	18.7± 0.03	1.23 ± 0.08	23

(Data represents mean ± SD, n=3)

Post compression studies:

The physical parameters like weight variation, hardness, thickness, friability of the tablets were within the pharmacopoeial limits and were shown in the (**Table 3**).

Table 3: Physico-chemical evaluation of Tablets

Formulations	Average Weight of tablets	Hardness (kg/cm²)	Thickness(mm)	Friability (%)	Drug content (%)
F1	--	3.8±0.98	6.18±0.02	--	97.26
F2	664.29 ± 1.51	8.2±1.09	6.01±0.05	0.18	99.16
F3	663.74 ± 1.98	8.7±0.84	5.95±0.07	0.08	98.85
F4	664.84 ± 1.59	9.6±0.72	5.97±0.06	0.06	99.15
F5	666.26 ± 1.81	9.7±0.81	5.96±0.08	0.06	97.75
F6	665.81 ± 1.87	9.9±0.21	5.93±0.04	0.05	98.89
F7	663.45 ± 1.98	9.8±0.37	5.94±0.02	0.04	98.73
F8	667.97 ± 1.61	10.02±0.16	5.98±0.03	0.02	99.61
F9	664.21 ± 1.96	9.9±0.14	5.97±0.05	0.03	99.87

(Data represents mean ± SD, n=3)

Estimation of drug content:

In the Ranolazine drug assay all the formulations was found in the range of 97 to 99%. Drug content analysis indicated that the Ranolazine was uniformly distributed in all the formulations, and the lower and higher yield is due to the result of processing conditions.

F1 formulation batch is prepared by dry granulation method and the resulted granules were showing poor flow properties, the tablets prepared from these granules failed in the friability test and weight variation test. Hardness of tablet was low and need to be improved. For this reason F2-F9 formulation, granules were prepared by wet granulation method.

In-vitro dissolution studies:

Tablets prepared from F1 formulation by dry granulation method were not subjected to further testing as they don't have sufficient hardness and failed in the friability test and weight variation test. Drug release studies of F2-F9 formulations were carried out in pH 1.2 acid buffer for 2hrs & in pH 6.8 phosphate buffer up to 24 hrs. Drug release profiles of all formulations were shown in (**Table 4**).

Table 4: Cumulative% Drug release of formulations F2-F9& Innovator

Time (hrs)	Cumulative % drug release*								
	F2	F3	F4	F5	F6	F7	F8	F9	Innovator
0	0	0	0	0	0	0	0	0	0
0.5	50.1±0.2	47.3±0.8	45.1±0.5	42.2±1.2	37.1±1.06	32.4±0.7	24.5±0.9	19.8±0.5	17.8±0.6
2	70.9±0.4	66.6±0.2	63.2±0.7	61.2±0.9	52.7±1.02	46.8±0.6	40.2±0.8	35.4±0.7	34.2±0.5
4	87.2±0.1	83.7±0.7	81.9±0.6	76.1±0.8	64.2±1.07	58.5±1.06	53.9±1.09	50.6±0.3	48.4±0.4
8	96.3±0.6	94.6±0.3	93.7±0.4	90.2±0.6	81.1±1.09	75.9±1.05	70.1±1.2	68.7±0.7	65.5±0.4
12	--	97.8±0.6	97.4±0.3	98.2±0.9	92.8±0.9	87.2±1.3	82.4±1.09	81.5±1.06	78.3±0.3
20	--	--	--	--	98.7±1.2	95.6±1.06	94.1±1.3	93.9±1.2	93.2±0.5
24	--	--	--	--	--	98.4±1.1	98.7±0.4	99.4±0.3	99.1±0.5

(Data represents mean ± SD, n=3

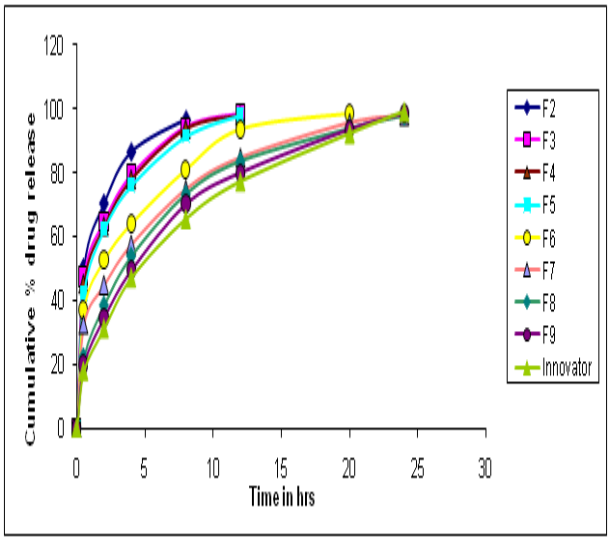

Figure 1: Cumulative% drug release plots for formulations F2-F9 with innovator

In (Figure 1) F2-F5 formulations Eudragit L 100-55 is used in 5% and HPMC K15M is used in 2% to 10%.In F2 formulation HPMC K15M is used in 4%.Tablets satisfy all the compression parameters but slight sticking problems were observed. In F3 formulation HPMC K15M concentration is increased from 4% of total formulation composition to 6%, to reduce the dissolution rate of the drug by increasing pH independent polymer alone. Magnesium stearate concentration is increased by 2mg to reduce sticking problems. Sticking problem was resolved. In F4 formulation HPMC K15 M concentration is further increased from 6% to 8% .In F5 formulation HPMC K15 M concentration is further increased from 8% to 10% of total composition. About 98.2% of drug is dissolved at the end of the 12hrs.

The results obtained from drug release studies of F2-F5 are more or less similar and the release is not extended beyond the 12hrs.It may be because of high solubility of drug in acid medium and the HPMC is not pH dependent polymer. Because of the above reasons even though HPMC K15M is a rapidly hydrating and high viscous polymer, it alone (with out increasing Eudragit concentration) could not sustain the release for 24hrs.

In order to extend the release time from 12hrs to 24 hrs. F6-F9 formulations, the pH dependent polymer (Eudragit L 100-55) concentration were increased from 5% to 10% and HPMC K 15M concentration was keeping constant at 6%. F6 formulation, the pH dependent polymer (Eudragit L 100-55) concentration is increased from 5% to 6%, the release was extended to 20hrs shown in (**Figure 1**). Even though the dissolution is still on higher side when compared to previous formulation. But, it sustains the release for more period. It is due to the increase in Eudragit polymer concentration.F7 formulation, Eudragit polymer concentration was increased from 6% to 8%. Dissolution was extended to 24hrs but it was not within the official limits. It means that with increase in Eudragit polymer alone the release was extended when compared to increase in HPMC

K15M alone. In F8 formulation, Eudragit concentration was further increased from 8 to 9% of total formulation. About 98.7% of drug was released at the end of 24 hrs but not with in official limits. In F9 formulation, Eudragit concentration was further increased from 9% to 10 % of total formulation. About 99.4% of drug was released at the end of 24 hrs and the drug release was within official limits and drug release was closer to that of innovator shown in (Figure 1).

Comparision of Cumulative % drug release of F9 -formulation with Innovator

In (**Table 5**) the formulation F9, the drug release profile was compared with innovator and dissolution data of F9 formulation was found to be closer to the Innovator. Complete release of drug was observed in a sustained way similar to that of Innovator product and found to be within the USP limits.

Table 5: Comparision of Cumulative % drug release of F9 -formulation with Innovator

Time (hrs)	Cumulative % drug release*	
	F9	Innovator
0	0	0
0.5	19.8±0.5	17.8±0.6
2	35.4±0.7	34.2±0.5
4	50.6±0.3	48.4±0.4
8	68.7±0.7	65.5±0.4
12	81.5±1.06	78.3±0.3
20	93.9±1.2	93.2±0.5
24	99.4±0.3	99.1±0.5

(Data represents mean ± SD, n=3)

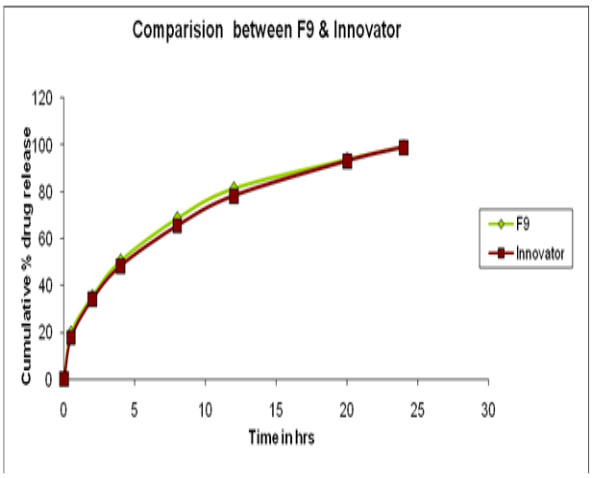

Fig 2: Comparison of Cumulative % drug release for formulation-F9 with Innovator

Based on the results obtained from the comparison plot, F9 formulation matches with the innovator product. Similarity factor 'f2' value was found to be 79.7.Based on similarity factor values, F9 formulation was selected as an optimized formulation.

Drug release kinetics from matrix tablets

In order to find out the drug release mechanism and kinetic, all formulations and Innovator were subjected to zero, first order and Higuchi, korsemeyer peppas plots. Based on R^2 values of first order and Higuchi, korsemeyer peppas, the F9 formulation indicated a good linearity with significantly high correlation coefficient values similar to that of Innovator. From the graphs various kinetic parameters were determined and shown in the (**Table 6**).

Table 6: Drug release kinetic parameters of formulations from F2-F9 and Innovator

Formulation	Zero order	First order	Higuchi	peppas	
	R^2	R^2	R^2	n value	R^2
F2	0.645	0.949	0.886	0.239	0.989
F3	0.643	0.973	0.874	0.238	0.982
F4	0.671	0.970	0.893	0.254	0.984
F5	0.715	0.983	0.919	0.269	0.992
F6	0.715	0.971	0.922	0.272	0.995
F7	0.759	0.964	0.939	0.300	0.990
F8	0.821	0.966	0.972	0.368	0.993
F9	0.849	0.951	0.983	0.427	0.994
Innovator	0.870	0.964	0.990	0.443	0.996

The release data indicated a good linearity with significantly high correlation coefficient values for the first order release rate then for the zero order release constants. Although it is desirable for a controlled release device to deliver the drug in zero order fashion it is extremely difficult to obtain such pattern as the kinetics of release is affected by physico-chemical compositions of matrix tablet, dissolution medium and processing variable. Plot of the amount of drug release Vs square root of time were found to be linear and the drug release mechanism from the matrix tablets might be diffusion type as proposed by Higuchi for all the formulations which ranges from (0.886-

0.983). Accordingly, the drug release from these matrix tablets involves penetration of dissolution fluid, leaching out of the drug through intestinal channel or pores.To further evaluate the release mechanism, the Korsemeyer peppas plots are drawn. Based on n values obtained it indicated that all the formulations followed fickian diffusion process which ranges from (0.239-0.427). It concludes that the drug release from the polymers is by diffusion alone

Stability studies:

The tablets of F-9 formulation were kept in stability chamber for three months at temperature of 40ºC/75% RH. These samples were compared with control samples for every month with respect to physical parameters, assay and drug release studies. It was seen that physically there was no change with respect to appearance, hardness, thickness. There was no significant change in dissolution profile and assay values from the initial results.

CONCLUSION

From this study one can conclude that for Ranolazine the pH dependent polymer controls the release effectively then pH independent high viscosity and rapid hydrating polymer. By increasing HPMC K 15 M concentration, drug release is not sustained more than 12hrs and the values obtained are more or less similar, it is because of high solubility of drug in acid medium. As Eudragit L100-55 polymer is pH dependent and is soluble at only pH greater than 4.5, by increasing its concentration the release was sustained for 24hrs.By comparing the drug release profiles of F2 to F9 formulations with innovator.F9 formulation matches with the innovator product (similarity factor 'f2' value was found to be 79.7) Release followed first order kinetics. Release data of the tablets more obeyed First order, Higuchi, Peppas equation models. Higuchi plots were linear indicating that the drug release from these tablets was diffusion controlled. The "n" value was in the range 0.23-0.42 with all the nine formulations developed, indicating that the fickian diffusion was the release mechanism. No significant change was observed in the drug content, physico-chemical properties and dissolution rate of these tablets after the storage period of 3months at 40º c and 75%RH. Accordingly it can be concluded that by F9 formulation one can expect an excellent in-vitro correlation & also increase the patient compliance.

REFERENCES

1. Swarbrick J, Boylan JC. In: Encyclopedia of Pharmaceutical Technology. Vol-2:ed 1.New York: Marcel Dekker, Inc ; 1998:338-339.
2. Jantzen GM, Robinson JR. Sustained-and controlled-release drug delivery systems. Banker G, Rhodes C, editors. Modern pharmaceutics. 3rd ed. NewYork: Marcel Dekker, Inc; 1996. 575-609
3. Qiu Y, Zhang G. Research and Development Aspects of Oral Controlled-Release Dosage forms in Handbook of Pharmaceutical Controlled Release Technology. In: Wise DL, editor. NewYork: Marcel Dekker Inc; 2000. 527-530.
4. Available from URL: http://www.RxList.com.
5. Available from URL: http://www.rxlist.com/ranexa-drug.htm.
6. Hasenfuss G, Maier LS. Mechanism of action of new anti-ischemic drug ranolazine.Clin Res Cardiol. 2008; 97(4):222–26.
7. Available from URL:http://en.wikipedia.org/wiki/Ranolazine.
8. www.freepatentsonline.com.
9. Robert M. Silverstein, Francesx Webster, "Spectrometric identification of organic compounds", 6th edition.
10. Aulton M.E. Flow properties - The Science of dosage form design second ed, 205-209.
11. Wolff,AndrewA.Sustained release ranolazine formulations.Patent EP1096937. 2007.
12. Jovanovis M, Jokic D, Duric Z, Tasic L & Jovicic G. Prepration and preliminary evaluation of sustained release tablets. 1990; 45:869.
13. Popli H, Sharma SN. Evaluation of sustained release formulations. The eastern pharmacist. Jan. 1990; 75-79.
14. Sauer D, Zheng W, Lonique B. Coots, James W. Influence of processing parameters Euro. J. Pharma. Biopharma 2007; 67: 464–475.
15. Aulton ME. Pharmaceutics: the Science of Dosage Form Design. 2.nd ed Living stone C. Elsevier Science Ltd. 2002; 315-20.

16. Guidance for industry. Extended release oral dosage forms: Development, evaluation and application of in vitro/in vivo correlations. U.S Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research (CDER). September.1997; BP: 1-27.
17. United State Pharmacopoeia 24, 2002, Pg. 1607.
18. Lachman L, Patric D. Akers J. kinetic principles and stability. Theory and practice of industrial pharmacy. 3rd ed Philadelphia: Varghese publishing house, 1987; 767.