International Journal of Farmacia

Journal Home page: www.ijfjournal.com

Formulation and evaluation of osmotic tablets of Ranolazine

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ABSTRACT

Ranolazine is a clinically effective antianginal agent that has been used as the sodium- dependent calcium ion influx inhibitor and inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle. Osmotic tablets of ranolazine were prepared by using polymers like HPMC K4M, lactose, povidone K-30, carbopol. The effect of the storage at high temperatures at 40°C, 50°C and 60°C for a period of 3 months on the chemical stability of the selected tablets and prediction of the shelf life was also assessed. Nine formulations were formulated. Pre-compression parameters such as Angle of repose, bulk density, Carr's index, Haunser ratio were evaluated. The purpose of this work was to formulate a solid dosage form for Ranolazine using the principles of osmosis which will bring down its dosing frequency to once a day and at the same time produce a zero-order release system.

Keywords: Osmotic tablets, HPMC, Osmogen, Zero-order release system.

INTRODUCTION

Among the various novel drug delivery systems available in market, per oral controlled release(CR) systems hold the major market share because of their obvious advantages of ease of administration better patient compliance, greater effectiveness in the treatment of chronic conditions [1], reduced side effects and greater patient convenience due to a simplified dosing schedule. Osmotically controlled oral drug delivery systems utilize osmotic pressure for controlled delivery of active agent(s) [2]. Alza Corporation of the USA was first to develop an oral osmotic pump. Ranolazine is a novel antianginal agent capable of producing *Anti-ischemic* therapy effects at plasma concentrations of 2 to 6 µmol/L without reducing heart rate or blood pressure. IUPAC name of ranolazine is N-(2, 6-dimethylphenyl)-2-[4-[2-hydroxy-3-(2-methoxyphenoxy) propyl] piperazin-1-yl]acetamide and the molecular weight 427.53657g/mol [3].

Ranolazine inhibits the late inward sodium current in heart muscle [5]. Inhibiting that current leads to reductions in elevated intracellular calcium levels [4]. This in turn leads to reduced tension in the heart wall, leading to reduced oxygen requirements for the muscle [6]. At therapeutic sub-toxic concentrations, Ranolazine has little effect on cardiac myocytes and conduction cells [7]. By blocking the calcium channels [8], Ranolazine inhibits the spasm of the coronary artery and dilates the systemic arteries, results in a increase of myocardial oxygen supply and a decrease in systemic blood pressure [9].

MATERIALS AND METHOD

Various materials used in preparing Ranolazine osmotic tablet formulations are ranolazine and

HPMC K4M, lactose, Povidone K30, carbopol, magnesium stearate, Sodium chloride, talc [10].

Methods

Preparation of calibration curve of Ranolazine

50 mg of Ranolazine is dissolved in a 50 ml volumetric flask with ethanol, made up the volume with pH 6.8 phosphate buffer [11]. From this solution 1ml is taken and diluted to 10 ml with phosphate buffer in a 10 ml volumetric flask [12]. From this stock solution 0.5ml, 0.75ml, 1ml, 1.25ml,1.5ml of solution is taken in different volumetric flasks and volume made up to 10 ml with pH 6.8 phosphate buffer .Absorbance is measured at 238nm using Beer's range (50-150 mcg/ml) [13].

Fourier Transforms Infra-Red Spectroscopy (FT-IR)

Fourier-transform infrared (FTIR) spectroscopy was performed on each of the samples to determine the structure of the organic compounds and to identify the presence of specific functional groups within a sample [14]. Furthermore, drug-polymer interactions were examined using the resulting spectra. The mixture was then ground to a fine powder using a mortar and pestle [15], and transparent discs were formed using a pellet press. The discs were then placed in the FTIR spectroscopy apparatus, and spectra were collected. The range of the collected spectra was 4000-400cm^{-1} [16].

Table 1: Ranolazine sustained release matrix tablets of F1-F9 formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ranolazine	500	500	500	500	500	500	500	500	500
HPMC K100 M	-	-	-	-	40	80	120	160	200
Carbopol	40	80	120	160	-	-	-	-	-
Lactose	228	180	132	84	156	148	100	52	44
Povidone K-30	8	8	8	8	8	8	8	8	8
Nacl	8	16	24	32	40	8	16	24	32
Mg. Stearate	8	8	8	8	8	8	8	8	8
Talc	8	8	8	8	8	8	8	8	8
Total Weight	800	800	800	800	800	800	800	800	800

RESULTS & DISCUSSION

Preparation of calibration curve of Ranolazine

50mg of Ranolazine active pharmaceutical ingredient (API) is dissolved in a 50 ml volumetric flask with ethanol. Then it is made up to volume with pH 6.8 phosphate buffer. From this solution 1ml is taken and diluted to 10 ml with pH 6.8 in a 10 ml volumetric flask. From this stock solution 0.5ml, 0.75ml, 1ml, 1.25ml, 1.5ml, of solution is taken in different volumetric flasks and volume made up to 10 ml with pH 6.8 phosphate buffer. Absorbance is measured at 238nm using Beer's range (50-150 mcg/ml).

Table 2: Preparation of standard curve of Ranolazine

S. No.	Ranolazine (µg /ml)	Absorbance
1	50	0.212
2	75	0.320
3	100	0.424
4	125	0.530
5	150	0.637

Standard calibration curve of Ranolazine

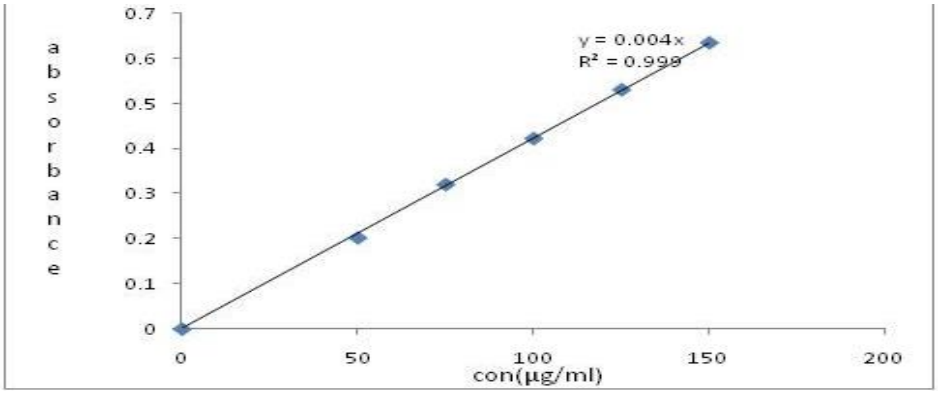

Fig 1: Standard calibration curve of Ranolazine in phosphate buffer pH 6.8

Fourier Transforms Infra Red Spectroscopy

FTIR studies revealed that there is no interactions of excipients with Ranolazine. All the absorption bands of the functional groups of ranolazine are visible when combined with excipients.

Table 3: Interpretation of pure drug

Functional Groups	Frequency	Observed Frequency
Methyl group	2872 cm^{-1}	2889 cm^{-1}
Pyridine	1622 cm^{-1}	1642 cm^{-1}
Aryl nitro compound	828 cm^{-1}	837 cm^{-1}

In vitro Dissolution studies

Table 4: Results of percentage cumulative drug release profile for F1-F9 formulations

Time Hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	20.45±0.5	15.0±04	16.36 ±0.3	19.77 ±0.4	18.40 ±0.3	14.61 ±0.5	16.70 ±0.1	15.20±02	14.27 ±0.1
2	44.65±0.2	26.59±0.3	28.23 ±0.2	42.27 ±0.2	32.04 ±0.5	30.52 ±0.7	31.70 ±0.5	28.63 ±0.3	25.5±0.3
4	66.13 ±0.3	42.61 ±0.6	40.22 ±0.5	61.36 ±0.3	50.93 ±0.3	46.06 ±0.2	48.06 ±0.5	45.18 ±0.6	39.36 ±0.2
8	82.5±0.2	61.02 ±0.2	53.86 ±0.2	82.84 ±0.2	75.22 ±0.4	62.34 ±0.6	62.04 ±0.5	60.09 ±0.3	57.04 ±0.6
12	99.20 ±0.3	82.84 ±0.5	73.29 ±0.6	97.84 ±0.3	80.52 ±0.4	80.02 ±0.51	83.86 ±0.1	76.43 ±0.62	74.38 ±0.3
16		98.52 ±0.2	85.66 ±0.6		87.84 ±0.3	85.45 ±0.2	98.18 ±0.3	83.52 ±0.	81.11 ±0.1
20			98.18 ±0.2		97.84 ±0.3	88.29 ±0.5		97.84 ±0.6	95.0±0.2
24						96.18±0.2			99.20 ±0.3

In vitro drug release studies revealed that release of Ranolazine from different formulations varies with characteristics and composition of matrix forming polymers. The release rate increased with decreasing concentration of HPMC. Eudragit is hydrophobic polymer which delays the drug release in F7 to F9 formulations.

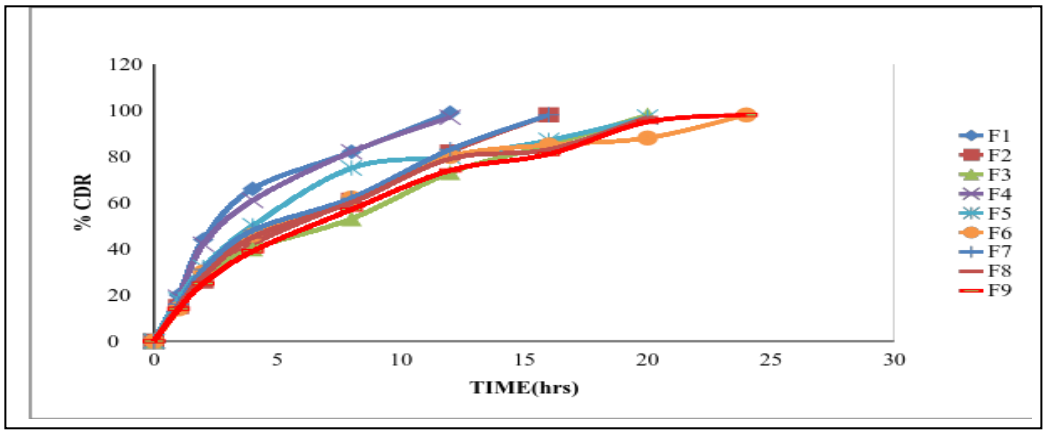

Fig 2: Percentage cumulative drug release profile of F1-F9 formulations

The above figure shows the in vitro release profiles of Ranolazine Osmotic tablets of formulations F1-F9. Effect of different polymers on the release profile of Ranolazine was studied.

Release kinetics and mechanism

To know the release mechanism and kinetics of Ranolazine optimized formulation F9 was fit into mathematical models of zero order, First order, Higuchi and Peppas models. The peppas model is widely used, when the release mechanism is not well known or more than one type of release could be involved. The semi-empirical equation (Peppas et al., 1985) shown as equation:

$Mt/M\infty = kt^n$

Where, $Mt/M\infty$ is fraction of drug released at time't', k represents a constant, and n is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process.

For non-fickian release, the value of n falls between 0.5 and 1.0; while in case of fickian diffusion, n = 0.5; for zero-order release (case II transport), n = 1; and for supercase II transport, n >0.89

Table 5: Kinetic modeling of F1-F9 formulations

Formulation code	Zero Order (R^2)	First Order (R^2)	Higuchi (R^2)	Hixon Crowell (R^2)	Korsemeyer Peppas	
					R^2	n
F1	0.873	0.9161	0.9785	0.9771	0.9345	0.607
F2	0.8856	0.9683	0.9872	0.9695	0.9967	0.664
F3	0.9565	0.8778	0.992	0.966	0.991	0.578
F4	0.8927	0.9689	0.9846	0.9902	0.9464	0.624
F5	0.8652	0.9526	0.9779	0.9689	0.9673	0.544
F6	0.8782	0.9292	0.9816	0.9711	0.957	0.571
F7	0.9442	0.8917	0.9906	0.9689	0.9802	0.5957
F8	0.9215	0.9211	0.9916	0.9747	0.9803	0.5957
F9	0.9313	0.9498	0.9827	0.9874	0.9887	0.4357

First order kinetics

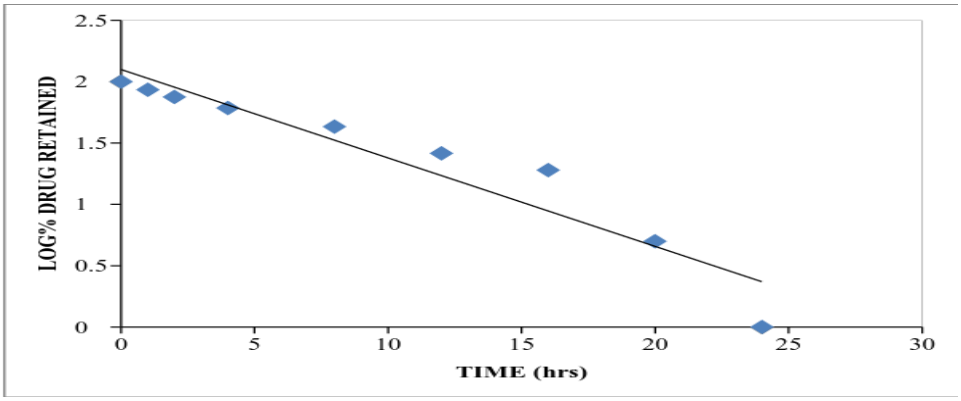

Fig 3: First order plot of optimized F9 formulation

Zero order kinetics

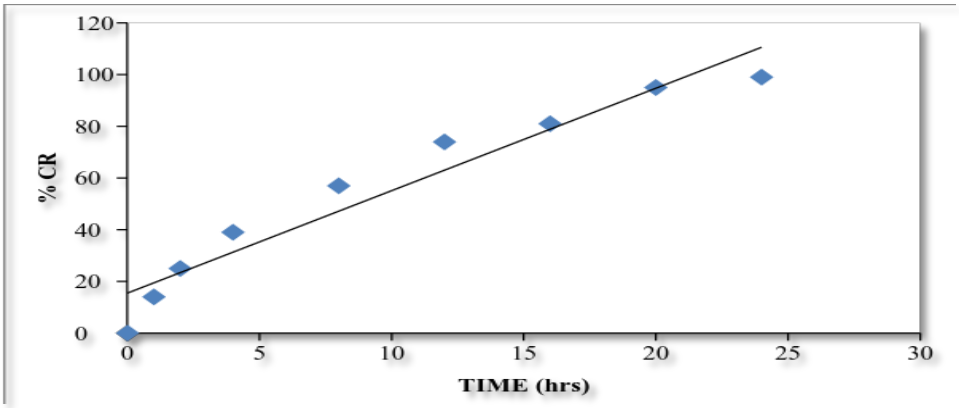

Fig 4: Zero order plot of optimized F9 formulation

Higuchi plot

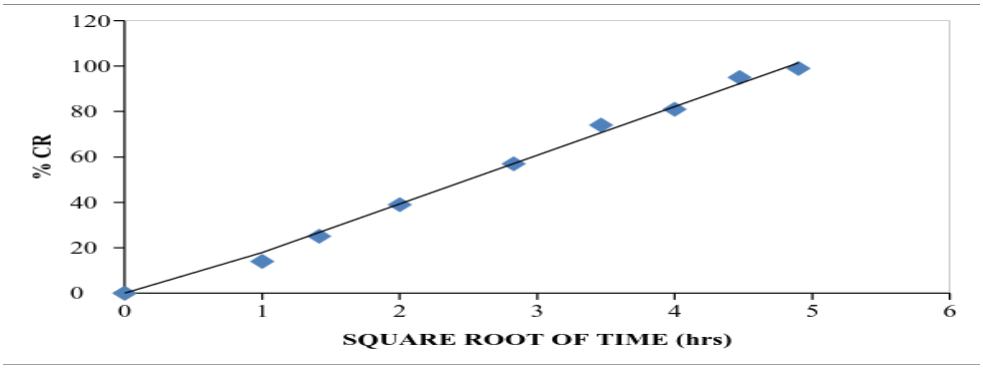

Fig 5: Higuchi plot of optimized F9 formulation

Hixon Crowell plot

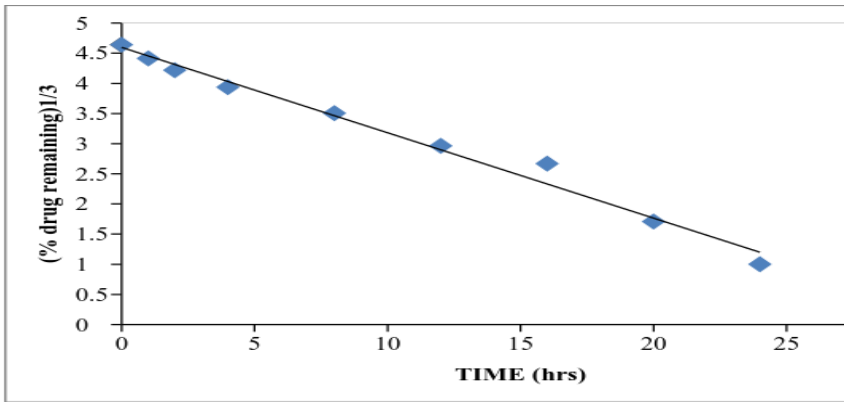

Fig 6: Hixon Crowell plot of optimized F9 formulation

Kores Meyer Peppas plot

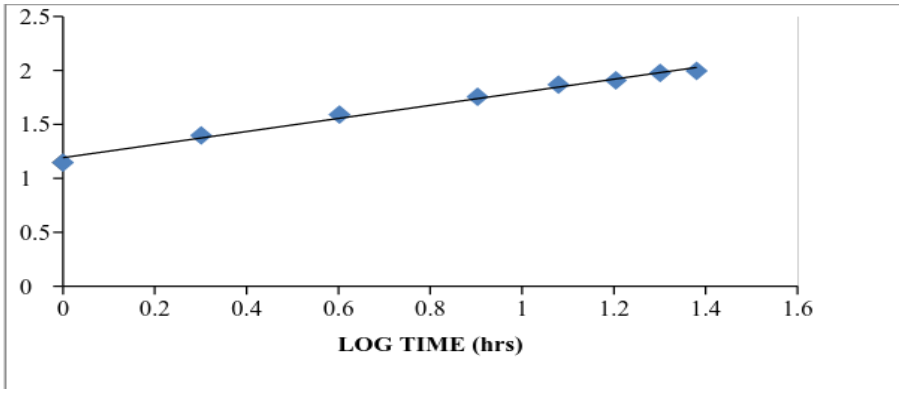

Fig 7: Kores Meyer Peppas plot of optimized F9 formulation

Stability Studies

There was no significant change in physical and chemical properties of the tablets of formulation F-9 after 3 Months. Parameters quantified at various time intervals were shown.

Table 6: Stability study data of optimized F9 formulation

Formulation Code	Parameters	Day 1 % CDR	30 days % CDR	60 days % CDR	90 days % CDR
F9	25^0C/60%RH	99.20	99.18	99.17	99.15
	30^0C/75% RH		99.18	99.17	99.15
	40^0C/75% RH		99.18	99.17	99.15

CONCLUSION

Ranolazine is used in angina.In the present work osmotic tablets were successfully formulated by using different polymers by wet granulation method. The drug-excipient interaction study was carried out using FTIR. In the drug-excipient interaction study, it was found that Ranolazine was having compatibility with all the excipients used in the formulation. The optimized formula showed, Hardness – 5.7 kg\cm^2,

Friability – 0.04, % CDR – 99.20. From the *in vitro* dissolution analysis the following conclusions are drawn. Formulation batches with HPMC K100 and Carbopol showed better release. It was observed that by increasing the viscosity of polymer a retarding effect on the release from the polymer matrix. From the dissolution profile modeling it was found that the optimized formulation F9 followed first order kinetics. When the stability results of best formulae was studied at 40^0 C AND 75% RH for 3 months were compared with their initial results it was found that there was no significant difference in hardness, friability, drug content and drug release of optimized formulation.

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