Australian Journal of Pharmaceutical Research

Journal homepage: www. http://mcmed.us/journal/ajpr

FORMULATION AND EVALUATION OF EXTENDED RELEASE TABLETS OF RANOLAZINE

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Article Info

Received 25/10/2013
Revised 15/11/2013
Accepted 18/11/2013

Key words:
Hydroxymethylcellulose, Ranolazine, Carbomer.

ABSTRACT

The present study was aimed to develop Ranolazine extended release tablets for the treatment of Angina, specifically reduces calcium overload in the ischemic myocyte through inhibition of the late sodium current (I_{Na}). Ranolazine extended release tablets enchance patient compliance and reduce adverse effects.A total of 9 formulations were developed using varying proportions of Hydroxy propyl methyl cellulose, carbomer as release retardant polymers by wet granulation technique. FT-IR studies revealed that there was no interaction between drug and polymers used.Before compression the granules were evaluated for precompression parameters such as bulk density, taped density, cars index, hausners ratio, angle of repose. After compression tablets were evaluated for appearance, weight variation, hardness, thickness, drug content, friability, in vitro release studies and stability studies.

INTRODUCTION

Presently, these conventional dosage forms are primarily, prescribed pharmaceutical products. To achieve and to maintain the concentration of an administered drug within therapeutically effective range, it is often necessary to take drug dose several times a day. This results in fluctuating drug levels in plasma [1-5]. In conventional oral drug delivery systems, there is a very little control over release of the drug. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses. Such situations often results in constantly changing, unpredictable and often sub or supra therapeutic plasma concentrations leading to marked side effects [5-9]. Controlled drug delivery systems have been introduced to overcome the drawback of fluctuating drug levels associated with conventional dosage forms.

MATERIALS

Microcrystalline cellulose 101 from Accent mirogel industry, Carbopol from MSN Pharma, Meglumine from MSN Pharma, Hydroxy propyl methyl cellulose from Dow Chemical company, Polyvidone from MSN Pharma, Magnesium stearate from EMCO industries, sodium hydroxide pellets from FINE industries, Aerosil from MSN Pharma and all are of pharmacerutical grade [10].

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Wet granulation method

Preparation of Extended Release Tablets:

- All the ingredients were weighed accurately as per the manufacturing formula.
- Ranolazine, microcrystalline cellulose, carbopol 974p and HPMC (Rutocel) were passed through #40 mesh sieve & collected in a polybag.
- Above sifted materials was loaded in a planetary mixer and mixed for 15 min at slow speed.
- About 0.5 gm of sodium hydroxide pellets was added in a 55 ml of purified water and added to the contents of planetary mixer.
- The wet dough mass was was passed through #16 meshes sieve and dried at 50◦-55◦C by using tray drier for 6 to 7hrs, till desired LOD is achieved.
- Oversized granules passed through 2.0 mm multimill at medium speed in forward direction.

- Finally milled granules was passed through #16 meshes sieve and loaded in a double cone blender.
- Magnesium stearate was passed through #40 meshes and it was added to the contents of double cone blender and mixed for 10 min.
- Material was loaded in a hopper and compresses the powder into tablets by using (Cad mach) compression machine with (17.5×8.0) mm standard concave punches. Check for weight variation, hardness (Hardnesstester, Pharmatest-PTB-311E), friability (Friabilator (USP), Electro lab- EF-2), thickness to meet the parameters [12-14].

PRECOMPRESSION PARAMETERS

The granules were evaluated for Angle ofrepose, Bulk density, Tapped density, Compressibility index and Hausner'sratio. The angle of repose was determined by fixed funnel method toassess the flow property of granules. Bulk density is the ratio between agiven mass of the powder or granules and its bulk volume. Tapped density is the ratio between a given mass of powder or granules and the constant or fixed volume of powder or granules after tapping. Bulk and tapped densitywere determined using digital bulkdensity apparatus. The compressibilityindex and the Hausner ratio are determined by measuring both the bulk volume and tapped volume of powder (or) granules.

Hausner's Ratio = Tapped density/Bulk density
Carr's index (%) = [(TD-BD) / TD] ×100
Where, TD = Tapped density, BD = Bulk density.

IR spectral analysis

FT-IR analysis of pure drug, individual polymer and combination of drug and polymers in higher concentration were taken for the study. Samples were compressed with potassium bromide and transformed into disk and scanned between 4000-400 cm in a SHIMADZU FT-IR (IR Affinity spectrophotometer

POST COMPRESSION PARAMETERS

Thickness, Diameter and Hardness

Thickness and diameter of the tablets were determined using Vernier caliper. Hardness or tablet crushing strength was measured using Monsanto tablet hardness tester

Weight variation test

Twenty tablets were selected at random and average weight was determined. The individual tablets were weighed and compared with average weight not more than two of the individual weights deviate from the average weight of tablets by more than 5%.

Friability test

The friability of tablets was determined by "Roche" friabilator. Ten tablets were taken and weighed. The tablets were subjected to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm for 4 minutes, dropping the tablets from a distance of six inches with each revolution. After operation, the tablets were dedusted and reweighed. The Percentage friability was determined using the formula:
Percentage Friability = [(Initial Weight – Final Weight)/ Initial Weight] × 100

Drug content estimation

Ranolazine content in the extended release tablets was estimatedby UV Spectrophotometric method based on measurement of absorbance at 233nm using 0.1 Hcl solution.

INVITRO DISSOLUTION STUDIES OF TABLETS [15,16]

Dissolution studies were carried out for all the formulations combinations in triplicate, employing USP XXVII paddle method and 900ml of 0.1N HCL as the dissolution medium. The medium was allowed to equilibrate to temp of 37°c $\pm$ 0.5°c. Tablet was placed in the vessel and the vessel was covered. the apparatus was operated for 24 hrs in 0.1N HCL at 50 rpm. At definite time intervals of 5 ml of the aliquot of sample was withdrawn periodically and the volume replaced with equivalent amount of the fresh dissolution medium. The samples were analyzed spectrophotometrically at 272 nm using uv-spectrophotometer

Release Kinetics

The analysis of drug release mechanism from a pharmaceutical dosage from is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to five popular release models such as zero-order, first-order diffusion and exponential equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi equation, erosion equation and Peppas-Korsemeyer equation. The results are given in Table 2 and 3.

Zero Order Release Kinetics

It defines a linear relationship between the fraction of drug released versus time.

$$Q = k_o t$$

Where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant.
A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First Order Release Kinetics

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most of the slow release tablets could be described adequately by apparent first-order kinetics. The equation that describes first order kinetics is

$$\ln (1-Q) = - K_1 t$$

Where, Q is the fraction of drug released at time t and k_1 is the first order release rate constant.

Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi's equation

It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$$Q=K_2 t^{1/2}$$

Where, K2 is the release rate constant.

A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependant.

Power Law

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Peppas and Korsemeyer equation (Power Law).

$$M_t/M_\alpha = K.t^n$$

Where, M_t is the amount of drug released at time t and M_α is the amount released at time α, thus the M_t/M_α is the fraction of drug released at time t, k is the kinetic constant and n is the diffusional exponent. To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted in Table-1. A plot between log of M_t/M_α against log of time will be linear if the release obeys Peppas and Korsemeyer equation and the slope of this plot represents "n" value.

RESULTS AND DISCUSSION

Table 1. Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion Exponent	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non-fickian) diffusion
0.89	Case II transport
n>0.89	Super Case II transport

Table 2. Composition of Ranolazine Extended Release Tablets

S.NO	INGREDIENT	F1mg/ 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
1	RANOLAZINE	500	500	500	500	500	500	500	500	500
2	MCC PH101	120	115	110	105	100	95	90	85	80
3	CARBOPOL974P	20	23	26	29	32	35	38	41	44
4	OPADRY ORANGE	15	15	15	15	15	15	15	15	15
5	POLYVIDONEk30	10	10	10	10	10	10	10	10	10
6	METHOCELK4M	8	10	12	14	16	18	20	22	24
7	MEGLUMINE	5	5	5	5	5	5	5	5	5
8	MAGNESIUM STEARATE	5	5	5	5	5	5	5	5	5
9	AEROSIL	5	5	5	5	5	5	5	5	5
10	NAOH	2	2	2	2	2	2	2	2	2
11	PURIFIED WATER	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

PRECOMPRESSION PARAMETER

Table 3. Micromeritic properties

Formulation code	Bulk density (gm /ml)	Tapped density (gm/ml)	Hausner ratio	Carr's index (%)	Angle of repose (θ)
F1	0.32	0.41	1.28	21.95	27.38
F2	0.30	0.38	1.26	21.052	28.14
F3	0.31	0.38	1.22	18.42	26.85
F4	0.33	0.37	1.12	10.810	27.12

F5	0.286	0.342	1.19	16.37	28.47
F6	0.301	0.350	1.16	14.00	30.96
F7	0.31	0.37	1.19	16.216	29.72
F8	0.32	0.38	1.18	15.789	24.41
F9	0.33	0.38	1.15	13.157	27.51

Table 4. Post compression studies

Formulation code	Weight variation n=20	Hardness (kg/cm^2) n=3	Friability (%) n=20	Thickness (mm) n=20	Content uniformity n=20
F1	694±0.23	11±o.57	0.49±0.1	5.9±0.58	99.28±
F2	690±0.62	10±0.62	0.57±0.42	6±0.82	97.16±
F3	689±0.18	13±0.46	0.38±0.35	5.7±0.51	98.94±
F4	691±0.42	9±0.34	0.24±0.15	5.8±0.75	99.68±
F5	687±0.26	10±0.54	0.39±0.21	5.4±0.6	99.41±
F6	693±0.34	9±0.26	0.46±0.55	6.06±0.78	98.19±
F7	692±0.23	11±0.37	0.42±0.11	6±0.98	100.26±
F8	689±0.37	10±0.48	0.29±0.03	5.9±0.2	99.68±
F9	691±0.29	9±0.68	0.37±0.015	5.8±0.3	100.12±

Fig 1. Comparision of invitro drug releases of formulation F4,F5, F6

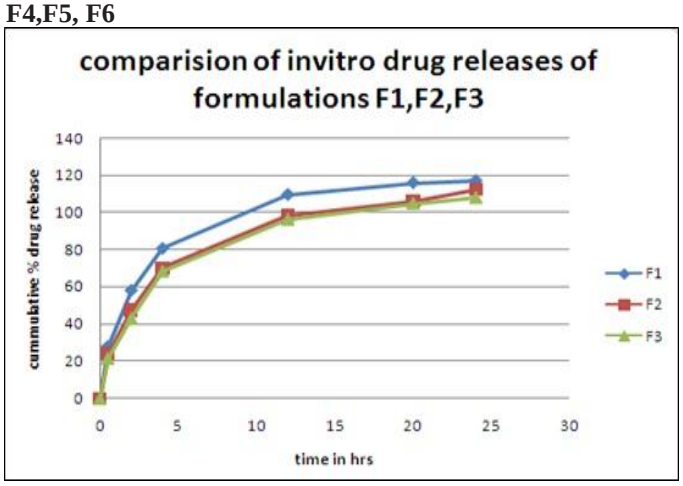


Fig 2. Comparision of invitro drug releases of formulation F4,F5, F6

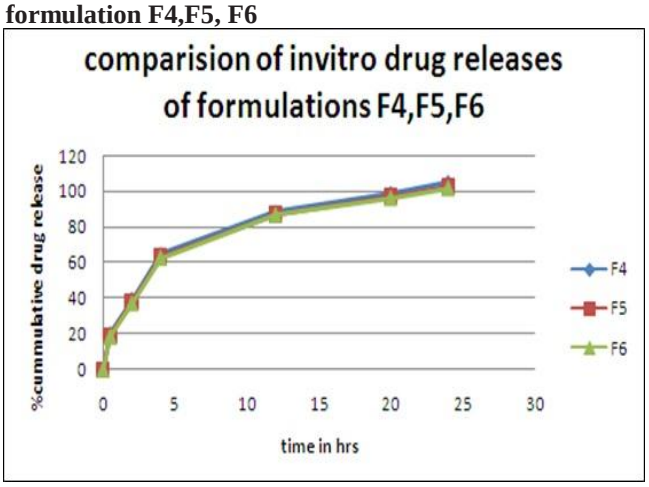


Fig 3. Comparision of invitro drug releases of formulation F7, F8, F9

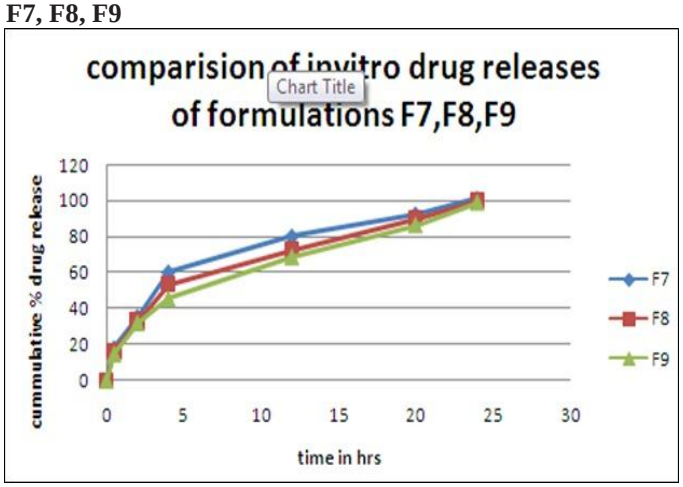
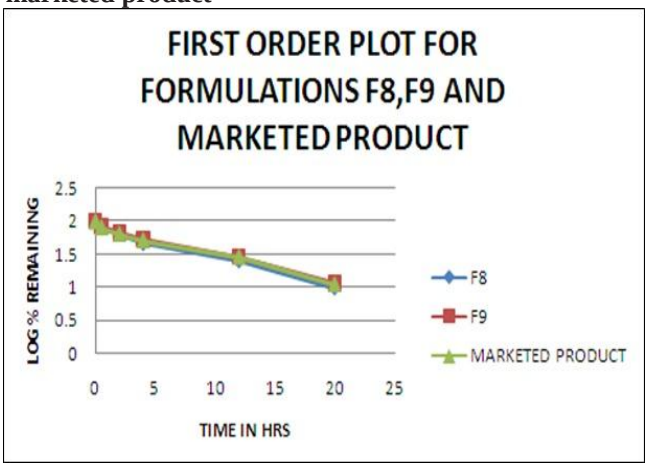


Fig 4. First order plot for formulation F8,F9 and marketed product



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