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FORMULATION DEVELOPMENT AND EVALUATION OF ONCE A DAY REGIOSELECTIVE DUAL COMPONENT GASTRORETENTIVE TABLET OF ROSUVASTATIN CALCIUM AND METOPROLOL SUCCINATE

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ABSTRACT

The aim of present investigation design regioselective dual component floating tablets of Metoprolol succinate and Rosuvastatin calcium, to give immediate release of Rosuvastatin and sustained release of Metoprolol. Bilayer floating tablets comprised two layers, i.e immediate release and sustained release layers. The immediate release layer comprised sodium starch glycolate as a super disintegrant and the sustained release layer comprised HPMC K100M, sodium alginate, xanthan gum as the release retarding polymers. Sodium bicarbonate and citric acid were used as a gas generating agent. Wet granulation method was used for formulation of the bilayer tablets. Accelerated stability studies were carried out on the prepared tablets in accordance with ICH guidelines. All formulations floated for more than 20hrs. More than 90% of Rosuvastatin was released within 120 min. HPMC K100M, sodium alginate and xanthan gum retarded the release of Metoprolol from the sustained release layer for 12h. After stability tests, degradation of both drugs were found but the drugs, contents were found to be within the range. The release of Metoprolol was found to follow Higuchi model and first order release models. Therefore, biphasic drug release pattern was successfully achieved through the formulation of floating bilayer tablets in this study.

KEYWORDS :

Regioselective, immediate release, sustained release, Accelerated.

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INTRODUCTION

Hypertension and hypercholesterolemia frequently coexist and may require concomitant drug treatment. Hypertension and hypercholesterolemia are major risk factors in the pathogenesis of coronary heart disease (CHD).[1-3] These two risk factors coexist in patients more frequently than would be expected by chance alone, and a syndrome of dyslipidemic hypertension has been identified. The current investigation aims at development of regioselective floating dual component (bilayer) tablets having different release patterns of Rosuvastatin calcium (ROSU) and Metoprolol succinate (METO) by using a gas generating agent.[2,4]

Metoprolol succinate is a white crystalline powder with high aqueous solubility and high permeability throughout gastrointestinal tract. The half-life of drug is relatively short approximately 4-7 hrs and in normal course of therapy drug administration is required every 4-7 hrs, thus warrants the use of sustained release formulation for prolong action and to improve patient compliance. At low doses, metoprolol selectively blocks cardiac β-1-adrenergic receptors with little activity against β2-adrenergic receptors of the lungs and vascular smooth muscle. Metoprolol is well absorbed after oral administration, Rapid and complete, 50%.[5-9]

Rosuvastatin is an antilipideamic agent that competitively inhibits hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase. HMG-CoA reducuase catalyzes the conversion of HMG-CoA to mevalonic acid, the rate-limiting step in cholesterol biosynthesis. Rosuvastatin belongs to a class of medications called statins and is used to reduce plasma cholesterol levels and prevent cardiovascular disease. Rosuvastatin acts primarily in the liver. It is completely absorbed in GIT.[10-15]

Effervescent floating dosage forms prepared with the help of swellable polymers such as HPMC K100M, sodium alginate, xanthan gum and effervescent compounds such as sodium bicarbonate and citric acid. When effervescent compound comes in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. The basic idea behind the development of such a system is to maintain a constant level of drug in the blood plasma in spite of the fact that the drug does not undergo disintegration. The drug usually keeps floating in the gastric fluid and slowly dissolves at a predetermined rate to release the drug from the dosage form and maintain constant drug levels in the blood.[15-18]

EXPERIMENTAL:

Materials:

Standard gift samples of Rosuvastatin calcium and Metoprolol succinate were provided by Aurobindo Pharma, Hyderabad and Wockhardt Pharmaceuticals Ltd, Aurangabad respectively.

HPMC K100M, sodium alginate, xanthan gum, Sodium starch glycollate (SSG), was obtained from Loba chemie., (Mumbai, India). All other ingredients were of laboratory grades.

Methods

Preparation of bilayer floating tablets

Bilayer floating tablets were prepared by wet granulation using sodium starch glycolate as a superdisintegrant, and HPMC K100M, sodium alginate and xanthan gum as the release controlling polymers, and sodium bicarbonate as a gas generating agent. The optimum concentrations of the above ingredients were determined under experimental conditions and on the basis of trial preparation of the tablets.[12,17,23] Preparation of bilayer floating tablets had two steps:[20-23]

Preparation of the sustained release layer: the ingredients (Table 1) were accurately weighed and added into the blender in ascending order. The powder mix was blended for 20 min. to obtain uniform distribution of the drug in formulation. To add isopropyl alcohol as granulating vehicle and to form granules by wet granulation method. 210 mg of the granule was accurately weighed and fed into the die of single punch tablet press (A Jaguar 4 8, Mumbai, India.) and compressed at low compression force using 8-mm concave punches.[16-22]

Table No. 1: Formulation of **Sustain release layer**

All the amounts are shown as milligrams.

INGREDIENTS	FORMULATION CODE									
	M1	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**
Metoprolol Succinate	70	70	70	70	70	70	70	70	70	70
HPMC K100M	90	80	70	60	50	90	80	70	60	50
Sodium Alginate	10	20	30	40	50	-	-	-	-	-
Xanthan Gum	-	-	-	-	-	10	20	30	40	50
PVP K30	12	12	12	12	12	12	12	12	12	12
Sodium Bicarbonate	18	18	18	18	18	18	18	18	18	18
Citric Acid	07	07	07	07	07	07	07	07	07	07
Magnesium Stearate	03	03	03	03	03	03	03	03	03	03
Indigo caramine	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Preparation of immediate of release layer: the ingredients (Table 2) were accurately weighed and added into the blender in ascending order. The powder mix was blended for 20 min to obtain uniform distribution of the drug in formulation. To add isopropyl alcohol as granulating vehicle and to form granules by wet granulation method. 70 mg of the granule was accurately weighed and manually fed into the die on controlled release layer and compressed at a optimum compression pressure by using 8-mm concave punches.[14-23]

Table no. 2: Formulation of immediate release layer

INGREDIENTS	FORMULATION CODE			
	R1	**R2**	**R3**	**R4**
Rosuvastatin Calcium	10	10	10	**10**
PVP K30	2	2	2	**2**
Sodium Starch Glycolate	3	3	4	**4**
Lactose	53	-	52	**-**
Microcrystalline cellulose	-	53	-	**52**
Magnesium Stearate	2	2	2	**2**
Isopropyl Alcohol	q.s.	q.s.	q.s.	**q.s.**

All the amounts are shown as milligrams.

Total weight of the single bilayer tablet= 210 mg

Physicotechnical parameter of regioselective tablet

Standard physical tests were performed for bilayer matrix tablets and average values were calculated. Weight variation was determined by weighing 20 tablets individually. Resistance to crushing was determined by taking 6 tablets from each formulation using a Pfizer hardness tester (Electrolab Pvt. Ltd., India). Thickness was determined by vernier calipers. Friability was determined by weighing 10 tablets after dusting and placing them in a Roche friabilator (Campbell Electronics, Mumbai, India).[17-22]

Floating characteristics:

Floating characteristics of the prepared formulations were determined by using USP type II paddle apparatus (Electrolab TDT-08L, Mumbai, India) in 900 ml of a pH 1.2 solution at 37±0.5°C for 24hrs. The time between the introduction of tablet and its buoyancy on the simulated gastric fluid (floating lag time) and the time during which the dosage form remain buoyant (floating duration) were measured. Also, the integrity of the tablets during the study was (matrix integrity) visually monitored.[1-6]

Drug content:

UV spectrophotometric method was developed and validated for simultaneous estimation of Metoprolol and Rosuvastatin from the prepared formulations as follows:

Metoprolol:

Twenty tablets were accurately weighed and the average weight was calculated. The tablets were then ground to a fine powder. An accurately weighed amount of the powder equivalent to 50 mg of Metoprolol was dissolved in methanol and volume was made to 50 ml. The solution was then filtered through a Whatmann filter paper No. 41. An aliquot of 1 ml was taken and diluted to 100 ml with pH 1.2 solution. For the assay of Metoprolol the absorbance of the sample solution was recorded at 274 nm. Absorbance to quantify Metoprolol in the sample solution using a calibration curve. The calibration curve for Metoprolol was plotted using the absorbance values of 10 standard solutions of Metoprolol over a concentration range of 10-100µg/ml.[1]

Rosuvastatin:

Above solution was used and to check absorbance at 241nm for the assay of Rosuvastatin, a difference spectrophotometric method was developed and validated to eliminate the interference of Metoprolol absorbance in sample solutions. The calibration curve for estimation of Rosuvastatin was obtained by plotting the difference of absorbance values at 241nm for 10 mixed standard solutions containing 1-12 µg/ml of Rosuvastatin against their concentrations.[1-2]

Swelling and Erosion studies:

The swelling behavior of dosage form can be measured by studying its dimensional changes, weight gain or water uptake ability. The water uptake study of the dosage form was conducted by using Type II USP dissolution apparatus in 900 ml of distilled water which was maintained at 37±0.5^{0}C and rotated at 50rpm. At selected intervals, the tablet was withdrawn and blotted with absorbent tissue to remove any excess dissolution medium on the surface and weighed. Percentage swelling of the tablet was expressed as percentage water uptake (%WU) calculated from following equation: [1-12]

$$\text{Degree of swelling (\% water uptake)} = \frac{Wt - Wo}{Wo} \times 100$$

Where, Wo is the initial weight of the dry tablet, and Wt is the weight of the wet, swollen tablet. Matrix erosion was determined after completion of swelling studies, on the same tablets used for the swelling determinations. After weighing, the hydrated matrices were dried in an oven at 50^{0}C for 24hrs and the remaining dry weight Wr, was determined. Matrix erosion was calculated according to the formula: [20-22]

$$\text{Erosion (\% mass loss)} = \frac{Wo - Wr}{Wo} \times 100$$

Drug release (Dissolution study):

The release of Metaprolol and Rosuvastatin from different formulations were determined using USP 23 paddle apparatus 2 (Electrolab TDT-08L, Mumbai, India) under sink conditions. The dissolution medium was 900ml of a pH 1.2 solution, at 37±0.5°C and the stirring speed was 50rpm. At predetermined time intervals 5ml of the samples were withdrawn by pipette pump with filter. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at 37±0.5°C. The samples were analyzed for drug release by measuring the absorbance at 241 and 274nm using UV-Visible spectrophotometer after suitable dilutions. For each formulation, the experiments were carried out in triplicate.

Kinetic modeling of drug release

To analyze the mechanism of drug release from the tablet, the dissolution data were fitted to the Zero order equation, first order equation**,** Higuchi's

equation and Korsmeyer-peppas equation equations.

Accelerated stability study of Regioselective dual component tablet:

In order to determine the change in in-vitro release profile and floating behavior on storage, accelerated stability study of dual component tablet was carried out according to ICH guidelines. The formulation (n=3) were sealed in aluminium packaging and kept at 40 ºC in a humidity chamber having 75% RH for 3 months. At the end of the period, samples were analyzed for drug content, floating characteristics, hardness values, and in vitro dissolution studies.

Assessment of similarity factor:

The similarity factor (*f*2 factor) was used to compare dissolution profiles of Metoprolol before and after the stability studies. The in vitro release profiles of the formulations before the stability studies were considered as reference and the profiles after the stability studies were considered as test. The similarity factors were calculated using BCP Disso software. The *f*2 factor is a logarithmic reciprocal square root transformation of the sum of squared error. The *f*2 factor was used to quantitate the agreement between two dissolution profiles. Dissolution tests were conducted under the same conditions. The values of *f*2 between 50 to 100 show similarity in in-vitro release profiles.

$$f_2 = 50 \times \log\left\{\left[1 + (1/n)\sum_{j=1}^{n}|R_j - T_j|^2\right]^{-0.5} \times 100\right\}$$

RESULTS

Floating characteristics

All formulations floated more than 22 hrs with a lag time of up to 140 sec. Swelling of the tablets was observed, which gave floating ability to formulations. A 18 mg concentration of sodium bicarbonate was found to be optimum for obtaining low lag time and prolonged floating duration. Floating duration and lag time were found to be dependent to the amounts of polymers incorporated in formulations.

Drug content:

Metoprolol (96.40%-99.20%) and Rosuvastatin (98%-99.12%) contents were found to be within the accept able range. Additives in formulations did not have any effect on drug content .

Table no.5: In vitro buoyancy study

Form Code	Floating lag time (sec) n=3	Floating duration (hrs) n=3
M1	40	24
M2	100	24
M3	55	24
M4	50	24
M5	100	24
M6	60	24
M7	140	22
M8	110	>24
M9	85	24
M10	40	>24

Table no. 6: Swelling Index (%water uptake study)

Form. code	Time in hour						% Erosion after 10hrs
	1	2	4	6	8	10	
M1	50	70	95	110	100	90	29.0
M2	40	50	65	80	70	40	31.0
M3	38	45	57	75	53	41	29.5

M4	34	41	52	59	51	38	31.4
M5	35	38	49	55	49	36	30.4
M6	40	55	68	90	80	65	32.3
M7	39	51	67	84	78	59	33.0
M8	35	52	65	79	71	57	34.2
M9	36	49	61	76	68	51	34.7
M10	30	42	55	70	61	45	35.2

Table no. 3: Evaluation of pre-compression parameters of developed formulations (Metoprolol succinate)

Formulation code	Angle of Repose(□)	Bulk Density	Tapped Density	Hausner's ratio	Carr's Index
M1	32.69	0.3281	0.3711	1.13	11.58
M2	34.81	0.3325	0.3843	1.15	13.479
M3	35.02	0.3319	0.3901	1.175	14.919
M4	36.11	0.3360	0.4005	1.191	16.104
M5	39.57	0.3448	0.4216	1.22	18.216
M6	33.53	0.3318	0.3792	1.142	12.50
M7	34.61	0.3368	0.3952	1.173	14.777
M8	36.13	0.3369	0.4061	1.205	17.04
M9	37.62	0.3372	0.4187	1.241	19.46
M10	39.85	0.3451	0.4311	1.249	19.948

Table no.4: Evaluation of Post-compression Parameters of developed formulations

Form Code	Thickness (mm) n=5	Diameter (mm) n=5	Hardness Kg/cm^3 n=5	% Friability	Uniformility of weight (mg) n=20	Mean drug content %
M1	4.75±0.05	8.01±0.01	4.6±0.2	0.55	210±02	98.12±0.23 (M)
						99.03±0.20 (R)
M2	4.64±0.03	7.99±0.02	5.2±0.4	0.61	213±04	96.56±0.63 (M)
						98.81 ±0.23 (R)
M3	4.88±0.02	7.98±0.03	4.5±0.5	0.68	210±05	99.20±0.21 (M)
						99.01±0.23 (R)
M4	4.78±0.04	8.02±0.02	5.0±0.2	0.53	211±04	98.52±0.01 (M)
						98.64±0.06 (R)
M5	4.40±0.05	7.99±0.0	4.6±0.3	0.34	210±03	97.20±0.17 (M)
						99.08±0.04 (R)
M6	4.81±0.02	8.00±0.02	5.2±0.2	0.54	212±02	97.60±0.12 (M)
						99.12±0.04 (R)
M7	4.94±0.01	8.02±0.02	5.5±0.1	0.23	210±04	98.00±0.23 (M)
						97.82±0.03 (R)
M8	4.52±0.02	8.01±0.02	5.0±0.3	0.46	214±03	98.80±0.02 (M)
						98.58±0.06 (R)
M9	4.91±0.05	8.00±0.02	4.8±0.4	0.39	210±02	96.40±0.02 (M)
						99.04±0.08 (R)
M10	4.84±0.03	7.99±0.02	4.9±0.3	0.49	215±04	97.65±0.21 (M)
						98.89±0.45 (R)

In vitro drug release:

Metoprolol

The release of Metoprolol was found to be a function of the polymer concentration. All formulations retarded the release of drug for 12 hrs. The effect of xanthan gum at different concentrations on the release of Metoprolol from tablet matrices was studied. Figure 2 and Figure 3 show the drug release profile of drug from sodium alginate, xanthan gum and HPMC K100M matrices, respectively. It was also observed that xanthan gum retarded the drug release more than HPMC K100M. The release data were fitted to different kinetic models and based on correlation coefficients (R), the best fitted models were determined (Table 7). Formulations M1 and M6 followed first order model while other formulations followed either Higuchi model.

Rosuvastatin

There was no significant effect on immediate release of Rosuvastatin from the immediate release layer. The amounts of drug release from all formulations were found to be more than 90% within 120 min.

Table no.7: comparison of Parameters for developed formulations before and after Stability study

Time	Form code	EVALUATION PARAMETERS					
		Appearance	**Hardness Kg/cm^3**	**% Drug Content**	**% CDR** after 12hrs Metoprolol	**Floating lag time** (sec)	**Floating duration** (hours)
Before study	**M1**	No change	4.6±0.2	98.12±0.23 (M) 99.03±0.20 (R)	64.95	40	24
	M6	No change	5.2±0.2	97.60±0.12 (M) 99.12±0.04 (R)	72.04	60	24
90 days	**M1**	No change	4.6±0.2	98.43±0.62 (M) 98.73±0.4 (R)	66.42	42	24
	M6	No change	5.2±0.2	97.60±0.12 (M) 99.12±0.45 (R)	72.88	55	24

Figure no.1: In vitro dissolution profile of Rosuvastatin Calcium sustained release layer (R1-R4)

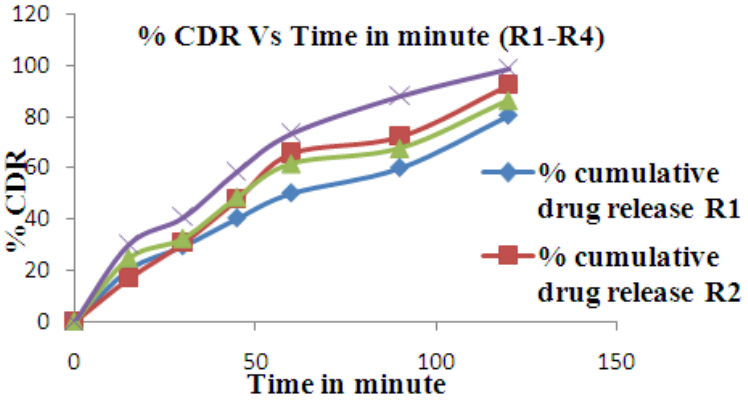


Figure no.2: In vitro dissolution profile of Metoprolol Succinate sustain release layer (M1-M5)

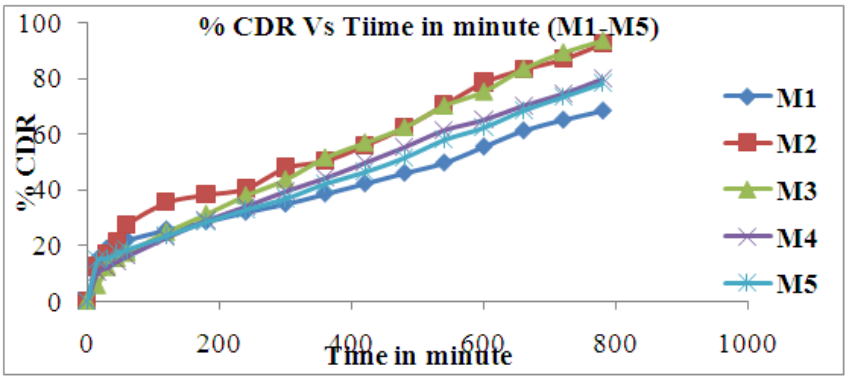
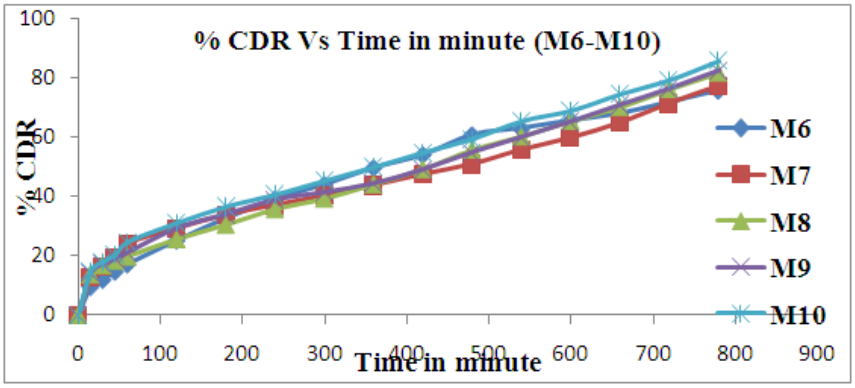


Figure no.3: In vitro dissolution profile of Metoprolol Succinate sustain release layer (M6-M10)



Similarity factor:

Similarity factors (f2) for all formulations are shown in Table 8. All formulations except mM6 showed (f2) value between 50 to 100 indicating similar release profiles of the formulations before and after stability studies. M6 showed a similarity value below 50, indicating dissimilar release profiles before and after the stability studies.

Tableno.8: Similarity factor analysis of various dissolution pairs

Sr. No.	Formulation code	f_2 for sustained release layer	f_2 for immediate release layer
1	M1	93.28	90.76
2	M6	88.99	91.78

CONCLUSION:

The design of two different release phases can be easily adjusted in both delivery rate and ratio of the dose fractions, according to the pharmacokinetics and therapeutic needs. The results obtained with the dissolution test show that the release profile is dependent on both the polymer type and amount in sustain release layer. Bilayer floating tablets having different release profiles for different drugs can be formulated using HPMC K100M, sodium alginate and xanthan gum (alone and in combination) to give sustained release of Metoprolol, and sodium starch glycollate to give immediate release of Rosuvastatin. Hence, this dosage form should be further evaluated for delivery of two drugs from, a single dosage form which could improve patient compliance and give better disease management.

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