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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF ONCE A DAY DUAL COMPONENT GASTRO RETENTIVE DRUG DELIVERY SYSTEM

***Vinchurkar Kuldeep, Mane Sheetal, Sainy Jitendra and Khan Masheer**

Indore Institute of Pharmacy, Shail's group, Opp. IIM, Rau-Pithampur Road, Rau, Indore - 453331, School of pharmacy, Devi Ahiliya Vishva Vidyalay, Indore – 452 012

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ABSTRACT

There is about 15-30 % incidence of co-existence of hypertension and hypercholesterolemia in India. This has more than additive adverse impact on vascular endothelium which leads to cardiovascular diseases. Hypertension and hypercholesterolemia are major risk factors in pathogenesis of coronary heart disease. Due to this, the patients may require concomitant treatment with antihypertensive and hypo-lipidemic agents. The combination of antihypertensive (beta blocker) and antihyperlipidemic (statin) drugs are reported to reduce cardiovascular events and progression of dyslipidemic hypertension. The purpose of this study was to prepare a bilayer gastro retentive tablet of Metoprolol succinate and rosuvastatin calcium using direct compression technology and optimize the type and concentration of polymer and superdisintegrant to give good drug release profile in patient having hypertension with hypercholesterolemia. Rosuvastatin is a competitive inhibitor of HMG co-reductase, has half-life of 19 h and bioavailability 20 % favors immediate release while Metoprolol succinate is a β_1-selective adrenergic receptor blocking agent and numbers of clinical trials have demonstrated the beneficial effects of Metoprolol therapy in heart failure, with decreased mortality due to both reduction in sudden death and death from worsening heart failure and it has half-life of 3 to 4 hours, and high stability and higher absorption window in acidic environment of stomach, favors development of sustained release floating formulation. The current investigation aims at development of safe, stable and efficacious dual component (bilayer) floating tablet formulation with differential release profiles of antihypertensive drug candidate (sustained release) and antilipidemic drug candidate (as fast release) component. A bilayer tablet was prepared in which, HPMC K100, K4M, K15M were used as gel forming agents while cross carmellose sodium, sodium starch glycolate and cross povidone alone used as a superdisintegrant. A sodium bicarbonate used as effervescent agent. The bilayer tablets were characterized by lag time, floating time, weight variation, drug content, dissolution profile and stability study. Best formulation F9, release 99.48% of Rosuvastatin calcium after 30 min and 96.6% of Metoprolol succinate after 12 hrs to achieve local therapy in the stomach, site-specific drug delivery reduces undesirable effects of side effects, reduced frequency of dosing with improved patient compliance and significant increase in bioavailability.

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INTRODUCTION

Globally, cardiovascular diseases are the number one cause of death and they are projected to remain so (Kishor, 2007). If current trends are allowed to continue, by 2030 an estimated 23.6 million people will die from cardiovascular disease. Hypertension is the primary cause of stroke, major risk factor for coronary artery disease like atherosclerosis and its complications and it is a major contributor to cardiac failure, renal insufficiency and high blood pressure is also called "the silent killer" because it often causes no symptoms for many years, even decades, until it finally damages certain critical organs. Hypercholesterolemia refers to elevated levels of lipids and cholesterol in the blood, and is also identified as dyslipidemia, to describe the manifestations of different disorders of lipoprotein metabolism (Cardiovascular disease and risk management, 2019). Hypertension and hypercholesterolemia are the major contributing factor to coronary heart disease. The prevalence of co-existence of hypertension with hypercholesterolemia is 15-30% in India which has more than an additive adverse impact on vascular endothelium which leads to cardiovascular diseases (Golomb, 2008; Yilmaz, 2018). Hypertension and hypercholesterolemia frequently coexist and may require concomitant drug treatment

Corresponding author: **Vinchurkar Kuldeep,**
Indore Institute of Pharmacy, Shail's group, Opp. IIM, Rau-Pithampur Road, Rau, Indore - 453331, School of pharmacy, Devi Ahiliya Vishva Vidyalay, Indore – 452 012.

which simultaneously prevents the morbidity rate (Kearney, 2004; Lardinois, 1988). Rosuvastatin Calcium is an antilipemic agent that competitively inhibits Hydroxymethylglutaryl - coenzyme A (HMG-CoA) reductase, HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonic acid, a rate limiting step in cholesterol biosynthesis and is used to reduce plasma cholesterol levels and prevent LDL-C. At usual starting doses, Rosuvastatin calcium is more efficient in reducing plasma low-density lipoprotein (LDL) cholesterol and achieving LDL cholesterol goals than atorvastatin, simvastatin, or pravastatin. It has a long biological half-life of 19 hours (Peppas, 1985). It has low bioavailability of about 20% (Peppas, 1985). All the above parameters suggest that Rosuvastatin calcium is a good candidate for immediate release dosage form. Metoprolol succinate is a β_1-selective adrenergic receptor blocking agent and numbers of clinical trials have demonstrated the beneficial effects of Metoprolol therapy in heart failure, with decreased mortality due to both reduction in sudden death and death from worsening heart failure[33]. Unlike other β1-selective blocker, Metoprolol does not exhibit membrane stabilizing or intrinsic sympathomimetic activity[30]. It has high aqueous solubility and high permeability throughout gastrointestinal tract (Dash, 2010).

It has a short biological half-life of 3-4 hours, hence for prolonged treatment sustained release formulation will be beneficial to reduce hypertension (Higuchi, 1963). Drug absorption in gastrointestinal tract is highly variable procedure and prolonging gastric retention of dosage form, extend the time for drug absorption. The current investigation aims at development of safe, stable and efficacious dual component (bilayer) floating tablet of ß-blockers and statins with differential release profiles to reduce cardiovascular events and progression of dyslipidemic hypertension by reducing dosing frequency, improve residence time of drug, combination therapy and improve patient compliance (Kumar, 2018; Lopes, 2016).

MATERIALS AND METHODS

Metoprolol succinate (Torrent Pharmaceuticals, Ahmedabad, India) and Rosuvastatin calcium (Zim Laboratory, Nagpur, India) were the active pharmaceutical ingredients. HPMC K-100M, K15M and K4M (Colorcon Asia Pvt. Ltd., Goa, India) were used as hydrophilic matrix forming polymer while sodium starch glycolate (Oxford Laboratory, Mumbai), cross carmellose sodium and cross povidone (Research Lab, Mumbai) were used as a superdisintegrant for making immediate release segment. Magnesium stearate (Oxford Laboratory, Mumbai) was used as glident, Sodium bicarbonate (Research Laboratory, Mumbai) was used as a gas generating agent, Microcrystalline cellulose PH102 (Research Laboratory, Mumbai) was used as a diluent.

Methods

Preparation of bilayer floating tablet: Bilayer floating tablet contains two layer i.e immediate release layer and floating sustained release layer.

Formulation of immediate release layer (IR): The immediate release layer were prepared by blending drug with different concentration of superdisintegrants (cross carmellose sodium, sodium starch glycolate, cross povidone as 2, 4, 6%w/w) and other excipients like microcrystalline cellulose and magnesium stearate. The blend so obtain used to prepare IR layer of drug in Bilayer floating tablet. For preliminary studies to optimize the IR formulations, a weighed quantity of above lubricated drug mixture blend was fed manually into the die and directly compressed using 8 mm flat faced punch of 10 station Rimek compression machine to get IR tablets (More, 2018; Jamshed, 2012). Nine formulation batches were made in order to achieve desired disintegration time and drug release. Formulation compositions of different immediate release batches are given in the Table 1.

Formulation of the floating sustained release (SR) layer: To prepare floating sustained release blend required quantity of drug and polymers (HPMC K4M, HPMC K15M and HPMC K100M), alkalizing agent (sodium bicarbonate) were weighed and passed through sieve with mesh #60 and were mixed homogeneously in a poly-bag for about 5-10 min and was taken in a mortar. To the mortar, magnesium stearate was added at the end and mixture was mixed for 2 minutes in a poly bag (Meenakshi, 2015; Raj, 2011). Formulation compositions of all batches are given in the Table 2. Bilayer floating tablets were prepared by direct compression method using 8 mm round concave punch of 12 station Rimek compression machine (Nayak, 2010; Singh, 2009). First the blend of floating sustained release layer were poured in the die cavity and the powder were compressed. After the compression, the upper punch was then lifted and the immediate release blend of drug were poured in the die, containing initially compressed sustained release layer and compressed to form bilayer tablet (Bhosale, 2017; Rao, 2019). The hardness was kept constant for all formulations and was measured using Pfizer hardness tester.

Postformulation study:

Appearance: The bilayer tablet was identified visually by checking the difference in the color, shape and texture.

Thickness: Thickness of the tablets was determined using digital Vernier caliper. The test was done in triplicate and average was determined.

Hardness: Hardness (crushing strength (kg/cm^2) of the tablets was tested using a Techno Pharma hardness tester (Pfizer) (Camarco, 2006; Jagdish, 2009).

Friability: Friability of tablet carried out by using Rolex tablet friabilator (Roche friabilator). This was determined by weighing 10 tablets before dusting, placing them in the friabilator and rotating the plastic cylinder vertically at 25 rpm for 4 min. The tablet was dedusted using soft muslin cloth and reweighed. The % friability was calculated according to formula (Jagdish, 2009; Asutoshkumar, 2010).

$$F = (1- W0 / W) \times 100$$

Where, W0 is the weight of the tablets before the test and W is the weight of the tablet after the test.

Floating lag time and Total floating time (*in vitro*): For this, 5 tablets of optimized formulations were used. The floating lag time was determined using a USP XXIV type II (paddle) apparatus containing 900 ml of 0.1N HCl and operated at 50

rpm. The time (sec) between the introduction of the tablet into the dissolution medium and its floating at the top of dissolution medium was noted. Subsequently the time (sec) for which the tablet remained afloat on the surface of the medium was also noted (Catalina, 2012; Geeta, 2010; Atram, 2009).

***In-vitro* disintegration time:** The disintegration time for all immediate release formulations was carried out using tablet disintegration test apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The medium, water was maintained at a temperature of 37° ± 2°C and time taken for the entire tablet to disintegrate completely was noted. Average of three determinations was taken (Kulkarni, 2009; Hilton, 1992).

***In-vitro* drug release study:** The release of Metoprolol Succinate and Rosuvastatin calcium were determined using USP dissolution test apparatus, Type II under sink conditions. The dissolution medium (900 ml) of pH 1.2 solutions maintained at 37 ± 0.5 and *50* rpm. At, predetermined time interval, 5 ml of the samples were withdrawn by pipette pump with filter (Lian-dong hu, 2011; Ibrahim, 2010). The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at 37 ± 0.5. The samples were analyzed for drug release by measuring absorbance at 241 and 274nm, for Rosuvastatin calcium and Metoprolol succinate respectively (Moursy, 2003; Stockwell, 1986; Khan rahman, 2006; Patra, 2007).

Swelling of matrix tablets: The extent of swelling was measured in terms of % of weight gained by the tablet. One tablet from each formulation was weighed and kept in petri dish containing 50 ml of 0.1N HCl buffer solution. At the end of specified time intervals tablets were withdrawn from petri dish and excess buffer blotted with tissue paper and weighed (Prajapati, 2009; Putta, 2011). The percentage of weight gained by the tablet was calculated by using following formula

$$\% \quad \text{Swelling} = \frac{\text{Wet weight of tablet} - \text{Dry weight of tablet}}{\text{Dry weight of tablet}} \times 100$$

Drug release kinetics: *In vitro* release data were subjected to model fitting analysis to know the order of drug release by treating the data according to zero order, first order and higuchi release kinetic equations and Korsmeyer-Peppas Eqn (Gande, 2011).

***In vivo* (x-ray) studies:** For this study, the tablets with 300 mg in weight were prepared consist of barium sulphate 80 mg (Part of the drug was replaced with BaSO4), HPMC (K100M) 100 mg, cross carmellose sodium 06 mg, sodium bicarbonate 20 mg and microcrystalline cellulose (PH102) 90 mg and magnesium stearate 04 mg (Raja Sekhar Reddy, 2014; Dash, 2010). The selection criteria for volunteer include (mean age 25 year, mean weight 60 ± *10* kg). Then, human volunteers were divided into group A and B.

(1) *Group A - fasted state*: The subjects fasted overnight then swallowed the floating tablet with 150 ml water. Afterwards the subjects were not allowed to eat.
(2) *Group B - feed state*: After a meal, the subjects swallowed the floating tablet immediately after ingestion of a routine diet composed of a bread and milk (150 g solid, 200 ml liquid). Afterwards the subjects were not allowed to eat.[36-37]

Stability studies: Selected formulation was stored at40 ± 2 and 75% ± 5%RH for three month and *in vitro* release studies were carried out (Peppas, 1985).

RESULTS AND DISCUSSION

Micromeritic properties of precompressional powder: In the present study, direct compression method was adopted for tableting. Hence the blend of drug and polymers should possess good flow and compaction properties. All the formulations exhibited the angle of repose value between 25.1-29.7, which was further supported by good compressibility index value of 21.1-24.7% and Hausner's ratio of 1.27-1.22, thus indicating the suitability of precompressional blends for compression into tablets. The results are shown in Table 3.

Physico-chemical evaluation of bilayer floating tablets: The prepared tablets were evaluated for their various physico-chemical properties. The tablets were white, circular in shape and were found to be uniform with respect to thickness (3.86 to 4.73 mm) and hardness (5.00 to 5.96 kg/cm2). The friability (0.23 to 0.83 %) and weight variation (300 to 302 mg) of different batch of tablets were found within acceptable limits. Drug content for metoprolol succinate (95.08 to 98.21 %) and Rosuvastatin Calcium (95.08 to 99.76 %) was found uniform within the batches of different tablets. The results of physico-chemical evaluation of tablets are given in Table 4.

Swelling study of bilayer floating tablets: Investigation of polymer swelling and erosion is a valuable exercise to better understand the mechanism of release and the relative importance of participating parameters. Swelling ratio describes the amount of water that is contained within the hydrogel at equilibrium and is a function of network structure, hydrophilicity and ionization of functional group. Swelling study was performed on all the batches of floating tablet for 24 hrs. The results of swelling index are given in Table 5, All the bilayer floating tablets swelled but remained intact without breaking throughout the period of swelling (12 hrs) in 0.1N HCl. The order of swelling index observed with different polymers was HPMC K100M (F9) > HPMC K15M (F6) > HPMC K4M (F3)

Buoyancy lag time and Total floating time: Gastro retentive buoyant tablets need to possess certain characteristics. Therefore experiments were conducted for buoyancy lag time as well as flotation period. Buoyancy lag time indicates how much time a tablet would take, under *in vitro* simulated conditions to float over the gastric fluid. The tablets were placed in a 250 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface for floating was determined as the buoyancy lag time. Sodium bicarbonate induces CO2 generation in the presence of hydrochloric acid. The gas generated is trapped and protected within the gel formed by hydration of the polymer, thus decreasing the density of the tablet below 1 gm/ml and the tablet becomes buoyant. The optimized concentration of sodium bicarbonate was found to be 25% of total tablet weight and it was maintained constant in all the floating tablets prepared. All floating tablets had buoyancy lag time in the range of 80 to 23 sec. The total floating time was found to be in the range of >24 to >19 hr, indicating a stable gel layer formation by all polymers and sodium bicarbonate that persists for a longer time.

Table 1. Formulation composition of different immediate release batches

Composition of immediate release layer									
Name of ingredient	IR1	IR2	IR3	IR4	IR5	IR6	IR7	IR8	IR9
Rosuvastatin Calcium	10	10	10	10	10	10	10	10	10
Sodium starch glycolate	2	4	6	-	-	-	-	-	-
Cross povidone	-	-	-	2	4	6	-	-	-
Cross carmellose sodium	-	-	-	-	-	-	2	4	6
Microcrystalline cellulose (MCC PH102)	86	84	82	86	84	82	86	84	82
Magnesium stearate	02	02	02	02	02	02	02	02	02
Total weight (mg)	100	100	100	100	100	100	100	100	100

Table 2. Formulation of bilayer floating tablet

Name of ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
IR9	100	100	100	100	100	100	100	100	100
Metoprolol succinate	70	70	70	70	70	70	70	70	70
Hydroxy propyl methyl cellulose K4M	60	80	100	-	-	-	-	-	-
Hydroxy propyl methyl cellulose K15M	-	-	-	60	80	100	-	-	-
Hydroxy propyl methyl cellulose K100M	-	-	-	-	-	-	60	80	100
Sodium bicarbonate	20	20	20	20	20	20	20	20	20
Microcrystalline cellulose (MCC PH102)	48	28	08	48	28	08	48	28	08
Magnesium stearate	02	02	02	02	02	02	02	02	02
Total weight (mg)	300	300	300	300	300	300	300	300	300

Table 3. Micromeritic properties of precompressional blends of bilayer floating tablets

Batch code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Carr's index (%)	Angle of repose
F1	0.57 ± 0.03	0.67 ± 0.01	1.30 ± 0.02	21.6 ± 0.10	27.5 ± 0.05
F2	0.55 ± 0.02	0.73 ± 0.02	1.22 ± 0.04	24.7 ± 0.10	29.7 ± 0.05
F3	0.57 ± 0.01	0.69 ± 0.01	1.24 ± 0.07	17.6 ± 0.05	28.0 ± 0.05
F4	0.52 ± 0.04	0.68 ±0.01	1.29 ± 0.05	16.1 ± 0.05	25.1 ± 0.05
F5	0.57 ± 0.02	0.67 ± 0.02	1.26 ± 0.01	20.8 ± 0.01	27.5 ± 0.01
F6	0.58 ± 0.01	0.73 ± 0.01	1.32 ± 0.01	21.1 ± 0.10	26.1 ± 0.01
F7	0.55 ± 0.01	0.73 ± 0.03	1.24 ± 0.07	17.6 ± 0.10	26.0 ± 0.05
F8	0.53 ± 0.02	0.72 ± 0.02	1.34 ± 0.07	21.8 ± 0.05	26.1 ± 0.01
F9	0.56 ± 0.03	0.71 ± 0.02	1.27 ± 0.02	21.1 ± 0.05	25.1 ± 0.05

*Average of 3 determinations ± SD

Table 4. Physico-chemical evaluation of bilayer floating tablets

Batch code	Hardness (kg/cm^3)	Thickness (cm)	Weight variation (mg)	Percentage of Friability (%)	Drug content (%)	
					Metoprolol Succinate	Rosuvastatin Calcium
F1	5.53 ± 0.05	4.12 ± 0.02	300 ± 0.02	0.53 ± 0.05	96.65 ± 0.90	98.42 ± 1.27
F2	5.96 ± 0.01	4.21 ± 0.02	300 ± 0.05	0.50 ± 0.00	98.21 ± 0.94	95.08 ± 1.80
F3	5.60 ± 0.01	4.01 ± 0.02	301 ± 0.01	0.76 ± 0.05	96.23 ± 0.54	98.08 ± 1.90
F4	5.00 ± 0.05	3.86 ± 0.02	300 ± 0.02	0.43 ± 0.05	95.08 ± 1.27	97.65 ± 0.90
F5	5.26 ± 0.05	4.81 ± 0.01	302 ± 0.01	0.83 ± 0.05	97.28 ± 1.26	98.86 ± 0.60
F6	5.36 ± 0.05	4.71 ± 0.02	300 ± 0.57	0.63 ±0.05	95.08 ± 1.80	96.82 ± 0.66
F7	5.53 ± 0.05	4.26 ± 0.01	300 ± 0.02	0.76 ± 0.05	96.65 ± 0.90	99.76 ± 0.90
F8	5.63 ± 0.05	4.33 ± 0.02	301 ± 0.02	0.23 ± 0.05	95.81 ± 0.90	96.65 ± 0.64
F9	5.06 ± 0.05	4.73 ± 0.02	302 ± 0.02	0.26 ± 0.05	97.07 ± 1.26	98.05 ± 0.90

All values are expressed as mean ± SD n=10, *n=20.

Table 5. Swelling index of bilayer floating tablet

Batch Code	Swelling index (%)				
	2 hrs	4 hrs	6 hrs	8 hrs	12 hrs
F1	0.275 ± 0.004	0.285 ± 0.004	0.298 ± 0.005	0.302 ± 0.003	0.305 ± 0.003
F2	0.280 ± 0.006	0.290 ± 0.006	0.300 ± 0.004	0.305 ± 0.003	0.306 ± 0.003
F3	0.284 ± 0.007	0.296 ± 0.005	0.302 ± 0.005	0.329 ± 0.005	0.345 ± 0.005
F4	0.290 ± 0.007	0.305 ± 0.008	0.315 ± 0.008	0.330 ± 0.008	0.340 ± 0.009
F5	0.300 ± 0.009	0.310 ± 0.009	0.320 ± 0.010	0.332 ± 0.009	0.349 ± 0.010
F6	0.316 ± 0.010	0.333±0.01	0.344 ± 0.012	0.350 ± 0.011	0.363 ± 0.011
F7	0.349 ±0.012	0.362 ± 0.014	0.375 ± 0.019	0.389 ± 0.018	0.399 ± 0.019
F8	0.369 ± 0.009	0.385 ± 0.011	0.399 ± 0.013	0.410 ± 0.018	0.426 ± 0.021
F9	0.379 ± 0.010	0.390 ± 0.012	0.400 ± 0.016	0.415 ± 0.018	0.435 ± 0.022

Table 6. Buoyancy lag time and total floating time of bilayer floating tablets

Batch Code	Floating lag time (sec)	Total floating time (hr)
F1	23	>19
F2	24	>21
F3	26	>21
F4	49	>21
F5	52	>23
F6	55	>24
F7	73	>23
F8	76	>24
F9	80	>24

Table 7: *In-vitro* disintegration time of rosuvastatin calcium ir tablets in 0.1n hcl

Batch code	Disintegration time (sec)
IR1	52.33 ± 2.51
IR2	46.66 ± 1.52
IR3	40.66 ± 1.15
IR4	38.66 ± 1.15
IR5	35.33 ± 1.15
IR6	31.66 ± 1.00
IR7	31.00 ± 2.88
IR8	27.66 ± 2.51
IR9	22.66 ± 2.51

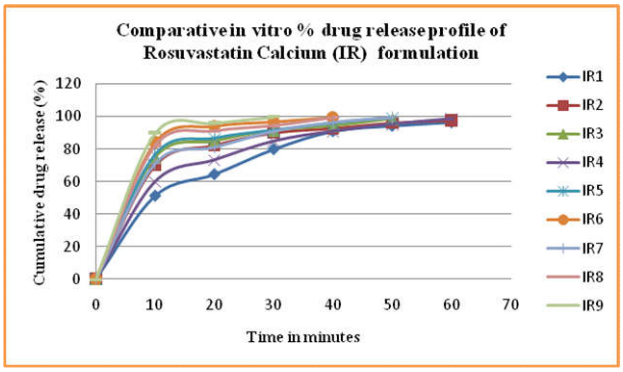


Fig. 1. Comparative *in-vitro* % drug release profiles of rosuvastatin calcium ir formulations

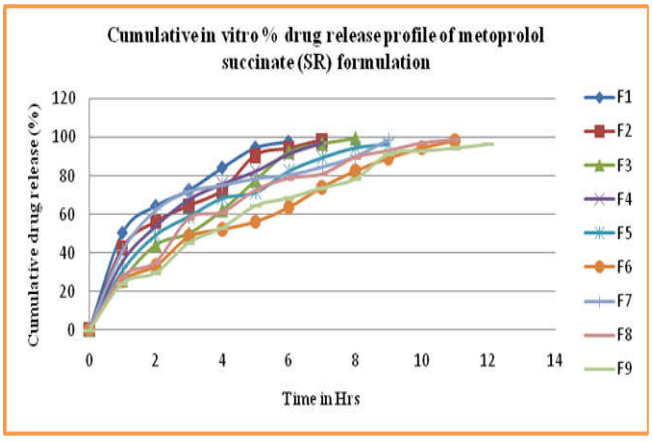


Fig. 2. Comparative in-vitro % drug release profiles of bilayer floating tablets

The results of the buoyancy lag time (BLT) and total floating time (TFT) for the different floating tablet formulations are given in Table 6.

***In-vitro* disintegration study:** The most important parameter that is needed to optimize during the development of immediate release tablets is disintegration time. Disintegration time is very important for an IR tablet which is desired to be less than 60 sec. In the present study three formulations IR1-IR9 containing SSG, CP and CCS disintegrated in 40.66, 31.66 and 22.66 sec respectively. CCS when it comes in contact with water, quickly wicks water into the tablet through capillary action to create internal pressure that disintegrates tablet. The results are given in Table 7.

***In-vitro* release profile of Rosuvastatin Calcium immediate release tablets in 0.1N HCl:** The dissolution was carried out in 900 ml of 0.1N HCl at 37±0.5˚C at 50 rpm using USP XXIV type-II (Paddle) dissolution apparatus for a period of 60 min. The IR tablets composed of Sodium stach glycolate, Cross povidone, Cross carmellose sodium as superdisintegrant (IR1-IR9) with different concentrations like 2, 4 and 6% showed drug release of about 98.63, 99.73 and 99.73% at the end of 50 (IR3), 40 (IR6) and 30 min (IR9) respectively. Among three superdisintegrants, Cross carmellose sodium has shown better drug release comparable to cross povidone and Sodium starch glycolate. Hence, formulation containing Cross carmellose sodium at 6% (IR9) was selected as best formulation for IR Layer. The results of *in-vitro* drug release of all IR tablets are given in Table 8 and depicted in Fig. 1.

***In-vitro* release profile of Metoprolol succinate bilayer floating tablets in 0.1N HCl:** IR layer of all bilayer floating tablets showed the burst release (100 mg) of Rosuvastatin Calcium within 30 min. Presence of super disintegrant (Croscarmellose sodium 6% w/w) in immediate release layer showed faster disintegration of the layer. This can be attributed to the extent of water uptake and consequently the strong swelling power of this disintegrant causing sufficient hydrodynamic pressure to induce complete disintegration. The release of Metoprolol succinate from bilayer tablets varied according to the types (HPMC K4M, K15M and K100M) and proportion of matrix forming polymers (30%, 40% and 50%). Ideally, a bilayer tablet should release the required quantity of drug in order to maintain an effective drug plasma concentration. In case of sustained release formulations F1- F9 comprising of different grades of HPMC K4M, K15M and K100M in varying concentration showed drug release between 96.6% at the end of 12 hrs respectively. The effect of polymer on release was studied by observing the release profile of sustained release formulations. In case of formulation (F9) containing HPMC K100M showed maximum drug release upto 12 hrs is due to highly viscous nature of HPMC K100M polymer, which results in strong gel strength that retards the drug release. In case of formulations composed of HPMC K4M and HPMC K15M the drug release drastically retarded below 12 hrs from the prepared bilayer floating tablets. This is due to the low viscous nature of polymers compared to HPMC K100M. The results of in-vitro drug release of all bilayer floating tablets are given in Table 9 and depicted in Fig. 2.

Release kinetic analysis: The kinetic values for the optimized formulations are shown in table no.10. The values of *in vitro* drug release of Metoprolol succinate were attempted to fit into various mathematical models, such as zero order, first order, higuchi matrix and Korsmeyer - peppas model and it was showed that developed batch followed zero order drug release kinetics as the plots shows highest linearity.

***In vivo* (x-ray) studies:** This study aimed to confirm that the formulation would actually float and be retained in the stomach.

Table 8. Comparative *in-vitro* % drug release profiles of rosuvastatin calcium ir formulations

Time in minutes	Cumulative drug release (%)								
	IR1	IR2	IR3	IR4	IR5	IR6	IR7	IR8	IR9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
10	51.24	69.97	74.93	60.06	76.59	84.3	71.08	82.1	89.81
20	64.46	82.1	84.85	73.28	86.51	94.22	81.00	90.91	95.87
30	79.89	89.81	91.46	84.85	91.46	96.97	90.91	94.22	99.73
40	90.91	92.57	94.22	90.91	95.87	99.73	96.42	99.18	-
50	94.22	95.87	98.63	95.32	99.18	-	99.42	-	-
60	96.42	97.53	-	98.63	-	-	-	-	-

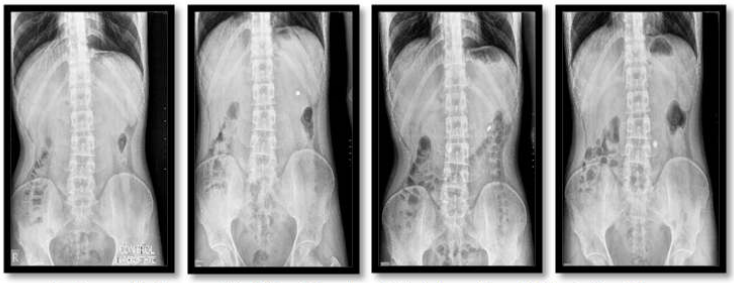
Table 9. Comparative *in-vitro* % drug release profiles of bilayer floating tablets

Time (hr)	Cumulative drug release (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	50.4 ± 0.24	42.6 ± 0.64	25.9 ± 0.04	35.5 ± 0.88	30.8 ± 0.38	25.3 ± 0.76	41.1 ± 0.21	27.8 ± 0.98	24.3 ± 0.21
2	64.3 ± 0.64	56.2 ± 0.22	44.2 ± 0.16	53.9 ± 0.10	49.2 ± 0.06	33.3 ± 0.62	62.2 ± 0.48	35.2 ± 0.68	29.8 ± 0.26
3	72.6 ± 0.02	64.4 ± 0.86	50.2 ± 0.32	67.9 ± 0.26	58.9 ± 0.07	48.4 ± 0.44	71.9 ± 0.62	57.9 ± 0.84	45.4 ± 0.18
4	84.2 ± 0.68	72.4 ± 0.94	62.2 ± 0.84	75.9 ± 0.08	68.3 ± 0.22	52.3 ± 0.32	75.1 ± 0.88	61.0 ± 0.78	53.2 ± 0.06
5	94.6 ± 0.36	90.6 ± 0.48	77.8 ± 0.86	82.5 ± 0.64	71.4 ± 0.62	56.2 ± 0.64	78.6 ± 0.12	72.4 ± 0.06	64.6 ± 0.06
6	97.6 ± 0.45	94.2 ± 0.24	92.5 ± 0.96	91.5 ± 0.54	82.4 ± 0.12	63.6 ± 0.72	80.5 ± 0.01	78.6 ± 0.10	68.6 ± 0.88
7	-	98.6 ± 0.21	96.8 ± 0.86	97.3 ± 0.44	89.4 ± 0.08	74.2 ± 0.08	84.6 ± 0.11	80.8 ± 0.66	73.9 ± 0.24
8	-	-	99.6 ± 0.78	-	94.5 ± 0.05	82.6 ± 0.10	90.2 ± 0.36	89.4 ± 0.56	78.6 ± 0.04
9	-	-	-	-	96.4 ± 0.34	89.3 ± 0.11	98.9 ± 0.33	92.9 ± 0.12	91.5 ± 0.35
10	-	-	-	-	-	94.6 ± 0.66	-	96.8 ± 0.44	93.1 ± 0.24
11	-	-	-	-	-	98.4 ± 0.06	-	98.6 ± 0.68	94.6 ± 0.08
12	-	-	-	-	-	-	-	-	96.6 ± 0.36

Table 10. Kinetic data of optimized formulation F9

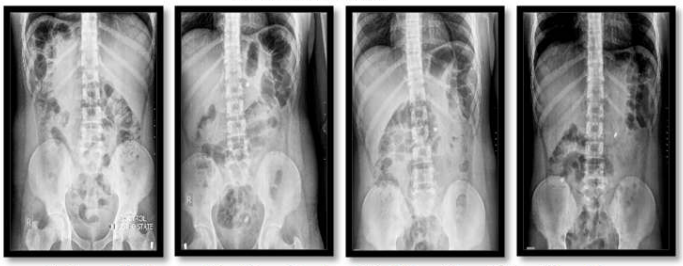
Formulation	Zero order	First order	Higuchi	Korsmeyer – pepps model	
F9	R2	R2	R2	R2	N
	0.9834	0.9647	0.9863	0.9906	0.8392

I. In fed- state



I) Controlled state. II) After 30 min. III) After 4 hr. IV) After 8 hr.

II. In fasted state



I) Controlled state. II) After 30 min. III) After 4 hr. IV) After 8 hr.

Fig. 3. *In vivo* (x-ray) studies

A radiological method was used to monitor the devloped formulation in the gastric region of human volunteers under fasting and feed counditions. It was found that the formulation remain buoyant in gastric contents in both feed and fast state for 8 hrs. The gastric resident time of optimized bilayer tablets was evaluated by counducting *in - vivo* X - ray studies in healthy human volunteers. From the radiographic images following results were obtained (Fig 3.). This analysis confirmed that, both the tablets were having similar values of above parameter mentioned.

So that, the *in-vivo* x- ray study results should be compared and the tablets were similar for *in-vitro* testing i.e., the mechanical strength, floating properties (Atram, 2009; Kulkarni, 2009; Hilton, 1992; Lian-dong hu, 2011; Ibrahim, 2010).

***Stability studies*:** Stability studies were conducted for the optimized formulations F9 at 40°C ± 2°C and 75% ± 5% RH for a period of 30 days. The samples were analyzed for physical appearance, hardness and uniformity of drug content

and *in-vitro* dissolution studies after 30 days. The results obtained were found to be within limit**.** There were no significant change observed in the physical appearance, hardness and drug content uniformity test was conducted at the end of 30 days. The in-vitro dissolution profile for formulations F9 stored at 40°C ± 2°C and 75% ± 5% RH exhibited 99.40% release of Rosuvastatin calcium after 30 min and 97.6 % release of Metoprolol succinate after 12 hrs. Therefore the stability studies revealed no change in physical appearance, hardness, drug content and not much change in in-vitro dissolution profiles. Hence these formulations were found to be stable at the above temperatures (40°C ± 2°C and 75% ± 5%RH).

Conclusion

From the results of above research work it can be concluded that, Increase in amount of superdisintegrant in formulation of immediate release layer increase in disintegration time and release of drug. Among the three superdisintegrants, sodium starch glycolate, cross povidone and cross carmellose sodium at three different concentrations (2%, 4% and 6%). Cross carmellose sodium (6%) is sufficient for complete release of Rosuvastatin calcium in 30 minutes. From the *in vitro* buoyancy study, it was observed that as the concentration of gas generating agent as increases, floating lag time decreases. Also, the polymer–gas generating agent ratio was found to be influence the floating lag time and total duration of floating. Thus floating lag time in order of HPMC K4M > HPMC K15M > HPMC K 100M but total duration of floating and tablet integrity was maintained for longer duration of time for high viscosity grades of polymer. Also, the drug-polymer ratio was found to be influence the release of drug from formulation. As the polymer level was increased, the drug release rate was found to be decreased. The drug release rate also influenced by viscosity grade of polymer (HPMC), as the polymer viscosity increased, the release of drug decreased. Thus, drug release rate in order of HPMC K100M > HPMC K15M > HPMC K4M.

From kinetic study data, it was observed that in optimized batch , Metoprolol succinate release from SR layer followed first order, higuchi model and non- Fickian diffusion release mechanism. HPMC K100M (50%) with gas generating agent sodium bicarbonate (10%) are suitable for sustained release of Metoprolol succinate over long period of time. From *in vitro* buoyancy studies, it was concluded that, developed batch F9 showed floating lag time 78 sec and total duration of floating up to 24 hrs. The dual component gastro retentive drug delivery system showed good floating and sustained release. *In vivo* study of optimized formulation F9, loaded with barium sulphate in fed as well as fasted state shows gastric retention period up to 8 hrs. Short term stability study indicates no appreciable changes in the drug content, floating lag time, total duration of floating and in vitro drug release rates of formulation F9.

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