Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2011, 3(3): 147-160
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Formulation and evaluation of floating pulsatile drug delivery system of Metoprolol tartrate

Anuradha K. Salunkhe*, Remeth J. Dias, Kailas K. Mali, Niranjan S. Mahajan and Vishwajeet S. Ghorpade

Department of Pharmaceutics, Satara College of Pharmacy, Satara, M.S. India

---

ABSTRACT

The objective of present investigation was to prepare and evaluate a floating pulsatile drug delivery system of metoprolol tartrate. The prepared floating pulsatile delivery system consisted of three different parts: a core tablet, containing the active ingredient, an erodible outer shell and a top cover buoyant layer. The rapid release core tablet (RRCT) was prepared by using superdisintegrants along with active ingredient. Dry coating of optimized RRCT was done by using different grades of hydroxy propyl methyl cellulose (HPMC) E5, E15, and E50 and upper most buoyant layer was prepared with HPMC K15M and sodium bicarbonate. Developed formulations were evaluated for their physical characteristics, drug content, in vitro disintegration time, in vitro drug release profile (lag time), floating lag time, floating time and in vivo X-ray study. On the basis of these evaluation parameters it was found that optimized floating pulsatile release formulation (FPRT) F9 showed floating lag time of 4 min, floating time of 12 hrs and release lag time of 6 hrs. The F9 formulation showed compliance with chronotherapeutic objective of hypertension.

Keywords: Chronotherapy, Floating pulsatile release tablet, Metoprolol tartrate, Lag time, Floating time.

INTRODUCTION

Conventional controlled release drug delivery systems are based on single-or multiple-unit reservoir or matrix systems, which are designed to provide constant or nearly constant drug levels over an extended period of time [1].

Chronopharmaceutics, the drug delivery based on circadian rhythm, is recently gaining much attention worldwide. Various diseases like asthma, hypertension, arthritis show circadian

variation, that demand time-scheduled drug release for effective drug action [2]. Results of several epidemiological studies have demonstrated the elevated risk of different pathologies during a 24 hr cycle. Blood pressure which rises notably just before waking up is usually responsible for attacks [3]. New technology based on pulsatile release control was developed to satisfy this requirement.

Zou H et al., developed a floating pulsatile release tablet of verapamil and observed the increase in drug release profile (lag time) by changing viscosity grades of hydroxyl propyl methyl cellulose (HPMC) [3]. Badve et al., developed hollow / porous calcium pectinate beads for floating pulsatile drug delivery [4].

The gastroretentive pulsatile drug delivery system is useful for those drugs which have pH dependent solubility, poor bioavailability in gastrointestinal tract (GIT) and narrow absorption window [5]. Overall, these considerations led to the development of oral pulsatile release dosage forms possessing gastric retention capabilities.

Metoprolol tartrate (MT) is a cardioselective β1 blocker and an effective antagonist of the inotropic and chronotropic responses to isoproterenol [6]. It is a typical drug used in therapy of hypertension. Absorption of MT takes place in duodenum and jejunum [7]. It also undergoes extensive first pass metabolism (40-60%). Previously, the attempts have been made in order to overcome the above drawbacks. Narendra C et al. formulated floating tablets of MT so as to release the drug for longer duration of time in upper part of GIT [8]. Aquil M et al. prepared transdermal patches of MT to avoid first pass metabolism of MT [9].

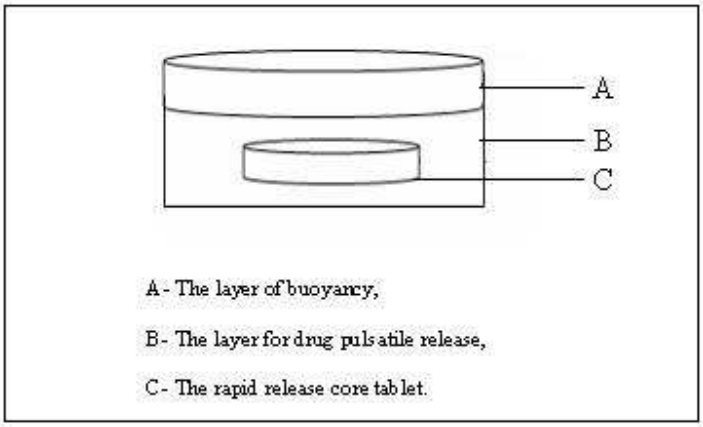

Figure 1. Design of floating pulsatile release tablet of MT

Generally in hypertension, the risk of getting heart attacks is just before the waking hours of the patient i.e. early in the morning and therefore the need of antihypertensive is typically felt during morning hours. For such cases, conventional formulations of MT cannot be administered before the symptoms get worsened because at that time patients are asleep. Thus taking into consideration the pharmacokinetics as well as objective of chronotherapy, we have made attempt to design and formulate floating pulsatile drug delivery of MT which when administered at bed time will deliver the drug in early morning hours.

The floating pulsatile drug delivery system was designed such that rapid release core tablet of MT was dry coated by the layer of HPMC to impart pulsatile release characteristics and the top cover buoyant layer ensured the floating of the system (figure 1). Developed formulations were evaluated for buoyancy studies, drug release studies and floating lag time studies

MATERIALS AND METHODS

Materials:

Metoprolol tartrate, crospovidone, croscarmellose sodium, polyvinylpyrrolidone (PVP) K- 30 were obtained as gift sample from Nicholas Piramal, Mumbai. HPMC (E5, E15, E50 and K15M) and microcrystalline cellulose were gifted by Cipla, Kurkumbh. Ethanol and hydrochloric acid used were of analytical reagent grade.

Methods:

Preparation of Rapid Release Core Tablet (RRCT)

Metoprolol tartrate RRCTs were prepared by wet granulation method (table 1). All the ingredients were passed through 60# mesh sieve separately and collected. The ingredients were weighed and mixed in a geometrical order. Then the mixture was wetted with a solution of PVP K-30 (10% w/v in ethanol). The wetted mass was again passed through 22# mesh sieve. The granules were dried in a circulating hot air oven (40ºC) for 6h and compressed by using 6 mm size punch to get a tablet of 60 mg weight using single punch tablet machine (Cadmach, Ahmedabad).

Table 1. Formulation of RRCT of Metoprolol Tartrate

Ingredients (mg)	RR1	RR2	RR3	RR4	RR5	RR6	RR7	RR8
Metoprolol tartrate	25	25	25	25	25	25	25	25
Croscarmellose sodium	1.2	1.8	2.4	3	--	--	--	--
Crospovidone	--	--	--	--	1.2	1.8	2.4	3
Microcrystalline cellulose	33.8	33.2	32.6	32	33.8	33.2	32.6	32
Total Weight (mg)	60	60	60	60	60	60	60	60

Evaluation of RRCT

Compatibility and physical characterization

The prepared RRCTs were evaluated for compatibility between drug and excipients using Fourier transform infrared spectroscopy (FTIR) [10]. The physical characteristics such as thickness, diameter, hardness and weight variation test were evaluated according to the Indian Pharmacopoeia (IP) 1996 [11].

Uniformity of content

20 tablets were weighed individually and powdered. The powder equivalent to about 0.12 gm of MT was transferred to a 100 ml volumetric flask. Then 75 ml of ethanol (95%) was added, mixed and filtered. 5 ml of filtrate was diluted with 50 ml ethanol and concentration of drug was determined by UV spectrophotometer (Schimadzu UV, 1700) at 274 nm [12].

In vitro disintegrating time

In vitro disintegration time of six tablets from each formulation was determined by using digital

tablet disintegration apparatus (Electrolab, ED- 2L). In vitro disintegration test was carried out at 37 ± 2 ^{0}C in 900 ml 0.1N HCl.

In vitro dissolution studies

The in vitro dissolution studies were carried out in 0.1N HCl (900 ml) at 37 ± 0.5^{o}C using USP dissolution apparatus type II. The speed of rotation was maintained at 50 rpm. Aliquots of dissolution medium were withdrawn at predetermined time interval and content of MT was determined by using UV spectrophotometer at 274 nm. The dissolution studies were conducted in triplicate.

Preparation of the Pulsatile Release Tablet (PRT)

The optimized RRCT was used for preparation of PRTs. Dry coating of optimized RRCT was done by using different grades of HPMC (E5, E15 and E50) at different concentrations (table 2). Final weight of tablet was adjusted to 360 mg. Dry coated tablet was prepared by placing 50% of pulsatile release layer in 10 mm die and RRCT was placed on it. Further remaining quantity of pulsatile release layer was added in cavity so as to cover the RRCT and finally compressed by using single punch tablet machine.

Table 2. The Composition of PRT of Metoprolol Tartrate

Polymer	Conc. in mg/ tablet					
HPMC E5	200	220	240	260	280	300
HPMC E15	200	220	240	260	280	300
HPMC E50	200	220	240	260	280	300

Evaluation of PRT

The formulated PRTs were evaluated for parameters like thickness, diameter, hardness and in vitro drug release (lag time). The optimization was done based on these results.

Swelling index

The swelling index of optimized PRT was compared with other PRTs with same concentration as that of optimized PRT by using USP dissolution apparatus type I. In this study six tablets were placed in the basket of dissolution apparatus by using 0.1N HCl as dissolution medium at 37± 0.5^{0}C. Tablets were withdrawn at a time interval of 30 min, blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, AX 120) [1]. Swelling index was calculated by using the following formula (eq. 1).

$$\text{Swelling Index} = \frac{\text{Wet weight of tablet - Dry weight of tablet}}{\text{Dry wet of tablet}} \quad \textbf{(1)}$$

Preparation of Floating Pulsatile Release Tablet (FPRT)

The composition of buoyant layer was optimized by using 3^2 full factorial design (table 5). In this study, two factors were evaluated each at three levels and experimental trials were performed at all nine possible combinations. The amounts of HPMC (X_1) and sodium bicarbonate (X_2) were selected as independent variables.

All the nine possible combinations of buoyant powder were filled into the die individually, followed by addition of optimized PRT and finally compression was done. These nine formulations were studied and optimized for floating lag time and floating time.

Evaluation of FPRT

FPRTs were evaluated for parameters like thickness, diameter, hardness, floating lag time, floating time and in vivo X- ray studies.

In vitro floating behavior of FPRT was studied by using dissolution apparatus type II in 900ml 0.1N HCl at 37 ± 0.5^0C. The speed of rotation was maintained at 50 rpm. The floating lag time (the period between placing FPRT in the medium and buoyancy) and floating duration of FPRT were determined by visual observation.

In vivo X-ray studies:

The Institutional Ethics Committee approved the in vivo studies. The in vivo X-ray studies of FPRTs were performed on three healthy human volunteers using Simence 300mA X- ray generating unit (Disha Diagnostic Centre, Satara, M. S., India). Volunteers aged 25-30 years and weighing 55-60 Kg were selected for these studies. The written consent of the human volunteers was taken before participation and the studies were carried under the supervision of an expert radiologist and physician.

The tablets of optimized FPRT formulation i.e. F9 were prepared by replacing MT with X-ray grade barium sulphate. The prepared tablet was administered to every subject with 200ml water after overnight fasting. After one hour a glass of plenty water was given to the every subject after tablet ingestion [13]. Gastric radiography was done at 0, 0.5, 2, 4, 6 and 8 hr.

Stability studies

A short-term stability study on optimized FPRT was carried out by storing the tablets at 40^0C/ 75% RH over a 6 months period according to ICH guidelines [12]. At the end of six months time interval, the tablets were examined for any physical characteristics, drug content, in vitro drug release (lag time), floating lag time and floating duration. Statistical analysis was performed on the drug content data and drug release parameters by using ‘t’ test.

RESULTS AND DISCUSSION

Rapid Release Core Tablet (RRCT) Characterization

Drug- Excipient interaction study

Infrared spectroscopy was used as means of studying drug-excipients interactions. It was found that there was no chemical interaction between MT and excipients used because there were no changes in the characteristic peaks of MT in the IR spectra of mixture of drug and excipients as compared to IR spectra of pure drug (figure 2). The drug exhibits peaks due to the secondary amine, carboxylic acid salt, aromatic ring, aromatic ether, isopropyl group and secondary alcohol.

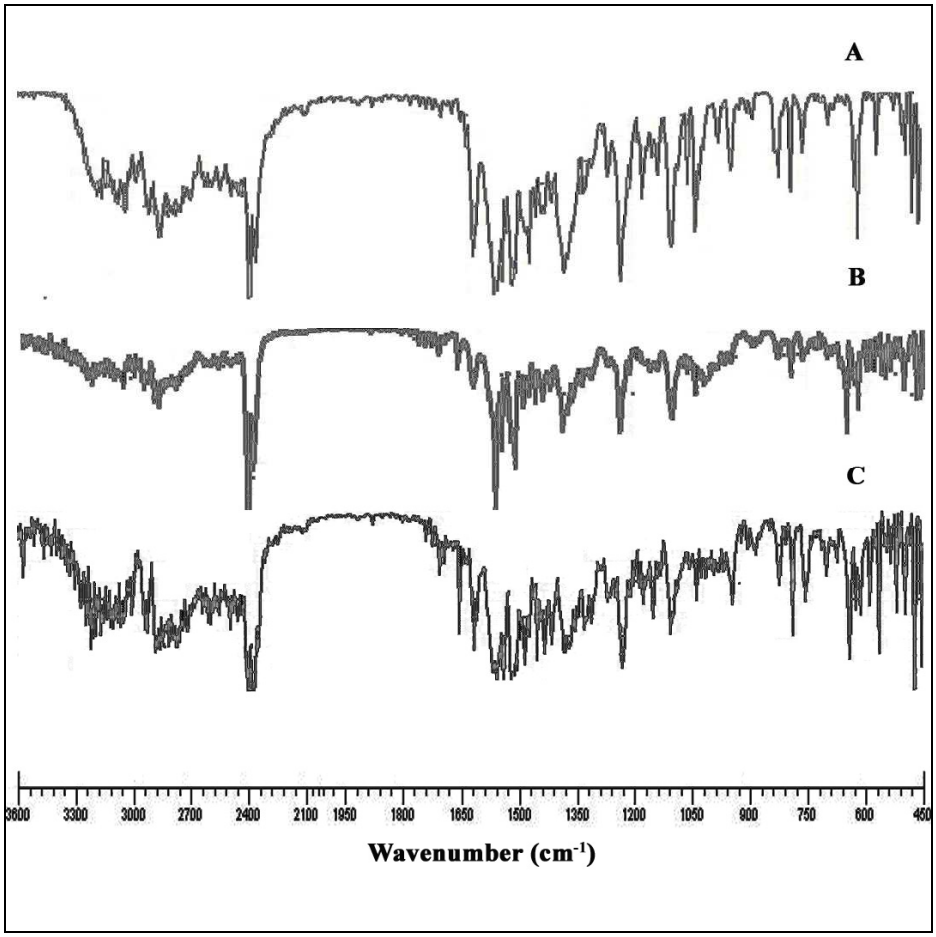

Figure 2. IR spectra of (a) Metoprolol tartrate; (b) Metoprolol tartrate, crosscarmellose sodium; and (c) Metoprolol tartrate, crospovidone

Physical characteristics of RRCT

Table 3: Evaluation of Metoprolol Tartrate RRCT

F.C.	Thickness* (mm) n=5	Diameter* (mm) n=5	Hardness* (kg/cm^2) n=6	In vitro disintegration time* (sec) n=6	In vitro % drug release*(%) n=3
RR1	2.4± 0.14	6±0	3.4± 0.14	173.3± 1.5	51.69± 1.1
RR2	2.44±0.089	5.99±0.1	3.44± 0.089	147± 1	61.48± 3.1
RR3	2.4± 0.14	6±0	3.52± 0.10	134± 2.3	80.31± 1.6
RR4	2.28± 0.17	6±0	3.4± 0.14	126.3± 1.5	97.65± 0.2
RR5	2.4± 0.14	5.99±0.17	3.4± 0.14	166.6± 1.5	64.84± 1.6
RR6	2.36± 0.16	6±0	3.32± 0.10	136.3± 1.5	76.36± 0.8
RR7	2.48± 0.10	6± 0	3.32± 0.10	125.6± 1.5	92.07± 0.2
RR8	2.32± 0.10	6±0	3.36± 0.16	117.6± 0.5	105±0.1

**values are expressed as mean± SD*

Eight formulations of MT RRCTs with varying concentration of croscarmellose sodium (RR1-RR4), crospovidone (RR5- RR8) were evaluated for tablet dimensions, hardness, weight

variation, uniformity of content, in vitro disintegration time and in vitro drug release study. It was found that all RRCTs showed tablet dimensions, hardness, weight variation, uniformity of content, in vitro disintegration time within the prescribed range as given in IP (table 3).

In vitro drug release of RRCT

In this study formulations containing crospovidone (RR5-RR8) showed fast drug release than the formulation containing croscarmellose sodium (figure 3). This may be because of the fact that crospovidone probably made larger pores with continuous network or skeleton providing enough pressure for faster disintegration and it also had capability to swell at least twice of its original volume when in contact with dissolution fluid [14]. Among eight formulations of MT RRCTs, it was observed that formulations containing crospovidone in concentration 5% (RR8) showed satisfactory hardness, uniformity of content , lowest disintegration time and highest drug release (table 3). So RR8 was considered as optimized formulation and was taken for further studies.

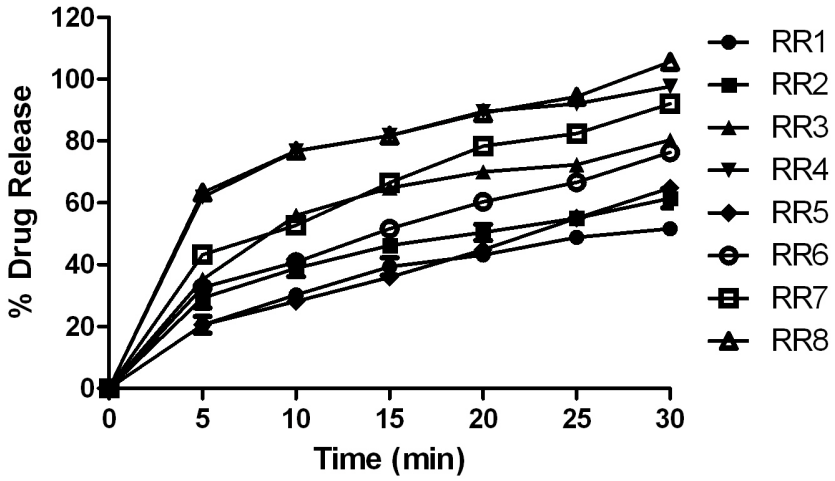

Figure 3. In vitro drug release profiles of Metoprolol tartrate from RRCT croscarmellose sodium and crospovidone.

Pulsatile Release Tablet (PRT) Characterization

Physical characteristics of PRT

For PRT characterization, total 18 formulations containing varying concentration (200- 300 mg) of HPMC E5, E15 and E50 were evaluated for thickness, diameter, hardness and drug release profile in terms of lag time. It was found that all PRT formulations showed satisfactory features in terms of thickness, diameter and hardness (table 4).

In vitro drug release (lag time) study

In vitro drug release (lag time) study of 18 formulations, showed differences in drug release (lag time) as shown in table 4. All the formulations coated with HPMC E5 and E15 have given the lag time of less than 3 hr and 5 hr respectively which was considered to be unsuitable for chronotherapeutic objective. The formulations coated with HPMC E50 in concentration of 280 mg showed sufficient lag time as compared to formulations coated with HPMC E5 and E15 with same concentration (Figure 4).

Table 4: Evaluation of Metoprolol Tartrate PRT

F.C.	Thickness* (mm)n=5	Diameter* (mm)n=5	Hardness* (kg/cm^2)n=6	Lag time* (min) n=3
E5$_{200}$	2.97±0.005	10± 0	4.3± 0.1	45
E5$_{220}$	3.25± 0.01	10± 0	4.4± 0.2	75
E5$_{240}$	3.47± 0.01	9.98± 0.005	4.4± 0.2	104
E5$_{260}$	3.77± 0.01	9.96± 0.005	4.4± 0.2	134
E5$_{280}$	3.99±0.005	10± 0	4.6± 0.1	165
E5$_{300}$	4.2± 0	10± 0	4.6± 0.08	195
E15$_{200}$	2.97±0.005	9.99± 0.01	4.6±0.1	149
E15$_{220}$	3.28± 0.01	9.99± 0.01	4.6± 0.1	180
E15$_{240}$	3.47± 0.01	10± 0	4.6± 0.1	210
E15$_{260}$	3.77± 0.01	10± 0	4.6± 0.2	240
E15$_{280}$	3.99±0.005	9.98± 0.01	4.5± 0.1	270
E15$_{300}$	4.2± 0	9.98± 0.01	4.5± 0.2	300
E50$_{200}$	2.97±0.005	9.99± 0.01	4.4±0.2	240
E50$_{220}$	3.28± 0.01	9.99± 0.01	4.6± 0.2	270
E50$_{240}$	3.47± 0.01	9.99± 0.01	4.6± 0.1	301
E50$_{260}$	3.77± 0.01	9.99± 0.01	4.6± 0	331
E50$_{280}$	3.99±0.005	9.99± 0.01	4.5± 0.2	360
E50$_{300}$	4.2± 0	9.99±0.01	4.5± 0.1	390

**values are expressed as mean± SD*

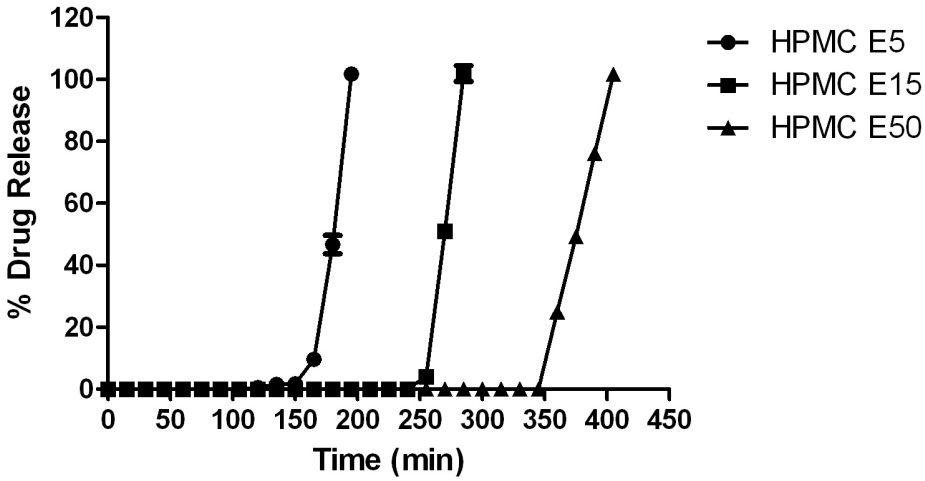

Figure 4. In vitro release profile of Metoprolol tartrate from PRT with 280mg different kinds of HPMC.

In this study (lag time) as the coated tablet i.e. PRT was placed in the dissolution medium, it was observed that the hydrophilic polymeric layer started erosion, which underwent progressive modification in terms of thickness and consistency. In the second phase of the dissolution procedure, the coating layer gradually started to erode up to a limiting thickness. After this stage, a shell was ruptured under the pressure applied by the swelling of the core tablet and MT was released. All of this process contributed to a lag time capable of exhibiting a pulsatile release of the drug. The drug release profiles relevant to the coated tablet showed that a lag phase was followed by the quick delivery of the drug. As the formulation coated with HPMC E50 in concentration of 280 mg showed sufficient lag time as compared to other formulations, this

formulation was considered as optimized formulation for FPRT.

Swelling index

The swelling behavior of optimized PRT containing HPMC E50 was compared with other PRTs containing HPMC E5 and HPMC E15 at same concentration i.e. 280 mg. The obtained results showed that the swelling front erodes faster for PRTs with HPMC E5 and the swelling front erosion was comparably slower in PRTs with HPMC E15 and E50 due to their marked viscosity properties (figure 5).

In swelling index study, an increase in thickness of rubbery layer of PRT with HPMC E50 was higher as compared with PRTs with HPMC E5 and HPMC E15. This result may be attributed to complete penetration of solvent and high viscosity of the HPMC E50 [15]. A direct correlation between swelling and lag time was observed and found that the formulations having maximum swelling indices showed higher lag time.

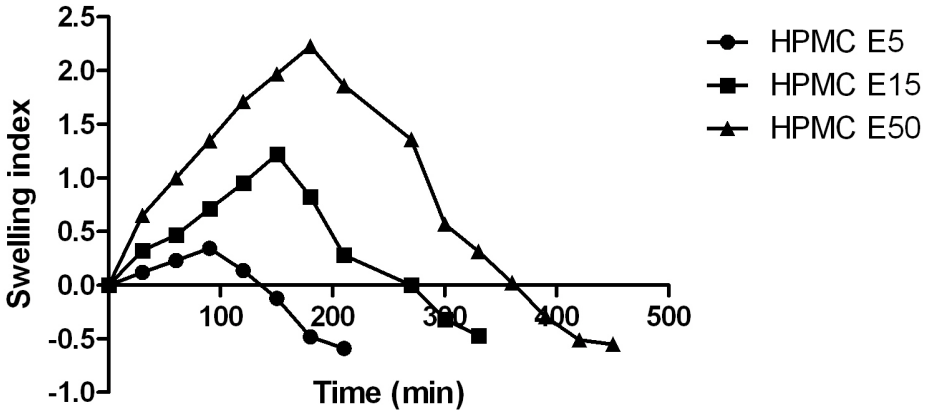

Figure 5. Swelling indices of PRT with HPMC E5, E15 and E50.

Floating Pulsatile Release Tablet (FPRT) Characterization

The composition of buoyant layer was prepared by using 3^2 full factorial design and evaluated for thickness, diameter, hardness, floating lag time and for floating time. It was found that all tablets form FPRT composition showed satisfactory results in terms of thickness, diameter and hardness (table 5).

Floating lag time and floating time study

In this study floating lag time for all compositions of FPRTs were found to be less than 14 minutes and floating time more than 12 hr (table 5).

Here FPRT with highest concentration of HPMC K15 M and sodium bicarbonate (F9) was selected for chronotherapy of hypertension because it showed least floating lag time of 4.6 minutes and highest floating time of 12 hr.

Table 5.Coded levels as per 3^2 full factorial designs with observed responses

F.C	X1	X2	Thickness* (mm) n=5	Diameter* (mm) n=5	Hardness* (kg/cm^2) n=6	Floating lag time (min) n= 3	Floating time (h) n=3
F1	-1	-1	4.1±0.005	10± 0	5.76 ± 0.08	13.6 ± 0.5	>12
F2	-1	0	4.1±0.005	10± 0	5.64 ±0.08	11.6±0.5	>12
F3	-1	+1	4.1±0.005	10± 0	5.52 ±0.17	6.6±0.5	>12
F4	0	-1	4.1±0.005	10± 0	5.56 ±0.17	11.3±0.5	>12
F5	0	0	4.1±0.005	10± 0	5.52 ±0.10	6.6±0.5	>12
F6	0	+1	4.1±0.005	10± 0	5.72 ±0.10	5.6±0.5	>12
F7	+1	-1	4.2± 0	9.98± 0.005	5.68 ±0.17	9.3±0.5	>12
F8	+1	0	4.1±0.005	9.96± 0.005	5.6 ±0.14	5.6±0.5	>12
F9	+1	+1	4.2± 0	10± 0	5.68 ±0.17	4.6±0.5	>12

**values are expressed as mean± SD*

Coded values	Actual values	
	X1	**X2**
-1	80	7.5
0	100	10
1	120	12.5

X1- HPMC K15; X2- Sodium bicarbonate

HPMC, a non ionic polymer with unique physicochemical properties, is used frequently as a controlled release polymer in swellable hydrophilic matrices. The popularity of this polymer may be attributed to its nontoxic nature and being relatively inexpensive. Sodium bicarbonate was included as a gas generating agent and this compound generates carbon dioxide on the reaction with acidic aqueous media, which help the tablet to become buoyant and remain entrapped in the gel layer. The amount of X1 (HPMC) and the X2 (Sodium bicarbonate) were chosen as independent variables in 3^2 factorial design. A statistical model used was

$$Y= b_o +b_1x_1+b_2x_2+b_{12}x_1x_2+b_{11}x_1x_1+b_{22}x_2x_2 \qquad \textbf{(2)}$$

Where Y is the dependent variable, b_o is the arithmetic mean response of the nine runs, and b_1 is the estimated coefficient for the factor x_1. The main effects (x_1 x_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (x_1 x_2) showed how the response changes when two factors are changed simultaneously. The polynomial terms (x_1 x_1, x_2 x_2) are included to investigate nonlinearity.

From the data of floating lag time parameters for factorial composition F1 to F9; polynomial equation for dependent variable has been derived using Design Expert software.
The equation derived for floating lag time was

$$Y = 67.788-0.5758\ x_1- 4.1233\ x_2+0.0115\ x_1x_2+1.7916\ x_1x_1+0.09066\ x_2x_2 \qquad \textbf{(3)}$$

In equation (3), negative sign for coefficient of x_1 and x_2 indicates that as the concentration of HPMC and gas generating ($NaHCO_3$) agent increases, floating lag time value decreases. The corresponding response surface plot and contour plot are given in figure 6 and 7.

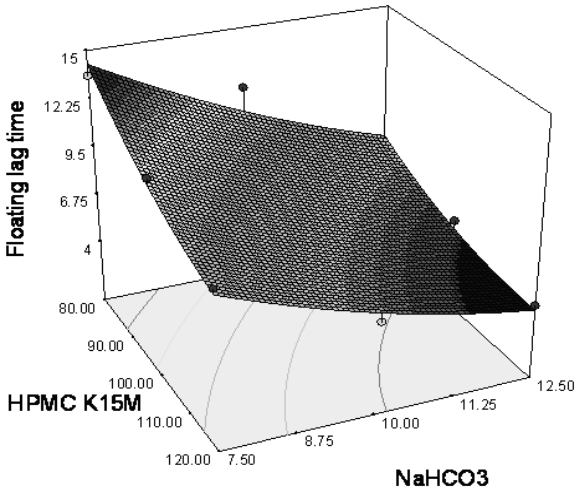

Figure 6. Response surface plot showing effect of factorial variables on floating lag

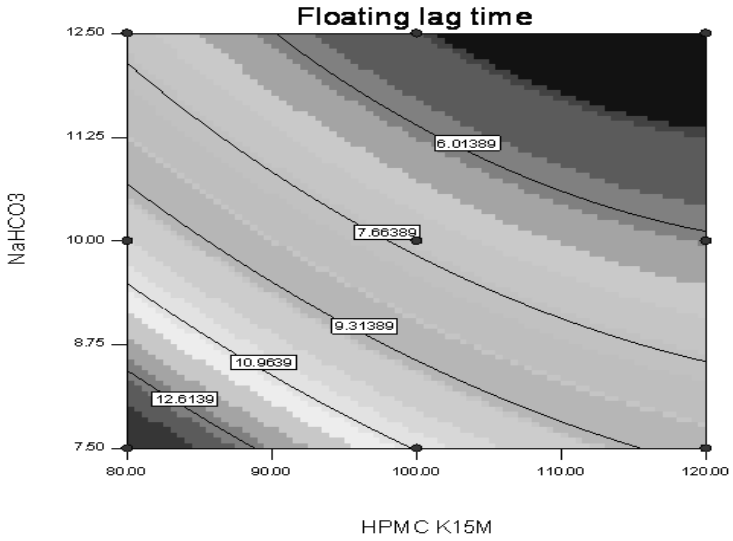

Figure 7. Contour plot showing relationship between various levels of HPMC and $NaHCO_3$ to attain fixed value of floating lag time.

In vivo X-ray studies:

Three volunteers were used to study the floating of tablets in fasted and fed conditions. After administration of barium floating placebo formulation, the radiographs were taken after 0, 0.5, 2, 4, 6 and 8 hr. The radiographs taken after 0.5 hr indicated the buoyancy of the tablets, in case of volunteers in fasted and fed state. The duration of tablet in stomach and upper part of intestine was monitored by radiograms (figure 8). It was observed that the tablet stayed in stomach for 6.5±0.5 hr.

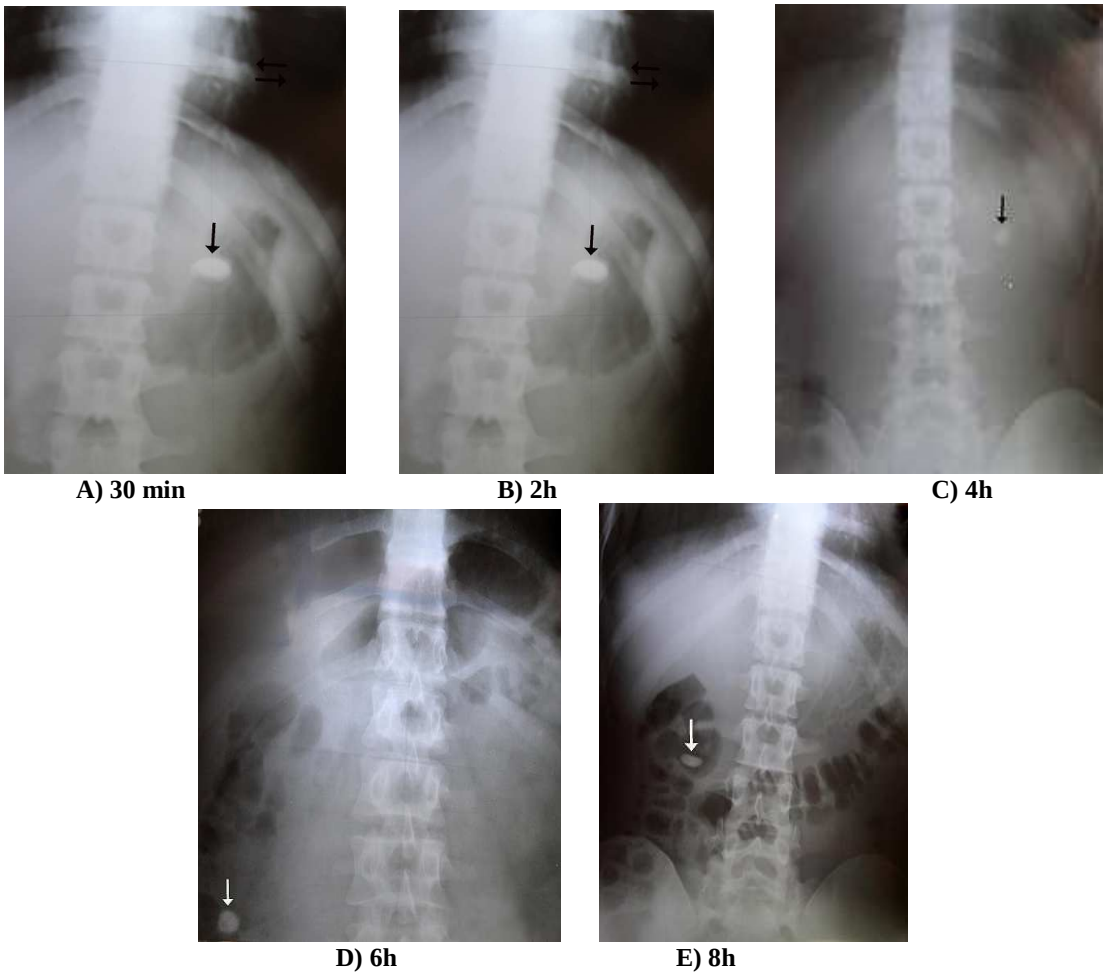

Figure 8. X ray radiograms of abdomen after administration of optimized FPRT in fasted state after (A) 30 min. and (B) 2h. Figures C and D after 3h taking liquid food and after 6h taking lunch respectively.

After 3 hours the liquid food was given to the healthy volunteer in fed state and radiographs were taken. Further it was observed that though the food emptied from the stomach, barium floating tablet remained at its place. This indicates that barium-floating tablet did not affect food emptying from the stomach and food did not affect swelling of tablet in the stomach.

The in vivo studies of optimized FPRT (barium floating tablet) indicated lesser floating lag time and increased gastric residence time.

Stability studies

Short-term stability studies of the optimized FPRT (F9) indicated that there were no significant changes ($p<0.05$) in physical parameters, in vitro dissolution studies, floating lag time and floating time at the end of six months period (table 6).

Table 6: Evaluation of FPRT (F9) after short term stability period

Parameters	Before	After
Thickness(mm)	4.2± 0	4.3± 0.11
Diameter(mm)	10 ± 0	10 ± 0
Hardness(kg/cm^2)	5.68± 0.17	5.69± 0.11
In vitro drug release (lag time) in min	360	360
Drug release (%)	105.6± 0.1	100.31±0.06
Floating lag time (min)	4.6±0.5	4.6±0.5
Floating time (h)	>12	>12

n=3; values are expressed as mean± SD

CONCLUSION

A chronotherapy based FPRT of MT was successfully developed. Taking into consideration the chronotherapy of hypertension, FPRT with highest concentration of HPMC K15M and sodium bicarbonate in buoyant layer and 280 mg concentration of HPMC E50 in pulsatile layer (formulation F9) gave satisfactory release lag time of 6 hr, 4.6 minutes floating lag time and more than 12 hr floating time. The in vivo X-ray study indicated that the FPRT may increase the gastric residence time. This FPRT may be used for administration at bed time which will release MT in the early morning when chances of hypertension are more. However there is further need for investigation for the clinical acceptance of this novel delivery system.

Acknowledgment
The authors are grateful to Prof. M. S. Jagtap, Chairman, Gourishankar Education Society, Satara for providing necessary facilities to carry out the research work.

REFERENCES

[1] S Sungthogjeen; S Puttipipatkhachorn; O Paeratakul; A Dasheveky; R. Bodmeire. *J. Contr. Rel.* **2004**, 95, 147-159.
[2] S Jessy; V Patole. *Dhaka uni. J. Pharm. Sci.* **2007**, 6, 37-41.
[3] H Zou; X Jiang; L Kong; S Gao. *J. Pharm. Sci.* **2008,** 97, 263-273.
[4] S Badve; P Sher; A Korde; A Pawar. Eur. *J. Pharm. Biopharm.* **2007,** 65, 83-93.
[5] BS Dave; AF Amin; MM Patel. *AAPS PharmSciTech.* **2004,** 5(2), 1-5.
[6] C Dollery. Therapeutics drugs, Churchill Livingstone, Edinburgh, **1999**; pp. M-139.
[7] C Narendra; MS Srinath; G Babu. *AAPS PharmSciTech.* **2006,** 7, 1-7.
[8] C Narendra; MS Srinath; A Moni. *CI & CEQ*. **2008**, 14, 17-26.
[9] M Aquil; Y Sultana. *Acta. Pharm.* **2003**, 53, 119-125.
[10] K Flory. Analytical profile of drug substances, Academic Press Elsevier, New York, **2005**; pp 325.
[11] Government of India, Ministry of health and welfare. Indian Pharmacopoeia, Controller of Publications, Delhi, **1996**; pp. A-80-81.
[12] International Conferences on Harmonization. Stability Testing of new Drug Substances and Products. Q 1 A (R2). 2003 [cited 2009 Sept 10]; Available from: http://www.emea.europa.eu.
[13] Z Rahman; M Ali; RK Khar. *Acta. Pharm.* **2006,** 56, 49-57
[14] RC Rowe; P Sheskey; P Weller. Handbook of Pharmaceutical Excipients, Fourth Edition, Pharmaceutical Press Publishers, Great Britain, **2005**; pp. 139-146.

[15] L Zema; A Maroni; A Foppoli; L Palugan; ME Sangalli; A Gazzanigi. *J. Pharm. Sci.* **2007**, 96,1527- 1536.