International Journal of Drug Delivery 6 (2014) 14-23
http://www.arjournals.org/index.php/ijdd/index

Original Research Article

ISSN: 0975-0215

Design and *In vivo* evaluation of Metoprolol Tartrate bilayer floating tablets in healthy human volunteers

Prasanna Kumari J*[1,4], Ramarao T[2], Jayaveera K N[3], Bhikshapathi D V R N[4], Madhusudan Rao Y[5]

*Corresponding author:

Prasanna Kumari J

[1]Research and Development Department, J.N.T.University, Hyderabad-500085, A.P, India.
[2]Avanthi Institute of Pharmaceutical Sciences, Hayathnagar, Hyderabad-501512, A.P, India.
[3]Department of Chemistry, J.N.T.University, Ananthapur-515002, A.P, India.
[4]Vijaya College of Pharmacy, Hayathnagar, Hyderabad-501511, A.P, India.
[5]Vaagdevi College of Pharmacy, Hanamkonda, Warangal-506001, A.P, India.

Abstract

The aim of the present investigation was to prepare bilayer floating tablets of metoprolol tartrate using the combination of superdisintigrants, HPMC K grade polymers and natural polymers like xanthan gum and guar gum by direct compression method. Bilayer floating tablets were prepared using optimized immediate release layer and floating layer as sustained release layer. The physico-chemical characteristics of the prepared tablets were evaluated and found to be satisfactory. All the prepared batches showed *in vitro* buoyancy. It was observed that the tablets remained buoyant for more than 12 h. Formulation F7 was selected as best formulation based on the *in vitro* characteristics and used *in vivo* radiographic studies by adding barium sulphate. These studies revealed that the tablets remained in the stomach for 210±5.4 min (n=3) in fasting human volunteers. Based on the *in vivo* performance in healthy subjects, the developed bilayer floating tablets showed superior bioavailability than the marketed tablets, the drug release was up to 12 h in controlled manner. The systemic availability of the best formulation was high after administration to obtain immediate action due to the immediate release layer, from sustained release layer the drug was released in controlled manner. It can be concluded that the best formulation F7 by choosing biphasic drug release pattern in a single dosage form could improve patient compliance and ensure better disease management.

Keywords: Metoprolol tartrate, superdisintigrants, HPMC, bilayer floating tablets, bioavailability

Introduction

Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action. Indeed, for controlled release system, oral route has gained more attention and success because gastro intestinal physiology offers more flexibility in dosage form design than other routes [1]. The benefits of long term delivery technology have not been fully realized for dosage forms designed for oral administration [2]. Development of oral controlled release systems has been a challenge to formulation scientists because of the difficulty in localizing the system in target areas of the gastrointestinal tract [3].

Gastroretentive drug delivery system is an approach to prolong the gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. These dosage forms can remain in the gastric region for longer period and hence significantly prolong the gastric retention time of the drugs [4]. Floating drug delivery systems are low-density systems that have sufficiently to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentration [5]. Bilayer tableting technology has been specially developed to provide two different release rates or biphasic release of a drug from a single dosage form [6].

Metoprolol tartrate is a selective β_1-blocking drug used for the management of moderate to severe essential hypertension [7]. Because of its relative short plasma half-life, patients are routinely asked to take metoprolol tartrate in divided daily doses, once every 6 to 8h. Such frequent drug administration may reduce patient compliance and therapeutic efficacy [8]. The multilayer tablet concept has been long utilized to develop sustained release formulations such a tablet has a fast releasing layer and may contain bi or tri layers to sustain the drug release [9]. The present study aims at formulating bilayer floating tablets of metoprolol tartrate with immediate release layer using super disintegrants like crospovidone, croscarmellose sodium and sodium starch glycolate in combination and alone, and a sustained release layer using hydroxy propyl methyl cellulose K-4M, K-15M, K-100M, Pvpk30 and sodium carboxy methyl cellulose polymers. The prepared tablets were evaluated for their compatibility studies, physico-chemical characteristics, *in vivo* radiographic and *in vivo* bioavailability studies.

Materials and Methods

Materials

Betaloc 100mg conventional tablet was purchased from AstraZeneca. Metoprolol tartrate was a generous gift from Dr. Reddy's Laboratories Limited, (Hyderabad, India). Hydroxy propyl methyl cellulose K4M, K15M and K100M were obtained from Colorcon Asia Private Limited, India. Xanthan gum, guar gum, crospovidone, croscarmellose sodium, sodium starch glycolate and PVP-K30 were gifted from MSN Labs Ltd, Hyderabad. All other chemicals used were of analytical grade.

Preparation of bilayer floating tablets

Formulation of immediate release (IR) layer

Eight formulation batches with different super disintegrants were made in order to achieve desired disintegration time and drug release. The composition of metoprolol tartrate immediate release tablets was shown in Table 1.

Table 1. Composition of metoprolol tartrate immediate release layer

Ingredients (mg)	IR1	IR2	IR3	IR4	IR5	IR6	IR7	IR8
Metoprolol tartrate	25	25	25	25	25	25	25	25
PVP K30	4	6	4	5	4	4	4	6
Crospovidone	10	15	-	-	-	12.5	-	10
Croscarmellose sodium	-	-	15	-	-	-	10	-
SSG	-	-	-	10	15	-	-	10
MCC	108	-	-	-	103	-	-	-
Lactose	-	101	103	107	-	-	-	96
DCP	-	-	-	-	-	105.5	108	-
Mg. Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total wt.	150	150	150	150	150	150	150	150

Formulation of floating sustained release (SR) tablets

Required quantity of metoprolol tartrate and other polymers was weighed and passed through sieve with mesh #40 and were mixed homogeneously in a poly-bag for about 5-10 min. The powder mass was passed through mesh #14. Finally the powder was lubricated with magnesium stearate and talc.

Formulation of floating bilayer tablets

The powder of floating sustained release layer was poured in the die cavity and the powder was compressed. After the compression, the upper punch was then lifted and the immediate release layer powder was placed in the die, containing initially compressed sustained release layer and compressed to form bilayer tablet. The composition of different formulations of metoprolol tartrate floating bilayer tablets are depicted in the Table 2.

Table 2. Composition of metoprolol tartrate floating bilayer tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
IR8	150	150	150	150	150	150	150
Metoprolol tartrate	75	75	75	75	75	75	75
HPMC K4M	130	-	130	-	-	-	-
HPMC K15M	-	130	-	-	-	-	-
HPMC K100M	-	-	-	130	130	130	150
Xanthan gum	10.5	35	17.5	10.5	10.5	35	17.5
Guar gum	10.5	-	17.5	10.5	10.5	3.5	17.5
$NaHCO_3$	60	60	60	60	60	60	60
Citric acid	-	-	-	-	-	-	10
SCMC	20	20	20	20	20	20	10
Lactose	24	10	25	39	14.5	-	5
MCC	-	-	-	-	-	21.5	-
Mg.Sterate	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	500	500	500	500	500	500	500

Evaluation of metoprolol tartrate bilayer floating tablets[10]

Thickness

The thickness of the prepared tablets was tested using vernier calipers. The test was done in triplicate and average thickness was determined.

Hardness

Hardness of prepared tablets was determined using Monsanto hardness tester and measured in terms of kg/cm^2.

Weight variation

Formulated tablets were tested for weight uniformity. Twenty randomly taken tablets were weighed together and the average weight was determined. Each tablet was then weighed individually and deviation from average weight was calculated. The percent weight variation was calculated by using the following formula.[10].

$$\% \text{ Weight variation} = \frac{\text{Average weight - Individual weight}}{\text{Average weight}}$$

Friability

The Roche friability test apparatus (Electrolab) was used to determine the friability of the tablets. Twenty pre-weighed tablets were placed in the apparatus operated for 4 min at a speed of 25 rpm. The tablets were removed from the friabilator, de-dusted and reweighed. The percentage friability was calculated according to the following formula [11].

$$\%\text{Friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

Drug content uniformity test

Ten tablets for each batch was weighed and powdered. A quantity of powder equivalent to 100mg of drug was taken into 100ml volumetric flask. The amount of drug present in the powder was determined by dissolving the powder mixture in 0.1N HCl and measure the drug content spectrophotometrically at 275nm using UV/Visible spectrophotometer (Shimadzu 1800) against 0.1N HCl blank [12].

Swelling studies

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[13]. The % of weight gained by the tablet was calculated by using the following formula:

Swelling Index (%) = M_t-M_0/M_0 X 100.

Buoyancy lag time determination & total floating time

The *in vitro* buoyancy was determined by the floating lag time. The tablet was placed in a 100 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 and further total floating time of all tablets was determined by visual observation [14].

In vitro disintegration time of immediate release layer

The disintegration time for all immediate release formulations was carried out using tablet disintegration test apparatus (Electrolab). 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 ^{0}C and time taken for the entire tablet to disintegrate completely was noted [15].

In vitro dissolution studies

In vitro drug release studies for the prepared immediate release layer and bilayer floating tablets were conducted for a period of 10 min and 12 h respectively using USP XXIV type-II (Paddle) dissolution apparatus (Electrolab) at 37±0.5 ^{0}C at 50 rpm using 900 ml of 0.1N HCl as dissolution medium. At predetermined interval of time, 5 ml of sample was withdrawn and replaced with fresh dissolution medium. The samples were filtered, suitably diluted and absorbance was analyzed using UV/Visible spectrophotometer (Shimadzu 1800) at 275 nm [16].

Kinetic modelling of drug release

The dissolution profiles of all the batches were fitted to zero order, first order, Higuchi[16] and Korsmeyer-Peppas equations [17].

Drug excipient compatibility studies

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. DSC scans of about 5 mg using an automatic thermal analyzer system preformed accurately weighed metoprolol tartrate and tablet containing the same amount of the drug. Sealed and perforated aluminium pans were used in the experiments for all the samples. Temperature calibrations were performed using indium as standard. An empty pan sealed in the same way as the sample was used as a reference. The entire samples were run at a scanning rate of 10^{0}C/min from 50-300 ^{0}C [18].

Stability studies

The stability studies were carried out as per ICH guidelines. The best formulation F7 was subjected to accelerated stability test by storing at 40±2ºC/75±5% relative humidity in an accelerated stability chamber (Remi, Mumbai). After specified period of time (1, 2 & 3 months) samples were withdrawn and floating lag time, total floating time and *in vitro* dissolution studies were conducted [19].

In vivo radiographic studies

The study protocol for radiographic studies was approved by the Institutional Human Ethics Committee (IHEC), Vaagdevi College of Pharmacy, Hanamkonda, Warangal, India. To make the best achieved X-ray opaque, 100 mg of the drug was replaced with barium sulphate and all other ingredients were kept constant. The study was conducted on three healthy male volunteers, each weighing between 55-70 kg and in the age group of 25±2 years. The tablets prepared for radiography (F7) were administered orally with a glass of water. During the study, the subjects were not allowed to eat but water was available ad libitum. After ingestion of the tablets, the volunteers were exposed to X-ray photography in the abdominal region at 0.5, 1.5, 3, 4 and 5 h after administration. The mean gastric residence time was calculated.

In vivo bioavailability studies

Six healthy male subjects were participated in this study (22-30 years, weighing 55-75 kg). Informed and signed consent and approval of the Human Ethical Committee were obtained. Metoprolol tartrate (F7) and reference product (Betaloc 100mg) was administered with a glass of water. The volunteers continued fasting for 4h, after which standard meal was provided. About 5 ml of blood was withdrawn at different time intervals such as 0, 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 h. Blood samples were collected from each subject's forearm vein using a sterile disposable needle and syrange into sterile glass centrifuge tubes containing 1 ml of 4% anhydrous sodium citrate solution. The samples were centrifuged immediately at 4000 rpm and the plasma was stored in light-protected container at -20 ^{0}C till analysis. The concentration of metoprolol tartrate from plasma was measured by using reversed phase HPLC. The chromatographic system consisted of a C18 column (Phenomenex) with a 5 µm particle size. The mobile phase used was phosphate buffer (adjusted to pH 3.5 with phosphoric acid) and acetonitrile (32:68). Plasma samples (250 µl) were transferred into a test tube to which internal standard (Pinacidil monohydrate 50µl) and 1 mL of acetic acid was added and vortexed for 3 min. To this, 1mL of chloroform was added and vortexed. The samples were centrifuged at 10,000 rpm for 10 min. The organic phase was transferred into another test tube and the solvent was evaporated to dryness. The residue was redissolved in 200 µL of mobile phase, of which 20 µL of the supernatant was injected for analysis [20].

Pharmacokinetic analysis

The pharmacokinetic parameters employed to evaluate were maximum plasma concentration (C_{max}), time to attain C_{max} i.e., T_{max} and $t_{½}$ values, area under plasma concentration–time curve from zero to the last sampling time (AUC_{0-t}), area under plasma concentration–time curve from zero to infinity ($AUC_{0-\infty}$) and mean residence time (*MRT*). AUC_{0-t} was calculated by the linear trapezoidal rule and $AUC_{0-\infty}$ from the following formula.

$AUC_{0-\infty} = AUC_{0-t} + C_t / K_E$

Results & Discussion

Physico-chemical parameters of metoprolol tartrate bilayer floating tablets

The prepared tablets were evaluated for different physico-chemical properties and the results are found to be within the pharmacopoeial limits, which depicted in Table 3.

Table 3. Physico-chemical parameters of metoprolol tartrate bilayer floating tablets

Formulation code	Weight variation (mg) (n = 20)	Hardness (kg/cm^2) (n = 3)	Thickness (mm) (n = 3)	Friability (%) (n = 20)	Content uniformity (%) (n = 10)
F1	500±0.9	4.9±0.11	5.02±0.04	0.42±0.03	97.34±0.35
F2	498±0.7	4.5±0.16	5.05±0.07	0.39±0.05	96.50±0.65
F3	499±0.4	5.1±0.14	5.06±0.09	0.43±0.02	98.55±0.50
F4	501±0.1	5.0±0.18	5.10±0.06	0.42±0.06	98.85±0.75
F5	502±0.3	5.2±0.02	5.03±0.03	0.45±0.04	98.90±0.55
F6	499±0.7	5.1±0.13	5.08±0.02	0.44±0.01	98.69±0.45
F7	501±0.7	5.1±0.13	5.10±0.02	0.42±0.01	99.19±0.45

Swelling studies of metoprolol tartrate bilayer floating tablets

The purpose of swelling study is to determine the water uptake capability of the polymer. All the formulations were evaluated for 12 h and the % swelling index of all the formulations at different time intervals i.e. from 0 to 12 h were shown in Table 4. From the

results it was concluded that the increased concentration of HPMC in the formulations increases the swelling indices. The best formulation F7 prepared by using HPMC K 100M showed highest swelling indices.

Table 4. Swelling index of metoprolol tartrate bilayer floating tablets

Time (h)	Swelling Index (%)*						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	43.32	46.89	41.34	56.32	58.12	57.36	60.33
2	64.52	71.52	62.12	82.56	84.52	80.52	85.12
3	74.08	80.08	73.09	95.03	94.08	96.07	99.07
4	86.61	91.61	84.66	113.31	112.61	110.41	110.61
6	98.12	112.12	96.14	125.78	129.12	128.17	132.14
8	108.31	125.32	104.12	140.12	145.32	144.52	153.32
10	124.71	140.46	122.75	155.61	162.71	160.71	168.82
12	146.30	164.60	141.29	181.28	184.29	182.24	191.23

*Mean ± SD (n=3)

Buoyancy lag time determination & total floating time

All the formulations had buoyancy lag time in the range of 23 to 78 sec. F1-F6 formulations shows buoyancy lag period of 25-78 sec. The best formulation F7 lag time was found to be 23 sec. The total floating time was found to be more than 12 h, which indicates a stable gel layer formation by all polymers and that $NaHCO_3$ remains for a longer time.

In vitro disintegration time of immediate release layer

In the present investigation 8 formulations were made with different superdisintegrants like crospovidone, croscarmellose sodium and SSG. The optimized formulation (IR8) prepared by using combination of superdisintegrants cross povidone and sodium starch glycolate disintegrated in lesser time i.e 39 sec compare with other formulations.

In vitro release profile of immediate release tablets:

The immediate release tablets of 8 formulations (IR1-IR8) prepared by using different superdisintegrants (Table 1) alone and in combination showed % drug release of about 98.08, 99.5, 98.4, 100.7 and 98.5 for IR1, IR2, IR4, IR5 and IR6 respectively at the end of 15 min. The formulations IR3 and IR7 showed the drug release of 100.8 and 99.55 at 20min and the drug release from the optimized formulation IR8 was found to be 99.5 at the end of 10 min. Among all the formulations IR8 consisting of crospovidone and sodium starch glycolate in combination considered as optimized formulation. IR8 was further used in the preparation of all bilayer floating tablets.

In vitro release profile of metoprolol tartrate bilayer floating tablets

All the sustained release formulations (F1-F7) are prepared with different grades of HPMC, natural polymers like xanthan gum, guar gum and sodium CMC showed drug release between 97.85 to 100% at the end of 10-12 h. Approximately 40% of the drug was released from the best formulation (F7) in the first hour as loading dose to attain quick action from the immediate layer. Formulation F7 containing the polymer HPMC K100M in higher concentration, results in strong gel strength that retards the drug release upto 12 h. The *in vitro* drug release profile of conventional dosage form (Betoloc 100mg) was found to be 98.40 after 30 min.

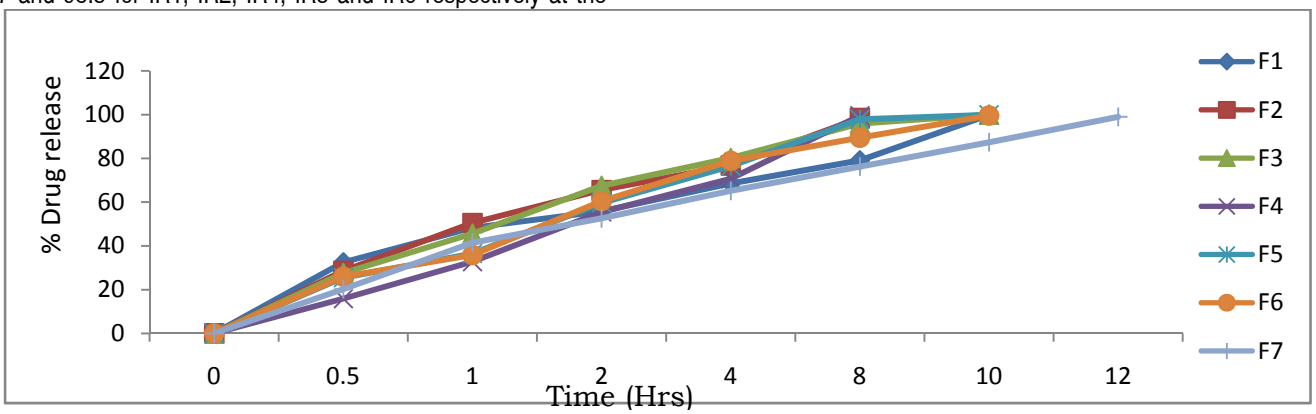


Figure 1. Comparative % drug release profiles of metoprolol tartrate bilayer floating tablets

Kinetic modelling of drug release:

To explore the mechanism of drug release from bilayer floating tablets, various kinetic models like zero order, first order, Higuchi and Korsmeyer-Peppas equations were applied to the different formulations. The release kinetics of best formulation (F7) was shown in Table 5. From the data it was concluded that the formulation F7 followed first order kinetics. When the drug release data was fitted to Higuchi equation, linear plots were obtained with high correlation coefficient values. The drug release was proportional to square root of time indicating that the drug release was diffusion controlled.

Table 5. Release kinetics of best formulation (F7) of metoprolol tartrate bilayer floating tablets

Zero Order		First order		Higuchi		Korsmeyer-Peppas	
r^2	*ko* (h^{-1})	r^2	*k1* (h^{-1})	r^2	*kH* ($h^{-1/2}$)	r^2	*n value*
0.905	5.62	0.921	-0.077	0.955	24.49	0.972	0.336

Drug excipient compatibility studies:

DSC studies:

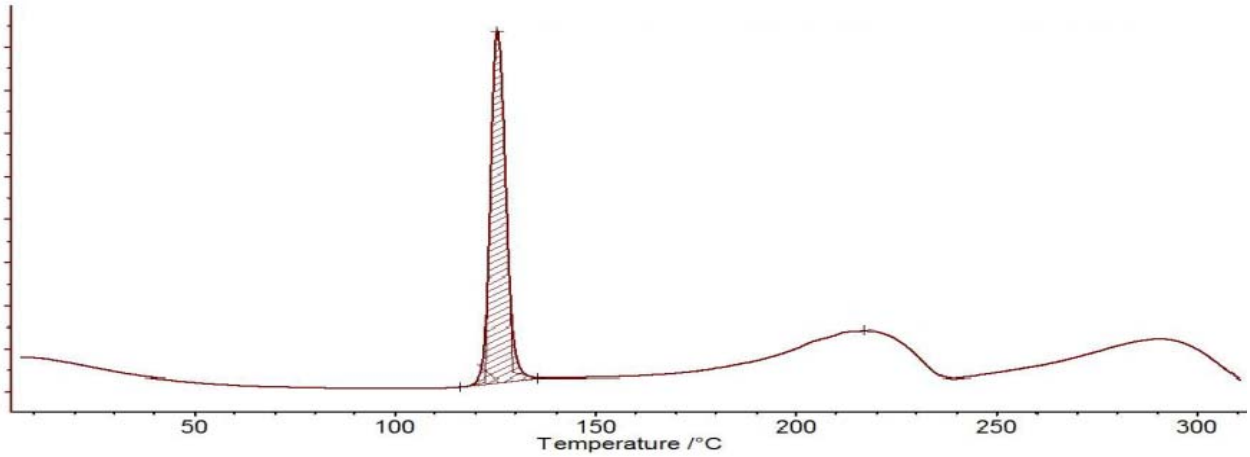


Figure 2. DSC thermogram of metoprolol tartrate pure drug

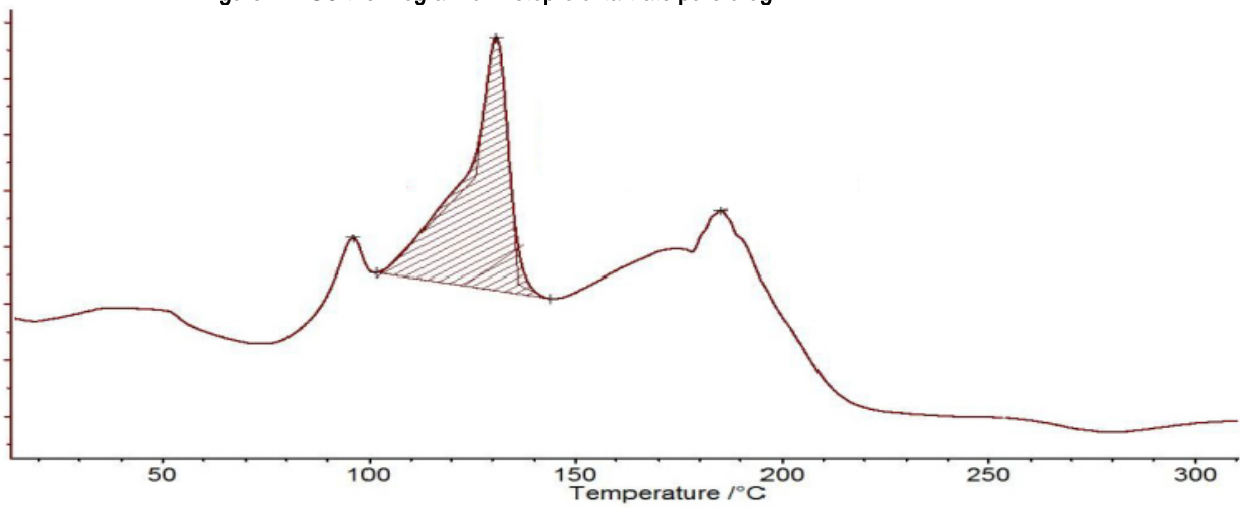


Figure 3. DSC thermogram of metoprolol tartrate best formulation (F7)

The DSC thermograms of the pure metoprolol tartrate (Figure 2) and best formulation (F7) (Figure 3) showed endothermic peaks at 122.4 and 125.6 ^{0}C respectively. It indicates that there is no interaction takes place between drug and other excipients used in the formulation.

Stability studies

The stability of best formulation F7 was tested at 40±2 ºC/75±5% relative humidity for 3 months. There was no significant change in floating lag time, total floating time and also *in vitro* drug release profile, where results are summarized in Table 6.

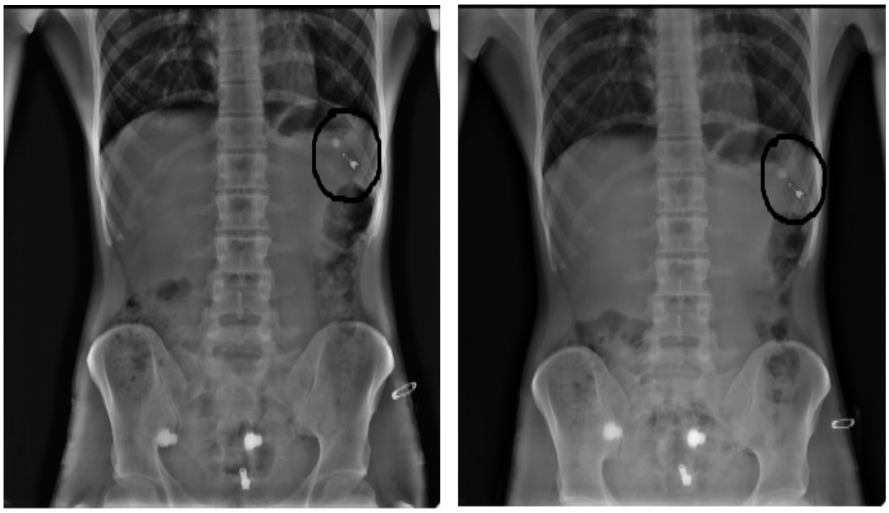
Table 6. Stability data of best formulation (F7)

Retest time for F7	Floating lag time(sec)*	Total floating time (h)*	*In vitro* drug release profile (%)*
0 days	23±1.5	>12 h	98.99
30 days	25±2.0	>12 h	96.24
60 days	26±1.0	>12 h	95.35
90 days	28±2.5	>12 h	94.35

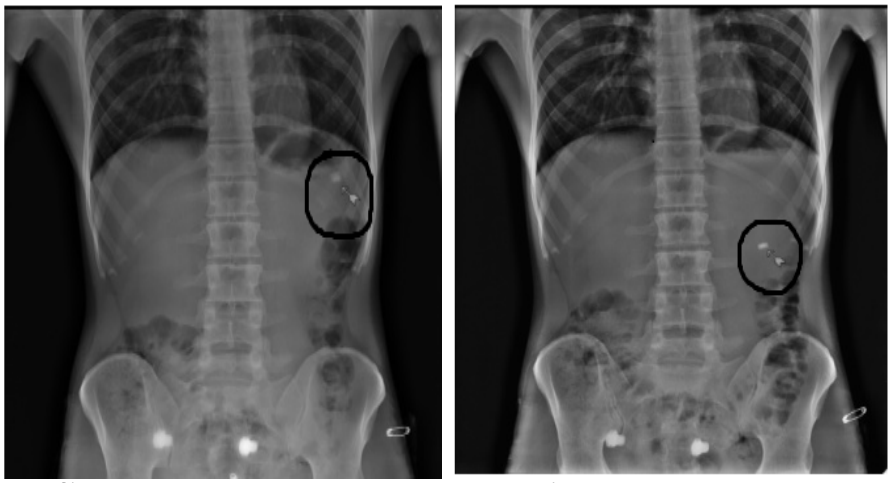
*Mean ± SD (n=3)

Intragastric behaviour of bilayer floating tablets

The radiographic images were taken at different periods post-administration of the barium sulfate-loaded tablet in three human volunteers (Figure 4. A-D). It is clear that the tablet appears more or less at the same position for the initial 3 h. This could be related to its floating ability. Later on, the tablet was slightly moved downwards, yet, remained within the stomach till the end of 4 h. The mean gastric retention period was found to be 210±5.4 min (n = 3). The increased gastric residence time favours increase in the bioavailability of drugs.



A) 30min B) 90 min



C) 3 h D) 4 h

Figure 4. Radiographic images showing the presence of a $BaSO_4$ loaded bilayer floating tablet (F7) in the stomach at a different time periods.

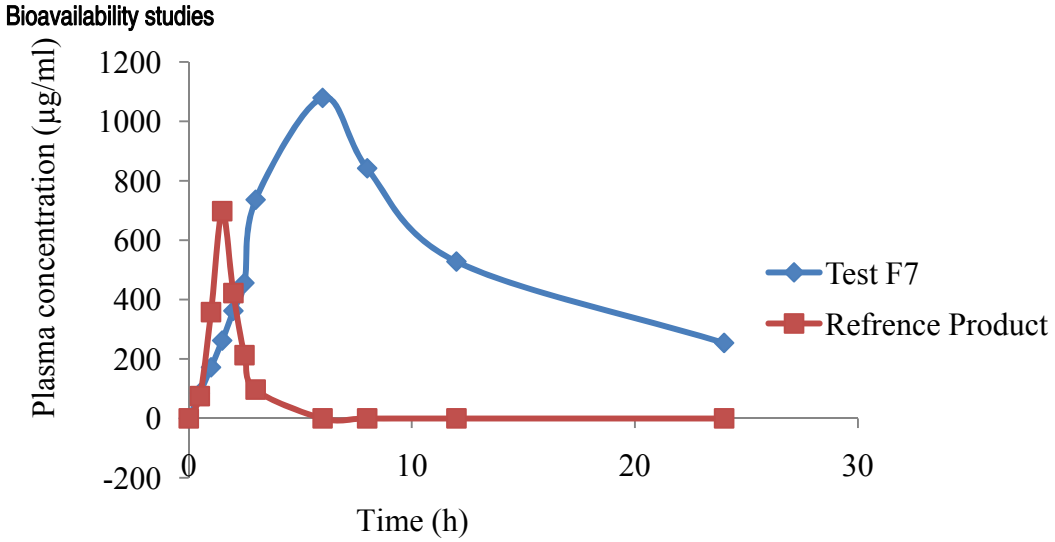


Figure 5: Comparative *in vivo* bioavailability profiles of the test formulation F7 and reference product (Betaloc).

Table 7. Pharmacokinetic parameters of test (F7) and marketed reference (Betaloc) formulation (n = 6)

Pharmacokinetic Parameters	Test formulation F7 Mean ± SD	Reference product Mean ± SD
C_{max} (µg/ml)	1094 ± 201	698±124
T_{max} (h^{-1})	6.3 ±1.2	1.5±0
AUC_{0-t} (µg h/ml)	4010 ± 689	1458±357
AUC_{0-} (µg h/ml)	4673 ± 776	2031±482
$t_{1/2}$ (h)	4.23 ± 0.44	0.50±1.25
MRT(h)	10.33 ± 0.86	3.75±0.37

Pharmacokinetic studies were carried out in healthy human volunteers for test formulation and reference drug and the results were depicted in Table 7. The comparison of plasma drug concentration of test formulation F7 and reference product was shown in Figure 5. C_{max} and T_{max} for test formulation and reference formulations was found to be 1094 ± 201 µg/ml, 6.3 ± 2 h and 698 ± 124 µg/ml, 1.5 ± 0 h respectively. In order to estimate the amount of drug absorbed from the test formulation, the relative bioavailability was calculated from the AUC $_{0-}$ of the reference and test formulation (2031 ± 482 µg h/ml and 4673 ± 776 µg h/ml). The AUC $_{0-t}$ of reference and test formulation was found to be 1458±357 µg h/ml and 4010 ± 689 µg h/ml. These results indicated that the bioavailability of the test formulation was increased significantly compare with reference one. The $t_{1/2}$ for test formulation and conventional product were 4.23 ± 0.44 h and 0.50±1.25 h, respectively. The MRT for test formulation was significantly longer than the reference (10.33 ± 0.86 h and 3.75±0.37).

Conclusion

In the present investigation, several formulations were prepared by using different polymers for immediate layer and sustained layer separately. Based on the evaluation parameters for immediate layer, IR8 was found to be optimized formulation upon its disintegration time i.e., 39 sec. For Sustained release tablet, F7 was decided as best formulation, because the lag time, buoyancy period and *in vitro* drug release was better than other formulations. The release pattern of bilayer tablet was best fitted to First order and Higuchi kinetic model with R^2 values of 0.921and 0.955 respectively. The value of n = 0.336 suggested that the drug is released from bilayer sustain dosage form by Fickian diffusion mechanism. *In vivo* radiographic studies revealed that the best formulation (F7) remained for 210 ± 5.4 min, which indicated that gastric retention time was increased by the floating mechanism which was considered desirable for improving the bioavailability of the drugs.

The comparison of *in vivo* bioavailability studies of test formulation and that of a reference formulation in healthy human volunteers confirmed that the test formulation increased the oral bioavailability with immediate action and later sustained action. Hence we can conclude from our study that the metoprolol tartrate bilayered floating tablets prepared by using hydrophilic and hydrophobic polymers are a promising alternative for the effective management of hypertension.

Acknowledgements

The authors acknowledge MSN labs ltd., Hyderabad and Colorcon Asia private ltd, India, for providing the excipients and Dr.Reddy's laboratories (Hyderabad, India) for providing the gift sample of metoprolol tartrate.

References

[1]. Priti T, Nidhi J, Pathak AK. Formulation and evaluation of bilayer floating tablets of Metoprolol tartrate. Int J Biomed Adv Res. 2012; 03(02): 122-128.

[2]. Patel N, Nagesh C, Patel J, Chandrasekhar S, Jani D. Formulation and evaluation of floating tablet containing Glipizide. Asian J. Pharm. Tech. 2012; 2(4): 135-140.

[3]. Harshal PG, Manohar VP, Bharat WT, Vinod MT, Patil VR. Formulation and *in vitro* evaluation of trifluoperazine hydrochloride bilayer floating tablet. Int J Pharm Bio. 2012; 2 (1): 166-172.

[4]. Nayak AK, Maji R, Das B. Gastroretentive drug delivery systems: a review. Asian J of Pharm and Clin Res. 2010; 3 (1): 2-10.

[5]. Chein YW. Novel Drug Delivery System, 2nd ed. Marcel Dekker Inc, New York, 1992; p. 1-3.

[6]. Fonner DE, Buck JR, Banker GS. Mathematical optimization techniques in drug product design and process analysis. J. Pharm. Sci. 1970; 59: 1587-1596.

[7]. Aqil M, Ali A, Ahad A, Sultana Y, Najmi AK, Saha N. A validated HPLC method for estimation of metoprolol in human plasma. Acta Chromatograph. 2007; 19: 130-140.

[8]. Hirtz J. The GIT absorption of drugs in man: a review of current concepts and methods of investigation. Br J Clin Pharmacol. 1985; 19: 77S-83S.

[9]. Baumgartner S, Kristl J, Vrecer F, Vodopivec P, Zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm. 2000; 195:125-135.

[10]. USP 27/NF 22, Asian edition, General test procedures, U.S. Pharmacopoeial convention, Rockville MD. 2004:1204.

[11]. Sharma D. Formulation development and evaluation of fast disintegrating tablets of salbutamol sulphate for respiratory disorders, ISRN Pharmaceu. 2013; 2013: 1-8.

[12]. Moiz Md, Prathima Srinivas M, Sadanandam M. Formulation and evaluation of bilayered tablets of montelukast and levocetrizine dihydrochloride using natural and synthetic polymers. Int J D Del. 2011; 3: 597-618.

[13]. Nerurkar J, Jun HW, Prince JC, Park MO. Controlled release matrix tablets of ibuprofen using cellulose ethers and carrageenans: effect of formulation factors on dissolution rate. Eur J Pharm Biopharm. 2005; 61: 56-68.

[14]. Puneeth KP, Kavitha K, Tamizh MT. Development and evaluation of rosiglitazone maleate floating tablets. Int J Appl Pharm. 2010; 2(2): 6-10.

[15]. Mohsin AA, Nimbalkar NE, Sanaullah S, Aejaz A. Formulation and evaluation of mouth dissolving tablets of amitryptyline hydrochloride by direct compression technique. Int J Pharm Sci. 2010; 2(1): 204-210.

[16]. Higuchi T. Rate of release of medicaments from ointment bases containing drugs in suspensions. J Pharm Sci. 1961; 50: 874-875.

[17]. Siepmann J, Peppas NA. Modelling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv D Del Rev. 2001; 48: 139-157.

[18]. Raghavendrarao NG, Sagar G, Tarun P. Formulation and evaluation of sustained release matrix tablets of tramadol hydrochloride. Int J Phar Pharmaceu Sci. 2009; 1: 60-70.

[19]. Sekar V, Chellan VR. Immediate release tablets of telmisartan using superdisintegrant-formulation, evaluation and stability studies. Chem. Pharm. Bull. 2008; 56(4): 575-577.

[20]. Mohan G, Ramesh B, Kishan V. Development of sustained release floating drug delivery system for norfloxacin: *In vitro* and *in vivo* evaluation. PDA J Pharm Sci Tech. 2011; 65(3): 198-206.