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THE PHARMA RESEARCH, A JOURNAL

The Pharma Research (T. Ph. Res.), (2011), 5(1); 52-61.
Published on- 15 Jun 2011

Original Article

ISSN 0975-8216

DESIGN, DEVELOPMENT AND *IN VITRO* EVALUATION OF FLOATING TABLETS OF ATENOLOL

Singh ajay[*1], Kumar pradeep[2], Malik anuj[3], Mittan singh dhirender[3], Bharali kumar rajib[3]

Affiliated to:

[1*] Department of Pharmaceutics, PES College of Pharmacy, Bangalore, Karnataka, (INDIA)
[2] Department of Pharmaceutical Analysis, SGCP, Baghpat, Uttar Pradesh, (INDIA)
[3] Department of Pharmacy, Al-Ameen College of Pharmacy, Bangalore, Karnataka, (INDIA)

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ABSTRACT

The objective of this work was to formulate and evaluate the floating tablets of atenolol. Tablets were prepared by direct compression method, where hydroxypropylmethylcellulose K-15M, sodium carboxymethylcellulose were used as swelling polymers, sodium bicarbonate as gas generating agent, dicalcium phosphate as diluent, magnesium stearate, talc as lubricant and glidant. Drug excipients compatibility studies were carried out by FTIR. Dissolution studies were carried out in medium 0.1 N HCl. The influence of different polymers like hydroxypropylmethylcellulose K-15M and sodium carboxymethylcellulose as well as their combinations on the drug release profiles was studied. The release mechanism of drug from tablets was evaluated on the basis Peppas model. The 'n' values of all the formulations were found in the range of 0.5637 to 0.712. This indicated that release of drug followed non-Fickian or anomalous transport. Other parameters such as thickness, hardness, friability and drug content were found well within the official limits. Tablets were also evaluated for swelling index, floating lag time and floating duration; all results were found to be promising. Based upon evaluation parameters, formulations F5 and F11 were selected as best formulation and subjected for stability studies as per ICH guidelines for 90 days. Scanning electron microscopy has been carried out for selected formulations F5 and F11, results showed that the polymer absorbed water during release studies, as it swells which resulted in the formation of pores through which drug diffuses into the release media.

Keywords: Floating drug delivery system (FDDS), compatibility, floating lag time (FLT), floating duration (FD), scanning electron microscopy (SEM).

INTRODUCTION

Tablets are one of the most commonly used and challenging of all pharmaceutical products to design and manufacture. However even for drugs with good compression and dissolution, and no bioavailability problems, tablet product design and manufacture can be challenging because of the many competing objectives of the dosage form. Action taken to improve one

objective or set of objectives may cause another objective or set of objectives to slip. Floating tablets can help to enhance the bioavailability of drugs with narrow absorption windows in the small intestinal region so drugs which does not undergo hepatic first pass metabolism can be delivered ideally by slow release from the stomach. In the present study atenolol was chosen as the drug of interest because of its low oral bioavailability (i.e. only 50%). It is also reported in the literature that 40 to 50% of drug is excreted unchanged in the feces and the drug is absorbed only from the upper GI tract. Atenolol did not undergo hepatic first pass metabolism, hence this is suitable candidate for formulating as floating drug delivery system.

Materials and Methods:

Atenolol was received as a gift sample from Torrent Pharmaceutical Ltd., Baddi, India; HPMC K 15M was purchaged from Colorcon Asia Pvt. Ltd., Goa, India. Sodium CMC was received from Micro Labs Pvt. Ltd., Peenya, India. Magnesium stearate from Reachem, Chennai, India; sodium bicarbonate and dibasic calcium phosphate and talc were supplied by S. D. Fine-Chem Ltd., Mumbai, India. All other chemicals were of analytical grade as received.

Compatibility Studies:

Active drug blended with individual excipients taken in 1:1 ratio. It was filled in closed vials and placed in stability chambers at 35 ± 2^0/60±5% RH. The compatibility studies were done by FTIR by using KBr pellet method. Samples were observed for any physical changes at the end of 1^{st}, 2^{nd} and 4^{th} week.

Preparation of tablets and solutions:

The drug and excipients **(Table 1)** were passed through 85 # size mesh prior to the preparation of the dosage form. The ingredients were weighed separately and mixed thoroughly to ensure uniform mixing. The tablets were prepared by direct compression technique using 10-station rotary machine.

TABLE 1: FORMULA FOR THE FLOATING TABLETS OF FORMULATION F1 TO F11

Ingedients	Qty/tab (mg)										
	F1	F2	F3	F4	F5	6	F7	F8	F9	F10	F11
Atenolol	100	100	00	100	100	100	100	100	100	100	100
HPMC K15 M	200	175	150	125	100	-	-	-	150	100	50
Sodium CMC*	-	-	-	-	-	200	175	150	50	100	150
DCP**	42	67	92	117	142	42	67	92	42	42	42
Sodium bicarbonate	50	50	50	50	50	50	50	50	50	50	50
Magnesium stearate	4	4	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4	4	4

*sodium carboxymethylcellulose, **di-basic calcium phosphate

One hundred and fourteen milligrams of atenolol was accurately weighed and transferred to 100 ml volumetric flask. To this, 50 ml of distilled water was added and the flask was agitated until the drug dissolved. The volume of the flask was made up to 100 ml with distilled water. Ten milliliters of the standard stock solution was again diluted to 100 ml with distilled water in a 100 ml of volumetric flask to get a concentration of 114 µg/ml. Aliquots containing 1, 2, 3, 4, and 5 ml of the above working solution was pipetted into labeled 50 ml volumetric flasks. Then the volume was made up to 50 ml with distilled water to get the concentrations within the Beer's range. The absorbance of these solutions were measured at 225 nm against the reagent blank using UV/Vis spectrophotometer **(Table 2)**

TABLE 2: DATA FOR CALIBRATION OF ATENOLOL IN DISTILLED WATER.

Concentration (µg/ml)	Absorbance
2.28	0.085
4.56	0.167
6.84	0.258
9.12	0.340
11.4	0.429

Data in triplicate

Percent drug Content:

Twenty tablets were weighed and triturated. The tablet triturate equivalent to 50 mg of the drug was weighed accurately, dissolved in distilled water and diluted to 100 ml with distilled water. Further dilutions were done suitably to get a concentration of 5µg/ml with distilled water. Absorbance was recorded at 225 nm against the reagent blank. The concentration of atenolol in µg/ml was determined by using standard curve and drug content was calculated [8].

Swelling Index:

The studies were carried out in petri dishes using 0.1N HCl. The prepared tablets were introduced in to the swelling media along with pre-weighed OHP sheet placing tablet on the OHP sheet. At predetermined time intervals the tablets were removed from the medium, excess water was blotted with tissue paper and immediately weighed. This procedure was repeated until the tablet reaches constant weight [9-11]. Swelling index was calculated using the following formula, % swelling Index = $W_O - (W_i+W_b)/ W_i * 100$, where, W_O = Weight of swollen tablet along with OHP sheet. W_i = Weight of initial tablet. W_b =Weight of OHP paper.

Buoyancy studies:

In vitro floating behavior of the tablets was studied by placing them in glass beaker filled with 900 ml of 0.1N HCl (pH 1.2). Floating lag time (time period between placing the tablet in the medium and tablet floating) and floating duration of the tablets were determined by visual observation. [12]

***In vitro* Release studies:**

In vitro release study was carried out by using USP XXII dissolution apparatus taking 900ml dissolution medium 0.1N HCl (pH 1.2) which

was maintained at temperature 37±0.5° with 50 rpm. Ten ml sample was withdrawn at every hour and was replaced with fresh dissolution medium. The samples were analyzed at λ_{max} of 225 nm using 0.1 N HCl (pH 1.2) as blank with Beer's range 1- 20 µg. Dissolution profiles of the formulations were analyzed by plotting a graph between percent drug released versus time. Bulk density, Tapped density (D_t), Angle of repose (θ), Carr's Consolidation Index (I), hardness, Friability (F) and Weight variation tests were also performed.

Data Analysis:

The results of *in vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows; Cumulative % drug released versus time (Zero –order kinetic model), log cumulative percent drug remaining versus time (First-order kinetic model), Log cumulative percent drug released versus log time (Peppas model).

Scanning Electron Microscopy (SEM):

Tablet powder was sputtered coated using pelco gold palladium coaters. The surface morphology of tablets was examined using SEM. The samples were placed in an evacuated chamber and scanned in a controlled pattern by an electron beam. Interaction of the electron beam with the specimen produces a variety of physical phenomena that were detected, photographed and provides information about the specimens.

Stability Studies:

Selected Formulations were stored at different storage conditions at elevated temperatures such as $25^0\pm2^0$/60±5% RH, $35^0\pm2^0$/60±5% RH and $40^0\pm2^0$/75±5% RH for 90 days. Samples were withdrawn at 10 days intervals and checked for drug content, physical changes, buoyancy, matrix integrity, hardness and friability.

Results and Discussion:

The aim of the research work was to formulate and characterize floating tablets of atenolol by using direct compression technique with (hydroxypropylmethylcellulose) HPMC K15 M, (sodium carboxymethyl cellulose) NaCMC as matrix polymers, sodium bicarbonate as gas generating agent[13], (di-basic calcium phosphate) DCP as diluent, and magnesium stearate, talc as lubricant and glidant respectively. The tablets were prepared by using generally regarded as safe (GRAS) approved excipients that were compatible with the drug (atenolol). The dosage forms containing atenolol, sodium bicarbonate, DCP and different polymers (HPMC and NaCMC) were prepared as floating tablets and evaluated. Atenolol calibration curve was prepared according to procedure given. Results were obtained with regression line y=0.0376x-0.0012, r^2=0.9998.

The drug-excipient interaction study was carried out using FTIR i.e. by KBr pellet method. In the drug-excipient interaction study, it was found that atenolol was having compatibility with all the excipients used in the formulation **(fig. 1).**

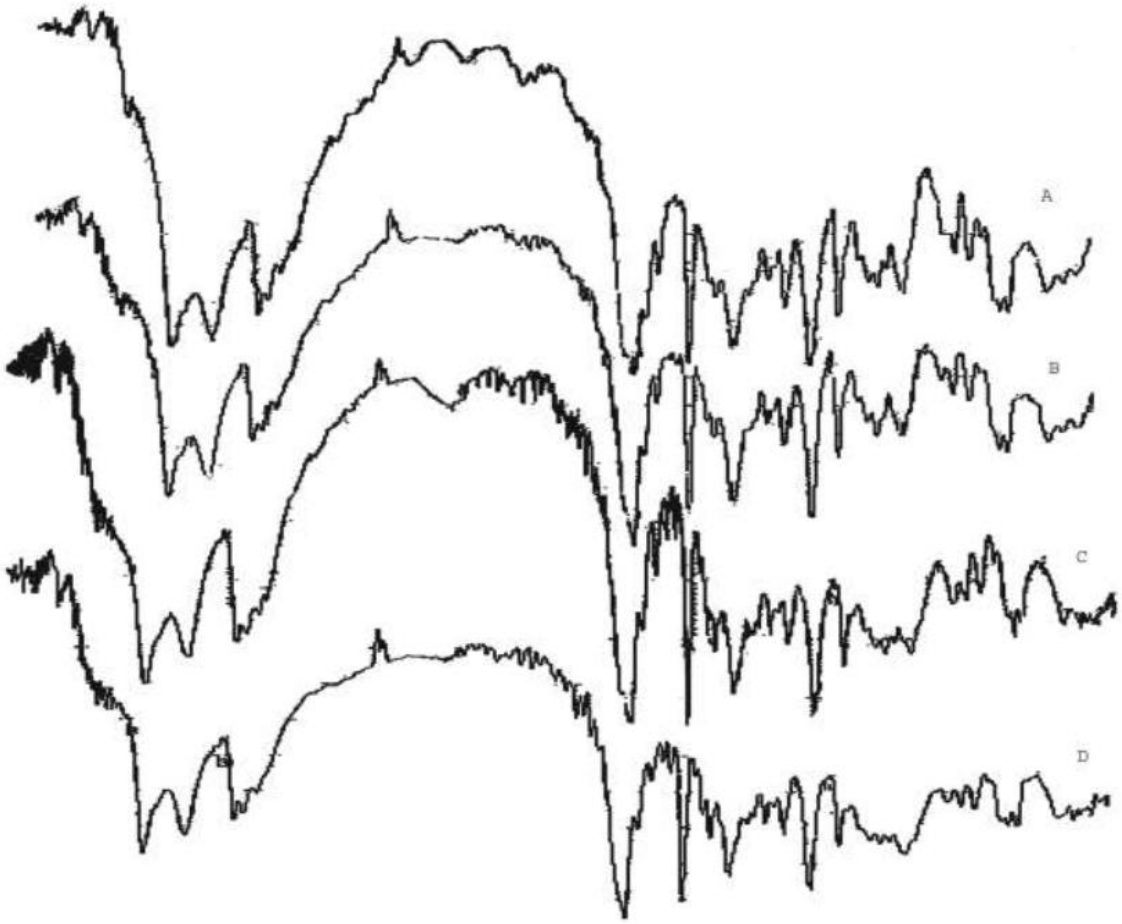

Fig. 1 -FTIR spectras

(A) pure drug; (B) drug with sodium carboxymethyl cellulose; (C) drug with hydroxyl-propylmethyl-cellulose K-15M; (D) formulation F11.

No significant change in the position of peaks was observed in the IR spectra of drug with excipients (1:1 ratio) compared to the spectra of the pure drug. Thus the chosen excipients for the formulations were found to be compatible with the active drug. There was no change in the physical appearance of the blend.

Flow properties play an important role in pharmaceuticals especially in tablet formulation. The bulk density **(Table 3)** of the powder was in the range of 0.429 to 0.438 g/ml; tapped density was in the range of 0.516 to 0.526 g/ml for all the formulations, which indicated that the powder was not bulky. The

angle of repose of all the formulations was in the range of 27.02^0 to 33.41^0, which indicate satisfactory flow of the powder. Carr's index was found to be in the range of 16.24-18.53 for all the formulations which indicate fair to passable powder.

TABLE 3: PRE-COMPRESSION PARAMETERS OF FORMULATION F1 TO F11

Formulations	Parameters			
	Bulk density (g/cc)	Tapped density(g/cc)	Angle of Repose (θ)	Carr's Index
F1	0.434	0.526	30.12	17.49
F2	0.430	0.521	29.05	17.32
F3	0.433	0.524	30.12	17.41
F4	0.436	0.527	32.45	17.53
F5	0.429	0.518	27.02	16.24
F6	0.435	0.516	33.41	18.19
F7	0.435	0.517	33.35	18.17
F8	0.436	0.520	32.53	18.53
F9	0.434	0.524	30.11	17.38
F10	0.430	0.522	29.08	17.34
F11	0.438	0.522	28.32	17.01

Data in triplicate

Prepared tablets were evaluated for weight variation, hardness and friability. The weight of all the tablets was found in range of 385 to 412 mg. Tablet hardness was found to be 4.8-5.8 $kg/cm^2$and friability was found to be between 0.185-0.215 for all the formulations that complies with the limits of Indian Pharmacopoeia 1996.

Swelling index for the formulations was carried out in 0.1N HCl. The rate of water uptake was more in the beginning. As time progressed the rate of water uptake slowed down. Formulations containing NaCMC as polymer showed increase in water uptake up to 4 hr only. These formulations showed decrease in % swelling index, which may be due to the solubility of NaCMC in 0.1N HCl which has led to the erosion of the tablet. Hardness, friability, thickness, drug content, floating lag time, floating duration and weight variation were within the prescribed limits of Indian Pharmacopoeia 1996 **(Table 4).**

TABLE 4: POST-COMPRESSION PARAMETERS OF FORMULATION F1 TO F11

Parameters	Formulations										
	F1*	F2*	F3*	F4*	F5*	F6!	F7!	F8!	F9*	F10*	F11*
Hardness kg/cm^2	4.8	5.2	5.0	5.4	5.2	5.6	5.4	5.8	5.0	4.8	5.2
Friability (%)	0.216	0.204	0.214	0.197	0.191	0.189	0.195	0.185	0.209	0.215	0.203
Thickness (mm)	2.92	2.92	2.91	2.92	2.91	2.94	2.94	2.96	2.94	2.92	2.92
Drug content (%)	95.06	94.70	97.05	98.45	95.04	98.34	95.67	97.23	96.09	95.56	98.05
% Swelling Index	220.3	207.9	186.6	185.5	175.7	125.0	129.8	119.4	243.5	252.0	260.3
Floating lag time (min.)	2.30	3.12	2.50	2.40	2.15	5.30	6.15	5.45	3.20	2.55	2.45

The weight variation study results of all the tablets were found between the ranges of 385 mg to 412 mg that complies within the IP limits (5%). *Floating duration of formulations is more than 10 h,! Formulations disintegrated after 5 h.

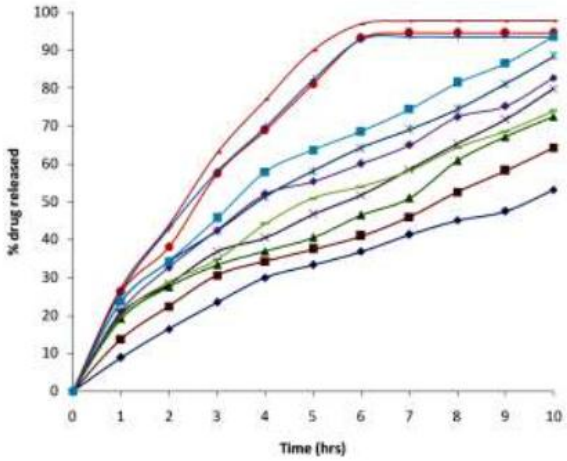

Fig. 2 Plot of cumulative percent drug release vs time profile for formulations F1-F11 of atenolol floating tablets

In-vitro release profile for given formulations of atenolol floating tablets, (F1), (F2), (F3), (F4), (F5), (F6), (F7), (F8), (F9), (F10) and (F11).

Formulations containing HPMC K15 M i.e., F1, F2, F3, F4 and F5 showed good buoyancy, more than 10 h and good matrix integrity also. But the release rate of the drug was found to be slow **(fig. 2)** in these formulations which may be due to the high viscosity of HPMC K15M. It was observed that as the amount of DCP increased in the formulations, the release rate was enhanced without any significant change in the FLT and FD of the formulations, which may be due to the solubility of DCP in 0.1N HCl. Formulations containing NaCMC i.e., F6, F7 and F8 were not able to maintain matrix integrity and got disintegrated rapidly within 5 h. Formulations F9, F10 and F11 were prepared using combination of polymers in order to overcome the low matrix integrity of NaCMC. It was reported in the literature that with increasing macromolecular weight of HPMC K15M polymer, the degree of entanglement of polymer chain increases, thus decreasing the mobility of macromolecules in the fully swollen systems leading to decreased drug diffusion coefficients and decreased drug release rates. Increase in the polymer molecular weight modifies the polymer dissolution behavior by decreasing the drug dissolution rate in turn affecting the drug release. Hence this may be the reason behind the decreased drug release from formulations containing HPMC K15 as polymer. Formulations containing only NaCMC showed good release but failed to maintain matrix integrity and disintegrated rapidly, which may be due to the water solubility of the polymer. Formulations F5 and F11 showed good drug release of 88.35% and 93.65%, respectively. Hence these formulations were subjected to stability studies. Formulations F5 and F11 were selected as optimised formulations as these formulations showed good buoyancy, matrix integrity, drug release rate and stability. Therefore these formulations were prepared in bulk and subjected to further stability studies.

In vitro drug release data of the floating tablets of selected formulations were evaluated kinetically by zero order kinetics; first order kinetics, and Peppas models. For planar geometry, the value of n = 0.5 indicates a Fickian diffusion mechanism, 0.5 to 1.0 indicates non-Fickian or anomalous transport, and n >1 implies case II (relaxation controlled) transport. The constant "n" and "k" were

calculated from the slope and intercepts of the plots of log (M_t/M_∞) vs. log t. The value of n calculated was in the range of 0.5637 to 0.712 which indicated that the release of drug followed non-Fickian or anomalous transport. For the selected formulations F5 and F11 the values of n were found to be 0.5637 and 0.5975 respectively, which indicated that release from these formulations followed non-Fickian or anomalous transport. For formulations F5 and F11 the regression (r^2) value of first order and zero order model fitting was found to be 0.9567, 0.9885 and 0.9348, 0.9753, respectively. As the regression value for zero order model fitting was found to be more compared to first order model in both the formulations, it was concluded that the formulations F5 and F11 followed zero order drug release.

SEM has been carried out for the best formulations F5 and F11 at 500 times magnification, which showed that as tablet absorbs water it swells and forms pores in the tablet through which drug release takes place, as shown in **fig. 3.**

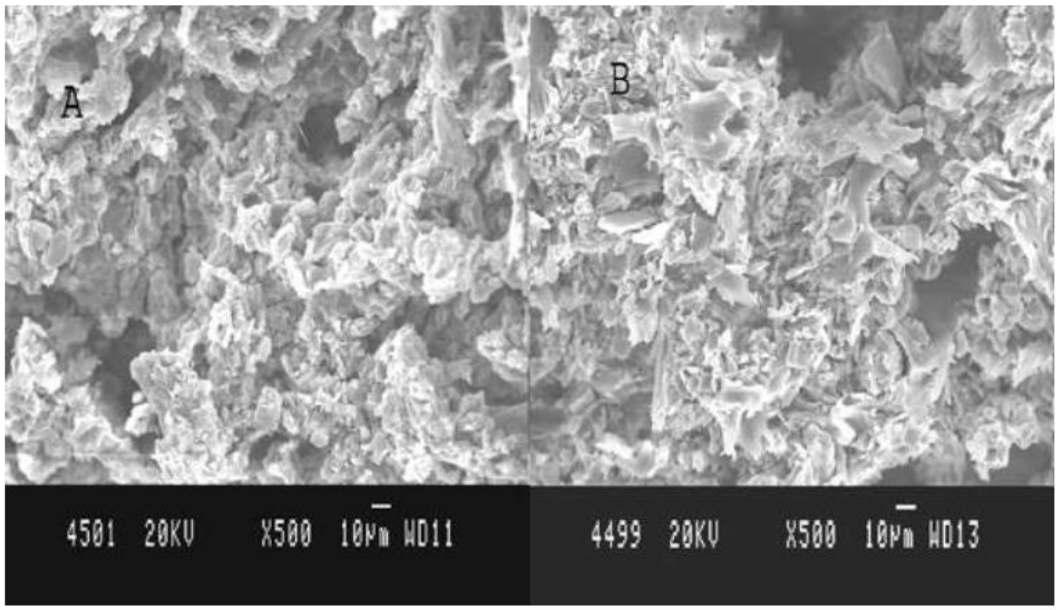

Fig.3 SEM image for formulation F5 at ×500 (A) and F11 at ×500 (B).
After dissolution indicating pore formation due to swelling of polymers

Stability studies were performed on selected formulations i.e. F5 and F11 at $25^0\pm2^0$/60±5% RH, $35^0\pm2^0$/60±5% RH and $40^0\pm2^0$/75±5% RH for 90 days. The formulations were checked for physical appearance, FLT, FD, drug content, hardness and friability etc. at intervals of 10 days. No physical change was observed in the formulations at all three stability conditions. No significant change was observed in drug content, FLT, FD, Hardness and friability of the

selected formulations at all three stability conditions. Hence, both the formulations were found to be stable.

The formulations F5 and F11 were found to be the best formulations which may be subjected to further evaluation in animal models.

Acknowledgements:

The authors wish to acknowledge Torrent Pharmaceutical Ltd., Baddi, India, for providing gift sample of atenolol and IISc Bangalore for SEM studies.

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