RESEARCH ARTICLE

Floating matrix tablets of atenolol: Formulation and *in vitro* evaluation

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The purpose of the study was to prolong the gastric residence time of atenolol by designing its floating tablets and to study the influence of different polymers on its release rate. Nine formulations of atenolol containing varying concentrations of polymers were designed by optimization. The floating matrix tablets of atenolol were prepared by direct compression method. The prepared tablets were evaluated for physicochemical parameters such as hardness, floating properties (floating lag time, floating time and matrix integrity), swelling studies and drug content. The physicochemical parameters of formulated tablets were found to be within normal range. A significant difference in drug release ($P < 0.0001$) and floating lag time ($P < 0.005$) at 0.5, one, four and eight hours were observed. The floating lag time of all the formulations was within the prescribed limit (<10 minutes). All the formulations showed good matrix integrity and retarded the release of drug for eight hours. The release pattern of atenolol was fitted to different models based on coefficient of correlation (r). All the formulations, except F2, F3 and F6 showed Korsemeyer-Peppas model as the best fit model. Formulation F2 and F3 showed first order model while F6 showed zero order model. Diffusion exponent (n) value was found in the range of 0.52-0.99 indicating diffusion as a release mechanism. The swelling studies of all the formulations showed that formulations containing Xanthan gum has higher swelling indices than HPMC K100M and HPMC K4M. It can be concluded that formulations with higher swelling indices retarded the release of drugs more than those with lower swelling indices.

Key words: *Atenolol, floating, swelling index*

INTRODUCTION

Floating drug delivery systems were first described by Davis in 1968.[1,2] It is possible to prolong the gastric residence time of drugs using these systems. Several techniques are used to design gastro retentive dosage forms. These include floating, swelling, inflation, adhesion, high-density systems and low density systems that increase the gastric residence time.[3-5] Gastric retention is useful for drugs which (i) act locally; (ii) have a narrow absorption window in the small intestinal region; (iii) unstable in the intestinal environment; (iv) low solubility at high pH environment.[6] Various dosage forms developed for gastric retention include, floating tablets,[7] floating beads,[8] pellets,[9] floating granules,[10] floating microspheres.[11] In this investigation, an attempt was made to design floating tablets of atenolol using different release retarding polymers along with a gas-generating agent.

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Atenolol is β-1 cardio selective adrenergic receptor blocker, widely used in the treatment of hypertension. The drug is insoluble in water and has half-life of six to eight hours with oral bioavailability of 50% due to smaller dose of drug (less than 50 mg).[12,13] In this study, an attempt was made to design and formulate the floating matrix tablets of atenolol so as to increase its gastric retention thereby ensuring slower and complete release of atenolol. Also, attempts were made to assess the effect of natural polymer, xanthan gum and semi synthetic polymers, hydroxypropylmethyl cellulose (HPMC) K4M and K100M on the release rate of drug. Sodium bicarbonate was used as a gas generating agent and dicalcium phosphate (DCP) was used as a channeling agent. The release pattern and swelling indices of all the formulations were analyzed using different mathematical models.[14]

MATERIALS AND METHODS

Materials

Atenolol and directly compressible lactose (DCL 15) were procured from Flamingo Pharmaceuticals, Mumbai M.S., India. Hydroxypropylmethyl cellulose (HPMC) of

two different viscosity grades (HPMC K4M, HPMC K100M) and xanthan gum (Rheogel®, Iranex, Rouen, France) 120-mesh size were received from Ajanta Pharmaceuticals Ltd, Mumbai, M.S., India. Other ingredients used were of analytical grade.

Methods

Preparation of floating tablets

Floating tablets of atenolol were prepared by direct compression method employing sodium bicarbonate as gas-generating agent. HPMC K4M, HPMC K100M and xanthan gum were used as rate controlling polymers. The concentrations of the above ingredients were optimized on the basis of trial preparation of the tablets.

All the ingredients [Table 1] were weighed accurately. The drug was mixed with the release rate retarding polymers and other excipients in ascending order of their weight. The powder mix was blended for 20 minutes to have uniform distribution of drug in the formulation. About 350 mg of the powder mix was weighed accurately and fed into the die of single punch machinery (Cadmach, Ahmedabad, India) and compressed at 3 N compression force using 10mm concave punches.

Floating characteristics

Floating characteristics of the prepared formulations were determined using USPXXIII paddle apparatus (Electrolab, TDT-06P, Mumbai, India.) under sink conditions. The dissolution medium was 900 ml of 0.1 N HCl (pH 1.2) and temperature of which was maintained to 37 plus/minus 0.5°C throughout the study. The time between the introduction of tablet and its buoyancy on the gastric fluid required for the tablet to float on the gastric fluid (floating lag time) and the time during which dosage forms remain buoyant (floatation duration) were measured. The integrity of the test tablets was observed visually during study (matrix integrity).

Drug content

Six tablets from each formulation were weighed and powdered. Powder equivalent to the average weight of the tablet was weighed accurately and transferred into a 100 ml volumetric flask and dissolved in a suitable quantity of methanol. The solution was made up to the mark and mixed well. A portion of sample was filtered and analyzed by a spectrophotometer (Shimadzu UV1700, Japan) at 225 nm.[15]

Drug release

Dissolution tests were conducted in triplicate for all formulations in a USPXXIII tablet dissolution apparatus (Electrolab, TDT-06P, Mumbai, India). The dissolution medium was 900 ml 0.1N HCl (pH 1.2) at 37 ± 0.5°C with a stirring speed of 50 RPM. At predetermined time intervals, two ml samples were withdrawn and sink conditions maintained. The samples were analyzed for drug release by measuring the absorbance at 225 nm using spectrophotometric method (Shimadzu UV, 1700, Japan). The drug release data was analyzed to study release kinetics using zero order, first order, Korsemeyer- Peppas and Higuchi equations.[16,17]

Zero order equation

$$\% \text{ Drug released} = kt \quad (1)$$

Where, k = constant, t = time

First order equation

$$\log \% \text{ unrelease d} = \frac{kt}{2.303} \quad (2)$$

Korsemeyer- Peppas equation,

$$\text{Log drug released} = \log k + n \log t \quad (3)$$

Where, n = release exponent

Higuchi's equation

$$\% \text{ Drug released} = kt^{0.5} \quad (4)$$

Per cent dissolution efficiency and mean dissolution time were calculated for all formulations.[18,19]

Table 1: Formulations of floating matrix tablets of atenolol

Ingredients/formulations	F1	F2	F3	F4	F5	F6	F7	F8	F9
Atenolol	50	50	50	50	50	50	50	50	50
HPMC K100M	35	70	105	-	-	-	-	-	-
HPMC K4M	-	-	-	35	70	105	-	-	-
Xanthan gum	-	-	-	-	-	-	35	70	105
Sodium bicarbonate	35	35	35	35	35	35	35	35	35
Dicalcium phosphate	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5
Magnesium stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Directly compressible lactose	205.5	170.5	135.5	205.5	170.5	135.5	205.5	170.5	135.5
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Total (mg)	350	350	350	350	350	350	350	350	350

Determination of swelling index

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium 0.1NHCl at 37 ± 0.5°C. After 0.5, one, two, three, four, five, six, seven and eight hours, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, AX 120). The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula.[20]

$$\text{Swelling index} = \frac{(\text{Wet weight of tablet - Dry weight of tablet})}{\text{Dry weight of tablet}} \quad (5)$$

Hardness

Hardness of the prepared formulations was determined using Monsanto hardness tester (Rolex, Chandigarh, India)[21] (n = 10).

Statistical analysis

Analysis of variance (ANOVA) was performed to find out significant difference in drug released at 0.5, one, four and eight hours, floating lag time at 0.5, one, four, eight hours, swelling index at one, four and eight hours from all formulations.

RESULTS AND DISCUSSION

Floating characteristics

When the floating matrix tablets containing gas-generating agents were exposed to 0.1N HCl, hydrochloric acid reacted with sodium bicarbonate in the floating tablet inducing CO_2 formation. The generated gas was entrapped into the matrix of swollen polymer matrix and well protected by gel formed by hydration of polymers, which led to floating of the dosage forms.[22,23]

A 10% concentration of sodium bicarbonate was found optimum to impart floating. It was observed that the concentration of sodium bicarbonate less than 10% led to slow reaction that prolonged the floating lag time up to 1.5 h. Hardness of four to 4.5 kg/cm^2 was found optimum to impart the compactness to the system. Swelling of the tablets depends on the type of polymer and its concentration. Floating lag time of the tablets was found to be the function of polymer concentration [Table 2]. This may be because at lower concentrations the polymers have less ability to form gel.[24]

All the formulations showed good matrix integrity probably because of the compactness of the system which is necessary to prevent the sweep of the tablet in lower part of gastrointestinal tract during interdigestive myoelectric cycle. The tablet floats on the dissolution medium for 24 hours because of the presence of internal voids in the dry center of tablets (porosity) due to increased bulk volume.

Drug content

Atenolol content was found within the specifications (92.5% to 107.5%).[25]

***In vitro* drug release**

In vitro dissolution studies for all the formulations showed controlled release of drug for eight hours. When the floating tablets were exposed to dissolution medium, the medium penetrated into the free spaces between macromolecular chains of the polymer. After solvation of the polymer chain, the dimension of the polymer molecule is increased due to the polymer relaxation by stress of the penetrated solvent. This led to swelling which is characterized by the formation of a gel like network surrounding the tablet. HPMC is a hydrophilic polymer that forms a surface barrier around the matrix tablet.[26] The higher rate and extent of drug release was observed from the formulations based on HPMC K4M and HPMC K100M than those based on Xanthan gum [Table 3]. It was observed that the formulations containing xanthan gum showed slower release of drug [Figure 1] than those containing HPMC K100M [Figure 2] and HPMC K4M [Figure 3]. This is because of higher degree of swelling due to water uptake and small amount of erosion due to polymer relaxation.

Under experimental conditions, the drug diffusivity in HPMC is higher than in xanthan gum gel. The release of atenolol from all the formulations fitted to different release kinetic models. The comparative effect of three different polymers on the

Table 2: Evaluation of physicochemical parameters of atenolol

Formulation code	Drug content % ± S.D (n=3)	Hardness ± S.D. (n=10)	Floating lag time (min.) ± S.D.	Floating duration (h) (n = 3)	Matrix integrity	Swelling index ± S.D (n = 3)
F1	98.25 ± 3.01	4.4 ± 0.28	7 ± 1.0	22.7 ± 0.05	Very good	0.771 ± 0.01
F2	102.03 ± 2.45	4.3 ± 0.18	6 ± 0.05	23 ± 1.00	Very good	1.0453 ± 0.01
F3	99.70 ± 3.5	4.5 ± 0.32	5 ± 1.75	24 ± 1.05	Very good	1.5026 ± 0.06
F4	100.81 ± 0.72	4.4 ± 0.31	9 ± 0.01	12 ± 0.05	Very good	0.6215 ± 0.03
F5	97.23 ± 0.25	4.4 ± 0.25	7 ± 0.03	15 ± 0.05	Very good	0.7310 ± 0.00
F6	99.17 ± 1.42	4.6 ± 0.36	6 ± 0.04	17 ± 0.05	Very good	0.9495 ± 0.01
F7	101.47 ± 2.89	4.3 ± 0.18	8 ± 0.17	24 ± 1.00	Very good	1.1277 ± 0.00
F8	100.01 ± 3.01	4.4 ± 0.12	6 ± 0.04	24 ± 0.05	Very good	1.4767 ± 0.018
F9	97.86 ± 3.5	4.5 ± 0.2	5 ± 0.01	24 ± 1.05	Very good	1.7695 ± 0.04

release profile of atenolol from the floating formulations in terms of percentage dissolution efficiency (%DE) showed that formulations containing xanthan gum retarded the release of drug than those containing HPMC K100M and HPMC K4M. It was observed that the formulations having low values of mean dissolution time (MDT) indicated the faster release of drugs than the other formulations [Table 3]. Formulations F2 and F3 were found to follow first order model (r value 0.98 and 0.82 respectively). Formulations F6 showed zero order release model (r value 0.99) while formulations F1, F4, F5, F7, F8 and F9 showed Peppas model (r value 0.96 to 0.99). When the drug release data was correlated to Korsemeyer Peppas equation that the value of diffusion exponent 'n' (0.52 to 0.99) indicated that the drug release was by Non- Fickian diffusion [Table 4].

Swelling index

The swelling of polymers used (HPMC K4M, HPMC K100M and xanthan gum) were determined by water uptake. It was observed that the swelling indices were increased with increase in polymer concentration. Formulations containing xanthan gum showed higher swelling indices as compared with other formulations containing the same amount of HPMC K4M and HPMC K100M

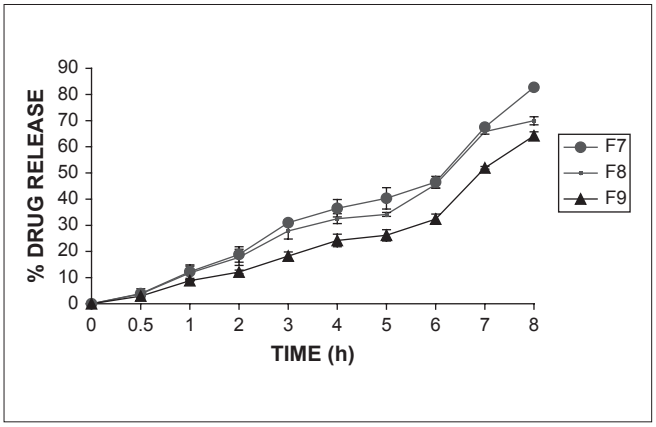

Figure 1: *In vitro* release profile of atenolol from formulations F7, F8 and F9 containing 20, 30 and 40% xanthan gum respectively

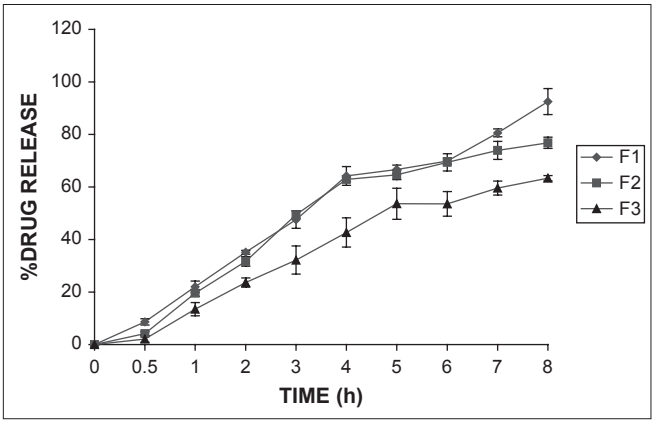

Figure 2: *In vitro* release profile of atenolol from formulations F1, F2 and F3 containing 20, 30 and 40% HPMC K 100 M respectively

Table 3: *In vitro* release profile of atenolol

Formulation code	% Drug release ± S.D.	% DE	MDT
F1	92.50 ± 4.98	53.89	3.95
F2	76.81 ± 2.16	50.88	4.01
F3	63.34 ± 1.02	34.73	4.03
F4	118.07 ± 5.80	58.93	3.02
F5	111.03 ± 5.61	50.73	3.34
F6	64.88 ± 2.07	33.27	3.79
F7	82.71 ± 2.33	36.65	4.49
F8	69.94 ± 1.54	33.68	4.54
F9	61.09 ± 1.54	25.47	5.50

(n = 3), DE- dissolution efficiency, MDT-mean dissolution time

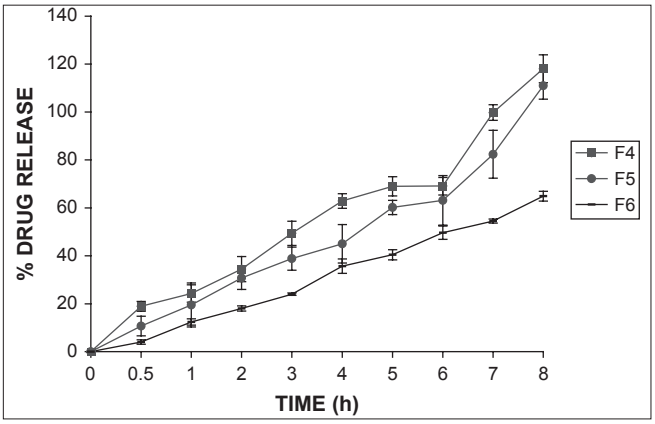

Figure 3: *In vitro* release profile of atenolol from formulations F4, F5 and F6 containing 20, 30 and 40% HPMC K 4 M respectively

Table 4: Analysis of *in vitro* release data of atenolol

Formulation code	Zero order		First order		Korsemeyer - Peppas			Best fit
	r	k	r	k	r	k	n	
F1	0.9600	12.49	0.9385	15.26	0.9849	18.55	0.79	Peppas
F2	0.9328	11.53	0.9834	15.53	0.9538	13.37	0.97	First
F3	0.7800	8.08	0.8228	13.45	0.3085	13.28	0.52	First
F4	0.9697	14.22	0.8835	14.50	0.9718	25.42	0.64	Peppas
F5	0.9597	12.66	0.9586	13.75	0.9699	17.72	0.96	Peppas
F6	0.9944	8.15	0.9867	14.26	0.9881	09.29	0.93	Zero order
F7	0.9805	9.30	0.9055	14.59	0.9836	09.35	0.99	Peppas
F8	0.9823	8.45	0.9453	14.85	0.9828	08.86	0.97	Peppas
F9	0.9139	8.77	0.9733	14.60	0.9945	15.17	0.59	Peppas

r- coefficient of correlation, k- constant, n-diffusion exponent

[Table 2]. This is because during dissolution a tablet containing xanthan gum instantly forms a viscous gel layer that slows down in sweep of dissolution fluid towards the core of matrix tablet. Swelling was a strong enough to avoid premature disintegration as well as burst effect and retarded the release of drug for a long period of time.[27] The results of these tests are provided in Figures 4-6. Usually swelling is essential to ensure floating. For floating the tablets, there should be appropriate balance between swelling and water uptake. It was observed that HPMC grade also affect the swelling. No effect of effervescence on the swelling index was observed. Swelling index values starts decreasing when polymer erosion starts in medium.[28]

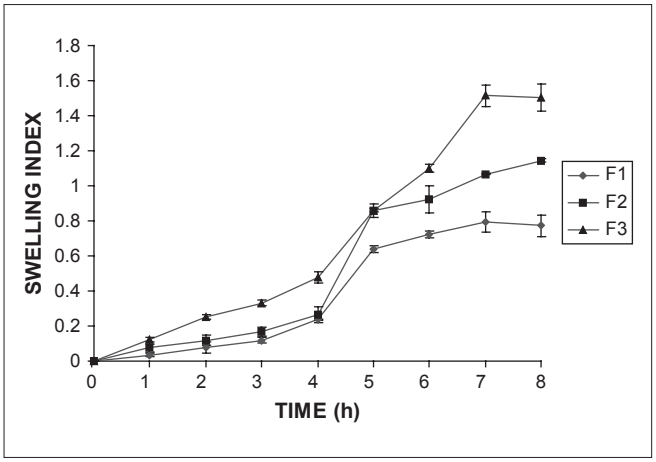

Figure 4: Swelling indices of atenolol from formulations F1, F2 and F3 containing 20, 30 and 40% HPMC K 100 M respectively

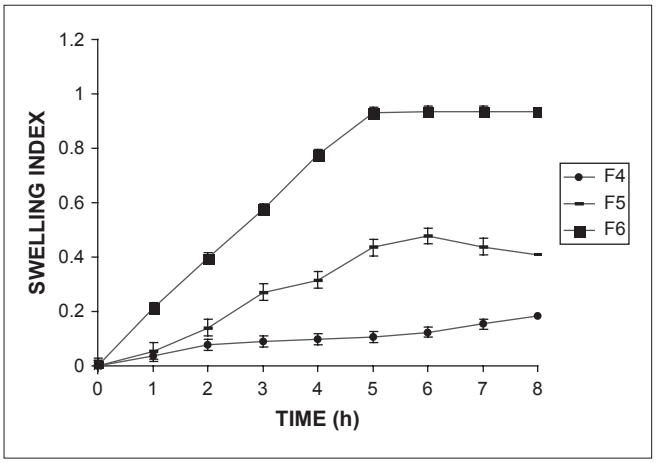

Figure 5: Swelling indices of atenolol from formulations F4, F5 and F6 containing 20, 30 and 40% HPMC K 4 M respectively

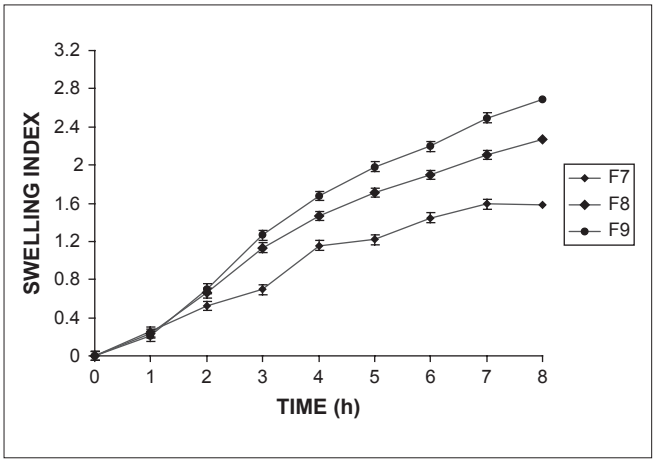

Figure 6: Swelling indices of atenolol from formulations F7, F8 and F9 containing 20, 30 and 40% xanthan gum respectively

It can be concluded that lesser floating lag time and prolonged floating duration can be achieved by using the polymer xanthan gum. It was also observed that formulations containing xanthan gum retarded the release of drug as the polymer swelling is crucial in determining the release rate. An inverse correlation between swelling and drug release was observed. It was found that the formulations with maximum swelling indices showed slower release of drugs.

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