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Development and characterization of floating tablets of atenolol

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ABSTRACT

A novel gastro retentive drug delivery system of Atenolol was formulated in an effort to increase gastric residence time and thereby increase drug bioavailability. Nine formulations of Atenolol tablets were prepared by direct compression and wet granulation technique using bees wax, ethyl cellulose and Cetosterol in varying proportions. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. Dicalcium phosphate was used as a channeling agent. The prepared tablets were evaluated for physicochemical parameters and found to be within range. The floating lag time of all the formulations was within the prescribed limit. In Vitro drug release studies were performed. Release pattern of Atenolol was fitted to different models based on coefficient of correlation (R).

Key Words: Effervescent floating, Atenolol, *In Vitro* dissolution.

INTRODUCTION

Drug absorption from the gastrointestinal tract is a complex procedure and is subjected to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment.

To formulate a successful stomach specific or gastroretentive drug delivery system, several techniques are currently used such as hydrodynamically balanced systems (HBS) / floating drug delivery system, low density systems, raft systems incorporating alginate gels, bioadhesive or mucoadhesive systems, high density systems, super porous hydrogels and magnetic systems,

Atenolol is a selective β_1 receptor antagonist, a drug belonging to the group of beta blockers, a class of drugs used primarily in cardiovascular diseases. Drug is insoluble in water and has half life of 6 to 8 hrs. In this study, an attempt was made to design and formulate the floating tablets of Atenolol using HPMC K100 and different hydrophobic substances like bees wax, Cetosterol and ethyl cellulose in varying proportions and their effect on release rate of drug is assessed. The release patterns of all the formulations were analyzed using different theoretical models [1-5]

MATERIALS AND METHODS

Materials

Atenolol was obtained as a gift sample from Fourrts India Pvt Ltd, Chennai. HPMC K100 was obtained as gift sample from MSN Laboratories Ltd, Hyderabad. Cetosterol was obtained from S. D Fine chemicals Ltd and Ethyl cellulose, xanthan gum, micro crystalline cellulose, sodium alginate were obtained from Loba Chemie Pvt Ltd.

Method

Preparation of floating tablet

Direct compression method was used in preparation of F1, F5, F6, F7 formulations. For each formulation of tablet drug, HPMC K100, NaHCO3,citric acid, ethyl cellulose(F5, F6. F7), sodium alginate, xanthan gum and diluents were blended homogeneously followed by addition of aerosil. The resultant mixture was further compressed into tablets using tablet machine. The final weight of each tablet formulation was 650mg.

Formulations containing bees wax and Cetosterol were prepared by melt granulation technique [6-8]

Physical Properties of floating tablets

The prepared tablets were tested for weight variation, drug content uniformity, hardness and friability.

Evaluation of tablets

Floating characteristics

Floating behavior studies were performed on the Atenolol floating tablets. The buoyancy of the tablets was studied at 37±0.5^{0}C, in 100 ml of simulated gastric fluid at pH 1.2 (without pepsin). The time of duration of tablet floatation was observed visually. The following parameters are determined: the time needed to go upward and float on the surface (floating lag time), floating duration and relative matrix integrity. The latter parameter was determined on the basis of visual inspection after the floating studies [9-12]

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Determination of Swelling Index

The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using 0.1N HCl (pH 1.2) as dissolution medium at room temperature. The swollen weight of the tablet was determined at predefined time intervals 0.5, 1, 2, 3, 4, 5, 6, 7 and 8h. The swelling index was calculated by the following equation [13]

$$\text{Swelling index} = \frac{Wt - W0}{W0}$$

In Vitro drug release

The release of drug from floating tablets was determined by using Dissolution Tester USP XXIII paddle apparatus with sinker. The dissolution test was performed using 900ml of 0.1N HCl solution at 37°C ± 0.5^{o}C temperature and at 50 rpm. At every 1 hour interval samples of 10ml are withdrawn from the dissolution medium and that amount was replaced with fresh medium to maintain the volume constant. The samples were filtered and diluted to a suitable concentration with 0.1 N HCl solution.The absorbance of these solutions was measured by using a UV-Visible double beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from standard curve [14-18]

RESULTS AND DISCUSSION

Gastro retentive tablets of Atenolol were developed to increase the gastric retention time of drug, so that they can be retained in the stomach for longer time and help in controlled release of drug. The Atenolol tablets were made using water soluble polymer HPMC K100 and xanthan gum. They are known to be beneficial in improving the buoyancy characteristics and drug release characteristics. PVP K30 was used as disintegrating agent. The composition of Atenolol tablets is given in Table I. The prepared Atenolol tablets were evaluated for thickness, weight variation, hardness, friability, drug content, swelling index, floating studies and *invitro* dissolution studies. All the studies were performed in triplicate and results are expressed as mean.

Physicochemical characterization

The results of physicochemical characterizations are given in Table II. The thickness of Atenolol tablets was measured by digital thickness tester and was ranged between 4.06 and 4.33mm. The weight variation for different formulations (F1 to F9) was found to be 0.320% to 0.750%, showing satisfactory results as per Indian pharmacopoeia (IP) limit. The hardness of Atenolol tablets was measured by Monsanto tester and was found between 3.2 and 6.1 kg/cm^2. The drug content uniformity varied between 96.53% to 102.36%. Good uniformity in drug content was found among different batches with drug content being more than 96%.

Floating studies

All the tablet formulations were prepared by effervescent approach. The invitro buoyancy of Atenolol tablets was induced by sodium bicarbonate and anhydrous citric acid. It was observed that the gas generated was trapped in the tablet and protected within the gel formed by hydration of polymer, thus decreasing the density of the tablet below 1, and the tablet becomes buoyant.

The tablets F1 containing HPMC with no hydrophobic release modifier exhibited lag time of 33s and floated till 18hrs. The tablets F2, F3, F4 with bees wax in increasing concentration exhibited lag time of 45s, 52s, 60s respectively, with a buoyancy of 18h and 12h. Formulations F5, F6, F7 with ethyl cellulose remained buoyant for more than 24hrs with a lag time of 28s, 19s and 13s respectively. Lag time found to decrease with increase in concentration of ethyl cellulose. Among all formulations F6 tablets showed shortest buoyancy lag time.

The Atenolol tablets of F8 and F9 with Cetosterol as release modifier exhibited lag time of 43s and 51s respectively. The buoyancy time of F8 and F9 was found to be 12h.

Swelling study

Swelling is also a vital factor to ensure buoyancy and drug dissolution of the matrix tablet. The floating tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release from the matrix tablet. Fig shows the swelling index of tablets of F1 to F9.

Atenolol floating tablets of F5 and F9 showed higher swelling index at the first 2h but could not maintain up to 8h. Tablets of F7 formulation showed constant increase in swelling index. Tablets of formulation F6 and F7 showed less swelling index at the beginning but was found higher at the end of 8h. Among all formulations F3 and F8 showed less swelling index. Formulation F7 showed highest swelling index.

***In vitro* dissolution studies**

In vitro dissolution studies of all the formulations of Atenolol tablets were performed by using type II paddle apparatus at a rotational speed of 50rpm. 0.1N HCl was used as the dissolution medium. The study was performed for 6h, and cumulative drug release was calculated at 1-h time intervals.

The results of *In vitro* dissolution studies are given in table III. All the tablet formulations showed more than 6% release within 1h, but F1 formulation containing only HPMC K100 polymer showed 15.91% drug release within 1h. It is generally believed that incorporation of lipophilic substances, which have relative density lower than 1, decrease the water intake and improve floating properties. Drug release in formulations F2, F3 and F4 with bees wax was found to be 76.48%, 73.04% and 70.18% respectively. Formulations F5, F6 and F7 with ethyl cellulose showed drug release of 84.07%, 78.48% and 74.18% respectively. Hydrophobic meltable materials like bees wax and Cetosterol showed decrease in the rate of drug release with increase in concentrations. Formulations with Cetosterol (F8 and F9) showed more decrease in release rate of the drug compared to other formulations.

The mechanism of release for the above formulations was determined by finding the R^2 value for each kinetic model. Zero order, First order, Higuchi, and korsmeyer-peppas corresponding to the release data of each formulation. For all the formulations the R^2 value of Higuchi is very near to 1 than the R^2 values of other kinetic models. Thus it can be said that the drug release follows Higuchi's model mechanism.

Table I composition of floating tablets of Atenolol (F1 to F9)

Raw Materials	F1	F2	F3	F4	F5	F6	F7	F8	F9
Atenolol	50	50	50	50	50	50	50	50	50
HPMC K100	150	150	150	150	150	150	150	150	150
Bees Wax	-	50	75	100	-	-	-	-	-
Ethyl Cellulose	-	-	-	-	25	50	75	-	-
Ceto sterol	-	-	-	-	-	-	-	25	37.5
NaHCO3	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
Citric acid	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75
Dicalcium phosphate	25	25	25	25	25	25	25	25	25
MCC	207.5	157.5	132.5	107.5	185.5	157.5	102.5	182.5	170
Xanthan Gum	50	50	50	50	50	50	50	50	50
Na alginate	50	50	50	50	50	50	50	50	50
PVP K 30	10	10	10	10	10	10	10	10	10
Aerosil	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Total Quantity(mg)	600	600	600	600	600	600	600	600	600

Table II physicochemical characterization of floating tablets of Atenolol (F1 to F9)

Evaluation parameters	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness (mm)	4.23	4.06	4.10	4.19	4.20	4.14	4.33	4.11	4.15
Wt variation (%)	0.636	0.397	0.383	0.616	0.479	0.750	0.550	0.616	0.320
Hardness (kg/cm^2)	4.1	5.5	5.8	6.1	3.2	3.7	4.1	4.6	4.8
Drug content (mg)	102.3	98.25	97.12	98.60	99.62	101.2	99.17	96.53	100.0
Lag time (s)	33	45	52	60	28	19	13	43	51
Buoyancy time (h)	18	18	18	12	>24	>24	18	12	12
Swelling index (h)	1.07	1.97	0.80	0.86	1.02	1.08	2.02	0.78	1.73

Table III Dissolution data of Atenolol floating tablets

Time (h)	% Cumulative drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	15.91	9.44	9.99	9.46	8.35	7.25	6.71	9.38	7.75
2	23.09	21.98	14.88	26.33	23.61	18.69	19.23	17.62	13.79
3	40.13	45.55	42.23	34.66	36.83	31.89	36.80	35.71	28.05
4	55.08	56.17	55.56	50.12	55.58	44.07	53.91	52.27	51.11
5	70.11	66.30	64.05	59.67	65.71	64.49	61.30	59.65	58.48
6	99.40	76.48	73.04	70.18	84.07	78.48	74.18	72.62	67.26

Table IV Kinetic treatment of dissolution profile of Atenolol tablets and mechanism of drug release

Formulations	Zero order		First order		Higuchi's		Korsmeyer -peppa's		
	K	R^2	K	R^2	K	R^2	n	K	R^2
F1	14.34	0.948	0.279	0.604	49.77	0.958	1.996	0.533	0.831
F2	12.32	0.964	0.107	0.976	14.29	0.979	1.928	0.547	0.809
F3	11.92	0.943	0.099	0.968	49.40	0.971	2.026	0.451	0.866
F4	10.90	0.970	0.085	0.983	42.63	0.994	1.902	0.517	0.816
F5	12.80	0.966	0.124	0.907	52.27	0.982	1.955	0.528	0.826
F6	11.96	0.947	0.108	0.906	51.26	0.969	2.088	0.392	0.902
F7	11.76	0.961	0.099	0.964	48.42	0.990	1.994	0.469	0.859
F8	11.54	0.958	0.096	0.960	47.64	0.985	1.960	0.477	0.853
F9	11.16	0.940	0.091	0.944	47.97	0.967	2.038	0.390	0.902

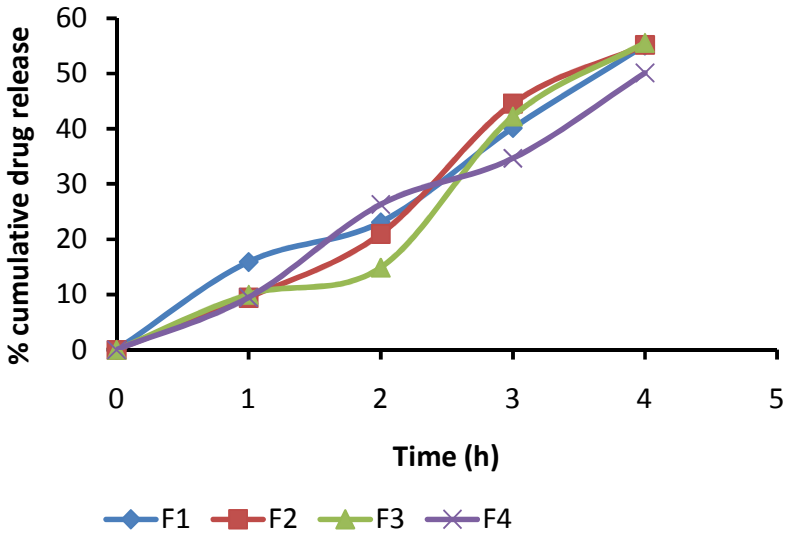

Fig I *Invitro* release profile of Atenolol formulations F1, F2, F3 and F4

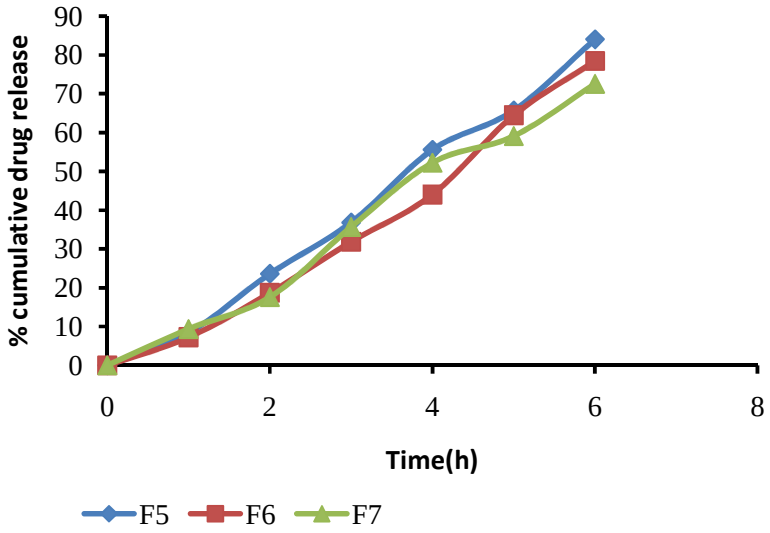

Fig II *Invitro* release profile of Atenolol formulations F5, F6 and F7

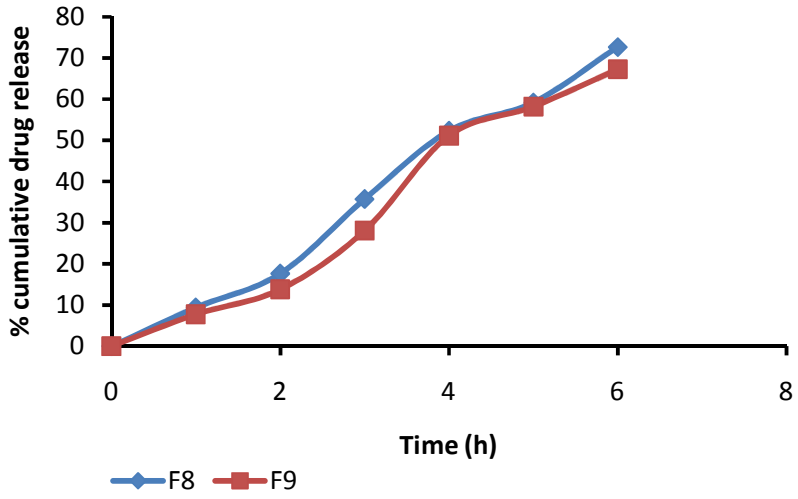

Fig III *Invitro* release profile of Atenolol formulations F8 and F9

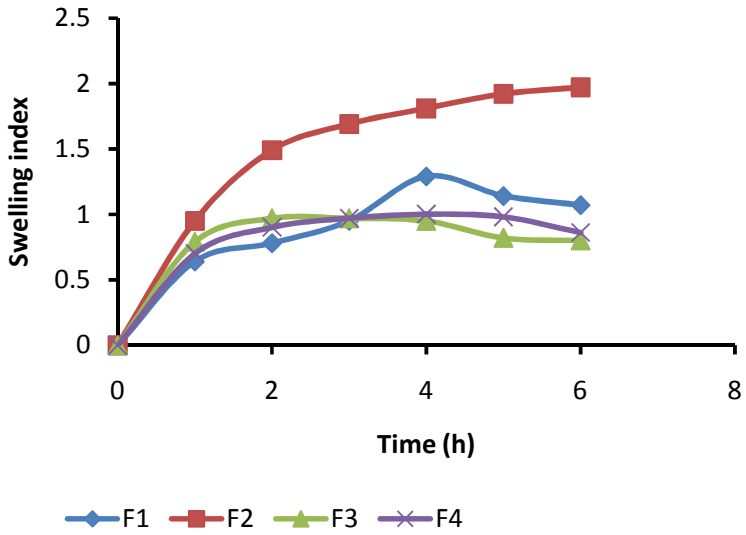

Fig IV Swelling indices of Atenolol from formulations F1, F2, F3, F4

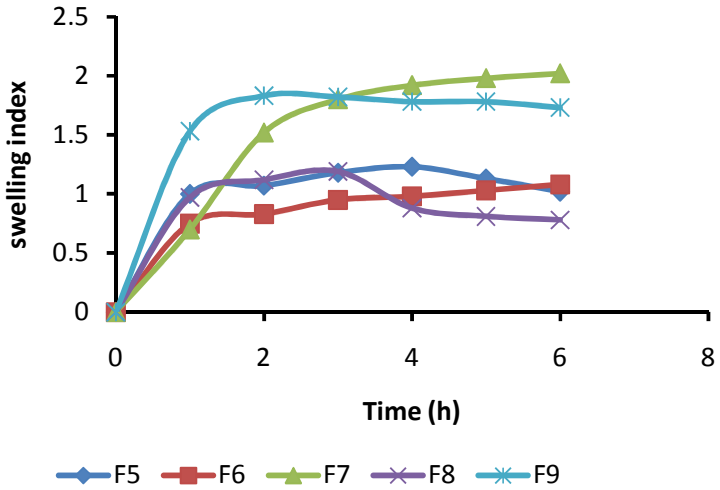

Fig V Swelling indices of Atenolol from formulations F5, F6, F7, F8, F9

CONCLUSION

An attempt was made to develop gastroretentive drug delivery system of Atenolol using HPMC K100 polymer and sodium carbonate and citric acid as effervescent agents. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment.

Nine formulations were prepared using different concentrations of hydrophobic release rate retarders. The main aim of this study was to investigate the effect of hydrophobic release rate modifiers on drug release and floating properties of the delivery system.

All the formulations were evaluated for hardness, friability, drug uniformity and weight variation it was observed that all the tablets of all batches had acceptable physical characteristics. Swelling index of tablets of F1 to F9 formulations was determined. Among all formulations F7 showed highest swelling index.

Formulations with lipophilic substances like bees wax and Cetosterol showed better floating properties than F1 and with increase in amount of bees wax and Cetosterol lag time was found to be increased. Formulations with ethyl cellulose found to have better floatation properties and their lag time was found to decrease with increase in concentration.

From the dissolution release profile it was observed that with increase in concentration of hydrophobic materials the drug release rate is decreased. Formulations with Cetosterol (F8 and F9) showed more decrease in release rate of the drug compared to other formulations. The drug release from floating Atenolol tablets is best explained by Higuchi's model. The effect of hydrophobic materials on the drug release profile and floating characteristics were studied.

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