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Effect of Polymer Concentration and Viscosity Grade on Atenolol Release from Gastric Floating Drug Delivery Systems

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Abstract

Gastroretentive floating drug delivery systems of atenolol, an antihypertensive drug with an oral bioavailability of only 50% (because of its poor absorption from lower gastrointestinal tract) have been designed. Hydroxypropyl methylcelluloses of different viscosity grades (K4M and 50 cps) were used as polymers and sodium bicarbonate as gas generating agent to reduce floating lag time. Tablets were prepared by direct compression method. The prepared formulations were further evaluated for hardness, friability, weight variation, drug content, swelling index, in vitro drug release pattern, short-term stability and drug-excipient interactions. Majority of the designed formulations displayed nearly first order release kinetics releasing more than 75% drug in 10 hours and remained buoyant for more than 24 hours. Drug release data shows that as the proportion and viscosity of polymer increases, drug release decreases. The formulation containing atenolol 50 mg, hydroxypropyl methylcellulose (50 cps) 100 mg and 37 mg sodium bicarbonate (20% w/w of tablet) as gas generating agent, appears to be a promising gastroretentive floating drug delivery system of the drug atenolol, releasing more than 90% of the drug in 10 hours.

Keywords: *Atenolol, gastroretentive floating drug delivery system, hydroxypropyl methylcellulose, hydrodynamically balanced system*

INTRODUCTION

Gastroretentive drug delivery 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. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastroretention helps to provide better availability of new molecular entities with new therapeutic possibilities and substantial benefits for patients.

The gastric emptying time has been reported to be from 2 to 6 hours in humans in the fed state[1]. Drugs that are required to be formulated into gastroretentive dosage forms include: (a) drugs acting locally and primarily absorbed in the stomach; (b) drugs that are poorly soluble at an alkaline pH; (c) those with narrow window of absorption; (d) drugs absorbed rapidly from GI tract and (e) drugs that degrade in colon. Various approaches have been worked out to improve the retention of oral dosage forms in the stomach. Depending on the mechanism of buoyancy, two distinctly different methods, viz., effervescent and non-effervescent systems have been used in the development of floating drug delivery systems[2]. Effervescent drug delivery systems utilize matrices prepared with swellable polymers such as methocel[3] or polysaccharides and effervescent components e.g., sodium bicarbonate and citric acid or tartaric acid[4].

Atenolol, a beta-blocker used in the treatment of hypertension and angina pectoris. It is incompletely absorbed from the gastrointestinal tract[5] and has an oral bioavailability of only 50%, while the remaining is excreted unchanged in faeces. This is because of its poor absorption in lower gastrointestinal tract[9]. It undergoes little or no hepatic first pass metabolism and its elimination half-life is 6 to 7 hours[6]. Therefore, it is selected as a suitable drug for the design of a gastroretentive floating drug delivery system (GFDDS)

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with a view to improve its oral bioavailability.

The objective of this work is to develop GFDDS of atenolol, employing swellable polymer hydroxypropyl methylcellulose (HPMC) of different viscosity grades (K4M and 50 cps) and sodium bicarbonate as gas generating agent, and to evaluate the effect of polymer concentration and viscosity on atenolol release from the prepared GFDDS.

MATERIALS AND METHODS

Atenolol IP and HPMC K4M were gift samples from M/s.Vapi Care Pharma Ltd., Vapi and M/s.Colorcon Asia Ltd., Goa respectively. HPMC 50 cps, sodium bicarbonate, talc and magnesium stearate were purchased from SD Fine Chem, Boisar, Maharashtra. All other chemicals used were of analytical reagent grade.

1. Preparation of Atenolol GFDDS:

In this work, direct compression method has been employed to prepare gastric floating drug delivery systems (GFDDS) of atenolol. HPMC of two different viscosity grades viz., K4M and 50 cps, with different concentration and fixed concentration of sodium bicarbonate (20% w/w) have been used for preparation of GDDS. Tablets were compressed on a single punch tablet machine (Cadmach, Ahmedabad, India) using 8 mm flat round punches.

The formulation codes for the prepared batches of GFDDS are given in Table 1. A batch of 50 tablets was prepared for each of the designed formulations.

2. *In Vitro* Characterization of GFDDS:

a) Drug Release Study: *In vitro* dissolution studies of GFDDS of atenolol were carried out in USP XXIII tablet dissolution test apparatus-II (Electrolab, Model:TDT-06N), employing paddle stirrer at 50 rpm and 900 ml of 0.1N HCl at 37±0.5ºC as dissolution medium. At predetermined time intervals, 5ml of the samples were withdrawn by means of a syringe fitted with a prefilter. The volume withdrawn at each interval was replaced immediately with same quantity of fresh dissolution medium maintained at 37±0.5ºC. The samples were analyzed for drug release by measuring the absorbance at 224.6nm using UV-visible spectrophotometer (Shimadzu UV-1700) after suitable dilution. All the studies were conducted in triplicate.

b) *In Vitro* Floating Studies: Floating time was determined by the same apparatus of dissolution study. The duration of floating is the time the tablet floats in the dissolution medium (including floating lag time, which is the time required for the tablet to rise to the surface), is measured by visual observation.

c) Swelling Index: The individual tablets were weighed accurately and kept in 50 ml of water. Tablets were taken out carefully after 60 minutes, blotted with filter paper to remove the water present on the surface and weighed accurately. Percentage swelling (swelling index) was calculated using the formula[7]:

$$\text{Swelling index} = \frac{\text{Wet weight - Dry weight}}{\text{Wet weight}} \times 100$$

a) Stability Studies: According to ICH guidelines for Accelerated stability testing of new drug substance, stability studies were performed at a temperature of 40±2ºC and 75%±5% RH, in Humidity chamber (Tempo, Mumbai), over a period of 6 months on the promising formulation (T_5) . The samples were analyzed at monthly intervals for any physical changes and drug content (by measuring the absorbance at 225.3 nm on methanolic extracts of the drug). At the end of storage period, dissolution test and *in vitro* floating studies were performed.

3b) Drug-Polymer Interaction Studies: IR spectroscopy is one of the most powerful analytical techniques, which offers the possibility of detecting chemical interaction. The IR spectra of atenolol, HPMC (50 cps) and promising formulation (T5) were obtained by KBr pellet method (Perkin-Elmer FTIR 1516 series spectrometer).

RESULTS AND DISCUSSION

In the present study, an attempt was made to design GFDDS of atenolol using hydroxylpropyl methylcellulose of different viscosity grades (K4M and 50 cps) as the polymers and sodium bicarbonate as a gas generating agent, to reduce floating lag time. The tablets were prepared by direct compression method. Six batches of formulations were designed and evaluated for various physical and floating characteristics, drug content uniformity and drug release profiles (Tables 2 and 3). Short term stability and drug- polymer interaction studies were also performed on the promising formulation.

The hardness of prepared GFDDS of atenolol was found to be in the range of 3.92 to 4.65 Kg/cm². The friability of all tablets was less than 1% and the percentage deviation from the mean weight of all the batches of prepared HBS were found to be within the prescribed limits as per IP. The low values of standard deviation indicate uniform drug content in all the batches prepared.

Swelling Index studies

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. Kinetics of swelling is important because the gel barrier is formed with water penetration. Swelling is also a vital factor to ensure floating and drug dissolution. To obtain floating, the balance between swelling and water acceptance must be restored.[7] The swelling index of the tablets increases with an increase in the polymer content and the content of gas generating agent ($NaHCO_3$) and was found to be in the range of 5.26 to 65.33.

***In Vitro* Floating Studies**

For all formulations, floating lag time was found to be in the range of 0.4 to 3.5 min. With increase in concentration of polymer of same viscosity grade, lag time increased and for same concentration of the polymers of different grades, lag time increases with increase in viscosity of polymer. All the designed formulations have displayed a floating time of more than 24 hours.

Floating mechanism

Effervescent Systems utilize effervescent reactions between carbonate/bicarbonate salts and gastric fluid to liberate CO_2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over gastric fluid. How the dosage form float is shown in the following figure (Fig.1)

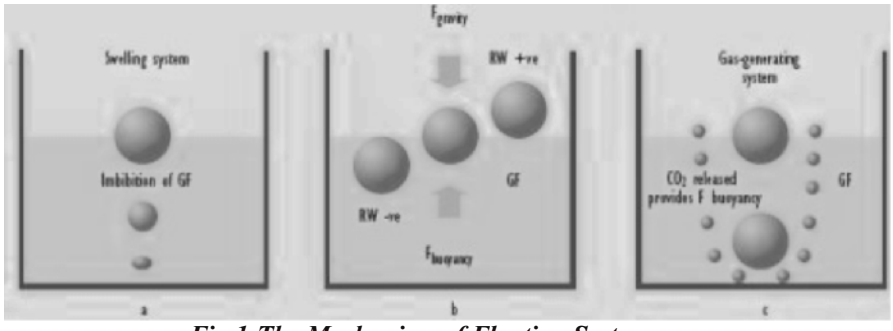

Fig.1:The Mechanism of Floating Systems

Drug Release Study:

The formulations T_1 to T_3 (prepared from HPMC K4M) have released only 67% to 76% drug in 10 h, whereas, the formulations T_4 to T_6 (prepared from HPMC 50 cps), have released 81 to 95% during the same period (Fig. 2). This increased drug release from the latter formulations can be attributed to the lower viscosity grade of HPMC. *In vitro* drug release data of all the formulations was subjected to goodness of fit test by linear regression analysis according to zero-order and first-order kinetic equations, Higuchi's and Korsmeyer–Peppas models (PCP DISSO 2000 V3 software) to ascertain the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in Table 4 and cumulative percent drug released vs time plots shown in Fig. 2 and 3.

From the above data, it is evident that except formulation T_3, all the formulations have displayed first order release kinetics ('r' values in the range of 0.9714 to 0.9933). Higuchi and Peppas data reveals that the drug is released by non-Fickian diffusion mechanism (n=0.48 to 0.79) except formulation T_3 (n=1.05), which displays zero-order release by erosion-dominated mechanism.

Formulation T_5 has displayed $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ values of 4.8, 6.4 and 8.2 h respectively (Table 3) and released nearly 91% drug in 10 h. Hence, this formulation was found to be promising (compared to T_4 which releases 95% drug in 10 h, in order to preclude any chances of dose-dumping from this formulation as it contains only 50 mg of the matrix polymer, i.e., HPMC 50 cps) and therefore, selected for accelerated stability study according to ICH guidlines.

Stability Studies

The results of accelerated stability study on the promising formulation T_5 indicated that there were no significant changes in physical appearance, drug content and dissolution profile ($p<0.05$).

Drug-Polymer Interaction Studies

IR spectrum of pure drug (atenolol) exhibits characteristic peaks at 3357.02 cm^{-1} and 1637.4 cm^{-1} due to N–H stretching and C=O stretching of amide group respectively. The peaks at 1417.27 and 1243.06 cm^{-1} are due to alcoholic –OH group. IR spectrum of formulation T_5 shows peaks at 3359.06 cm^{-1} and 1637 cm^{-1} due to N–H stretching and C=O stretching of amide group respectively. The peaks at 1416.53 cm^{-1} and 1243.04 cm^{-1} are due to alcoholic –OH group. The presence of above peaks confirm undisturbed drug in the formulation; hence there are no drug-carrier interactions. IR spectra of atenolol, HPMC (50 cps) and T_5 shown in figure-4.

CONCLUSION

The results of the study indicated that as the proportion and viscosity of the matrix polymer increases, cumulative percent drug release in 10 h decreases. Hence, these two factors have a great influence on the overall performance of the designed GFDDS formulations. The formulation (T_5) containing atenolol 50 mg, HPMC (50 cps) 100 mg and 37 mg sodium bicarbonate (20% w/w of tablet) as gas generating agent, appears to be a promising GFDDS of atenolol, releasing nearly 91% of the drug in 10 h.

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Table 1: Composition of atenolol GFDDS formulations

Ingredients(mg/tablet)	T_1	T_2	T_3	T_4	T_5	T_6
Atenolol	50	50	50	50	50	50
HPMC K4M	50	100	150	--	--	--
HPMC 50 cps	--	--	--	50	100	150
NaHCO	3 25	37	50	25	37	50
Magnesium stearate	2.5	3.7	5.0	2.5	3.7	5.0
Purified Talc	1.25	1.85	2.50	1.25	1.85	2.50

Table 2: Evaluation of atenolol GFDDS formulations

Formulation code	Mean Hardness	Friability (%) kg/ cm²	Average weight mg	Mean% content*	Swelling Index* ±SD	Floating lag (min)	Floating time (hr)
T_1	4.18	0.51	126.45	96.30±1.17	5.26±0.152	3.5	24
T_2	4.59	0.54	185.75	94.92±3.10	14.33±0.25	2.71	24
T_3	4.77	0.57	250.25	97.71±1.69	40.50±1.47	0.70	24
T_4	3.92	0.64	125.95	96.60±1.02	8.60±0.257	3.1	24
T_5	4.46	0.61	185.60	94.49±0.54	22.36±1.15	2.20	24
T_6	4.65	0.56	249.00	93.65±1.72	65.33±0.32	0.41	24

* Average of three determinations

Table 3: Dissolution parameters of atenolol GFDDS formulations

Sl. No.	Formulation Code	$t_{50\%}$(h)	$t_{70\%}$(h)	$t_{90\%}$(h)	Cumulative percent drug release in 10 h
1.	T1	4.9	7.6	>10	76.44
2.	T2	5.2	8.9	>10	72.67
3.	T3	5.5	>10	>10	67.19
4.	T4	4.5	6.2	8.0	95.21
5.	T5	4.8	6.4	8.2	90.65
6.	T6	5.9	8.2	>10	81.34

Table 4: Kinetic data of atenolol GFDDS formulations

Batch		Zero order	First order	Higuchi 's equation	Peppas equation
	r	0.9798	-0.9919	0.9823	0.9945
T 1	a	8.6400	2.0060	-7.9368	1.1924
	b	7.7062	-0.0669	27.0450	0.7220
	r	0.9185	-0.9714	0.9751	0.9292
T 2	a	17.2527	1.9016	1.2920	1.3343
	b	6.3074	-0.4735	23.2690	0.5559
	r	0.9742	-0.9858	0.9657	0.9836
T 3	a	3.2768	2.0200	-11.6286	0.8621
	b	7.3175	-0.5430	25.2148	1.0547
	r	0.8891	-0.7715	0.9689	0.9125
T 4	a	25.9400	1.8920	5.2363	1.5022
	b	7.5259	-0.0840	28.4053	0.4813
	r	0.9336	-0.9871	0.9710	0.9605
T 5	a	14.9350	1.9933	-6.2388	1.2654
	b	8.8811	-0.1029	32.1101	0.7584
	r	0.9861	-0.9762	0.9786	0.9851
T 6	a	4.7137	2.0313	-6.7894	1.1144
	b	7.8644	-0.6660	25.7071	0.7890

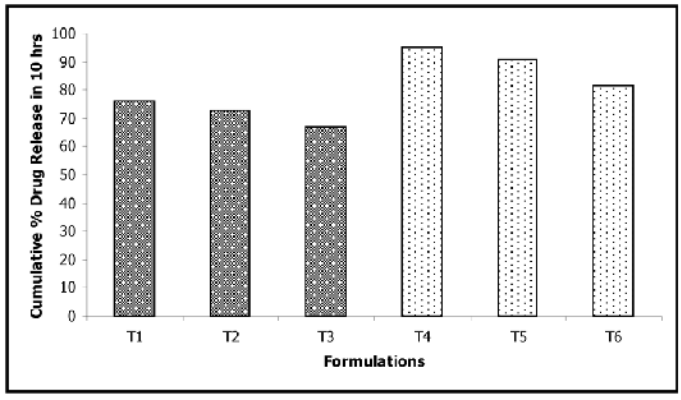


Fig. 2: Effect of polymer concentration and viscosity grade on atenolol release from GFDDS (T_1 to T_3 – HPMC K4M; T_4 to T_6 – HPMC 50 cps)

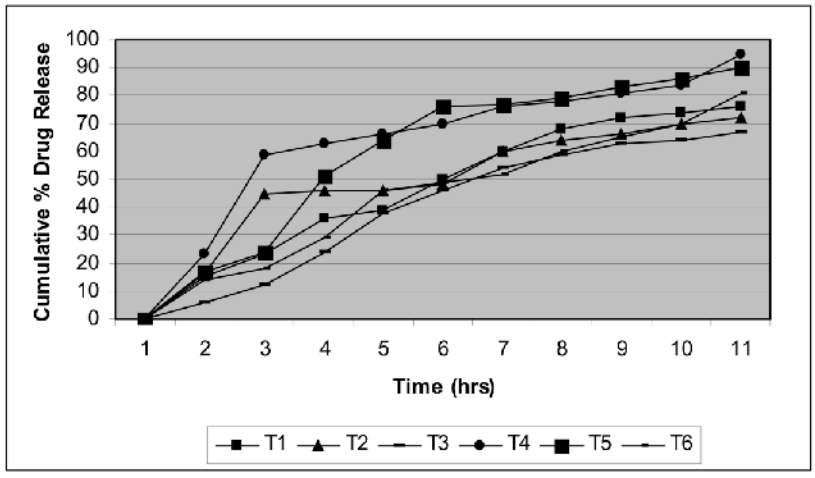


Fig. 3: Cumulative Percent Drug Released Vs Time Plots (Zero Order) of formulations T1, T2, T3,T4,T5 and T6

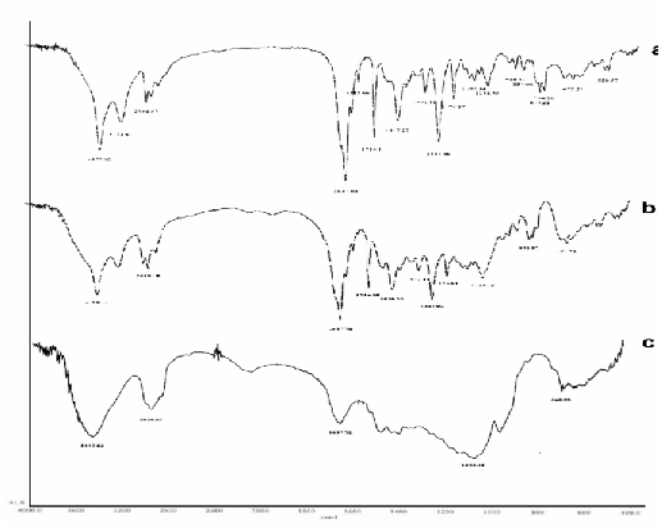
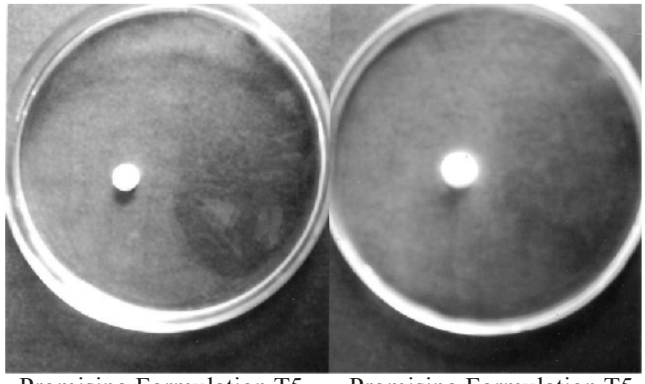


Fig. 4: Ik Spectra of (a) Atenolol IP; (b) HPMC (50 cps); (c) Formulation T5



Promising Formulation T5 Before Swelling (t= '0'min)

Promising Formulation T5 After Swelling (t= '60' min)

Fig.5: Determination of Swelling Index

Fig.6: Determination of Floating time and Floating lag time

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