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Original Article

Formulation and Evaluation of Gastroretentive Floating Drug Delivery System of Atenolol

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ABSTRACT

Atenolol is an antihypertensive drug and the elimination half life is 3-4 hours. The main aims of prepared Atenolol floating tablets are to increase the retention time in gastric and also to improve the bioavailability. Atenolol was selected as a drug because it is incompletely absorbed from the gastrointestinal tract and has an oral bioavailability of only 50% while remaining drug is excreted unchanged in feces. This is because of poor absorption in lower gastrointestinal tract. The floating Atenolol tablets were formulated by using HPMC K100M, HPMC K4M, HPMC K15M as the release retardant polymers, and sodium bicarbonate used as a gas generating agent to reduce the floating lag time. Direct compression method was used to prepared the tablets and then evaluated for friability, hardness, weight variation, total floating time, floating lag time, dissolution rate.

Keywords: Atenolol, Floating tablets, HPMC, Dissolution, Gastro Retentive.

1. INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Over 90% of the formulations manufactured today are ingested orally. This shows that this class of formulations is the most popular worldwide and the major attention of the researcher is towards this direction. Effective oral drug delivery may depend upon the factors such as

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gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed.

Dosage forms that can be retained in the stomach are called as gastroretentive drug delivery system. GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavalability. The floating tablets has bulk density lower than the gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.

Requirements for Gastric Retention[8,9]

To achieve gastric retention the dosage form must satisfy certain requirements. The dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served the device should be removed from the stomach with ease.

2. MATERIALS AND METHOD

Atenolol, HPMC K 15M, HPMC K 100M, Sodium Carbonate, Micro Crystalline Cellulose, Magnesium Sterate and Talc. All other chemicals used were of analytical grade.

METHOD

Preparation of Atenolol floating tablets

All the formulations were prepared by direct compression method using different viscosity grades of HPMC polymers in various ratios (designated as F-1 to F-8 in Table). The Atenolol and all other ingredients were individually passed through sieve ≠ 40. All the ingredients were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with talc. The single punch tablet machine (CADMACH) was used for the compression of the floating tablets. Use of ingredients in the formulation: Sodium bicarbonate was used as the gas generating agent to reduce the floating lag time. HPMC K4M and HPMC K100M were used as the release retardant polymer to obtain prolonged release of the drug up to 8 hours. Microcrystalline cellulose (MCC) was used as the diluent. Magnesium stearate and talc were used as the lubricants. The tablets were prepared by using the direct compression method.

Table 1: Composition of floating tablets of Atenolol

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Atenolol	50	50	50	50	50	50	50	50	50
HPMC K15M	50	100	150	_	_	_	_	_	_
HPMC K100M	_	_	_	50	100	150	_	_	_
HPMC K4M	_	_	_	_	_	_	50	100	150
Sodium bicarbonate	45	45	45	45	45	45	45	45	45
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Microcrystalline cellulose	154	99	49	154	99	49	154	99	49

Evaluation of Tablets [10-13]

The formulated tablets were evaluated for the following physicochemical characteristics:

General Appearance

The general appearance of a tablet, its visual identification and 'elegance' is essential for consumer acceptance. This includes tablets shape, size, colour, presence or absence of an odour, taste, texture, physical flaws, consistency and legibility of any identifying marking.

Hardness

Hardness of the tablet was determined by using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced

against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

Weight Variation

10 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it was within the permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

Friability test[14]

Friability of the tablets was determined using Roche friabilator. This device subject the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm for 4 minutes and dropping the tablets at a height of 6 inches in each revolution. Pre-weighed sampleof tablets was placed in the friabilator and were subjected to 100 revolutions. For the tablets with an average weight of 0.65g or less take a sample of whole tablets corresponding to about 6.5g and for tablets with an average weight of more than 0.65g take a sample 10 whole tablet. The friability is determined by the formula.[82]

Percentage friability = (initial weight-final weight) /initialweight × 100

Drug content

20 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of Atenolol was transferred in to a 100 ml volumetric flask and the volume adjusted to 100 ml with 0.1N hcl. Further 1ml of the above solution was diluted to 100 ml with 0.1N hcl and the absorbance of the resulting solution was observed at 224.5 nm.

***In vitro* Buoyancy studies**

The *in vitro* buoyancy was determined by floating lag time, and total floating time. The tablets were placed in a 100 ml beaker containing 0.1N hcl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and the duration of the time the tablet constantly floats on the dissolution medium was noted as the Total Floating Time respectively (TFT).

Dissolution Study [15]

Release studies were performed in USP basket method. 900 ml of 0.1N HCL was placed in the vessel and the medium was allowed to equilibrate to temp of 37+0.5 °C. Tablet was placed in the vessel and the basket, the apparatus was operated for 8 hours at 50 rpm. At definite time intervals, 5 ml of the fluid was withdrawn; filtered and again 5 ml of the fluid was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed spectrophotometrically at 224.5 nm.[83]

FTIR studies

The FTIR spectra of the drug (alone), and the drug-polymer (mixture) were recorded, From the infrared spectra it is clearly evident that there were no drug-polymer interactions of the drug.

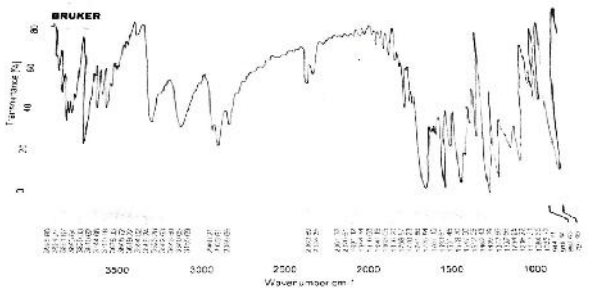

Fig 1: FTIR Peak of Atenolol

Table 2. FTIR Peak of Atenolol

Functional group	Characteristic frequency	Observed frequency
O-H	3400-3500	3443
H-N	3500-3100	3502
C-H	2900-2880	2855
C=C	1680-1620	1631
$C=CH_2$	1000-600	883

3. RESULTS AND DISCUSSIONS

Table 3. Precomposition parameter of blend

Parameters	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)	Hausner's Ratio	Angle of Repose (º)
F1	0.401±0.001	0.500±0.05	18±0.64	1.24±0.005	24.972±0.005
F2	0.400±0.002	0.491±0.05	18.5±0.64	1.22±0.005	23.534±0.005
F3	0.399±0.001	0.499±0.04	20±0.65	1.25±0.005	22.464±0.004
F4	0.397±0.001	0.495±0.04	19.7±0.63	1.24±0.004	22.822±0.004
F5	0.394±0.002	0.495±0.05	20±0.64	1.25±0.005	23.575±0.003
F6	0.404±0.001	0.505±0.05	20±0.64	1.25±0.004	21.802±0.005
F7	0.397±0.001	0.495±0.04	22±0.63	1.28±0.004	20.976±0.005
F8	0.402±0.001	0.502±0.05	20±0.63	1.25±0.003	19.479±0.005
F9	0.397±0.001	0.495±0.05	22±0.64	1.28±0.003	22.727±0.004

(Mean±S.D) (n=3)

Table 4: Post compression parameter.

Parameters	Avg.Weight	Hardness (kg/cm^2)	Friability	% Drug content (mg)	Buoyancy Lag Time (min)	Total floating time (hrs)
F1	299±0.57	7.3±0.05	0.31±0.06	99.12±0.057	5±0.05	>8
F2	303±0.57	7.4±0.05	0.51±0.05	98.11±0.057	9±0.05	>8
F3	298±0.57	8±0.04	0.51±0.05	98.01±0.056	8.2±0.04	>8
F4	289±0.56	7.5±0.04	0.31±0.06	98.45±0.056	6±0.06	>8
F5	287±0.56	7.7±0.03	0.31±0.06	99.02±0.057	6±0.05	>8
F6	302±0.55	7.4±0.05	0.41±0.06	97.12±0.055	8.3±0.04	>8
F7	292±0.56	7.3±0.05	0.31±0.05	98.11±0.057	8.5±0.04	>8
F8	293±0.57	7.9±0.05	0.41±0.05	99.06±0.056	8.6±0.05	>8
F9	285±0.57	7.7±0.05	0.31±0.05	98.12±0.055	8.5±0.05	>8

(Mean±S.D) (n=3)

Table 5: Dissolution profile data

Time	Cumulative % drug dissolved								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0

0.5	17	17	16.4	16	15	14	13	12	10
1	29.14	28.74	27.128	24.72	23.5	22.68	20.66	18.64	15.4
2	38.516	36.508	35.264	27.808	26.364	26.328	25.068	23.008	20.104
3	42.068	44.62	43.152	32.748	31.276	30.24	32.556	30.256	27.296
4	56.076	52.68	51.184	40.376	39.076	35.42	37.384	38.84	38.224
5	66.348	57.884	56.96	46.344	45.02	42.092	43.296	44.784	41.76
6	70.604	62.772	61.632	52.016	51.868	50.884	50.312	48.832	45.752
7	73.72	72.736	69.176	60.184	59.436	59.436	57.852	56.144	54.208
8	77.072	76.076	75.248	71.296	70.336	69.34	67.724	65.584	62.416

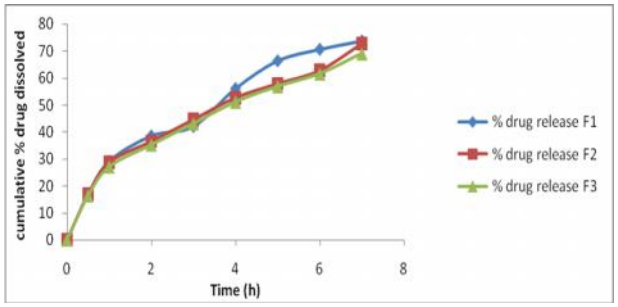

Fig 2: Dissolution profile data of F1-F3

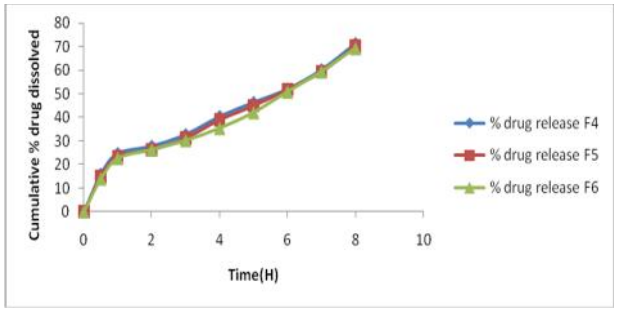

Fig 3: Dissolution profile data of F4-F5

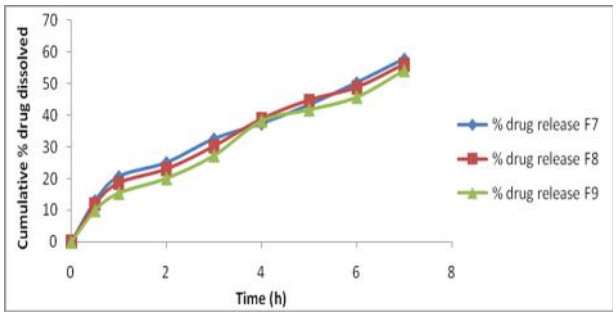

Fig 4: Dissolution profile data of F7-F8

Table 6: Regression coefficient

Formulation	R^2		
	Zero order	First order	Higuchi
F1	0.933	0.985	0.988
F2	0.920	0.986	0.955
F3	0.930	0.989	0.996
F4	0.955	0.944	0.963
F5	0.962	0.944	0.959
F6	0.961	0.944	0.946
F7	0.958	0.966	0.971
F8	0.967	0.979	0.972
F9	0.975	0.981	0.963

4. DISCUSSION

The objective of the present study was to prepare Floating tablets of Atenolol. These were developed to prolong the gastric residence time and to increase the drug bioavailability. Atenolol was chosen as a model drug because it is better absorbed in the stomach than the lower gastro intestinal tract. The tablets were prepared by direct compression technique, using polymers such as HPMC K15M, HPMC K100M, HPMC K4M and other standard excipients. Tablets were evaluated for physical characteristics such as hardness, floating capacity and weight variation. The *in vitro* release characteristics were evaluated for 8 hrs. Totally 9 different formulations of Atenolol were prepared by using three different polymers like HPMC K15M, HPMC K100M, HPMC K4M and diluent microcrystalline cellulose in different concentrations. The amount of drug released from all the formulations depends upon the concentration of the polymer used. Finally, the retardant effect of the polymer on the drug release can be indicated as

HPMC K15M > HPMC K100M>HPMC K4M.

The data from in vitro study was fitted into equation for the zero-order, first-order and higuchi release model and regression coefficient values were computed and results are shown in Table 5 However drug release was also found to be very close to zero order kinetic, indicated that concentration was nearly independent of drug release.

5. CONCLUSION

The Atenolol is a selective β1-adrenoreceptor blocking agent which is used in the treatment of hypertension. In this study Atenolol tablets were prepared by using different polymers like HPMC K15M, K100M and HPMC K4M. Eight formulations of floating tablets of Atenolol were developed by direct compression method. The best formulation F1 can successfully be employed as a controlled release floating drug delivery system. The floating tablets of Atenolol increase the gastric residence time and eventually improve the bioavailability of the drug. Based upon the FTIR studies we conclude that there is no drug excipients interaction. The F1 Formulation was found to be best, Floating lag time decreased because of the concentration of sodium bicarbonate. In which the amount of polymer in the tablet formulation decreased and then increased the drug release of the tablets.

The stability method can be defined as validated quantitative analytical method that can detect the change with the time in the chemical, physical or microbiological properties of the drug substance and drug product. When the formulation was stored at accelerated condition (45±2 ^{0}C and 75±5% RH) for

three months. Stability studies showed no significant changes were observed.

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