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Formulation Development and In-Vitro Evaluation of Gastroretentive Floating tablets of Atenolol

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Abstract
The purpose of the study was to prolong the gastric residence time and increase the bioavailability of atenolol by designing its floating tablets and to study the influence of different polymers on its release rate. It was selected as a model drug, because it is poorly absorbed from the lower GIT. The tablets were prepared by direct compression technique, using different polymers such as hydroxy propyl methyl cellulose (HPMC K4M, K15M), Guargum (GG) and sodium bicarbonate alone or in combination, and other standard excipients. The physical characteristics of tablets were evaluated viz. hardness, thickness, weight variation, swelling index and floating capacity. Further, tablets were evaluated for *in-vitro* drug release characteristics for 12 hr. The effect of effervescent on buoyancy and drug release pattern was also studied. *In vitro* drug release mechanism was evaluated by linear regression analysis. The formulation used by high percentage of guargum provides significantly greater swelling index compared with other formulations. The tablets were exhibited desired floating and prolonged drug release up to 12 hrs.
Keywords: Atenolol, Floating tablets, swelling Index, HPMC K4M and K15M, Sodium bicarbonate.

INTRODUCTION

Drug that are easily absorbed from the gastrointestinal tract and have a short half-life are eliminated quickly from the blood circulation, so they require frequent dosing. To avoid this drawback, the floating drug delivery system formulations have developed in an attempt to release the drug slowly in to the gastro intestinal track and maintain an effective drug concentration in the serum for long period [1, 2]. Floating drug delivery systems (FDDS) were first described by Davis in 1968 [3, 4]. It is possible to prolong the gastric residence time of drugs using these systems, and beside this, other systems include swelling, inflation, adhesion, high-density systems and low density systems that increase the gastric residence time [5, 6, 7]. Gastric retention is useful for drugs which (i) act locally (ii) unstable in the intestinal environment (iii) have a narrow therapeutic absorption window in the small intestinal region (iv) low solubility at high pH environment [8].

Atenolol is a cardio selective β-1 adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic activities and it has been used for the treatment of hypertension [9]. It is poorly absorbed from the lower gastrointestinal tract. The oral bioavailability of atenolol has been reported to be 50% [10]. The human jejunal permeability and extent of adsorption is also low [11]. Thus, it seems that an increase in GRT may increase the extent of absorption and bioavailability of the drug. The drug is slightly water soluble and has elimination half life, after an oral dose, of six to seven hours. It is prescribed widely in diverse cardiovascular diseases, for example hypertension, arrhythmias, angina pectoris, and myocardial infarction [12, 13].

Based on this, an attempt was made through this investigation to formulate floating tablets of Atenolol using different polymers and their combinations. The prepared tablets were evaluated for physical characteristic such as weight variation, hardness, thickness, drug content uniformity, floating capacity, and swelling index. All the tablets were evaluated for *In-vitro* drug release.

MATERIAL AND METHODS

Material

Atenolol received as gift sample from Zydus-cadila, Ahmadabad, India. Other chemicals and polymers such as hydroxy propyl methyl cellulose (HPMC K4M and K15M), were obtained from the Dow chemicals, USA. Guargum and Sodium bicarbonate were received from Loba chemical Pvt, Ltd., Mumbai, India. Avicel supplied by BASE chemicals, Switzerland.

Methods

Atenolol floating tablets were prepared by direct compression method using sodium bicarbonate as gas-generating agent. HPMC K4M, HPMC K15M and guargum were used as rate controlling polymers. All the ingredients were weighed accurately and mixed homogeneously in the

Table 1: Composition of Atenolol floating tablets formulations

S.no	INGREDIENTS	Quantity used in mg						
		F1	F2	F3	F4	F5	F6	F7
1	Drug	50.0	50.0	50.0	50.0	50.0	50.0	50.0
2	HPMC K4M	26.0	25.4	24.2	24.7	25.6	26.4	24.0
3	HPMC K15M	41.0	48.9	37.2	36.0	42.4	36.8	39.0
4	Guargum	6.5	6.0	10.5	11.5	6.5	10.0	9.5
5	$NaHCO_3$	22.5	25.8	26.0	24.8	22.5	24.4	24.9
6	Avicel pH 102	52.0	51.9	50.1	51.0	51.0	50.4	50.6
7	Mg Stearate	2	2	2	2	2	2	2

weight proportion mentioned in Table 1. Drug and excipients were passed through sieve no 80#. These ingredients were mixed uniformly for 3 minutes. Then the powder blend was lubricated with magnesium stearate, and compressed with the help of CDM3-16 station rotary tablet compression machine using flat-faced punches (diameter 12mm).

Measurements of flow properties

The flow properties of granules (before compression) were characterized in terms of Angle of repose [14], Tapped density, Bulk density [15], Carr's Index and Hausner ratio [16].

Weight variation and hardness

Weight variation test was done as per USP methods (Shimadzu, Japan), Hardness was measured with Monsanto Tester (Paramount science Instruments, India) and Thickness was done by Screw-gauge micrometer (Campbell Electronics, Mumbai, India.)

Assay of tablets

Six tablets from each batch were weighed and powdered. Powder equivalent to the average weight of the tablet was accurately weighed and transferred into a 100ml volumetric flask and dissolved in a suitable quantity of buffer pH 1.2. The solution was made up to the mark and mixed well. A portion of the sample was filtered and analyzed by a UV spectrophotometer (Double beam 1700, Shimadzu, Japan) at 224nm.

Buoyancy/Floating Test

In vitro buoyancy studies were performed for all the formulations as per the method described by Rosa et al [17]. The randomly selected tablets from each formulation was determined by using the USP (Type II) dissolution apparatus containing 900ml 0.1N HCl at 75rpm. The time (minutes) taken by the tablet to reach the top from the bottom of the flask (Floating Lag Time or FLT) and the time for which the tablet constantly floated on the surface of the medium (duration of floating or Total floating time (TFT)) was measured.

Swelling index

The swelling index of the tablets was determined in 0.1N HCl (pH 1.2) at room temperature. This property of the formulation was determined by various techniques [18].The water uptake study of the tablet was done using USP dissolution apparatus II. The medium used was 0.1N HCl, 900 ml, rotated at 50rpm. The medium temperature was maintained at 37 ± 0.5° C throughout the study. After selected time intervals, the tablets were withdrawn, blotted to remove excess water, and weighed. The swelling characteristics of the tablets were expressed by the following equation,

$$\text{Swelling index} = \frac{(\text{Weight of the swollen tablets} - \text{Initial weight of the tablets}) \times 100}{\text{Initial weight of the tablets}}$$

***In vitro* release**

The *In- vitro* release study for all the formulations were carried out USP dissolution apparatus (Type II). The dissolution medium was used pH 1.2 (900ml). The rotation speed was 50rpm. The temperature was maintained at 37 ± 0.5^{o} C. Five milliliters of sample was withdrawn at predetermined time intervals and the volume of the dissolution medium was maintained by adding the same volume of fresh prewarmed buffer every time. The absorbance of the withdrawn samples was measured spectrophotometrically at 224nm.

Release kinetics

Release kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero order (cumulative amount of drug release versus time) [19], first order (log cumulative percentage of drug remaining versus time) [20], Higuchi square root (cumulative percentage of release versus square root of time) [21] and Korsmeyer- Peppas model (log cumulative percentage of drug released versus log time) [22] .The criteria for selecting the most appropriate model was chosen on the basis of goodness of fit test.

Table 2: Evaluation of flow properties*

S.no	Angle of repose (Ø)	Tapped Density (g/ml)	Bulk Density (g/ml)	Compressibility Index (%)	Hasuren's Ratio
1	21.15±0.29	0.512±0.02	0.541±0.01	24.24±0.05	1.10±0.004
2	25.44±0.25	0.540±0.01	0.430±0.02	21.15±0.02	1.39±0.002
3	22.35±0.25	0.419±0.04	0.422±0.04	26.73±0.01	1.60±0.005
4	21.30±0.11	0.496±0.02	0.583±0.05	24.05±0.02	1.81±0.001
5	24.19±0.02	0.483±0.02	0.525±0.04	20.19±0.01	1.19±0.004
6	26.19±0.41	0.519±0.05	0.571±0.02	21.07±0.04	1.15±0.002
7	25.67±0.25	0.455±0.01	0.467±0.01	22.52±0.04	1.39±0.002

* All values are expressed as mean ± SD n=5.

RESULT AND DISCUSSION

Evaluation of Atenolol Granules

The granules of various formulations were prepared and evaluated for the bulk density, tapped density, compressibility index, and hausner's ratio. The results of angle of repose (Ø) ranged from 21.15± 0.29 to 26.67 ± 0.25. Bulk density and tapped density were found 0.421 ± 0.06 to 0.538 ± 0.03g/ml and 0.419 ± 0.04 to 0.540 ± 0.01 g/ml. The bulk density depends on particle size, shape and cohesiveness of the particles. The Hausner's ratio was found from 1.19 ± 0.004 to 1.39 ± 0.002, which is well within the specified 1.50 and the granules is possible. The addition of glidiant normally improves the flow during possible. The compressibility index (%), ranged from 20.19 ± 0.01 to 26.73 ± 0.01 as indicates pass to possible flow properties. All these results were given in Table 2.

Weight variation and Assay of tablets

The percentage of weight variation of each tablet from average was less than 5%, which proved good uniformity. The assay for drug content in all the batches of atenolol tablets was in the range 90 to 110% (i.e., a variation of ± 5%).

Hardness and thickness

The hardness of prepared tablets was observed within the range of 2.5-3.5 kg/cm2. Thickness of all tablets was found in the range of 3-4mm.

Buoyancy/Floating Test

Floating test of fabricated tablets was determined in 0.1N HCl and the result was shown in Table 3. The formulation containing high percentage HPMC K4 exhibited FLT of 28 sec. incorporation of high concentration sodium bicarbonate in this formulation, shows less FLT. Tablets of batches F 2 and F 3 showed less FLT and less floating duration. The incorporation of percentage guargum to formulations containing HPMC K4M and HPMCK15M, increased the floating duration. HPMC takes more time in swelling and is also able to maintain the integrity of the tablets.

Table 3: Evaluation of atenolol floating tablets formulations

Parameters	F 1	F 2	F3	F4	F 5	F 6	F 7
FLT (sec)	21	7.5	10	16	13	28	17
Floating duration (hrs)	24	18	23	24	24	21	18

Swelling index

Tablet composed of polymeric matrices build a gel layer around the tablets core when they come in contact water. This gel layer govern 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[19]. Guargum based formulations F3, F4 showed higher swelling index and faster rate of swelling. The combination of HPMC K15M and K4M resulted in a higher swelling index compared with HPMC K15M alone. HPMC K15M exhibited low swelling index, but there was no decrease in swelling rate, because it has high viscosity and high water retention property.

In vitro releases

Floating formulation mainly affected by physiological conditions such as food transport, gastrointestinal motility, and so on[23]. A study on floating tablets of Atenolol has indicated lower bioavailability of drug. The reason for this lower bioavailability is attributed to small size of the dosage form, causing too short residence time.

Different polymers and their combinations were used in the formulation of floating tablets. It was observed that the type of polymer influences the drug release pattern. The percentage release profile was shown in Table 4. A significantly higher rate and extent of drug release was observed from batches based on Guargum and sodium bicarbonate than based on HPMC. The combination of high percentage Guargum and sodium bicarbonate formulations (F4, F6, and F7) were provide drug release for longer time, different concentration of HPMC K15M did not affect the drug release. HPMC K15M formulatins

drug release was lesser owing to its high viscosity. But, addition of HPMC K4M increased the drug release, but the increase was not significant. The percentage of drug release at the end 12hr was found to be 92%, 100% from batches. F7, F6.

Release kinetics

The drug release kinetics of Atenolol, release data was analyzed according to different kinetic equations. Such as zero order, first order, Higuchi's model, Korsmeyer-peppas, and Hixson-crowell. The data were analyzed by the regression coefficient method and regression coefficient value (r^2) of all batches is shown in Table 5. The formulations F4, F6 and F7 were followed Korsmeyer–peppas model, whereas remaining all the formulations showed Higuchi's release kinetics. The in vitro release profiles of drug from all these formulations could be best expressed by Higuchi's equation as the plots showed highest linearity (r^2=0.95 to 0.99). To confirm the diffusion mechanism, the data were fitted into Korsmeyer-Peppas equation. The formulations showed good linearity (r^2 = 0.965 to 0.98) with slope (n) between 0.469 - 0.558.

Table 4: Percentage drug release of Atenolol floating tablets

Time (hrs)	Percentage drug Release *						
	F 1	F2	F3	F4	F5	F6	F7
0.5	21±1.19	19±0.92	26±1.98	21±1.46	15±1.71	23±1.14	19±1.68
1	34±2.50	21±1.85	38±2.14	30±1.30	25±1.69	38±1.71	27±1.20
2	38±1.23	32±1.63	46±1.95	43±2.50	41±2.16	44±1.96	40±1.89
4	45±1.66	40±2.37	52±2.07	54±1.53	54±1.96	55±1.37	46±2.17
6	64±1.20	58±1.07	67±1.76	76±1.44	67±0.91	84±2.08	81±1.28
8	77±2.85	64±1.85	71±1.87	78±2.37	74±1.20	87±1.57	86±1.86
12	86±1.32	76±1.76	88±1.79	91±1.40	88±1.55	100±1.49	92±2.05

* All values are expressed as mean ± SD n=5.

Table 5: Release kinetics data for different formulations

S.no		Formulations						
		F1	F2	F3	F4	F5	F6	F7
1.	Zero order							
	r^2	0.865	0.8157	0..5187	0.7752	0.8382	0.7673	0.8687
	K	5.732	6.2498	7.4664	7.9868	7.4532	8.7398	8.2479
2.	First order							
	r^2	0.447	0.478	0.395	0.4622	0.5037	0.4505	0.588
	K	3.5339	3.7497	3.3967	3.4872	3.6219	3.3928	3.5591
3.	Higuchi							
	r^2	0.9644	0.9515	0.9533	0.9672	0.9829	0.9531	0.9705
	K	0.0462	0.0543	0.0441	0.0423	0.0458	0.0386	0.0411
4.	Korsmeyer-peppas							
	N	0.558	0.469	0.632	0.619	0.449	0.612	0.667
	K	16.70	17.32	18.91	19.69	17.46	20.09	20.84
	r^2	0.988	0.975	0.985	0.977	0.965	0.991	0.993

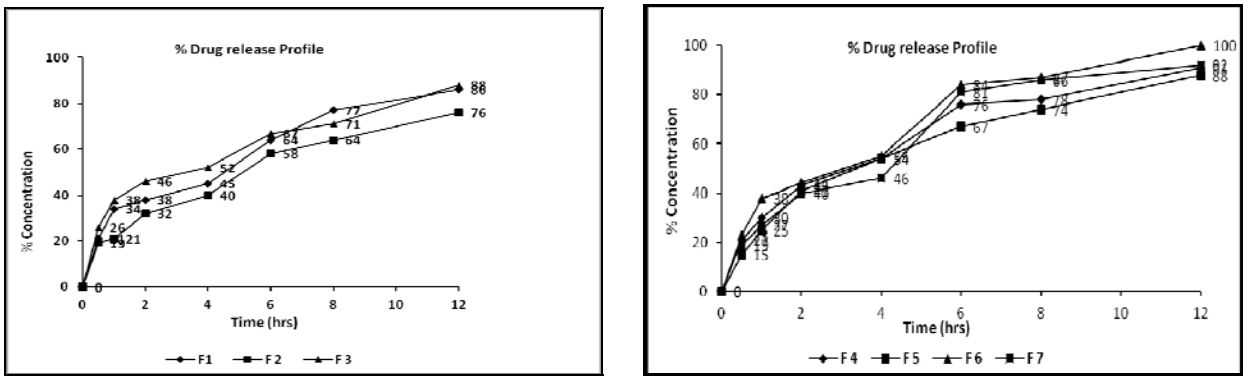

Figure: 1. Dissolution profiles of Atenolol floating tablets

CONCLUSION

The gastroretentive floating tablet of atenolol 50 mg were formulated as an approach to increase gastric residence time and thereby improve its bioavailability. The hydroxy propyl methyl cellulose polymers (HPMC K4M and HPMC K15M), showed better control over the drug release. Formulated tablets were showed acceptable weight variation, hardness and uniformity of drug content. A lesser FLT and a prolonged floating duration could be achieved by sodium bicarbonate and GG exhibited higher swelling index. Formulation F4, F6, F7 gave better controlled release compared to other formulations. Polymer swelling is crucial in determining the drug release rate and is also important for flotation. The release kinetics data was analyzed according to different kinetic equations. The data were analyzed by the regression coefficient method and regression coefficient values (r2) of all batches are shown in Table 6. Analyze the regression coefficient value for all batches. The formulations F4, F6 and F7 were followed Korsmeyer –peppas model, whereas remaining all the formulations showed Higuchi's release kinetics. The formulations showed good linearity (r^2 = 0.95 to 0.98) with slope (n) between 0.470-0.586. The objective of formulating a floating dosage form of Atenolol by using optimized techniques has been achieved.

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