Research Article

FORMULATION AND EVALUATION OF FLOATING MATRIX TABLET OF ATENOLOL FOR GASTRO-RETENTIVE DRUG DELIVERY

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ABSTRACT

The purpose of this research was to develop gastro-retentive delivery system of atenolol which, after oral administration should have the ability to prolong gastric residence time with desired *in vitro* release profile. Atenolol was chosen as a model drug because it is poorly absorbed from the lower gastrointestinal tract. The tablets were prepared by direct compression technique, using natural gum such as xanthan gum and guar gum, alone or in combination. The tablets were evaluated for physical characteristics viz. hardness, friability, weight variation, content uniformity, and floating capacity. Further, tablets were evaluated for *in vitro* release characteristics for 8 hr. Among all the formulations, tablets containing combination of xanthan gum and guar gum showed better floating capacity as well as sustained release of atenolol at the end of 8 hr. The mechanism of release of atenolol from the floating tablets was found to be diffusion couple with erosion. It was concluded that the tablets prepared by combination of xanthan gum and guar gum had efficient floating and sustained release capacity as compared to tablets prepared by using natural gum alone.

Keywords: Atenolol, Gastro-retentive floating tablet, Xanthan gum, Guar gum

INTRODUCTION

Atenolol is a cardioselective β-blocker widely prescribed for asymptomatic condition such as hypertension. It is poorly absorbed from the lower gastrointestinal tract. The oral bioavailability of atenolol was reported to be 50%[1]. The human jejunal permeability and extent of absorption is low[2]. Thus, it seems that an in gastric residence time may increase the extent of absorption and bioavailability of drug. The recommended adult oral dosage of atenolol is 50 mg twice daily for the effective treatment of hypertension. However, fluctuations of drug concentration in plasma may occur, resulting in side effects or a reduction in drug concentration at receptor side. As the drug is effective when the plasma fluctuations are minimized, therefore sustained release dosage form of atenolol is desirable. The short biological half life of drug (6 to 8 h) also favors development of sustained release formulations.

There are several approaches have been reported for prolonging the residence time of drug delivery system in a particular region of the gastrointestinal tract, such as floating drug delivery systems, swelling and expending systems, polymeric bioadhesive systems, swelling and expanding systems, modified shape systems, high density systems and other delayed gastric emptying devices[3]. Floating drug delivery system or hydrodynamically balanced systems were first described by Davis (1968). The floating of FDDS occurs due to their lower bulk density than the gastric contents or due to gaseous phase formed inside in the environment[4,5]. It is applicable for those drugs which (i) act locally; (ii) have a narrow absorption window in the small intestinal region; and (iii) unstable in the intestinal environment[6].

In recent years, the natural hydrophilic polymer based matrix tablets as carrier for controlled release delivery has been widely and successfully use due to their ease of manufacturing, relatively low cost, favorable *in vivo* performance and versatility in controlling the release of drug with wide range of physicochemical properties[7]. Natural gums are biodegradable and non toxic, which hydrate and swell on contact with aqueous media and these have been used for the preparation of dosage form[8]. Xanthan gum is a linear, high molecular weight extracellular heteropolysaccharide, produced commercially by viscous fermentation of gram negative bacterium *Xanthomonas campesteris*. The molecule consists of backbone identical to that of cellulose, with side chains attached to alternate glucose residues[9]. It is a hydrophilic polymer widely used as thickening agent in the food industry, and in the pharmaceutical industry, it is used as a hydrocolloid to thicken, suspend, emulsifying, and stabilize water-based systems[10]. Xanthan gum has been also used as effective excipients for sustained release formulation; it not only retards drug release, but also provides time-independent release kinetics[11,12]. Guar gum is an interesting excipients for preparation of hydrophilic matrix tablets because of its unique properties such as swelling, gel formation, non toxicity and biodegradability. Guar gum is a polysaccharide, found in the seeds of the plant *Cyamopsis tetragonolobus*. Researchers have been used guar gum, either alone[13,14], or in combination,[15,16] for fabricating sustained release dosage forms.

In the present research work an attempt was made to prepare floating tablets of atenolol using xathan gum and guar gum alone and their combination. The prepared tablets were evaluated for physical characteristics such as hardness, weight variation, drug content uniformity, and floating capacity. All the tablets were evaluated for *in vitro* release characteristics.

MATERIALS AND METHODS

Atenolol was obtained as gift sample from Cipla Ltd, Mumbai, India. Xanthan gum and guar gum were purchased from Himedia, Mumbai, India. Sodium bicarbonate was received from B. D Pharmaceutical Works, Howrah, India. Citric acid and magnesium stearate were obtained from Loba Chemie Pvt Ltd., Mumbai, India. Talc was purchased from Nice Chemie Pvt. Ltd., Mumbai, India. Lactose was purchased from Reidel India Chemicals, Mumbai, India.

Methods

Calculation of theoretical release profile of atenolol from matrix tablets

The total dose of atenolol for twice a day sustained release formulation was calculated as per Robinson Eriksson equation[17] using available pharmacokinetic data[18]. Pharmacokinetic studies show that 25 mg of atenolol produce expected therapeutic effects within 2 h with a half life of 6 h. Thus, the first order overall elimination rate constant, $k_e=0.693/6=0.1155$ mg/h. Hence, the availability rate $R=k_eD=0.1155\times25=2.8875$ mg/h where, D is the initial dose of drug. The maintenance in conventional dose $D_m=Rh=2.8875\times11=31.7625$ mg, where h is the number of hours for which sustained action is desired. Thus, total dose$=D+D_m=25+31.7625=56.7525$. $D_{corrected}=D-Rt_P=56.7625-2.8875\times2=50.9875$ mg where t_P is the time period required to achieve a peak plasma level. Hence an oral controlled release formulation of atenolol should contain a total dose of 50.9875 mg ($\approx$50mg) and should release 25 mg in 1 h like conventional tablets, and 2.8875 mg per hour up to 12 h thereafter.

Preparation of floating table

Floating matrix tablet of atenolol were prepared by direct compression method according to the formula given in Table 1. Atenolol (50 mg) was mixed with the required quantity of polymer xanthan gum and guar gum alone or in combiantation, sodium bicarbonate (14 mg), citric acid (7 mg), and lactose in mortar and pastel for 15 min. The powder blend was then lubricated with talc (2.8 mg) and magnesium stearate (1.4 mg) for additional 3 min and prior to the compression; the prepared powder blend was evaluated for several tests as mentioned below. The powder blend was then compressed into tablets manually on single punch tablet punching machine (Kilburns, Allahabad, India) using 6 mm standard flat punch.

Evaluation of powder blend

Bulk density and tapped density

Both poured (or fluff) bulk (D_o) and tapped bulk densities (D_F) were determined, according to the method reported by Raghuram et al.[19], whereby a quantity (3 g) of granules from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 mL measuring cylinder. After the initial volume was observed, the cylinder allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in the volume was noted. The value of bulk density and tapped density were calculated by using equation:

$$\text{Bulk density } (D_O) = \frac{\text{Weight of powder}}{\text{Volume of powder}} \qquad (1)$$

$$\text{Tapped density } (D_F) = \frac{\text{Weight of powder}}{\text{Volume of powder after tapping}} \qquad (2)$$

Compressibility index

The Carr's compressibility index and Hausner's ratio were calculated from the values of bulk density and tapped density[20].

$$\text{Compressibility \%} = \frac{D_F - D_O}{D_F} \times 100 \qquad (3)$$

$$\text{Hausner's ratio} = \frac{D_F}{D_O} \qquad (4)$$

Evaluation of tablet

Prepared tablet were evaluated for quality control tests like weight variation test, hardness test, friability test, content uniformity study, and *in vitro* release study.

Weight variation test

To study weight variation, tablets from each formulation were selected at random and average weight was determined using an electronic balance. Then individual tablets were weighed and the individual weight was compared with an average weight. Weight values were reported in mg. Mean and SD were calculated.

Hardness test

For each formulation, the hardness of six tablets was determined using a hardness tester (Monsento, Mumbai, India). Hardness values were reported in kg/cm^2. Mean and SD were calculated.

Friability test

For each formulation, six tablets were weighed. The tablets were placed in a Roche friabilator (Labotech, Mumbai, India) and subjected to 100 rotations in 4 min. The tablets were then dedusted and reweighed. The friability was calculated as the percent weight loss.

Drug content uniformity study

Five tablets were weighed individually, then placed in a mortar and powdered with a pestle. An amount equivalent to 25 mg drug (100 mg) was extracted with 100 mL of 0.1M HCl (pH 1.2), stirred for 15 min using magnetic stirrer (Labotech, Mumbai, India). The solution was filtered through a filter (0.22 μm pore size), properly diluted with 0.1 M hydrochloric acid and the drug content was measured using UV-VIS spectrophotometer at 225 nm.

Buoyancy study

The *in vitro* buoyancy was characterized by floating lag time and total floating time. The test was performed using USP 24 type II apparatus (Timestan, Kolkata, India) at 100 rpm in 900 mL of 0.1M HCl (pH 1.2) maintained at 37±0.5°C. The time required for tablet to rise to the surface of dissolution medium and duration of time the tablet constantly float on dissolution medium were noted as floating lag time and total floating time, respectively ($n = 3$)[21].

In vitro drug release study

The *in vitro* drug release study was performed using USP 24 type II apparatus (Timestan, Kolkata, India) at 50 rpm in 900 mL of 0.1M HCl (pH 1.2) maintained at 37±0.5°C. The samples were withdrawn at predetermined time intervals for period of 8 hr and replaced with the fresh medium. The samples were filtered through 0.45 μm membrane filter, suitably diluted and analysed at 225 nm using double beam UV-VIS spectrophotometer (Thermo electron corporation, Mumbai, India). The content of drug was calculated using equation generated from calibration curve. The test was performed in triplicate and the mean value was used to construct the release profile.

Determination of release kinetics and release mechanism

The rate and mechanism of release of atenolol from the prepared floating tablets were analyzed by fitting the dissolution data into following equations:

$$\text{Zero order kinetics: } F = k_o t \qquad (5)$$

$$\text{First order kinetics: } \ln(1 - F) = -k_1 t \qquad (6)$$

To describe the drug release behavior from polymeric systems, the dissolution data were also fitted according to the well-known exponential Korsmeyer-Peppas equation[22].

$$M_t/M_\infty = kt^n \qquad (7)$$

Where M_t/M_∞ is the fraction of drug release at time t, and k is the kinetic constant, n is the release exponent (indicating the general operating release mechanism). For tablets, depending on the aspect ratios, n value between 0.43 and 0.5 indicating Fickian (case I) diffusion-mediated release, non-Fickian (Anomalous) release, coupled diffusion and polymer matrix relaxation, occurs if $0.5 < n < 0.89$, purely matrix relaxation or erosion-mediated release occurs for n=1 (zero-order kinetics), and super case II type of release for n>0.89.

Statistical analysis

To evaluate contribution of each factor with different levels on responses, two way analysis of variance (ANOVA) was performed using Sigma Stat software (Sigma Stat 2.03, SPSS, Chicago, Illinois, USA).

RESULTS AND DISCUSSION

Atenolol floating tablets were prepared by using xanthan gum and guar gum as a polymeric retardant materials and sodium bicarbonate and citric acid as gas forming agent to float the tablets in stomach. Carbon dioxide which is formed by combination of citric acid with sodium bicarbonate is just entrapped by the polymer and decreases the density of tablet below the density of gastric fluid which results in floating of the tablet.

The micromeritics parameters of the powder blend of different formulation batches are shown in Table 2. Angle of repose and compressibility index was found to be in the range of 31.54°±2.87 to 36.97°±0.57 and 14.51±0.20 to 22.16±0.68, respectively. The bulk density and tapped density of the prepared powder blend was fond to be in the range of 0.70±0.01 to 0.90±0.01 gm/cm^3 and 0.87±0.02

to 1.06±0.02 gm/cm³, respectively. The result of angle of repose indicates good flow property of the granules and the value of compressibility index further support for the good flow property.

The tablets of all formulations was found to be off white, smooth, flat faced circular with no visible cracks. The physicochemical properties of all the formulations are shown in Table 3. The hardness of the tablets was measured by Monsento hardness tester and was found in between 2.76±0.79 to 3.62±0.42 kg/cm². The friability was measured by Roche friabilator and was found to be within acceptable range. The weight variation of the tablet formulations was found to be in the range of 137.72±1.48 to 141.08±1.29 mg. The drug content estimations showed values in the range of 97.31±1.03% to 102.44±2.65%, which reflects good uniformity in drug content among different formulations. All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality.

All the tablets were prepared by effervescent approach. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1M hydrochloric acid). The combination of sodium bicarbonate and citric acid provided desired floating ability and therefore this combination was selected for the formulation of the floating tablets. It was observed that formulation S1 and S4 content little amount of polymeric material; therefore unable to hold the carbon dioxide within the tablet matrix as a result they are not floated. Whereas, all the other formulations shows appreciable floating lag time less than 6 min. Table 3 shows formulations S6 and S7 are able to float above the dissolution medium for more than 8 hr, which is our desired goal.

In vitro dissolution studies of all the formulations of floating tablets of atenolol were carried out in 0.1N HCl solution (pH 1.2). The *in vitro* release profile of the different formulations is shown in Figure 1. The release profile of different formulations shows that S1 and S4 released the whole drug within 6 h. Formulation S2, S3, S5, S6 and S7 released the drug within the range of 70-80 % within the time of 8 h. Whereas, formulation S2, S3, S5 and S6 shows burst release of drug. The formulation S7 released the drug in the same manner of theoretical release profile as calculated using Robinson Erickson equation.

The *In vitro* drug release data was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of zero order and first order plots were compared, it was observed that 'r' values of zero order plots were in range of 0.946 to 0.998 for the formulations S1, S2, and S3 indicating drug release from formulations was found to follow zero order kinetics. Whereas formulations S4, S5, S6, and S7 shows 'r' values of first order plots in the range of 0.832 to 0.989, indicating drug release form formulations was found to follow first order kinetics.

It is notable that the 'r' values of the linear regression for Higuchi's plot were found to be in the range of 0.821 to 0.961 indicating that the data fits the Higuchi's model well and the drug release was found to be predominantly controlled by diffusion process.

When the *In-vitro* dissolution data were fitted to exponential model, the 'r' values were found to be in range of 0.904 to 0.998 in most of the formulations, indicating the data fits the exponential model well. The slopes (n) values of exponential equation were found to be <0.45 indicating the drug release is governed by Fickian diffusion mechanism except in formulation F7 the n vale was found to be >0.45 to <0.89 indicating the drug release is governed by non-Fickian diffusion.

Table 1: Composition of different formulations tablets

Ingredient	Formulation						
	S1	S2	S3	S4	S5	S6	S7
Atenolol	50	50	50	50	50	50	50
Xanthan gum	14	28	42	-	-	-	14
Guar gum	-	-	-	14	28	42	14
Sodium bicarbonate	14	14	14	14	14	14	14
Citric acid	07	07	07	07	07	07	07
Talc	2.8	2.8	2.8	2.8	2.8	2.8	2.8
Magnesium stearate	1.4	1.4	1.4	1.4	1.4	1.4	1.4
Lactose	50.8	36.8	22.8	50.8	36.8	22.8	36.8
Total weight	140	140	140	140	140	140	140

Table 2: Micromeritics properties of powder blend of different formulation (S1-S7)

Parameter	Formulation						
	S1	S2	S3	S4	S5	S6	S7
Angle of repose (º)	33.51±1.64	33.00±3.16	31.54±2.87	36.97±0.57	34.10±1.10	36.25±0.95	36.42±0.64
Bulk density (gm/cm³)	0.82±0.01	0.82±0.01	0.90±0.01	0.70±0.01	0.75±0.02	0.72±0.01	0.82±0.02
Tapped density (gm/cm³)	1.02±0.01	1.03±0.01	1.06±0.02	0.87±0.02	0.97±0.04	0.98±0.02	0.99±0.03
% compressibility	19.11±1.17	20.43±1.15	14.51±0.20	18.82±3.41	22.16±0.68	21.56±3.21	20.23±0.75
Hausner's ratio	1.23±0.01	1.26±0.02	1.17±0.01	1.23±0.05	1.19±0.01	1.26±0.02	1.19±0.01

Table 3: Physicochemical and buoyancy properties of the tablets of different formulations (S1 to S7).

Parameter	Formulation						
	S1	S2	S3	S4	S5	S6	S7
Hardness (kg/cm²)	3.62±0.42	3.48±0.34	2.94±0.81	3.01±0.25	2.96±0.56	2.76±0.79	3.08±0.16
Weight variation (mg)	140.26±1.89	137.72±1.46	138.12±0.89	141.08±1.29	139.26±2.01	138.45±1.08	139.0±1.97
Friability (%)	0.42±0.02	0.28±0.03	0.20±0.02	0.08±0.01	0.09±0.03	0.07±0.01	0.05±0.003
Content uniformity (%)	99.95±1.89	101.21±2.06	99.01±0.92	97.31±1.03	102.44±2.65	98.78±0.71	99.82±0.54
Floating lag time (min)	-	5.12±0.56	6.23±0.42	-	3.12±0.23	5.06±0.51	5.36±0.41
Floating time (h)	-	5.06±0.29	6.28±0.49	-	6.39±0.38	8.82±0.53	12.23±0.44

Table 4: *In vitro* release kinetics parameters

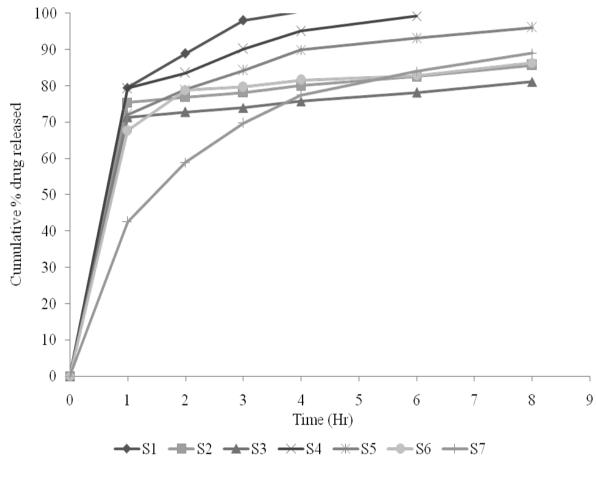| Formulation	Zero order		First order		Higuchi		Korsemeyer-Peppas	
	k_0	R^2	k_1	R^2	k_H	R^2	n	R^2
S_1	7.197	0.946	0.516	0.927	21.91	0.975	0.361	0.983
S_2	1.455	0.998	0.033	0.991	5.600	0.977	0.128	0.909
S_3	1.391	0.998	0.025	0.994	5.357	0.977	0.129	0.909
S_4	4.129	0.950	0.291	0.954	14.58	0.978	0.270	0.964
S_5	3.290	0.892	0.121	0.989	13.28	0.961	0.286	0.989
S_6	2.082	0.725	0.043	0.832	8.617	0.821	0.213	0.904
S_7	6.140	0.861	0.100	0.978	25.00	0.943	0.587	0.992

Fig. 1: *In vitro* release profile of atenolol from different formulations (S1-S7)

CONCLUSION

In the present study gastro-retentive floating tablets of atenolol were successfully prepared by direct compression method using natural gums like xanthan gum and guar gum. Fabricated tablets showed acceptable weight variation, hardness, and uniformity of drug content. The overall results explained that the tablets prepared by combination of xanthan gum and guar gum could be more efficient on floating and sustained release of atenolol as compared to the tablets prepared by using natural gum alone. Thus, proper selection of the ratio of xanthan gum and guar gum, desired drug release was achievable. Extensive studies on similar formulations are essential to establish a successful formulation from the biopharmaceutical viewpoint.

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