Original Article

Dual-pulse Release System of Atenolol: Preparation and *in-vitro* Characterization

Sonam Sanjayrao Kunjekar, Dilesh Jagdish Singhavi*, Tejaswini Balkrishna Parshuramkar, Shagufta Khan

Institute of Pharmaceutical Education and Research, Borgaon (Meghe), Wardha, Maharashtra, INDIA.

ABSTRACT

Aim: Hypertension exhibits a circadian rhythm and drugs need to be released at the time when the blood pressure is elevated most. This elevation is pronounced at 7 pm and at 4 am. Atenolol is an anti-hypertensive drug with an absorption window mainly in the upper section of the gastrointestinal tract. The present investigation was aimed at designing floating pulsatile capsules for dual release of atenolol in the stomach for effective management of hypertension. **Materials and Methods:** The floating pulsatile capsules designed had different components: a formaldehyde-treated capsule body; an untreated cap; a polymer plug layer, containing a polymer; two atenolol-containing immediate-release tablets and a swellable polymer layer. The polymer plug layer was made of hydroxypropyl methylcellulose (K4M or E50) and xanthan gum alone or in combination. The capsules were characterized for weight variation, percent drug content, *in-vitro* release behaviour and floating property. **Results:** The outcomes of the *in-vitro* studies showed that lag duration between the two pulses of drug release from the formulations can be adjusted by manipulating the composition of the plug layer. The optimized floating pulsatile capsule provided the first pulse of the drug immediately after administration to cover the first point of the symptoms. It provided the drug release from second pulse after a lag time of 8 hr for covering up the second point of the symptoms in the early morning. **Conclusion:** Thus, the dual-release floating pulsatile capsule designed may be used for chronological treatment of hypertension.

Keywords: Hypertension, Pulsatile, Floating, Lag time, Capsule, Plug layer.

INTRODUCTION

Most drug delivery systems available in the market rely on controlled drug delivery. It has multiple benefits such as constant drug release at site of action, avoidance of side effects and improved patient compliance. But this type of a release pattern is not advantageous in some pathophysiological conditions. Such conditions need the drug to be released only at the time when symptoms are exhibited after the administration of the dosage form. A pulsatile formulation is a system which provides a fast and transitory release of the drug after a predetermined off-release period, i.e., lag time.[1] Single-pulse and buoyant double-pulse core-in-cup tablets have been designed for valsartan.[2] A reasonable lag time can be obtained by controlling the polymer concentration in the plug layer. Pulsatile drug delivery systems are attracting more attention because they release drugs at specific sites at desired times in the required amounts, thereby improving the patient compliance.[3] Bussemer and co-workers designed pulsatile release capsules that have a lag time because of a rupturable coating. The lag time was adjustable by manipulating the mechanical strength and permeability of the rupturable coating.[4]

Hypertension is an elevated blood pressure condition. It is a main cause of various diseases such as coronary heart disease, heart stroke, loss of sight and kidney damage. Hypertension exhibits a circadian rhythm. There are two peaks in blood pressure elevation: one is in the evening, at about 7 pm

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Correspondence:
Dr. Dilesh Jagdish Singhavi
Institute of Pharmaceutical Education and Research, Borgaon (Meghe), Wardha-442001, Maharashtra, INDIA.
E-mail: dileshsinghavi@rediffmail.com

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and the other is in the early morning, between 4 am and 8 am.[5] The treatment of this condition therefore needs a pulsatile system to be developed. The system should provide two pulses of drug release. Atenolol (AT) was selected as the model drug because it is an effective beta-adrenergic blocking agent and is a valuable candidate in the treatment of time-related blood pressure elevation. The site of absorption of AT is the upper segment of the gastrointestinal tract (GIT). Therefore development of a pulsatile drug delivery system alone is not sufficient for effective delivery of AT in the upper part of the GIT during both the peak points of the hypertension symptoms. Improving the gastric residence time is also needed to cover the two peak points. The floating-pulsatile concept has been used to enhance residence time of dosage form in the vicinity of upper part of GIT with maintaining a lag phase in drug release followed by a rapid release of the drug.[6] The aim of the present investigation was to formulate and evaluate dual-release floating pulsatile capsules of AT.

MATERIALS AND METHODS

Materials

AT was donated from Kopran Research Laboratories Limited, Mumbai, India. Xanthan gum, hydroxypropyl methylcellulose K4M (HPMC K4M), hydroxypropyl methylcellulose E50 (HPMC E50), Carbopol 934P, polacrilin potassium, microcrystalline cellulose (MCC) and lactose were obtained from Loba Chemie Pvt. Ltd., Mumbai. Other reagents and chemicals used for experiments were of analytical grade.

Methods

Design of the Floating Pulsatile Capsule

The floating capsules were prepared with two parts, a body and a cap. A layer of Carbopol was introduced in the body and a circular polymeric disc of thickness 1 mm was placed above this layer as a separator.[7] An immediate-release tablet of AT was placed over the disc. The drug would be released from this tablet after a specific period (lag time). Another separating disc was placed above the tablet of AT. A polymer layer was introduced above this second disc to introduce a lag time before drug release. Over this polymer layer, a circular separating ring band was placed. Another immediate-release tablet of AT was placed over the separating ring band A gelatin cap was provided over the enteric body (Figure 1). When the capsule is ingested, the acidic environment would dissolve the gelatin cap quickly, but the enteric body would remain intact. As a result, the formulation mixture would get exposed to the acidic environment only from the upper side.

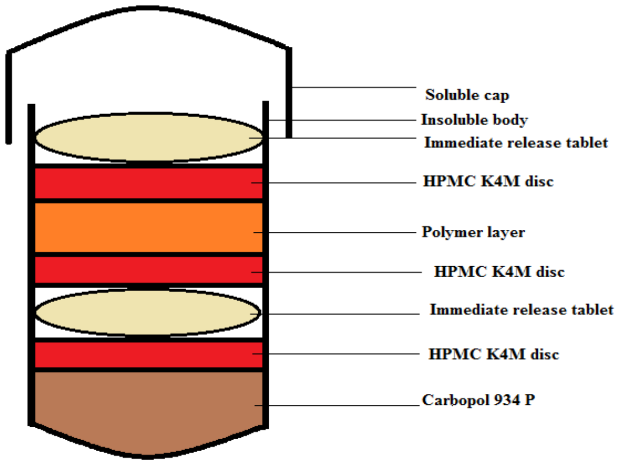

Figure 1: Design of floating pulsatile capsule.

Table 1: Composition of immediate-release AT tablets with disintegration time.

Sr. no.	Ingredients (mg)	Batch			
		B1	B2	B3	B4
1	AT	25	25	25	25
2	Polacrillin potassium	2	4	6	8
3	Lactose	30	28	26	24
4	MCC	42	42	42	42
5	Magnesium stearate	1	1	1	1
	Total	100	100	100	100
Disintegration Time* (Sec)		600.67 ± 6.11	473.33 ± 10.96	414.67 ± 5.50	538 ± 5.29

Each value represent mean ± standard deviation (n=3)

Formulation of Immediate-Release Tablet

Direct compression technique was applied to prepare immediate-release tablets. A mixture of AT, polacrilin potassium, MCC, Avicel PH-102 and lactose was dry blended for 20 min, after which magnesium stearate was added. The resulting mixture was further blended for 10 min. The blended powder was compressed using a single-punch tablet compression machine with a 6 mm punch and die to produce core tablets. Flat punches were used to make tablets weighing 100 mg each (Table 1). Each tablet formulation was monitored for weight variations, hardness, friability, thickness and drug content.[8]

In-vitro Release Behaviour Study

An *in-vitro* release behaviour study of the prepared tablets was done using a USP Type-2 (paddle method)

apparatus. Five hundred millilitres of 0.1 N HCl with pH 1.2 was utilized as the dissolution medium. The rotation speed was kept at 100 rpm and the temperature was set to 37 ± 0.5°C.[8,9] Ten-millilitres aliquots were taken at particular time intervals up to 60 min and examined using a double-beam UV spectrophotometer at 222.40 nm.

Preparation of Separating Polymer Disc

HPMC solution (4% w/w) was prepared in water containing glycerol (5%, v/v). The mixture was poured into a petridish and allowed to dry at 45°C for 12 hr. The dried film was cut using a punch to obtain uniform circular discs with a thickness of 1 mm and a diameter of 6.0 mm.[10]

Fabrication of Cross-Linked Gelatin Capsule Body

The gelatin capsule bodies were treated with formalin to modify its solubility behaviour. Remarkable decrease in the solubility of gelatin body was observed due to exposure to formalin vapours. This might due to cross-linking between amino group gelatin amino group and aldehyde group of the formaldehyde.[11]

The bodies of hard gelatin capsules (size 0) were removed from the caps. Twenty-five millilitres of formaldehyde solution of different concentrations (15%, 25% and 40%, v/v) was introduced into a desiccator followed by addition of a bit of potassium permanganate in order to form formalin vapours. By keeping on the wire mesh, the empty bodies of the capsules was treated with formaldehyde vapours for various time intervals. Because the caps were not exposed to these vapours, they remained non-enteric. After tightly closing the desiccator, the reaction was allowed to proceed for 12 hr. Then the bodies were exposed to 50°C for 30 min to make sure the completion of the reaction between the gelatin and the vapours of formaldehyde. The bodies were kept for drying at room temperature to ensure elimination of remaining formaldehyde. The solubility of the treated capsule bodies was tested in 0.1 N HCl. The time taken by treated capsule body to dissolve or to form a softy fluffy mass was noted.[11]

Formulation of Floating Pulsatile Capsules

Fifty milligrams of Carbopol 934P was introduced in each enteric gelatin body. A separating polymeric discs was placed over the Carbopol 934P layer. An immediate-release tablet was placed over the disc and another separating disc was placed over the tablet. A polymer plug was provided over the disc. Polymer plugs of different compositions (Table 2) were used in different capsules. Another separating disc was placed over the polymer. An immediate-release tablet was placed over the disc and the body was sealed with a hard gelatin cap.[7]

Parameters for Floating Pulsatile Capsules

Weight Variation Test

Ten capsules with each formulation were weighed. Weight variation (%) was determined using the formula[9]

$$\text{Weight variation} = \frac{(\text{Weight of capsule} - \text{Average weight of capsule})}{\text{Average weight of capsule}} \times 100 \quad (1)$$

In-vitro Floating Time Study of Different Polymers

The USP dissolution apparatus was used in this test. Five hundred millileters of 0.1 N HCl (pH 1.2) was used as medium and it was maintained at 37 ± 0.5°C. Each capsule formula was placed in the medium and tested. The duration for which the capsule remained buoyant in the solution was noted. This duration was considered the floating time.[9,10]

In-vitro Dissolution Study

The *in-vitro* release profile of AT from the developed formulations was examined using the USP II dissolution apparatus. Five hundred milliliters of 0.1 N HCl (pH 1.2) at 37 ± 0.5°C was used as dissolution medium and the paddle rotation speed was kept at 100 rpm. From the dissolution apparatus, samples (10 ml) were taken out hourly upto 12 hr and displaced with fresh dissolution medium. Using a double-beam UV spectrophotometer, the absorbance was examined at 226.40 nm. The percentage cumulative drug release was calculated using the standard calibration curve.[5,7,12,13]

Stability Study

A stability study was performed on of the optimized formulation (B3). The tablets (enclosed in aluminium foil) were kept at 40 ± 2°C and 75 ± 5% relative humidity for the period of 3 months. They were examined visually at 1-month intervals for any physical changes.[14]

RESULTS AND DISCUSSION

Immediate-release core tablets of AT were formulated to obtain a pulsed release of the drug. The tablets were prepared using polacrilin potassium as a superdisintegrant at different concentrations (2%, 4%, 6% and 8%, w/w). The tablets were examined for various physicochemical parameters, like weight-variability, friability and hardness, as per procedure specified in the Indian Pharmacopoeia. All the parameters were found to be within the prescribed limits. The dissolution study

showed that when the tablets came in contact with the dissolution medium, they disintegrated rapidly. It was observed that formulation B3 (concentration of polacrilin potassium 6%) had a reduced disintegration time (414.67 ± 5.50sec) compared with formulations B1 and B2 (polacrilin potassium concentrations 2% and 4%, respectively) (Table 1). Increasing the polacrilin potassium concentration from 2% to 6% increased the rate and extent of liquid uptake and penetration into the tablets, as a result of which the integrity of the tablet was disrupted quicker. Thus the drug particles were exposed to the dissolution medium very quickly. Further increasing the polacrilin postassium concentration to 8% w/w increased the disintegration time (538 ± 5.29 sec) and reduced the drug release (81.03 ± 1.52%) in batch B4 (Figure 2). Gelling of polacrilin potassium may have occurred in batch B4, hindering the disintegration and dissolution of the drug. The solubility study showed that capsule bodies exposed to the vapours of a 40% (v/v) formaldehyde solution exhibited enteric behavior for more than 12 hr. This duration is longer than those of capsule bodies exposed to vapours of 15% and 25% formaldehyde solutions. Therefore capsule bodies exposed to a 40% formaldehyde solution were selected.

The floating pulsatile capsules were successfully formulated according to the design mentioned in the Figure 1. The floating pulsatile capsules were subjected to a weight variability study, which was examined according to the method given in the Indian Pharmacopoeia. All the parameters were found to be within the prescribed limits, that is, the average weight variation was not more than 7.5%[15] (Table 2). All the capsules were able to provide a dual release of the drug. When a capsule was in put in the 0.1 N HCl, the cap of the capsule dissolved within 5 min and the first immediate-release tablet came into direct contact with the medium. A rapid drug release followed within 20–30 min. Then the polymer plug layer came into direct contact with the medium, which swelled, as a result of which there was a lag time. After this lag time, there was a rapid release of the drug from the second tablet (a second pulse) (Table 2 and Figure 3). The *in-vitro* release profiles of different batches revealed that all the batches exhibited a dual pulse release pattern.

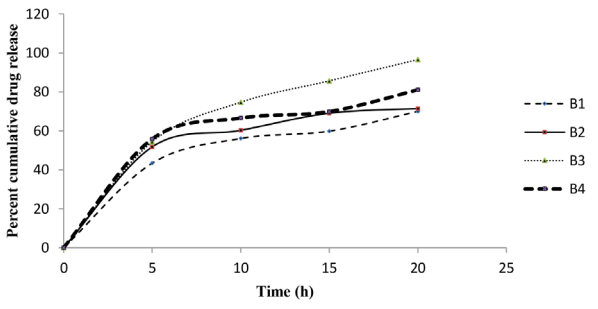

Figure 2: *In-vitro* dissolution profiles of AT from batches B1, B2, B3 and B4.

Table 2: Composition of plug layer and physical parameters of floating pulsatile capsules.

Batch	Amount of polymer (mg)			Average weight variation** (mg)	Floating time* (hours)	Lag time* (hours)
	HPMC K4M	HPMC E50	Xanthan gum			
S1	100	—	—	452.10 ± 1.43	> 12	10
S2	—	100	—	455.60 ± 1.65	> 12	8
S3	—	—	100	445.31 ± 1.97	> 12	9
S4	50	50	—	437.20 ± 1.54	> 12	9
S5	50	—	50	442.43 ± 1.39	> 12	9
S6	—	50	50	465.69 ± 1.42	> 12	9

*Mean ± SD (n = 3), **mean ± SD (n = 10)

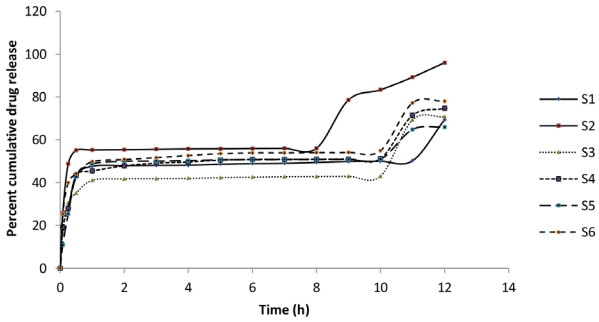

Figure 3: *In-vitro* dissolution profiles of AT from batches S1 to S6 in 0.1N HCl.

The first pulse of drug release (43.25 ± 0.21 %) of the capsules of batch S1 took place within 30 min. After a lag time of 10 hr, there was a second pulse of drug release from the second tablet. There was a cumulative release of 69.41 ± 0.29% after 12 hr. The lag time in drug release might be due to the presence of the viscosity-enhancing polymer HPMC K4M, which resisted erosion. The hydration and swelling of this polymer increased the path length, which increased the lag time[2]. In contrast, with the capsules of batch S2, the drug releases in the first pulse was 55.08 ± 0.35%.

This batch had HPMC E50 (100 mg) as a plug layer. The total drug release of this batch was 96.02 ± 0.21% at the end of 12 hr, with a lag time of 8 hr between the two drug-release pulses. HPMC E50 is characterized by its low viscosity solution forming capacity. It forms a gel on hydration subsequently dissolves in the dissolution medium.[15]

Formulation S3 (with a plug layer of xanthan gum alone) exhibited a drug release of 70.72 ± 0.32% up to 12 hr, with a lag time of 9 hr between the two pulses of drug release. Xanthan gum developed a weak gel structure compared with HPMC K4M.This was responsible for the shorter lag time compared with formulation S1. Formulation S4 (polymer plug layer of HPMC K4M and HPMC E50) exhibited a drug release of 74.65 ± 0.18% drug after 12 hr, with a lag time of 9 h between the two pulses of drug release. The lag time of formulation S4 was higher than that of formulation S2 and lower than that of formulation S1. This might be due to the combination of the highly viscous HPMC K4M and the comparatively low-viscosity HPMC E50. Formulation S5 (containing a combination of HPMC K4M and xanthan gum in the polymer plug layer) exhibited a drug release of 65.98 ± 0.20% after 12 hr, with a lag time of 9 hr. Xanthan gum, along with the viscosity-enhancing polymer HPMC K4M, gets hydrated when it comes in contact with an aqueous medium, forming a gel structure. This led to the lag time of 9 hr. Formulation S6 (polymer plug layer of HPMC E50 and xanthan gum) exhibited a drug release of 77.98 ± 0.22% after 12 hr. Both the polymers form gels, but xanthan gum forms a gel slowly compared with HPMC E50 and is responsible for the lag time of 9 hr. The optimized batch S2 with desired lag time of 8 hr. between two pulse releases was selected for the stability study. It was observed that this batch was stable for a period of 3 months at 40 ± 2°C and 75 ± 5% RH.

CONCLUSION

The major objective of this investigation was to fabricate a floating pulsatile capsule to provide a dual-pulse release in order to cover the two periods of peak blood pressure elevation in hypertension. The findings of the *in-vitro* studies suggest that the prepared capsule was successful in providing a dual pulse drug release in the upper portion of the GIT. The lag time between the two pulses of drug release can be adjusted by changing the ratio and types of the polymers in the plug layer.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ABBREVIATIONS

AT: Atenolol; **GIT:** Gastrointestinal tract; **MCC:** Microcrystalline cellulose; **HPMC:** Hydropropyl methylcellulose; **min:** Minute; **mm:** millimeter; **mg:** milligram; **°C:** Degree Centigrade; **mL:** milliliter; **rpm:** Revolutions per minute; **RH:** Relative Humidity.

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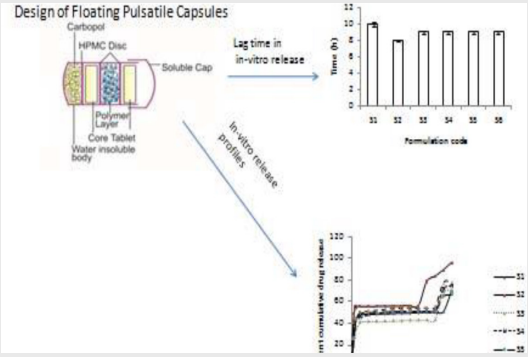
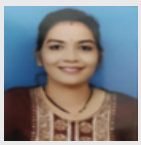
PICTORIAL ABSTRACT



SUMMARY

- In this research work, floating pulsatile capsules were developed by using formaldehyde treated enteric capsule body, untreated cap, immediate release tablet containing drug, plug layer, separating polymeric disc and swellable polymer. The capsule body was made enteric by using formaldehyde vapour treatment, while the cap was untreated. The capsule was filled with swellable polymer (carbopol), followed by separating HPMC disc, immediate release tablet, again HPMC disc then polymer layer (containing HPMC K4M, HPMC E50, Xanthan gum alone or in combination) and HPMC disc followed by immediate release tablet. Floating pulsatile capsules were examined for in - vitro floating behaviour, *in-vitro* drug release, weight variation and stability study.
- Depending on nature, combination and ratio of polymers used in plug layer, most of the formulations showed buoyancy for more than 12 hr. Batch S2 containing HPMC E50 (100 mg) in polymer layer showed drug release 96.02 ± 0.21% upto 12 hr and the desired lag time of 8 hr.

About Authors



Ms. Sonam Sanjaykumar Kunjekar is currently working as Senior Quality Assurance Executive in SSM Formulations Pvt. Ltd. Hinganghat, Wardha, Maharashtra.

Dr. Dilesh Jagdish Singhavi is presently Associate professor at the Institute of Pharmaceutical Education and Research, Wardha, Maharashtra. He has more than 17 Years of experience in Teaching and Academic Research. He is actively involved in development of floating drug delivery systems, pulsatile drug delivery systems and Multiparticulate drug delivery systems.

Ms. Tejaswini Balkrishna Parshuramkar is currently working as Research Associate in Callidus Research Laboratory pvt ltd Pune Maharashtra.

Dr. Shagufta Khan is currently Professor at the Institute of Pharmaceutical Education and Research, Wardha, Maharashtra. She has the teaching and research experience of more than 20 years. She is keenly involved in designing Nanocarriers for drug delivery and targeting.

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