Research Article

Evaluation of Pulsatile Tablet in Capsule Pulsatile Release Device

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ABSTRACT

In this investigation, a novel oral pulsatile drug delivery system was developed based on a tablet in a capsule device, where a core tablet surrounded coating material. The system consists of two parts, one part consists of Amlodipine immediate release blend and other part consists of Olmesartan coated tablet. The core containing Olmesartan as a bioactive compound was prepared by direct compression method. The coating materials consisted Eudragit RL 100 and Eudragit RS 100 was used in different concentration. The tablets prepared were evaluated for Swelling Index, In vivo X ray study (on rabbit) and *in-vitro* drug release study. *In-vitro* drug release studies were carried out using pH 1.2 for Amlodipine blend and pH 6.8 phosphate buffer for Olmesartan for 6 hrs. From the obtained results formulation of tablet in capsule device, shows best results.

Keywords: Pulsatile drug delivery system, Amlodipine, Olmesartan, Tablet in capsule device, Eudragit.

INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance. However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as Pulsatile release. A Pulsatile drug delivery system is characterized by a lag time that is an interval of no drug release followed by rapid drug release.[1,2]

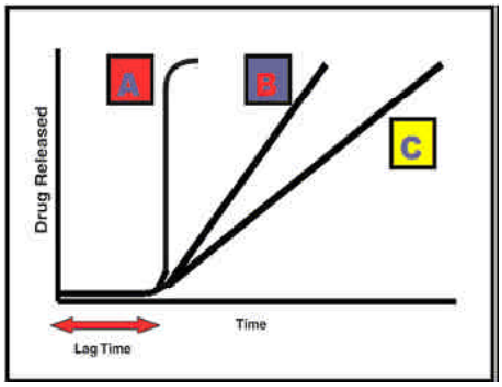

Figure 1: Sigmoidal release pattern

In this context, the aim of the research was to achieve a so-called sigmoidal release pattern (pattern A in Figure). The characteristic feature of the formulation was a defined lag time followed by a drug pulse with the enclosed active quantity being released at once. Thus, the major challenge in the development of Pulsatile drug delivery system is to achieve a rapid drug release after the lag time. Often, the drug is released over an extended period of time (patterns B & C in Figure). In chronopharmacotherapy (timed drug therapy) drug administration is synchronized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient. By basing drug delivery on circadian patterns of diseases drug effect can be optimized and side effects can be reduced. If symptoms occur at day time a conventional dosage form can be administered just prior the symptoms are worsening. If symptoms of a disease became worse during the night or in the early morning the timing of drug administration and nature of the drug delivery system need careful consideration. Control release systems for 12 or 24 hr drug release are not suitable for diseases, which follow circadian variation. In that condition there is requirement for time or pulsatile drug delivery system.'[4]

Necessities of Pulsatile DDS:[4-6]

1. **First pass metabolism**:

Some drugs, such as beta blockers, and salicylamide, undergo extensive first pass metabolism and require fast drug input to saturate metabolizing enzymes in order to minimize pre-systemic metabolism.

2. **Biological tolerance**:

Drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g., biological tolerance of transdermal nitroglycerin, salbutamol sulphate.

3. **Special chronopharmacological needs**:

Circadian rhythms in certain physiological functions are well established. It has been recognized that many

symptoms and onset of disease occur during specific time periods of the 24 hour day, e.g., asthma and angina pectoris attacks are most frequently in the morning hours.

4. **Local therapeutic need**:

For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects.

5**. Gastric irritation or drug instability in gastric fluid:**

Protection from gastric environment is essential for the drugs that undergo degradation in gastric acidic medium (eg. peptide drugs), irritate the gastric mucosa (NSAIDS) or induce nausea and vomiting.

Therefore, in this present research investigation an attempt will be made to formulate time controlled tablet in capsule Pulsatile drug device. The proposal consists of Amlodipine blend which is inserted with Olmesartan coated tablet in capsule size 0.

MATERIAL AND METHODS

1) Measurement of swelling index

The swelling ability of the coated tablets in physiological media was determined by swelling them to their equilibrium. The tablets were weighed (W0) and placed separately in petri dish (having the internal diameter of 10 cm) containing 10 ml of 0.1 N HCl for 2 h followed by pH 7.4 phosphate buffer for 3h and finally pH 6.8 phosphate buffer for 7h. At the end of 2, 5 and 12 h, tablets were removed and excess media over the surface of tablets were soaked using filter paper.[7,8]

Swelling Ratio of compressed tablet in capsule calculated by,

$$SR = \frac{Wf - W1 \times 100}{W1}$$

Where,

Wf-Final weight of tablet

W1-Initial weight of tablet

SR-Swelling Ratio

2) *In Vitro* release study of Amlodipine blend

Prepared blend of Amlodipine was kept in hard gelatin capsule and dissolution studies were performed using a USP XXIII dissolution apparatus I (basket type) (TDT-08L, Electrolab) in 900 ml medium at 37±0.5°c at a rotation speed of 50 RPM. In vitro release study was carried out in acidic media at pH 1.2 for 2 h. Five milliliters sample was withdrawn at specific intervals and replace with a fresh dissolution medium. These samples were filtered using a 0.45 um membrane filter.

The concentration of samples was analyzed using UV spectrophotometer at wavelength 360 nm.

Standard Solution - 0.2 mg/ml of USP Amlodipine dissolved in methanol. Dissolved in methanol to volume, shown in table 2.[9,10]

3) *In vitro* release study of coated Olmesartan tablets

In vitro drug release studies were performed using USP XXIII dissolution apparatus II paddle type (TDT-08L plus, Electrolab, Mumbai, India)) in 900 mL medium at 37.0±0.5 C, at a rotation speed of 50 rpm. Dissolution media selected was 0.1 N HCl (pH 1.2) and phosphate buffer of pH 6.8. Dissolution test was performed for 2 h in 0.1 N HCl (pH 1.2) and for 6 h in phosphate buffer (pH 6.8) respectively. Five milliliters sample was withdrawn at specific intervals and replaced with a fresh dissolution medium. These samples were filtered using a 0.45 µm membrane filter. The concentration of samples was analyzed using UV spectrophotometer at 265 nm, shown in table 3.[11-13]

4) *In vitro* release study of tablet in capsule formulation

In vitro drug release studies were carried out in a USP XXIII dissolution apparatus I basket type (TDT-08L plus, Electrolab, Mumbai, India)) in 900 mL medium at 37±0.5 C at a rotation speed of 50 rpm. The capsule was placed in the basket. Hard gelatin capsule (500mg) containing optimized batches of Amlodipine blend and coated Olmesartan tablet were transferred to the dissolution medium. For simulating conditions of the GI tract, dissolution tests were carried out in media with pH 1.2 and pH 6.8 (phosphate buffers). The study was performed for 2 h for acidic stage (pH 1.2) and for 6 h in the 6.8 pH phosphate buffer. 5 mL sample was withdrawn at predetermined time intervals and replaced with fresh dissolution media. The withdrawn samples were filtered through membrane filter 0.45µm and analyzed using UV spectrophotometer using multicomponent method for first 2 h at λ max 350 nm respectively. After 2 h dissolution sample were analyze by UV spectrophotometer at λ max 265 nm.[14,15]

5) Stability Studies

Accelerated stability study of an optimized batch of tablet in capsule formulation was carried out as per ICH guidelines at 40 ± 20C and 75 ± 5 % RH in an environmental test chamber (Multitech) for a period of 3 months. These samples were kept in glass vials without rubber plugs. After 90 days, the samples were analyzed for the *in vitro* drug release.[16,17]

6) *In Vivo* Study

This study was carried out at GSN Pharma pvt. Ltd., Central animal house (Registration No. – 769/2011/CPCSEA, Hyderabad). The in vivo study was carried out by administering optimized enteric coated tablets to male albino rabbits. Six rabbits weighing 2.1-2.6 kg were used for the study. Rabbits were housed in a 12 hr light dark, constant temperature. After that x ray was

done and coated tablets position seen at respected time intervals.

RESULTS AND DISCUSSION

1) Swelling Ratio of tablet

Swelling index of the coated tablets was attributed to fluid uptake by ERS and ERL content in the preparation, since ERS and ERL were the only component in the final enteric coated tablets having swelling abilities. Maximum swelling index was observed by using Eudragit RL and Eudragit RS. Showing good swelling ratio in 6.8 pH, which shown in table 1.

Table 1: Swelling Index

pH	Swelling Ratio
1.2	16.2
6.8	27.2

Table 2: *In Vitro* release of Amlodipine at pH 1.2

Time in Min.	Absorbance	% Drug Release
5	0.0059	3.2
10	0.061	32
15	0.112	60
20	0.177	98

Table 3: *In vitro* release of Olmesartan Tablet in pH 1.2 up to 2 hrs and 6.8 pH till 6th hr

Time in Min.	Absorbance	% Drug Release
30 (1.2 pH)	0.0	0
60	0.0	0
90	0.0012	1
120	0.0023	2
150 (6.8 pH)	0.0623	10
180	0.1234	35
240	0.189	55
320	0.4578	94
360	1.172	98.9

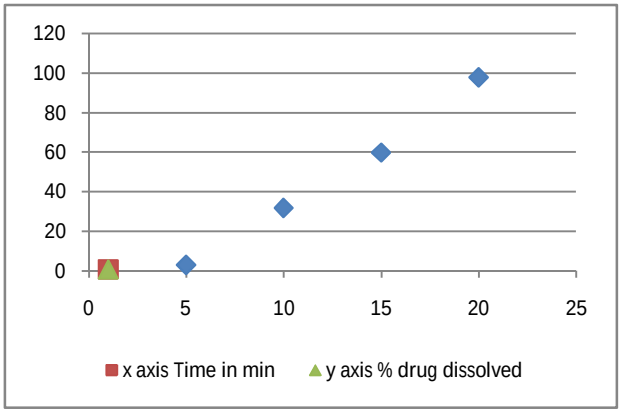

Figure 2: Amlodipine dissolution in 1.2 pH

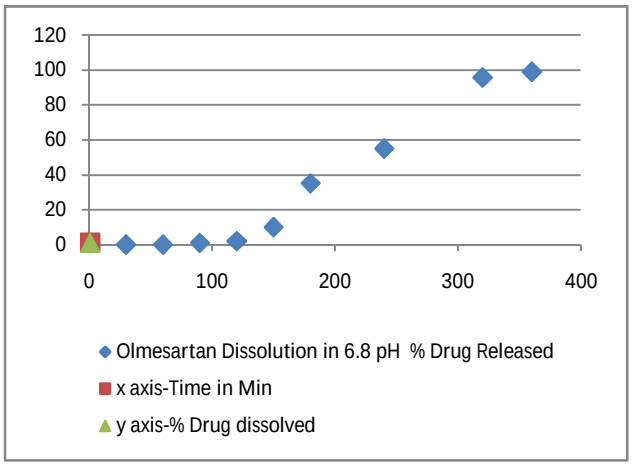

Figure 3: Olmesartan coated tablet dissolution in 6.8 pH

2) *In Vivo* Study

In vivo study is carried out on 6 rabbits. They were feed with Olmesartan coated tablet. After that X ray study is carried out. Tablet was not dissolved in 1.2 pH and remain undissolved up to 3-5 hrs in rabbits.

3) *In vitro release* profile of stability batch

Table 4: *In vitro* release of optimized stabilized batch

Time In Min.	Amlodipine Blend	Olmesartan Coated Tablet
0	0	0
30	97.6%	0
60	-	2
90	-	3
120	-	8
150	-	11
180	-	39
240	-	53
320	-	81
360	-	96

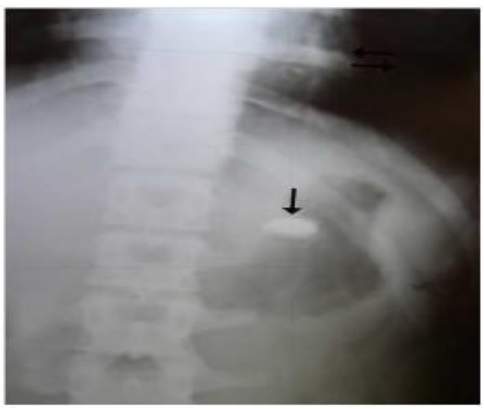

Figure 4: Position of enteric coated tablet in 1.2 pH up to 2 hrs in rabbit

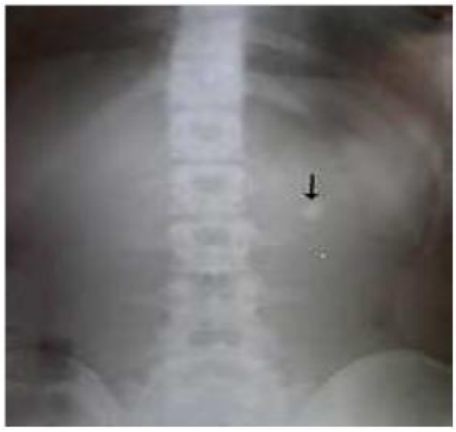

Figure 5: Position of enteric coated tablet in 6.8 pH up to 6 hrs in rabbit

The effect of temperature and time on the physical and chemical characteristic of the tablet in capsule device. From the dissolution profile of the stability batch, results indicate that there wasn´t significant changes in the *in vitro* drug release of Amlodipine blend and Olmesartan coated tablet respectively from the prepared tablet in capsule formulation.

CONCLUSION

From the above results, it can be concluded that the prepared Tablet in Capsule pulsatile drug delivery system can be considered as one of the promising formulation technique for chronotherapeutic management of hypertension.

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