Design and Evaluation of Pulsatile Drug Delivery of Losartan Potassium

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ABSTRACT: The study was designed for the investigation of pulsatile device to achieve time or site specific release of Losartan potassium based on chronopharmaceutical considerations. The basic design involves the preparation of cross linked hard gelatin capsules by using formaldehyde, then the drug diluent mixture were prepared and loaded in, which was separated by using hydrogel plugs of different polymers of different viscosities. Prepared formulations were subjected to evaluation of various parameters like weight variation, percentage drug content, *in vitro* drug release and stability studies. Weight variation and percentage drug content results showed that they were within the limits of official standards. The *in-vitro* release studies revealed that the capsules plugged with polymer HPMC showed better pulsatile or sustained release property as compared to the other formulations. The stability studies were carried out for all the formulations and formulations F1 & F2 were found to be stable.

Key words: Chronopharmaceutics, HPMC, Losartan potassium, Pulsatile.

INTRODUCTION

Traditionally, drug delivery has meant to get a simple chemical absorbed predictably from the gut or from site of injection. A second-generation drug delivery goal has been the perfection of continuous and constant rate (zero order) delivery of bioactive agents. However, living organisms are not "zero order" in their requirement or response to drugs. They are predictable resonating dynamic systems, which require different amounts of drugs at predictably different times within the circadian cycle in order to maximize desired and minimize undesired drug effects. Due to advances in chronobiology, chronopharmacology and global market constraints, the traditional goal of pharmaceutics (eg. design drug delivery system with a constant release rate) is becoming obsolete.[1]

Chronotherapeutics refer to a clinical practice of synchronizing drug delivery in a manner consistent with the body's circadian rhythm including disease states to produce maximum health benefit and minimum harm.[2]

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Pulsatile Drug Delivery Systems

Pulsed or pulsatile drug release is defined as the rapid and transient release of certain amount of drug molecules within a short period of time immediately after a predetermined off-release period. Recent studies have revealed that diseases have a predictable cyclic rhythm that the timing of medication can improve the outcome of desired effect. This condition demands release of drug as a "pulse" after a lag time. Such systems are called as pulsatile drug delivery system.[3]

By optimizing timing of the drug administration, plasma peak is obtained, at an optimal time and number of doses per day can be reduced. When there are no symptoms there is no need of drugs, hence saturable first pass metabolism and tolerance development can also be avoided.[4]

Hypertension is defined conventionally as blood pressure ≥ 140/90. Elevated arterial pressure causes pathological changes in vasculature and hypertrophy of left ventricles: as a consequence, hypertension is the principle cause of stroke which leads to disease of coronary arteries with myocardial infarction and is the major contributor to cardiac failure.[5,6]

Losartan potassium is a selective, competitive angiotensin II (receptor type 1 (AT_1)) antagonist, reducing the end organ responses to angiotens in II. Reduction in blood pressure occurs independently on the status of the renin-angiotensin system. It is used in the treatment of hypertension and other disorders that follow circadian rhythm, such as diabetic mellitus, angina pectoris, and rheumatic diseases. Losartan potassium is well absorbed after oral administration and bioavailability of about 33% and plasma half-life ranging from1.5 to 2.5h.[7,8]

Based on the concept that a formulation on leaving the stomach, arrives at ileocaecal junction in about 6 hours after administration and difference in pH throughout GIT, a time and pH dependent pulsatile (modified pulsincap), drug delivery system was designed.

MATERIALS AND METHODS

Materials. Losartan potassium was obtained as a gift sample from Microlabs Pvt. Ltd, Banglore. Lactose, Hydroxypropyl methyl cellulose and Carboxymethyl cellulose sodium from S.D. Fine Chem. Ltd, Mumbai, India. Empty capsules shells from Yarrow Chemical Products, Mumbai, India.

Preparation of formaldehyde treated crossed-linked gelatin capsule.[9,10] About 100 hard gelatin capsules size '1' were taken. Their body was separated from the cap and placed on a wire mesh. Then 25 ml of 37% v/v of formaldehyde solution was taken in a beaker and kept in an empty glass dessicator. To this 2.5 g of potassium permanganate was added. On the top of beaker a wire mesh containing the body of the capsule was kept and immediately the dessicator was tightly closed and sealed. The body of the capsule was made to react with formaldehyde vapors for 4 hrs. Then they were removed and kept on a filter paper and dried for 48 hrs in an open atmosphere to facilitate removal of residual formaldehyde. These capsule bodies were rejoined with untreated cap and stored in a polythene bag for further studies.

Formulation of sustained release pulsin capsules.[9]

Preparation of physical mixture of drug and polymer. 25 mg of each of Losartan potassium and lactose were mixed in a mortar and this mixture was stored in polythene bag. Various formulations by using different polymers as hydrogel plugs are given in Table 1.

Table 1. Composition of different formulations.

Formu-lation code	Polymer	Grades	Drug-lactose mixture	Amount of polymer used/plug
F1	HPMC	5CPS	50 mg	100 mg
F2	HPMC	15CPS	50 mg	100 mg
F3	Sodium CMC	200-300CPS	50 mg	100 mg
F4	Sodium CMC	500-800CPS	50 mg	100 mg

Filling of capsules. Hard gelatin capsules of size '1' with formalin treated body and untreated cap were taken for filling. Twenty capsules for each formulation were prepared by manually as follows:

The cap and body of the known weight of capsule was separated individually by hand. The drug-lactose mixture (50mg) equivalent to 25mg of drug (Losartan potassium) was filled in to the body of capsule; this forms the second dose of the drug. The quantity of the polymer as specified in Table 1 for different formulations was weighed and filled above drug-lactose mixture, then pressed tightly with a glass plunger; this forms plug 2 of the formulation. Similarly, first dose of the drug-lactose mixture placed and polymer forms plug 1 of the capsule. Now, the drug-lactose mixture was weighed and placed in soluble cap to form the immediate release (dose) of drug. Finally the cap was locked into the capsule body and stored in tightly packed container for further studies.

Evaluation of formaldehyde treated capsules. Various physical and chemical tests were carried out simultaneously for both formaldehyde treated and untreated capsules. The identification attributes like color, odor, lock ability, stickiness and shape were checked manually. The size of the capsules, i.e. length, external diameter and thickness was determined by using Vernier calipers.

Qualitative test for free formaldehyde

Standard formaldehyde solution. A suitable volume of formaldehyde solution was diluted with water to give a solution containing 20 µg/ml of formaldehyde.

Sample solution. Twenty five formaldehyde treated bodies were cut into small pieces and taken into a beaker containing distilled water (40 ml). This was stirred for 1hr with a magnetic stirrer, to solubilize the free formaldehyde. The solution was filtered into a 50 ml volumetric flask, washed with distilled water and volume was made up to 50 ml with washings.

Procedure. To 1 ml of sample solution in a test tube, 4 ml of water and 5 ml of acetyl acetone solution were added, the test tube was placed in a water bath at 40^{o}C for 40 min. At the same time reference solution was placed in the same manner using 1 ml of standard formaldehyde solution. The sample solution was not more intensely colored than the standard solution inferring that less than 20 µg/ml of free formaldehyde was present in 25 capsules body.[9]

Evaluation of modified pulsincap

***In vitro* release profile.** *In vitro* dissolution profile of each formulation was determined by employing USP XXIII apparatus by rotating basket method in different media like stimulated gastric fluid (pH 1.2 buffer) for 2 hrs (since the average gastric emptying time is 2hrs), and colonic fluid pH 6.8 buffer for subsequent 10hrs. The dissolution media were maintained at a temperature of 37± 5ºC, the speed of rotation of basket maintained were 50 rpm. Pulsing capsules were placed in basket in each dissolution vessel to prevent floating. Five ml of the samples was withdrawn from dissolution media at suitable intervals and same amount was replaced with fresh buffer. The absorbance was measured at 204 nm. Data obtained was also subjected to kinetic treatment to understand release mechanism.

Drug content. The contents of capsule was placed into 100 ml volumetric flask and the volume was made up with pH 6.8 phosphate buffer. The solution was shaken for 1 hr and kept for 24 hrs. From the stock solution, 1ml solution was taken in 10 ml volumetric flask and the volume was made with pH 6.8 phosphate buffer. Solution was filtered and absorbance was measured spectrophotometrically at 204 nm against pH 6.8 phosphate buffer as a blank. Then the amount of drug present in one capsule was calculated.

Stability studies. The optimized formulation was subjected for three months stability studies. The selected formulations were stored in ambered color glass bottle, which were closed tightly. They were then stored at 25ºC/60% RH, 40ºC/75% RH for 3 months and evaluated for drug content, by *in vitro* dissolution studies.

RESULTS AND DISCUSSION

Pulsatile drug delivery system of Losartan potassium for the treatment of hypertension were prepared by hand filling method, using polymers like HPMC and sodium CMC of different grades.The physico- chemical evaluation data of empty gelatin capsules presented in Table 2 indicates that thickness of the capsule ranged from 0.17 - 0.21mm. When compared to the untreated capsules, formalin treated capsules were found to be thicker and showed better sustaining release activity. The individual weights of each capsule were quite uniform and cross-linking did not show any significant change in weight. Average weight of capsules was in the range of 0.0734 - 0.075 mg.

The length of caps was 9.54 and 9.6 mm, whereas body length was 16 and 16.4 mm for untreated and formalin treated respectively. The external diameter was found to be 6.2 and 6.5 for untreated and treated, respectively, which are shown in Table 2. This maybe due to cross linking that leads to decrease in percentage moisture.

The solubility studies on both formalin treated and untreated capsule shells was carried out for 24 hrs. The study shows in case of untreated capsules that both body and cap were dissolved within 15 minutes, whereas in formalin treated capsules only cap dissolved within 15 minutes and the body remained intact. The compatibility studies done by

FTIR studies indicated that there was no chemical interaction between the drug and excipients used.

The amount of physical mixture was found to be 149.8 to 152.4mg as per the combination drug, diluents and hydrogel plug of polymer. The amount of Losartan potassium in each capsule was in between 73.97 to 75.04 mg and it equals to three individual doses separated by hydrogel plug. The theoretical drug loading for each dose is equivalent to 25 mg. The percentage drug content was from 98.75 - 100.25 the data are shown in Table 3.

Table 2. Physical characteristics of empty gelatin capsules with and without cross-linking.

Type of capsules	Length (mm)		External diameter (mm)		Thickness (mm)		Avg weight of empty capsules (mg)
	Cap	Body	Cap	Body	Cap	Body	
Untreated	9.6	16.4	6.9	6.5	0.19	0.17	0.075
Formalin Treated	-	16.0	-	6.2	-	0.21	0.073

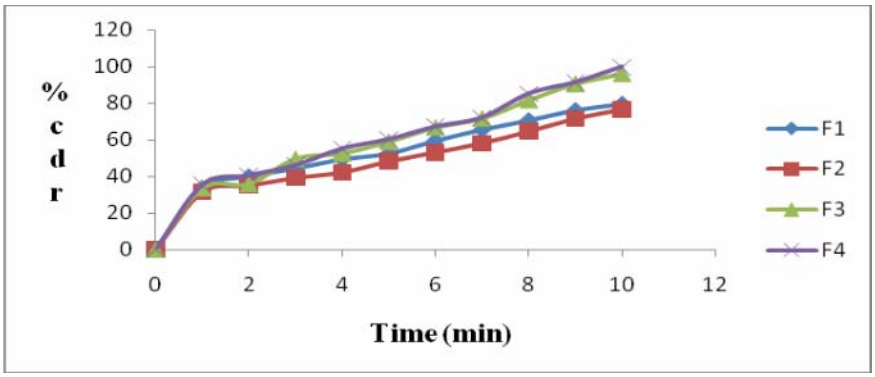

Figure 1. Cumulative percentage release Vs time profile of formulation

Table 3. Amount of physical mixture and drug loading per capsule.

Formu-lation code	Amount of physical mixture filled (mg)	Amount of drug per capsule (mg)	Percentage drug content
F1	150.2 ± 1.0	74.82 ± 0.18	99.25 ± 0.75
F2	151.6 ± 2.3	75.04 ± 0.40	98.75 ± 1.20
F3	149.8 ± 2.1	73.97 ± 1.00	99.87 ± 0.30
F4	152.4 ± 1.2	74.65 ± 0.35	100.25 ± 0.25

From the *in vitro* dissolution studies it was found that all the caps were separated from the body thereby releasing the immediate release dose of 25mg within 15 minutes. The polymer plugs swelled in alkaline medium and the plug ejection time was found to be between 4-5hrs in all formulations. About 5-10% of the first loading dose was found to be released even before the plug was ejected. It may be due to the diffusion of the loading dose through the hydrogel plug into the dissolution medium. The dissolution profiles of all the formulations have been shown in Figure 1. From the figure it was observed that there is a higher initial release rate, which is a characteristic property of the matrix formulations.

All the formulations show linearity with respect to zero order and first order kinetics. The regression values of zero order kinetics of formulations F1, F2, F3 and F4 were 0.917, 0.890, 0.941 and 0.942, respectively. The regression values of first order kinetics of formulations F1, F2, F3 and F4 were 0.972, 0.949, 0.845 and 0.744, respectively. From the release kinetic data it can be concluded that the drug release followed mixed order kinetics.

To ascertain the drug release mechanism, the *in-vitro* data were also subjected to Higuchi's model. R^2 values of formulations F1, F2, F3& F4 were 0.972, 0.951, 0.960 and 0.958, respectively. The formulations were subjected to Peppa's plots, 'n' value ranges from 0.415 to 0.482 indicating that the drug release was by non- Fickian diffusion mechanism.

The stability studies showed no change in the physical changes and appearance. The data given in Table 4 indicates that there is no significant change in content estimation and dissolution profile.

Table 4. *In-vitro* drug release after stability studies of formulations F1 and F2.

Room temperature		At 40°/75 RH.	
F1	F2	F1	F2
0	0	0	0
33.09	29.46	30.72	27.96
39.51	34.39	37.40	32.94
43.99	38.50	40.05	37.52
48.81	41.73	45.88	40.96
52.04	47.41	48.55	46.82
58.96	52.53	54.91	52.121
65.28	57.46	63.86	56.41
69.89	63.96	67.56	62.90
74.76	70.94	70.73	69.27
78.96	76.12	74.06	74.29

CONCLUSION

In the present work an attempt was made to develop sustained release pulsatile capsules of Losartan potassium on the lines of novel drug delivery systems. The first step in preparing such type of drug delivery system is to develop capsules with soluble cap and insoluble body. It was done by exposing the separated body of capsule to formaldehyde vapors, which causes a cross linking of the gelatin molecule and making the body insoluble.

All the prepared formulations were subjected to various evaluation parameters like melting point, solubility studies, compatibility studies, weight variation and drug content uniformity. The results of all the evaluation parameters were found to be satisfactory.

The capsules were also subjected to *in vitro* drug release studies in pH 1.2 and pH 6.8 phosphate buffer solution. The results showed that, in all the formulations the caps dissolved within 15 minutes, and then there was a higher initial release of drug followed by a slow and a nearly constant release of drug over a period of 8 to 10 hours depending on the type and amount of polymer used.

Further the release data was fitted to various mathematical models such as Higuchi, Korsmeyer-Peppa's, zero order and first order to evaluate the kinetics of drug release. The drug release follows mixed order kinetics and mechanism was found to be non-Fickian diffusion.

The best formulations were subjected for stability studies and results showed that there was no significant change in physical appearance, drug content as well as dissolution study.

Hence it can be concluded that mixing of the drug with a blend of polymers and filling the mixture into cross linked gelatin capsules prolongs the release of drug. When the two doses of drug were placed between the two polymer plugs within the cross linked capsules showed pulsatile release.

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