



Research Article

Formulation and Evaluation of Chronomodulated Pulsincap Therapeutic System for Early Morning Surge in Blood Pressure

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ABSTRACT

The objective of this study was to design and developed a capsule dosage form which contains the drug closed with plug, which is removed after a predetermined lag time and the drug is release from the insoluble capsule body early in the morning hours. This delivery system was helpful to control early morning surge in blood pressure because cardiovascular events occur more frequently in the morning. Initially core tablet was prepared by using Captopril as a model drug, which is having Angiotensin-converting enzyme inhibition activity and different concentration of crosscarmellose sodium as a super disintegrant by the direct compression method by using 6 mm flat faced punch. Formulation was developed by filling core tablets in formaldehyde treated empty capsule body and sealed by using plugs of different polymers like guar gum, HPMC K4M, Sodium alginate and Xanthum Gum. Core tablet was evaluated for different evaluation parameters and the formulation which shows least disintegration time has been selected for further study. After complete wetting of the plug, it formed a soft mass, which was then easily ejected out of the capsule body expose the core tablet of captopril to pH 6.8 phosphate buffer (simulated colonic fluid). From in vitro dissolution study it was concluded that, the drug release is directly proportional to concentration of polymer used in erodible tablet plug.

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INTRODUCTION

The rationale of the present study is to develop a drug delivery system which provides required dose at the required time without any failure. Pulsatile drug delivery system solves this problem, a single capsule ingested at the bedtime releases drug early in the morning which gives protection from cardiovascular events. High blood pressure or hypertension as a disease is known medically most common chronic illness [1-4]. Plasma norepinephrine level and plasma renin activity are elevated in the morning; both hormones have potential to induce coronary vasoconstriction. This is the Renin-Angiotensin-Aldosterone System (RAAS) is activated in the morning, and may contribute to the morning BP surge and to morning increase in cardiovascular risk. Chronomodulated pulsatile therapeutic system releases a therapeutic agent at a rhythm that ideally matches the biological requirement of a given disease therapy.

The oral controlled-release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time, thereby ensuring sustained therapeutic action. However, there are certain conditions for which such a release pattern is not suitable [5]. Diseases where a constant drug levels are not preferred, but need a pulse of therapeutic concentration in a periodic manner acts as a push for the development of Pulsatile Drug Delivery System [6].

Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount [7]. The concept of chronotherapeutics originates from the finding of the major disease conditions such as asthma, cardiac disorders, allergic rhinitis, and arthritis following circadian example of symptom outburst.

Captopril HCL is chemically (2S) -1-[(2S) -2-methyl-3-sulfanylpropanoyl] pyrrolidine-2-carboxylic acid having Angiotensin-Converting Enzyme Inhibitor activity used in Management of hypertension. Rapidly absorbed following oral

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administration in fasting individuals, with peak blood concentration attained in 1 hour. Approximately 60–75% of an oral dose is absorbed. Hypotensive effect may be apparent within 15 minutes and usually is maximal in 1–2 hours after a single oral dose [8–11]. HPMC K4M and Guar gum, sodium alginate and Xanthan gum are used as erodible plug materials in different concentration and its effect on lag time is studied [12].

MATERIAL AND METHOD

Captopril HCL was supplied from Wockhardt limited Aurangabad, INDIA. Hydroxy propyl Methyl Cellulose K4M and Crosscarmellose sodium was procured from Leben laboratories Pvt. Ltd., Akola. Guar gum, Xanthan gum and Sodium alginate was obtained from Loba Chemie. Pvt. Ltd., Mumbai. All other Excipients used in our work were of analytical grade.

Preparation of core tablet of Captopril

The core tablet of Captopril was prepared by direct compression technique. Avicel 581 was used as a diluent, Crosscarmellose Sodium was added to obtain a fast disintegrating tablet. The composition of core tablets was as shown in Table 1.

Table 1: Composition of Core Tablet.

Name of Ingredients	Quantity (mg/tablet)
Captopril	25.0
Crosscarmellose sodium	3.5
Magnesium stearate	3.5
Avicel 581	38.0
Total weight	70.0

Post-compression Study of core tablet

Shape and appearance

Tablets were examined under a lens for the shape of the tablet, and color was observed by keeping the tablets in light.

Uniformity of thickness

Thickness and diameter of core tablets were measured using a Vernier caliper.

Weight variation test

To study weight variation, 20 tablets were weighed on an electronic balance separately and average weight was calculated and the test was performed according to the official method.

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Hardness of core tablets was determined using a Monsanto hardness tester.

Friability test

The friability of 10 tablets was determined using the Roche friabilator (Electrolab, Mumbai, India). Friability can be determined by following equation:

$$\% \text{ Friability} = 100 \left[1 - \frac{W_0}{W} \right]$$

Uniformity of content

Five tablets were powdered in a mortar and pestle and a quantity equivalent to 25 mg of Captopril was accurately weighed and dissolved in a suitable volume of 6.8 pH phosphate buffer. After making suitable dilutions the final solution was analyzed spectrophotometrically at 212 nm.

In-vitro Disintegration test for core tablet

Tablet disintegration was carried by placing one tablet in each tube of the basket and top portion of the each tube was closed with disc and run the apparatus containing pH 6.8 phosphate buffer maintained at 37°C as the immersion liquid. The assembly was raised and lowered between 30 cycles per minute. The time taken for the complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded. The experiment was carried out in triplicate.

In-vitro drug release study of core tablets

In-vitro dissolution study was carried out using USP Type II (paddle type) apparatus (Electrolab TDT-08L). 6.8 pH phosphate buffer as a dissolution medium was used. Release pattern was studied visually by taking samples of 5 ml at the specific time intervals 0.5min, 1 min, 2 min, 3 min, 4 min and 5 min also the sample was analyzed at 212 nm using a UV spectrophotometer.

Preparation of erodible tablet of different polymer

Erodible tablet formulations containing different polymer were prepared by direct compression technique it includes weighing polymer and adding directly compressible Avicel 581. Magnesium stearate and talc were added to each blend and further mixed. The resultant blends were tableted to 100 mg using 6 mm flat-faced punches on Tablet punching machine.

Table 2: Result of Pre-compression Study of Powder Blend of Core Tablet.

Property Studied	Loose Bulk Density (g/ml) \pm SD	Tapped Bulk Density (g/ml) \pm SD	Carr's Index (%) \pm SD	Hausner's Ratio	Angle of Repose (ϕ)
Result	0.530 \pm 0.015	0.583 \pm 0.026	9.09 \pm 0.24	1.11	28.36

Table 3: Result of Post Compression Study of Core Tablet.

Test	Thickness(mean \pm SD, mm) (n=3)	Average Weight (mg)	Hardness (mean \pm SD,kg/cm ²) (n=3)	Friability %	Drug content %	Disintegration time (min)
Result	1.3 \pm 0.15	70.2	3.6 \pm 0.21	0.784 \pm 0.1	98.67	2.12

Table 5: The composition of Erodible Tablet

Sr.no.	Batch Contents	G1	G2	G3	H1	H2	H3	S1	S2	S3	X1	X2	X3
1	Guar gum	25	50	75	-	-	-	-	-	-	-	-	-
2	HPMC K4M	-	-	-	25	50	75	-	-	-	-	-	-
3	Sodium alginate	-	-	-	-	-	-	25	50	75	-	-	-
4	Xanthum gum	-	-	-	-	-	-	-	-	-	25	50	75
5	Avicel 581	73	48	23	73	48	23	73	48	23	73	48	23
6	Mag. Stearate	1	1	1	1	1	1	1	1	1	1	1	1
7	Talc	1	1	1	1	1	1	1	1	1	1	1	1
Total		100	100	100	100	100	100	100	100	100	100	100	100

(Note: All values in mg)

Table 6: Evaluation Study of Physical Parameter of Erodible Tablet Formulations.

Property Studied	Thickness (mm) \pm SD	Hardness (kg/cm ²) \pm SD	Friability % \pm SD	Average Weight (mg)
G1	1.9 \pm 0.018	4.13 \pm 0.14	0.30 \pm 0.33	99.9
G2	2.1 \pm 0.021	3.83 \pm 0.17	0.55 \pm 0.14	99.75
G3	2.2 \pm 0.038	3.41 \pm 0.21	0.65 \pm 0.15	99.85
H1	3.8 \pm 0.022	4.53 \pm 0.2	0.86 \pm 0.29	98.45
H2	4.1 \pm 0.015	4.21 \pm 0.17	0.65 \pm 0.24	100.05
H3	4.2 \pm 0.024	4.17 \pm 0.29	0.40 \pm 0.14	100.9
S1	2.4 \pm 0.015	4.73 \pm 0.47	0.20 \pm 0.24	98.7
S2	2.5 \pm 0.023	5.10 \pm 0.14	0.25 \pm 0.17	99.15
S3	2.4 \pm 0.034	5.57 \pm 0.5	0.40 \pm 0.24	99.7
X1	2.4 \pm 0.012	4.11 \pm 0.42	0.25 \pm 0.27	100.00
X2	2.4 \pm 0.034	4.62 \pm 0.54	0.40 \pm 0.21	99.85
X3	2.6 \pm 0.014	4.97 \pm 0.24	0.45 \pm 0.37	99.5

Evaluation of erodible tablets of different polymers

HPMC K4M and Guar gum, sodium alginate and Xanthan gum are used as erodible plug materials in different concentration and further evaluated for different post-compressional parameters.

RESULTS AND DISCUSSION

Data obtained from the Preformulation studies of the pure drug shows that a flow property of the pure drug is fair. So, it requires modifying its flow properties in order to obtain the tablets

having a uniform weight. Direct compression method is used for the manufacture of core tablet. Previously, all the pre-compression parameters are studied on the powder blend, which is used for compression. The powder blend shows excellent flow property. Pre-compression parameters studied are given in **Table 2**.

Formulations prepared were randomly picked from each batch examined under the lens for shape and in the presence of light for color. Tablets showed standard concave surfaces with a

circular shape. Tablets were white in color. Thickness of the tablets was measured using vernier calipers by picking three tablets randomly. The results of thickness for tablets are shown in **Table 3**. The mean thickness of the tablets (n=3) was 1.3 ± 0.1 mm. The weight variation of a tablet is shown in **Table 3**. All the tablets passed the weight variation test, i.e., average percentage weight variation was found within the pharmacopoeial limits of $\pm 10\%$.

Hardness or crushing strength of the tablets was found 3.5 kg/cm^2 . The low standard deviation values indicated that the hardness of all the formulations was almost uniform and the tablets possess good mechanical strength with sufficient hardness. Friability values for tablet were found to be 0.784 %. The obtained results were found to be well within the approved range ($<1\%$) in all the designed formulations. That indicated tablets possess good mechanical strength. The results are tabulated in **Table 3**. The percent drug content was found to be 98.67 %.

Table 4: *In-vitro* Dissolution Study of Core Tablet

Time (sec)	Absorbance	%drug release
0	0	0
30	0.025	5.10
60	0.112	22.85
120	0.198	40.40
180	0.321	65.51
240	0.421	85.91
300	0.449	91.63
360	0.456	93.06

In-vitro disintegration time for core tablet was found to be 2.1 min which indicates that the concentration of cross-carmellose sodium used is sufficient and there is no need to use unnecessarily higher concentration. Table no. 4 shows U.V. absorbance of sample obtaining at different time interval and Figure no. 1 indicate % drug release curve. The core tablet shows more than 90 % of drug release within 5 minutes upon contact with dissolution medium. When the formaldehyde treated capsules were subjected to solubility studies in different buffer solutions for 24 hours, only the cap dissolved within 15 minutes, while the capsule body remained intact for about 24 hours.

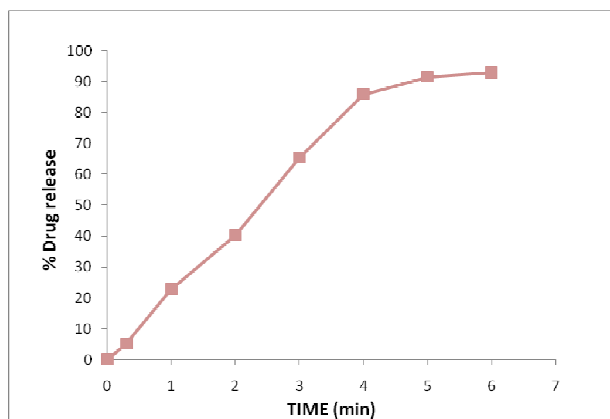


Figure 1: Dissolution Profile of Core Tablet.

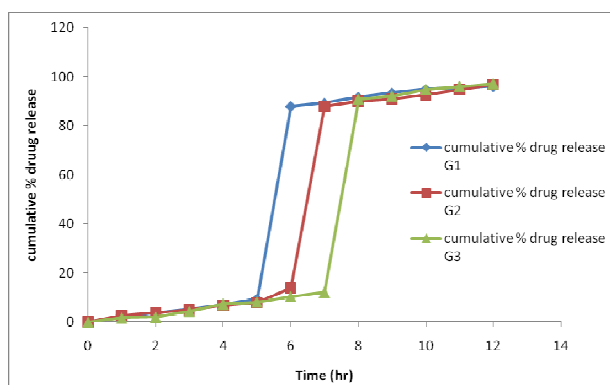


Figure 2: Dissolution Profile of Pulsincap Technology Guar Gum as Hydrogel Plug In Erodible Tablet.

Evaluation of erodible tablets of different polymers

Four different polymers i.e. guar gum, HPMC K4M, sodium alginate and Xanthan gum were separately used for the preparation of hydrogel plug in erodible tablet. All polymers were used in three different concentration 25 mg, 50 mg and 75 mg in three batches. Composition of erodible tablet formulations is shown in Table n.05.

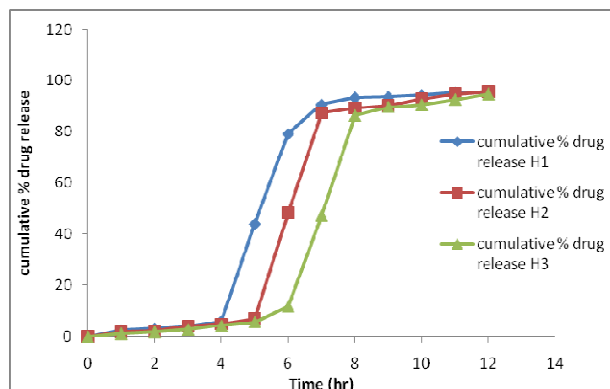
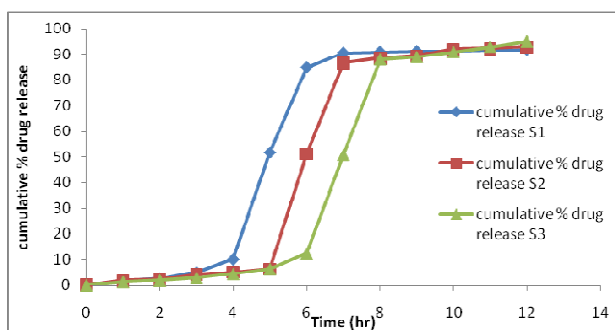
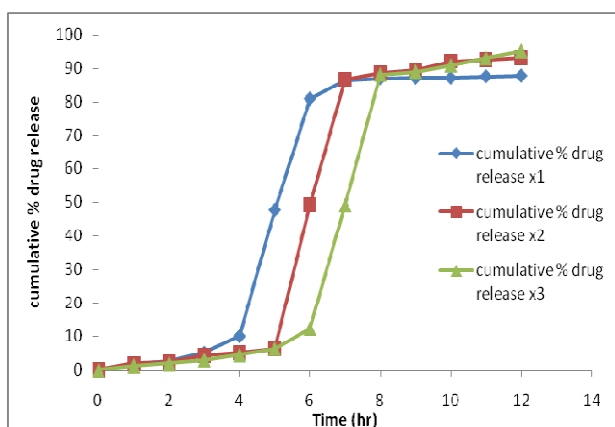


Figure 3: Dissolution Profile of Pulsincap Technology HPMC K₄M as Hydrogel Plug In Erodible Tablet.

Table 7: In-vitro Dissolution Study of Pulsincap formulations

Time (hrs)	Cumulative % drug release											
	G1	G2	G3	H1	H2	H3	S1	S2	S3	X1	X2	X3
1	2.09	2.72	1.67	2.51	1.88	1.25	1.67	1.88	1.25	1.67	1.88	1.25
2	3.97	3.97	2.09	3.14	2.3	1.88	2.51	2.3	1.88	2.51	2.31	1.88
3	5.23	5.02	4.39	3.97	4.18	2.93	5.01	4.18	2.92	5.02	4.18	2.92
4	7.11	6.9	7.32	6.06	5.01	4.39	10.03	5.01	4.39	10.03	5.01	4.39
5	9.41	7.94	8.15	44.11	7.1	5.85	51.64	6.27	6.28	47.67	6.27	6.27
6	88.01	14.01	10.45	79.23	48.5	11.91	84.88	51.21	12.33	80.91	49.13	12.33
7	89.26	87.8	12.13	90.73	87.38	47.45	90.52	86.55	50.81	86.55	86.55	49.12
8	91.78	89.9	90.94	93.45	89.27	86.34	90.94	88.43	88.22	86.97	88.43	88.22
9	93.45	90.73	92.2	93.66	90.31	89.69	91.15	89.48	89.05	87.18	89.48	89.05
10	94.91	92.61	94.91	94.29	92.82	90.52	91.19	91.98	90.94	87.17	91.99	90.94
11	95.33	94.7	96.17	95.12	94.7	92.61	91.56	92.41	93.03	87.61	92.41	93.03
12	96.17	96.79	97.21	95.24	95.74	94.71	91.77	93.03	95.12	87.82	93.03	95.12

**Figure 4:** Dissolution Profile of Pulsincap Technology Sodium Alginate as Hydrogel Plug In Erodible Tablet.**Figure 5:** Dissolution Profile of Pulsincap Technology Xanthum Gum as Hydrogel Plug In Erodible Tablet.

Erodible tablet formulations were subjected for evaluation of Shape, thickness, hardness, friability and weight variation. The data obtained from post-compression parameter such as thickness, hardness, friability, and weight variation of Erodible tablet are shown in **Table 6**.

In all formulation, the hardness test indicates good mechanical strength. Hardness was ranged from 3.41 to 5.57 Kg/cm². Friability was ranged from 0.20 to 0.86. Friability is less than 1% which indicated that tablets had good mechanical resistance. In weight variation test all tablets are in the percentage limit allowed.

In vitro drug release study of Pulsincap technology

In-vitro drug release profiles of pulsatile device were found to have very good sustaining efficacy. During dissolution studies, it was observed that, for 2 hours in 0.1 N Hydrochloric acid, all capsules having erodible tablet plug of different polymer have negligible drug release.

Erodible tablet absorbed the surrounding fluid, swelled and released the drug through the swollen matrix. After complete wetting of the plug, it formed a soft mass, which was then easily ejected out of the capsule body expose the core tablet of captopril to pH 6.8 phosphate buffer solution, after that core tablet due to presence of superdisintegrant show rapid disintegration and maximum drug release achieve in colonic fluid after lag time. Cumulative % drug release data of all batches is given in **Table 7**.

CONCLUSION

From in vitro dissolution study it was concluded that in-vitro drug release profiles of pulsatile device were found to have very good sustaining efficacy, it was observed that drug release is directly proportional to concentration of polymer used in erodible tablet preparation.

From obtained results, it was found that Guar gum shows high sustaining capacity.

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