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RESEARCH ARTICLE

Design and Development of Losartan Potassium Press Coated Tablets for Pulsatile Drug Delivery

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Abstract

The objective of the present study was to design and evaluate time-dependent pulsatile delivery systems (PDDS) of losartan potassium pulsatile press coated tablets. Losartan potassium (LP) is angiotensin II (AG II) receptor antagonists to treat hypertension. LP pulsatile systems are time-controlled drug delivery systems which are designed to mimic the circadian rhythm of the body and deliver the drug at a specific time. LP core tablets were prepared by direct compression method using a single punch machine. The prepared tablets were shielded with a combination of different grades of Hydrosy propyl methyl cellulose (HPMC) and Ethyl cellulose (EC) as coated materials. Prepared core and pulsatile tablets were optimized and evaluated for various properties like diameter and thickness, uniformity of weight, hardness, friability, disintegration time, drug content and *in vitro* dissolution studies. The drug release profile LP pulsatile tablet batch of LH-3 designated as the optimized batch that shows the lag time 8 hrs with complete drug release of 99%. LP pulsatile tablets will be taken at bedtime, releasing the drug in the morning hrs when the symptoms are more prevalent can prove to be a revolution in the treatment of hypertension.

Keywords: *Ethyl cellulose, Hydroxy propyl methyl cellulose, Losartan potassium, Pulsatile drug delivery.*

Introduction

Pulsatile release dosage form predictably releases the drug and maintains plasma drug level in the therapeutic range. This system created a new pattern of drug release, which is connected to the chronopharmacology. The term "chrono" denotes to the observation of every metabolic activity undergoes rhythmic changes with time [1].A pulsatile drug delivery system (PDDS) that can be administered at night (before sleep) but that release drug in the early morning would be a promising chronopharmaceutic system [2]. PDDS is generally a time- and site-specific delivery system which is designed to release the active material rapidly in a burst manner (fast release mode) within a short period immediately after a predetermined off-release period called lag time or delay time [3, 4].The main rationale for the use of PDDS is the delivery of those drugs which exhibits biological tolerance, especially upon a constant drug release, such as a zero-order release, decreasing the drug efficiency [5]. This is a proper system for chronotherapy, especially for the diseases that are predictable cyclic rhythms. The effectiveness of medication regimen can recover both efficiency of the treatment and compliance of the patients [6, 7]. LP is a selective, competitive angiotensin II (receptor type 1 (AT1)) antagonist, reducing the end-organ responses to angiotensin II. Reduction in blood pressure occurs independently on the status of the renin-angiotensin system.

LP used in the treatment of hypertension and other disorders that follow a circadian rhythm, such as diabetic mellitus, angina pectoris, and rheumatic diseases. Additionally, LP is well absorbed after oral administration and bioavailability of about 33% and plasma half-life ranging from 1.5 to 2.5 hrs [8]. LP can be used for the therapy of symptoms or disease that becomes worse during night or in the early morning according to circadian rhythms and chronobiology.

In these cases, conventional drug delivery system is inappropriate for the delivery of drug, as they cannot be administrated just before the symptoms are worsened during sleeping hours [9].Current research aims to develop a pulsatile chrono pharmaceutical drug delivery system of LP for synchronization of drug delivery to the circadian rhythm of hypertension and to control the onset of drug action by drug release lag time.

Materials

Losartan potassium was received as a gift sample from Macleod Pharma, Mumbai, (AR. No.755045. Batch No. 6 LK 002), Microcrystalline cellulose (MCC) was supplied from Signet chemical Mumbai. Cross povidone, magnesium stearate, lactose monohydrate was purchased from Loba chemie Mumbai. Hydroxy propyl methyl cellulose with different viscosity grade (HPMC 50 cps, K4M and K100) and sunset red were supplied by M.J Biopharm Mumbai. Ethyl cellulose and talc were bought from Micro fine chemicals. Mumbai .

Pre-formulation Studies

Drug-excipient compatibility study (by FT-IR) and pre-compression parameters such as angle of repose, bulk and tapped densities, compressibility index was done for lubricated LP compression blend as per USP pharmacopoeia specification.

Preparation of LP core Tablets

Preparation of rapid release inner core tablet was a very important part of formulation consideration, in this study fast dissolving tablets a super disintegrant cross povidone [10, 11] was used for the preparation of core tablet. The tablets were prepared using different excipients (MCC, magnesium stearate and lactose monohydrate) and they were blended with 50 mg active ingredient (LP) to get 150 mg core tablet that can drug release within few minutes as soon as the outer press coating materials are dissolved or eroded. Compression of LP core tablets was prepared by single compression tablet machine using 8 mm flat punch.

Preparation of LP Press-coated Tablets

As given in table 1 the various formulation compositions containing HPMC, EC, MCC, talc, magnesium stearate and colorant were used to formulated from LH-1 to LH-12 by direct compression method. The prepared core tablet (150 mg) was placed centrally and then remaining 150 mg of powder blend was filled in 11 mm die cavity. The total weight of 300 mg LP press coated tablet was compressed in single punch tablet compression (Fig. 1).

Table 1: Formulation composition of press-coating material

Ingredients	LH-1	LH-2	LH-3	LH-4	LH-5	LH-6	LH-7	LH-8	LH-9	LH-10	LH-11	LH-12
Losartan Potassium	10	10	10	10	10	10	10	10	10	10	10	10
HPMC K 4 M	81	99	117	135	NA	NA	NA	NA	NA	NA	NA	NA
HPMC K 100 M	NA	NA	NA	NA	81	99	117	135	NA	NA	NA	NA
HPMC 50 CPS	NA	NA	NA	NA	NA	NA	NA	NA	81	99	117	135
Ethyl Cellulose	45	45	45	45	45	45	45	45	45	45	45	45
MCC (Avicel pH 102)	146	128	110	92	146	128	110	92	146	128	110	92
Talc	9	9	9	9	9	9	9	9	9	9	9	9
Magnesium Stearate	9	9	9	9	9	9	9	9	9	9	9	9
Color	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
TOTAL	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**

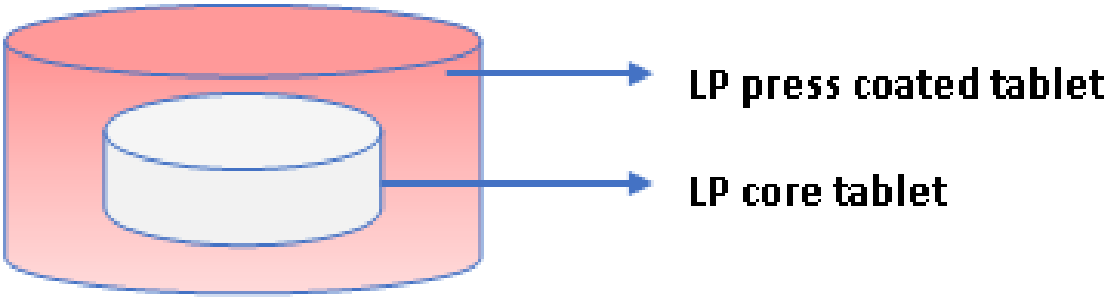


Fig. 1: Schematic diagram of Losartan potassium Pulsatile tablet

Post compression Evaluation of LP core and Press-coated Tablets

Core and press coated tablets were evaluated for post compression-tests such as thickness, hardness, friability, weight variation and uniformity of drug content according to the USP pharmacopoeia specification**.**

In vitro Drug Release Study (LP press coated pulsatile tablets)

The *in-vitro* release patterns of press coated pulsatile tablets containing LP was performed at 37±5ºC using 0.1 N Hydrochloric acid (HCl) for first 2 hrs and then continuously in pH 6.8 phosphate buffer solution in USP apparatus II with paddle speed 100 rpm. Aliquot of 10 ml filtered was manually withdrawn at predetermined time intervals and replaced with 10 ml of fresh respective media. The sample suitably diluted with respective media, then analyzed at 205 nm using a UV spectrophotometer [12].

Drug Release Models

There are two significant characteristics of drug delivery system in describing drug dissolution profile are drug release mechanisms and kinetics. The kinetics of the drug release from matrix tablet, mathematical models namely zero-order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models were used. The measurement to select the most appropriate model is based on the goodness – or fit test [13].

Stability Studies

Accelerated stability studies were carried out at 40 ± 2°C/ 75 ± 5 % RH for optimized formulation (LH-3). The changes in physical appearance, drug content and *in vitro* release studies were observed for a specific time up to 60 days.

Results and Discussion

Drug-excipient Compatibility Study

From the FT-IR spectrum, it was observed that there were no changes in these main peaks in IR spectra of a drug and mixture of drug and excipients, which showed there were no physical interactions between drug and polymers used. FT-IR studies had indicated that no interaction between drug and polymers, and compatible with the formulation components (Fig. 2).

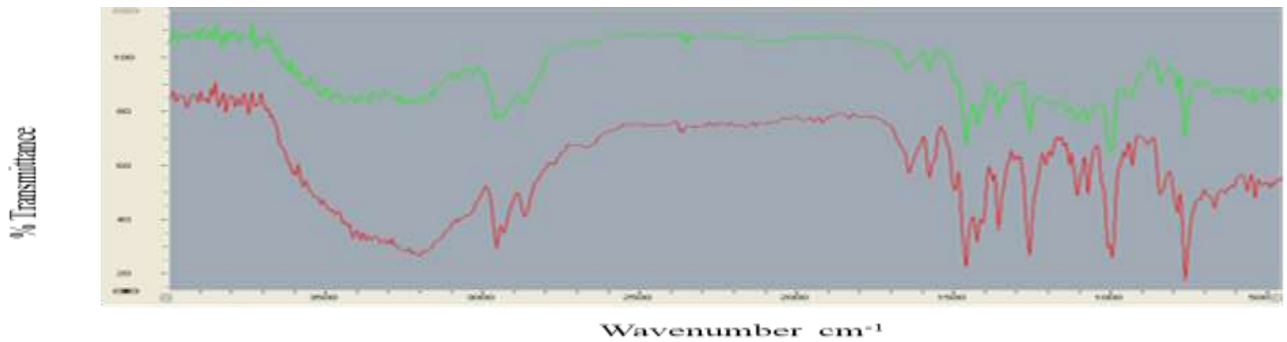


Fig. 2: FT-IR graph of LP and LP core tablet blend

Pre-compression Evaluation of Powder Mixture of Core Tablet

As per USP Pharmacopeial specification, powder mixture was evaluated for angle of repose, bulk density, tapped bulk density, bulkiness and Carr's index.

Pre-compression parameters of powder mixture of core tablet as shown in table 2. An angle of repose of powder mixture was 33º, categorized as good flowing. Bulk density and tapped bulk density of powder mixture were 0.4166 gm/cm^3 and 0.4545 gm/cm^3 respectively.

Compressibility index of 8.33 % indicates that the core tablet blend had excellent compressibility characteristics [14, 15].

Table 2: Pre-compression evaluation powder mixture

Parameter	Observation
Angle of repose	32º69′
Loose bulk density(LBD)	0.4166 gm/cm^3
Tapped bulk density (TBD)	0.4545 gm/cm^3
Bulkiness	2.400 gm/cm^3
Compressibility index (Carr's index)	8.33 %

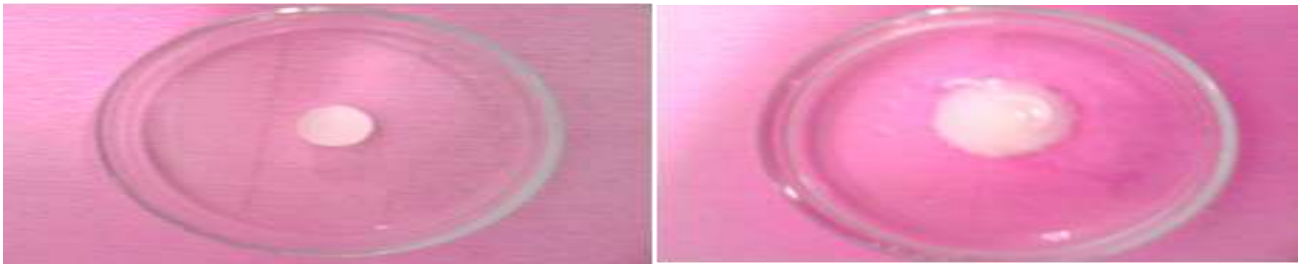
Post-compression Evaluation of LP core and Press-coated Tablets

The LP core tablets were evaluated for thickness, hardness, average weight, friability and *in vitro* disintegration study. The thickness of the core tablets was 2.3 mm. Hardness and average weight of core tablets was 4.50 ± 0.25 kg/cm^2 and 151.5 mg respectively. Friability of core tablets was 0.74l5 (%) which passes USP/NF limits that are less than 1% loss during friability test (Table 3).

Table 3: Post-compression evaluation of LP core tablet

Parameter	Observation
Thickness	2.3 mm
Hardness	4.50±0.25 Kg/cm^2
Average Weight	151.5 mg
Friability	0.7415 %

The fast disintegrating time was observed by visual observation of the LP core tablet in petri dish (medium: 0.1 N HCl) and was determined as time point when the core tablet disintegrates completely (n=3) [16, 17]. The LP core tablet was disintegrated completely within 2 min, consisted of achieving rapid drug release (Fig. 3). LP core tablet had cross povidone as a super disintegrant, which caused to disintegrate rapidly the LP after the press coated polymers released.



Initial

After 2 mins

Fig. 3: *In vitro* disintegration of LP core tablet

Post-compression Evaluation Press coated LP Pulsatile Tablets

The post-compression data of the press coated LP pulsatile tablets are shown in table 4. Tablets from different batches were evaluated to ensure their weight uniformity; none of batch crossed the USP limit. Prepared tablets showed similar values for hardness, and thickness and none of the batches exceeded the maximum acceptable weight loss during friability testing. Results showed that all batches fell in the acceptable pharmacopeial limit. The uniformity of drug content was almost the same in all prepared batches.

Table 4: Post-compression evaluation Press coated LP Pulsatile tablets

Batch	Weight variation (mg)	Hardness Kg/cm^2	Thickness (cm)	Friability (%)	Uniformity of Drug content (%)
LH-1	300.10 ±0.56	6.8	3.9	0.5±±0.14	99.65
LH-2	301.12 ±0.64	6.5	4	0.54±0.11	98.85
LH-3	299.98 ±0.75	6.5	4	0.52±0.13	99.06
LH-4	298.26 ±0.60	7.5	3.8	0.54±0.14	98.50
LH-5	300.22 ±0.66	6.8	3.8	0.56±0.11	97.05
LH-6	303.26 ±0.57	6.5	3.9	0.53±0.14	98.44
LH-7	300.31 ±0.55	6.5	3.8	0.57±0.13	98.68

LH-8	302.06 ±0.60	7	4	0.53±0.14	99.30
LH-9	300.21 ±0.55	6.8	4	0.52±0.13	98.55
LH-10	301.35 ±0.64	6	3.8	0.54±0.14	98.00
LH-11	298.98 ±0.60	6.5	3.8	0.56±0.11	99.45
LH-12	299.96 ±0.60	6.5	3.8	0.52±0.13	99.66

In vitro Drug release Study (Press coated pulsatile tablets)

The *in vitro* drug release was carried out in 0.1 N HCl followed by pH 6.8 phosphate buffer medium. The tablets were found to be stable at 0.1 N HCl and later in pH 6.8 the press coated tablet gets released by eroding the outer coat layer which is shown in Fig. 4. [18].

0.1 N HCl (2 hrs) **PH 6.8 phosphate buffer**

Fig. 4: *In vitro* dissolution LP press coated tablet

LH-1 to LH-4 batch showed a lag time of 4 to10 hrs (Fig. 5), LH-4 batch contains 45 % HPMC K4M and 15 % EC observed the highest lag time of 10 hrs. After the lag time, press coating material got eroded and core tablet come in contact with dissolution medium within a few min the core tablet dissolved completely and released 99% drug in 20 hrs.

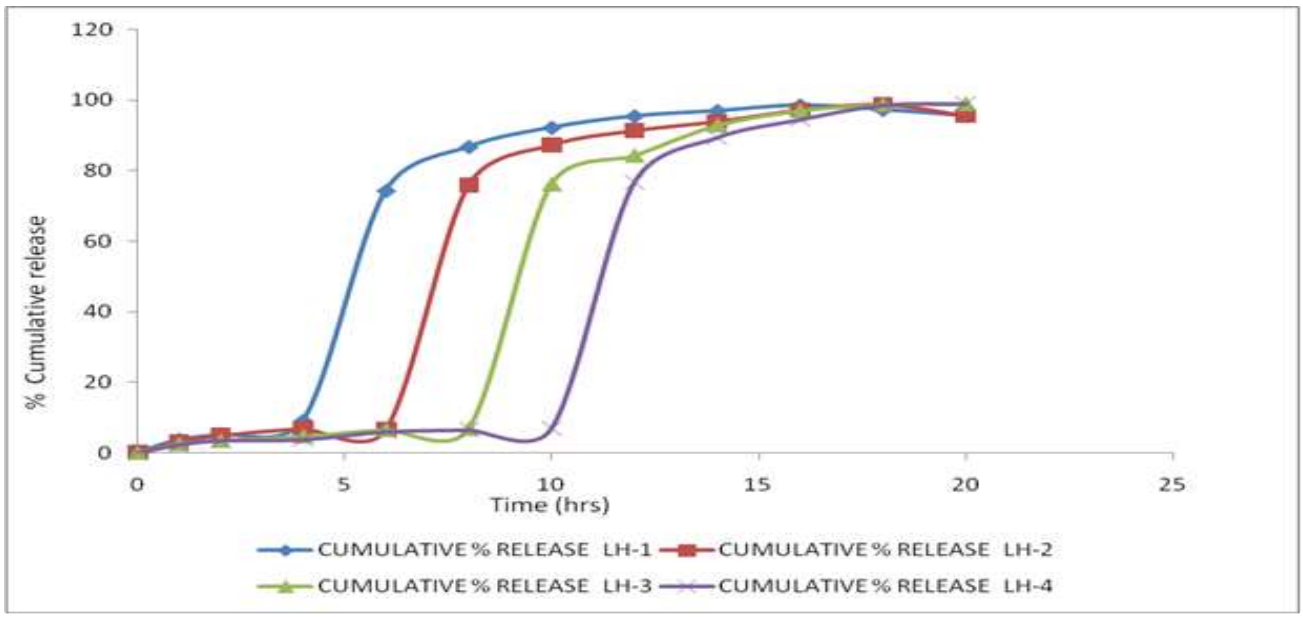


Fig. 5: Comparative *in vitro* release profile of LP pulsatile tablet containing HPMC K 4 M

LH-5 to LH-8 batch containing different concentration HPMC K 100 M showed lag time from 8 to 12 hrs (Fig. 6), lag time increase with increasing concentration of HPMC. After coating material got completely eroded and core tablet disintegrated and released drugs around 100 % in 25 hrs.

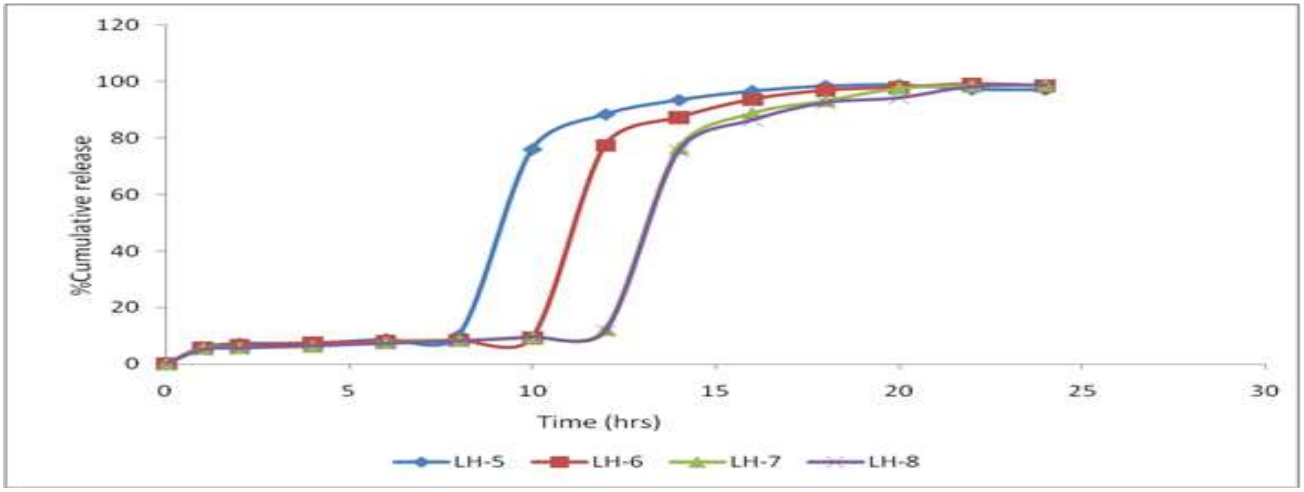


Fig. 6: Comparative *in vitro* release profile of LP pulsatile tablet containing HPMC K100 M

LH-9 to LH 12 batch containing HPMC 50 cps showed the lowest lag time of 2 to 4 hrs (Fig. 7), amongst all three HPMC grade. HPMC 50 cps batch tablets were completely disintegrated and released 100 % drug within 10 hrs.

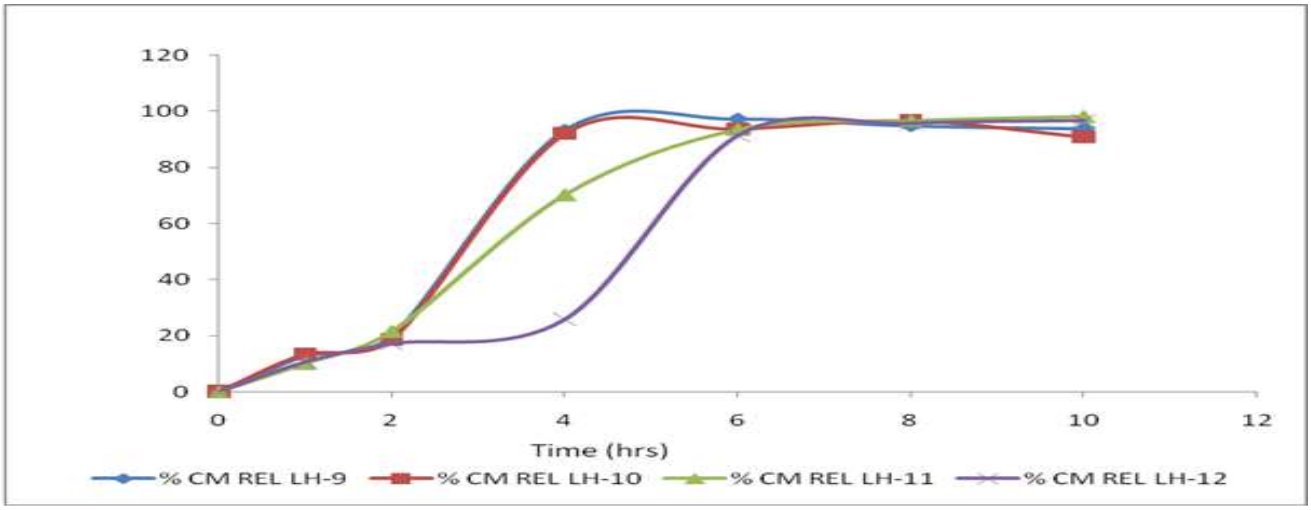


Fig. 7: Comparative *in vitro* release profile of LP pulsatile tablet containing HPMC 50 CPS

Depending on the different viscosity grade of the HPMC (the molecular weight of the polymer) and EC polymer a wide range of toughness and strength of the combination can be exhibited, which may eventually reflect on the release of the press coat. EC with a medium range of viscosity can be the proper candidates with the desired mechanical properties creating a wide range of lag times with no sensitivity to the coating weight [19].

The press coated tablet has been structured in such a manner that it releases the drug after the lag time i.e., better absorb at intestinal environment. Also this support for justifying the dosage form for its chronotherapeutic property. The above data reveals that batch containing a composition of HPMC K4M 39% and EC 15%, LH-3 as outer barrier layers and which was suitable to achieve the 8 hrs lag time, So it was the best composition for pulsatile release and direct compression was the best method.

Drug release Models

The drug release data of optimized formulation (LH-3) were fitted to models representing zero order, Higuchi's and Korsmeyer's - Peppas equation kinetics to know the release mechanisms (table 5). It was observed that the correlation coefficient values are higher (r^2 = 0.924) with the zero-order kinetics (Fig.8) [18, 20]. To find the drug release mechanism, the *in-vitro* data were also subjected to Higuchi diffusion.

The 'r' value of Higuchi diffusion was 0.9861, for LH-3 LP press coated tablets. It suggests that the Higuchi diffusion plots of LH-3 batch was fairly linear because 'r' values near about 1, so it confirms the drug release by Higuchi diffusion mechanism. The similar finding was reported by researchers for time programmed

pulsincap system for chronotherapeutic delivery of losartan potassium [9]. The n value of peppa's plot confirms that it obeys non fickian type of drug release.

Table 5: Drug Release Mechanisms and Kinetics (LH-3)

Time (hrs)	%CDR	log % CDR	% CDR (x)	log % cum. drug remaining	log T	√T	(x)⅓
0	0		100	2		0	4.641
1	2.3	0.36172	97.7	1.98989	0	1	4.605
2	3.5	0.54406	96.5	1.98452	0.3010	1.4142	4.586
4	3.78	0.5774	96.22	1.98326	0.6020	2	4.582
6	6.03	0.78031	93.97	1.97298	0.7781	2.449	4.546
8	6.54	0.8155	93.46	1.97062	0.9030	2.828	4.538
10	6.9	0.8388	93.1	1.96894	1	3.1622	4.532
12	76.62	1.8843	23.38	1.36884	1.0791	3.4641	2.859
14	89.32	1.9509	10.68	1.02857	1.14612	3.7416	2.202
16	94.44	1.9751	5.56	0.7450	1.2041	4	1.771
18	98.51	1.9934	1.49	0.1731	1.2552	4.2426	1.142
20	98.93	1.9953	1.07	0.02938	1.3010	4.4721	1.022

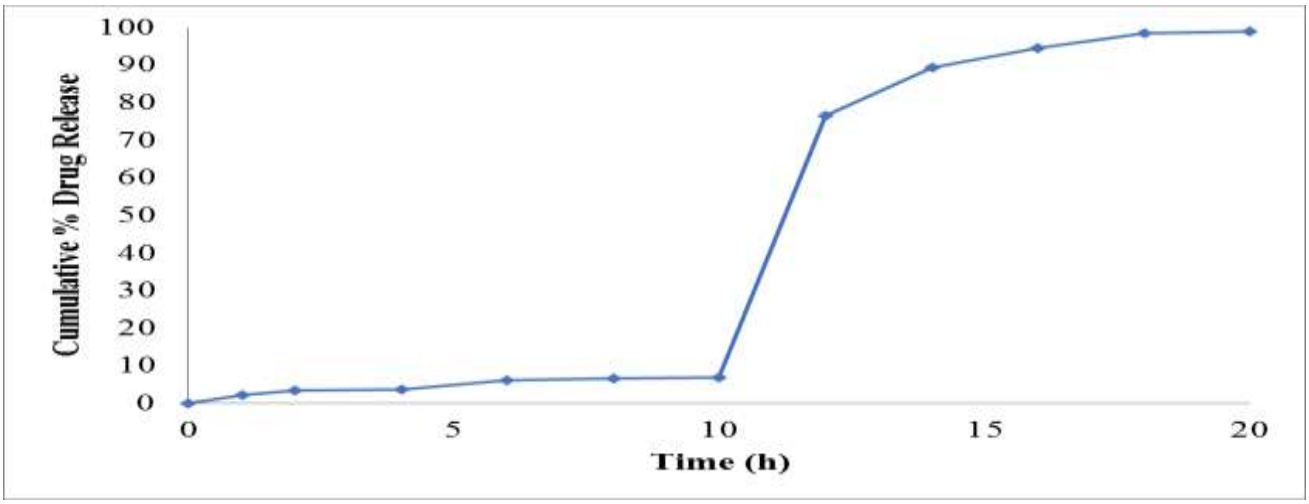


Fig. 8: Zero Order Drug Release Kinetics

Stability Studies

Results of accelerated stability studies reveal that the tablets did not show any change in physical appearance during the study period, drug content (n=3; mean ± SD) was found to be 98.4±0.38% (data not shown). The dissolution profile of these tablets (shown in Fig. 9) also not showed any significant variation [21, 22]. This signifies that optimized batch has stability and potency at accelerated conditions within 2 months.

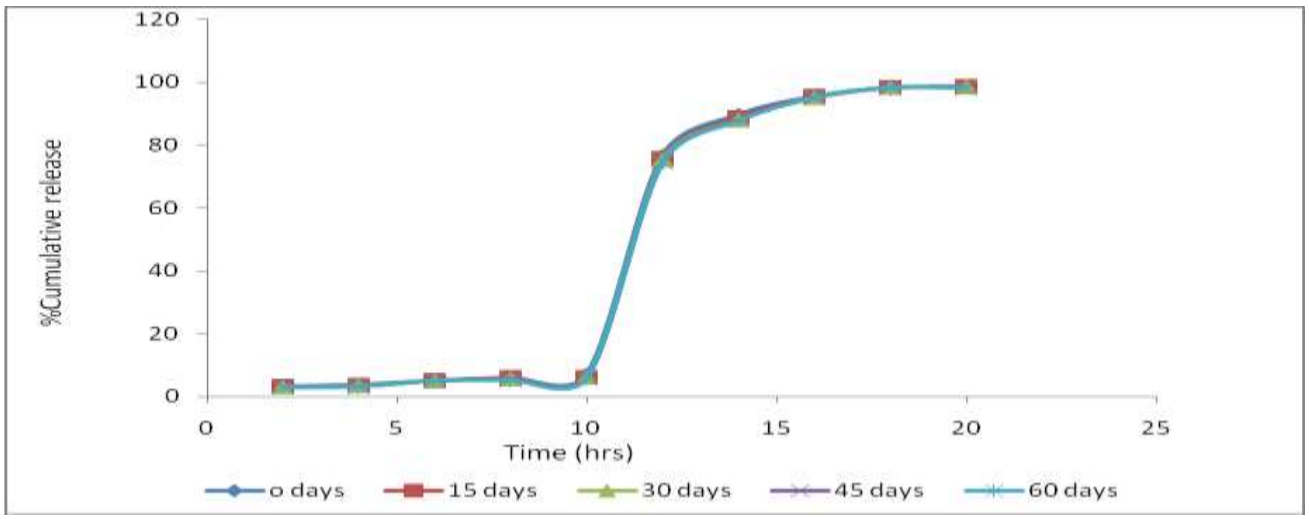


Fig. 9: I*n vitro* release profile of LP pulsatile tablet (LH-3)

Conclusions

A satisfactory attempt was made to develop pulsatile system of LP and evaluated it. The prepared formulations showed satisfactory results and achieved the objective of pulsatile drug release in the desire timeline. The accelerated stability study for LH-3 press

coated LP tablets indicates no significant difference in in vitro release profile after a period of 2 months. Hence, it can be concluded that by altering the amount of the outer coating material different lag times can be obtained.

The batch LH-3 of direct compression having specified composition of ethyl cellulose and HPMC K4M has shown a required lag time of 8 hrs and can be considered a suitable composition of outer barrier layer and direct compression can be considered as best method for pulsatile drug delivery system to treat hypertension as a chronotherapeutics approach.

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