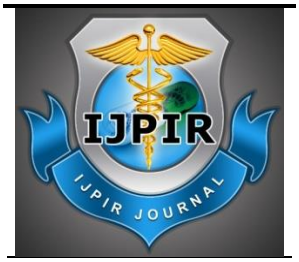
Research Article



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Chronomodulated drug delivery system of losartan potassium: Formulation and *in vitro* evaluation

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ABSTRACT

Objective*:* The purpose of current investigation is to design and evaluate press coated tablets of losartan potassium for chronotherapy of hypertension.
Methods: The core tablets of losartan potassium were formulated by direct compression method using super disintegrants (croscarmellose sodium and crosspovidone). The optimized core tablet is coated with guar gum and ethyl cellulose polymer blend using compression coating technique, which were further evaluated for physical parameters, drug content, swelling studies, drug release, stability studies and FTIR studies.
Results and Discussion*:* The pre, post compression parameters and drug content results of both tablets were within the specified limits of pharmacopeia. Swelling studies of PCT indicates that addition of ethyl cellulose decreased swelling index due to hydrophobic nature. The optimized press coated tablet (LPCT3) showed negligible drug release (< 10%) in 6 h lag time followed by drug release (98.9±1.28%) in 10 h which is suitable for chronotherapy. Stability studies indicates that there is no significant difference in drug release during storage condition. FTIR studies indicates that there is compatibility between drug and excipients.
Conclusion: Press coated tablets with polymer blends of guar gum and ethyl cellulose resulted in drug release after a predetermined lag time which is suitable for chronotherapy of hypertension.

Keywords: Losartan Potassium, Press coated tablets, Hypertension

INTRODUCTION

Innovative drug delivery systems have emerged from considerable technological advancements in formulations, biodegradable polymers, and pharmacokinetics during the last 30 years. Due to circadian rhythm, people's physiological and biochemical state fluctuate within each 24 h period, making continuous drug administration into the body unnecessary and undesired. Certain ailments like asthma, peptic ulcers, cardiovascular disease, cancer and rheumatoid arthritis exhibit circadian cycles in its pathogenesis. Nowadays, based on the concept of chronotherapeutics [1], chronotherapeutic systems are having a great deal of interest and awareness because they provide drugs at a precise moment based on the disease pathophysiological demand, leading in enhanced

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therapeutic efficacy and patient compliance [2]. The pulsatile or sigmoidal system is another name for a chronomodulated system. A chrono modulated drug delivery system delivers drug quickly and transiently after a specified lag time [3]. These systems are beneficial for drugs with chrono pharmacological behaviour (night-time dosing), first pass metabolism, and a particular absorption site in the gastrointestinal tract (GIT).

Hypertension is a sever condition that affects about 90% of individuals with cardiovascular disease (CVD) and is a high-risk factor for CVD, that can lead to sudden death [4-6]. Blood pressure (BP) fluctuates throughout the day, with a morning surge (between 6 a.m. and noon) associated with activation of renin-angiotensin-aldosterone and sympathetic nervous system prior to waking. Morning BP spikes have been linked to an increased incidence of heart mortality and myocardial infarction [7 & 8]. The morning activation of catecholamines, renin, and angiotensin correlates to increased blood pressure [9].

Compression coating, also known as press coating, is a simple and innovative strategy of creating a pulsatile drug delivery system that has a number of benefits. The tablet may be coated thickly quickly, and there is no need for a particular coating solvent or coating apparatus [10]. It is used to protect moisture-, light-, oxygen- or acid-sensitive drugs [11], to mix and isolate distinct drugs [12], and to change timings of drug release (prolonged pulsatile and programmed release of several drugs in single tablet) [13]. A core tablet is coated by hydrophobic/hydrophilic polymer blend. After a specific amount of time has passed, the outer polymer coating may erode, burst, or disintegrate, releasing the drug from the core tablet due to penetration of water to barrier coating layer causing rupture [14].

Losartan Potassium (LP) is a non-peptide antagonist of angiotensin II type I (AT1) receptor, used for treatment of hypertension, especially nephropathy in diabetic individuals [15]. It inhibits the renin-angiotensin system by preventing angiotensin II from binding to its receptors [16]. On repeated oral administration, it is quickly absorbed from the gut and metabolised (14 % of dose) by CYP2C9 into an active carboxylic acid metabolite (E3174) [17]. It has a 33 % oral bioavailability and a plasma elimination half-life of 2 to 2.5 hours [16, 18 & 19], there by requiring 2-3 times daily dosing which often leads to patient non-compliance [20]. It belongs to class I of Biopharmaceutical Classification System (BCS). It is taken once daily with dose of 25, 50, 100 mg depending on the need for prevention, treatment, and in severe conditions.

MATERIALS AND METHODS

Materials

Losartan Potassium was a gift sample from Dr. Reddy's Laboratory Pvt. Ltd. Hyderabad, India. Crosscaramellose Sodium (CCS) and Crosspovidone (CP) were gift sample from Hetero Drugs, Hyderabad, India. Guar Gum (LR grade) was obtained from Aurobindo Pharma Pvt. Ltd. Hyderabad. Ethocel™ was supplied from Colorcon Asia Pvt. Ltd., Goa, India. Avicel PH 102, Talc and Magnesium stearate were supplied from S. D fine Chemicals Ltd., Mumbai, India. All other chemicals were analytical quality.

Methods

Pre-formulation study

The organoleptic characteristics of the LP drug sample were studied (physical state, colour, odour and taste). A capillary tube technique was employed to assess the melting point.

Drug solubility studies were conducted in various media (distilled water, methanol, pH 6.8 phosphate buffer). An excess quantity of LP drug was introduced into a 25 ml flask containing medium, further they were agitated on a rotary shaker at 37°C for 24 h. Then, they were kept for another 24 h without disturbing to achieve equilibrium. Solutions were filtered through a 0.45µm filter, diluted appropriately and determined by a UV-Visible Spectrophotometer at 230nm (Shimadzu Corporation, Japan) [21].

Preparation of LP core tablets

Core tablets (LRRCT1-LRRCT4) weighing 100mg were developed by direct compression technique using various concentrations of super disintegrants (croscarmellose sodium, CCS; crosspovidone, CP). For a batch of 100 tablets, drug, super disintegrants and diluents were accurately weighed (Table 1), sieved through ≠ 30 sieve, transferred to polybag and mixed for 5 min. Magnesium stearate and talc were added to previous blend and re-blended for 2 mim, further, the mixture was compacted into tablets using a 16 stations rotary punching machine with 6mm round flat punches (Cadmach, Ahmedabad, India) [22].

Table 1: Composition of Losartan Potassium core tablets

Formulation	LP (mg)	CCS (mg)	CP (mg)	Avicel PH102 (mg)	Talc (mg)	Magnesium Stearate (mg)	Total Weight (mg)
LRRCT1	50	2	-	45	2	1	100
LRRCT2	50	4	-	43	2	1	100
LRRCT3	50	-	2	45	2	1	100
LRRCT4	50	-	4	43	2	1	100

Preparation of LP press coated tablets

Optimized LP core tablet (LRRCT4) was press coated with varying compositions of Guar gum (hydrophilic polymer) and Ethyl cellulose (hydrophobic polymer) polymer blend (Table 2). For a batch of 100 tablets, the necessary amounts of polymer blend were weighed and blended for 5 min. Magnesium stearate and talc were added, sifted through # 30 sieve and re-blended for 2 min. Half of the coating material was placed in the die cavity, accompanied by carefully positioned core tablet in the centre, then remaining half of the coating material was filled in die cavity and compacted with 16 stations rotary punching machine (Cadmach, Ahmedabad, India) using 9 mm round, flat punches to produce press coated tablets (PCT) weighing an average of 201.5 mg.

Table 2: Composition of Losartan Potassium press coated tablets

Formulation	Guar gum (mg)	Ethocel (mg)
LPCT1	0	100
LPCT2	25	75
LPCT3	50	50
LPCT4	75	25
LPCT5	100	0

Each formulation contains 1% Talc and 0.5% Magnesium Stearate

Pre-compression studies of core and press coated powder mixture

Various pre-compressional assessment criteria were applied to the powder mixture of all core and coated formulations. Pre-compression parameters were used to assess the flowability of the powder blend of core and PCT and were determined using the following equations.

$$Tan\theta = \frac{h}{r} \qquad (1)$$

Where, *h* is the height of the cone formed by powder blend, *r* being the radius of the cone base and θ is the angle of repose.

$$Carr's\ Index\ (\%) = \frac{TD - BD}{TD} \times 100 \qquad (2)$$

$$Hausner's\ Ratio = \frac{TD}{BD} \qquad (3)$$

Where, the tapped density is TD and the bulk density is BD.

Post compression studies of core tablets and press coated tablets

The formulated core and coated tablets of LP were characterized for various physical properties as per standard procedures.

Diameter and *thickness* are crucial characteristics of tablet identification as it ensures uniformity of size, which were determined using vernier calliper and average values with ± SD were recorded in mm. *Hardness* of the tablets was measured by Monsanto hardness tester and recorded in kg/cm^2 [23]. *Weight variation* was conducted by randomly selecting 20 tablets, weighed each and the mean weight of tablet was determined further, compared with individual tablet weight. Weight variation for each formulation was computed by using formula.

$$\%\ Weight\ Variation = \frac{Average\ weight\ of\ tablet - weight\ of\ each\ tablet}{Average\ weight\ of\ tablet} \times 100 \qquad (4)$$

Friability test was carried out by taking 5 tablets in triplicate. The tablets were weighed and were placed in Roche friabilator (Electro labs, Model EF2, Mumbai, India) and rotated at speed of 25 rpm for 4 minutes. The tablets were dedusted to remove impacted powder and reweighed again to know loss in weight which represents mechanical strength of tablet. Friability was calculated by following formula.

$$\%\ Friability = \frac{Initial\ Weight - Final\ Weight}{Initial\ Weight} \times 100 \qquad (5)$$

Drug content

Drug content was determined to ensure dose uniformity in each tablet. In mortar and pestle, 5 tablets were crushed into fine powder and the powder equivalent to 50 mg of drug was taken and transferred to volumetric flask containing 100 ml of pH 6.8 phosphate buffer. It was agitated continuously on rotary shaker and it was left aside for one hour to ensure complete dissolution further filtered using 0.45 µm filter, diluted appropriately before being analysed by a UV- Visible spectrophotometer (Shimadzu Corporation, Japan) at 230nm [4].

Disintegration time

Disintegration study was conducted using USP disintegration apparatus (Electrolab, Model, ED-2L Mumbai, India) in triplicate as method described in the BP. Tablets were kept in each of the basket's six tubes having water as disintegration fluid at 37±2°C. The time required for complete disintegration leaving no residue on wire screen, was observed for each formulation of core tablets.

Swelling studies

The swelling characteristics of press coated tablets were assessed by keeping tablets in the USP dissolution type I apparatus containing 900ml of 0.1N HCl pH 1. 2 for 2 h continued by pH 6.8 phosphate buffer for 8 hrs at 37±0.5°C. At specified time intervals, the tablets were taken out, blotted with tissue paper to remove excess water and then weighed. The wet tablet weight (*wt*) and initial tablet weight (*wi*) were weighed to determine the swelling index as follows.

$$Swelling\ Index = \frac{wt - wi}{wi} \times 100 \qquad (6)$$

Lag time and in vitro dissolution studies

Drug release studies of core tablets was conducted in pH 6.8 phosphate buffer, 900 ml for 90 min using USP Type II dissolution apparatus (Electro lab, TDT-08L) at 50 rpm and 37±0.5°C.

Lag time is the time taken for the drug to release less than 10% of drug. Lag time of press coated tablet was evaluated at the time of drug release studies by visually inspecting the tablet, further time is recorded when the outer coating is ruptured [24].

Drug releases studies of press coated tablets was carried out successively in two distinct appropriate dissolution media to determine their ability to provide the requisite lag time before drug release using USP Type II dissolution apparatus (Electro lab, TDT-08L, Mumbai, India). The study was conducted in 0.1N HCl (pH 1.2) for 2 h and continued by pH 6.8 phosphate buffer, 900 ml at 50rpm and 37±0.5°C. At predefined time intervals, sample was withdrawn and examined by UV-Visible spectrophotometer at 230nm (Shimadzu Corporation, Japan) [4 & 24].

Stability studies

Optimized press coated tablet (LPCT3) was subjected to accelerated stability studies (40±2ºC/75±5% RH) for 6 months in stability chamber (Hicon, Delhi, India) as stated in ICH Q1A (R2) guidelines (FDA, 2003) to find any visual physicochemical modifications done in the formulation after storing it at elevated temperature and humidity conditions. Tablets were enclosed in air tight amber coloured wide-mouth glass container. Physical parameters, content uniformity and percent drug release of optimized tablet were assessed at specified time intervals [25].

Fourier transform infrared spectroscopy study (FTIR)

Fourier transform infrared spectrophotometer (Shimadzu, Model 84005, Japan) was used to record the spectra of the drug and optimized formulation. Approximately, 2mg of sample was crushed with dried KBr completely and uniformly mixed. Then small portion of mixture was compacted to form transparent pellets at 10 tones pressure using automatic IR press, further, the spectra of pure drug and optimized press coated tablet were recorded at 400-4000cm^{-1}.

RESULTS AND DISCUSSIONS

Pre-formulation study

The organoleptic properties of LP sample were found to be off white to white crystalline powder with bitter taste as given in officials (Indian pharmacopoeia). LP melting point was found to be 262°C (263-265°C).[26] According to existing literature on LP's solubility profile, it is freely soluble in water. The outcomes of LP solubility in water, methanol and pH 6.8 phosphate buffer were found to be 0.810 mg/ml, 0.819 mg/ml and 0.769 mg/ml, respectively.

Pre-compression studies of core and press coated powder mixture

The core blend and coated powder blend with different ratio of Guar gum and Ethyl cellulose were evaluated for precompression parameters (Table 3). The results of precompression parameters were found to be within required limits indicating that all the formulations posses good to excellent free flowing property.

Table 3: Pre-compression parameters for LP core and press coated powder blend

Formulation	Angle of Repose[a] (θ)	Bulk Density[a] (gm/cc)	Tapped Density[a] (gm/cc)	Carr's Index[a] (%)	Hausner's Ratio[a]
LRRCT1	25.4±0.12	0.36±0.005	0.42±0.005	14.29±0.42	1.17±0.05
LRRCT2	24.8±0.18	0.32±0.006	0.38±0.007	15.79±0.36	1.19±0.04
LRRCT3	26.2±0.23	0.39±0.005	0.44±0.008	11.36±0.24	1.13±0.07
LRRCT4	24.4±0.27	0.36±0.004	0.42±0.006	14.29±0.36	1.17±0.03
LPCT1	25.3±0.15	0.41±0.008	0.47±0.005	12.77±0.29	1.15±0.05
LPCT2	26.9±0.14	0.36±0.006	0.43±0.004	16.28±0.35	1.19±0.06
LPCT3	26.3±0.16	0.38±0.008	0.45±0.007	15.56±0.24	1.18±0.08
LPCT4	24.5±0.13	0.40±0.007	0.46±0.009	13.04±0.18	1.15±0.09
LPCT5	24.1±0.20	0.42±0.009	0.47±0.007	10.64±0.45	1.12±0.01

[a]Each value represents the mean ±Standard Deviation SD (*n* =3)

Post compression studies of core and press coated tablets

The post compression parameters of core and coated tablets were evaluated and results were presented (Table 4). *Diameter* and *thickness* of core and coated tablet was within acceptable limit. *Hardness* of core and coated tablets were in the range of 2.89±0.56 to 3.05±0.06 kg/cm^2 and 4.86±0.03 to 4.98±0.63 kg/cm^2, respectively which indicates that tablet possess good mechanical strength with sufficient hardness. *Weight variation* of core and coated tablets were in the range of 99.8±0.22 to 101.0±0.44 mg and 200.5±0.45 to 201.3±0.24 mg, respectively. The percentage standard deviation of all the tablets were within pharmacopeial limits which indicates the uniformity of tablets. *Friability* of both tablets was less than 1% indicating greater mechanical resistance and stability to transportation.

Drug content

Drug content of tablets were found to contain 98.05±0.45 to 99.72±0.19 % of labelled amount which indicates uniformity of drug content as per pharmacopeial limits.

Table 4: Post compression studies of LP core and press coated tablets

Formulation	Thickness[a] (mm)	Diameter[a] (mm)	Hardness[a] (kg/cm^2)	Weight Variation[a] (mg)	Friability (%)	Drug Content[a] (%)	Disintegration Time[a] (sec)
LRRCT1	2.20±0.05	6.03±0.06	3.05±0.06	99.9±0.10	0.82	99.09±0.04	65.8±1.64
LRRCT2	2.21±0.01	6.00±0.04	2.96±0.11	99.8±0.22	0.75	98.05±0.45	42.8±1.06
LRRCT3	2.21±0.03	6.02±0.06	3.01±0.12	101.0±0.44	0.89	99.52±0.06	54.4±0.99
LRRCT4	2.24±0.04	6.01±0.04	2.89±0.56	99.8±0.05	0.87	99.48±0.12	36.54±1.20
LPCT1	3.62±0.03	9.00±0.03	4.86±0.03	200.5±0.45	0.49	99.24±0.25	-
LPCT2	3.63±0.04	9.02±0.07	4.92±0.42	201.4±0.27	0.28	99.45±0.26	-
LPCT3	3.62±0.06	9.04±0.06	4.98±0.63	201.3±0.24	0.34	99.83±0.32	-
LPCT4	3.64±0.04	9.03±0.07	4.94±0.52	201.8±0.34	0.46	99.43±0.25	-
LPCT5	3.62±0.03	9.04±0.04	4.93±0.43	201.4±0.25	0.33	99.63±0.32	-

[a]Each value represents the mean ±Standard Deviation SD (n =3)

Disintegration studies

Results of disintegration studies of core tablets (LRRCT1-LRRCT4) were presented (Table 4). An increase in concentration of super disintegrant, decreased disintegration time. When compared with formulation containing CCS, formulation containing CP showed less disintegration time which may be due to excellent wicking or capillary action for water absorption [26].

Swelling studies

Swelling studies of coated tablets were carried out and presented (Figure 1). Increasing the concentration of ethyl cellulose decreased swelling index and drug release which indicates that it is hydrophobic insoluble polymer. The results revealed that ethyl cellulose was an excellent erosion-controlling polymer in guar gum press coatings.

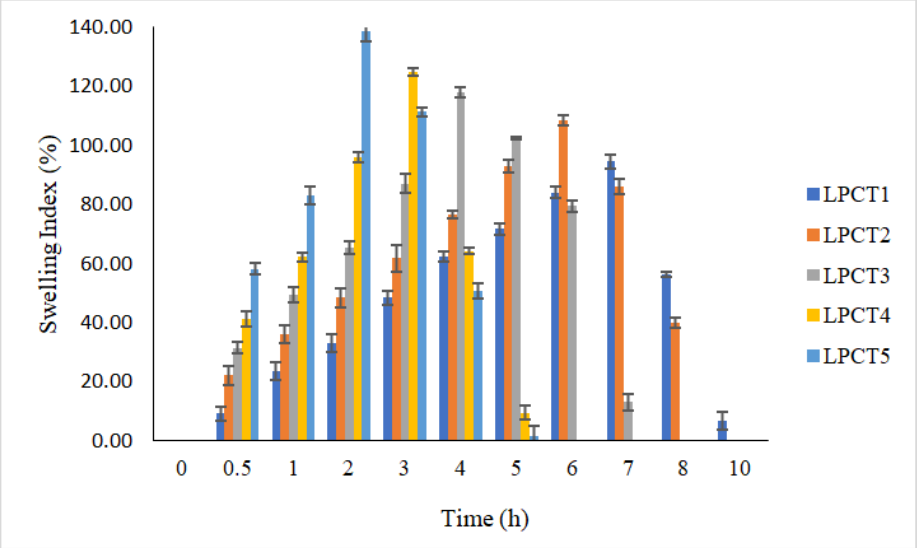

Fig 1: Swelling studies of LP press coated tablets (mean ±SD; *n* =3)

Lag time and in vitro dissolution studies

Drug release studies of core tablet was conducted and the results were shown (Figure 2). The drug release from core tablet containing CCS (LRRCT1-LRRTCT2) was found to be 89.45±1.86 % at 90 min and 98.32±1.89 at 90 min, respectively. Where as the drug release from core tablet containing CP (LRRCT3-LRRCT4) was found to be 99.45±2.99 at 90 min and 98.64±1.96 at 60 min, respectively. From the outcomes, it shows that an increase in amount of super disintegrant, increased drug release. CP containing formulation showed rapid release than CCS containing formulations which may be due to the fact that CP made large pores with continuous skeleton requiring sufficient pressure for rapid disintegration and possess ability to swell when exposed to dissolution fluid [27]. Formulation containing CP in concentration 4% (LRRCT4) showed good hardness and content uniformity, lowest disintegration time and rapid drug release. So, LRRCT4 formulation batch is optimized and it was press coated with outer barrier polymer blend.

Lag time of press coated tablets was assessed by recording the time where the drug release is less than 10% from tablet [28]. Lag time results were within the range of 2 h to 7 h. The formulation (LPCT3) showed a desired lag time i.e., 6hr with complete drug release in 10 h. Formulation containing guar gum alone showed less lag time when compared with formulations containing polymer blend and ethyl cellulose alone. Incorporation of ethyl cellulose (water insoluble), increase the lag time by delaying the erosion of guar gum and decreasing solvent intake [29].

Drug release studies of press coated tablets was performed and the results were shown (Figure 3). Drug release from press coated tablet (LPCT1-LPCT5) showed 75.45±3.57% at 12h, 89.42±1.45% at 12h, 98.9±1.28% at 10h, 98.45±3.14 at 8h and 99.62±2.08% at 8h, respectively. The results revealed that ethyl cellulose alone resulted in more lag time and diminished drug release due to its hydrophobic nature and insolubility over the whole pH range. In other words, excessive ethyl cellulose can bring unwanted proportion of lag time could not cut off and the drug release did not begin until whole lag time finished. Hence, combining guar gum provides a drug release after a desired lag time due to its hydrophilicity and swelling properties. It also suggests that drug release mechanism of PCTs formulated with polymer blend of guar gum and ethyl cellulose is that guar gum imbibes, swells and finally forms an aqueous passage from coating surface to drug layer after definite time which depends on composition of polymer blend. PCT coated with alone guar gum resulted in limited lag time of drug release due to its high hydrophilicity. Hence, drug release rate after lag time was depend on composition of polymer blend. The formulation containing polymer blend of ethylcelluloes (50%) and guar gum (50%) (LPCT3) showed drug release of 98.9±1.28% at 10h with lag time of 6 h is optimized which can be considered as one of the good tools for chronotherapy of hypertension with improved patient compliance.

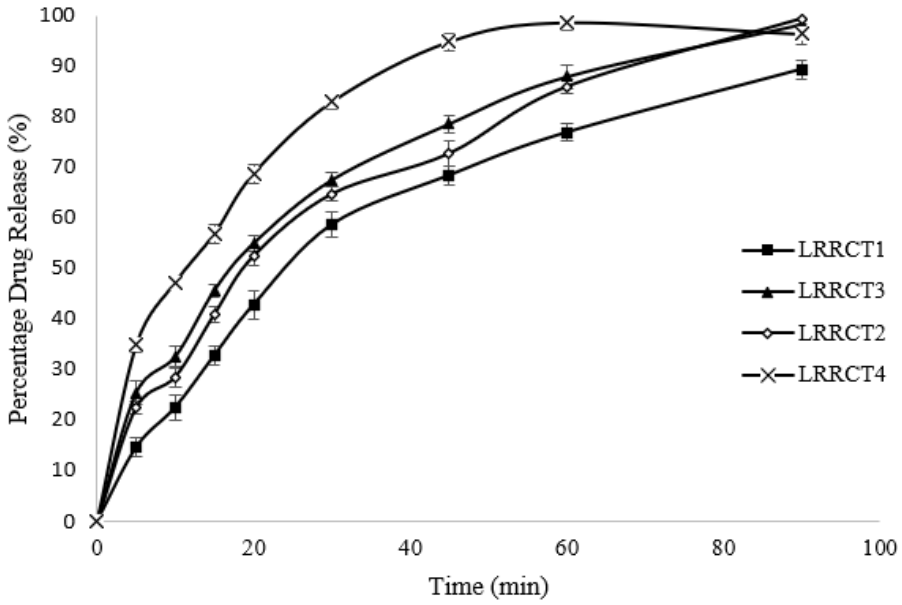

Fig 2: Drug release profiles of LP core tablets (mean ±SD; *n* =3)

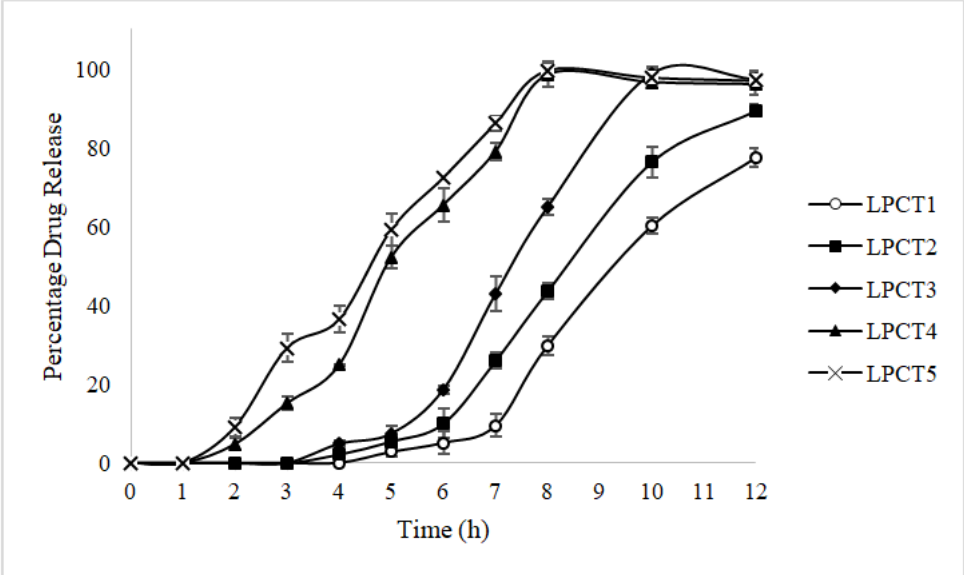

Fig 3: Drug release profiles of LP press coated tablets (mean ±SD; *n* =3)

Stability studies

Stability studies of optimized press coated tablet (LPCT3) were performed by examining the tablet for various parameters (physical parameters, content uniformity and dissolution studies). The stability studies outcome concluded that there are no significant changes in physical parameters and content uniformity. Release of drug from optimized formulation was found to be almost similar during storage period with that optimized tablet before storage as shown (Figure 4). Form release studies, it is confirmed that there is no significant difference in drug release before, during and after storage with similarity factor $f2>50$.

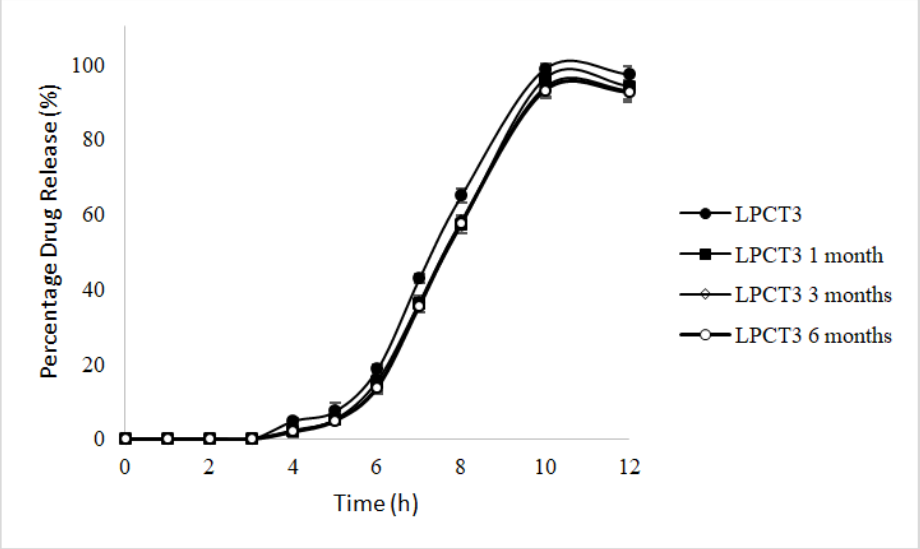

Fig 4: Drug release profiles of optimized LP press coated tablet during stability studies (mean ± SD; *n* =3)

Fourier transform infrared spectroscopy study (FTIR)

The spectra of pure drug LP showed characteristic peaks at 3204 cm^{-1} (OH stretching), 2929 cm^{-1} (CH stretching), 1580 cm^{-1} (C=N stretching), 1460 cm^{-1} (C=C stretching) and 762 cm^{-1} (C-Cl stretching), respectively. The optimized press coated tablet (LPCT3) showed almost same drug characteristic peaks with slight variation in the spectra (Figure 5), which indicates the retention of chemical identity of drug and compatibility between drug and excipients.

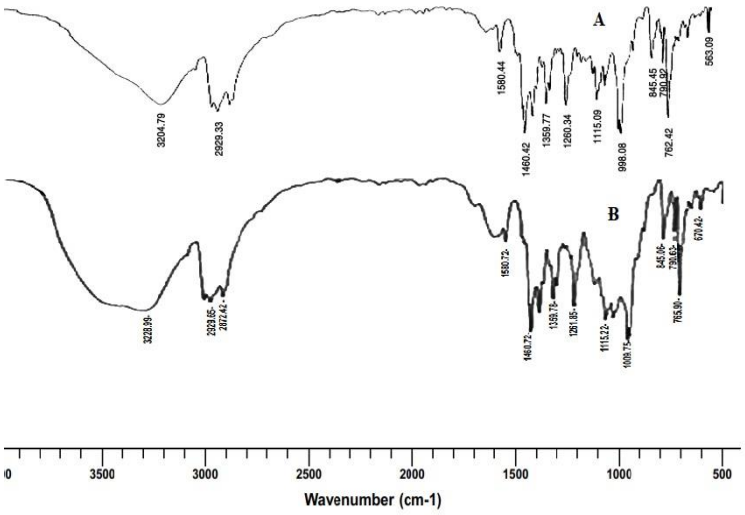

Fig 5: FTIR studies of a) Losartan Potassium and b) Optimized PCT (LPCT3)

CONCLUSION

The lag time and time-controlled drug release from press coated tablet can be modified by varying the proportion of blend of guar gum and ethyl cellulose in outer barrier layer. The optimized formulation (LPCT3) showed drug release of 98.9±1.28% at 10h with lag time of 6 h which make this formulation useful for chronotherapy of hypertension which follows circadian rhythm. The beneficial outcome of this study encourages the use of polymer blend of guar gum and ethyl cellulose in development of chronotherapeutic system used to treat hypertension that follows circadian rhythm.

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