INTRODUCTION
Traditionally, drug delivery has meant to get a simple chemical absorbed predictably from the gut or from site of injection [1]. Oral controlled drug delivery 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. The oral controlled release system shows the typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby sustaining therapeutic action. But there are certain conditions which demand release of drug after a lag time, i.e., chronopharmacotherapy of disease which shows circadian rhythms in their pathophysiology [2]. A number of common diseases which shows circadian rhythms in their pathophysiology include rheumatoid arthritis, allergic rhinitis [3], hypertension [4, 5] and cancer [6].
Hypertension is a chronic disorder present in over 90% of all patients with cardiovascular (CV) disease and is a major risk factor for CV disease which sometimes leads to sudden death [7-9]. Ambulatory blood pressure (BP) exhibits a diurnal variation with increase in the morning (between 6 am and noon; BP surge) with activation of the sympathetic nervous system prior to awakening. The morning BP surge was reported to be associated with high risk of cardiac death, ischemic and hemorrhagic stroke [10, 11]. These changes in blood pressure corresponds the morning activation in catecholamines, renin, and angiotensin [12].

Treatment of this disease condition occurring in the early hours is not convenient by using conventional immediate release dosage form. Hence, chronotherapeutic drug delivery system (ChDDS) may be useful for such patients since the drug is released at a predetermined lag time. Chronotherapeutics refers to a treatment method in which in vivo drug availability is timed to match the rhythms of disease, in order to optimize therapeutic outcomes and minimise side effects [7, 13 & 14]. It is designed such that drug release is modulated in a manner that ensures that maximum concentration (Cmax) of the drug is reached at the maximum intensity of the disease condition. Cmax of the drug is normally reached within 1 - 2 h for many conventional dosage forms and this may not match with the maximum intensity of the disease state. Hence, for effective therapy, it is always advisable to provide maximum drug concentration at maximum intensity of disease condition.

Angiotensin II receptor blockers selectively and specifically antagonize the action of angiotensin II, a potent vasoconstrictor impacting BP regulation. Angiotensin II receptor blockers are becoming increasingly popular for the treatment of hypertension because they are effective and well tolerated [2]. Losartan potassium is the first orally active, highly specific, non-peptide angiotensin II receptor antagonist which blocks the renin–angiotensin system by suppressing the effects of angiotensin II at its receptors. It is a weakly acidic yellowish white crystalline powder with a pKa of 4.9 [7, 15 & 16]. It is a salt of 2-n-butyl-4-chloro-5- hydroxymethyl-1-[2-((1H-tetrazol-5-yl)biphenyl-4-yl)methyl] imidazole with a biological half life of 2-2.5h [7, 15 & 16]. It is used in the treatment of hypertension particularly in diabetic patients for nephropathy [16]. Its adult dose is 25mg, 50 mg and 100 mg once daily based on the requirement as prophylactic, for treatment and in severe conditions [17]. It is almost completely absorbed from following oral administration but its bioavailability has been limited (33%) due to extensive first pass metabolism [10]. It can used for the therapy of symptoms or disease that according to circadian rhythms and chronobiology become worse during night or in early morning (fax and mulcuhy1991) [2]. For these cases conventional drug delivery system are inappropriate for the delivery of drug, as they cannot be administrated just before the symptoms are worsened because at that time the patients are sleeping [2]. Hence, an attempt was made to formulate pulsatile drug delivery system of losartan potassium which can deliver the drug after lag time of 5-6 h.

Chronomodulated drug delivery system (ChDDS) can be defined as a system where drug is released suddenly after a well-defined lag time according to the circadian rhythm of the disease [18, 19]. ChDDS can be classified according to the pulse-regulation of drug release into three main classes; time-controlled pulsatile release (single or multiple unit system), internal stimuli induced release and external stimuli-induced pulsatile release systems [20]. PDDS can also be classified according to the dosage form into three main types; capsules, pellets and tablets among which the ‘core-in-cup’ tablet system. The core-in-cup tablet system consists of three different parts: a core tablet, containing the active
ingredient, an impermeable outer shell and a top cover plug layer of a soluble polymer [21].

The objective of the present investigation is to design and evaluate Losartan Potassium pulsatile core-in-cup tablets as to optimize the drug release after a certain lag time expecting an improvement in its bioavailability and to meet therapeutic needs relating to particular pathological conditions.

MATERIALS
Losartan Potassium was obtained from Cirex Pharma Pvt Ltd, Hyderabad, India. Cellulose Acetate Propionate was obtained from S.D. Fine Chem. Ltd., Mumbai. Sodium Alginate (SA, 200 cps of 1% w/v aqueous solution), Sodium Carboxy Methyl Cellulose (Na CMC, 1500 cps of 1% w/v aqueous solution) and Hydroxy Propyl Methyl Cellulose K4M (HPMC 4000) was obtained from ozone international Mumbai. All other reagents and chemicals used were analytical grade.

METHODS
Flowability Studies
The angle of repose of the core formulation mixture was determined by the fixed funnel method [22]. The fluff bulk density (FBD) and tapped bulk density (TBD) were determined by using a tapped density tester (Copley, UK). The Compressibility Index (Carr’s Index) (%) and the Hausner ratio were calculated as follows: [19]

\[
\text{Carr’s Index (\%)} = \frac{TBD - FBD}{TBD} \times 100
\]

\[
\text{Hausner Ratio} = \frac{TBD}{FBD}
\]

Solubility Studies
Losartan Potassium solubility was investigated in 0.1 N HCl, phosphate buffer (pH 6.8) and distilled water. A known excess amount of Losartan Potassium was added to a flask containing 25mL of each medium. The flasks were shaken for 24 h in a water bath at 37°C and then they were left to attain equilibrium for another 24 h. Solutions were filtered, diluted and analyzed using UV-Visible spectrophotometer (PG Instruments limited, T-80 UV-Visible Spectrophotometer) at 230nm [19].

Tablet Preparation
The tablets were prepared using Rimek Mini Press-I with suitable flat face punches. The system is consisted of a core-in-cup tablet (Figure 1). The core tablet was made of 50 mg of Losartan Potassium using flat punches (6mm). An impermeable coating cup consisting of cellulose acetate propionate was applied under the bottom and around the core tablet. The cellulose acetate propionate powder (100mg) used in the under bottom coating layer was filled into a die of 10mm diameter and then was gently compacted to make a powder bed with a flat surface. The core tablet was in turn carefully placed in the center of the powder bed. Next, the die was filled with the remainder of the coating powder (65 mg) so that the surrounding surfaces of the core tablet were fully covered. On the top was added the hydrophilic swellable material (30, 60, 90 or 120 mg), which consists of sodium alginate or sodium carboxy methyl cellulose or HPMC K4M. Last, the bed was compressed to produce the desired core-in-cup system using Rimek Mini Press-I, (total weight 240, 270, 300 or 330 mg). The composition of core-in-cup formulations was depicted in Table 1 [21].
Physicochemical Characterization of Tablets

The prepared core tablets were subjected to uniformity of thickness and diameter using Vernier calipers. The tests were carried out on 20 randomly selected tablets [19].

Tablet tensile strength is the stress needed to fracture a tablet by diametral compression. It is given by Fell and Newton as in Equation.

\[ T = \frac{2P}{\pi D t} \]  

Where, \( P \) is the fracture load that causes tensile failure of a tablet of diameter \( D \), and thickness \( t \). The fracture load (kg) of ten tablets was determined individually with a Monsanto hardness tester (Tab Machines, Mumbai, India), using the procedure of Brook and Marshal [23]. The mean values of the fracture loads were used to calculate \( T \) values for the various tablets [7].

Table 1: Composition of Losartan Potassium core-in-cup formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Losartan Potassium (Mg)</th>
<th>Cellulose Acetate (Mg)</th>
<th>Sodium Alginate (Mg)</th>
<th>Hpmc K4m (Mg)</th>
<th>Sodium Carboxymethyl Cellulose (Mg)</th>
<th>Total Weight (Mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSA-1</td>
<td>50</td>
<td>160</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>240</td>
</tr>
<tr>
<td>LSA-2</td>
<td>50</td>
<td>160</td>
<td>90</td>
<td>-</td>
<td>-</td>
<td>270</td>
</tr>
<tr>
<td>LSA-3</td>
<td>50</td>
<td>160</td>
<td>60</td>
<td>-</td>
<td>-</td>
<td>300</td>
</tr>
<tr>
<td>LSA-4</td>
<td>50</td>
<td>160</td>
<td>120</td>
<td>-</td>
<td>-</td>
<td>330</td>
</tr>
<tr>
<td>LHPC-1</td>
<td>50</td>
<td>160</td>
<td>-</td>
<td>30</td>
<td>-</td>
<td>240</td>
</tr>
<tr>
<td>LHPC-2</td>
<td>50</td>
<td>160</td>
<td>-</td>
<td>60</td>
<td>-</td>
<td>270</td>
</tr>
<tr>
<td>LHPC-3</td>
<td>50</td>
<td>160</td>
<td>-</td>
<td>90</td>
<td>-</td>
<td>300</td>
</tr>
<tr>
<td>LHPC-4</td>
<td>50</td>
<td>160</td>
<td>-</td>
<td>120</td>
<td>-</td>
<td>330</td>
</tr>
<tr>
<td>LSCMC-1</td>
<td>50</td>
<td>160</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>240</td>
</tr>
<tr>
<td>LSCMC-2</td>
<td>50</td>
<td>160</td>
<td>-</td>
<td>-</td>
<td>60</td>
<td>270</td>
</tr>
<tr>
<td>LSCMC-3</td>
<td>50</td>
<td>160</td>
<td>-</td>
<td>-</td>
<td>90</td>
<td>300</td>
</tr>
<tr>
<td>LSCMC-4</td>
<td>50</td>
<td>160</td>
<td>-</td>
<td>-</td>
<td>120</td>
<td>330</td>
</tr>
</tbody>
</table>

LSA: Formulation containing Sodium Alginate, LHPC: Formulation containing Hydroxy Propyl Methyl Cellulose K4M, LSCMC: Formulation containing Sodium Carboxy Methyl Cellulose
Weight variation test of tablet (n=20) was carried out as per official method [24, 25].

The disintegration time method described in the British Pharmacopoeia [26] was followed using water maintained at 37±2°C as the disintegration fluid. Six tablets were placed in disintegration apparatus (Electrolabs, Model, ED-2L Mumbai, India)) for each determination. It was carried out in triplicate and the mean results reported [16].

Percent drug content of Losartan Potassium can be determined using 5 tablets which were weighed and crushed to fine powder. The powder equivalent to 50 mg of drug was weighed out, transferred to a 100 ml volumetric flask and made up the volume with phosphate buffer (pH 6.8). The resulting solution was filtered and 1ml of it diluted to 10 ml with phosphate buffer. The absorbance of the resulting solution was measured at 230 nm using a spectrophotometer and the drug content was computed [7].

Lag Time
The lag time was determined by visual observation of the pulsatile tablet in USP II paddle apparatus (medium: 0.1 N HCl for 2 h followed by phosphate buffer, pH 6.8, at 37°C, rotation speed 50 rpm) and was determined as time point, when the outer coating ruptured (n=3) [25].

In Vitro Drug Release
The in vitro dissolution study of various pulsatile tablets was carried out in 900 ml of 0.1 N HCl for first 2 h, followed by 900 ml of phosphate buffer (pH 6.8). The dissolution medium was maintained at temperature 37±0.5°C. The paddle speed was set at 50 rpm. At different time intervals 5 ml of sample was withdrawn and analysed by UV/Vis spectrophotometer at 230 nm. At each time of withdrawal, 5 ml of fresh corresponding medium was replaced into dissolution vessel. The time when 10% or more of Losartan Potassium dissolved in medium was defined as end of lag time in this experiment. The test was performed in triplicate [25].

Stability Studies
The selected formulations were tested for their stability according to the International Conference of Harmonization (ICH) guidelines under both standard long-term and accelerated storage conditions. Tablets were enclosed in polyethylene Petri dishes. Half of the tablets was loaded in a desiccator containing anhydrous CaCl₂ kept at 25°C and 60% RH for 3 months. The other half was kept in a stability cabinet (Climacell-MMM, Germany) adjusted at 40°C and 75% RH for 3 months. At specified time intervals, the tablets were examined for their physical appearance and in vitro drug release [19].

Fourier Transform Infra Red (FTIR) Studies
The FTIR spectrum of the different samples were recorded with an infra-red spectrometer (Shimadzu, Model 84005, Japan) using potassium bromide discs prepared from powdered samples. The spectrum was recorded in the region of 4000 to 400 cm⁻¹ [7].

RESULTS AND DISCUSSION

Flowability Studies
For direct compression of materials, it is required to possess good flow and compacting properties. According to USP, values for angle of repose 31-35° generally indicate good flow property. A Hausner ratio of less than 1.25 and Carr’s index of 16-20 indicate fair flow [27].

Losartan potassium exhibited angle of repose, Carr’s index and Hausner ratio 24°±1.2°, 8.336±0.58% & 1.09 ± 0.1, respectively, which indicated the good flow property.

Solubility Studies
The available literature on solubility profile of losartan potassium indicated that the drug is freely soluble in water. The results of losartan potassium solubility in water, 0.1N HCl & phosphate buffer pH 6.8 were found to be 1.239 gm/ml, 1.377 gm/ml and 1.289 gm/ml respectively.
Physico-Chemical Characterization of Tablets
The thickness of core tablet and core-in-cup tablets was found to be 2.32±0.45 mm and 3.32±0.04 to 5.83±0.09 mm respectively. The diameter of core tablets and core-in-cup tablets was found to be 6.01±0.01 mm and 10.03±0.02 mm to 10.04±0.01 mm respectively. The core tablets and core-in-cup tablets showed a uniform thickness and diameter as shown in Table 2 & 3.

The hardness of the core tablet and core-in-cup tablets was found to be 2.5±0.25 kg/cm² and 5.50±0.02 to 8.50±0.01 kg/cm² respectively as shown in Table 2 & 3

The friability of core tablet and core-in-cup formulations was found to be 0.7415% and 0.69 to 0.83% respectively which was within the pharmacopeia limits as shown in Table 2 & 3.

The weight variation of core tablet and core-in-cup tablets were found to be within the range of 49.16±0.47 mg and 241.5±1.3 to 335±0.08 mg as shown in Table 2 & 3. All the tablets passed weight variation tests as the average % weight variation was within 7.5% i.e. in the pharmacopeia limits.

The disintegration time of core tablet was found to be 22±0.05 sec as shown in Table 2.

The drug content of core-in-cup tablets was found to be within the range of 97.23% to 99.01% i.e., in the pharmacopeia limits as shown in Table 3.

Table 2: Physico-chemical characterization of Losartan Potassium core tablet

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness*</td>
<td>2.32±0.45 mm</td>
</tr>
<tr>
<td>Diameter*</td>
<td>6.01±0.01 mm</td>
</tr>
<tr>
<td>Hardness*</td>
<td>2.50±0.25 kg/cm²</td>
</tr>
<tr>
<td>Weight variation</td>
<td>49.16±0.47mg</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.7415 (%)</td>
</tr>
<tr>
<td>Disintegration time</td>
<td>22±0.05sec</td>
</tr>
</tbody>
</table>

Each value represents the mean ±SD (n=3).

Table 3: Physico-chemical characterization of Losartan Potassium core-in-cup tablet formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Hardness* (kg/cm²) ±SD</th>
<th>Thickness* (mm) ±SD</th>
<th>Diameter* (mm) ±SD</th>
<th>Weight variation (mg) ±SD</th>
<th>Friability (%)</th>
<th>Drug content (%) ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSA-1</td>
<td>5.50±0.02</td>
<td>3.32±0.04</td>
<td>10.02±0.06</td>
<td>241.5±1.30</td>
<td>0.72</td>
<td>97.56±2.03</td>
</tr>
<tr>
<td>LSA-2</td>
<td>5.60±0.06</td>
<td>4.81±0.03</td>
<td>10.01±0.07</td>
<td>273.5±0.60</td>
<td>0.74</td>
<td>98.67±1.80</td>
</tr>
<tr>
<td>LSA-3</td>
<td>6.50±0.01</td>
<td>5.25±0.08</td>
<td>10.03±0.02</td>
<td>299.0±0.07</td>
<td>0.74</td>
<td>97.67±2.30</td>
</tr>
<tr>
<td>LSA-4</td>
<td>6.51±0.02</td>
<td>5.81±0.03</td>
<td>10.01±0.01</td>
<td>332.0±0.08</td>
<td>0.75</td>
<td>98.01±0.09</td>
</tr>
<tr>
<td>LHPC-1</td>
<td>6.00±0.05</td>
<td>4.12±0.04</td>
<td>10.04±0.01</td>
<td>243.0±0.05</td>
<td>0.73</td>
<td>97.78±1.18</td>
</tr>
<tr>
<td>LHPC-2</td>
<td>5.50±0.03</td>
<td>4.35±0.07</td>
<td>10.04±0.02</td>
<td>26.84±0.06</td>
<td>0.73</td>
<td>98.89±1.06</td>
</tr>
<tr>
<td>LHPC-3</td>
<td>8.00±0.05</td>
<td>5.22±0.03</td>
<td>10.03±0.06</td>
<td>301.8±0.70</td>
<td>0.77</td>
<td>99.01±0.25</td>
</tr>
<tr>
<td>LHPC-4</td>
<td>8.50±0.01</td>
<td>5.83±0.09</td>
<td>10.02±0.07</td>
<td>332.0±0.70</td>
<td>0.79</td>
<td>97.23±1.25</td>
</tr>
<tr>
<td>LSCMC-1</td>
<td>4.50±0.05</td>
<td>4.10±0.09</td>
<td>10.00±0.02</td>
<td>242.0±0.08</td>
<td>0.69</td>
<td>97.99±1.89</td>
</tr>
<tr>
<td>LSCMC-2</td>
<td>4.50±0.03</td>
<td>4.35±0.07</td>
<td>10.00±0.02</td>
<td>271.5±0.60</td>
<td>0.68</td>
<td>97.78±1.18</td>
</tr>
<tr>
<td>LSCMC-3</td>
<td>5.50±0.02</td>
<td>5.32±0.03</td>
<td>10.05±0.02</td>
<td>310.0±0.07</td>
<td>0.75</td>
<td>98.89±1.06</td>
</tr>
<tr>
<td>LSCMC-4</td>
<td>6.59±0.04</td>
<td>5.83±0.09</td>
<td>10.01±0.03</td>
<td>335.0±0.08</td>
<td>0.83</td>
<td>99.01±0.25</td>
</tr>
</tbody>
</table>

Each value represents the mean ±SD (n=3).
Lag Time and In Vitro Drug Release Studies

Sodium Alginate, Sodium CMC and HPMC K4M were chosen as the most suitable plug polymers for designing of Losartan Potassium core-in-cup tablet formulations based on a number of preliminary studies, as shown in Table 1. To choose the most appropriate plug polymer among them, further release studies were conducted.

Figure 2 shows the in vitro release profile of formulations containing Sodium Alginate (LSA1 to LSA4). LSA1, LSA2, LSA3 & LSA4 showed a lag time of 1 h, 2 h, 2 h & 2 h respectively with drug release of 97.48% at 5 h, 96% at 6 h, 98.04% at 6 h & 98.61% at 7 h, respectively.

Figure 3 shows the in vitro release profile of formulations containing HPMC K4M (LHPC1 to LHPC4). LHPC1, LHPC2, LHPC3 & LHPC4 showed a lag time of 3 h, 3 h, 5 h & 7 h respectively with drug release of 96.92% at 8 h, 97.19% at 9 h, 98.74% at 10 h & 97.96% at 11h, respectively.

Figure 4 shows the in vitro release profile of formulations containing NaCMC (LSCMC1 to LSCMC4). LSCMC1, LSCMC2, LSCMC3 & LSCMC4 showed a lag time of 2 h, 3h, 3h and 3 h, respectively with drug release of 97.7% at 7 h, 96.37% at 7 h, 95.97% at 8 h & 98.65% at 8 h, respectively.

In all formulations containing Sodium Alginate, NaCMC & HPMC K4M, an increase in the polymer quantity results to a increase in lag time and decrease of the release rate of the drug from the system [21].

Upon contact of the core-in-cup tablet with the medium, the plug layer, consisting of SA, NaCMC or HPMC, absorbs water. Consequently, the polymer swells and expands. By time the swelling and expansion of the plug increases creating a barrier which delays the contact of liquids with the surface of the core tablet. This process varies with the nature of the polymer used. It is also suggested that the swelling of the plug layer may destabilize the plug itself and gradually leads to its erosion or removal. Therefore, the swelling and destabilization of the plug polymer control the rate by which the plug layer polymer erodes. At the end, according to the properties of each polymer, the plug is completely eroded and water ingress into the core increases heavily resulting in rapid drug release [19, 28].

In formulations containing LSA1 to LSA4, Sodium Alginate shrinks at low pH. In gastric fluid the hydrated Sodium Alginate is converted into a porous, insoluble alginic acid skin. After passed into the higher pH medium, the alginic acid is converted to soluble viscous layer. The pH dependent behavior and rapid dissolution of sodium alginate in higher pH range results in release of Losartan Potassium at pH 6.8. Sodium Alginate can be used as a biological on-off switch with which the release of drugs can be controlled by the external pH change due to its swelling behavior [19, 28].

In formulations containing NaCMC (LSCMC1 to LSCMC4), NaCMC, as a polyelectrolyte gel, is very sensitive to pH changes. The neutralization of charges in acid medium affects the polymer chain conformation and leads to a tight network structure. The chain arrangement generates a system of connected channels in the gel matrix that controls the drug release process in a biological environment. In phosphate buffer pH 6.8, NaCMC gels show a lower dynamic viscosity in comparison with that in an acid medium. The system has a liquid-like character and looser structure of NaCMC. This behavior is typical for normal solutions of conformationally disordered (random coil) polymers interacting by physical entanglement. The weak gel structure determines the ability of NaCMC polymer chains to disentangle from the polymer network and dissolve. This results in a faster erosion of hydrogel matrix and enhances the drug release [19, 29].

According to the previous facts, NaCMC was expected to show faster dissolution behavior. Unexpectedly, Sodium Alginate exhibited much faster dissolution...
upon elevating the pH of the medium than NaCMC. This could be resulted from the higher viscosity of the used grade of NaCMC relative to that of SA. NaCMC, with the higher viscosity, displays the most rapid and the greatest bulk swelling which lasts longer than SA. After maximum swelling of both polymers was achieved, a tendency to rapid decrease of swelling was observed, which appeared to be greater for SA, followed by NaCMC. Apparently, NaCMC, the polymer with the maximum volume increase, exhibited the slower drug release [19, 21].

In formulations containing HPMC K4M (LHPC1 to LHPC4), the sensitivity of HPMC gel (plug layer) to pH changes is not significant in comparison with the NaCMC or SA gels. Its rheological properties are not influenced by the medium pH. The system keeps its elastic characteristic at pH 1.0, which determines its ability to retain the network structure for a long period of time. In pH 6.8, the elastic viscosity is almost the same. This behavior indicates the absence of entanglement coupling [29].

As HPMC K4M, was characterized by its high viscosity, gel layer was sufficiently resistant to extensive erosion even after thorough hydration which was accompanied by path length increase [30]. Therefore, it was logic to get the lowest drug release in comparison with Sodium Alginate and NaCMC which have lower viscosities.

Accordingly, in vitro release rate of Losartan Potassium from LHPC3 was the most convenient one among the previously studied tablet formulations showing an optimum lag time of 6hrs followed by a drug release after changing pH from 1.2 to 6.8.

Each value represents the mean ±SD (n=3).

Figure 2: In vitro drug release profile of formulations containing sodium alginate (LSA1 TO LSA4)

Each value represents the mean ±SD (n=3).

Figure 3: In vitro drug release profile of formulations containing HPMC K4M (LHPC1 to LHPC4)
Each value represents the mean ±SD (n =3).

**Figure 4: In vitro drug release profile of formulations containing Sodium CMC (LSCMC1 to LSCMC4).**

**Stability Studies**
LHPC3 tablets were kept at 25 °C and 60% RH for 3 months (standard long-term storage conditions) and 40°C and 75% RH for 3 months (accelerated storage conditions). The rate of drug release from LHPC3 did not change significantly (P > 0.05) after storage under both regular and accelerated conditions. In addition, LHPC3 did not show dramatic changes in appearance during the study period. A slight plug layer swelling was observed at the end of the study period under accelerated storage conditions which did not affect the drug release profile significantly (P > 0.05).

**FTIR Studies**
In order to investigate if there is any interaction between added excipients and Losartan Potassium in the core-in-cup tablet, the FTIR of the Losartan Potassium, cellulose acetate propionate, HPMC K4M and the optimized formulation LHPC3 were determined as shown in Figure 5. All the characteristic peaks observed for both drug and excipient remained unchanged and the spectra data was superimposed. This observation ruled out the possibility of chemical interaction and modification between the Losartan Potassium and added excipients during the production process.

**Figure 5: FTIR Spectrum of (A) Losartan Potassium (B) HPMC K4M (C) Cellulose Acetate Propionate (D) Optimized Formulation LHPC3.**
CONCLUSION
A chronomodulated core-in-cup drug delivery system for oral use was developed and evaluated. The formulation consisted of a core tablet, containing the drug, an impermeable outer shell and a top cover swellable layer. The results suggested that the described system released the drug after a certain lag time, which could be modified by several factors. The quantity of material in the top layer and polymer characteristics are important factors in controlling the lag time and drug release. The lag time increases by increasing the quantity of the hydrophilic top cover layer. In contrast, drug release was found to decrease. Thus, we concluded that the top cover layer and especially the erodible polymeric material, from which this layer consists, regulate the performance of the system. Formulation LHPC3 with a predetermined lag time of 5 h with drug release of 98.74% was taken as the optimized formulation and no modification and/ or chemical interaction throughout the process of formulation. Hence from the above study it was concluded that HPMC K4M is suitable for the development of chronotherapeutic drug delivery systems with Losartan Potassium. Thus this approach can provide a useful means for pulsatile/programmable release and may helpful for patients with morning surge. This work can also be extended for variety of drugs suitable for chronotherapy.

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