



Design and evaluation of time programmed pulsincap system for chronotherapeutic delivery of losartan potassium

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ABSTRACT

In the present work an attempt has been made to develop and evaluate a time or site specific pulsatile drug delivery system. The basic design consists of an insoluble hard gelatin capsule body, filled with Eudragit microcapsules of Losartan potassium and sealed with a hydrogel plug. The entire capsule was enteric coated, so that the variability in gastric emptying time can be overcome and a colon-specific release can be achieved. The Losartan potassium microcapsules were prepared by solvent evaporation method with Eudragit L-100 and S-100 (1:2) by varying drug to polymer ratio and evaluated for the particle size, angle of repose, percentage yield, drug content, SEM, IR and in-vitro release study. Most of the isolated microcapsules were of particle size range 135 to 655mm, the angle of repose was in the range of 23° 95" to 30° 40". Bulk and tapped densities showed good packability and Carr's index ranges from 15.71 to 19.11. The drug loaded microcapsules show 68.93 ± 0.37 to 80.12 ± 0.62 drug entrapment. The in-vitro, drug release studies were carried out using pH 6.8 phosphate buffer for 12 hrs. At the end of 12th hrs the drug release in the range of 84.96 ± 1.53 to 98.45 ± 0.24 and from the obtained results; one of better formulation was selected for further fabrication of Pulsatile capsule. Different grade of HPMC hydrogel polymer were used as plugs in different ratios, to maintain a suitable lag period and it was found that the drug release was controlled. The entire capsule was enteric coated with 5% CAP, so that colon specific release can be achieved. The formulated pulsatile device was evaluated weight variation, thickness of CAP, IR, and in-vitro release study. The in-vitro release studies of pulsincap system revealed that colon specific release has been achieved, increasing the hydrophilic polymer content resulted in delayed release of losartan potassium from microcapsule.

Keywords: Pulsatile; Colon-specific device; Chronotherapeutics; Eudragit microcapsule; Losartan Potassium.

INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. The oral controlled release system shows a typical pattern of drug release in which the drug concentration is maintained in therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained 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. In this condition to emulate innate circadian rhythms, reasonable and generally accepted rationale is a delivery system capable of releasing drugs in a pulsatile fashion rather than continuous delivery at predetermined time or site following oral administration. Such a release pattern is known as "pulsatile release".

Pulsatile drug delivery system is defined as the rapid and completely release the drug after a lag time, thus provide spatial & temporal delivery and increasing patient compliance have generated increasing interest during recent years for a number of disease and therapies. Such systems are advantageous for drug with an extensive first pass metabolism, nearly constant drug level at the site of action, prevention of peak-valley fluctuation, reduction in dose

of drug, reduced dosage frequency, avoidance of side effects, improved patient compliance and adaptation of therapy to chronopharmacological need. Pulsatile drug delivery systems are usually of reservoir type, where by a drug reservoir is surrounded by a diffusional barrier. This barrier erodes, dissolves or ruptures after a specified lag time, followed by rapid drug release

In general, pulsatile drug delivery system can be classified in to time controlled and site specific delivery systems. Drug release from the former group is primarily activated by plug ejection or a barrier coating that dissolves, erodes or ruptures after a certain lag time, while release from the latter group is primarily regulated by the biological environment in the gastrointestinal tract such as the pH or presence of enzyme. Based on the plug ejection mechanism, various capsular delivery systems were designed. Capsular delivery system intended for pulsatile release generally consists of an insoluble body and soluble cap, body contained in active contents into the capsule body. When this capsule came in contact with the body fluid, it swelled, create the pressure inside of body and after a lag time, the plug pushed itself outside the capsule and rapidly released the polymer it is formed from, the plug delays the onset of release through its erosion or swelling processes until timed removal from the capsule body and resulting release of drug content in to the aqueous medium. In addition, Stimuli induced pulsatile drug delivery, in these systems there is release of the drug after stimulation by any biological factor like temperature, or any other chemical stimuli.

Angiotension II receptor blocker selectively and specifically antagonize the action of angiotensin II, a potent vasoconstrictor impacting BP regulation Angiotension II receptor blocker are becoming increasingly popular for the treatment of hypertension because they are effective and well tolerated. Losartan potassium is the first orally active angiotensin II receptor antagonist, losartan is extensively metabolized in liver. It is widely prescribed in the treatment of hypertension. It undergoes extensive biotransformation and has an elimination half life 1.5 – 2hr. it can be 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). For these cases conventional drug delivery system are inappropriate for the delivery of drug, as they cannot be administered just before the symptoms are worsened because at that time the patients are sleeping.

The goal in drug delivery research is to develop formulations to meet therapeutic needs relating to particular pathological conditions. Research in the chronopharmacological field has demonstrated the importance of biological requirement of a given disease therapy and thus to manage the disease while minimizing treatment's side effects. The aim of this study is the investigation of predictable pulsatile formulations of losartan potassium consisted of insoluble capsules body, this can be achieved by a bed time administration of a drug delivery system which with a delayed start of drug release can provide adequate protection in the early mornings. So colon specific drug delivery systems can be utilize for chronotherapeutic drug administration.

EXPERIMENTAL SECTION

Materials: Losartan potassium was obtained from Karnataka Antibiotics Pvt. Ltd., Bengaluru. Eudragit L-100 and Eudragit S-100 were supplied as gifts by Degussa India Pvt Ltd., Mumbai. Hydroxypropylmethylcellulose (HPMC K4M, HPMC E15, and HPMC E50) was obtained from Colorcon Asia Pvt. Ltd., Goa. Cellulose acetate phthalate was obtained Spectrochem Pvt Ltd., Mumbai. Span-80 was obtained Research Lab. Mumbai. Acetone, Liquid paraffin, n-Hexane were obtained from S.D.Fine. Chem. Ltd., Mumbai.

Preparation of microcapsules:

Accurately weighted Eudragit L-100 and S-100 in 1:2 ratios were dissolved in 10 ml of acetone to form a homogenous polymer solution. Core material, i.e. Losartan potassium was added to the polymer solution and mixed thoroughly. This organic phase was slowly poured at 15°C into liquid paraffin (100 ml) containing 1% w/w of Span-80 with stirring at 1000 rpm to form a smooth emulsion. Thereafter, it was allowed to attain room temperature and stirring was continued until residual acetone evaporated and smooth-walled, rigid and discrete microcapsules were formed. The microcapsules were collected by decantation and the product was washed with n-Hexane, four times and dried at room temperature for 3 hrs. The microcapsules were then stored in a dessicator over fused calcium chloride.

Four batches were prepared with different proportions of core to coat materials (drug: polymer = 1:0.5, 1:1, 1:1.5 & 1:2 (w/w) named LM 1-4, respectively).

Evaluation of microcapsules:

Percent yield value of Microcapsules: The percent yield values of each batch of microcapsules were obtained on weight of dried microsphere and respect to the total solid material amount in the dispersed phase. The yield of microcapsules preparation was calculated using the formula:

$$\text{Percent yield} = \frac{\text{The amount of microcapsules obtained (g)}}{\text{The theoretical amount (g)}} \times 100$$

Sieve analysis: Separation of the microcapsules into various size fractions was carried out using a mechanical sieve shaker. A series of ten standard stainless steel sieves were arranged in the order of decreasing aperture size. 10 g of drug-loaded microcapsules was placed on the upper most sieves. The sieves were shaken for a period of about 10 min. and then the particles on the screen were weighed. The procedure was carried out three times for each product.

$$\text{Average Size} = \frac{\sum nd}{\sum n}$$

Where, **n** is the number of microcapsules and **d** is the size of microcapsules

Study of External morphology: Scanning Electron Microscopy has been used to determine shape, particle size distribution, surface topography, texture and to examine the morphology of fractured or sectioned surface. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large part to simplicity of sample preparation and ease of operation.

SEM studies were carried out by using JEOL JSM T-330 A Scanning microscope (Japan). The microcapsules were coated uniformly with gold by using ion sputter coater, after fixing the sample in individual brass stabs. All samples were randomly examined for surface morphology of microspheres by using Scanning electron microscope.

Study of Micromeritic properties:

Angle of repose⁹¹ A glass filling funnel is held in place with a clamp on the ring support over a glass plate. Microspheres were weighted passed through the funnel, which was kept at a height 'h' from the horizontal surface. The passed microspheres formed a pile of a height 'H' above the horizontal surface and the pile was measured and the angle of repose was determined for all the batches by using the formula.

$$\text{Angle of repose } (\theta) = \tan^{-1}(H/R)$$

H = Height of the pile and R= Radius of the pile.

Bulk density and Tapped density: Bulk and tapped densities were measured by using 10ml of graduated cylinder. The sample poured in cylinder was tapped mechanically for 100 times, then tapped volume was noted down and bulk density and tapped density were calculated. Each experiment for micromeritic properties was performed in triplicate manner.

Carr's index: Compressibility index (Ci) or Carr's index value of microspheres was computed according to the following equation:

$$\text{Carr's index} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100$$

Hausner's ratio: Hausner's ratio of microparticles was determined by comparing the tapped density to the bulk density using the equation:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \times 100$$

Drug content: In a 100 ml volumetric flask, 25 mg of crushed microcapsules were taken, and volume was made up to mark with pH 6.8. The flask was shaken for 12 hours using an orbital shaker incubator. Then the solution was filtered and from the filtrate appropriate dilutions were made and absorbance was measured at 219.4 nm.

In-vitro dissolution studies: *In-vitro* dissolution profile of each formulation was determined by employing USP XXIII rotating basket method (900 ml pH 6.8 phosphate buffer, 100 rpm, 37^o±0.5^oC). Microcapsules equivalent to 100 mg of Losartan potassium was loaded into the basket of the dissolution apparatus. 5 ml of the sample was

withdrawn from the dissolution media at suitable time intervals and the same amount was replaced with fresh buffer. The absorbance of the filtrate was determined at wavelength of 219.4 nm against pH 6.8 as blank. The amount of drug present in the filtrate was then determined from the calibration curve and cumulative percent of drug release was calculated. Data obtained was also subjected to kinetic treatment to obtain the order of release and release mechanism.

Preparation of cross-linked gelatin capsules:

Hard gelatin capsules of 100 in number were taken. Their bodies were separated from the caps. 25 ml of 15% v/v formaldehyde was taken into dessicator and a pinch of potassium permanganate was added to it, to generate formalin vapors. The wire mesh containing the bodies of the capsule was then exposed to formaldehyde vapors. The dessicator was tightly closed. The reaction was carried out for 12 hrs after which the bodies were removed and dried at 50°C for 30 minutes to ensure completion of reaction between gelatin and formaldehyde vapors. The bodies were then dried at room temperature to facilitate removal of residual formaldehyde. These capsule bodies were capped with untreated caps and stored in a polythene bag.

Test for formaldehyde treated empty capsules:

Solubility studies for treated capsules: solubility tests were carried out for normal capsules and formaldehyde treated capsules for 24hrs. ten capsules were randomly selected and then subjected to solubility studies in buffer of pH 1.2, 7.4 and 6.8. A single capsule was placed in the buffer solution and stirred for 24hrs. The time at which the capsule dissolves was noted

Chemical test: Standard solution used is Formaldehyde solution (0.002 w/v) and Sample solution is Formaldehyde treated bodies (about 25 in numbers) were cut into small pieces and taken into a beaker containing distilled water. This was stirred for 1 hr with a magnetic stirrer, to solubilize the free formaldehyde. The solution was then filtered into a 50 ml volumetric flask, washed with distilled water and volume made up to 50 ml with the washings. To 1 ml of sample solution, 9 ml of water was added. 1 ml of resulting solution was taken into a test tube and mixed with 4 ml of water and 5 ml of acetone reagent. The test tube was warmed in a water bath at 40°C and allowed to stand for 40 mins. The solution was not more intensely colored than a reference solution prepared at the same time and in the same manner using 1 ml of standard solution in place of the sample solution. The comparison should be made by examining tubes down their vertical axis.

Formulation of pulsatile (modified pulsincap) drug delivery system:

Formaldehyde treated hard gelatine capsules were chosen for the formulation. The bodies and caps were separated manually. Microcapsules equivalent to 150 mg of the Losartan potassium were accurately weighed and filled into the treated bodies by hand filling. The capsules containing the microcapsules were then plugged with different grades like hydroxyl propyl methylcellulose at different concentration like HPMC K4M, HPMC E15, and HPMC E50 – 20, 30, 40 mg. The joint of the capsule body and cap was sealed with a small amount of the 5% ethyl cellulose ethanolic solution. The sealed capsules were completely coated with 5% Cellulose Acetate Phthalate (CAP) to prevent variable gastric emptying. Coating was repeated until an 8-12% increase in weight is obtained. % Weight gain of the capsules before and after coating was determined. The whole system thus produced is modified pulsincap.

In vitro release profile:

Dissolution studies were carried out by using USP XXIII dissolution test apparatus. In order to simulate the pH changes along the GI tract, 900 ml of three dissolution medium with pH 1.2 buffer for 2 hours, pH 7.4 buffer for 3 hours, pH 6.8 buffer for subsequent hours. Rotation was 100 rpm and Temperature was maintained at 37°C ± 0.5°C. 5 ml of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed and the amount of losartan released was determined by UV absorption spectroscopy.

RESULTS AND DISCUSSION

Percentage Yield: It was observed that as the polymer ratio in the formulation increases, the product yield also increases. Highest percentage yield of the formulation LM-4 and lowest percentage yield of formulation LM-1. Percentage yield of the all formulation varies from 79.93 to 91.26%.

Particle Size Analysis: The mean particle size of the microcapsules significantly increased with increase in polymer concentration and was ranged in between 261.34 to 372.85 μm (Fig 2). The reason must be, the various manufacturing parameters (apparatus design, type of stirrer, stirring speed, viscosity of emulsion phases and the stabilizer concentration) affect particle size. Here, investigated the effects of polymer concentration, thus the effects

of polymer concentration, thus the inner phase viscosity and the stirring speed of the system on particle formulation and particle size, while keeping the other parameters constant. Increasing the polymer ratio caused the mean microcapsule size to shift towards a higher particle size. Higher concentration of polymer produced a more viscous dispersion, which formed larger droplets, so increases the size of microspheres.

More than 98.0% of the isolated microspheres were of particle size range 135 to 655 μm . Most of the microcapsules were collected more percentage above sieve 287.5 μm (sieves 44/60) by LM-1 to LM-4 formulations (Fig 1).

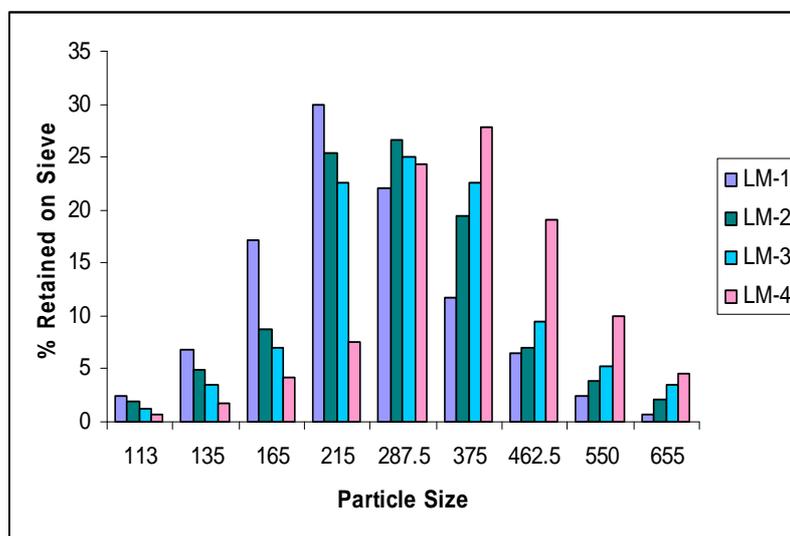


Fig 1: Particle Size Distribution of Different Formulations of Losartan potassium Microcapsules (n = 3)

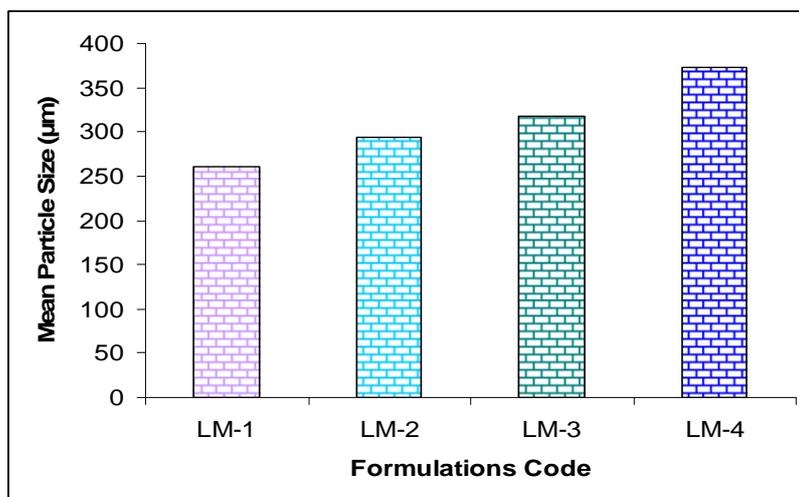


Fig 2: Average Particle Size of Different Formulation of Losartan Potassium Microcapsules

Scanning Electron Microscopy: Scanning electron microscopy was performed to characterize the surface of the formed microcapsules. Particles from LM-1 and LM-2 were rough surfaced but spherical, where as LM-3 and LM-4 (Fig: 3) were found to be spherical, smooth and discrete.

Micromeritic properties

Angle of repose: All formulations showed excellent flowability as expressed in terms of angle of repose value in the range 23° 95'' to 30° 40''. The better flow property indicated that the Losartan potassium microspheres produced are aggregated [Table-1]

Bulk and Tapped density: bulk and tapped densities showed good packability of the microspheres [Table-23]

Carr's index (Ci): Carr's index ranges from 15.71 to 19.11. F9 had lowest Carr's index indicating excellent compressibility [Table-1]

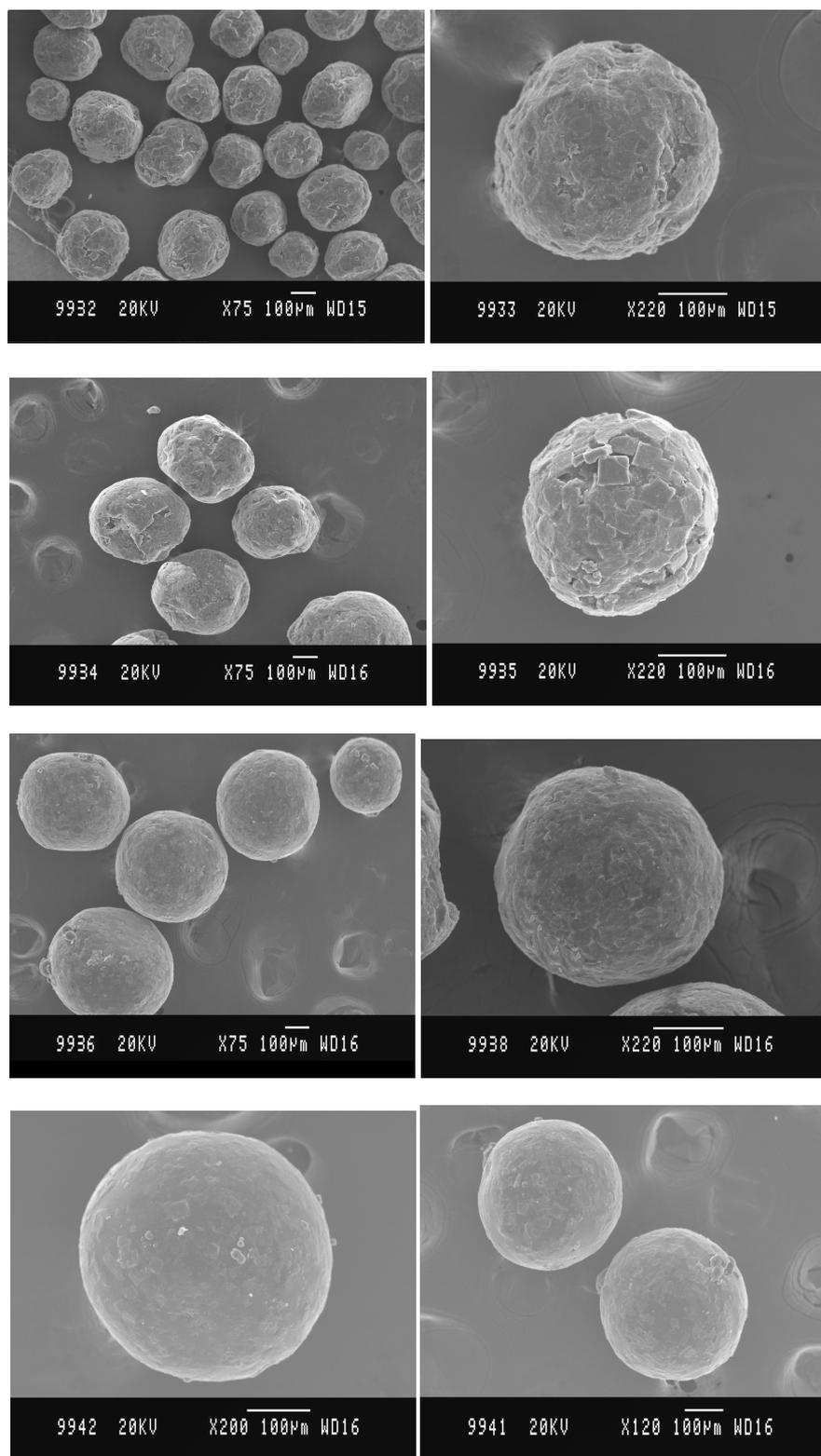


Fig 3: Scanning Electron micrographs of Losartan Potassium microcapsules for DM-1, DM-2, DM-3 and DM-4 formulations

Hausner's ratio: Hausner's ratio ranges from 1.195 to 1.307 indicates that all preparation showed that they had good flow properties [Table-1].

Drug Content and Entrapments Efficiency: It was observed that entrapment efficiency increases with an increase in polymer concentration which may be due to the increase in viscosity of the Eudragit S-100 / Eudragit L-100 solution with increase in concentration prevents drug crystals from leaving the droplets. The combination of Eudragit S-100 and Eudragit L-100 shows the high entrapment efficiency to comparisons of individual polymer of

Eudragit S-100 and Eudragit L-100. The encapsulation efficiency was good for the preparation, but highest for LM-3 formulation. (as shown in Fig: 4)

Table 1: Micromeritic Properties of Different Formulation of Losartan Potassium Loaded Microcapsules

Sl.No.	Formulation Code	Angle of Repose (θ) Mean \pm SD*	Bulk Density (g/ml) Mean \pm SD*	Tapped Density (g/ml) Mean \pm SD*	Carr's index (ci) (%)	Hausner's ratio
1	LM-1	30°39'' \pm 0.128	0.398 \pm 0.0034	0.477 \pm 0.0066	16.56 \pm 0.201	1.195 + 0.035
2	LM-2	28°52'' \pm 0.211	0.432 \pm 0.0032	0.526 \pm 0.0051	17.87 \pm 0.125	1.375 + 0.030
3	LM-3	26°55'' \pm 0.176	0.474 \pm 0.0059	0.586 \pm 0.0031	19.11 \pm 0.059	1.370 + 0.015
4	LM-4	23°91'' \pm 0.096	0.456 \pm 0.0055	0.541 \pm 0.0087	15.71 \pm 0.236	1.307 + 0.020

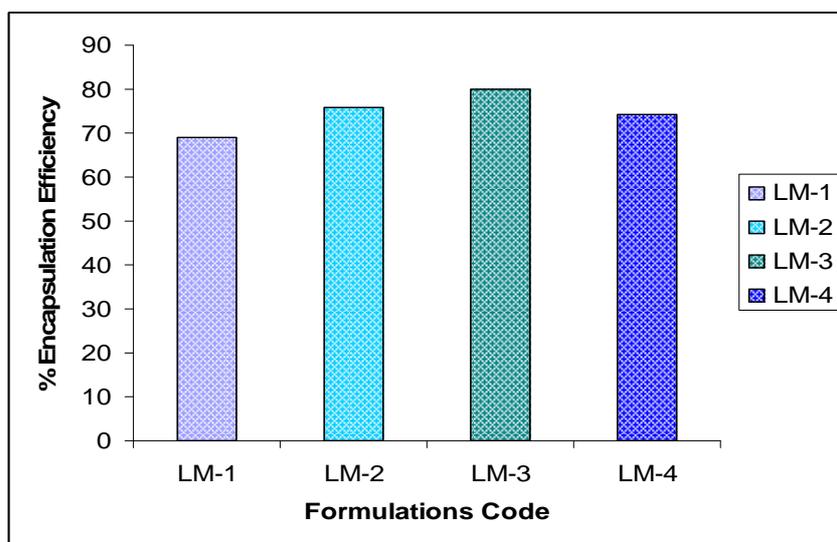


Fig 4: Comparison of Encapsulation Efficiency of Different Formulation of Losartan Potassium Microcapsules

In-vitro dissolution studies:The *In-vitro* release studies of Losartan potassium from prepared microcapsules were carried in pH 6.8 buffer as a dissolution medium for a period of 12 hrs. The drug release from the formulations decreased with increase in the amount of polymer added in each formulation. The release showed a biphasic release with an initial burst effect. In the first 30 min. drug release was 30.96%, 26.72%, 19.99% and 14.69% for LM-1 to LM-4 respectively. The mechanism for the burst release can be attributed to the drug loaded on the microcapsule or imperfect entrapment of drug.

The overall cumulative % release for LM-1, LM-2, LM-3 and LM-4 were found to be 98.45%, 94.01%, 90.09%, and 84.96% at the end of 12th hrs. (As shown in Fig: 5)

The release of the drug is dependent on the microcapsules size, as expected. Drug release is faster from spheres of smaller size owing to the decreased diffusional path length and the increased surface area in contact with the dissolution medium.

To obtain the values of the release constant and to understand the release mechanism the release data was fitted to various mathematical models such as Higuchi Matrix, Zero order, First order and Hixson Crowell etc.

The 'r' values for zero order kinetics of LM-1, LM-2, LM-3 and LM-4 were 0.9055, 0.9365, 0.9606 and 0.9797 respectively. The 'r' values for first order of LM-1, LM-2, LM-3 and LM-4 were 0.8606, 0.9450, 0.9599 and 0.9586 respectively.

The 'r' values indicate the drug release follows zero order. To ascertain the drug release mechanism, the in-vitro data were also subjected to Higuchi diffusion. The 'r' values of Higuchi diffusion was 0.9861, 0.991, 0.993 and 0.9815 for formulation LM-1, LM-2, LM -3 and LM-4 respectively. It suggests that the Higuchi diffusion plots of all the formulations were fairly linear because 'r' values near about 1 in all the cases. So it confirms the drug release by Higuchi diffusion mechanism.

The 'r' values of Hixson-Crowell were 0.9427, 0.9849, 0.9893 and 0.9854 for formulation LM-1, LM-2, LM-3 and LM-4 respectively. The 'r' value of formulation LM-4 was near about 1 compared to all model. So it confirms the drug release by Hixson-Crowell's mechanism.

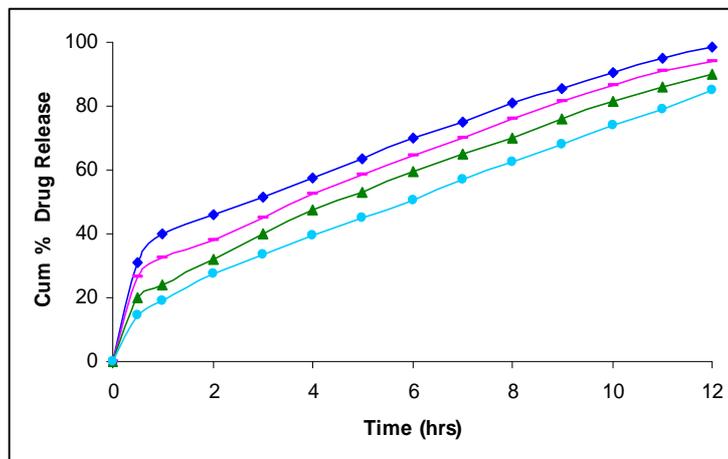


Fig 5: Comparative Plots of Zero Order (Cumulative % Drug Release versus Time)

Formaldehyde treatment of hard gelatin capsules: The bodies of hard gelatin capsules were made insoluble by formaldehyde treatment. This was done by exposing the bodies of the capsules to vapors of formaldehyde; the caps were not exposed leaving them water-soluble. The capsules were tested for physical and chemical changes caused by exposure to vapors of formaldehyde.

Dimensions: On formaldehyde treatment, the '0' size capsule bodies showed a significant decrease in length and diameter.

Solubility studies: When the capsules were subjected to studies in different buffers, the untreated caps disintegrated within 10 minutes in all the media whereas the treated bodies remained intact for about 24 hours.

Qualitative test for free formaldehyde: Limit test for the presence of residual formaldehyde was carried. The sample solution was not more intensely colored than the standard inferring that less than 20 $\mu\text{g/ml}$ of free formaldehyde is present in 25 capsules bodies as per the I.P.

Formulation of modified pulsincap: Microcapsules equivalent to 100 mg of Losartan potassium were filled into the treated bodies and plugged with different polymers like HPMC K4M, HPMC E15, HPMC E50 at different concentrations. The filled capsules were completely coated with 5% CAP cast solution. These pulsatile drug delivery systems were then evaluated for thickness of the CAP coating and *in-vitro* release.

Thickness: The thickness of the cap coating was measured by using screw gauge. The values ranged from 0.055-0.064 mm.

***In-vitro* release studies:** *In-vitro* release profiles of pulsatile device during 24 hrs studies were found to have very good sustaining efficacy. During dissolution studies, it was observed that, the enteric coat of the cellulose acetate phthalate was intact for 2 hours in pH 1.2, but dissolved in intestinal pH, leaving the soluble cap of capsule, which also dissolved in pH 7.4, and then the exposed polymer plug 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; releasing the Eudragit microcapsules into simulated colonic fluid (pH 6.8 phosphate buffer). With all the formulations, there was absolutely no drug release in pH 1.2, thus indicating the efficiency of 5% CAP for enteric coating. Very slight release was observed in pH 7.4.

a) Formulations with HPMC K4M as hydrogel plug: With formulations F1 (20 mg), F2 (30 mg), at the end of 5th hour there was 7.06% and 4.96 % cumulative drug release was found.

In case of F1 and F2 it was observed that polymer concentration was sufficient to retard the drug release in small intestinal fluid and the plug ejected out in colonic fluid, releasing the entire drug in colonic pH, in a controlled manner. At 24 hours, 95.23 % and 91.18 % of drug release was found in F1 and F2 respectively.

With F3, a decrease in expelling power of plug was observed which might be due to inadequate wetting of the polymer. It was observed that plug ejected after 6 hrs and at the end of 24 hrs 85.90% of drug release was observed. (as shown in Fig: 6)

b) Formulation with HPMC E50 as hydrogel plug: With formulation F4 (20 mg), F5 (30 mg), at the end of 5th hour 19.54% and 6.96 % of drug was released respectively and At the end of 24th hour F4 formulation had released 97.01 % of drug, whereas F5 formulation released 94.22 % of drug up to 24 hours in controlled manner.

In case of F6, decrease in expelling power of plug, due to inadequate wetting of polymer at higher concentration. At the end of 24th hr 87.18 % of drug was released. (as shown in Fig: 7)

c) Formulations with HPMC E15 as hydrogel plug: With formulations F7 (20 mg), F8 (30 mg) and F9 (40 mg), at the end of 5th hour around 8.07 %, 7.34 %, 5.94 % of drug release was observed respectively. F7 released 98.97 % of drug within 24 hrs where as F8, F9 released 95.23 % and 93.05 % of drug at the end of 24th hour. (as shown in Fig: 8)

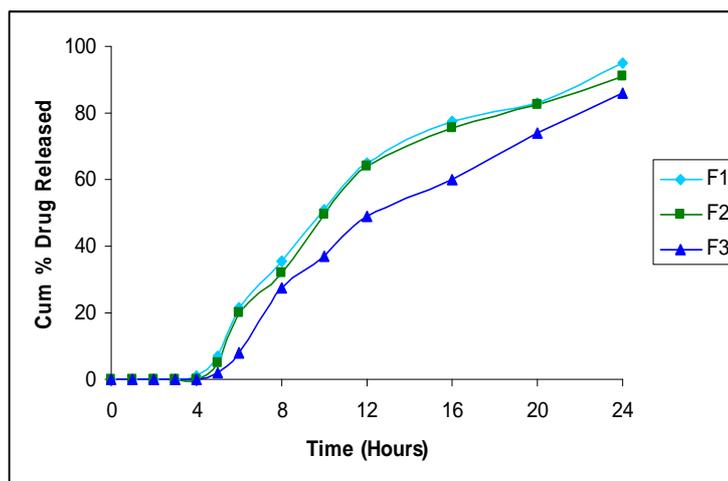


Fig 6: Comparative *in-vitro* release profile of formulations F1, F2, F3.

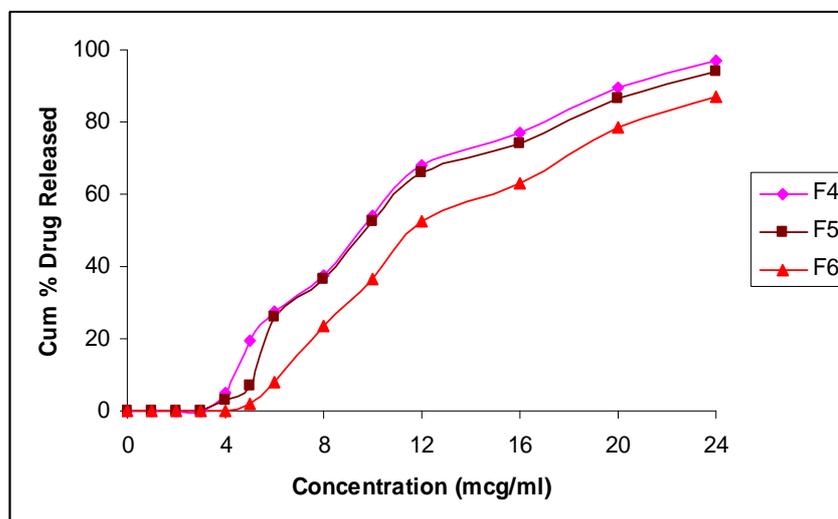


Fig 7: Comparative *in-vitro* release profile of formulations F4, F5, F6.

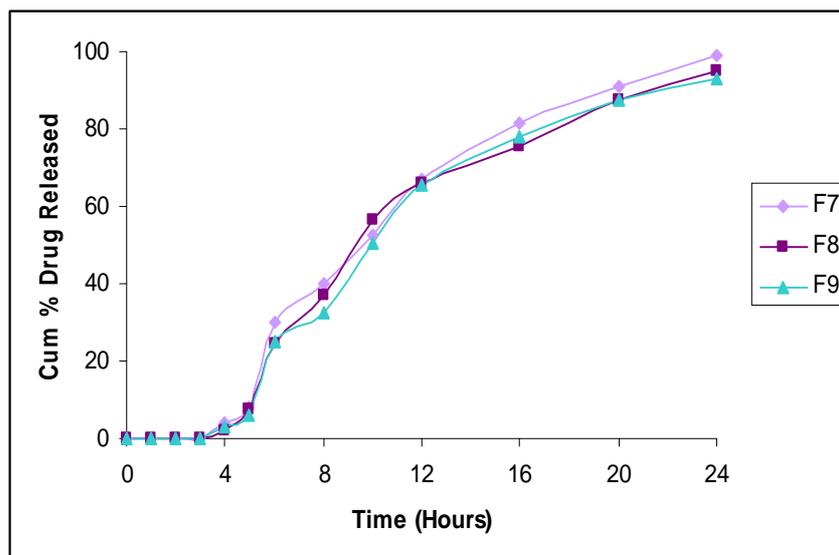


Fig 8: Comparative *in-vitro* release profile of formulations F7, F8, F9.

CONCLUSION

In this study demonstrate that the Losartan potassium microcapsules could be successfully colon targeted by design of time and pH dependent modified chronopharmaceutical formulation. Pulsatile drug release over a period of 3-24hrs, consistent with the requirements for chronopharmaceutical drug delivery was achieved from insoluble gelatin capsules, in which microencapsulated Losartan potassium was sealed by means of a suitable hydrogel plug. Thus the designed formulation can be considered as one of the promising formulation for preparing colon-specific drug delivery systems because colonic delivery system was valuable when a delay in absorption is therapeutically desirable in treatment of diseases like hypertension, which is influenced by circadian rhythms.

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