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DESIGN AND CHARACTERIZATION OF PULSATILE DRUG DELIVERY OF LOSARTAN POTASSIUM

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Abstract:
In the present study, an effort was made to develop the pulsatile drug delivery of Losartan potassium to the colon. A time delayed capsule was prepared by sealing the microspheres inside the insoluble hard gelatin capsule body with erodible hydrogel plug. The microspheres were prepared by emulsion solvent evaporation technique.. Optimized microsphere formulations were selected based on dissolution studies. The entire device was enteric coated, so that the variability in gastric emptying time can be overcome and a colon-specific release can be achieved. Hydrogel plug (HPMCK100 and lactose in 1:1 ratio) having 4.5kg/cm^2 hardness and 100 mg weight was placed in the capsule opening and found that it was satisfactory to retard the drug release in small intestinal fluid and to eject out the plug in colonic fluid and releasing the microspheres into colonic fluid after a lag time criterion of 5 hours. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used. FTIR study confirmed that there was no interaction between drug and polymer. Among all the formulations Losartan potassium micropheres prepared with cellulose acetate in 1:2 ratio shown prolonged release for a period of 12 hours. The obtained results revealed the capability of the system in delaying drug release for a programmable period of time and can prevent a sharp increase in the blood pressure during the early morning hours, a time when the risk of hypertension is the greatest.

Keywords: *Losartan potassium; Hypertension; Pulsatile;Microspheres; Hydrogel Plug; Solvent evaporation*

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INTRODUCTION:

Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount. These systems are beneficial for drugs having high first-pass effect; drugs administered for diseases that follow chronopharmacological behavior, drugs having specific absorption site in GIT, targeting to colon, and cases where night time dosing is required [1]. Cardiovascular events occur more frequently in the morning, and ambulatory blood pressure (BP) exhibits a diurnal variation with increase in the morning(morning BP surge). The morning BP surge was reported to be associated with high risk of cardiac death, and ischemic and hemorrhagic stroke [2]. Losartan potassium is the first orally active angeotensin II receptor antagonist, losartan is extensively metabolized in liver[3]. It is widely prescribed in the treatment of hypertension. It undergoes extensive biotransformation and has an elimination half life of 1.5 – 2hr. It can use for the therapy of symptoms or disease that according to circadian rhythms and chronobiology become worse during night or in early morning. 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[4]. Due to its short biological halflife and low bioavailability, it requires frequent administration. Thus chronopharmaceutical drug delivery system will synchronize the drug delivery with the circardian variation in periods of increased risk which is highly desirable for hypertensive patients. The main objective of present work is to formulate and evaluate the chronopharmaceutical drug delivery system containing losartan potassium for the treatment of hypertension which is used to deliver the drug at specific time as per pathophysiological needs of the disease and improvement of therapeutic efficacy and patient compliance.

The pulsatile drug delivery of Losartan potassium can be taken before bed time (10 pm) and capable of releasing drug at 3.00 am by proportioning drug concentration in the early morning hours when free cholesterol levels are more prevalent[5]. The intentionally delaying the drug absorption for a specified time period of 5 hours(lag time) was controlled by hydrogel plug which will be taken at bed time with a programmed start of drug release early in morning hours

MATERIALS AND METHODS:

Losartan potassium was a gratis sample obtained from Ranbaxy Lab. Ltd. (India).Eudragit RLPO and Eudragit RSPO were obtained from Himedia; Mumbai. HPMC K100, carbapol, Na CMC and Methyl Cellulose were purchased from SD fine chemicals, Mumbai. All reagents used were of analytical-reagent grade.

Preparation of Cross-Linked Gelatin Capsules:

Approximately 100 number size 0 hard gelatine capsules were taken. Bodies were separated from cap, 25 ml of 15% (v/v) formaldehyde was taken into desiccators and a pinch of potassium permanganate was added to it, to generate formalin vapours. The wire mesh containing the empty bodies of capsule was then exposed to formaldehyde vapours. The caps were not exposed leaving them water-soluble. The desiccators were tightly closed. The reaction was carried out for 12 h after which the bodies were removed and dried at 50^0C for 30 min to ensure completion of reaction between gelatin and formaldehyde vapours. The bodies were then dried at room temperature to facilitate removal of residual formaldehyde[6]. These capsule bodies were capped with untreated caps and stored in a polythene bag.

Table 1: Preparation of Losartan potassium microspheres

Polymer employed			
Eudragit RLPO		**Eudragit RSPO**	
Formulation Code	**Core: Coat**	**Formulation Code**	**Core: Coat**
F-1	**1:1**	**F-4**	**1:1**
F-2	**1:1.5**	**F-5**	**1:1.5**
F-3	**1:2**	**F-6**	**1:2**

Preparation of Hydrogel Plug:
Plug for sealing the capsule body was prepared by compressing equal amount of equal amount of HPMC K100: lactose, carbapol: lactose, Na CMC: lactose, and Methyl Cellulose: lactose using 7 mm punches and dies on rotary tablet press keeping varying thickness and hardness values of tablet plug[7] .

Preparation of microspheres:
All the microspheres formulations were prepared by emulsion solvent evaporation technique [8] and the composition was shown in table 1. The effect of various formulation and processing factors on microspheres characteristics were investigated by changing polymer: drug ratio. Weighed amount of Losartan potassium and polymer in 1:1 ratio were dissolved in 10ml of chloroform. The homogeneous drug and polymer organic solution was then slowly added in a thin stream to 100ml of liquid paraffin containing 1% surfactant (span 80) with constant stirring for 1h. The resulting microspheres were separated by filtration and washed with petroleum ether. The microspheres finally air dried over a period of 12 hrs and stored in a desiccator. In case of 1:1.5and 1:2 core:coat ratios, the corresponding polymer get varied respectively.

Designing of Pulsincap:
The Pulsincap was designed by filling the microspheres equivalent to 50mg of Losartan potassium into the formaldehyde treated bodies by hand filling. The capsules containing the microspheres were then plugged with optimized hydrogel plug. The joint of the capsule body and cap was sealed with a small amount of the 5% ethyl cellulose ethanolic solution[9]. The sealed capsules were completely coated by dip coating method with 5% cellulose acetate pthalate in 5:5 (v/v) mixture of acetone: ethanol plasticized with n-dibutylphthalate (0.75%), 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[10].

Physicochemical Characterization of Hydrogel Plug
Hydrogel Plugs were studied for hardness, friability, weight variation and lag time[10].

Drug content uniformity:
Then encapsulated microspheres equivalent to 50mg of Losartan potassium were taken into mortar and grounded with the help of pestle. The grounded power mixture was dissolved in 6.8 pH buffer , filtered and estimated spectrophotometrically at 285 nm[11].

***In vitro* release profile of pulsatile capsule:**
Drug release studies of pulsincaps were carried out using a USP XXIII dissolution rate test apparatus (Apparatus 2, 100 rpm, 37 °C) for 2 hr in 0.1 M HCl (900 ml) as the average gastric emptying time is about 2 hr. Then the dissolution medium was replaced with pH-7.4 phosphate buffer (900 ml) for 3hr as the average small intestinal transit time is about 3 hr. After 5 hr, the dissolution medium was replaced with pH 6.8 phosphate buffer (900 ml) and tested for subsequent hours. Nine hundred milliliters of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at 37±0.5ºC. Five milliliters of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 285 nm, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times [12].

Drug excipient compatability studies:
The IR Spectra for the formulation, pure drugs and excipients were recorded on JASCO FT-Infra Red Spectrophotometer using KBr pellet technique[13] at the resolution rate of 4 cm^{-1}. Spectrum was integrated in transmittance mode at the wave number range 380 to 4368 cm^{-1} .

RESULTS AND DISCUSSION:

Pulsincap dosage form was a capsule which consists of a water insoluble body and a water soluble cap. The microspheres were sealed within the capsule body by means of a hydrogel plug. When the pulsing cap was swallowed, the water soluble cap dissolves in the gastric juice and the exposed hydrogel plug begins to swell. At predetermined time after ingestion, the swollen plug was ejected out and the encapsulated drug formulation was then released into the colon, where it is dissolved and then absorbed into blood stream. In the present study, capsule bodies which were hardened with formaldehyde treatment for 12 hrs were used for the preparation of pulsincaps. It was sealed with unhardened cap of the capsule. The microspheres were prepared by emulsion solvent evaporation technique .The method employed gave discrete, spherical, non-sticky and free flowing microspheres. As aggregates these microspheres were also non-sticky and free flowing. The formation of a stable emulsion in the early stages is important if discrete microspheres are to be isolated. An optimal concentration of emulsifier is required to produce the finest stable dispersion. Below optimal concentration the dispersed

globules/droplets tend to fuse and produce larger globules because of insufficient lowering in interfacial tension, while above the optimal concentration no significant decrease in particle size is observed, because a high amount of emulsifying agent increases the viscosity of the dispersion medium. The optimal concentration of surfactant was found to be 1.0%. Microscopic examination of the formulations revealed that the microspheres were spherical and appeared as aggregates or discrete particles.

All the formulations offered good flow properties. The particle size of the microspheres ranged between 613.23and 662.53µm. The use of the surfactant permits the remarkable reduction in the size of the microspheres as the result of decrease in the interfacial tension. All formulations had a narrow particle size distribution. The mean particle size of microspheres was influenced by the type of polymer proportion in the formulation. The mean size increased with increasing polymer concentration. It would appear that increasing polymer concentration produced a significant increase in viscosity of the internal phase, thus leading to an increase of emulsion droplet size and finally a higher microspheres size. Microspheres were developed with 1:1, 1:1.5, 1:2, ratios of core: coat to determine the affect of coating material concentration on the release rate of Losartan potassium. These microspheres were characterized for Drug Content and % Encapsulation Efficiency. The results are given in Table 2. The technique also showed good entrapment efficiency. Hydrogel Plugs were evaluated for hardness, friability, weight variation and lag time and the results were shown in Table 3. The formulations fitted with the various hydrogel plugs HP1,HP2, HP3, HP4 shown 0.4% , 7.14% , 15.63 % and 18.21 % of drug release respectively at the end of 5th hour . It was observed that 100 mg hydrogel plug (HPMC K100: lactose in 1:1 ratio) having 4.5kg/cm^2 hardness was satisfactory to retard the drug release in small intestinal fluid and to eject out the plug in colonic fluid and releasing the microspheres into colonic fluid. This suggested that the lag time could also be adjusted and influenced by the plug composition**.**

During dissolution studies, it was observed that, the enteric coat of the cellulose acetate phthalate was intact for 2 hrs in pH 1.2, but dissolved in intestinal pH, leaving the soluble cap of capsule, which also dissolved in pH 7.4, then the exposed polymer plug absorbed the surrounding fluid, swelled and released the drug through the swollen microspheres. After complete wetting of the plug, it formed a soft mass, which was then easily ejected out of the capsule body; releasing the microspheres into simulated colonic fluid (pH 6.8 phosphate buffer). From the *In-vitro* release studies of device, it was observed that with all formulation, there was absolutely no drug release in simulated gastric fluid (acidic pH 1.2) for 2 hours and in simulated intestinal fluid (pH 7.4 phosphate buffer). Burst effect was found in colonic medium (pH 6.8 phosphate buffer).

In-vitro release profiles in colonic medium were found to have very good sustaining efficacy. Pulsin caps loaded with Losartan potassium microspheres prepared with Eudragit RLPO in 1:1,1:1.5 and 1:2 ratios shown sustained drug release for a period of 10 hours (5th hour to 15th hour), 11 hours (5th hour to 16th hour) and 12 hours(5th hour to 17 hour) respectively. respectively and are shown in figure 1.Pulsin caps loaded with Losartan potassium microspheres prepared with Eudragit RSPO in 1:1,1:1.5 and 1:2 ratios shown sustained drug release for a period of 9.5 hours (5th hour to 14.5th hour), 10.5 hours (5th hour to 15.5th hour) and 11.5 hours(5th hour to 16.5 hour) respectively and are shown in figure 2.

Table 2: Evaluationl data of Losartan potassium microspheres

Formulation	Angle of Repose	Bulk Density (g/cm^3)	Tapped density (gm/cm^3)	Carr's Index	Hausner's Ratio	Average Particle Size (µm)	% Drug Content	% Encapsulation Efficiency
F-1	26.52	0.522	0.619	15.67	1.185	561.28	48.23	96.46
F-2	26.14	0.524	0.620	15.48	1.183	579.16	39.11	97.77
F-3	25.73	0.527	0.622	15.27	1.180	588.24	32. 62	97.95
F-4	27.64	0.514	0.611	15.87	1.188	522.17	48.56	97.12
F-5	26.93	0.519	0.614	15.49	1.183	548.28	39.29	98.22
F-6	26.10	0.521	0.616	15.42	1.182	568.19	32. 41	98.21

Table: 3 Evaluation characteristics of hydrogel plugs prepared with various natural polymers

Hydrogel Plug Code	Composition (1:1)	Weight (mg)	Thickness (mm)	Hardness (kg/cm2)	Lag time (hours)
HP1	HPMC K 100 : Lactose	100±1.4	3.16	4.7	5
HP2	Carbopol : Lactose	100±1.1	3.29	4.2	4.5
HP3	Na CMC : Lactose	100±1.5	3.24	3.8	4
HP4	Methyl Cellulose : Lactose	100±1.2	3.54	3.5	3

Table: 4 In-vitro disssolution kinetics parameters of Losartan potassium microspheres

Formulation	Correlation coefficient				Release kinetics			Diffusion Exponent value(n)
	Zero order	First order	Higuchi	Peppas	K_o (mg/hr)	T_{50} (hr)	T_{90} (hr)	
F1	0.9990	0.6859	0.9271	0.9968	4.90	5.1	9.1	0.8732
F2	0.9983	0.8085	0.9352	0.9983	4.54	5.5	9.9	0.8651
F3	0.9965	0.7450	0.9355	0.9989	4.16	6	10.8	0.8594
F4	0.9907	0.8211	0.9561	0.9956	6.41	3.9	7.0	0.7385
F5	0.9895	0.8206	0.9573	0.9971	5.81	4.3	7.7	0.7508
F6	0.9925	0.8353	0.9506	0.9964	5.07	4.93	8.88	0.7643

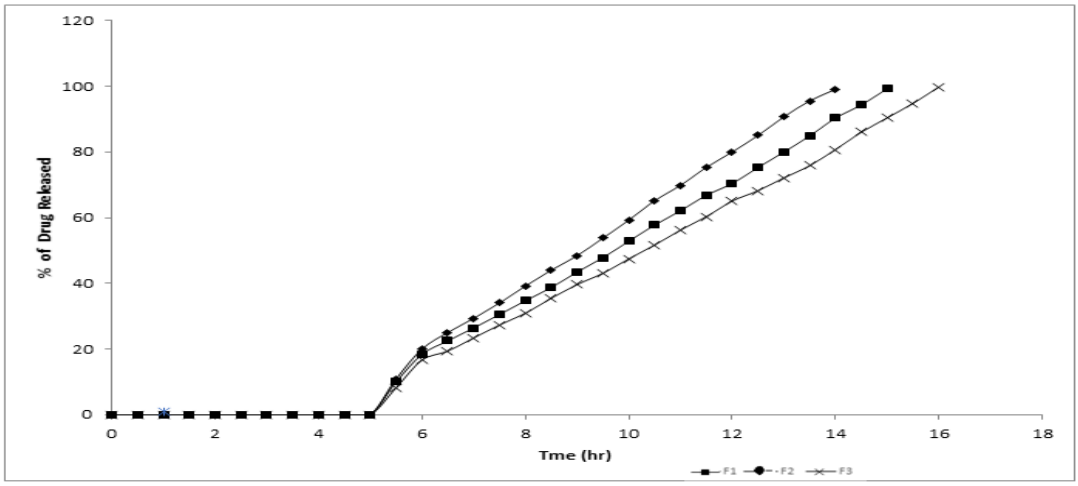

Fig 1: Comparative *In-vitro* drug release profiles plot of Losartan potassium microspheres prepared with Eudragit RLPO in different ratios

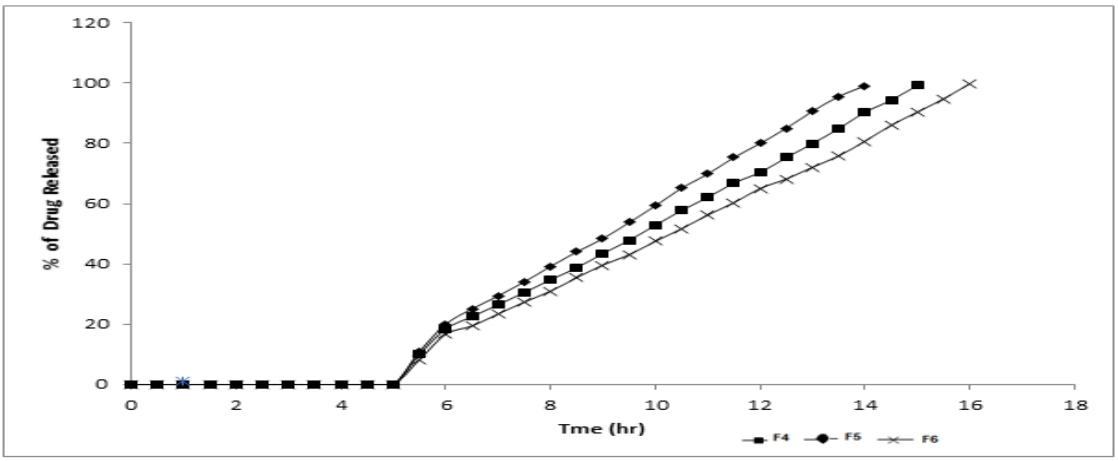

Fig 2: Comparative *In-vitro* drug release profiles plot of Losartan potassium microspheres prepared with Eudragit RSPO in different ratios

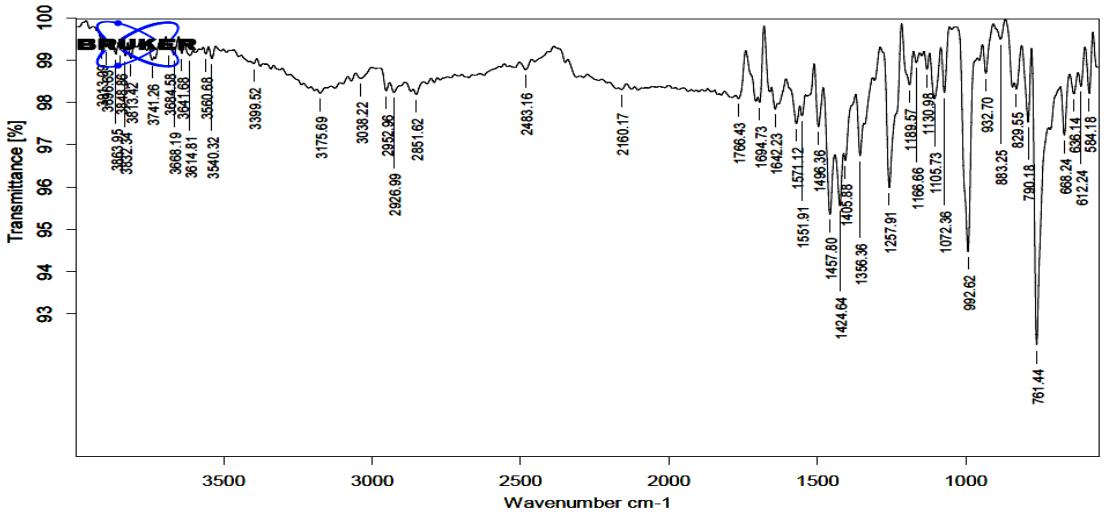

Fig 3: FTIR spectrum of pure Losartan potassium

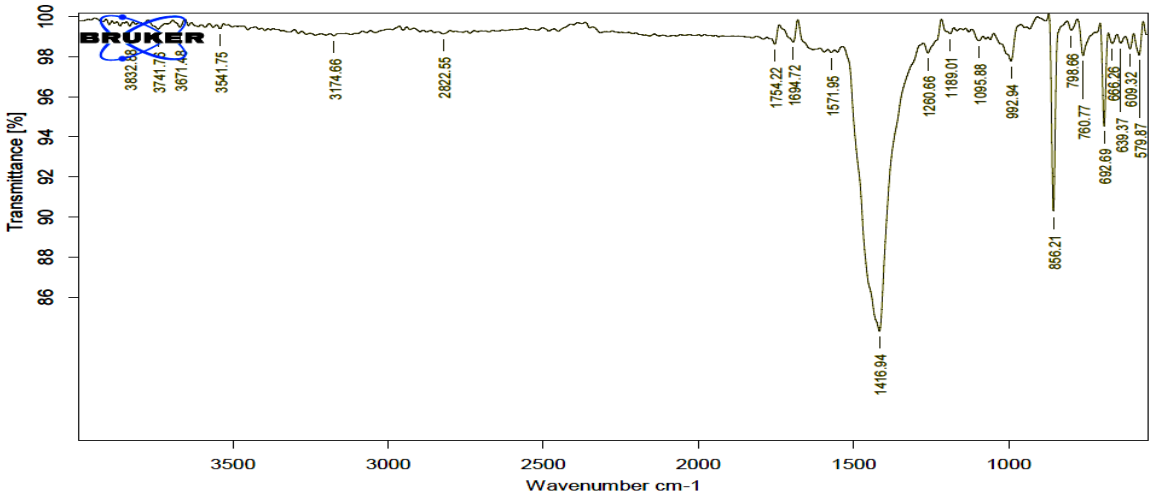

Fig 4: FTIR spectrum of optimized formulation

The correlation coefficient values for dissolution kinetics data was shown in the Table 4. These values clearly indicated that the drug release followed zero order kinetics and the mechanism of drug release was governed by
peppas - korsmeyer model. The exponential coefficient (n) values were found to be in between 0.7551 to 0.9730 indicating non fickian diffusion mechanisam.
The FTIR spectrum of Losartan potassium pure drug (Figure 3) appeared at 3038.22,3399.52,1130.98,1642.23,1356.36,1571.12 and 2926.99 denoting stretching vibration of C-H-,N-H-,O-H-,C=N,C-N,N=N and aromatic ring, respectively. The FTIR spectrum (Figure 4) of optimized formulation (F4) showed the same peaks. There were no change or shifting of the characteristic peaks in drug and excipient mixtures suggested that there was no significant drug polymer interaction which indicates the stable nature of the drug in all formulations. From the figures it was observed that similar peaks were also reported in optimized formulation. There was no change or shifting of characteristic peaks in drug loaded microspheres suggested that there was no significant drug polymer interaction which indicates the stable nature of the drug in optimized formulation.

CONCLUSION:

Among all the formulations Pulsin caps loaded with Losartan potassium microspheres prepared with Eudragit RSPO in 1:2 ratio shown prolonged release for a period of 12 hours. The obtained results showed the capability of the system in delaying drug release for a programmable period of time and the possibility of exploiting such delay to attain colon targeting. In accordance with the chronomodulated therapy of hypertension, the lag time criterion of 5 hours and sustained release for a period of 12 hours was satisfied. The dosage form can be taken at bed time and will release the contents in the early morning hours when hypertension is more prevalent.

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