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Research Article

**PREPARATION AND EVALUATION OF PULSATILE DRUG
DELIVERY OF MONTELUKAST SODIUM****M.Rama Krishna^{1*}, A. Prameela Rani² and V.Saikishore³**¹Department of Pharmaceutics, Avanthi Institute of Pharmaceutical Sciences, Hyderabad 501512.²Department of Pharmaceutics, Acharya Nagarjuna University, Nagarjunanagar-522510.³Department of Pharmaceutics, Bapatla College of Pharmacy, Bapatla-522101.**Abstract:**

In the present study, an effort was made to develop a novel dosage form by using a chronopharmaceutical approach for the treatment of nocturnal asthma using Montelukast sodium as a model drug. 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 (HPMCK4 and lactose in 1:1 ratio) having 4.5kg/cm² 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 Montelukast sodium microspheres prepared with Eudragit L100 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 incidence of asthmatic attacks, during the early morning hours, a time when the risk of asthmatic attacks is the greatest

Keywords: Montelukast sodium; Asthma; Pulsatile; Microspheres; Hydrogel Plug; Solvent evaporation**Corresponding author:****M.Rama Krishna,**

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INTRODUCTION:

Recently pulsatile systems are gaining a lot of interest and attention, as they deliver the drug at the right site of action at right time and in right amount, thus providing spatial and temporal delivery and increasing patient compliance. A pulsatile release profile is characterized by a lag time followed by rapid and complete drug release, which is useful for the treatment of certain diseases which exhibit circadian rhythm such as asthma, gastric ulcer, hypertension, ischemic heart disease and arthritis [1]. Asthma is one of the most common ailments with the largest circadian variation. It is a disease of lung airways (bronchi) characterized by hyper-responsiveness to a variety of stimuli. Nocturnal asthma, a condition prevalent in two-thirds of the asthmatics, is defined as a variable night time exacerbation of the underlying asthma condition associated with increase in symptoms and need for medication, increased airway responsiveness and worsening of lung function. Symptoms typically occur between midnight and 8 am, especially around 4.00 am [2].

It is inconvenient for a patient to take medicine at midnight. In this condition, a drug delivery system that can release the drug at a predetermined time to guarantee therapeutic efficacy is a prerequisite. This can be achieved by developing a pulsed release system capable of delivering the drug at the required time after a well-defined lag time [3]. Montelukast sodium is an orally administered drug of choice in the treatment of asthma in adults and children. It is a potent, selective and orally acting leukotriene receptor antagonist used in the prophylaxis and treatment of asthma by inhibiting physiological actions of the cysteinyl leukotrienes (LTC₄, LTD₄ and LTE₄). Montelukast has a biological half-life of about 2.5-5.5 hrs and 64 % bioavailability. Development of pulse release formulation of Montelukast can be advantageous, that can provide specific lag time and increase compliancy of the dosage form towards patient's side [4].

The aim was to have a lag time of 5 h, i.e., the system is to be taken at bed time (9 pm) and is expected to release the drug after a period of 5 h, i.e., at 2 am. Literature evidence shows that the peak plasma concentration of Montelukast sodium is reached approximately 2 h after oral administration. Therefore, the drug concentration would be at its maximum level, when asthma attacks are more prevalent, i.e., at 4 am. A pulsatile dosage form, taken at bedtime with a programmed start of drug release in the early morning hours, can prevent a sharp increase in the incidence of asthmatic attacks, during the early morning hours (nocturnal asthma), a

time when the risk of asthmatic attacks is the greatest [5].

MATERIALS AND METHODS:

Metoprolol succinate was a gratis sample obtained from Aurobindo Pharma limited; Hyderabad. Eudragit S-100, Eudragit L-100 were obtained from Himedia; Mumbai. HPMC K4, 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 gelatin 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°C 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.

Preparation of Hydrogel Plug:

Plug for sealing the capsule body was prepared by compressing equal amount of equal amount of HPMC K4: 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 Montelukast sodium and polymer in 1:1 ratio were dissolved in 10ml of acetone. 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 dessicator. In case of 1:1.5 and 1:2 core: coat ratios, the corresponding polymer get varied respectively.

Table.1: Preparation of Montelukast sodium microspheres

Polymer employed			
Eudragit S100		Eudragit L100	
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

Designing of Pulsincap:

The Pulsincap was designed by filling the microspheres equivalent to 10 mg of Montelukast sodium 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 phthalate 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 10mg of Montelukast sodium 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 342 nm [11].

In vitro release profile of pulsatile capsule:

Drug release studies of pulsincaps were carried out using a USP XXIII dissolution 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±0.5°C. Five milliliters of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 342 nm, by UV absorption spectroscopy and the cumulative

percentage release was calculated over the sampling times [12].

IR spectral studies:

The IR Spectra for the formulation, pure drugs and excipients were recorded on JASCO FT-Infra Red Spectrophotometer using KBr pellet technique¹³ at the resolution rate of 4 cm⁻¹. Spectrum was integrated in transmittance mode at the wave number range 560 to 3560 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.

Table 2: Evaluation data of Montelukast sodium microspheres

Formulation	Angle of Repose	Bulk Density (g/cm ³)	Carr's Index	Hausner's Ratio	Average Particle Size (µm)	% Drug Content	% Encapsulation Efficiency
F-1	27.18	0.905±0.01	15.7±0.04	1.17±0.04	140.48±0.02	46.42±0.03	92.84±0.02
F-2	22.85	0.928±0.02	13.6±0.03	1.15±0.03	156.12±0.04	37.41±0.02	93.52±0.05
F-3	21.16	0.941±0.03	12.8±0.02	1.14±0.05	179.54±0.06	32.09±0.03	96.28±0.02
F-4	27.68	0.770±0.04	15.8±0.05	1.20±0.03	147.84±0.06	45.8±0.06	91.60±0.03
F-5	25.12	0.784±0.05	14.6±0.03	1.18±0.05	163.17±0.05	36.93±0.02	92.32±0.05
F-6	22.17	0.812±0.03	12.8±0.04	1.14±0.02	189.65±0.05	31.77±0.05	95.31±0.04

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

Hydrogel Plug Code	Composition (1:1)	Weight (mg)	Thickness (mm)	Hardness (kg/cm ²)	Lag time (hours)
HP1	HPMC K 4 : Lactose	100±1.2	3.44± 0.10	4.7±0.03	5±0.01
HP2	Carbopol : Lactose	99 ±1.1	3.42±0.12	4.6±0.01	4.5±0.02
HP3	Na CMC : Lactose	100±1.2	3.41±0.08	4.3±0.04	4.1±0.02
HP4	Methyl Cellulose : Lactose	99 ±1.1	3.43±0.09	4.1±0.02	3.0±0.01

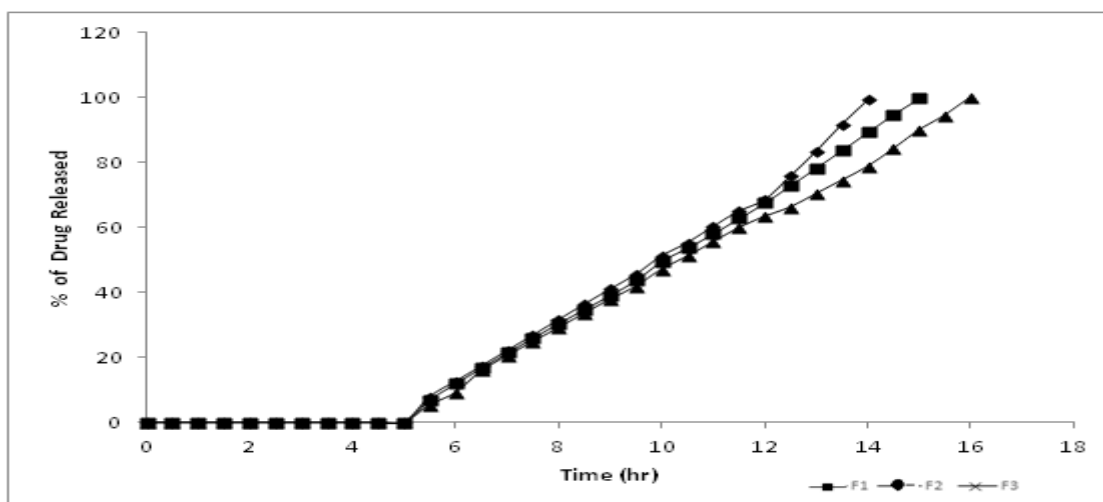
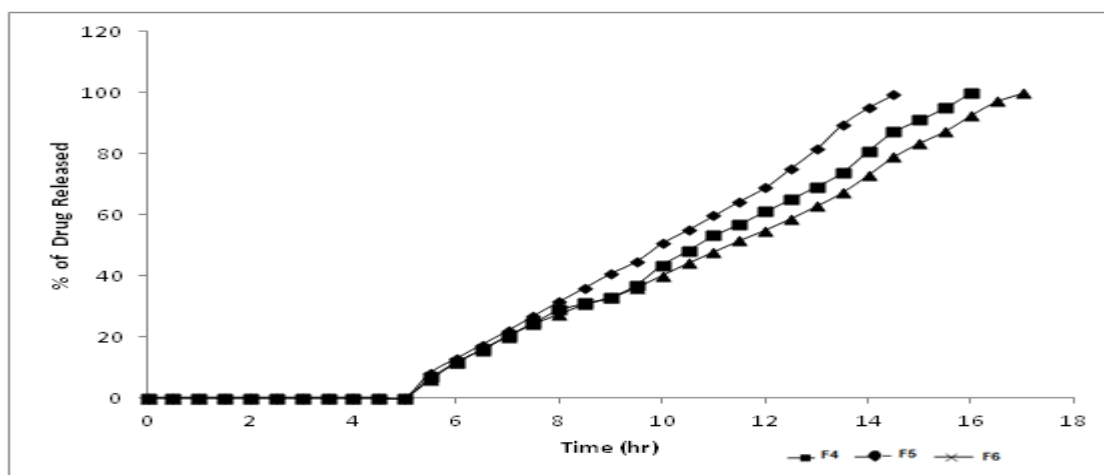
All the formulations offered good flow properties. The particle size of the microspheres ranged between 140.48±0.02 and 179.54±0.06. The use of the surfactant permits the remarkable reduction in the size of the microspheres as the result of decrease in the interfacial tension. All formulations had a 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, and ratios of core: coat to determine the affect of coating material concentration on the release rate of Montelukast sodium. 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 0.31% , 6.76 % ,

13.24 % and 17.22 % of drug release respectively at the end of 5th hour . It was observed that 100 mg hydrogel plug (HPMC K4: lactose in 1:1 ratio) having 4.5kg/cm² 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 buffers).

Table 4: In-vitro disssolution kinetics parameters of Montelukast sodium microspheres

Formulation	Correlation coefficient				Release kinetics			Diffusion Exponent value(n)
	Zero order	First order	Higuchi	Peppas	K_0 (mg/hr)	T_{50} (hr)	T_{90} (hr)	
F1	0.9937	0.7583	0.9189	0.9754	1.28	4.9	8.8	0.8727
F2	0.9992	0.7572	0.9261	0.9985	1.23	5.1	9.1	0.9019
F3	0.9986	0.7482	0.9329	0.9990	1.12	5.6	10.0	0.9412
F4	0.9979	0.7834	0.9234	0.9953	1.28	4.9	8.8	0.8653
F5	0.9979	0.7636	0.9251	0.9965	1.12	5.6	10.1	0.8794
F6	0.9968	0.7615	0.9219	0.9960	1.02	6.1	11.0	0.8744

**Fig 1: Comparative *In-vitro* drug release profiles plot of Montelukast sodium microspheres prepared with Eudragit S100 in different ratios****Fig 2: Comparative *In-vitro* drug release profiles plot of Montelukast sodium microspheres prepared with Eudragit L100 in different ratios**

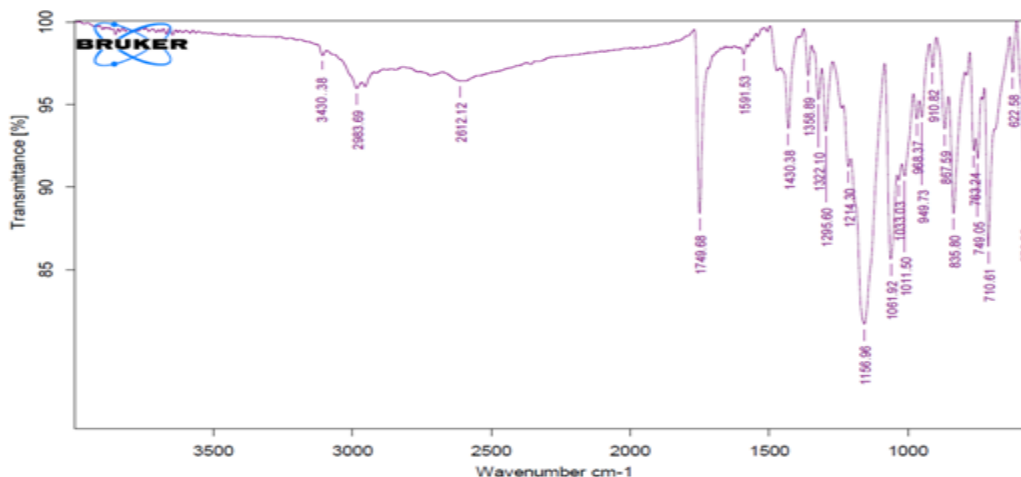


Fig 3: FTIR spectrum of pure Montelukast sodium

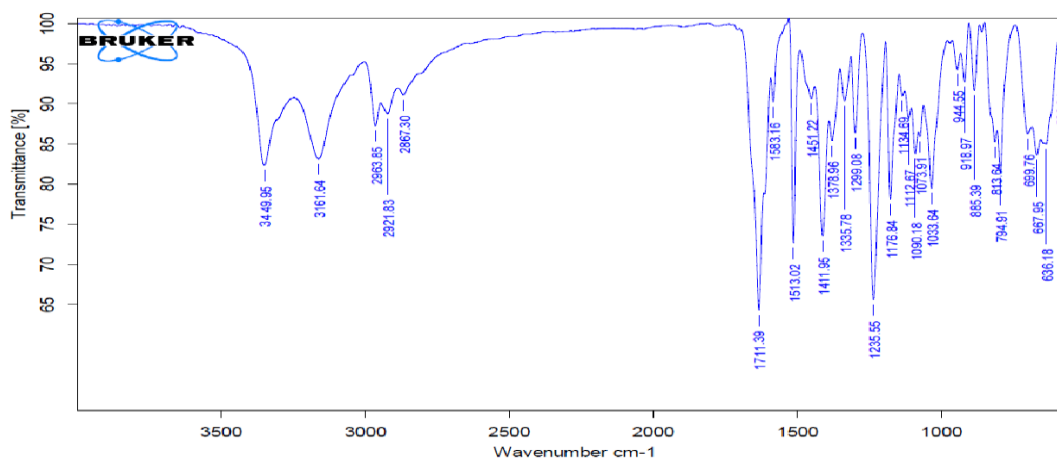


Fig 4: FTIR spectrum of optimized formulation

In-vitro release profiles in colonic medium were found to have very good sustaining efficacy. Pulsin caps loaded with Montelukast sodium microspheres prepared with Eudragit L100

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), 11 hours (5th hour to 16th hour) and 12 hours (5th hour to 17th hour) respectively. and are shown in figure 1. Pulsin caps loaded with Montelukast sodium microspheres prepared with Eudragit S 100 in 1:1,1:1.5 and 1:2 ratios shown sustained drug release for a period of 8 hours (5th hour to 13th hour), 9 hours (5th hour to 14th hour), and 10.5 hours (5th hour to 15.5 hour) respectively and are shown in figure 2. 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 0.8727 to 0.9412 indicating non fickian diffusion mechanism.

The FTIR spectrum of Montelukast sodium pure drug (Figure 3) showed characteristic peaks at 3430.38 cm⁻¹, 2983.69 cm⁻¹, 1749.68 cm⁻¹, 835.80 cm⁻¹ and 1430.38 cm⁻¹ denoting stretching vibration of N-H stretching, C-H stretching, C=O stretching C-Cl Stretching and C-C Stretching respectively. The FTIR spectrum (Figure 4) of optimized formulation (F4) showed characteristic peaks at wave numbers were 3449.95 cm⁻¹, 2921.83 cm⁻¹, 1711.39 cm⁻¹, 813.64 cm⁻¹ and 1451.22 cm⁻¹ denoting stretching vibration of N-H stretching, C-H stretching, C=O stretching C-Cl Stretching and C-C Stretching respectively. 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 Montelukast sodium microspheres prepared with Cellulose acetate 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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