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DESIGN AND CHARACTERIZATION OF CHRONOPHARMACEUTICAL DRUG DELIVERY OF PROPRANOLOL HYDROCHLORIDE

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ABSTRACT: Objectives: In the present study, an effort was made to develop a novel pulsatile dosage form for the treatment of hypertension using Propranolol hydrochloride as a model drug. A time-delayed capsule was prepared by sealing the pellets inside the insoluble hard gelatin capsule body with an erodible hydrogel plug. **Methods:** The pellets were prepared by the Fluidized Bed Wurster (bottom spray) technique. 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 4.5 kg/cm^2 hardness and 100 mg weight was placed in the capsule opening and found suitable to avoid the drug release in small intestinal fluid and eject the plugin colonic fluid, releasing the pellets into colonic fluid after a lag time criterion of 5 h. Three dissolution media with pH 1.2, 7.4 and 6.8 were consecutively used to simulate the pH changes along the GI tract. **Results:** FTIR study confirmed that there was no interaction between drug and polymer. Among all the formulations Propranolol hydrochloride pellets coated with Eudragit FS 30D in 35% w/w concentrations shown prolonged release for a period of 12 h. **Conclusion:** The obtained results revealed capability of system in controlling drug release for a programmable period of time and prevent a sharp increase in the incidence of blood pressure, during the early morning h, a time when the risk of hypertension attacks is maximum.

INTRODUCTION: Pulsatile drug delivery system is one type of drug delivery system, where the delivery device is capable of releasing drugs after predetermined time-delay (*i.e.*, lag time). The approach is based on the principle of delaying the time of drug release until the system transits through to the colon.

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For drugs required to be targeted in the colonic region (distal organ) the delivery system should prevent the release of drug in the upper two-third portions in the gut. Drugs with idiosyncratic pharmacokinetics or pharmacodynamics or drugs with extensive first-pass metabolism, require the pulsatile release of the drug.

A pulsatile release system is beneficial for the adaptation of drugs to suit circadian rhythms of body functions or diseases [1]. Several functions (*e.g.*, BP, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms. Cardiac events also occur with a circadian pattern [2].

The cardiovascular events are more commonly occur in the morning and the incidence of sudden cardiac death is up to 70% between 7 am and 9 am than during the rest of the day. Similarly, the stroke and ventricular arrhythmias occur with greater frequency in the morning hours due to the plasma catecholamine and cortisol, as well as vascular tone and effective circulating volume, which are also highest in the morning h [3]. Propranolol Hydrochloride is a non-selective β-adrenergic blocking agent. It has been widely used in the treatment of hypertension and many other cardiovascular disorders.

Propranolol Hydrochloride is subjected to an extensive and highly variable hepatic first-pass metabolism following oral administration, with reported systemic bioavailability of between 15 and 23% [4]. As it's biological half-life is about 3.9 h and is eliminated rapidly, repeated daily administration is needed to maintain effective plasma levels that make it a suitable candidate to be delivered through the colon route at a controlled rate. Administration of drugs through colon route bypasses the first-pass metabolism and thereby increases the bioavailability.

Prolonged-release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve a longer duration of action. 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 [5]. The aim was to have a lag time of 5 h, *i.e.*, the system is to be taken at bedtime (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 Propranolol hydrochloride is reached approximately 2 h after oral administration. Therefore, the drug concentration would be at its maximum level, when hypertension 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 h, which is highly desirable for hypertensive patients.

MATERIALS AND METHODS: Propranolol hydrochloride was a gratis sample obtained from Natco Pharma; Hyderabad. Eudragit FS 30D was obtained from Evonik Industries AG, Darmstadt, Germany. HPMC K4, Cellulose acetate phthalate 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 the cap, 25 ml of 15% (v/v) formaldehyde was taken into desiccators and a pinch of potassium permanganate was added to generate formalin vapors. The wire mesh containing the empty bodies of the capsule was then exposed to formaldehyde vapors. 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 ºC for 30 min to ensure completion of the reaction between gelatin and formaldehyde vapors. The bodies were then dried at room temperature to facilitate the 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 the equal amount of HPMC K4: lactose, to attain the weights of 75 mg, 100 mg, 125 mg and 150 mg using 7 mm punches and dies on rotary tablet press keeping varying thickness and hardness values of tablet plug [7].

Preparation of Pellets by Fluidized Bed Wurster (Bottom spray) Technology: The composition of various Propranolol hydrochloride controlled-release pellets were given in **Table 1**. All the ingredients were weighed out as per the given formula. The pellets of Propranolol hydrochloride were prepared by using sugar spheres. The required quantity of sugar spheres (sugar spheres USP-NF) was sifted through mesh #30. Mesh #30 passed sugar spheres were sifted through mesh #35 and retain were collected. First, seal coating was done prior to drug loading on sugar spheres because they were very small in size and brittle in nature, so in order to reduce the fine generation and prevent agglomeration they were made hard by seal coating [8].

TABLE 1: PROPRANOLOL HYDROCHLORIDE FORMULATIONS WITH EUDRAGIT FS 30D IN DIFFERENT CONCENTRATIONS

Seal Coating	Functional category	DF1	DF2	DF3
Sugar spheres (30/35)	Base pellets	144	144	144
Hydroxy propyl methyl cellulose 5 cps	Sealing polymer	6	6	6
Purified water (10% solids)		q.s	q.s	q.s
weigh of pellets after seal coating		150	150	150
Drug Loading				
Seal coated pellets		150	150	150
Propranolol HCl	Active ingredient	90	90	90
Povidone K30	Binder	30	30	30
Cross povidone	Pore former	30	30	30
Purified water (15% solids)		q.s	q.s	q.s
weigh of pellets after drug loading		300	300	300
ER Coating				
Drug Loaded Pellets		300	300	300
Eudragit FS 30D	Sustained-release polymer	35	26.25	17.5
Hydroxy propyl methyl cellulose 5 cps	Pore former/emulsifier	3	2.25	1.5
Polysorbate 80	Plasticizer	7	5.25	3.5
Talc	Anti tacking agent	10	3.75	2.5
weigh of pellets after SR Coating		350	337.5	325
Final weight of Pellets/capsules		350	337.5	325

Step 1 - Seal Coating: Required quantity of water was taken into a suitable vessel and hydroxypropyl methylcellulose 5 cps was added slowly under continuous stirring for a period of 45 min to get the 10% w/v solution of HPMC E5. Sugar spheres were loaded into fluidized-bed drier and 10% w/v solution of HPMC E5 was atomized on to the Sugar spheres while the air is allowed to circulate into the basket at an airflow rate of 2000 - 4500 cfm to keep the materials under the fluidized state. The process of fluidization was continued for 10 min. The drug-loaded pellets from the Fluidized Bed Coater were spread into the trays uniformly and dried at 60 °C temperature for about 3 h. After drying, the pellets were sifted by using vibro sifter to remove fines and collect the uniform sized pellets.

Step 2 - Drug Loading: Equal quantities of Propranolol hydrochloride and cross-carmellose sodium were taken into a bowl and mixed with a gloved hand. To the mixer, another equivalent quantity of Propranolol hydrochloride was added and mixed with help of gloved hand and the remaining quantity of the drug was loaded into the blender and mix with the powder for 10 min. The required quantity of water was taken and kept it under stirring, polyvinyl pyrrolidone K-30 was added to the vortex of the solution under stirring and stirred for 20 min. Then the dispersion was passed using nylon cloth (mesh number 20). Sugar pellets were charged into a fluidization basket. The drug and cross carmellose powder blends were also charged into the fluidized basket and povidone solution were atomized on to the materials while the air is allowed to circulate into the basket at an airflow rate of 2000 - 4500 cfm to keep the materials under the fluidized state. The process of fluidization was continued for 10 min. The drug-loaded pellets from the fluidized bed coater were spread into the trays uniformly and dried at 60 °C temperature for about 3 h. After drying the pellets were sifted by using vibro sifter to remove fines and collect the uniform sized pellets.

Step 3 - Extended Release Coating: Aqueous dispersion of Eudragit NM 30 D / Eudragit RL 30D /Eudragit FS 30D were prepared by diluting with water to get different levels of polymeric coating (35% w/w, 26.25% w/w and 17.5.% w/w respectively) to coat over drug layered pellets. Hydroxypropyl methylcellulose 5 cps was added as Pore former in the coating solution. The required quantity of Polysorbate 80 and talc was also added to the aqueous dispersion as Plasticizer and Anti tacking agent, respectively. The drug-coated pellets were charged into a fluidization basket. An aqueous dispersion of Polymer solution was atomized on to the materials while the air is allowed to circulate into the basket to keep the materials under the fluidized state. The process of fluidization was continued for 10 min. The finally coated pellets

were dried at ambient conditions for 2 h and sifted through vibro sifter to collect uniform sized pellets. The optimized process variables for different stages of the coating were specified in **Table 2**.

TABLE 2: OPTIMIZED PROCESS VARIABLES FOR DIFFERENT STAGES OF COATING

Process Variables	Coating stages of E. R. coated pellets		
	Seal Coating	Drug Layering	ER Coating
Inlet air temperature (^{0}C)	35–38	55–80	35–40
Out let Air temperature	30–36	50–75	30–35
Product bed temperature (^{0}C)	33-37	40-46	33-37
Atomization air pressure (bar)	1.2-1.3	1.2-1.5	1.2
Relative humidity (%)	32-33%	32-33%	32-33%
Blower drive speed (rpm)	30-37	45-55	40-45
Spray rate (gm/min)	3-5	3-15	3-10
Air Flow (cfm)	2000 - 4500	2000- 4500	2000- 4500

Designing of Pulsincap: The Pulsincap was designed by filling the pellets equivalent to 90 mg of Propranolol hydrochloride into the formaldehyde-treated bodies by filling manually. The capsules containing the pellets were then plugged with an optimized hydrogel plug.

The joint of the capsule body and cap was sealed with a small amount of 5% ethylcellulose ethanolic solution [9]. The sealed capsules were completely coated by a dip-coating method with 5% cellulose acetate phthalate in 5:5 (v/v) mixture of acetone: ethanol plasticized with n-dibutyl phthalate (0.75%), to prevent variable gastric emptying. The 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 [11].

Drug Content Uniformity: The encapsulated pellets equivalent to 90 mg of Propranolol hydrochloride were taken into mortar and grounded with the help of pestle. The grounded powder mixture was dissolved in 6.8 pH buffer, filtered and estimated spectrophotometrically at 237 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 h. In 0.1 M HCl (900 ml) as the average gastric emptying time is about 2 h. Then the dissolution medium was replaced with pH-7.4 phosphate buffer (900 ml) for 3 h as the average small intestinal transit time is about 3 h. After 5 h, the dissolution medium was replaced with pH 6.8 phosphate buffers (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 the temperature was maintained at 37 ± 0.5 ºC. Five milliliters of dissolution media were 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 potassium bromide pellet technique at the resolution rate of 4 cm^{-1}. Spectrum was integrated into transmittance mode at the wavenumber range 560 to 3560 cm^{-1} [13].

RESULTS AND DISCUSSION: Pulsincap dosage form is a capsule which consists of a water-insoluble body and a water-soluble cap. The pellets 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 a 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 the bloodstream. In the present study, capsule bodies that were hardened with formaldehyde treatment for 12 h were used for the preparation of pulsincaps. It was sealed with an unhardened cap of the capsule. The pellets were prepared by emulsion Fluidized Bed Wurster (bottom spray) technology. Due to high solubility, the sugar spheres immediately get dissolved in aqueous media without a build-up of sufficient osmotic pressure in the core. In order to retard the dissolution rate of nonpareil seeds, a film of hydroxypropyl methylcellulose 5 cps is applied on nonpareil seeds. Drug layering was performed by

coating aqueous suspension of the drug over seal coated pellets. Seal coated pellets were further coated with drug layering suspension up to the desired weight build-up having the same concentration of the drug. Binder concentration was optimized in the drug layer to achieve proper film formation and minimize the production of fines during coating.

An aqueous dispersion of Eudragit FS 30D was prepared by diluting with water to coat over drug layered beads, along with hydroxypropyl methylcellulose 5 cps as a binder in coating solution & formulation. The variable selected was % weight build-up (% coating) of the extended-release polymer. To optimize % coating of extended-release polymer, three formulations with different levels of polymeric coating (35% w/w, 26.25% w/w and 17.5. % w/w respectively) were manufactured. These pellets were characterized for percentage yield, size analysis, drug content and flow properties. The results were given in **Table 3** & **4**. Hydrogel Plugs were evaluated for hardness, friability, weight variation and lag time and the results were shown in **Table 5**. The formulations fitted with the various hydrogel plugs HP1, HP2, HP3, HP4 shown 17.67%, 14.06%, 7.24% and 0.26% of Propranolol hydrochloride release respectively at the end of 5^{th} h. It was observed that 150 mg hydrogel plug (HPMC K4 and lactose in 1:1 ratio) having 4.8 kg/cm^2 hardness was satisfactory to retard the drug release in small intestinal fluid and eject the plugin colonic fluid, releasing the pellets into the colonic fluid.

TABLE 3: PERCENTAGE YIELD, MEAN PARTICLE SIZE AND DRUG CONTENT OF PROPRANOLOL HYDROCHLORIDE PELLETS COATED WITH EUDRAGIT FS 30D IN DIFFERENT CONCENTRATIONS

Formulation	% yield	Average Particle Size (µm)	% of drug loading
PF1	96.29	691.31 ± 0.03	97.68 ± 0.02
PF2	96.81	679.43 ± 0.06	97.43 ± 0 .06
PF3	97.18	663.41 ± 0.04	96.83 ± 0.05

TABLE 4: FLOW PROPERTIES OF PROPRANOLOL HYDROCHLORIDE PELLETS COATED WITH EUDRAGIT FS 30D IN DIFFERENT CONCENTRATIONS

Formulation	Angle of repose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's Index (%)	Hausner's Ratio
PF1	25.42	0.908 ± 0.03	1.066 ± 0.04	14.82 ± 0.04	1.17 ± 0.03
PF2	24.13	0.917 ± 0.04	1.081 ± 0.07	15.17 ± 0.05	1.18 ± 0.02
PF3	22.72	0.920 ± 0.06	1.086 ± 0.06	15.28 ± 0.04	1.18 ± 0.03

TABLE 5: EVALUATION CHARACTERISTICS OF HYDROGEL PLUGS

Hydrogel plug code	Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Lag time (h)
HP1	75 ± 1.3	2.62 ± 0.03	4.1 ± 0.03	3.5
HP2	100 ± 1.1	3.42 ± 0.04	4.3 ± 0.02	4
HP3	125 ± 1.4	4.25 ± 0.06	4.6 ± 0.04	4.5
HP4	150 ± 1.2	5.12 ± 0.08	4.8 ± 0.01	5

This suggested that the lag time could also be adjusted by changing the plug composition. Composition for a pulsatile capsule containing Propranolol hydrochloride pellets coated with Eudragit FS 30 D in different concentrations on the basis of design summary were specified in **Table 6**.

TABLE 6: COMPOSITION FOR PULSATILE CAPSULE CONTAINING PROPRANOLOL HYDROCHLORIDE PELLETS COATED WITH EUDRAGIT FS 30 D IN DIFFERENT CONCENTRATIONS ON THE BASIS OF DESIGN SUMMARY

Formulation code	Weight of the empty body	Weight of pellets /capsule	Hydrogel plug	Total weight of capsule with cap (mg)	Wt. capsule After cellulose acetate phthalate coating (mg)
PF1	60.03	350	150	590.03	598.91
PF2	60.04	337.5	150	577.55	586.15
PF3	60.01	325	150	565.03	574.08

During dissolution studies, it was observed that the enteric coat of the cellulose acetate phthalate was intact for 2 h 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 pellets. After the complete wetting of the plug, it formed a soft mass, which was then easily ejected out of the capsule body, releasing the pellets into the simulated colonic fluid (pH 6.8 phosphate buffer). A pulsatile device consisting of Propranolol

hydrochloride pellets coated with Eudragit FS 30 D in different concentrations, sustained drug release for a period of 12 h (5^{th} h to 17^{th} h), 11 h (5^{th} h to 16 h) and 9.5 h (5^{th} h to 14.5 h) respectively. Comparative *in-vitro* drug release profiles plot of Propranolol hydrochloride pellets coated with Eudragit FS 30 D in different concentrations were shown in **Fig. 1**.

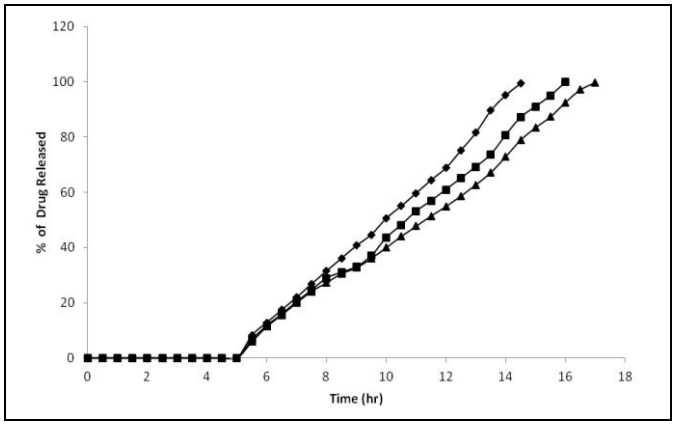

FIG. 1: COMPARATIVE *IN-VITRO* DRUG RELEASE PROFILE PLOT OF PULSATILE DEVICE CONSISTING OF PROPRANOLOL HYDROCHLORIDE COATED WITH EUDRAGIT FS 30 D IN DIFFERENT CONCENTRATIONS
(-□-)PF1: pellets coated with 35% of Eudragit FS 30 D(-♦-)PF2: pellets coated with 26.25% of Eudragit FS 30 D (-■-) PF3: pellets coated with 17.5% of Eudragit FS 30 D

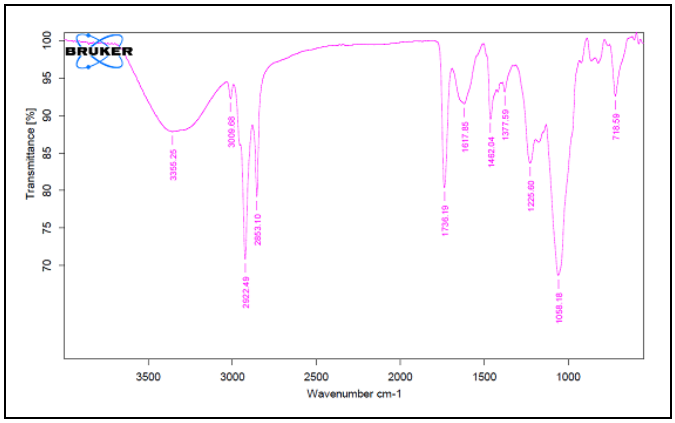

FIG. 2: FTIR SPECTRUM OF PURE PROPRANOLOL HYDROCHLORIDE

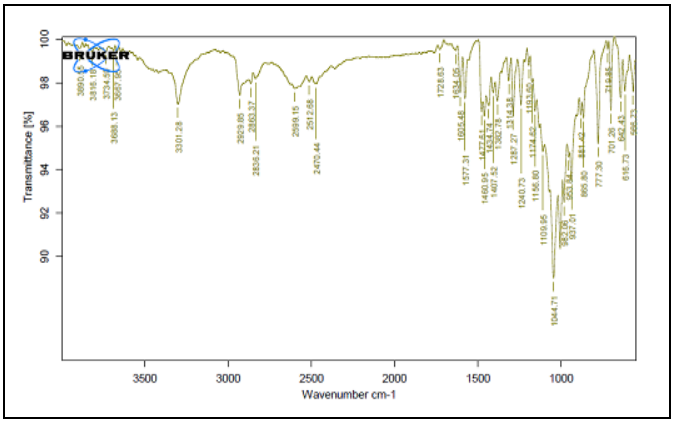

FIG. 3: FTIR SPECTRUM OF OPTIMIZED PROPRANOLOL HYDROCHLORIDE FORMULATION

To ascertain the mechanism of drug release, the dissolution data were analyzed by zero-order, first-order, Higuchi and Peppas equations. When the amount of drug release values were plotted against time, straight lines were obtained in all the cases indicating that the rate of drug release from these microparticles followed zero-order kinetics. The plot of log % Drug Released *vs.* log time (Peppas plots) was drawn. The plots were found to be linear with all pellets. Release Kinetics of pellets, the time required to get 50% drug release (T50) and 90% drug release (T90) was calculated and shown in **Table 6**. The exponential coefficient (n) values were found to be in between 0.7555 to 0.9576, indicating that the drug release followed non fickian mechanism. These results indicated that the release rate was found to decrease with an increase in the concentration of coating material applied. The FTIR spectrum of Propranolol hydrochloride pure drug **Fig. 3** showed characteristic peaks at 2853.10 cm^{-1}, 1617.85 cm^{-1}, 1462.04 cm^{-1} and 1225.06 cm^{-1} denoting stretching vibration of C=H stretching, C=C stretching, CH Deformation and C-O Stretching respectively. The FTIR spectrum of optimized formulation (F4) showed characteristic peaks at wave numbers were 2836.21cm-1, 1634.05 cm^{-1}, 1434.74 cm^{-1} and 1287.27 cm^{-1} denoting stretching vibration of C=H stretching, C=C stretching, CH Deformation, and C-O Stretching respectively. There is no change or shift of the characteristic peaks in drug and excipient mixtures suggesting 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 the optimized formulation. There was no change or shift of characteristic peaks in drug-loaded pellets suggesting that there was no significant drug-polymer interaction which indicates the stable nature of the drug in the optimized formulation.

CONCLUSION: Among all the formulations Pulsin caps loaded with Propranolol hydrochloride pellets coated with 35% of Eudragit FS 30 D shown prolonged release for a period of 12 h. 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 chrono-modulated therapy of hypertension, the lag time criterion of 5 h and sustained release for a period of 12 h was satisfied. The dosage form can be taken at bedtime and will release the contents in the early morning hours when hypertension is more prevalent.

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