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FABRICATION, OPTIMIZATION AND EVALUATION OF CHRONOTROPIC DRUG DELIVERY SYSTEM OF CAPTOPRIL

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Keywords:

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ABSTRACT: The present investigation was based on the development and evaluation of chronotropic capsules for hypertension treatment. Captopril has ACE inhibitor action to prevent the circadian rhythm related to hypertension. The solubility of captopril in the GI tract was pH-dependent *i.e.*, captopril soluble only at 1.2 pH, show better stability, and absorbed in the upper part of the gastrointestinal tract. Captopril has 1-2 h half-life ($t_{1/2}$) and 3.7 pKa value. For the optimization of formulation 3^2 factorial designs was used and in these methods, two independent variables at three levels were selected. The direct compression method was used for the preparation of pulsincap plugs. The dissolution profile of formulated batch F1 to F9 at the end of 9 h was found in the range of 92.50 to 99.60% in different pH of phosphate buffer. From the results, it was found that formulation F5 was shown the most similar dissolution profile because the similarity value was found to be above 90%. The swelling index was found higher in formulation F5 and time for erosion was 78 minutes for F5 formulation. Statistically, the formulation was optimized, and P and R^2 values for the response variable (time of erosion of plug) were observed 0.0152 & 0.7130, respectively. The second response variable % drug release showed the P & R^2 values as 0.0016 & 0.8225 respectively. P-value and R^2denote that model was significant for the formulation in the correspondence of major response variables.

INTRODUCTION: The oral controlled drug delivery system in which the drug release pattern follows zero-order kinetics and maintained therapeutic window for a longer duration, by which ensuring novel therapeutic action [1]. For various diseases, (*e.g.*, hypertension, bronchial asthma) as well as manage body functions (level of many hormones, blood pressure, *e.g.*, cortisol, renin, and aldosterone) affected by circadian rhythm, to diminish these disorders, chronotropic drug delivery system is an effective and optimal approach.

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Alongside it, some drugs required controlled, targeted, and absorption in accordance with circadian rhythm. To achieve this special situation, drugs can be developed with a new advanced drug delivery dosage form called chronotropic drug delivery system [2].

A chronotropic oral drug delivery system has advantages over the conventional oral dosage form in that the drug can be released at a specific time period. The chronotropic delivery system is the quick and transient drug release of certain drug concentration or drug molecules within a minimum time interval quickly after a predetermined off release interval.

This type of drug delivery has the advantages such as targeted drug delivery of fixed amount of drugs which are employed to treat various diseases which shows circadian rhythm in the pathophysiology of

hypertension-related with captopril, avoidance of drug degradation in the upper gastrointestinal tract, *e.g.* peptides and proteins and for time-dependent drug delivery like hormones and other drugs *e.g.*, isosorbide dinitrate to diminish normal hormonal secretion in the body that can be achieved by chronotropic release of hormone from the administered drug in suitable dosage form [3, 4, 5]. The goals of such a strategy are to improve the efficacy of medications for BP control, reduce medication-induced adverse effects and, most importantly, decrease patient cardio-vascular risk as well as renal and all other end-organ injuries that are consequences of hypertension [6, 7, 8]. As a model drug, captopril was selected because it shows ABC inhibitory action to prevent the circadian rhythm related to hypertension. The solubility of captopril in the GI tract was ph-dependent *i.e.*, captopril soluble only at 1.2 pH, show better stability, and absorbed in the upper part of the gastrointestinal tract. Captopril has 1-2 h half-life ($t_{1/2}$) and 3.7 pKa values [9, 10, 11]. Hypertension's pathophysiology depends upon circadian rhythm, *i.e.*, highest plasma concentration of angiotensin and renin in early morning [12, 13]. Disease pathophysiologies as well as pharmacokinetic parameters indicate that captopril is a suitable drug to prepare chronotropic granules loaded capsules. The objectives of the research were to fabricate, optimize, and characterize the prepared oral chronotropic delivery system.

MATERIALS AND METHODS:

Materials: Captopril I.P. was obtained as a gift sample from Torrent Pharmaceutical, Ahmadabad, India. All other polymers and chemicals were analytical grade and provided by Shriram College of pharmacy, Banmore, Morena.

Methods:

Compatibility Analysis (FTIR): FTIR spectrum of captopril was obtained by means of an FTIR spectrophotometer. The potassium bromide disk method was employed for the preparation of samples, and IR spectra were accumulated at 400-4000 cm^{-1} wave no. After generating IR spectra, it was interpreted for corresponding fundamental groups. FTIR studies of captopril, HPMC, Eudragit RL100, Cellulose acetate phthalate, Sodium lauryl sulfate, and physical mixture of drugs with polymers were carried out to find out the interaction. The spectral are shown in **Table 3.**

Standard Curve of Captopril in pH 1.2 Buffers (0.1N HCl): Concentrated 8.5 ml HCl was taken and dissolved in 1000 ml of distilled water. The pH of the solution was then adjusted to 1.2 using a pH meter. A stock solution of the drug was prepared by using 100 mg of Captopril.

The drug was dissolved in 0.1N HCl and stirred for some time. The volume of the solution was made up to 100 ml, with the subsequent addition of 0.1N HCl to it followed by continuous shaking. From the stock solution, 1 µg/ml of the drug concentration solution was made and analyzed spectro-photometrically. The absorbance of each solution was noted at 201 nm. The λ_{max} of captopril was performed in triplicate, and mean absorbance was considered. The calibration curve was constructed by plotting the absorbance versus concentration **Fig. 2**.

Preparation of Captopril Granules: First of all, the ingredients were mixed and then moistened with a 10% PVP solution in ethanol. The mixture was granulated by passing through a 24-mesh screen then dried at 140º to 150 ºC. The mixture was sized through a 44-mesh screen; talc was added & mixed well.

TABLE 1: FORMULA FOR GRANULES

Ingredient	Quantity per Capsule	Quantity for 50 Capsules
Captopril	25 mg	1250 mg
Lactose (fine powder)	115 mg	5750 mg
Corn starch	50 mg	2500 mg
Talc	10 mg	500 mg
SLS	1%	100 mg
PVP (10% solution)	q. s.	q. s.

Preformulation Study:

Physical appearance Study: In this study, the physical appearance of drug and polymer was observed, and it confirms the physical state, taste, odor, color, and melting point, and it was compared with the standard which gave in the pharmacopeia.

Angle of Repose (θ): The angle of repose of prepared granules was determined according to fixed standing funnel method [14]. (n=3)

$$\theta = \text{Tan}^{-1}\, h / r$$

Where, θ denotes as angle of repose, r-radius and h-height of pile

Bulk Density and Tapped Density: Bulk and tapped densities were determined by using 100 ml of measuring cylinder. The pre-weighed granules were filled in a measuring cylinder, and volume was measured. For the determination of tapped density, granules filled cylinder was tapped until obtaining zero difference of tapped volume. Each experiment was performed in a triplicate manner to get reproducible results. Final calculations were calculated by using the following formula [14]:

$$Bd = m / v$$

Where, Bd = Bulk density (gm/ml), M = Mass of granules (gm) and V = Volume of granules (ml)

$$Td = M / T$$

Where, Td = Tapped density (gm/ml), M = Mass of granules (gm), Tv = Tapped granules

Carr's Index: The compressibility index of the prepared granules was determined by calculating bulk and tapped densities. It is a simple parameter to determine the Bd and Td of granules and the rate at which it packed down. The formula for Carr's index is as below [14]:

$$\text{Carrs index (\%)} = Td – Bd / Td \times 100$$

Where, Bd = Bulk density, td = Tapped density

Hausner's Ratio (HR): Hausner's ratio of granules was calculated by comparing bulk density tothe tapped density by using the following formula.

$$HR = Td / Bd$$

Where, HR is Hausner's ratio, Td is tapped density and Bd is bulk density. Lower Hausner's ratio (< 1.25) indicates better flow properties than higher ones (> 1.25).

Granules Size: Granules' size was analyzed by the sieving method.

Development and Optimization of Pulsing-Capsule (Pulsincap) Formulations by using 32 Factorial Design: For the optimization of formulation 32 factorial designs were used, and in these methods, two independent variables at three levels were selected. Detail of these factors is shown in the table.

TABLE 2: TWO INDEPENDENT VARIABLE AND THREE LEVELS

Factor	Level		
	Low (1)	Medium (0)	High (1)
Independent variables			
HPMC (mg)	15	20	25
Eudragit RL 100 (mg)	15	40	75
Dependent variables			
DV1 = Time of erosion of plugs			
DV2 = % Drug release			

Preparation of Hydrogel Plug: The direct compression method was used for the preparation of pulsincap plugs. The granules and polymers mixed blend was sieved through a sieve no.45 and compressed with a single punch. Magnesium stearate and isopropyl alcohol dispersion were used as an external lubricant for the reduction of sticking of plugs to the punches.

Preparation of Cross-linked Gelatin Capsules: First of all, formaldehyde 15% v/v (25 ml) was placed in desiccators, and a minute quantity of $KMnO_4$ was employed in it for generating formalin vapors. The empty hard gelatin capsule bodies (50 mg capacity) were fixed with wire meshes and allowed to interact with formaldehyde vapors. The interaction was allowed for 24 h than after bodies of capsules were detached and dried at 50 °C for 30 min for completion of interaction with formaldehyde vapors and gelatin. Then hard gelatin capsule bodies were allowed to dry at room temperature to remove the rest of the formaldehyde concentration. The caps were not exposed to formaldehyde vapors, leaving them water-soluble. Then these bodies were capped with capsule cap.

TABLE 3: COMPOSITION OF PULSING CAPSULE FORMULATION

Formulation	Components in mg (% w/w)		
	Weight of Captopril in Granules	HPMC	Eudragit RL100
F1	200	15 (0)	15 (-1)
F2	200	15 (0)	40 (0)
F3	200	15 (0)	75 (1)
F4	200	20 (-1)	15 (-1)
F5	200	20 (-1)	40 (0)
F6	200	20 (-1)	75 (1)
F7	200	25 (1)	15 (-1)
F8	200	25 (1)	40 (0)
F9	200	25 (1)	75 (1)

Tests for Formaldehyde-treated Empty Capsule Bodies: Different physical characters were

evaluated such as visual inspection, attributes, solubility, and dimension changes.

Qualitative Chemical Tests for Free Formaldehyde: The standard formaldehyde solution was used for comparison with a sample solution. For the preparation of the sample first, formaldehyde-treated capsule bodies were cut into small pieces and placing them into a distilled water containing beaker. This sample solution was stirred for an hour for the solubilization of free formaldehyde. The sample solution was filtered then filtrates washed by using distilled water and volume made up to 50 ml. In brief, 9 ml of water was added to a 1 ml sample solution. From the resulting solution, 1 ml was withdrawn into a test tube then mixed with 5 ml acetone and 4 ml of water. The test tube was allowed to warm at 40 °C on to the water bath for 40 min. Then compare the intensity of the color of a sample solution with the reference solution in the same manner and the same time using 1 ml of the reference solution. The comparison was made by inspecting tubes down at eye levels.

Formulation of a Pulsatile Drug Delivery System: The treated caps and bodies of hard gelatin capsules were detached manually. Captopril granules were weighed accurately and filled into the formaldehyde-treated bodies manually. The granules containing capsules were then plugged with various concentrations of polymers, *i.e.*, Eudragit RL100 and HPMC. Then bodies and caps of capsules were joined together and then coated these capsules by dipping in a solution of plasticizer and 5% CAP (cellulose acetate phthalate) in acetone: ethanol (1:1 v/v) to prevent variable gastric emptying. The coating was managed until an 8-10% increased. The percentage weight gain of the pulsincap before and after coating was calculated [15] **Table 4**.

Evaluation of Designed Pulsatile Capsule: The thickness of the coating of cellulose acetate phthalate coating was evaluated by a screw gauge. Capsules sample (10) were randomly taken and weighed, and calculated for % weight variation. The parameters standard was met if none of the individual weights is less than 92.5% or more than 107.5% of the mean [16].

***In-vitro* Dissolution Analysis:** *In-vitro* dissolution studies were carried out on the pulsincap at 37 ± 0.5 °C at 100 rpm using USP Dissolution apparatus-II.

RESULTS AND DISCUSSION:

Compatibility Analysis (FTIR): IR studies of drug captopril, HPMC, Eudragit RL100, cellulose acetate phthalate, and sodium lauryl sulfate were carried out, and observed absorption peaks were compared with peaks of the group present in the drug respective polymers. There was no interaction reported between the drug and polymers used.

TABLE 4: INTERPRETATION OF CAPTOPRIL IR SPECTRA

S. no.	Wave No. (Peak) in cm^{-1}	Interpretation
1	2980.35	$-CH_3$ Asymmetric stretching
2	2879.27	$-CH_2$ Stretching
3	2566.22	-SH Stretching
4	1748.25	-C=O Stretching (COOH group)
5	1589.59	-C=O Stretching (amide group)
6	1332.08	-OH Bending
7	1228.23	-CN Stretching

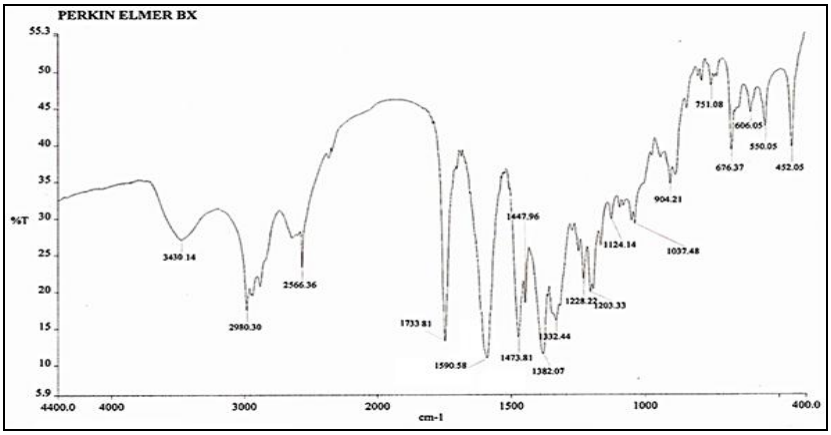

FIG. 1: IR GRAPH FOR DRUG POLYMER INTERACTION

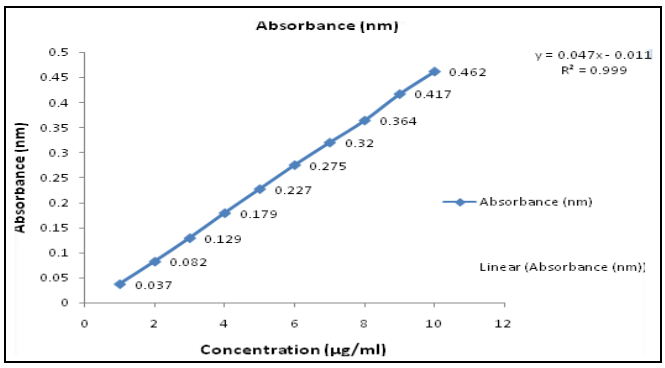

FIG. 2: STANDARD CURVE OF CAPTOPRIL IN pH 1.2 BUFFER (0.1N HCL)

Pre-formulation Study:

Physical appearance Study: The physical appearance of the drug was revealed as white of the crystalline powder, bitter in taste and slight sulfurous odor.

Angle of Repose (θ), Bulk Density and Tapped Density: Values of the angle of repose, bulk density, and tapped density are expressed in the table.

TABLE 5: ANGLE OF REPOSE, BULK DENSITY AND TAPPED DENSITY VALUES

Granules Code	Angle of Repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)
	Mean	Mean	Mean
A	23.45	0.4	0.56
B	22.15	0.46	0.63
C	21.17	0.47	0.52

Carr's Index (CI): Carr's index ranges from 5.88-9.25%. The formulation code C of granules had the lowest C_i index indicating excellent compressibility **Table 6.**

Hausner's Ratio and Granule size: It was ranging from (1.06-1.10), *i.e.*, all three preparations showed that they had good flow properties. Upon considering the micrometric properties of all the three formulations, formulation code C of granules had the best flow properties since it had a high angle of repose value (23.17), Carr's index (5.88), and Hausner's ratio (1.06) **Table 6.**

TABLE 6: CARR'S INDEX (CI), HAUSNER'S RATIO AND PARTICLE SIZE VALUES

Granules Code	Carr's Index (C_i) (%)	Hausner's Ratio	Granules size (mm)
	Mean	Mean	Mean
A	6.12	1.06	0.721
B	9.25	1.10	0.611
C	5.88	1.06	0.669

Effect of Formaldehyde Treatment on the Dissolution of Body and Cap: The solubility of hard gelatin capsules was modified by using the treatment of formaldehyde. Formaldehyde vapors were allowed to react gelatin capsules and the solubility of capsules was decreased because of cross-linking of amino groups present in gelatin and aldehyde groups of formaldehyde. Formaldehyde treated body of capsules was shrunken during the observation. 250 mg Capsules observed as decreased in diameter and length after the formaldehyde treatment.

TABLE 7: DISSOLUTION TIME OF CAP (MIN) AND DISSOLUTION TIME OF CAPSULE BODY (HRS)

S. no.	Dissolution time of Cap (Min)	Dissolution time of Capsule Body (h)	Normal Capsules (Min)
1	19 ± 0.7	24 ± 1	25 ± 1
2	20 ± 0.9	24 ± 0.9	24 ± 1
3	22 ± 0.6	24 ± 0.7	26 ± 0.9
4	21 ± 0.8	24 ± 1	25 ± 0.9
5	18 ± 0.7	24 ± 0.8	25 ± 1
6	19 ± 0.9	24 ± 0.9	25 ± 0.7
7	21 ± 0.7	24 ± 0.7	26 ± 1
8	19 ± 0.8	24 ± 0.8	25 ± 1
9	20 ± 0.6	24 ± 0.7	26 ± 1
10	19 ± 0.9	24 ± 0.7	25 ± 1

The stability parameter was performed for formaldehyde-treated capsules and normal capsules for 24 h.

Cap and body of formaldehyde-treated capsules were dissolved within about 20 min and 24 min, respectively, while normal capsules were dissolved within about 25 min. The formaldehyde capsules were tested for the presence of free formaldehyde.

The sample solution was not more intensely colored than the standard solution. Values of dissolution time of cap (min) and dissolution time of capsule body (hrs) are expressed in **Table 7**.

Thickness of Coating and Weight Variation: The thickness of the coating of cellulose acetate phthalate coating was evaluated by a screw gauge. The thickness range was observed 0.48-0.6 mm for all formulations. Capsules sample (10) were randomly taken from each batch and weighed and calculated for % weight variation. A maximum % deviation was observed for F4 (7.43 ± 0.7%), and the minimum was observed for F5 (6.39 ± 0.7%). Values of thickness and % weight variation are expressed in **Table 8.**

TABLE 8: THICKNESS AND % WEIGHT VARIATION

Formulation code	Thickness (mm)	Weight Variation (%)
F1	0.5±0.01	6.87±0.4
F2	0.6±0.02	7.43±0.7
F3	0.5±0.02	6.51±0.6
F4	0.6±0.02	7.42±0.5
F5	0.5±0.01	6.39±0.7
F6	0.48±0.01	6.98±0.6
F7	0.49±0.01	6.74±0.7
F8	0.5±0.01	6.81±0.6
F9	0.5±0.01	6.95±0.6

Evaluation of Pulsincap: Captopril release from pulsincap was studied for 10 h. Dissolution study of pulsincap indicated that the cellulose acetate phthalate was worked good enteric-coated polymer and intact for 2 h at stomach pH but dissolved at near to basic pH (intestinal pH), thus detached the soluble cap of the capsule. The polymer plug absorbs the fluid of the intestine and swells; then drug release takes place. From the data of all formulations, it was observed that there was no drug release at stomach pH, it was observed that 5% of cellulose acetate phthalate has good efficiency for enteric coating.

Influence of Plug Weight on Pulsatile Release Capsule: The lag time was controlled by the weight of the plug; it increased with increasing plug weight.

When comparing two different types of polymers, it was found that pulsatile prepared using Eudragit RL100 required higher weight in the plug compared to HPMC to achieve the same lag time. HPMC had the maximum lag time, and Eudragit RL100 had the minimum lag time because it's poor compressibility.

Determination of the time of Erosion of the Plugs: The time for complete erosion of the plugs (compressed plugs: 55,45,35,25, & 15 mg 12-5N) was determined with a disintegration tester in pH 7.4 PBS.

TABLE 9: EROSION PROPERTIES, SWELLING AND DISSOLUTION OF PLUG

Formulation	Dissolution	Swelling	Time of Erosion (min)
F1	++	+	89
F2	+	+	74
F3	+	+	51
F4	+	0	42
F5	+	++	78
F6	+	+	65
F7	+	+	47
F8	+	+	39
F9	+	0	53

++ Very good; + good; 0 not good.

ANOVA for Quadratic Model:
Response 1: Time of Erosion of Plug:

TABLE 10: ANOVA RESPONSE FOR TIME OF EROSION OF PLUG

Source	Sum of squares	DF	Mean square	F	P	R^2	Model
Regression	3248.03	5	649.61	4.97	0.0152	0.7130	Significant
Residual	1307.72	10	130.77				
Total	109.57	15	-				

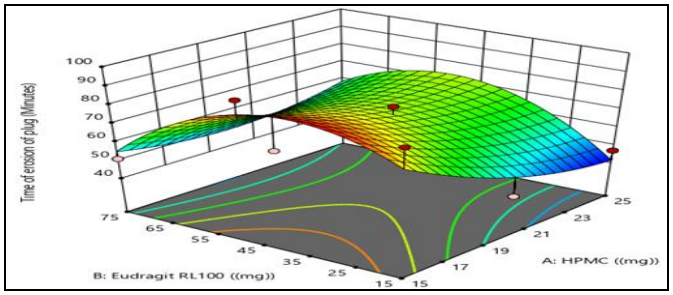

FIG. 3: RESPONSE GRAPH FOR TIME OF EROSION OF PLUG

***In-vitro* Dissolution Analysis:** *In-vitro* dissolution studies were carried out on the pulsincap at 37 ± 0.5 °C at 100 rpm using USP Dissolution apparatus-II The *in-vitro* dissolution studied was performed in three different pH media to the changes along the GI tract, with pH 1.2 (*i. e.* Simulated gastric fluid pH); pH 6.8 and 7.4 (*i. e.* Simulated intestinal fluid pH) were sequentially

used (referred to as sequential pH change method). Capsules were tied to paddle with a thread, in dissolution media consisting of 900 ml of 0.1N (pH 1.2), hydrochloric acid, and dissolution was performed for 2 h (the average gastric empty time is 2 h).

Then removed the first media, and the fresh pH 6.8 phosphate buffer solution (PBS) was added. After the intestinal transit time (for small intestine 3 h) removed the second media and the fresh pH 7.4 phosphate buffer solution (PBS) was added and at the 1 h interval sample ware withdrawn. The withdrawn sample was analyzed by a UV-visible spectrophotometer at 201 nm.

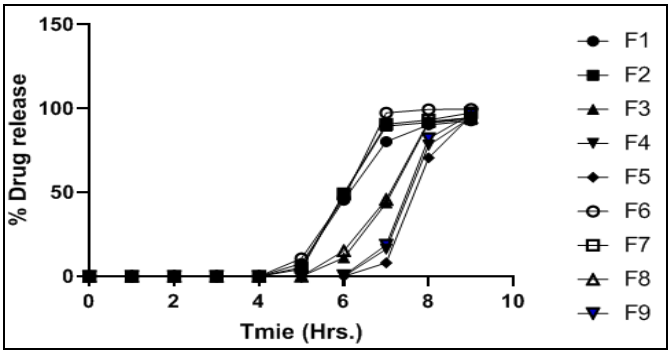

FIG. 4: GRAPH OF COMPARATIVE RELEASE STUDY OF FORMULATION

Finally, the drug content in all fluids was determined from the calibration curve of Captopril to determine the release pattern in **Table 11.**

TABLE 11: COMPARATIVE RELEASE STUDY OF FORMULATION (F1-F9)

Time (h)	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
0	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00
1	00.00	00.00	00.00	00.00	00.0	00.00	00.00	00.00	00.00
2	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00
3	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00
4	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00
5	07.70	04.30	00.00	00.00	00.00	10.70	05.30	00.00	00.00
6	45.32	48.90	11.12	0.1	00.00	46.30	49.20	15.22	0.51
7	80.20	89.40	43.70	16.17	8.00	97.30	90.60	45.70	18.70
8	90.20	91.60	91.40	78.10	70.6	99.30	93.10	92.20	82.10
9	92.50	93.30	94.40	94.60	95.50	99.50	97.30	94.40	96.40

ANOVA for Quadratic Model:
Response 2: % Drug Release:

TABLE 12: ANOVA RESPONSE FOR % DRUG RELEASE

Source	Sum of squares	DF	Mean square	F	P	R^2	Model
Regression	43.87	5	8.77	9.27	0.0016	0.8225	Significant
Residual	9.47	10	130.77				
Total	53.34	15	-				

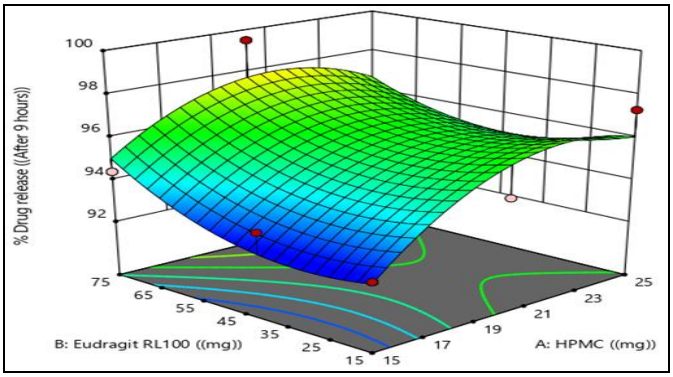

FIG. 5: RESPONSE GRAPH FOR % DRUG RELEASE

CONCLUSION: The present investigation was based on the development and evaluation of chronotropic capsules for hypertension treatment. The instant release of captopril after a lag time is an essential need of a chronotropic drug delivery system, which was achieved by developed preparations. The pH-sensitive coating and hydrogel plug polymers such as hydroxypropyl methylcellulose and Eudragit RL 100 were found to be responsible for delaying the release. Thus, this approach can provide a useful means for pulsatile/programmable release (with a single pulse) of captopril and may help for patients with morning surge.

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CONFLICTS OF INTEREST: Authors declare no conflict of interest.

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