IJPSR (2025), Volume 16, Issue 4 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 10 November 2024; received in revised form, 06 December 2024; accepted, 11 December 2024; published 01 April 2025

MICROSPONGE BASED CANDESARTAN CILEXETIL LOADED PULSINCAP FOR ACHIEVING CHRONOMODULATED DRUG DELIVERY

J. Gomathi *, M. F. Farzana Affrin and B. Veeralakshmi

Department of Pharmaceutics, C. L. Baid Metha College of Pharmacy, Affiliated to The Tamil Nadu, Dr. M. G. R. Medical University, Chennai - 600097, Tamil Nadu, India.

Keywords:

Pulsincap, Candesartan cilexetil, Chronomodulated, Microsponges, hydrogel plug, Hypertension

Correspondence to Author:
Dr. J. Gomathi

Associate Professor,
Department of Pharmaceutics, C. L. Baid Metha College of Pharmacy, Affiliated to The Tamil Nadu, Dr. M. G. R. Medical University, Chennai - 600097, Tamil Nadu, India.

E-mail: gomathidinesh1@gmail.com

ABSTRACT: Candesartan Cilexetil (CC) traditional dosage form has poor bioavailability and quick first pass metabolism, which leads to rapid elimination of the drug from the system and reduced plasma drug concentration during early morning heart attack incidence. The primary purpose of the Candesartan Cilexetil chronotherapeutic formulation is to optimally release the medicine in greater amounts in the early morning hours (when it is most needed) and in lower amounts at night (when it is least needed). Because systolic and diastolic blood pressures increase fast in the early morning by at least 15 to 25 mmHg and peak late in the day, Candesartan Cilexetil was successfully developed as microsponges to enhance its solubility and bioavailability and delivered as the pulsatile release (Pulsincap dosage form) for delivering the drug after the lag time of 5-6 h for the chronomodulated release of the drug. Microsponges and Pulsincap were subjected to various formulation parameters like FTIR, DSC, encapsulation efficiency, SEM, *in-vitro* dissolution and kinetic study. F9 formulation was selected as best formulation as it offered a required lag time of 5 h and achieved a cumulative percent drug release of 95.87% over a period of 24 h. The drug release of F9 follows zero order kinetics. From the outcomes, it is evident that the solubility and bioavailability can be improved and the drug can be delivered as pulsatile delivery for an effective treatment of the morning spike of hypertension.

INTRODUCTION: Pulsatile drug delivery systems are single-unit devices, often in capsule form. The typical design of such devices comprises an insoluble capsule body containing medication and a plug. The plug is removed after a particular period of time due to swelling, erosion, or dissolution. One such approach is the Pulsincap system, which comprises a water-insoluble capsule body filled with the drug formulation.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.16(4).962-73

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.16(4).962-73

The open end of the body is sealed with a swellable hydrogel stopper. When the plug comes into touch with dissolving media or gastrointestinal fluids, it expands and eventually pushes itself out of the capsule. The medication is then released quickly [1, 2].

These systems are useful for medications that have high first-pass effects, pharmaceuticals employed to treat diseases with chrono-pharmacological behaviour, drugs with a particular absorption site in the GIT, drugs that target the colon, and conditions that require midnight administration [3]. Chronotherapeutics is the clinical field of synchronizing drug delivery with the body's chronological cycle, including disease states, in

order to get maximal health benefits with the least amount of side effects [4]. Ischemic cardiovascular conditions like angina pectoris and hypertension have become more common. The most common cause of these episodes is high blood pressure, which increases significantly prior to waking up. If certain diseases develop symptoms late at night or early in the morning, treating them using immediate-release dosage forms may be impracticable. In theory, using modified-release forms of dosage with zero-ordered drug release can lead to constant and controlled amounts of drugs in plasma throughout the day [5, 6].

Candesartan Cilexetil (CC) is an angiotensin II receptor blocker and one of the most prevalent antihypertensive drugs. Chemically, it is a tetrazole derivative which is clinically used in the form of an ester prodrug. During the absorption process from GIT, CC is bioactivated by ester hydrolysis and liberates the free drug, Candesartan. It is characterized by poor aqueous solubility and low dissolution rate which resulted in a very low bioavailability, only 15%. So, the main objective of the present work was to develop a pulsatile capsules of Candesartan Cilexetil which releases a drug after a predetermined lag time and it is controlled by a hydrogel plug of polymers [7-11].

MATERIALS AND METHODOLOGY:

Materials: Candesartan Cilexetil and HPMC K4M were offered as free samples by Saimirra Innopharm Pvt Ltd. Chennai, India. Ethyl cellulose (EC) (Loba Chemicals Private Limited, Hyderabad), polyvinyl alcohol (Qualigens). Dichloromethane is from Fisher Scientific, Mumbai. All additional compounds used are of pharmaceutical and analytical grade.

Methodology:

Drug-Characterization:

UV-spectroscopy:

Preparation of Primary Stock I Solution: Pure Candesartan Cilexetil of 10mg was weighed and dissolved in methanol in a 100 ml volumetric flask. The primary stock solution of CC was prepared with methanol at a concentration of 1000µg/ml.

Preparation of Stock II Solution: Prepare stock II at a concentration of 100 µg/ml from the primary stock solution I. The aforementioned stock solution was then further diluted with methanol to produce working standard solutions of 10, 20, 30, 40, and 50 µg/ml. The solution was scanned in the wavelength range of 200nm – 400nm. The maximum wavelength of CC was determined to be 254nm [12-17].

Design of Formulation: Candesartan Cilexetil Microsponge Formulation by Quasi-Emulsion Solvent Diffusion Technique [6]:

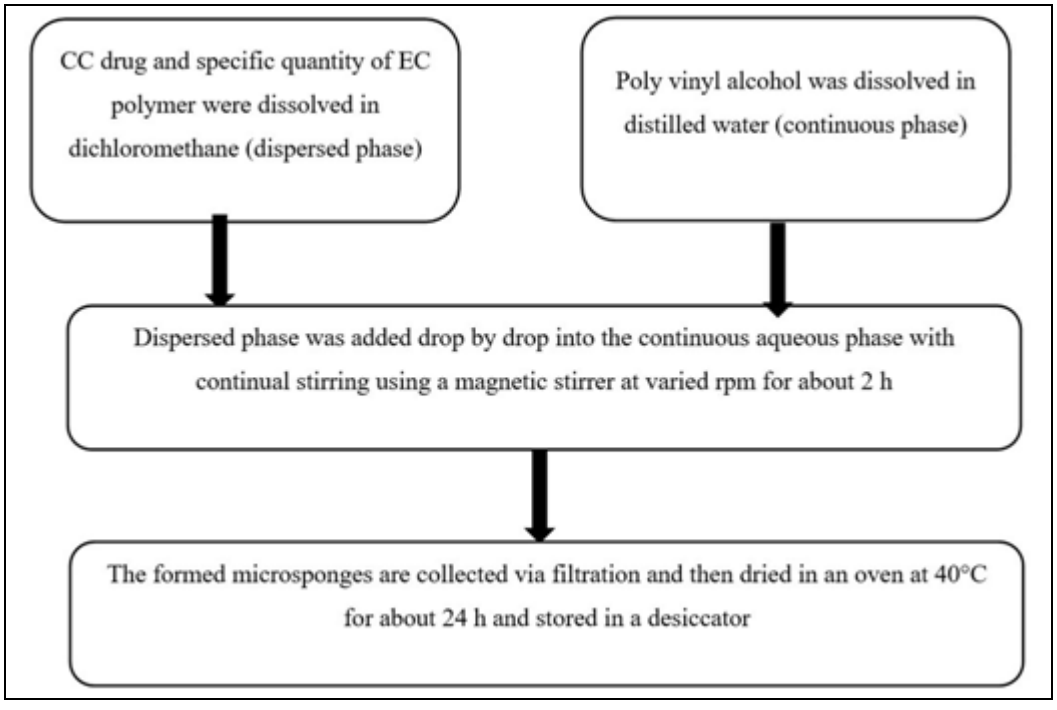

TABLE 1: FORMULATION OF CANDESARTAN CILEXETIL MICROSPONGES BY QUASI-EMULSION SOLVENT DIFFUSION TECHNIQUE

Formulation	Drug: Polymer Ratio	DCM (mg)	PVA (mg)	DW (ml)	Stirring Rate (rpm)
F1	1:4	20	400	150	400
F2	1:4	20	400	150	700
F3	1:4	20	400	150	1000
F4	1:5	20	500	150	400
F5	1:5	20	500	150	700
F6	1:5	20	500	150	1000
F7	1:6	20	600	150	400
F8	1:6	20	600	150	700
F9	1:6	20	600	150	1000

DCM - Dichloromethane, PVA - Poly vinyl alcohol, DW - Distilled water

Characterization of Encapsulated Microsponge Formulations:

Drug Polymer Interaction Study: The drug's and polymer's interaction were studied using an FTIR spectrometer. The sample was produced by combining it with potassium bromide (KBr), triturating it in a glass mortar, and then transferring it to the sample container. The spectrum was studied using different frequencies ranging from 4000-400cm^{-1}. The FTIR spectra of pure drug, drug and polymer and prepared CC microsponges were carried out using an FTIR spectrometer, Shimadzu (Japan).

Differential Scanning Calorimetry: Thermal analysis using DSC was done on the drug, and microsponges F9 to validate the compatibility between the drug and excipients. Weighed samples were sealed in an aluminium pan. Samples were heated at a rate of 10°C per minute in the presence of nitrogen throughout a temperature range of 0 to 300°C.

X-Ray Diffraction Studies: X-ray diffraction studies were performed using a Philips PW 3710 X-ray diffractometer (XRD) to identify the crystallinity of the pure drug Candesartan Cilexetil and Candesartan Cilexetil microsponges preparation [18-20].

Percentage Production Yield: The microsponges that had been prepared were collected and weighed. The yield was estimated by dividing the observed weight by the total weight of all non-volatile components.

%Yield = (weight of microsponge) / (theoretical weight of microsponge) × 100

Percentage Entrapment Efficiency: 100 mg of drug-containing microsponges were weighed and maintained in a 100ml phosphate buffer solution of pH 6.8 for 12 h with continuous stirring. Using a UV spectrophotometer (Shimadzu, Japan), filtered samples were further examined at 254 nm next to a blank.

% Entrapment Efficiency = (Actual drug in microsponge) / (theoretical drug conc) × 100

Particle size: The particle size was evaluated using a particle size analyser (Malvern 2000 SM; Malvern Instruments, Malvern, UK). To evaluate particle size, the samples must be prepared by taking a microsponge formulation and diluting it with distilled water. 10µl of the sample is placed in a 2ml standard volumetric flask and its total volume is filled with distilled water. After that, the sample is placed into the plastic cuvette for study.

Scanning Electron Microscopy: Scanning electron microscopy (SEM) was used to see how the surface of the microsponge was shaped and how they were constructed. The microsponge powder was sparingly sprinkled over a double-sided adhesive tape that was previously adhered to aluminium stubs to create the sample. The stubs were then subjected to fine-coat ion sputtering for gold coating. After being coated with gold, the samples were randomly tested for particle size and surface morphology.

***In-vitro* Release Studies of Microsponges:** The dissolution rates of the produced microsponges are determined using the USP paddle technique at 50 rpm in 900 ml phosphate buffer pH 6.8 as the dissolution media, which is kept at 37±0.5°C. The samples were collected at predetermined intervals and replaced with new medium. The collected samples were filtered using Whatman filter paper

and should be analysed spectrophotometrically at 254nm [21, 22].

Preparation of Cross-linked Gelatin Capsules: Formalin treatment has been employed to modify the solubility of gelatin capsules. Exposure to formalin vapours results in an unpredictable decrease in the solubility of gelatin owing to the cross-linkage of the amino group in the gelatin molecular chain aldehyde group of formaldehyde by Schiff's base condensation.

Method: The size 0 hard gelatin capsule was taken. Bodies were removed from the cap, and 25 ml of formaldehyde (15%v/v) was added to desiccators with a pinch of potassium permanganate to produce formalin vapours. After that, the wire mesh containing the empty capsule bodies was subjected to formaldehyde vapours. The caps were not exposed, making them water-soluble. The desiccators were firmly closed. The capsule bodies were removed and dried at 50°C for 30 min to ensure the completion of the reaction between gelatin and formaldehyde vapours. The capsule bodies were then dried at room temperature in order to facilitate the removal of residual formaldehyde. These capsule bodies were sealed with untreated caps and kept in a polythene bag.

Evaluation of Cross-linked Capsule:

Solubility Study of Treated Capsules: In varied time intervals, the capsule bodies were exposed to a 15% formaldehyde solution. Following that, the exposed capsule bodies were dried in a hot air oven. Body solubility was investigated in 0.1N HCl. The time it takes for the capsule to disintegrate or form a soft fluffy mass was recorded.

Qualitative Test for Free Formaldehyde: The standard is a formaldehyde solution, and the test solution is a formaldehyde-treated body of about 25 capsules cut into small pieces and placed in a beaker filled with distilled water. To dissolve the free formaldehyde, this was agitated for 1 h using a mechanical stirrer. The solution was then filtered into a 50ml volumetric flask, rinsed with distilled water, and the total volume was made up to 50 ml using the washings.

Method: 1 ml of sample solution and 9 ml of water were mixed together. One millilitre of the resultant solution was placed in a test tube and mixed with 4 ml of water and 5 ml of acetone reagent. The test tube was placed in a 40°C water bath and left to stand for 40 min. The solution was less strongly coloured than a reference solution made at the same time and in the same way, but with 1 ml of standard solution as compared to the sample solution. The comparison was conducted by looking down the vertical axis of the tubes [23-25].

Preparation and Evaluation of Hydrogel Plug: HPMCK4M was employed to create the hydrogel plug. It was made by the direct compression technique with lactose. And the prepared hydrogel plug was studied for average weight, thickness and hardness.

Determination of Swelling Index of Hydrogel Plug: Hydrogel plugs were immersed in three distinct pH levels. At 2, 4, 6, 8, 10, 12 h, the plugs were carefully removed and their weights were accurately determined.

$$\% \text{ Swelling Index} = (\text{wet weight} - \text{dry weight}) / (\text{wet weight}) \times 100$$

In-vitro **release of Pulsatile Capsule:** The USP Type I dissolving test apparatus (Basket technique) was used for the dissolution studies. Three dissolving media with pH 1.2, 7.4, and 6.8 were employed successively to imitate pH variations along the GI tract (sequential pH change approach).

The pH 1.2 had been used for 2 h before being removed and replaced with new phosphate buffer pH 7.4. After 3 h, the medium was withdrawn and a colonic fluid phosphate buffer pH 6.8 was added for further investigation. Each time, 900 ml of the dissolving media was utilised. The rotation speed was set to 100 rpm, and the temperature was kept at 37±0.5°C.

At specified time intervals, 10 ml of dissolving medium were removed and replaced with new dissolution medium. UV absorption spectroscopy was used to analyse the withdrew samples, and the cumulative percentage of drug release was determined [26-28].

In-vitro **Release Kinetics:** To examine the probable processes of Candesartan Cilexetil microsponge release from the constructed pulsincap, drug release data were fitted to multiple

models, namely Higuchi, Korsmeyer Peppas, zero-order, and first-order kinetics.

Accelerated Stability studies as per ICH Guidelines: The ICH guideline Q1A (R2) stability testing of novel drug substances and products describes the design of stability studies to support the filing of NDAs and MAAs. Following the ICH guidelines, the stability of the developed pulsincaps containing microsponges during storage was investigated in a stability chamber (Thermolab scientific) and was subsequently tested for physical stability (colour change), and release characteristics (dissolution study) at monthly intervals for a maximum of six months to determine the storage stability of the formulations [29-32].

RESULTS AND DISCUSSIONS:

UV-Spectroscopy: In this study, UV-spectroscopy analysis of Candesartan Cilexetil revealed a maximum absorption wavelength within the range of 254-258 nm. A calibration curve constructed for concentrations between 10-50 µg/ml demonstrated excellent linearity, as indicated by a regression coefficient (R^2) of 0.999. These findings confirm that Candesartan Cilexetil follows Beer-Lambert's law within the tested concentration range, making this method suitable for its quantitative analysis.

Fourier Transform Infrared Analysis: FTIR analysis of Candesartan Cilexetil (CC), its physical mixture with polymers, and CC-loaded microsponges demonstrated that key functional groups responsible for its pharmacological activity remained unchanged.

This stability indicates that CC is compatible with Ethylcellulose, as no significant interactions affecting its structure were observed. These results confirm the suitability of Ethylcellulose as a polymer for formulating CC-loaded microsponges.

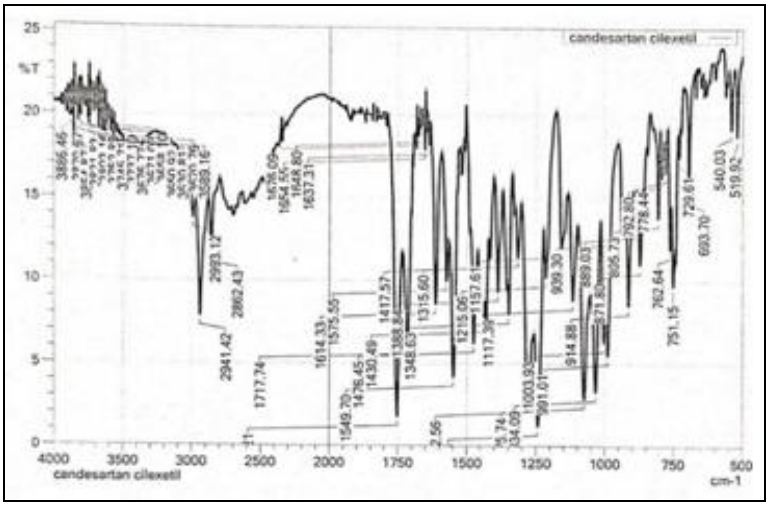

FIG. 1: FTIR OF PURE DRUG (CANDESARTAN CILEXETIL)

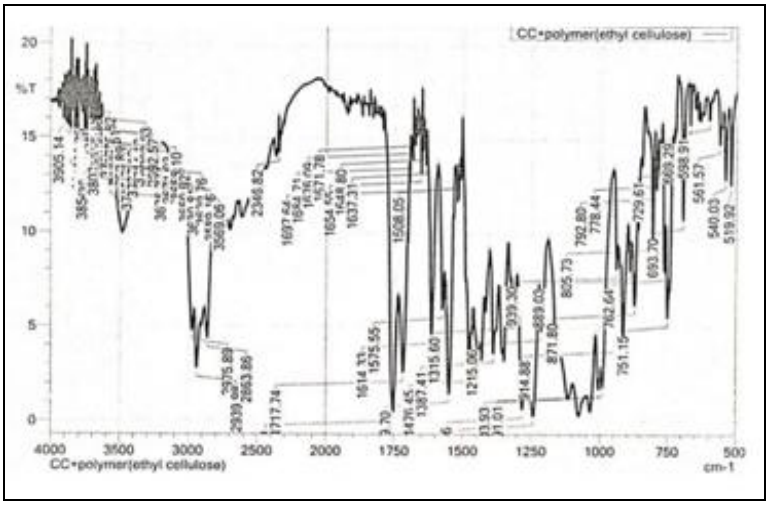

FIG. 2: FTIR OF CANDESARTAN CILEXETIL AND ETHYL CELLULOSE

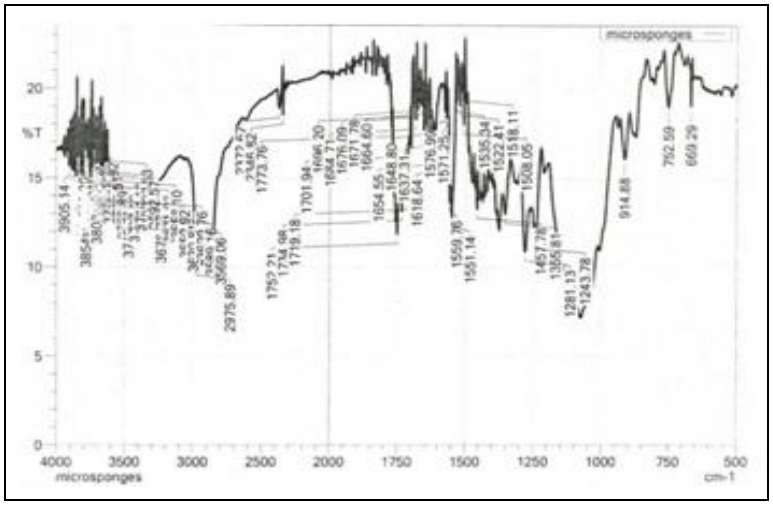

FIG. 3: FTIR OF PREPARED CANDESARTAN CILEXETIL MICROSPONGES

Differential Scanning Calorimetry (DSC): Differential Scanning Calorimetry (DSC) thermograms showed a prominent endothermic peak for pure Candesartan Cilexetil (CC) at 173.8°C, confirming its pure crystalline state. In contrast, the thermogram of the formulated CC microsponges (1:6 ratio) displayed no distinct melting peak, indicating an amorphous structure. This result aligns with expectations, as cross-linked polymer-based microsponges generally lack a defined melting point.

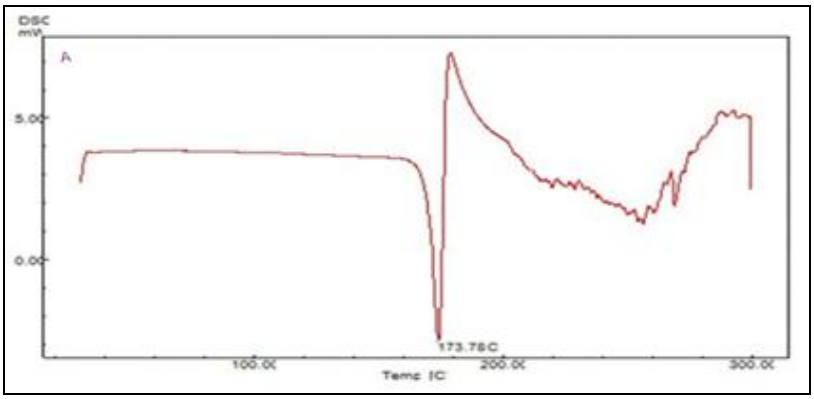

FIG. 4: (A) DIFFERENTIAL SCANNING CALORIMETRY THERMOGRAM OF A CANDESARTAN CILEXETIL (PURE DRUG)

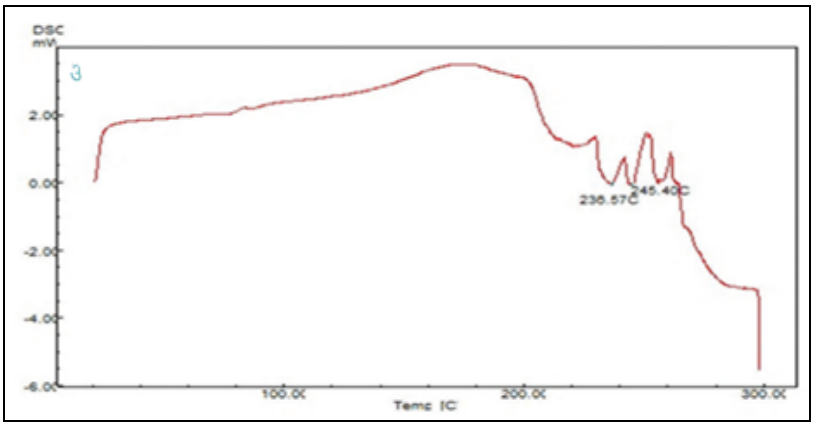

FIG. 4: (B) DIFFERENTIAL SCANNING CALORIMETRY THERMOGRAM OF OPTIMIZED CANDESARTAN CILEXETIL MICROSPONGES (F 9)

X-Ray Diffraction Analysis: X-ray diffraction (XRD) analysis of pure Candesartan Cilexetil confirmed its crystalline nature, as indicated by sharp, distinct peaks at specific diffraction angles

(2θ) of 9.9819°, 17.2137°, 18.6489°, 19.8632°, 21.5225°, 23.8034°, 25.5001°, 27.7464°, and 29.1848°, consistent with reported values. In contrast, the optimal microsponge formulation (F9) lacked these characteristic peaks, suggesting that Candesartan Cilexetil was transformed into an amorphous or disordered crystalline phase in the microsponge matrix. This structural shift is likely due to the microsponges' cross-linked polymeric network, which contributes to the drug's amorphous dispersion, enhancing solubility and potentially improving bioavailability.

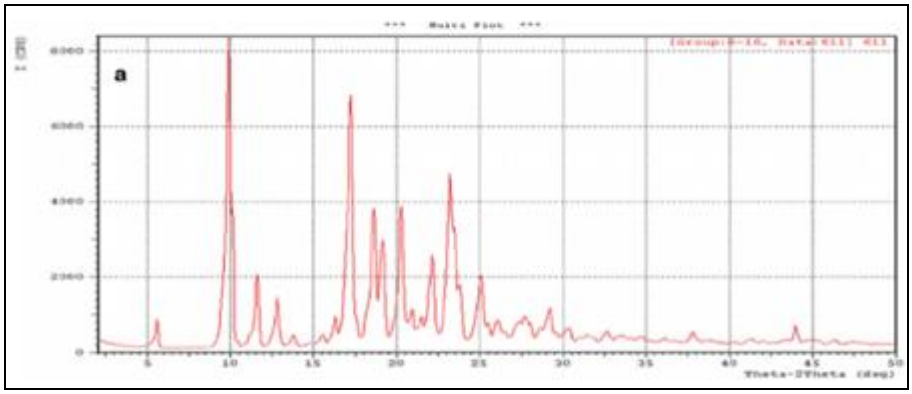

FIG. 5: (A) XRD ANALYSIS OF CANDESARTAN CILEXETIL PURE DRUG

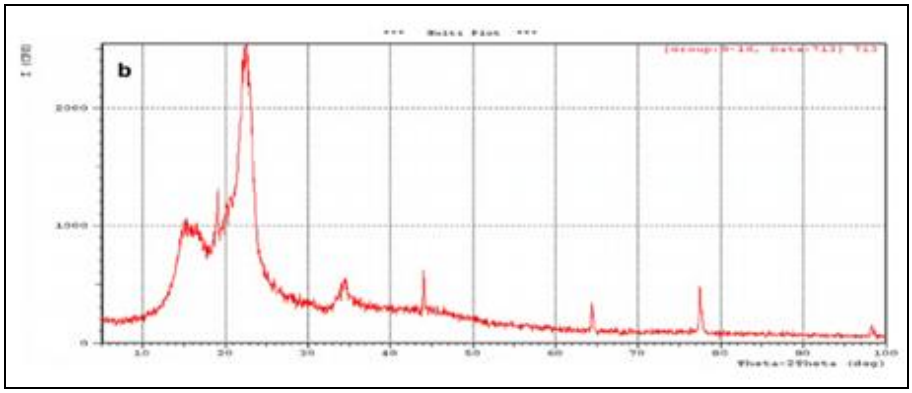

FIG. 5: (B) XRD ANALYSIS OF CANDESARTAN CILEXETIL MICROSPONGES OPTIMIZED FORMULATION (F9)

Production Yield of Candesartan Cilexetil Microsponges Formulation: The production yield of Candesartan Cilexetil microsponges formulation is given in **Table 2.** The production yield was found to increase with the increase in the drug: polymer ratio and also with high stirring rate.

Particle Size and Entrapment Efficiency of Candesartan Cilexetil Microsponges: The mean particle size of the Candesartan Cilexetil microsponges was calculated, and it was discovered that the microsponges particle size increased with an increase in polymer concentration and decreased at higher rpm. **Table 2** displays the Candesartan Cilexetil microsponge formulation's particle size and entrapment efficiency. The entrapment efficiency was found to be in the range of 34.9 to 84.49%. The formulation F9 possessed a higher entrapment efficiency of about 84.49%.

TABLE 2: PROPERTIES OF PREPARED MICROSPONGES

Formulation Code	%Production Yield	Particle Size (µm)	%Entrapment Efficiency
F1	52.2	84.1	34.9
F2	58.6	46.14	67.08
F3	62.6	67.3	51.9
F4	59.39	63.12	46.83
F5	67.2	57.51	59.76
F6	63.6	46.77	71.4
F7	80.3	49.10	69.9
F8	80.5	61.82	51.82
F9	84.2	29.8	84.49

Scanning Electron Microscopy: SEM indicates that the outer surface of the optimized F9 formulation was smooth and dense, whereas the shape of microsponges created by the quasi-emulsion solvent diffusion approach was spherical and homogeneous, with no drug crystals on the surface. The higher the rate of stirring, higher is the early solvent drag on diffusion and consequently, the agglomeration of microsponge.

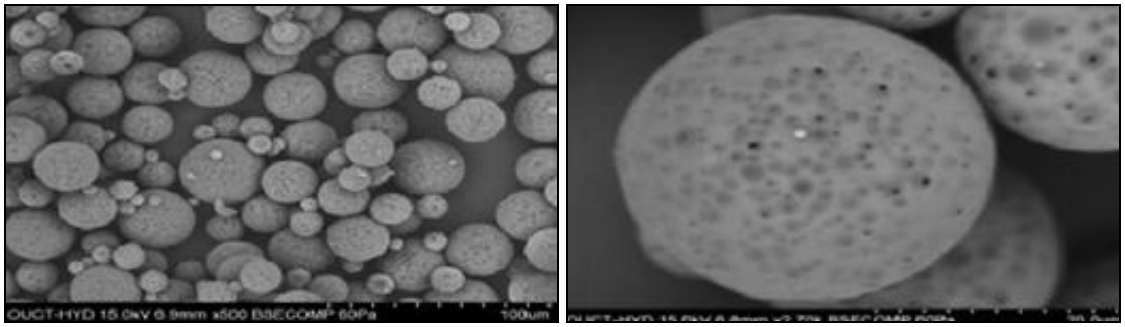

FIG. 6: SEM IMAGES OF CANDESARTAN CILEXETIL LOADED OPTIMIZED MICROSPONGES (F9)

***In-vitro* Drug Release of Candesartan Cilexetil Microsponges:** The dissolution rates are inversely linked to particle size according to surface area relationships. The effectiveness of the microsponges entrapment was significantly impacted by the drug-polymer ratio. A higher polymer content indicated improved drug encapsulation performance. After 8 h of dissolution testing, it was discovered that the drug release rates for formulations F1, F2, F3, F4, F5, F6, F7, F8, and F9 were 12.70%, 23.66%, 28.50%, 30.56%, 34.42%, 44.46%, 72.55%, 88.02%, and 93.40%, respectively. The study found that the drug releaseof F9 formulation was superior than the other formulations.

TABLE 3: PERCENTAGE DRUG RELEASE OF CANDESARTAN CILEXETIL MICROSPONGES

Formulation Code	Percentage Drug Release (%)							
	1h	2h	3h	4h	5h	6h	7h	8h
F1	0.5715	0.9171	1.9135	3.8695	5.2155	5.77651	9.8122	12.7290
F2	1.0962	1.6472	2.172	3.964	7.9010	8.0886	15.718	23.665
F3	1.9982	2.5513	3.6067	5.6784	10.1805	10.977	23.995	28.505
F4	2.7306	2.9860	4.442	7.327	10.887	11.594	12.972	30.56
F5	5.789	6.547	8.327	8.841	11.136	12.992	15.969	34.422
F6	7.970	9.861	11.296	12.391	12.66	15.691	24.14	44.46
F7	14.54	18.50	27.52	33.98	37.39	39.88	54.90	72.55
F8	16.674	28.60	35.87	38.761	54.42	58.63	73.86	88.02
F9	29.69	34.82	44.74	71.75	75.49	81.69	87.78	94.26

Evaluation of Cross-Linked Gelatin Capsules [33]:

Physical Test:

Identification: The size "0" capsules with white caps and white bodies. The capsules are odourless, soft, and sticky when handled with wet fingers. After treatment with formaldehyde, there were no significant changes in the capsules. The treated capsules are not tacky when handled with wet fingers.

Chemical Test:

Solubility Study for Treated Capsules: When the capsules were put through a solubility test in 0.1N HCl for 24 h, it was discovered that the body and cap of the untreated capsules dissolved in 15 min. In case of formaldehyde treated capsules, cap dissolved in 15 min and body of the capsules last for around 24 h without breaking. The study also found that the treated capsule retained its physical integrity throughout the process of breakdown.

Qualitative test for free Formaldehyde: The presence of free formaldehyde was checked in the formaldehyde-treated capsules. Less than 20 µg of free formaldehyde are contained in 25 capsules, according to the observation that the sample solution was not more strongly coloured than the reference solution.

Evaluation of Hydrogel Plug: The hydrogel plug was prepared using HPMC k4M polymer by direct compression method using lactose and the average weight was found to be 99.8±0.25mg, hardness and thickness were in range of 2.98±0.017 kg and 2.60±0.09mm respectively.

TABLE 4: EVALUATION OF HYDROGEL PLUG

Average Weight (mg)±SD	Hardness (kg)±SD	Thickness (mm)±SD
99.8±0.25	2.98±0.017	2.60±0.09

% Swelling Index of Hydrogel Plug: % Swelling index test for prepared hydrogel plug was carried out at various buffer solution (pH 1.2, pH 7.4, pH 6.8) and the swelling index of the plug at pH 1.2 after 12 h was found to be 78.55%, at pH 7.4 was found to be 81.41% and at pH 6.8 the swelling index reported as 83.2%.

***In-vitro* Release Study of Candesartan Cilexetil Loaded Pulsincap Formulations (F1-F9):** The *in-vitro* release study of candesartan cilexetil-loaded pulsincap formulations (F1-F9) was conducted in media with varying pH levels (1.2, 7.4, and 6.8) to simulate stomach, small intestine, and colonic conditions. All formulations showed no drug release for the initial 2 hours, indicating stability in the acidic pH of the stomach.

The graphical data in **Fig. 7** demonstrates that drug release from the pulsincap formulations commenced after a lag time of approximately 5 h, aligning with the anticipated colonic release. Formulations with higher polymer concentrations showed prolonged lag times, contributing to controlled release. The optimized formulation, F9, exhibited 95.87% drug release at the end of 24 h with a lag time of about 5 h.

The results of the *in-vitro* release study indicate that the pulsincap formulations (F1-F9) successfully delayed the release of candesartan cilexetil, with no release observed during stomach and small intestine transit times. This 5-hour lag time aligns well with the typical gastrointestinal transit, ensuring targeted release in the colon. The data suggests that higher polymer concentrations effectively prolong the lag time, providing control over the release onset. The F9 formulation, which released 95.87% of the drug over 24 h, demonstrated an optimal release profile with a sustained and complete release post-lag time. This makes F9 suitable for targeted colonic delivery, which could enhance the therapeutic efficacy of candesartan cilexetil.

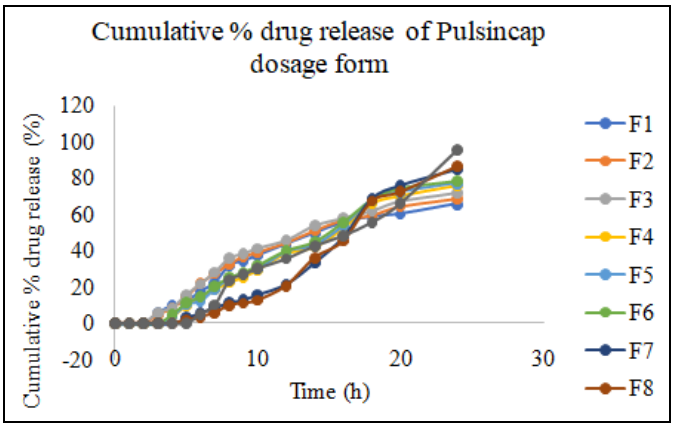

FIG. 7: CUMULATIVE % DRUG RELEASE OF PULSINCAP FORMULATIONS (F1-F9)

Release Kinetics of Candesartan Cilexetil Loaded Pulsincap Formulations (F1-F9): *In-vitro* release studies were conducted for candesartan cilexetil loaded pulsincap formulations (F1-F9) loaded with microsponges to evaluate their release kinetics. The release data was analysed using multiple kinetic models zero-order, first-order, Higuchi, and Korsmeyer-Peppas to determine the mechanism and rate of drug release. Among the models tested, zero-order kinetics showed the highest linearity for formulation F9, with a correlation coefficient (R^2) of 0.955, indicating that the drug release from this formulation proceeds at a constant rate.

The results indicate that formulation F9, when loaded into the pulsincap system, follows zero-order release kinetics, which suggests a steady, concentration-independent drug release rate. This characteristic is desirable for formulations intended for controlled drug delivery, as it ensures consistent drug levels over time. The high correlation coefficient (R^2=0.955) further supports the accuracy of the zero-order model in predicting the release behaviour of F9. Consequently, this optimized formulation could be particularly beneficial in maintaining therapeutic drug levels, providing a sustained-release profile suitable for extended therapeutic applications.

TABLE 5: *IN-VITRO* KINETIC DATA OF PULSINCAP LOADED CANDESARTAN CILEXETIL MICROSPONGES

Formulation code	Zero-order kinetics		First-order kinetics		Higuchi model		Korsmeyer-peppas model	
	Slope	R^2	Slope	R^2	Slope	R^2	R^2	N
F1	3.205	0.976	0.022	0.992	0.054	0.962	0.972	1.185
F2	3.318	0.976	0.023	0.994	0.052	0.965	0.957	1.213
F3	3.44	0.975	0.025	0.995	0.050	0.965	0.960	1.184
F4	3.650	0.991	0.027	0.975	0.047	0.934	0.968	1.507
F5	3.746	0.990	0.028	0.974	0.045	0.934	0.969	1.517
F6	3.805	0.991	0.029	0.975	0.045	0.938	0.974	1.435
F7	3.920	0.959	0.032	0.913	0.039	0.858	0.993	2.116
F8	3.908	0.955	0.032	0.905	0.038	0.848	0.989	2.530
F9	3.960	0.955	0.039	0.693	0.041	0.804	0.829	1.688

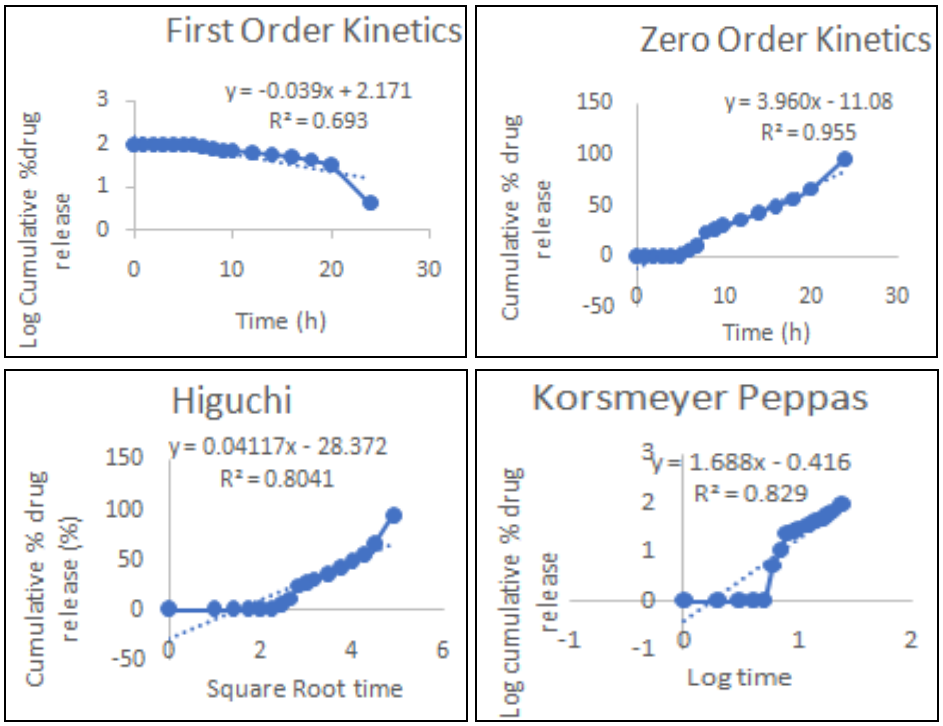

FIG. 8: RELEASE KINETIC DATA OF PULSINCAP LOADED OPTIMIZED CANDESARTAN CILEXETIL MICROSPONGE (F9)

Accelerated Stability Studies: Formulation F9, loaded with Candesartan Cilexetil microsponges, was tested under accelerated conditions (40°C ±2°C / 75% ±5% RH) for six months. The aim was to assess physical and chemical stability.

Physical Characteristics: No changes in appearance, texture, or capsule integrity were observed. The formulation maintained its structural integrity.

Drug Release: The release profile remained consistent, with no significant deviations in dissolution rates, indicating stable microsponge performance.

Formulation F9 showed no significant changes over six months under stress conditions, confirming its stability and suitability for long-term storage.

TABLE 6: STABILITY STUDIES OF OPTIMIZED PULSINCAP LOADED CANDESARTAN CILEXETIL MICROSPONGES

Testing time	Change in physical appearance of the pulsincap		Percent drug release (%)
	Colour	Odour	
Initial	NC	NC	97.52
30 days	NC	NC	96.87
60 days	NC	NC	95.75
90 days	NC	NC	95.19

120 days	NC	NC	95.48
150 days	NC	NC	95.27
180 days	NC	NC	95.04

NC- No Change

CONCLUSION: This study successfully developed a pulsatile drug delivery system for Candesartan Cilexetil aimed at chronomodulated release to improve bioavailability and effectively control early morning hypertension. Candesartan Cilexetil, a BCS class II drug with low solubility and poor bioavailability, was formulated as microsponges to enhance its release profile and absorption in the gastrointestinal tract. Nine formulations (F1-F9) were prepared, varying polymer concentrations and process parameters, to achieve optimal release characteristics. *In-vitro* release studies demonstrated that the optimized formulation (F9), loaded in a pulsincap system, provided a 5-hour lag time, with no drug release during the initial stomach (pH 1.2) and small intestine (pH 7.4) phases. This delay aligns with gastrointestinal transit, allowing targeted release in the colonic environment (pH 6.8). The release profile showed that formulation F9 released 95.87% of Candesartan Cilexetil over 24 h, ensuring sustained release that matches the circadian rhythm of hypertension, which often peaks in the early morning hours.

The investigation further confirms that increased polymer concentration effectively extends the lag time, enhancing control over release onset. This property is advantageous for chronotherapy, as it allows drug administration at night with delayed release targeting early morning hypertension. The F9 formulation provides an improved therapeutic approach, potentially increasing patient compliance by reducing the need for early morning dosing and minimizing side effects associated with fluctuations in blood pressure. Overall, the pulsincap system for Candesartan Cilexetil offers an effective, targeted release for managing early morning hypertension, aligning drug delivery with the body's biological clock, and enhancing both patient outcomes and adherence.

ACKNOWLEDGEMENT: We would like to express our sincere gratitude to the Principal and Vice Principal of C. L. Baid Metha College of Pharmacy for their constant support and encouragement throughout this research. Our heartfelt thanks are also extended to the department staff for their valuable contributions and assistance. Special thanks to Saimirra Innopharm Pvt. Ltd., Chennai, India, for providing the free samples used in this study. We also acknowledge Loba Chemicals Private Limited, Hyderabad and Fisher Scientific, Mumbai.

CONFLICT OF INTEREST: The authors declare no conflict of interest.

REFERENCES:

1. Anusha V, Umashankar MS and Kumar YG: Pulsatile drug delivery system an innovative method to treat chronotherapeutic diseases by synchronizing drug delivery with circadian rhythm. Journal of Applied Pharmaceutical Science 2023; 13(12): 66-78.
2. Yadav R, Jha M, Jat D and Jain DK: Present scenario of pulsatile drug delivery system. IJCAAP 2023; 7(4): 171-8.
3. Graf TP, Qiu SY, Varshney D, Laracuente ML, Euliano EM, Munnangi P, Pogostin BH, Baryakova T, Garyali A and McHugh KJ: A scalable platform for fabricating biodegradable microparticles with pulsatile drug release. Advanced Materials 2023; 35(22): 2300228.
4. Gao J, Karp JM, Langer R and Joshi N: The future of drug delivery. Chemistry of Materials 2023; 35(2): 359-63.
5. Arif Muhammed R, Mohammed S, Visht S and Omar Yassen A: A review on development of colon targeted drug delivery system. International Journal of Applied Pharmaceutics 2024; 16(2): 12-27.
6. Kurapati P and Chinni S: Pulsatile drug delivery systems of esomeprazole: optimization through quality by design. Indian Journal of Pharmaceutical Education and Research 2024; 58(2): 417-31.
7. Ali DS: Chemometric methods for simultaneous determination of candesartan cilexetil and hydrochlorothiazide in binary combinations. Journal of Analytical Methods in Chemistry 2023; 2023(1): 5107317.
8. Aly UF, Sarhan HA, Ali TF and Sharkawy HA: Applying different techniques to improve the bioavailability of candesartan cilexetil antihypertensive drug. Drug Design Development and Therapy 2020; 14: 1851-1865.
9. Leorita M, Ikawati Z, Endro-Nugroho A and Setyopranoto I: Comparison of the efficacy and tolerability of candesartan cilexetil between hypertension patients of muna and tolaki ethnicity. Research Journal of Pharmacy and Technology 2024; 17(4): 1503-9.
10. Soh MS, Won KH, Kim JJ, Lee SY, Hyon MS, Youn HJ, Rha SW, Kim DI, Ahn Y, Kim BJ and Choi DJ: Phase III randomized clinical trial of efficacy and safety of amlodipine and candesartan cilexetil combination for hypertension treatment. Scientific Reports 2024; 14(1): 22940.
11. Gomathi J, Veeralakshmi B and Farzana Affrin MF: Pulsatile Drug Delivery: A Strategy For Treating Chronotherapeutic Ailments. International Journal of Current Pharmaceutical Research 2023; 15(4): 1-8.

12. Jagdale SC, Phule PS and Chavan GJ: Formulation and evaluation of modified pulsincap drug delivery system of rizatriptan benzoate. International Journal of Pharmacy and Pharmaceutical Sciences 2014; 6(5): 48-52.
13. Hans M, Dua JS, Prasad DN and Sharma D: Formulation and evaluation of fluconazole microsponge using Eudragit L 100 by quasi emulsion solvent diffusion method. Journal of Drug Delivery and Therapeutics 2019; 9(3): 366-373.
14. Dhurke R and Ramyasree D: Pulsatile delivery system for antihypertensive drug. Current Aspects in Pharmaceutical Research and Development 2022; 9: 100-10.
15. Singh HN, Saxena S, Singh S and Yadav A: Pulsatile drug delivery system: Drugs used in the pulsatile formulations. Research Journal of Pharmaceutical Dosage Forms Technology 2013; 5(3): 115-121.
16. Al-Edresi S, Hamrah KA and Al-Shaibani A: Formulation and validation of Candesartan cilexetil-loaded nanosuspension to enhance solubility. Pharmacia 2024; 71: 1-3.
17. Guan H, Wang M, Yu S, Wang C, Chen Q, Chen Y, Zhang W and Fan J: Candesartan cilexetil formulations in mesoporous silica: preparation, enhanced dissolution *in-vitro*, and oral bioavailability *in-vivo*. Journal of Pharmaceutical Sciences 2024; 113(10): 3045-53.
18. Chabane A, Bouchal F, Hentabli M, Ayachi N, Slama HE, Rezgui F and Hammoumraoui L: Investigation of the candesartan cilexetil antihypertensive drug microencapsulation by PLA-PVP K30 biodegradable polymers: Experimental optimization and release kinetics modelling. The Canadian Journal of Chemical Engineering 2023; 101(8): 4446-59.
19. Biharee A, Bhartiya S, Yadav A, Thareja S and Jain AK: Microsponges as drug delivery system: Past, present, and future perspectives. Current Pharmaceutical Design 2023; 29(13): 1026-1045.
20. Kumar N and Akhtar S: Microsponges: a futuristic approach for oral drug delivery and current status. Indian J of Public Health Res and Devel 2022; 13(2): 101-109.
21. Mandal S, Bhumika K, Kumar M, Hak J, Vishvakarma P and Sharma UK: A novel approach on micro sponges drug delivery system: method of preparations, application, and its future prospective. Indian Journal of Pharmaceutical Education and Research 2024; 58(1): 45-63.
22. Raj R, Mazumder R, Mishra R, Mishra R and Singh Baghel D: Role of Chronotherapy in the management of hypertension: an overview. Current Drug Therapy 2024; 19(7): 794-808.
23. Sekhar R, Alam MS, Ahsan I, Raja S, Mohamed T and Nabi SS: Development of platform technology for gastro-resistant soft gel capsules by using cross-linking technique. Drug Delivery Letters 2021; 11(4): 325-34.
24. Luo S, He Y, Zhu L, Si T and Sun Y: Comprehensive evaluation on the encapsulation performances of melamine-formaldehyde microcapsules affected by core oils. Colloids and Surfaces A: Physicochemical and Engineering Aspects 2023; 659: 130794.
25. Lobel BT, Baiocco D, Al-Sharabi M, Routh AF, Zhang Z and Cayre OJ: Current challenges in microcapsule designs and microencapsulation processes: A review. ACS applied materials & interfaces 2024; 16(31): 40326-55.
26. Elghamry AF, Zalat ZA, Abu El-Enin AS and Elewa HA: Formulation and evaluation of colon targeted pulsincap delivery of Carvedilol for treatment of hypertension. Azhar International Journal of Pharmaceutical and Medical Science 2023; 3(1): 15-31.
27. Ye T, Zou L, Wang Y and Ma G: Engineered self-healing single-cavity microcapsules for pulsatile release of drug delivery. Particuology 2023; 80: 53-60.
28. Ishrath A, Devadas V and Ahmed MM: Formulation, development and characterization of diltiazem pulsin cap for pulsatile drug delivery. American Journal of Pharm Tech Research 2019; 9(5): 97-113.
29. Reddy G, Jat RK and Manjanna KM: Formulation and evaluation of pulsatile drug delivery of albuterol sulphate and theophylline drugs using modified pulsincap technology. Journal of Drug Delivery and Therapeutics 2024; 14(2): 127-133.
30. Patil IS, Patil OA, Mandake GC and Nitalikar MM: Development and evaluation of telmisartan pulsatile drug delivery by using response surface methodology. Asian Journal of Pharmaceutical Research 2018; 8(4): 205-214.
31. Hu S, Xu C, Zhang Y, Du Y, Tang J and Chen L: Preparation of enteric capsules with pulsatile drug delivery potential using pullulan and polyacrylic acid resin III. Arabian Journal of Chemistry 2024; 17(4): 105691.
32. Dash SK, Sahoo RK, Padhan A, Khan AS, Karna N, Nanda N and Dash S: Pulsatile drug delivery system (PDDS): a chronotherapeutic approach for optimum therapy. Journal of Pharmaceutical Research International 2022; 34(31B): 28-45.
33. Kanugo A and Dhage R: pH-dependent pulsatile delivery of Ambrisentan for the treatment of hypertension. Journal of Research in Pharmacy 2023; 27(2): 848-859.

How to cite this article:
Gomathi J, Farzana Affrin MF and Veeralakshmi B: Microsponge based candesartan cilexetil loaded pulsincap for achieving chronomodulated drug delivery. Int J Pharm Sci & Res 2025; 16(4): 962-73. doi: 10.13040/IJPSR.0975-8232.16(4).962-73.