Predictable Pulsatile Release of Candesartan Cilexetil for Chronotherapeutics of Hypertension

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Abstract

The present investigation aimed with the development of time dependent press coated pulsatile drug delivery of Candesartan cilexetil for early morning rise in blood pressure. Core tablets were prepared with different concentrations of superdisintegrants for immediate release. Core tablets were coated with combinations of hydrophilic polymer HPMC and hydrophobic polymer ethyl cellulose in various proportions, which prolong the lag time. Core and coated tablets were evaluated for weight variation, hardness, friability, content uniformity and *in-vitro* dissolution studies. Fourier Transform Infrared Spectroscopy (FTIR) was also performed to detect the possible drug excipients interactions. The results showed that the release lag time of Candesartan cilexetil increased when the quantity of ethyl cellulose increased thus decreasing the drug release. Stability study of the optimized batch was performed at 40°C and 75% RH for 3 months according to ICH guidelines.

Introduction

The temporal rhythm of body functions has been shown to affect not only the severity of a number of diseases but also the pharmacokinetics and pharmacodynamics of most bioactive compounds in use. Accordingly, chronotherapeutics treatments, tailored to supply the patient with the appropriate dose of the required drug at the perfect time, are gaining an increasing interest. Many diseases follow a well-defined circadian pattern such as hypertension, allergic rhinitis, osteoarthritis, rheumatoid arthritis, nocturnal asthma, angina pectoris and peptic ulcer [1].

The concept of the chronopharmacokinetics and chronotherapy of drugs have been extensively utilized in clinical therapy for improving drug efficacy and preventing side effects and tolerance of drugs. In order to emulate innate circadian rhythms, a reasonable and generally accepted rationale is a delivery system capable of releasing drugs in a pulsatile fashion rather than continuous delivery at predetermined times or sites following oral administration [2].

Pulsatile drug delivery system (PDDS) can be defined as a system where drug is released suddenly after a well-defined lag time according to the circadian rhythm of the disease. This system aim to deliver a drug via the oral route at a rate different than constant, (i.e., zero order release). PDDS are characterized by a least two distinctive drug release phases following a predetermined lag time. Drug's release may be controlled by time, by site or a combination of the two parameters [3].

Pulsatile drug delivery systems are usually of reservoir type, whereby a drug reservoir is surrounded by a diffusion barrier. This barrier erodes, dissolves or ruptures after a specified lag time, followed by a rapid drug release [4].

Materials and Methods

Materials

Candesartan Cilexetil was obtained as gift sample from Mylan Laboratories Hyderabad. HPMC various grades and Ethyl cellulose grades was received as gift samples from Colorcon, Goa. All other chemicals were of analytical pharmaceutical grade.

Methods

FT-IR studies: Drug excipients interactions play a crucial role with respect to stability and potency of the drug. FT-IR techniques have been used to study the physical and chemical interaction between drug and excipients used. IR spectrum of pure drug and excipients were observed between 4000-400^{-1} cm. (Shimadzu IRAffinity-1s FTIR).

Solubility enhancement studies: Candesartan cilexetil is a hydrophobic drug belongs to BCS class II having bioavailability of 15-40%. Attempt had made for improving dissolution of Candesartan cilexetil using liquisolid technique.

Preparation of core tablet: The composition of Candesartan cilexetil was depicted in Table 1. All of the powders used were passed through sieve no. 44 separately. The desired quantity of the previously weighed solid Candesartan cilexetil was dissolved in liquid vehicle Tween 80. The resulting wet mixture was then blended with dibasic calcium phosphate to form simple admixture. Sodium starch glycollate, cross carmellose sodium, cross povidone, magnesium stearate and talc were added to admixture and mixed by geometric addition technique. Finally, 175 mg of the blend was weighed and compressed using Rimek mini press II machine. (Karnavati Engineering Ahmadabad, India).

Optimization of core tablets: The core tablets were optimized based on the disintegration time and dissolution studies by using different superdisintegrants.

Preparation of mixed blend for barrier layer: The various compositions containing HPMC and ethyl cellulose grades were shown in Table 2. Different compositions were weighed, dry blended for 20 min and used as press coating material to prepare pulsatile tablets.

Formulation of pulsatile tablet: Press coated tablets were prepared using various compositions given in Table 2. HPMC and ethyl cellulose were used for release retarding outer shells. Half of the total quantity of coating powder blend was filled in die cavity to make a powder bed at the bottom. The previously compressed core tablet was placed in the centre on the above powder blend. The remaining equivalent powder

Ingredients (mg)	CT1	CT2	CT3
Candesartan cilexetil	8	8	8
Tween 80	q.s.	q.s.	q.s.
Dibasic calcium phosphate	155	155	155
Sodium starch glycollate	5.25	-----	-----
Cross carmellose sodium	-----	5.25	-----
Cross povidone	-----	-----	5.25
Magnesium stearate	1.75	1.75	1.75
Talc	1.75	1.75	1.75
Total weight	**175**	**175**	**175**

Table 1: Composition of core tablets.

Coating material	PT1	PT2	PT3	PT4	PT5	PT6	PT7	PT8	PT9	PT10	PT11	PT12
HPMC K15M	50	100	150	50	100	150						
HPMC K100 M							50	100	150	50	100	150
EC 7	150	100	50				150	100	50			
EC 10				150	100	50				150	100	50
Total weight (mg)	375	375	375	375	375	375	375	375	375	375	375	375

Table 2: Composition of press coated tablets.

was filled in the die, and the content was compressed using a flat punch [5-10].

Evaluations

Flowability studies

The flow properties of the pulsatile systems were estimated by determining the angle of repose, Carr's index and Hausner's ratio. The angle of repose was measured by the fixed funnel and free-standing cone method. The bulk density and tap densities were determined for the calculation of Hausner's ratio and Carr's index which was calculated as follows:

Compressibility index=Tapped-bulk × 100/tapped

Hausner's ratio=Tapped density/Bulk density

Weight variation test

Weight variation test performed as per Indian pharmacopoeia (IP) by weighing 20 tablets individually on digital electronic balance, calculating the average weight and comparing the individual tablets weights to the average.

Tablet thickness, hardness and friability test

The prepared core and coated tablets thickness were measured by Vernier Caliper. The hardness of tablets was evaluated by using Monsanto hardness tester. Friability test was performed by using Roche friabilator (Electrolab, Mumbai, India).

Disintegration test

The in-vitro disintegration time for immediate release core tablets was determined by using disintegration test apparatus as per IP. Placed one tablet in each of the six tubes of the basket, was positioned in 1 L of beaker at 37°C ± 0.5°C. The time taken for the complete disintegration of the tablets was noted.

In-vitro dissolution test

The dissolution rates of all formulations were measured in dissolution test apparatus (Electrolab TDT-O8 L.) In-vitro dissolution studies were carried out using USP type II apparatus (Paddle method) at a speed of 50 rpm at 37 ± 0.5°C using 0.1 N HCl initially for 2 hrs and replaced with phosphate buffer of pH 6.5. Appropriate aliquots were withdrawn at suitable time intervals and filtered through Whatman filter paper and diluted as per need with phosphate buffer 6.5. The samples were analyzed spectrophotometrically at 251 nm by UV visible spectrophotometer (Shimadzu 1800) (Figures 1-7).

Drug content uniformity

In order to carry out drug content uniformity, tablets were crushed and powdered quantity equivalent to one tablet was diluted with 100 ml of phosphate buffer of pH 6.5. Further suitable dilutions were done. The absorbance was recorded at 251 nm on UV spectrophotometer (Shimadzu 1800.) The study was carried out in triplicate.

Stability studies

The aim of stability studies was to check the quality of drug product varies with time under the influence of environmental factors such as temperature, humidity and light. The accelerated stability study was carried out as per the ICH guidelines for 3 months of an optimized formulation. The sample were packed in an aluminium foil placed in a tightly closed high density polyethylene bottle and kept at 40 ± 2°C and relative humidity at 75 ± 5%. Samples were taken at regular time interval of 1 month for a period of 3 months and analyzed. Any changes in evaluation parameters, if observed were noted. Test were carried out in triplicate and mean value was noted with standard deviation.

Release kinetics

To determine the release mechanism and kinetics, the results of the in-vitro dissolution study of formulated pulsatile tablets were fitted into various kinetics equations, such as zero-order, first order, Higuchi's model, Korsemeyer-Peppas model and Hixson-Crowell model. Correlation coefficient values (R^2) were calculated from the linear curves obtained by regression analysis of the above plots [11-15].

Results and Discussion

FT-IR spectrum

The FTIR spectra of Candesartan cilexetil exhibited distinctive peaks at 1715 cm^{-1} due to C=O stretching of carboxylic acid, 1075 cm^{-1} due to ethereal linkage and 3068 because of aromatic C-H stretching. The spectrum found that there were no interactions of drug with excipients. Hence it indicates no change in chemical integrity of the drug. FTIR spectrums were shown in Figures 2-4.
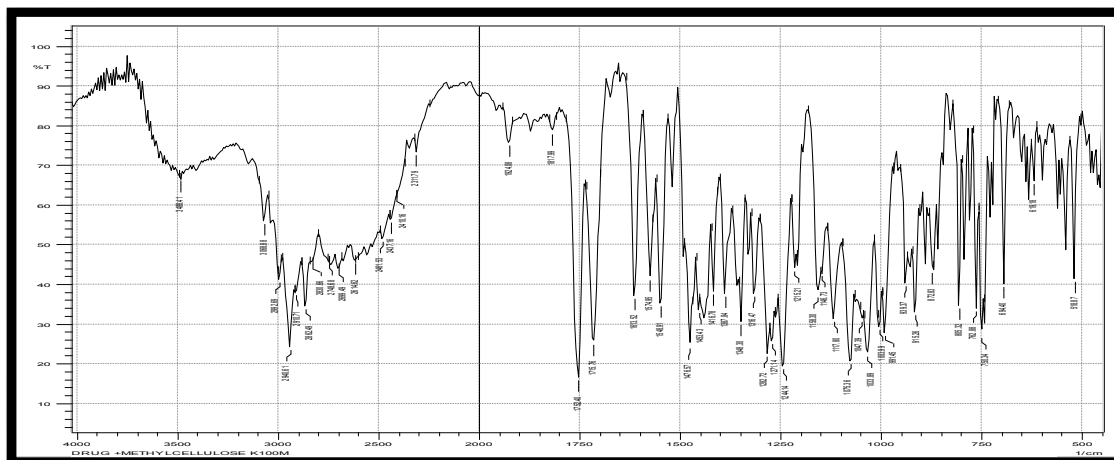
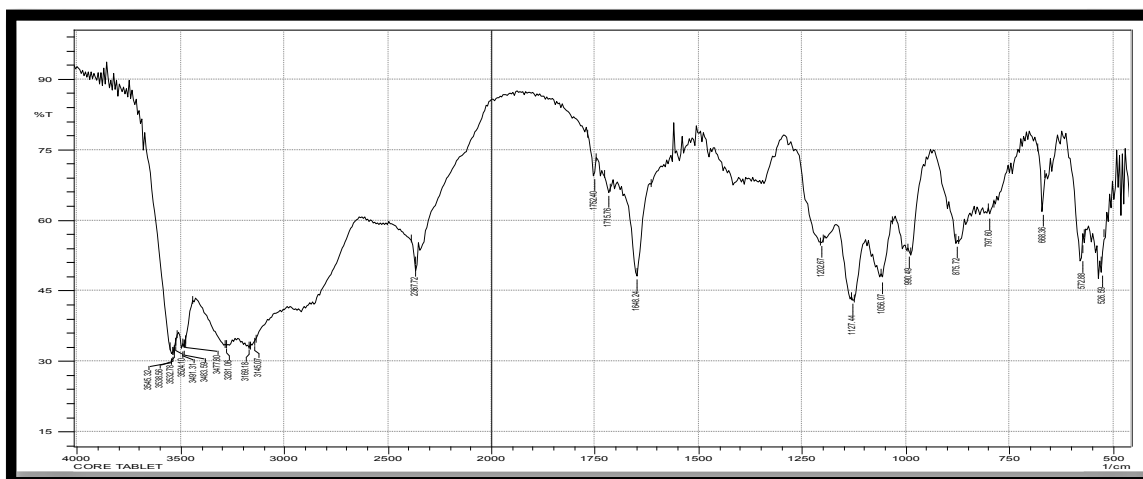**Figure 1:** FTIR spectrum of pure Candesartan cilexetil.
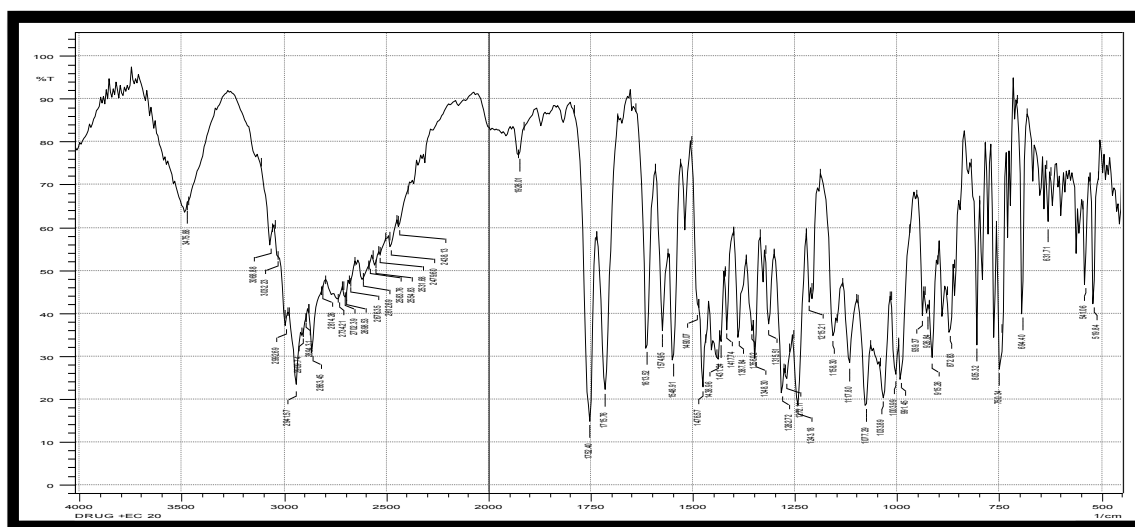

Figure 2: FTIR spectrum of core tablet.

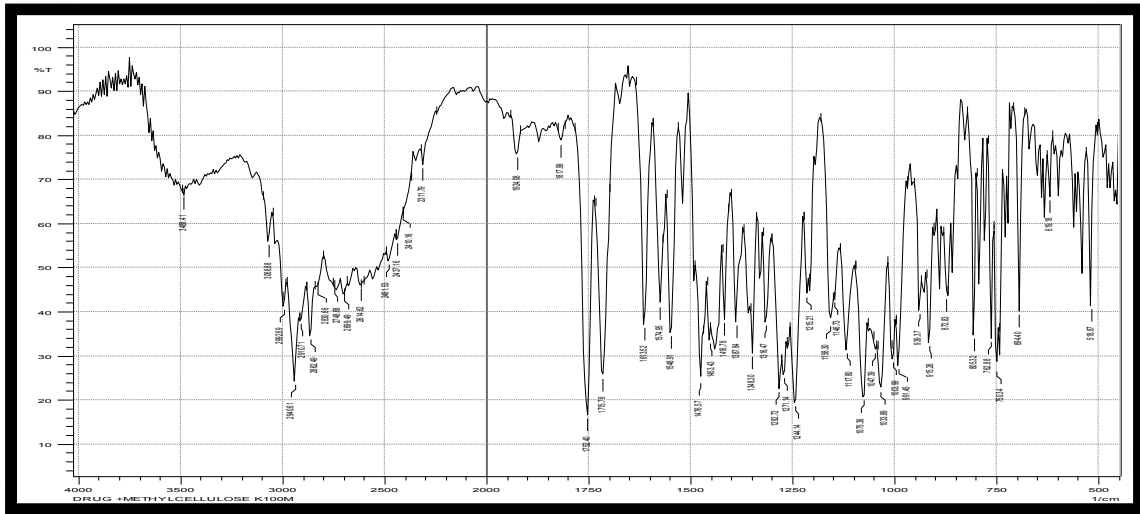**Figure 3:** FTIR spectra of Candesartan with ethyl cellulose.

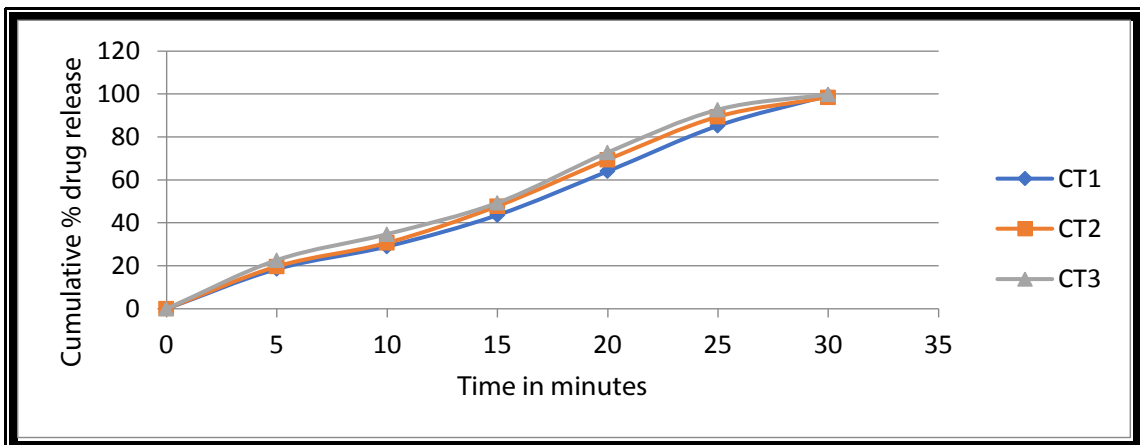**Figure 4:** FTIR spectra of Candesartan cilexetil with HPMC.
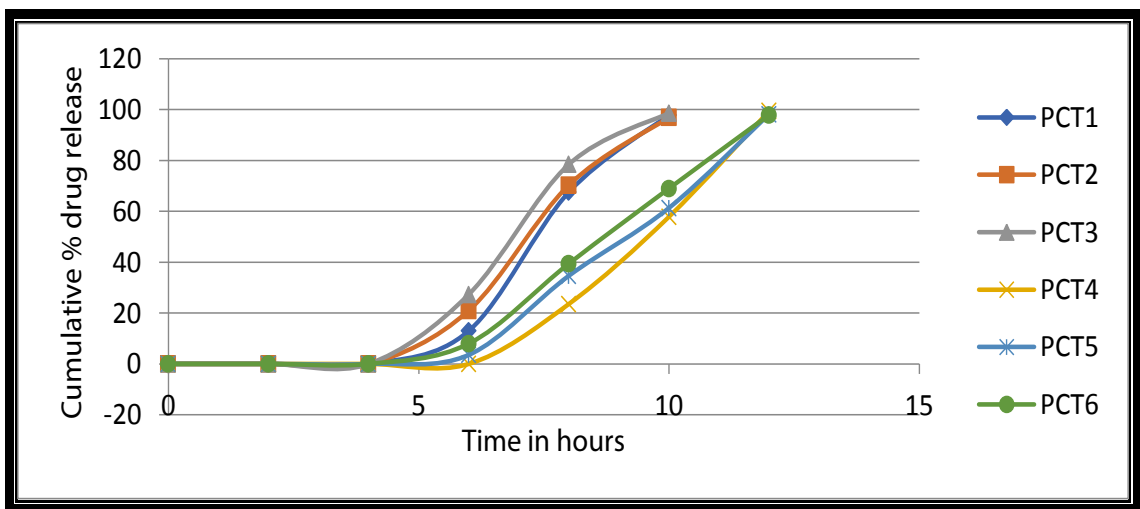

Figure 5: *In-vitro* dissolution of core tablets.

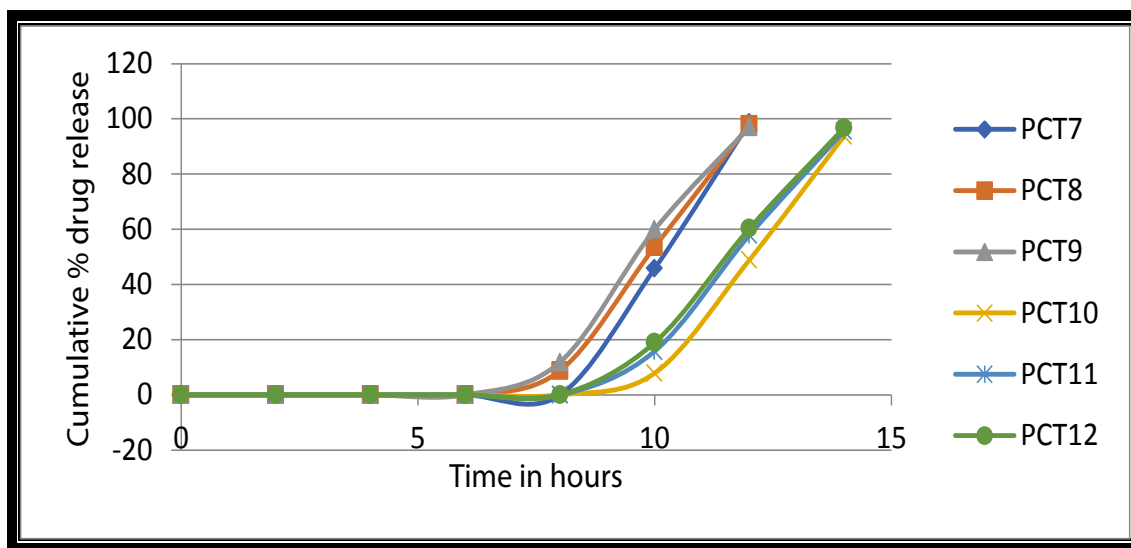**Figure 6:** *In-vitro* dissolution data of PCT1 to PCT6.

Figure 7: *In-vitro* dissolution data of PCT 7 to PCT 12.

Solubility enhancement

Attempt has been made to find highest solubility of Candesartan cilexetil in various nonvolatile solvents. Polyethylene glycol 400, Span 80, Tween 80 and Glycerin were used as nonvolatile solvents. Among all of them, highest solubility was found to be in Tween 80. Hence, Tween 80 was used as solubilizing agent for Candesartan cilexetil.

Flowability studies

The flow properties of powder blends were estimated by determining the angle of repose whose values found to be in the range of 26.32-30.54 indicating good flow. Compressibility index values were in the range of 17.04 to 19.96%. Hausner's ratio was found to be in the range of 1.20 to 1.24. The values of all parameters were within the prescribe limits given by USP XXVII and results were shown in Tables 3-6.

Post compression parameters of core tablets

Weight variation of all core tablets were found in the range of 173 ± 0.35 to 177 ± 0.46. It indicates that all the tablets were passes for the pharmacopeia limits of ± 7.5%. Hardness of core tablet was found in the range of 5 to 5.2 kg/cm^2. Friability values found to be 0.36 to 0.41. Drug content was found to be in the range of 98.33 ± 0.43 to 99.78 ± 0.29.

In-vitro dissolution study

In-vitro drug dissolution studies were carried out in USP type II paddle apparatus for pulsatile tablets. The drug released from various core tablets CT1-CT3 were found to be 99.30%, 98.48% and 99.78% respectively. CT3 was selected for compression coating because of least disintegration time and highest drug release. Dissolution data shows that difference in lag time was observed for various combinations as PCT1-PCT3, PCT4-PCT6, PCT7-PCT9, PCT10-PCT12 shown lag time of 4 hrs, 6 hrs, 8 hrs and 10 hrs respectively.

The data obtained from *in-vitro* release studies of optimized batch PCT4 were fitted into various kinetic models such as zero order, first order, Higuchi model, Hixson model and Korsemeyer-Peppas model to find out the mechanism of drug release from pulsatile tablets. Regression coefficient value R^2 values were shown in Table 7. Results

Batch code	Bulk density	Tapped density	Carr's index (%)	Angle of repose (Θ)	Hausner's ratio
CT1	0.473	0.591	19.96	30.54	1.24
CT2	0.479	0.585	18.11	28.13	1.22
CT3	0.477	0.575	17.04	26.32	1.20

Table 3: Flow properties of powder blends.

Batch code	Weight variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Disintegration time (Sec)	Drug content (%)
CT1	172 ± 0.18	5.0	0.41	42	98.33 ± 0.43
CT2	176 ± 0.52	5.1	0.38	40	99.15 ± 0.22
CT3	177 ± 0.34	5.2	0.36	37	99.78 ± 0.13

Table 4: Evaluation of core tablet.

shown that formulation batch PCT4 follows zero order kinetics which was more than all models value indicated that drug concentration was independent on time.

Conclusion

The aim of designing pulsatile drug delivery of Candesartan cilexetil was to prevent early morning rise in blood pressure which leads to hypertension and other cardiovascular problems. To achieve this goal, pulsatile tablets containing inner rapid releasing core was prepared and further compression coated with suitable combinations of hydrophilic and hydrophobic polymer namely HPMC and ethyl cellulose respectively. HPMC have swelling and erodible nature while ethyl cellulose having rupturable behavior. PCT4 was chosen as optimized batch which meet the requirement and having lag time of 6 hrs which releases 98.32% of drug within 12 hrs. Optimized batch evaluated for stability and found to be successful.

Batch code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm²)	Friability (%)	Drug content (%)
PCT1	372 ± 0.56	4.74 ± 0.13	9.2	0.22	98.26 ± 0.47
PCT2	376 ± 0.37	4.72 ± 0.19	9.3	0.20	98.67 ± 0.63
PCT3	378 ± 0.46	4.71 ± 0.11	9.1	0.18	99.03 ± 0.38
PCT4	374 ± 0.28	4.73 ± 0.08	9.2	0.21	98.32 ± 0.73
PCT5	373 ± 0.39	4.74 ± 0.15	9.4	0.15	97.56 ± 0.65
PCT6	375 ± 0.45	4.75 ± 0.17	9.1	0.19	98.28 ± 0.37
PCT7	377 ± 0.57	4.76 ± 0.14	9.0	0.25	98.73 ± 0.24
PCT8	376 ± 0.32	4.76 ± 0.11	8.9	0.27	98.64 ± 0.18
PCT9	374 ± 0.36	4.73 ± 0.13	9.2	0.21	98.52 ± 0.35
PCT10	372 ± 0.24	4.77 ± 0.15	9.1	0.19	99.13 ± 0.46
PCT11	379 ± 0.18	4.78 ± 0.19	9.3	0.21	99.50 ± 0.58
PCT12	377 ± 0.26	4.75 ± 0.15	9.1	0.20	99.63 ± 0.69

Table 5: Evaluation of press coated pulsatile tablet.

Parameters	Initial	After 1 month	After 2 month	After 3 month
Appearance	White	No change	No change	No change
Hardness	9.2	9.1	8.9	8.7
Drug content	98.32	98.04	97.76	97.58

Table 6: Accelerated stability studies for optimized batch PCT 4.

Batch	Zero order (R²)	First order (R²)	Higuchi model (R²)	Hixson model (R²)	Korsemeyer-Peppas model (R²)
PCT4	0.748	0.497	0.608	0.253	0.636

Table 7: Release kinetics models for optimized batch PCT 4.

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