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FORMULATION AND EVALUATION OF ORAL PULSATILE DRUG DELIVARY SYSTEM OF CANDESARTAN CILEXETIL

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ABSTRACT

Pulsatile Drug Delivery systems (PDDS) is a novel method, it is basically time-controlled drug delivery systems in which the system controls the lag time and drug is released in an immediate or extended fashion. The present investigation was conducted for formulation and evaluation of pulsatile release tablets of candesartancilexetil for the treatment of cardiovascular diseases. The compression coated tablets consisted of a core tablet containing drug with syntheticsuperdisintegrant, which was further coated by erodible outer layer consisted of HPMC K4 and HPMC K100. After carrying outpreformulation studies the formulated tablets were evaluated for post post-compression parameters like weight variation, thickness, hardness, friability, drug content and in-vitro study of drug release. The best formulation was selected on the basis of post-compression parameters and was subjected to accelerated stability studies for 3 month. Amongst 6 formulations prepared, F6 produced convincing results with a maximum cumulative drug release of 99.1% in 8 hours. Also the formulation didn't show any significant changes during 3 month period of stress testing. By virtue of its release pattern and delivering the drug at the right time, right place and in right amounts, the developed delivery system holds good promises of benefiting the patients suffering from hypertension.

KEYWORDS: Pulsatile drug delivery, candesartan, control release, HPMC.

INTRODUCTION

Pulsed or pulsatile drug release is defined as the rapid and transient release of a certain amount of drug molecules within a short time - period immediately after a predetermined off - release period 1. Pulsatile drug delivery systems are characterized by at least two distinctive drug release phases following a predetermined lag time. Drug release may be controlled by time, by site or by combination of the two parameters.

Delivery systems with a pulsatile release pattern are receiving increasing interest for the development of dosage forms, because conventional systems with a continuous release are not ideal. Most conventional oral controlled drug delivery systems release the drug with constant or variable release rates. A pulsatile release profile is characterized by a time period of no release rates (lag time) followed by a rapid and complete release 2.

Chrono-pharmacotherapy, the drug regime based on circadian rhythm, is recently gaining more attention worldwide. Pulsatile drug delivery system has great importance not just for the treatment of disease that are influenced by the circadian rhythm of the body, but also for the potential it holds to prevent the down regulation of drug receptor and to achieve efficient therapeutic effects.

Many systems in the human body such as cardiovascular, pulmonary, hepatic and renal systems show variations in their function throughout a typical day.

In cardiovascular diseases the focus is to optimally deliver the antihypertensive drug in higher amount in early morning and lower amount at night. Holter monitoring of the electrical properties of heart has revealed that 24 hours variation in the occurrence of ventricular premature beats with the peak in events in diurnally active person between 6 am and noon 3, 4.

Candesartan cilexetil is an angiotensin - receptor blocker (ARB) that may be used to treat hypertension. Candesartan lowers blood pressure by antagonizing the rennin-angiotensin-aldosterone system (RAAS); it competes with angiotensin II for binding to the type-I angiotensin II receptor subtype and prevents the blood pressure increasing effects of angiotensin II. Unlike angiotensinconverting enzyme inhibitors (ACE), ARBs do not have the adverse effect of dry cough. Candesartan may be used to treat hypertension, isolated systolic hypertension, left ventricular hypertrophy and diabetic

nephropathy. It may also be used as an alternative agent for the treatment of heart failure, systolic dysfunction, myocardial infarction and coronary artery disease 5.

MATERIALS AND METHODS

Candesartan cilexetil was received from hetro drugs Hyderabad. Crosscarmellose is obtained from Merck Mumbai. Sodium starch glycolate obtained from S.D.Fine Chem. crospovidone is obtained from colorcon. MCC is obtained from S.D.Fine Chem. Magnesium stearate is obtained from Mallinckrodt Chemical. Mannitol is obtained from S.D.Fine Chem. Sodium CMC is obtained from S.D.FineChem. Karaya gum is obtained from S.D.Fine Chem. Sodium alginate is obtained from S.D.Fine Chem. HPMC grades such as E15,K4M,K100, ethyl cellulose and EC10. All other excipients and chemicals are of pharmaceutical and analytical grades.

METHODS

Calibration curve of candesartan cilexetil

Preparation of stock solution

10 mg of drug weighed and transferred into 10ml volumetric flask and add 5 ml of methanol and stirred well vertex for 1min and then add remaining methanol to make up the volume.

Method used in present research work

An UV-VIS Spectrophotometric method based on the measurement of absorbance at 251 nm in methanol stock solution was used in the present research work for the estimation of candesartan cilexetil.

For the estimation of candesartan cilexetil in aqueous fluid the stock solution was subsequently diluted to get a series of dilutions 2, 4, 6, 8 and 10µg/mL of solution and the absorbance was measured at 251 nm (UV-VIS spectrophotometer, SL-218,Elico) against the same dilution as blank. The absorbance values of candesartan celixetil at different concentrations were given in graph.

FT - IR Studies: FT - IR spectroscopy was carried out to check the possible interactions between drug with excipients and polymers. IR spectrum of pure drug and polymers were observed between 4000 400cm-1.

Enhancement of Solubility: Candesartan cilexetil has very poor solubility in water. Hence an attempt was carried out to enhance the solubility dissolution and bioavailability of the drug by using super disintegrants.

Formulation of fast dissolving Tablets

Tablets containing 150mg of candesartan cilexetil were prepared by direct compression method employing different super disintegrant in different ratios. Similarly candesartan cilexetil fast dissolving tablets employing sodium starch glycolate, crossCarmellose sodium and cross povidone.

Table 1: Fast dissolving tablets of candesartan celixetil employing three super disintegrates.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Candesartan	16	16	16	16	16	16	16	16	16
SSG	3	5	7	-	-	-	-	-	-
CCS	-	-	-	3	5	7	-	-	-
CP	-	-	-	-	-	-	3	5	7
MMC	49	49	49	49	49	49	49	49	49
MANNITOL	78	76	74	78	76	74	78	76	74
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Total weight(mg)	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

Formulations of pulselate tablets: the optimised fast dissolving tablets were press coated with 200mg of different time released polymers as given data in table 2.

Table 2: Composition of press coated tablets.

Press coating materials (mg)	HPMC K4	HPMC K100
F6PD1	200	------
F6PD2	150	50
F6PD3	100	100
F6PD4	50	150
F6PD4	------	2000

Evaluations

Flow Property of Powders: The flow properties of powder blends were carried out as bulk density, tapped density, Carr's index, angle of repose and Hausner's ratio.

Weight Variation Test: All the prepared tablets were evaluated for its weight variation as per I.P. All the tablets pass the test for weight variation if average percentage weight variation was found according the pharmacopoeia limits of ± 7.5%.

Hardness and Friability: Hardness of all the tablets was determined by manual Monsanto hardness tester. The hardness of three tablets in each batch was measured and average was calculated in terms of kg/cm2. Friability represents mechanical strength of tablets. Rotary friabilator was used to determine the friability. In this test, twenty tablets which was previously weighed subjected to rotation at 25 rpm for 100 revolutions.

Tablets were dusted and reweighed; the loss in weight was calculated by following equation,

$$\text{Percept friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}}$$

Dissolution of Tablets: In vitro dissolution study was performed by using type II apparatus (paddle method) at a speed of 50 rpm at 37 ± 0.5 °C using 0.1 N HCl for 2 hrs initially and replaced with 6.8 pH phosphate buffer. Sample was withdrawn at regular intervals and analyzedspectrophotometrically at 251nm using UV visible spectrophotometer. (Elico 218).

Content Uniformity: For the determination of drug content ten tablets were selected randomly, crushed and powdered quantity equivalent to one tablet was diluted with 100ml of phosphate buffer of pH 6.8. Then aliquots of the filter was diluted and analyzedspectrophotometrically at 251nm. The drug concentration was calculated and reported in standard deviations.

Stability Studies: The present investigation of stability testing is 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 month for 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 (R2) were calculated from the linear curves obtained by regression analysis of the above plots.

RESULT AND DISCUSSION

Calibration of Candesartan Cilexetil: Standard calibration curve of Candesartan cilexetil was carried out in 0.1N HCL buffer and phosphate buffer of pH 6.8. The curves shown linearity which was indicated in Fig.1.

FT-IR Studies: FT-IR spectrum of pure drug shows characteristic absorption peaks and found that there were no interactions of drug with excipients and polymers. Hence it indicates no change in chemical integrity of the drug. FT-IR spectrums were shown in Fig. 2.

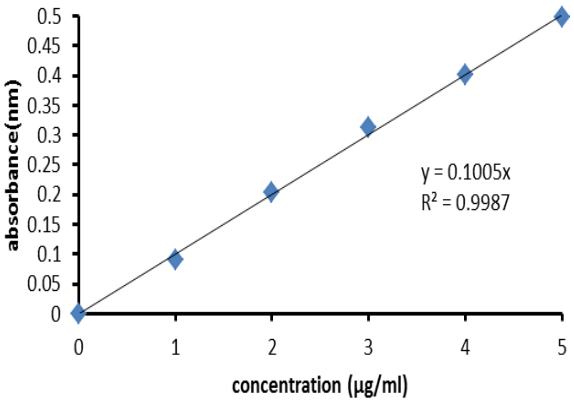

Fig. 1: Calibration curve of candesartan celixetil in phosphate buffer of ph 6.8.

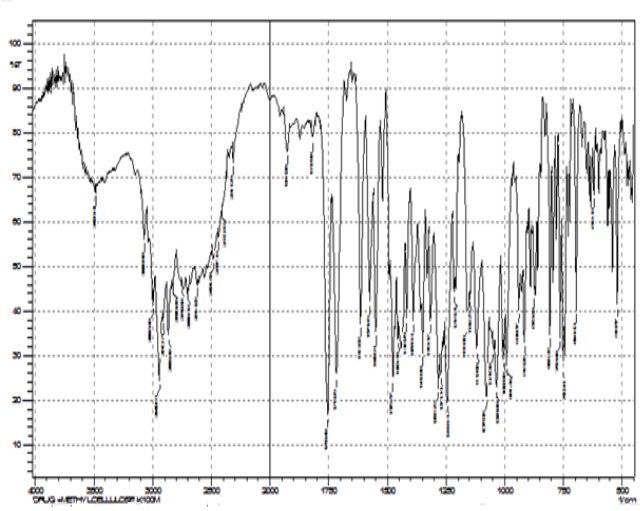

Fig. 2: FT-IR spectrum of pure candesartan cilexetil.

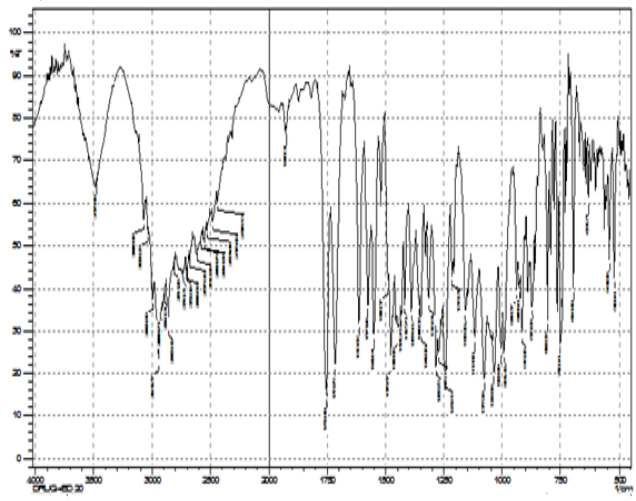

Fig. 3: FT-IR spectrum of core formulation.

Solubility Enhancement: Candesartan cilexetil is a hydrophobic drug having very low water solubility. Attempt was carried out to enhance the solubility dissolution and bioavailability of the drug using various

super disintegrant hencecross caramelouse sodium was selected as solubilising agent for candesartan celixetile.

Pre Compression Parameters: The formulation powders were subjected for pre compression evaluations parameters such as bulk density, tapped density, compressibility index, angle of repose and Hausner's ratio. The values of all parameters were within prescribed limits as per USP XXVII and indicate good flow properties. The results were shown in Table 3.

Table 3: Pre compression parameters.

CODE	bulk density	Tapped density	Carr's index	Angle of repose (Ɵ)	Hausner's ratio
F1	0.490	0.594	19.1%	30.14	1.23
F2	0.473	0.578	18.7%	29.93	1.27
F3	0.476	0.587	17.82%	29.14	1.31
F4	0.491	0.593	17.91%	28.78	1.41
F5	0.483	0.589	17.23%	27.12	1.17
F6	0.452	0.569	18.91%	28.17	1.29
F7	0.476	0.572	18.72%	29.37	1.12
F8	0.469	0.463	18.93%	30.18	1.79
F9	0.472	0.473	19.24%	27.42	1.78

Post parameters

In order to check the quality control standards, various tests such as weight variation, hardness and friability, disintegration, thickness, dissolution and content uniformity were performed. The weight variation of all core and coated tablets passed the test indicating average percentage weight variation was found within the pharmacopoeia limits.

Table 4: Evaluations of core tablets.

Code	Weight variation	Hardness(kg/cm2)	Friability (%)	Disintegration time(sec)	Drug content (%)
F1	150±0.21	3.8	0.35	52	98.45±0.39
F2	150±0.37	4.3	0.32	41	98.79±0.37
F3	150±0.26	4.5	0.39	49	99.07±0.24
F4	150±0.21	4.9	0.41	44	99.72±0.49
F5	150±0.39	4.4	0.79	40	100.19±0.27
F6	150±0.42	4.5	0.31	39	99.13±0.79
F7	150±0.38	4.9	0.39	49	98.87±0.69
F8	150±0.71	4.3	0.36	61	98.54±0.13
F9	150±0.82	4.1	0.31	58	99.19±0.29

Table 5: evaluation of coated tablets.

Batch code	Weight variation	Thickness (mm)	Hardness (Kg/cm2)	Friability (%)	Drug content (%)
F1	350±0.48	4.73	9.7	0.27	98.46±0.64
F2	350±0.41	4.75	9.5	0.31	98.83±0.49
F3	350±0.17	4.77	9.3	0.19	98.19±0.29
F4	350±0.30	4.79	9.4	0.22	99.67±0.16
F5	350±0.43	4.76	9.2	0.28	97.62±0.65
F6	350±0.57	4.78	9.3	0.29	99.21±0.53
F7	350±0.15	4.73	9.9	0.31	98.39±0.28
F8	350±0.47	4.72	9.1	0.38	98.79±0.43
F9	350±0.26	4.75	9.2	0.19	99.19±0.47

Hardness of core tablets was found in the range of 3.8 to 4.9 kg/cm 2 and for coated tablets 9.1 to 9.7 kg/cm2. Friability values for core and coated tablets were found to be 0.46 to 0.53 and for coated tablets 0.31 to 0.79 respectively. The drug content for core tablets was found in the range of 98.45 ± 0.37 to 99.07 ± 0.27 and for coated tablets as 97.34 ± 0.52 to 99.73 ± 0.68 respectively.

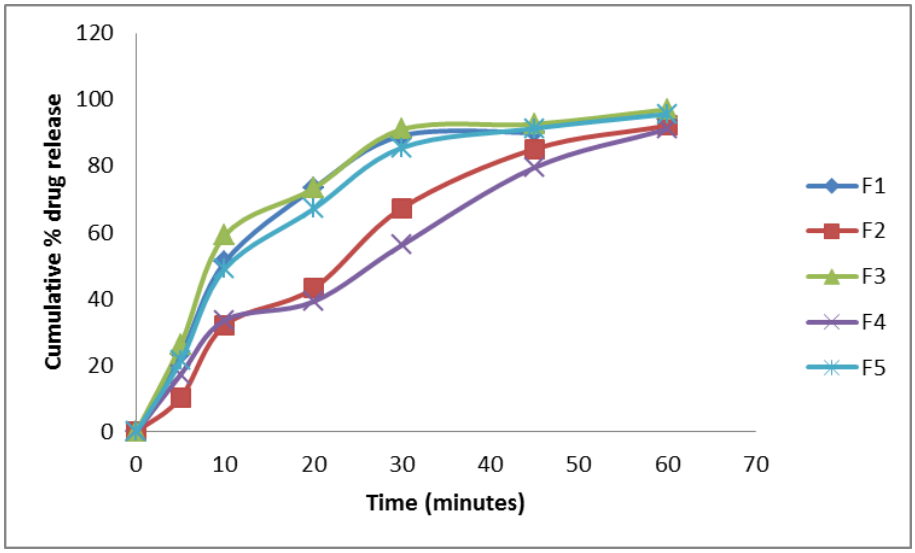

Fig. 4: Dissolution of core tablets f1 to f5.

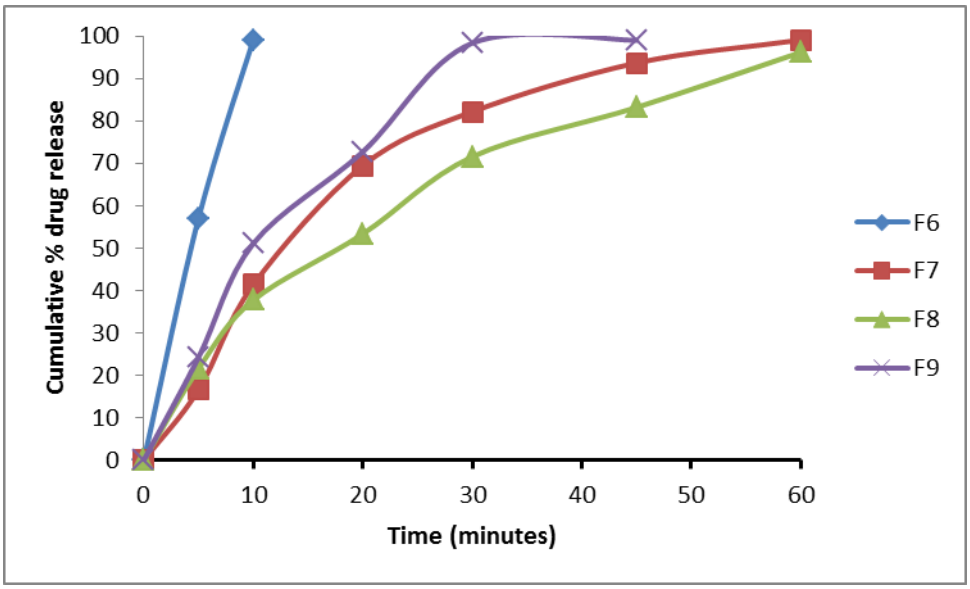

Fig. 5: Dissolution of core tablets f6 to f9.

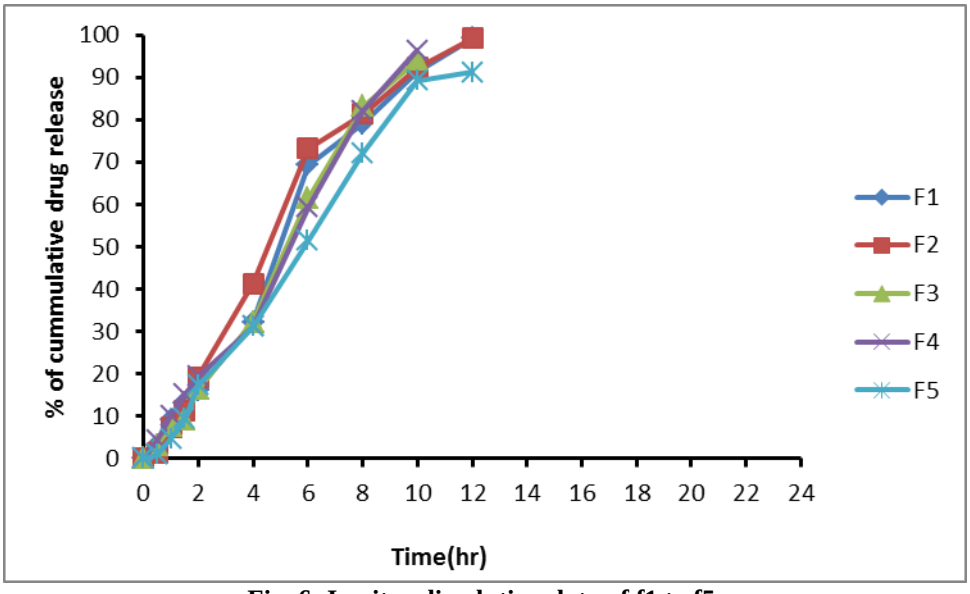

Fig. 6: In vitro dissolution data of f1 to f5.

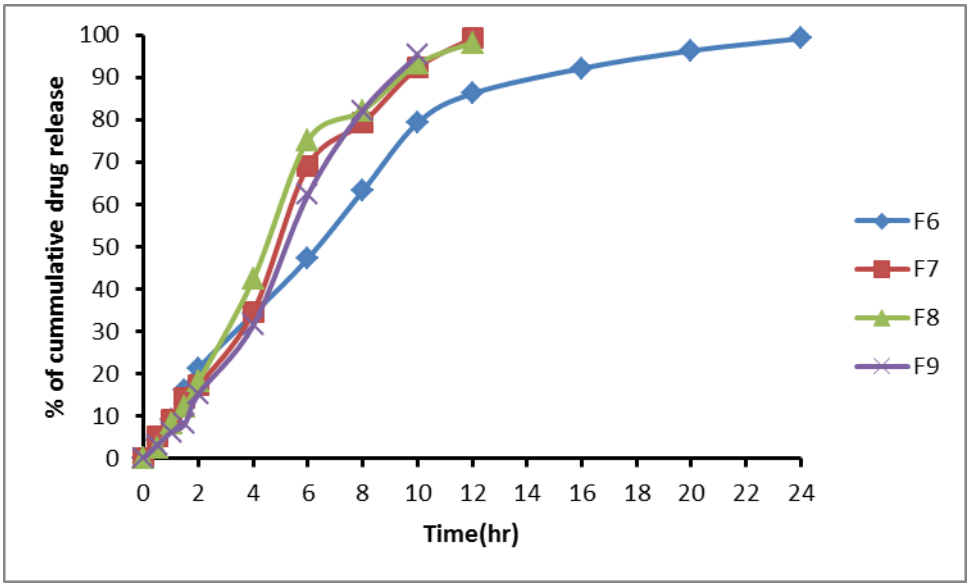

Fig. 7: In vitro dissolution data of f6 to f9.

Table 6: Accelerated Stability Study Of Optimized Batch F10.

Parameters	Initial	After1 month	After2 months	After 3 months
Appearance	White	No change	No change	No change
Hardness	9.7	9.5	9.4	9.3
Drug content	98.76	98.63	98.52	98.25

Table 7: Dissolution Kinetics Models.

Batch code	Zero order	First order	Higuchi (R2)	Hixson (R2)	Korsemeyer-Peppas (R2) F1
F1	0.915	0.035	0.659	0.023	0.925
F2	0.935	0.023	0.759	0.025	0.932
F3	0.967	0.025	0.513	0.016	0.956
F4	0.845	0.039	0.745	0.026	0.859
F5	0.961	0.015	0.845	0.040	0.542
F6	0.715	0.0502	0.521	0.18	0.645
F7	0.763	0.515	0.476	0.543	0.665
F8	0.759	0.642	0.526	0.705	0.569
F9	0.779	0.615	0.559	0.741	0.774

The data obtained from in-vitro release studies of all batches were fitted into various kinetics models such as zero order, first order, Higuchi model, Hixson model and Korsemeyer-Peppas model to find out the release mechanisms of drug release from pulsatile tablet. Regression coefficient values R2 were shown in Table 7. Results shown that formulation batch F9 follows zero order kinetics which was found to be more than all models value indicated that drug concentration was independent on time.

CONCLUSION

The basic objective of developing pulsatile tablet of Candesartan cilexetil was to prevent the cardiovascular complications such as early rise in blood pressure followed by heart failure. For achieving this goal, pulsatile drug delivery was formulated containing inner immediate release tablet and outer coating with combinations of hydrophilic HPMC E15, HPMC K4M, HPMC K100, HPMC CE10 and hydrophobic ethyl cellulose polymers. HPMC was selected because of its swelling and erodible behaviour and ethyl cellulose of its rupturable behaviour. Optimized batch was selected as F6 as having highest lag time of 4 - 5 hrs.and released 99.12% of drug after 8 hr. It was observed that low hydrophilic and high hydrophobic polymer combination was responsible to achieve the desired lag time. Optimized batch F6 checked for its stability and found to be successful.

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