Available online on www.ijddt.com
International Journal of Drug Delivery Technology 2017; 7(3); 184-189
doi: 10.25258/ijddt.v7i03.9562
ISSN: 0975 4415

Research Article

Development of Pulsatile Drug Delivery for Chronotherapeutics of Hypertension

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Received: 5th June, 17; Revised 1st Sept, 17, Accepted: 13th Sept, 17; Available Online: 25th Sept, 2017

ABSTRACT
The goal of present work was to investigate the effects of rupturable material ethyl cellulose combines with erodible material Klucel EXF on the pulsatile release pattern of Candesartan cilexetil in order to prevent morning rise in blood pressure. A tablet prepared by compression coating method contains core and coat components. Core consists of active ingredients with its various superdisintegrants where as coat contains different grades of ethyl cellulose and Klucel HXF in various combinations. All these tablets were evaluated for its micromeritics, weight variations, hardness, friability and in vitro dissolution testing. Drug-excipients interactions were carried out by FTIR. Dissolution studies were carried out in simulated gastric fluid followed by phosphate buffer of pH 6.5. The optimized formulation PT6 which give lag time of 6 hrs and released 99.10 % within 7 hr, as well as found to be stable in ICH stability testing guidelines.

Keywords: Pulsatile, Candesartan cilexetil, Klucel HXF, Ethyl cellulose.

INTRODUCTION

In cardiovascular disease capillary resistance and vascular reactivity are higher in the morning and decreases later in the day. Platelet agreeability is increased and fibrinolytic activity is decreased in the morning leading to a state of relative hypercoagulability of the blood. Because of this reason the frequencies of myocardial infarction and of sudden death are prone during from morning to noon[1]. The time of a drug administration can play a key role in determining the efficacy and tolerability of a pharmacological therapy. Indeed, the temporal rhythm of bodily functions have been shown to affect not only the incidence or severity of a number of disease conditions but also the pharmacokinetics as well as pharmacodynamics of most bioactive compounds in use. Accordingly, chronotherapeutics treatments tailored to supply the patient with the appropriate dose of the required drug when this is especially needed are gaining increasing interest[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[3]. PDDS is capable of providing one or more rapid release pulses at predetermined lag times which results in better absorption of the active solute, and thereby provides more effective plasma concentration time profile[4].

Angiotensin II receptor blocker (ARB) selectively and specifically antagonize the action of angiotensin II, a potent vasoconstrictor impacting BP regulation. ARBs are becoming increasingly popular for the treatment of hypertension because they are effective and well tolerated[5]. Candesartan cilexetil is an ARB that may be used to treat hypertension. Candesartan lowers blood pressure by antagonizing the rennin-angiotensin-aldosterone system; it competes with angiotensin II for binding to the type-I angiotensin II receptor subtype and prevents blood pressure increasing effects of angiotensin II[6].

MATERIALS AND METHODS

Candesartan cilexetil was received from Mylan Laboratories Hyderabad. Ethyl cellulose grades were gifted by Colorcon Asia Pvt. Ltd. Goa. Dibasic calcium phosphate (anhydrous DC grade), Magnesium stearate and Talc supplied by Nitika Pharmaceuticals Nagpur. All other reagents and chemicals are of pharmaceutical and analytical grades.

Drug interactions studies

The physicochemical compatibilities of the drug and the used excipients were tested by FTIR. IR spectrum of pure

Table 1: composition of core tablet.

Ingredients	C1	C2	C3
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 (mg)	175	175	175

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Table 2: combination of coating material.

Coating material	PT1	PT2	PT3	PT4	PT5	PT6	PT7	PT8	PT9
Klucel EXF		50	100	150	200	50	100	150	
EC 10	200	150	100	50					
EC 20						150	100	50	200
Total weight	200	200	200	200	200	200	200	200	200

Table 3: Flow property of powders.

Batch code	Bulk density	Tapped density	Carr's index (%)	Angle of repose (Θ)	Hausner's ratio
CT1	0.470	0.584	19.52	29.96	1.24
CT2	0.472	0.580	18.62	29.37	1.22
CT3	0.476	0.571	16.63	26.73	1.19

Table 4: Evaluation of core tablets.

Batch code	Weight variation	Hardness (Kg/cm^2)	Friability (%)	Disintegration time (sec)	Drug content (%)
CT1	174±	4.9	0.43	44	98.67±0.63
CT2	177±	4.7	0.47	41	98.46±0.45
CT3	176±	4.8	0.45	39	98.23±0.56

Table 5: Evaluation of coated tablets.

Batch code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
PT1	375±0.15	4.73	9.0	0.24	98.38±0.51
PT2	378±0.25	4.75	9.2	0.22	98.81±0.24
PT3	372±0.29	4.75	8.9	0.29	98.34±0.38
PT4	374±0.37	4.74	9.1	0.24	97.37±0.78
PT5	376±0.24	4.77	9.2	0.21	99.13±0.34
PT6	375±0.44	4.78	9.1	0.23	98.76±0.49
PT7	374±0.26	4.74	9.0	0.25	97.94±0.84
PT8	377±0.41	4.73	9.1	0.23	98.45±0.57
PT9	373±0.34	4.72	8.9	0.27	99.27±0.63

drug and excipients were observed between 4000-400 cm^{-1}. (Shimadzu IRAffinity-1s FTIR)

Enhancement of solubility

Candesartan cilexetil belongs to BCS class II indicates low solubility and having bioavailability of 15-40 %. Hence, attempt had made for enhancing solubility dissolution and bioavailability of Candesartan cilexetil using liquisolid Compaq technique.

Formulation of core tablet

The composition of Candesartan cilexetil was depicted in Table 1. All of the powder used was 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 above admixture and mixed by geometric addition technique. Finally, 175 mg of the blend was weighed and compressed by 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.

Formulation of pulsatile tablet

Press coated tablets were prepared using various compositions given in Table 2. Ethyl cellulose was 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 was filled in the die, and the content was compressed using a flat punch.

Evaluations

Flow property

The flow properties of the pulsatile systems were evaluated 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.

Weight variation test

Weight variation test were carried out as per the specifications given in IP. Twenty tablets were selected randomly and weighed. Average weight was determined and test will passes when the tablets weight lies within pharmacopoieal limits.

Hardness and Friability

Tablet hardness is defined as force required to break a tablet in a diametrically compression test. Determination of hardness is required to assess the resistivity of tablets

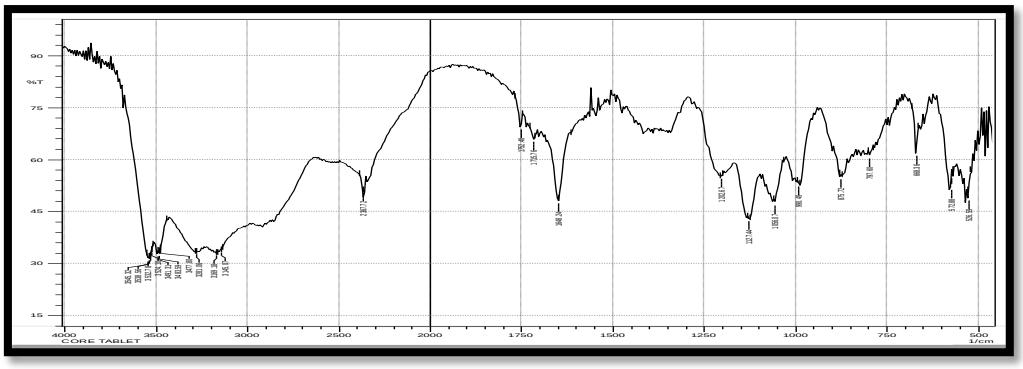

Figure 1: FTIR spectra of pure Candesartan cilexetil.

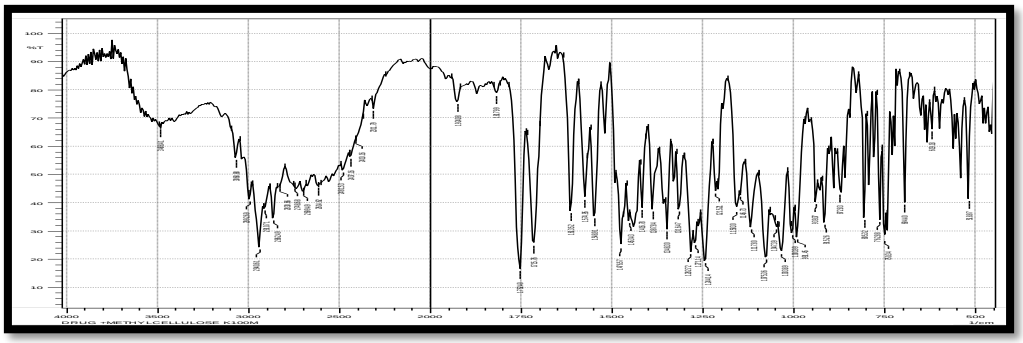

Figure 2: FTIR spectra of core tablets.

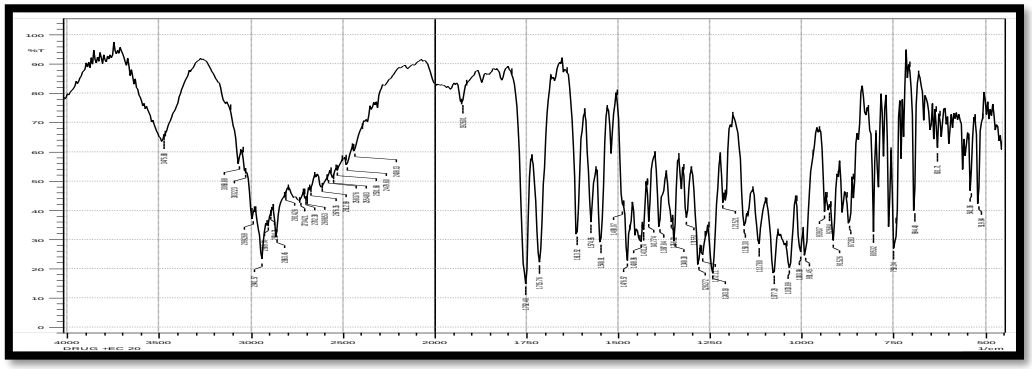

Figure 3: FTIR spectra of Candesartan cilexetil with Ethyl cellulose.

against mechanical shocks during their handling in manufacturing, packaging and shipping operations. Tablet hardness was measured by using Monsanto hardness tester. For each formulation the friability of tablets was determined using Roche friabilator (Electrolab Mumbai India). In this test tablets were subjected to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. The tablets were then dusted and reweighed.

Disintegration test

The in-vitro disintegration time for rapid 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 complete disintegration of the tablets was noted.

In-vitro dissolution test

In-vitro dissolution studies were carried out by USP type II paddle method apparatus. Dissolution test was performed at a speed of 50 rpm at 37±0.5 °C using 0.1 N HCl initially for 2 hrs and then replaced with phosphate buffer of pH 6.5. Appropriate aliquots were withdrawn at suitable time intervals and filtered through Whatman filter paper which was further diluted with phosphate buffer 6.5. The samples were analyzed spectrophotometrically at 251 nm by using UV visible spectrophotometer (Shimadzu 1800.) The results were shown in triplicates.

Content uniformity

Ten tablets were randomly selected, weighed and powdered with mortar and pestle. The quantity of powder equivalent to one tablet weight was transferred carefully into a 100 ml volumetric flask and dissolved the drug with phosphate buffer of pH 6.5. Then the solution was filtered

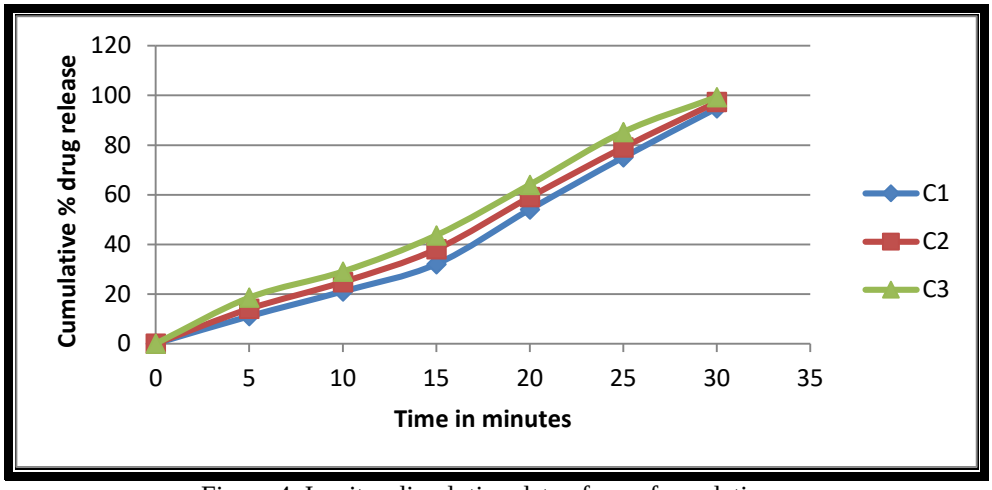

Figure 4: In-vitro dissolution data of core formulations.

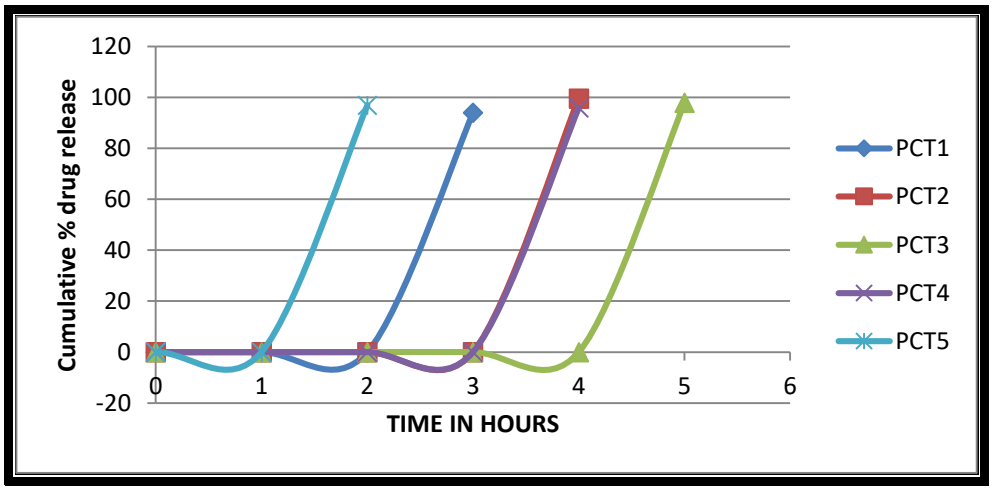

Figure 5: In-vitro dissolution data of PT1-PT5.

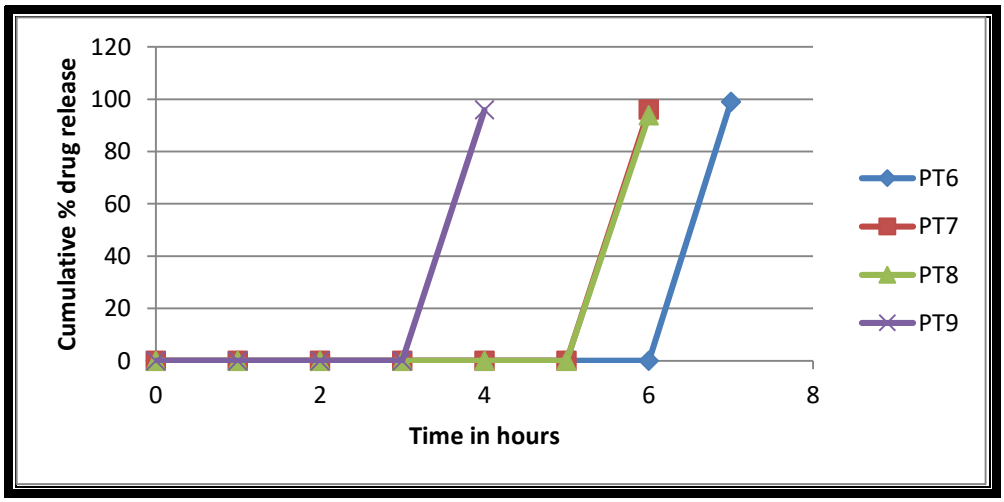

Figure 6: In-vitro dissolution data of PCT6-PCT9.

though a membrane filter (0.45 mm) and diluted. The filtrate was measured spectrophotometrically at 251 nm using UV visible spectrophotometer.

Stability studies

The accelerated stability study was carried out as per the ICH guidelines for optimized batch. 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 interval of 1 month for a period of 3 months and analyzed. The samples were evaluated for their physical characteristics and drug content.

RESULTS AND DISCUSSION

Table 6: Accelerated stability study of optimized batch PT6

Parameters	Initial	After 1 month	After 2 month	After 3 month
Appearance	White in colour	No change	No change	No change
Hardness	9.1	8.9	8.7	8.6
Drug content	98.76	98.53	98.37	98.09

FTIR studies

The FTIR spectra of Candesartan cilexetil shown 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 Fig. 1 to 3.

Enhancement of solubility

Determination of solubility was carried out in different non volatile solvents such as PEG 400, span 80, glycerin, tween 80. Highest solubility was found to be in tween 80. Hence, tween 80 was used as solubilizing agent in core formulation for Candesartan cilexetil.

Flowability studies

Flow properties were carried out by determining the angle of repose whose value found to be in the range of 26.73 to 29.96 indicating good flow. Carr's index values were in the range of 16.63 to 19.52 % . Hausner's ratio was found to be in the range of 1.19 to 1.24. The values of all parameters was found to be within the prescribe limits given by USP XXVII and results shown in Table 3.

Evaluation of core tablets

Weight variation of all tablets was found in the range of 171±0.30 to 178±0.24. Results indicate that all the tablets were passing the weight variation test of 7.5± %. Hardness of core tablet was found in the range of 4.7 to 4.9 kg/cm^2. Friability values found to be 0.35 to 0.42. Drug content was found in the range of 98.23±0.56 to 98.67±0.63.

In-vitro dissolution

The drug released from core tablet batches were found to be 99.63 %, 98.87 % and 99. 86 % respectively. CT3 was selected for inner core tablet for press coating pulsatile tablets because of least disintegration time of 39 sec and highest dissolution rate of 99.86 % within 30 minutes. Dissolution study was also carried out for press coated pulsatile tablets indicating that difference in lag time was observed with various combinations.

In-vitro dissolution studies shown that batches of PT1 – PT5 having lag time of 2 hr, 3 hr, 4 hr, 3 hr, 1 hr respectively. Similarly, PT6-PT9 batches shown lag time of 6 hr, 5 hr, 5hr, and 3 hr respectively. Batches of PT1 to PT5 having less viscosity of ethyl cellulose which provides highest lag time up to 4 hrs whereas PT6-PT9 batches containing higher viscosity grades of ethyl cellulose and with erodible material Klucel EXF able to give highest lag time of 6 hrs which meet the demands for pulsatile drug delivery. In-vitro drug release was found to be highest in PT 6 which gives 99.10 % within 7 hrs.

CONCLUSION

The aim of current investigation was to develop pulsatile drug delivery of antihypertensive agent which is capable of reducing number of cardiovascular complications like early morning rise in blood pressure, myocardial infarction, heart failure etc. To provide the prompt relief from these symptoms Candesartan cilexetil was chosen pulsatile drug delivery. Core tablet containing Candesartan with different superdisintegrants was prepared and coated with various combinations of ethyl cellulose as rupturable material and Klucel EXF as erodible material. Optimized batch was chosen as PT6 having highest lag time of 6 hrs followed by burst release which released 99.10 % of drug within 7 hrs, thus fulfilling the demand of chronotherapeutics drug delivery. Patients are advice to take this pulse tablet at bed time after 10 pm so that it will get relief from early morning rise in blood pressure.

ACKNOWLEDGEMENT

Thanks you Mylan laboratories Hyderabad for providing gift sample of Candesartan cilexetil, Colorcon Asia Pvt. Ltd. Goa for providing ethyl cellulose grades and also to Nitika Chemicals for the gift samples of dibasic calcium phosphate, magnesium stearate and talc.

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