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PH Dependent Pulsatile Drug Delivery for Chronotherapeutics of Cardiovascular Diseases

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ABSTRACT

The objective of current investigation was to formulate an effective drug delivery system for the patients suffering from cardiovascular problems such as early rise in blood pressure, myocardial infarction and heart failure etc. To achieve this goal, pulsatile drug delivery was selected because it delivers the drug at right time and at right situation. Candesartan cilexetil was selected for pulsatile drug delivery in order to provide relief from various cardiovascular problems. Core tablets were formulated with different superdisintegrants for immediate release. Core tablets were further compression coated with various suitable combinations of hydrophilic polymer HPMC K15M and enteric polymers Eudragit L 100 and S100 respectively for definite lag time. The formulated tablets were evaluated for its micromeritics properties followed by weight variation, hardness, friability, content uniformity and in-vitro dissolution test. The drug-excipients interactions were carried out by FTIR studies. Optimized batch PT9 were also evaluated for accelerated stability studies which found to be successful.

Keywords: Pulsatile, Candesartan cilexetil, HPMC K15M, Eudragit L 100, Eudragit S 100, FTIR, Cardiovascular problems

INTRODUCTION

Chronopharmacology is the study of how the effects of drugs vary with biological timing and endogenous periodicities, which is relevant to many diseases, such as ischemic heart disease and hypertension, which are frequently occurred before down. The circadian rhythm showed that drug pharmacokinetics and the effects of therapies changed with the time of drug administration. Therefore, maintaining an adequate blood concentration during the episodes of a disease not only improves efficacy but also reduces the side effects of the drug.

Delayed-release drug delivery system (DDS) is a Chronopharmacology and hominal physiology based DDS, mainly applied for the treatment of diseases exhibiting circadian rhythm, for instance, ischemic heart disease, asthma and intestinal diseases. Patients may take drug before going to sleep at around 10 pm, and active components in the medicine will be released after several hours delay and take effect at night during the episodes of the disease [1].

Pulsatile drug delivery systems release the drug rapidly and completely after a lag time, thus provide spatial and temporal delivery and increasing patient compliance, have generated increasing interest for number of diseases and therapies [2,3]. The pulsatile release of an active agent is desirable when treating disease that require drug delivery in a manner to maintain therapeutic levels albeit circadian rhythms [4].

Candesartan cilexetil was chosen as it is angiotensin II receptor blocker used to treat hypertension, myocardial infarction, left ventricular hypertrophy and diabetic nephropathy. It is also used for heart failure, systolic dysfunction and coronary artery diseases. Candesartan lowers the blood pressure by antagonizing the rennin-angiotensin-aldosterone systems; it competes with angiotensin II for binding to the type-I angiotensin II receptor subtype and prevents blood pressure increasing effects of angiotensin [5]. The objective of designing work was to develop effective drug delivery which provides relief from early morning rise in blood pressure and myocardial infarction which leads to mortality in many patients.

MATERIALS AND METHODS

Candesartan cilexetil was received from Mylan laboratories Hyderabad. HPMC K15M received as gift sample from Colorcon Asia Pvt. Ltd Goa and Eudragit L100, S 100 grades gifted by Evonic Degussa Mumbai. Dibasic calcium phosphate, magnesium stearate and talc gifted by Nitika Chemicals, Nagpur. All other reagents and chemicals were pharmaceutical analytical grades.

Enhancement of solubility

Dissolution is a rate determining step towards drug absorption and bioavailability. Candesartan cilexetil is a hydrophobic drug as belongs to BCS class II drug indicating low solubility. Hence attempt was carried out to enhance the solubility, dissolution and ultimately bioavailability of drug. Liquisolid Compaq technique was used for enhancement of solubility which involving various nonvolatile solvent [6-10].

FTIR studies

FTIR technique checks any kind of interactions between drug and excipients. Initially spectrum of pure drug was determined by its bonding and stretching followed by with all formulation variables between the ranges of 4000-400 cm^{-1}.

Formulation of core tablet

The formulation variables were given in Table 1. All the ingredients used were passed through sieve no. 44 separately. The required quantity of the previously weighed solid Candesartan cilexetil was dissolved in tween 80 which is a non-volatile solvent. The resulting wet mass was then blended with dibasic calcium phosphate to form simple admixture. Remaining ingredients were added in the formulation according to their geometrical order. Finally, powder blend containing 175 mg was accurately weighed and compressed using Rimek mini press II machine at Karnavati Engineering Ahmadabad, India.

Table 1: Composition of core tablets.

Ingredients (mg)	**CT1**	**CT2**	**CT3**	**CT4**	**CT4**	**CT6**
Candesartan cilexetil	8	8	8	8	8	8
Tween 80	q.s	q.s.	q.s.	q.s.	q.s.	q.s.
Dibasic calcium phosphate	157	157	157	155	155	155
Sodium starch glycollate	5.25	--	--	7	--	--
Cross carmellose sodium	--	5.25	--	--	7	--
Cross povidone	--	--	5.25	--	--	7
Magnesium stearate	1.75	1.75	1.75	1.75	1.75	1.75
Talc	1.75	1.75	1.75	1.75	1.75	1.75
Total weight	175	175	175	175	175	175

Optimization of core tablets

Core tablet which should be part of pulsatile tablets selected on the basis of disintegration time and dissolution release data.

Composition of coating layer

The different composition of HPMC K15M and Eudragit L100, Eudragit S 100 for press coated pulsatile tablets was shown in (Table 2) All the ingredients were accurately weighed and dry blended for 20 minutes and finally used for press coating materials.

Table 2: Compositions of coating materials.

Ingredients (mg)	**PT1**	**PT2**	**PT3**	**PT4**	**PT5**	**PT6**	**PT7**	**PT8**	**PT9**	**PT10**
HPMC K15M	50	100	150	--	200	50	100	150	50	--
Eudragit L100	150	100	50	200	--	--	--	--	50	--
Eudragit S 100	--	--	--	--	--	150	100	50	100	200
Total weight	200	200	200	200	200	200	200	200	200	200

Formulation of pulsatile tablet

Compression coated tablets were formulated by using different compositions given in Table 2. Powder blends were properly mixed and half of the total quantity of coating powder blend was filled in die cavity to provide a bed at the bottom. The core tablet was placed in the centre on the above powder blend and remaining half quantity of powder was filled in the die. Finally, material was compressed by using a flat punch to get desired tablet weight.

Evaluations

Flow-ability study

Flowing characteristics of powder blends such as Carr's index, angle of repose and Hausner's ratio were determined. Angle of repose was determined by the fixed funnel and free standing cone method. The bulk density and tapped density values were evaluated for the calculation of Carr's index and Hausner's ratio.

Weight variation test

Weight variation test performed with the specifications provided by the Indian pharmacopoeia (IP). The procedure involved weighing of 20 tablets individually on a precise digital balance and calculating their average weight. Weight variation test will pass when not more than 2 tablets weight was not in limits.

Tablet thickness, hardness and friability test

The thickness of all the tablets was measured by Vernier caliper scale. Hardness of all tablets was determined by using Monsanto hardness tester. Friability was tested by Roche friabilator (Electrolab, Mumbai, India).

Disintegration test

In-vitro disintegration test was performed by using disintegration test apparatus as per the specifications given by IP. Process involved keeping one tablet in each six tube of the basket which was positioned in 1 L of basket at 37°C ± 0.5. The time taken for the complete disintegration was noted when all the particles must be passing through the sieves.

Dissolution study

In-vitro drug dissolution was carried out in ten station dissolution test apparatus. (Electrolab, India). *In-vitro* dissolution studies were performed by 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 hours and replaced thereafter with phosphate buffer of pH 6.5. Appropriate aliquots were withdrawn at suitable time intervals and filtered through Whatman filter paper and diluted with phosphate buffer pH 6.5. The samples were analyzed spectrophotometrically at 251 nm by using UV visible spectrophotometer. (Shimadzu, 1800 Japan)

Content uniformity

Tablets should comply for content uniformity so as to provide therapeutic response. Ten tablets were selected randomly, crushed and powdered quantity equivalent to one tablet was diluted with phosphate buffer of pH 6.5. The absorbance was recorded at 251 nm on UV spectrophotometer and reported the value with standard deviation.

Stability studies

The stability studies were performed for an optimized batch according to the guidelines given by ICH. 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% for 3 months. Samples were taken at regular interval of 1 month and analyzed. Any changes in evaluation parameters, if observed were noted.

RESULTS AND DISCUSSION

FTIR spectra shown characteristic peaks which interpret identity of Candesartan cilexetil. The stretching of carboxylic acid observed at 1075 cm^{-1} due to presence of C=O, 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 its different excipients. FTIR spectrum was shown in (Figures 1-4) [11-15].

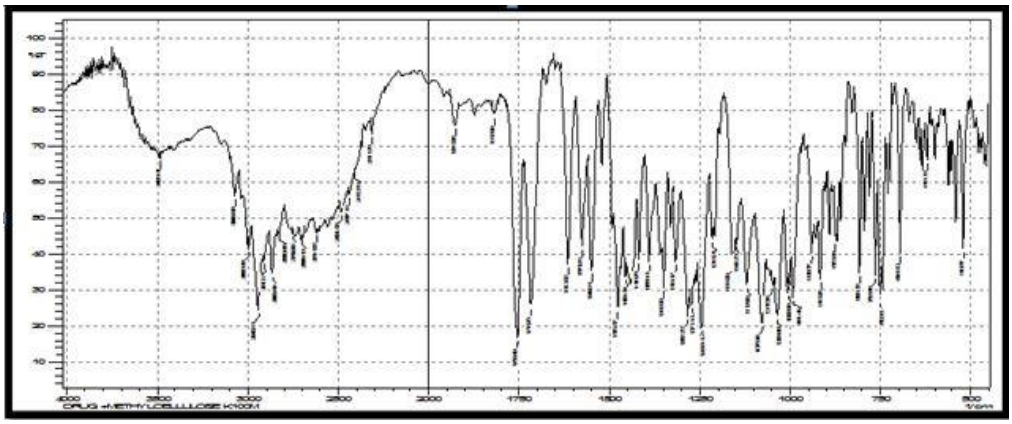

Figure 1: FTIR spectrum of candesartan cilexetil.

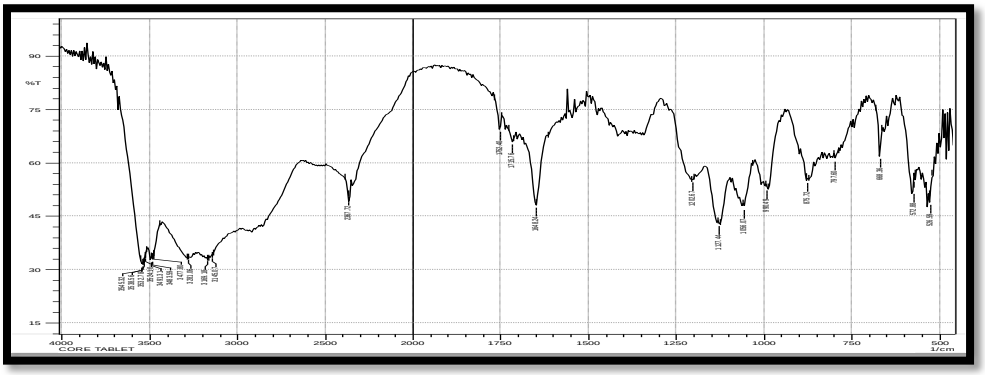

Figure 2: FTIR spectrum of core tablet.

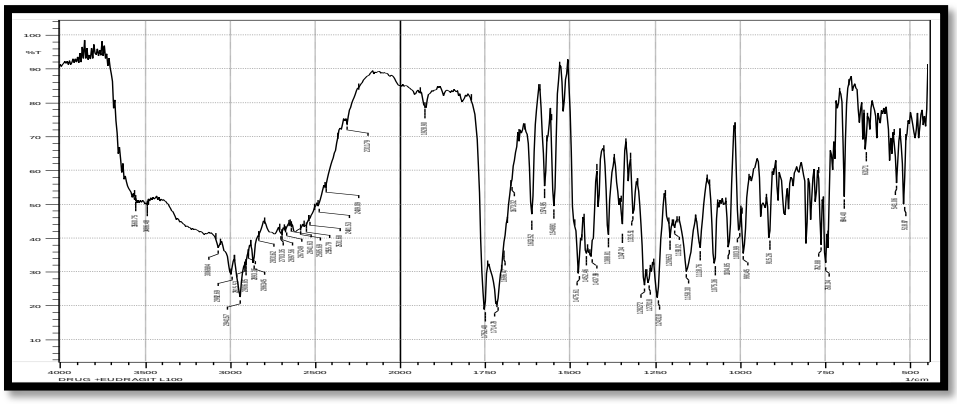

Figure 3: FTIR spectrum of Candesartan cilexetil with HPMC.

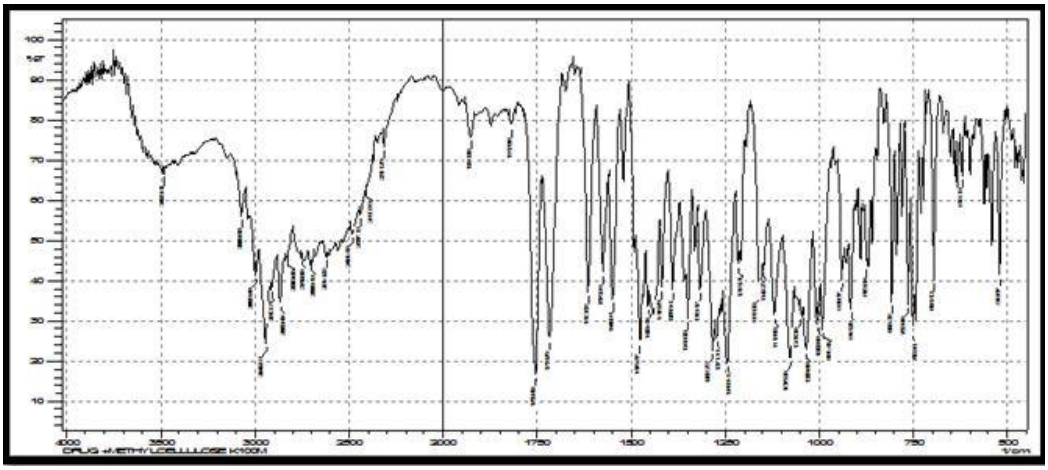

Figure 4: FTIR spectrum of candesartan cilexetil and Eudragit S 100.

Solubility enhancement

Solubility of Candesartan cilexetil was enhanced by liquisolid Compaq technique using various non-volatile solvents such as span 80, polyethylene glycol, glycerin, tween 80 etc. Among all the solvents highest solubility was found in tween 80. Hence, tween 80 was chosen as solubility enhancer in core tablet for Candesartan cilexetil.

Flow-ability studies

The flowing characteristics such as Carr's index, angle of repose and Hausner's ratio were measured. Compressibility index was found to be in the range of 17.69 to 19.46%. Angle of repose was observed as 26.57 to 29.83. Hausner's ratio was also evaluated whose value lies in the range of 1.21 to 1.24. From these results it was observed that powder blends having good flowing nature and suitable for direct compression (Table 3).

Table 3: Flowing characteristics of powder blends.

Batch code	Bulk density	Tapped density	Carr's index (%)	Angle of repose (Ɵ)	Hausner's ratio
CT1	0.480	0.596	19.46	29.83	1.24
CT2	0.476	0.586	18.77	28.24	1.23
CT3	0.479	0.582	17.69	26.57	1.21
CT4	0.481	0.588	18.19	27.68	1.22
CT5	0.477	0.581	17.90	27.13	1.21
CT6	0.473	0.578	18.16	27.79	1.22

Evaluation of tablets

Weight variation test were carried out which passes as all the tablets were found within the pharmacopoeial limits. Weight variation of all core tablets were found in the range of 173 ± 0.42 to 178 ± 0.57. Hardness of core tablets was found to be 4.6 to

4.8 kg/cm^2. Friability of core tablets was in the range of 0.47 to 0.55%. Disintegration time was observed in the range of 31 to 43 seconds. Content uniformity was found to be in the range of 98.12 ± 0.84 to 99.08 ± 0.60% (Tables 4 and 5).

Table 4: Evaluation of core tablets.

Batch code	Weight variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Disintegration time (sec)	Drug content (%)
CT1	178 ± 0.57	4.7	0.51	43	98.40 ± 0.67
CT2	173 ± 0.38	4.8	0.47	40	98.12 ± 0.84
CT3	177 ± 0.82	4.7	0.50	38	99.08 ± 0.60
CT4	174 ± 0.63	4.6	0.54	36	98.57 ± 0.47
CT5	175 ± 0.53	4.6	0.55	31	98.86 ± 0.68
CT6	173 ± 0.42	4.7	0.52	32	98.74 ± 0.75

Table 5: Evaluation of press coated tablets.

Batch code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)
PT1	379 ± 0.42	4.71	8.8	0.30	97.86 ± 0.57
PT2	377 ± 0.40	4.73	9.1	0.26	98.62 ± 0.76
PT3	372 ± 0.53	4.76	8.9	0.28	98.34 ± 0.82
PT4	376 ± 0.38	4.75	9.0	0.27	98.92 ± 0.74
PT5	378 ± 0.32	4.74	9.2	0.25	98.85 ± 0.86
PT6	373 ± 0.34	4.73	9.1	0.24	98.03 ± 0.92
PT7	375 ± 0.56	4.76	8.9	0.29	98.37 ± 0.67
PT8	373 ± 0.58	4.77	8.8	0.31	99.13 ± 0.58
PT9	378 ± 0.67	4.72	9.0	0.29	98.60 ± 0.62
PT10	372 ± 0.75	4.74	8.9	0.30	98.22 ± 0.73

In-vitro dissolution study

In-vitro drug release studies were carried out by using USP type II paddle method. Core tablets containing various concentrations of superdisintegrants were observed. Among all the formulation batches highest drug release was observed with CT 5 as 99.35 within 15 minutes and also lowest time taken to disintegrate the tablet. So, CT5 was chosen as core inner tablet for all press coated pulsatile tablets. A core formulation CT1-CT3 releases the drug as 97.43%, 98.56%, and 99.87% within 25 minutes respectively. Whereas batches containing CT4 and CT6 releases 97.60% and 98.96% respectively. Rapid release of core tablets was observed in CT4-CT 6 due to higher concentration of superdisintegrants as compared as CT1-CT3 (Figures 5 and 6).

In press coated batches PT1-PT5 containing HPMC K15M and Eudragit L 100 combinations difference in lag time was observed. Batches PT1-PT5 shown 4 hrs, 4 hrs, 3 hrs, 2 hrs and 2 hrs respectively. In PT5-PT10 batches difference in lag time was also observed as 4 hrs, 4 hrs, 3 hrs, 6 hrs and 3 hrs respectively. It was observed that HPMC K15M and Eudragit L 100 combinations release the drug quickly as compared with HPMC K15M and Eudragit S 100. As HPMC is hydrophilic in nature and Eudragit L 100 dissolves rapidly in pH above 6 as compared with Eudragit S 100 which dissolves above pH 7.

Hence slow drug release was observed among these batches. All of the batches only PT9 will meet the desired lag time as it contains HPMC K15M, Eudragit L100 and Eudragit S100 which releases 99.57% within 7 hrs. Hence, PT9 was selected as optimized batch (Figures 7 and 8, Table 6).

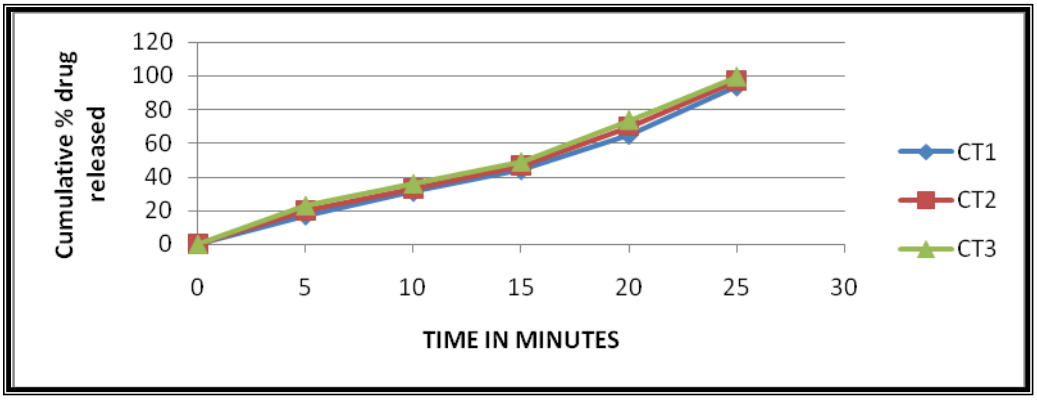

Figure 5: *In-vitro* dissolution data of core tablets CT1-CT3.

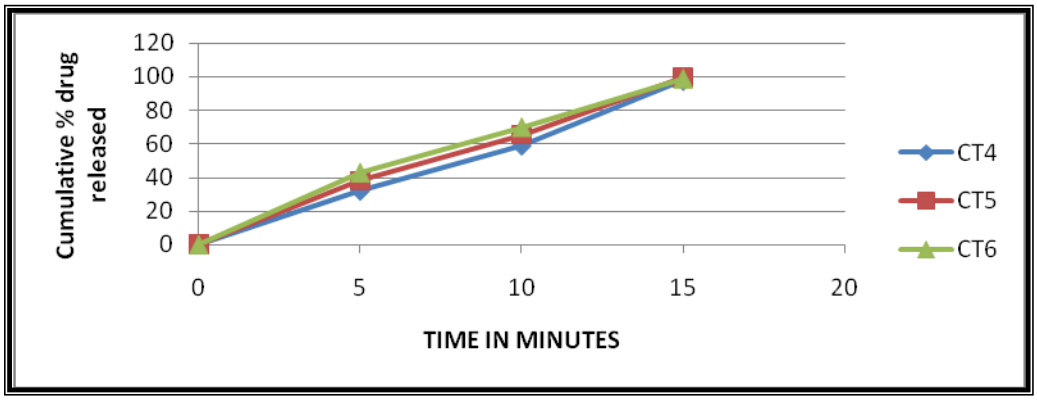

Figure 6: *In-vitro* dissolution data of core tablet core tablets CT4-CT6.

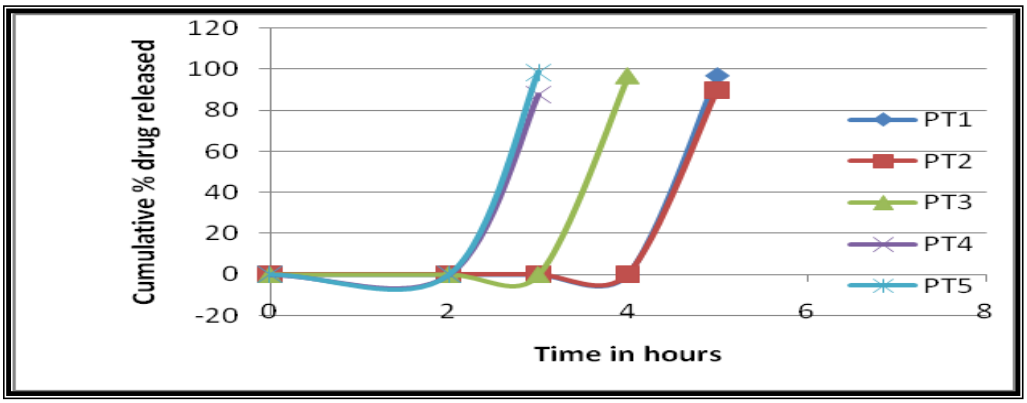

Figure 7: *In-vitro* dissolution data of PT1-PT5

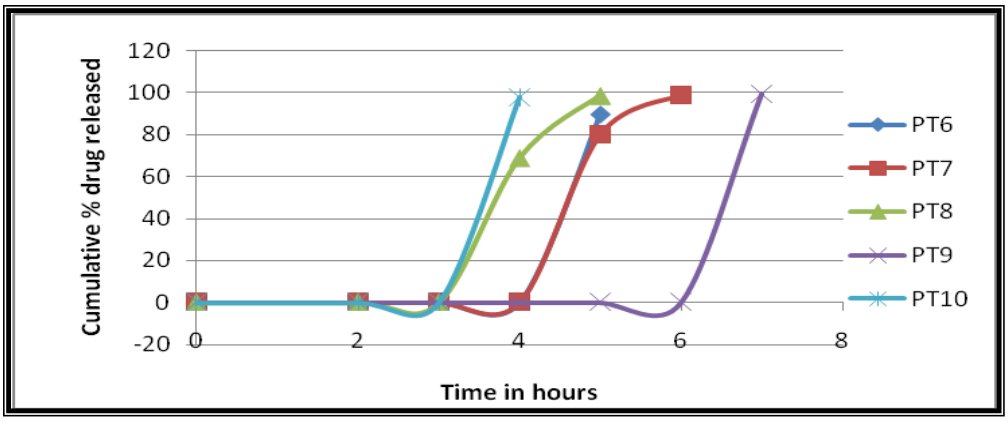

Figure 8: *In-vitro* dissolution data of PT6-PT10.

Table 6: Accelerated stability studies for optimized batch PT9.

Parameters	Initial	After 1 month	After 2 month	After 3 month
Appearance	White in colour	No change	No change	No change
Hardness	9.0	8.8	8.6	8.5
Drug content	98.60	98.35	98.02	97.69

CONCLUSION

The purpose of designing pulsatile drug delivery was to provide relief from various cardiovascular problems like early morning rise in blood pressure, myocardial infarctions which arises in early morning. Conventional tablets don't provide the relief from above problems. Hence pulse tablets containing rapid release Candesartan cilexetil was formulated which was coated with suitable combinations of hydrophilic and enteric polymers so as give desired lag time. Patients suffering from cardiovascular problems are recommending taking this pulse tablet before sleep at 10 pm which releases its drug completely in morning hours. Optimized batch PT9 was tested and found to be successful.

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