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DEVELOPMENT AND CHARACTERIZATION OF PULSATILE DRUG DELIVERY SYSTEM OF LERCANIDIPINE

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KEYWORDS:

PDDS, Hypertension, Lag time, Superdisintegrant, Press coated tablets, Polymers.

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ABSTRACT

In present study, pulsatile release tablets of Lercanidipine was prepared using press coating technique for chronotherapeutic management of hypertension. These systems are designed according to the circadian rhythm of the body that are to be dosed at bed time but show rapid and complete drug release after a lag time during early morning hours. The pulsatile tablets were prepared by applying a barrier layer on core tablets. The Lercanidipine core tablets were prepared by direct compression method, using crospovidone as superdisintegrant in different concentration range of 2% - 5% and the outer barrier layer was formulated with HPMC and Ethyl cellulose. Compatibility studies were carried out by FTIR for all the excipients showed that the polymers used were compatible with drug. Mixtures of different weight ratio of HPMC K4M and EC (150:50, 200:00, 100:100, 00:200, 150:50) were press coated over Lercanidipine core tablets to release the drug after a desired lag time of about 5 h. Prepared press coated tablets were evaluated for all characteristic test parameters. The effect of polymer on the lag time of drug release was investigated. Formulations C5 (150: 50) compression coated tablets achieved a burst release of Lercanidipine after 5 hr which is applicable for pulsatile drug delivery of Lercanidipine for hypertension. The stability study results revealed that there were no significant changes after 56 days.

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1. INTRODUCTION

Now-a-days, the emphasis of pharmaceutical researchers is turned towards the development of more efficacious drug delivery systems with already existing molecule [1]. Modified release dosage forms have a great importance in this regard. Such systems control the release pattern of drug, either with constant or variable rates drug is released with predetermined release rates. However, there are certain diseased conditions such as hypertension, bronchial asthma, myocardial infarction, rheumatic disease, arthritis, cancer, ulcers, diabetes, and hypercholestrolemia for which such a release pattern is not suitable. These conditions demand release of drug after a lag time that makes available the drug at the time of maximum need of the disease following the principles of chronotherapy. This condition can be achieved by pulsatile drug delivery system which is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after a predetermined off- release period i.e. lag time. A pulse has to be generated in such a way that a complete and rapid drug release is achieved after the lag time so as to match body's circadian rhythms with the release of drugs [2]. Lag time is defined as the time gap between when the dosage form is placed into an aqueous environment and the time at which the active ingredient begins to get released from the dosage form [3].

Blood pressure (BP) exhibits a diurnal variation with higher values during early morning (4.00-6.00 hr) and as the day progress; it shows lowest level during night. Conventional dosage forms are not completely effective in such case. It requires a specific type of delivery system which deliver the antihypertensive drug in higher amounts in early morning hours (i.e.at time of greatest need) and lower amounts at night (i.e.at the middle of sleep cycle when the need of drug is less).

Lercanidipine is an antihypertensive (blood pressure lowering) drug. It belongs to the dihydropyridine class of calcium channel blockers, lercanidipine blocks L-type calcium channels in the smooth muscle cells of blood vessels, relaxing them and thus lowering blood pressure. This drug has pKa value of 9.36. Hence, its main site of absorption is intestinal region. So to make out the maximum therapeutic benefit of drug and for effective chronotherapeutic management of hypertension, PDDS of lercanidinpine has been developed and evaluated to release the drug after the desired lag time of 5 hrs for providing the relief from hypertension during early morning hrs.

2 . MATERIALS

Lercanidipine was procured from Torrent Pharmaceuticals, excipients used viz. crospovidone, directly compressible, directly compressible microcrystalline cellulose, talc, magnism stearate, HPMC K4M, Ethyl cellulose, Xanthan gum were provided by Rayat institute of pharmacy, Railmajra SBS Nagar, Punjab.

3. METHOD

Compression coating technique is used to prepare pulsatile tablets. It consists of two steps:

- Preparation of lercanidipine core tablets using crospovidone as superdisintigrant.
- Preparation of compression coated pulsatile tablets by applying barrier layer of polymers on core tablet.

3.1 PREPARATION OF LERCANIDIPINE CORE TABLETS

The core tablets of Lercanidipine were prepared by direct compression method. Core tablets were formulated using various concentrations of super disintegrant and directly compressible excipients as describe in table 1. Accurately weighed quantity of lercanidipine, microcrystalline cellulose, crospovidone, talc and magnesium stearate were passed through 40# sieve and dry blended for 10 min. The resultant powder mixtures were compressed into tablets (average tablet weight = 80 mg) by using single station punch- tableting machine [4-5].

Table 1: Formulation of Drug Loaded Core Tablet

Formulation Ingredients	F1	F2	F3	F4
Lercanidipine (mg)	20	20	20	20
MCC (PH-102) (mg)	55.2	54.4	53.6	52.8
Crospovidone (%)	2	3	4	5
Talc (%)	2	2	2	2
Magnesium stearate (1%)	1	1	1	1
Net Weight (mg)	80	80	80	80

3.2 CHARACTERIZATION PARAMETERS

3.2.1 Fourier Transforms Infra Red Spectroscopy (FTIR)

The interference study was carried out using FTIR analysis. IR spectrum of mixture of drug – polymers i.e. Lercanidipine, ethyl cellulose and HPMC K4M was analysed between wavelength 4000 cm^{-1}- 400 cm^{-1}, no interaction was detected between Lercanidipine and exicipients . After analyzing FTIR study it was clear that the drug and polymers can be safely used in formulating pulsatile drug delivery system. The results are shown in Figure 1.

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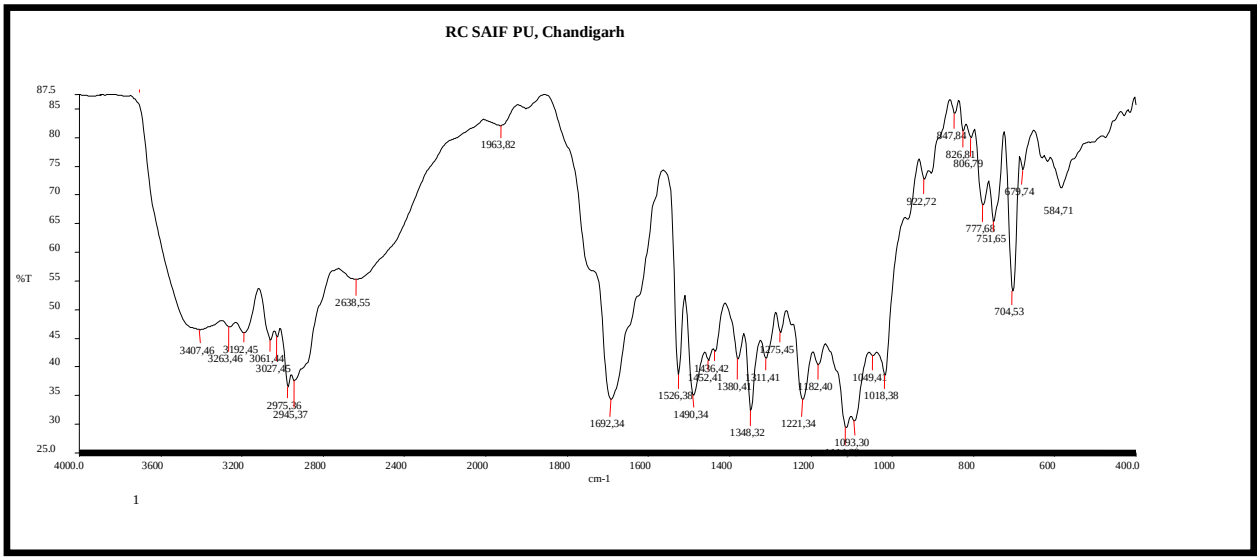

Figure 1:FTIR of Lercanidipine + Ethyl cellulose+ HPMC K4M

3.2.2 Pre Compression Parameters

The prepared powder blend was evaluated for various parameters like bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio [6]. The results are shown in table 3.

3.2.3 Post Compression Parameters

The prepared Lercanidipine core tablets were tested for weight variation, hardness, thickness, drug content, disintegration time, friability and in vitro dissolution study. The results are shown in table 4.

a. Weight variation test

Weighed individually 20 tablets and calculated the average weight. Not more than two of the individual weight deviate from the average weight by more than the percentage shown in the table and none deviates by more than twice that percentage IP official limit of percentage deviation of tablet.

b. Thickness

The thicknesses of tablets were determined by using screw gauge and the standard deviation was calculated. [7].

c. Hardness test

For each formulation, the hardness of tablets was determined using the Monsanto hardness tester. Three tablets were chosen randomly and tested for hardness. The average hardness of the tablets was noted [8].

d. Friability

Ten tablets were weighed and placed in the Roche Friabilator and apparatus was rotated at 25 rpm for 4 min. After revolution the tablets were dusted and weighed. The friability was calculated by the formula given below.

$$F = (1- Wo/W) \times 100$$

Where, Wo is the weight of the tablets before the test and W is the weight of the tablet after the test [9].

e. Disintegration test

The test of disintegration was carried out in disintegration test apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top, and held against a 10 mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of tablets, one tablet was placed in each tube and basket rack was positioned in a 1 liter beaker containing phosphate buffer pH 6.8 such that the tablet remains 2.5 cm below the liquid. The temperature of the buffer was maintained at 37±2ºC. The time taken for the complete disintegration of the tablets was noted [10].

f. Drug content

Ten tablets were powdered and the blend equivalent to 20 mg of Lercanidipine was weighed and dissolved in suitable quantity of phosphate buffer of pH 6.8. The solution was filtered, suitably diluted and the drug content was analyzed spectrophotometerically at 241 nm. Each sample was analyzed in triplicate [11].

g. In- Vitro Drug Release of Drug Loaded Core Tablet

In vitro drug release of Lercanidipine from compression coated tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml phosphate buffer pH 6.8. Temperature was maintained at 37 ± 0.5 ºC. The sped of rotation of paddle was set at 50 rpm. At a predetermined time interval of 1 min. 5 ml samples were withdrawn, filtered through Whatman filtered paper. Absorbance of solution was checked by UV spectrophotometer at 241 nm and drug release was determined from standard curve. The results are shown in table 5.

3.3 PREPARATION OF COMPRESSION COATED PULSATILE TABLETS

Coating of core tablets to provide lag time was done using two polymers. Different Formulations (C1-C4) of coating layer with ethyl cellulose and HPMC K4M were prepared for optimizing the desired lag time. Xanthan gum was added to improve the adhesion properties of the coating layer along with talc as glidant and magnesium stearate as lubricant. Required weight of coating powder was weighed and used in two steps. First half coating powder was filled into the die and core tablet was placed in the centre of die. Tablet was slightly pressed to fix the coating around and under the core tablet, then left amount of coating powder was filled in the die above the tablet surface and compressed by using 12 mm flat faced punch tooling. Table 2 shows different ratio of HPMC K4M and ethyl cellulose in the outer coating layer.

Table 2: Composition of Compression Coated Tablets

Formulation composition	C1	C2	C3	C4	C5
Core tablet formulation					
Lercanidipine (mg)	20	20	20	20	20
MCC (mg)	52.8	52.8	52.8	52.8	52.8
Crosspovidone (%)	5	5	5	5	5
Talc (%)	2	2	2	2	2
Magnesium Stearate (%)	1	1	1	1	1
Coating layer formulation					
HPMC: EC (mg)	50:150	200:00	100:100	00:200	150:50
Xanthan gum (mg)	20				

3.4 CHARACTERIZATION OF COMPRESSION COATED TABLET

The prepared compression coated tablets were evaluated for weight variation, thickness, hardness, friability, drug content and the results has been shown in table 6. Lag time determination and in-vitro dissolution study for coated tablets were also performed.

3.4.1 Lag time Determination by Rupture test

The lag time of pulsatile release tablets is defined as the time when the outer coating starts to rupture. It was determined visually by using USP dissolution testing apparatus II (900 ml buffer 37.0 ± 0.5 at 50 rpm). Initially tablets were subjected to dissolution in HCl buffer pH 1.2 for 2 hrs and after that media was changed to phosphate buffer pH 6.8. The time at which the outer coating layer starts to rupture was noted [12].The results have been shown in table 7.

4.2.2 *In-Vitro* Drug Release of Compression Coated Tablets

In-Vitro drug release of Lercanidipine from compression coated tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml HCl buffer of pH 1.2 which was replaced with phosphate buffer pH 6.8 after two hrs. Temperature was maintained at 37 ± 0.5 ºC. The speed of rotation of paddle was set at 50 rpm. At a predetermined regular time interval, 5 ml of samples were withdrawn filtered through Whatman

filter paper. Absorbance of solution was checked by UV spectrophotometer at 241 nm and drug release was determined from standard curve. The results have been shown in table 8.

4. STABILITY STUDY

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light and to establish a retest period for the drug substance or shelf life for the drug product and recommended storage conditions.

4.1 Protocol for Stability Study

a. Test design: The tablets were packed in aluminum foil and stored in stability chamber at accelerated conditions i.e. 40ºC/75% RH for a period of 56 days.

b. Test Criteria: The samples were withdrawn after the specified time interval i.e. 7, 14, 21, 28, 35, 42, 49 and 56 days respectively and were evaluated for the following parameters:

Physical Appearance (change in shape, discoloration)

Drug Content

5. RESULTS AND DISCUSSION

5.1 Pre compression characterization

The value of angle of repose for all the formulations was found between 27.33±0.78º to 29.56±0.03º. The bulk density and tapped density of blends for all the formulation determined and used to calculate Carr's index and Hausner's ratio values. The values for both the parameters were found in the range indicating optimum flow properties of the formulation blend. The values are given in table 3.

Table 3: Precompression Characterization of Powder Blend

Formulation code	Angle of repose (θ) ±SD	Bulk Density (g/cc) ± SD	Tapped Density (g/cc)) ± SD	Carr's Index (%) ± SD	Hausner's ratio ± SD
F1	28.39±1.43	0.374±0.042	0.437±0.027	11. 04±0.48	1.15±0.028
F2	27.33±0.78	0.365±0.018	0.424±0.044	12.21±0.58	1.11±0.014
F3	27.48±1.78	0.368±0.027	0.437±0.018	11.29±0.21	1.13±0.012
F4	29.56±0.03	0.381±0.002	0.458±0.030	13.12±0.47	1.16±0.045

5.2 Post compression characterization of core tablets

The weight of the core tablets was found between 79.71±2.52 to 81.33±1.56 mg. The percentage deviation for all the tablet formulations was found to be within the specified limits and hence all the formulations complied with the test for weight variation. Core tablets from all batches showed

acceptable thickness values in the range 3.07±0.06 to 3.11±0.04 mm. The hardness of the tablets was found to be ranging between 4.9±011 to 5.1±0.25 kg/cm^2. The friability of all the formulations was evaluated using Roche Friabilator. It was observed in range (0.189±0.03 to 0.312±0.01) indicating that the friability was within the prescribed limits. The tablets showed variation in the values of disintegration time due to different concentration of Superdisintegrant in the formulation ranging from 10.23±1.19 to 61.19±0.31 seconds. Drug content of all the formulations were found to have more than 96% of drug. The results are given in table 4. In- vitro drug release of Lercanidipine from core tablets was determined in phosphate buffer pH 6.8. The results are given in table 5.

Table 4: Post compression Characterization of Core Tablets

Formulation code	Weight variation (mg) ± SD	Thickness (mm) ± SD	Hardness (Kg/cm^2) ±SD	Friability (%) ± SD	Disintegration Time (s) ± SD	% Drug content
F1	79.71 ±2.52	3.07 ±0.06	4.9 ±0.15	0.312 ±0.01	61.19 ±0.31	96.25± 0.15
F2	80.57 ±1.24	3.11 ±0.04	5.0 ±0.32	0.272 ±0.06	57.34 ±1.17	96.76 ±0.02
F3	81.33 ±1.56	3.11 ±0.02	5.1 ±0.25	0.299 ±0.03	35.00 ±1.20	97.51 ±0.11
F4	80.67 ±2.12	3.10 ±0.02	4.9 ±0.11	0.189 ±0.03	10.23 ±1.19	98.34 ±0.07

Table 5: Data of % Cumulative Drug Released from Core Tablet

Time (min)	% Cumulative Drug Release			
	F1	F2	F3	F4
0	0	0	0	0
2	43.47	54.15	67.25	70.13
4	59.76	61.72	71.51	78.26
6	65.22	72.32	79.21	85.45
8	76.65	87.43	81.65	91.56
10	88.31	90.46	94.35	95.67
12	88.49	90.51	94.61	95.88
15	88.51	91.12	94.67	96.06

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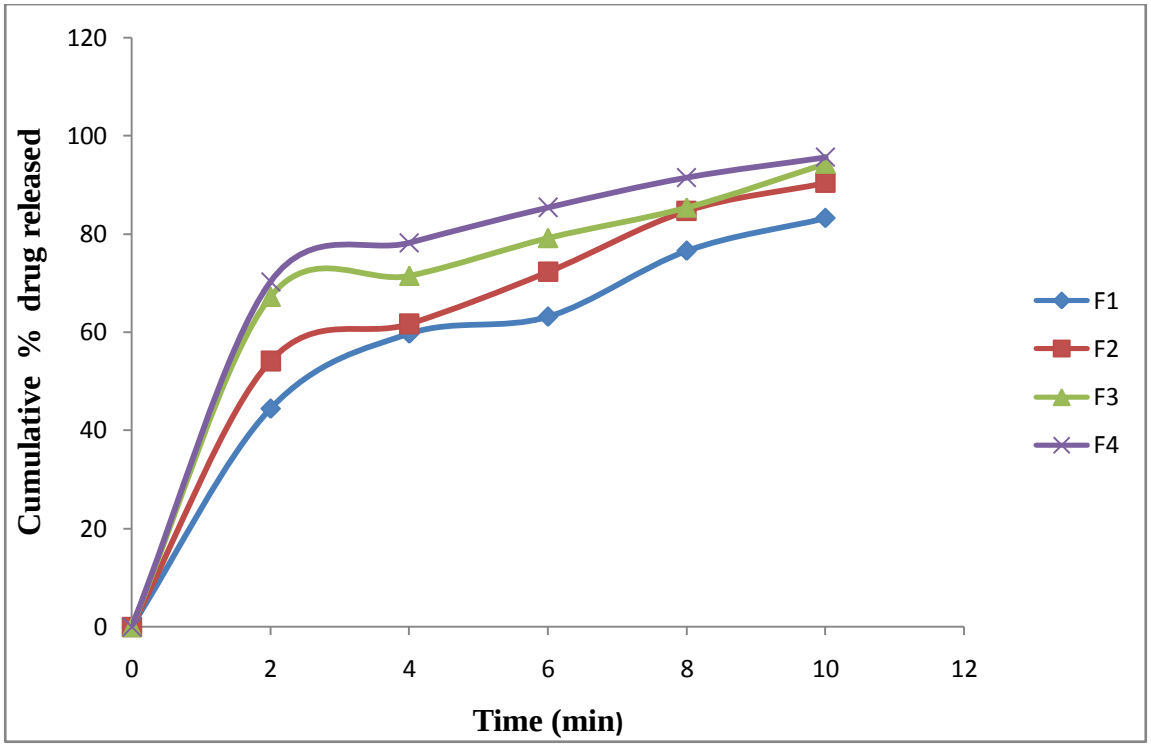

Figure 2: Graph Showing % Cumulative Released from Core Tablets

5.3 Characterization of Compression coated Tablets

The compression coated tablets were evaluated for weight variation, thickness, hardness, friability, drug content. The weight of the coated tablets was found between 300.46±1.10 and 302.00±1.25 mg depending upon the weight of coating layer. Coated tablets from all the batches showed uniform thickness values in the range of 4.91±0.01 to 5.27±0.04 mm. The hardness of the tablets was found to be ranging between 6.0±0.13 to 6.5±0.02 kg/cm^2. The friability of all the formulation was evaluated using Roche Friabilitor and the friability of tablets was found to be ranging 0.54±0.01 to 1.00±0.05 %. The observed values have been shown in table 6.

Table 6: Results of Evaluation Parameters of Compression Coated Tablets

Formulation code	Weight variation (mg)±SD	Hardness (kg/cm^2)±SD	Thickness (mm)±SD	Friability (%)±SD
C1	301.70±1.44	6.5±0.02	5.24±0.05	0.67±0.08
C2	300.53±1.67	6.0±0.15	5.19±0.02	0.54±0.01
C3	302.11±1.10	6.5±0.00	4.91±0.01	0.83±0.05
C4	302.00±1.25	6.0±0.35	5.13±0.05	1.00±0.05
C5	300.46±1.15	6.0±0.13	5.27±0.04	0.78±0.09

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To determine the period of no drug release lag time of compression coated tablets was observed. Each formulation (C1-C5) showed distinct lag time as given in table 7. In- vitro drug release of Lercanidipine from compression coated tablets was determined using dissolution test apparatus. The test was performed at 37± 0.5ºC using HCl buffer (pH1.2) replaced with phosphate buffer (pH 6.8) after two hrs. Absorbance was checked by UV of solution was checked by using spectrophotometer at 241nm. The results are given in table 8.

Table 7: Lag time of Lercanidipine Compression Coated Tablets

Formulation Code	Lag Time (hrs)
C1	4
C2	2.5
C3	6.5
C4	1.5
C5	5

When, HPMC K4M used alone (C2), showed lag time of only 2.5 hr. This is probably because of hydration and swelling of outer barrier layer or water penetration through outer barrier layer, it formed a mechanically weak sweallable layer, which could rupture easily upon exposure to the dissolution medium and resulting development of internal pressure within tablet core and drug release was initiated [13]. With Ethylcellulose alone (C4), showed lowest lag time as compared to any weight ratio of mixture of HPMC K4M and EC. Ethylcellulose is semipermeable in nature, although it is naturally insoluble in water. Water penetrates faster the coating layer of the core tablet when used alone. After hydration of core, the drug was released [14]. When ethyl cellulose was used in combination with HPMC K4M, it causes synchronization between swelling and erosion of the polymer in maintaining a constant stable gel layer for a long period of time. Upon contact with dissolution medium HPMC K4M hydrated and formed compact with ethylcellulose. The hydrophobicity of ethylcellulose retards the hydration of HPMC K4M. Therefore dissolution medium did not penetrate the outer coating layer, but the coating eroded slowly. The active erosion rate of outer barrier layer depends upon the composition of the formulation which determines the lag time of press coated tablets [15].

Table 8: Data of % Cumulative Drug Release Study from tablet Formulations Coated with HPMC K4M and Ethyl Cellulose

Time (min)	% Cumulative Drug Release Study of Lercanidipine Compression Coated Tablets of Formulation				
0	0	0	0	0	0
30	0	0	0	0	0
60	0	0	0	0	0
90	0	0	0	0	0
120	0	0	0	93.23	0
150	0	94.15	0	93.88	0
180	0	94.67	0	94.67	0
210	0	94.79	0		0
240	0		0		0
270	94.34		0		0
300	95.78		0		0
330	95.29		0		94.23
340			0		95.34
350			92.16		95.78
360			93.54		96.32
370			93.68		96.71

The period of lag time was different and dependent on the weight ratio of mixture of HPMC K4M and EC. The results indicate that the lag time of a press coated tablet can be modulated by combining EC with HPMC K4M in different weight ratio. The system was found to be satisfactory in terms of release of the drug after a predetermined lag time of 5-6 hrs and thus the dosage forms can be taken at bedtime, so, that the content will be released in the morning hours, i.e., at the time of symptoms of hypertension. Lag time can be controlled by adjusting the mixture containing different weight ratio of HPMC K4M and EC.

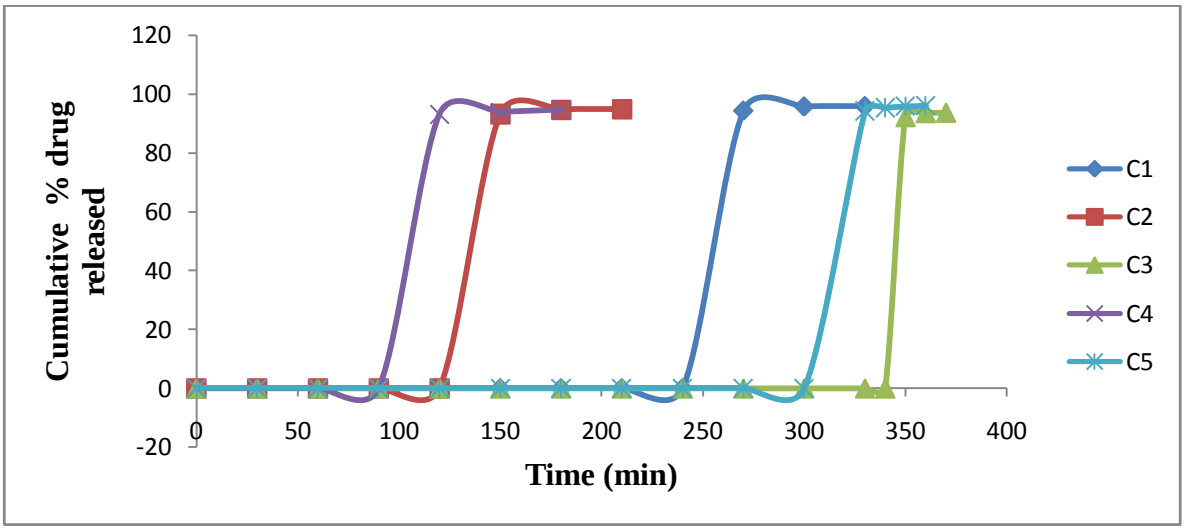

Figure 3: Graph Showing Cumulative % Drug Released from Coated Tablets

A plot between % cumulative drug released and time (Figure 3) showed that formulations coated with HPMC K4M and EC provided rapid and complete drug released after a lag time, which is applicable for pulsatile drug delivery.

Among all the formulation C5 containing HPMC K4M: EC in 150:50 was found to provided better integrity, lag time of 5 hrs and good dug release profile which is desirable for chronotherapeutic treatment of hypertension by Lercanidipine and hence selected for conducting the stability study. The formulation C5 was subjected to stability study at 40 ºC and 75% RH for 56 days. No changes in shape and colour were observed. The results for drug content are shown in table 9.

Table 9: Observation of Drug content during Stability Study

Time (days)	Accelerated Conditions	
	Physical Appearance	Drug Content
0	+	98.54± 0.26
7	+	98.31±0.47
14	+	98.04±0.09
21	+	97.67±0.17
28	+	97.50±0.38
35	+	97.35±0.03
42	+	97.12±0.21
49	+	96.73±0.07
56	+	96.41±013

(+ indicated no change in physical appearance)

6. CONCLUSION

The pulsatile type release of Lercanidipine is successfully achieved by press coating technique using combination of time dependent rupturable and erodible polymers. Ethyl cellulose was chosen because of its rupturable behavior and HPMC K4M was chosen because of its swelling and erodible behavior. Lercanidipine press coated tablets were prepared using different weight ratios (W/W) of HPMC K4M and EC. The lag time found to be influenced by different weight ratios of polymer. The formulation C5 was found to be satisfactory in terms of burst release of the drug after a predetermined lag time of 5 hrs. Hence the presented system was designed to be dosed at bed time to achieve a rapid and complete drug release after desired lag time during early morning hours which not possible by administering conventional dosage form.

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