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Volume 2, Issue 5, 2017**RESEARCH ARTICLE****DESIGN AND EVALUATION OF CHRONOTHERAPEUTIC PULSATILE DRUG DELIVERY SYSTEM OF CILNIDIPINE****Nweje-Anyalowu Paul C¹, Anyalogbu Ernest AA², White Alalibo Jim³**¹Department of Biochemistry, Clifford University, Owerri, Abia State Nigeria.²Department of Biotechnology, Federal University of Technology, Owerri, Imo State, Nigeria.³Department of Laboratory Services, University of Abuja Teaching Hospital, Abuja, Nigeria*Corresponding Author's Email: paul.nwejeanyalowu.77852@unn.edu.ngDOI: <http://doi.org/10.22270/ujpr.v2i5.R4>

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ABSTRACT:

At present scenario the drug regimen based on circadian rhythm is recently gaining much attention worldwide by researchers. Justification behind it is that, there are various diseases like asthma, hypertension, and arthritis show circadian variation that demand time scheduled drug release for effective drug action. A chronodelivery system, based on biological rhythms, is a state-of-the-art technology for drug delivery. The aim of present work is formulate and evaluate a press coated pulsatile release tablets of Cilnidipine using an admixture of hydrophilic polymer i.e. hydroxypropyl methyl cellulose (HPMC) and pH sensitive polymers (ethyl cellulose, eudragit S-100) in order to achieve a predetermined lag time for chronopharmacotherapy of Hypertension. Cilnidipine is the novel calcium antagonist accompanied with L-type and N-type calcium channel blocking function used for the treatment of hypertension. The tablets prepared were evaluated for different properties like bulk density, tapped density, Angle of repose and Carr's index), hardness, thickness, weight variation, friability, drug content uniformity and *in vitro* drug release study.

Keywords: Chronotherapy, pulsatile, hypertension, circadian variation, press coated tablets.

INTRODUCTION

A pulsatile release profile is characterized by a lag time followed by rapid and complete drug release. Pulsatile drug delivery systems are designed according to the circadian rhythm of the body¹. Chronomodulated system is also known as pulsatile system or sigmoidal release system related to biological rhythms. Circadian rhythm regulates many functions in human body like metabolism, physiology, behavior, sleep pattern, hormone production. Many diseases such as cardiovascular, asthma, peptic ulcer, arthritis etc. follow the body's circadian rhythm and shows circadian pattern². These conditions could be taken by timing and adjusting the administration of drugs according to the circadian rhythm of the disease. These systems are designed in a manner that the drug is available at the site of action at the right time in the right amount³. Disease conditions where constant drug levels are not preferred but need a pulse of therapeutic concentration in a periodic manner acts as a push for the development of pulsatile drug delivery system. A time delayed release profile is characterized by a lag time followed by rapid and complete drug release⁴.

Cilnidipine is the novel calcium antagonist accompanied with L-type and N-type calcium channel blocking function. Cilnidipine decreases blood pressure and is used to treat hypertension⁵. Due to its

blocking action at the N-type and L-type calcium channel, Cilnidipine dilates both arterioles and venules, reducing the pressure in the capillary bed. Cilnidipine is vasoselective and has a weak direct dromotropic effect, a strong vasodepressor effect, and an arrhythmia-inhibiting effect⁶. Hypertension is the most powerful risk factor for the cardiovascular diseases, including stroke, coronary artery disease, heart failure, chronic kidney disease, and aortic and peripheral arterial diseases.

Morning hypertension is a condition characterized by high blood pressure ($\geq 135/85$ mm Hg) in the morning and controlled levels throughout the day⁷. Heart attacks and stroke usually occur in the morning because of morning hypertension. Between 4:00AM and noon, the body releases certain hormones that boost energy and increase morning alertness, but this also results in a sharp increase in blood pressure⁸.

So for effective treatment such type of drug delivery system required which provide minimum amount of drug release at night highest at morning. Through pulsatile delivery system this type of release can be provide. Thus, this study focus on the development of press coated pulsatile tablets of Cilnidipine for providing the relief from hypertension deliver the drug at specific time as per pathophysiological needs of the disease and improvement of therapeutic efficacy and patient compliance.

MATERIAL AND METHOD

Material

Cilnidipine was obtained from Swiss pharma ltd, Lagos, Nigeria. Lactose was obtained from Givanas Nigerian Ltd, microcrystalline cellulose, Crospovidone, Magnesium stearate and dicalcium phosphate were obtained from Chemiron International Limited, Lagos, Nigeria. HPMC, EC and talc were obtained from Avro Pharma Limited, Lagos, Nigeria Eudragit S 100 was obtained from Archy Pharmaceutical Nigeria Limited. All other chemicals and reagents used were either of analytical or pharmaceutical grades.

Tablet Manufacturing Method

1. Formulation of core tablets by direct compression

The core tablets containing Cilnidipine were prepared by using the composition shown in table 1. All excipients were mixed for 25 min and passed through a 40 mesh size sieve and directly compressed in to 70 mg tablets using 6 mm round flat punches on a rotary tablet machine⁹.

2. Preparation of press coated pulsatile tablets

The core tablets were press coated with polymer blend. Polymer blend was composed of HPMC, EC and Eudragit S 100 in different concentrations. Half of the coating material was placed in the die cavity, the core tablet was carefully positioned in the centre of the die and cavity was filled with the other half of the coating material. Coating materials was compressed around the core tablet using of 10mm punch¹⁰. The compositions were as shown in table 2.

EVALUATION OF CORE TABLETS

A. Precompressional studies

1. Determination of angle of repose

The angle of repose of blend was determined by the funnel method. The accurately weight blend was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the blend. The blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation¹¹.

$$\tan \theta = \frac{h}{r}$$

Where, h and r are the height and radius of the powder cone.

2. Determination of bulk density and tapped density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2gm of blend previously shaken to break any agglomerates formed, then it was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations¹².

$$LBD = \frac{\text{Weight of the granules}}{\text{Untapped Volume of the packing}}$$

$$TBD = \frac{\text{Weight of the granules}}{\text{Tapped volume of the packing}}$$

3. Determination of Compressibility Index

The Compressibility Index of the blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down¹³. The formula for Carr's Index is as below:

$$\text{Carr's Index (\%)} = \frac{TBD - LBD}{TBD} \times 100$$

4. Hausner's Ratio

Hausner's Ratio was determined by following equation¹⁴:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

B. Post-compressional studies:

1. Uniformity of thickness

Thickness of Cilnidipine tablets were measured using a calibrated dial calipers. Three tablets of each formulation were picked randomly and dimensions determined. It is expressed in mm and standard deviation was also calculated¹⁵.

2. Weight variation test

Twenty Cilnidipine tablets were selected randomly from each batch and weighed individually to check for weight variation¹⁶.

3. Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Hardness of Cilnidipine tablets was determined using a validated dial type hardness tester. It is expressed in kg/cm². Three tablets were randomly picked from each batch and analyzed for hardness. The mean and standard deviation were also calculated¹⁷.

4. Friability

Twenty Cilnidipine tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes¹⁸. After revolutions the tablets were weighed again. The percentage friability was measured using the formula,

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

5. Drug content

Three Cilnidipine tablets were weighed individually and triturated. Powder equivalent to the average weight of the tablet was weighed and drug was extracted in water for 6 hours. The solution was filtered through 0.45μ membrane. The absorbance was measured at 291 nm after suitable dilution¹⁹.

6. Lag time of coated tablets

The lag time of pulsatile release Cilnidipine tablets is defined at the time when the outer coating starts to rupture. It was determined visually by using USP dissolution testing apparatus II (900ml buffer 37.0±0.5°C, 50 rpm). Coated Cilnidipine tablets were evaluated for lag time in pH 6.8 and 7.4 phosphate buffer respectively. Coated tablets were placed in 900 ml of above mentioned buffers, agitated at 75 rpm and maintained at 37±0.5°C. The time taken for outer coating to rupture was monitored and reported as lag time²⁰.

7. Dissolution studies of the coated tablets

Drug release study of coated Cilnidipine tablets was carried out using USP XXIII dissolution test apparatus I. Initially tablets were placed in 900 ml of 0.1 N HCl for 2 hours maintained at $37 \pm 0.5^\circ\text{C}$, 75 rpm followed by pH 6.8 phosphate buffer for 3 hours and pH 7.4 for 5 hours. Aliquots of predetermined quantity were collected manually at definite time intervals replacing with fresh buffer to maintain sink condition and analyzed for drug content using a UV-visible spectrophotometer at λ_{max} of 291 nm^{21} .

RESULTS AND DISCUSSION

In the present study, an attempt was made to design pulsatile drug delivery system of Cilnidipine for the effective treatment early morning hypertension. The pulsatile drug release tablets were prepared by compression coating method and consisted of two different parts: a core tablet, containing the active ingredient and an erodible outer coating layer of polymer. Based on preliminary trials, the core tablets of Cilnidipine were prepared by using different ingredients including microcrystalline cellulose, crospovidone, lactose, magnesium stearate, dicalcium phosphate and talc by direct compression technique.

Results of the pre-compression parameters performed on the blend for batch (Table 3). The results of Hausner's ratios were found to in the range of 1.188 ± 0.11 to 1.213 ± 0.09 .

The result of angle of repose ranged between 25.26 ± 0.07 to 28.32 ± 0.15 . The values are less than 30, indicate good flow properties of powder base. This was further supported by lower compressibility index values. Generally, compressibility index values up to 15% results in good to excellent flow properties. To obtain desired lag time before drug release, the core tablets were coated with varied ratio of HPMC, EC, Eudragit S 100 polymers to achieve barrier properties by compression coating technique. The compression coated tablets were evaluated for weight variation, thickness, hardness, friability, drug content and lag time.

The hardness of tablets of all the formulations ranged between 4.93 ± 0.08 to $5.96 \pm 0.11 \text{ kg/cm}^2$.

The formulation CPT1 showed a comparatively high hardness value of $5.96 \pm 0.11 \text{ kg/cm}^2$. This may be due to presence of higher amount of ethyl cellulose, which is generally responsible for more hardness. The percentage friability of tablets of all the formulations ranged between 0.68 ± 0.21 to 0.82 ± 0.06 . Percentage friability for all the formulations was below 1% indicating that the friability is within the prescribed limits. The weight variation of tablets of all the formulations ranged between 242.42 ± 0.12 to 322.34 ± 0.09 . The average percentage deviation of all the tablet formulations was found to be within the limit, and hence all the formulations passed the test for uniformity of weight as per the official requirements.

Satisfactory uniformity in drug content was found among different batches of tablets, and percentage of drug content was more than $97.42 \pm 0.12 \%$.

Lag time of all the formulations was found between 255.47 ± 0.13 to 300.58 ± 0.14 . A Cumulative percent

drug released versus time showed in (Figure 1) the dissolution rate was inversely proportional to the coated level applied. The quick release was observed in tablets containing ethylcellulose, it may be due to high solubility of EC at pH 6.8. This polymer characteristic gives to the matrix a quick gel erosion rate and a high erosion degree of the overall system. Maximum drug release 94.39% was shown by the tablets of batch CPT1 and lowest release 73.54% by the tablets of batch CPT3 in the 10hrs study.

CONCLUSION

A satisfactory attempt was made to develop pulsatile release Cilnidipine tablets using pH sensitive polymers (ethyl cellulose, eudragit S-100) and swellable hydrophilic polymer (HPMC) to mimic the circadian rhythm. Prepared pulsatile drug delivery systems were evaluated for hardness, friability, weight variation, drug content uniformity, *in vitro* drug release.

Based on different evaluation parameters formulation of batch CPT1 was concluded as an optimum formulation. The system released the drug rapidly after a certain lag time due to the rupture of the polymers film. Pulsatile release Cilnidipine tablets can be taken at bedtime so that the content will be released in the morning hours *i.e.* at the time of symptoms. From the above results, it can be concluded that the prepared pulsatile drug delivery system can be considered as one of the promising formulation technique for chronotherapeutic management of hypertension.

CONFLICT OF INTERESTS

There are no conflicts of interest.

REFERENCE

1. Parmar RD, Parikh RK, Vidyasagar G, Patel DV, Patel CJ, Patel BD. Pulsatile drug delivery systems: an overview. *Int J pharm sci nanotech*. 2009; 2(3):605-614.
2. Korner A, Larsson A, Andersson A, Piculelle L. Swelling and polymer erosion for polyethylene oxide tablets of different molecular weights polydispersities. *J Pharm Sci*. 2009; 99:1225-1238.
3. Hong-Liang Lin, Shyr-Yi Lin, Ying-Ku Lin, Hsiu-O Hoa, Yo-Wen Lo and MingThauSheu. Release characteristics and *in vitro-in vivo* correlation of pulsatile pattern for a pulsatile drug delivery system activated by membrane rupture via osmotic pressure and swelling. *Europ J Pharm Biopharm*. 2008; 70:289– 301.
4. McConville J, Ross A, Florence A, Stevens H. Erosion characteristics of an erodible tablet incorporated in time delayed capsule device. *Drug Dev. Ind. Pharm*. 2005; 31:35-42.
5. Minami J; Kawano Y, Makino Y, Matsuoka H, Takishita, S. Effects of cilnidipine, a novel dihydropyridine calcium antagonist, on autonomic function, ambulatory blood pressure and heart rate in patients with essential hypertension". *British J Clin Pharmacol*. 2017; 50 (6): 615–620.
6. Shetty R; Vivek G; Naha K; Tumkur A, Raj A, Bairy KL. Excellent Tolerance to Cilnidipine in Hypertensives with Amlodipine - Induced Edema. *North American J Med Sci*. 2017; 5 (1): 47–50.
7. Matsui Y, Eguchi K, Shibasaki S, Ishikawa J, Hoshida S, Pickering TG, Shimada K, Kario K. Effect of doxazosin on the left ventricular structure and function in morning hypertensive patients: the Japan Morning Surge 1 study. *J Hypertens*. 2008; 26:1463–1471.

8. Marfella R, Siniscalchi M, Nappo F, Gualdiero P, Esposito K, Sasso FC, Cacciapuoti F, Di Filippo C, Rossi F, D'Amico M, Giugliano D. Regression of carotid atherosclerosis by control of morning blood pressure peak in newly diagnosed hypertensive patients. *Am J Hypertens*. 2005; 18:308–318.
9. Andrea Gazzaniga, Luca Palugan, Anastasia Foppoli, Maria EdvigeSangalli. Oral pulsatile delivery systems based on swellable hydrophilic polymers. *European J Pharma Biopharm*. 2008; 68: 11– 18.
10. Janugade BU, Patil SS, Patil SV, Lade PD. Formulation and evaluation of press coated montelukast tablets for pulsatile drug delivery system. *Int J Chem Tech Research*. 2009; 1(3): 690-691.
11. Hiroyuki M, Yutaka O, Masato I, Tomoaki H, Katsuhide T. Formulation approach for nicorandil pulsatile release tablet. *Chem Pharm Bull*. 2008; 56(4):464-467.
12. Gandhi SD, Pandya PR, Jani GK, Upadhyay NN, Nagaich U. Formulation development and evaluation of colon targeted tablets of Secnidazole for the treatment of amoebiasis. *Int J Pharm Sci Rev Res*. 2010; 5(3):64-71.
13. Bauskar M, Nandedkar S, Wagh R. Formulation, design and optimization of pulsatile release tablet of Doxofylline with swelling and erodible layers for treatment of nocturnal asthma. *Int J Pharm Pharm Sci*. 2012; 3(5):218-223.
14. Lin SY, Kawashima Y. Current status and approaches to developing press-coated chronodelivery drug systems. *J Control Release*. 2012; 157:331-53.
15. Singh S, Koland M. Formulation and evaluation of pulsatile drug delivery systems of glipizide for the management of type-II diabetes mellitus. *J Drug Del Therap*. 2016; 6:11-18.
16. Akila RM, Sharma B. Chronotherapeutic formulation of metformin hydrochloride. *Der Pharmacia Sinica*. 2013; 4:67-71.
17. Janugade BU, Patil SS, Patil SV, Lade PD. Press coated tablet of Montelukast sodium. *Int J chem Tech res*. 2009; 1(3): 690-691.
18. Dandale SS, Deshmane SV, Biyani KR. Formulation and evaluation of pressed coated pulsatile tablet containing nifedipine. *Int J Biol Pharm Res*. 2013; 4(7): 471-474.
19. Efentakis M, Koligliati S, Vlachou M. Design and evaluation of a dry coated drug delivery system with an impermeable cup, swellable top layer and pulsatile release. *Int J Pharm*. 2006; 311:147–156.
20. Kikuchi A, Okano T. Pulsatile drug release control using hydrogels. *Adv Drug Deliv Rev*. 2002; 54:53-77.
21. Igwe J Chibueze, Emenike IV, Oduola AR. Formulation and evaluation of Finasteride sustained-release matrix tablets using different rate controlling polymers, *Univ J Pharm Res*. 2016; 1(2): 25-31.

Table 1: Composition of Cilnidipine core tablets

Ingredients	Quantity (mg)
Cilnidipine	50
Microcrystalline cellulose	90
Crospovidone	3
Lactose	30
Magnesium stearate	4
Dicalcium phosphate	90
Talc	5
Total	272

Table 2: Compression coat formula for different Cilnidipine tablet batches

Ingredients (mg)	Batch Code			
	CPT1	CPT2	CPT3	CPT4
Core tablet	272	272	272	272
HPMC	40	60	80	100
EC	40	60	80	100
Eudragit S 100	40	60	80	100

Table 3: Pre compression parameters for coating materials

Batch code	Bulk density (LBD)	Tapped density (TBD)	Carr's index	Hausner's ratio	Angle of repose (degree)
CPT1	0.506± 0.06	0.603± 0.08	16.08± 0.06	1.191± 0.15	25.26± 0.07
CPT2	0.513± 0.25	0.614± 0.11	16.4± 0.09	1.196± 0.08	26.03± 0.13
CPT3	0.526± 0.18	0.625± 0.24	15.8± 0.11	1.188± 0.11	28.32± 0.15
CPT4	0.543± 0.09	0.652± 0.33	16.7± 0.08	1.213± 0.09	27.51± 0.08

Table 4-Post compression parameters for coated tablets

Batch code	Hardness (Kg/cm ²)	Thickness (mm)	% Friability	Weight variation	% Drug content	Lag Time (min)
CPT1	5.96± 0.11	4.72± 0.08	0.75± 0.12	273.25± 0.09	97.42± 0.12	255.47± 0.13
CPT2	4.93± 0.08	5.24± 0.06	0.81± 0.13	242.42± 0.12	99.21± 0.06	278.34± 0.07
CPT3	5.25± 0.06	5.31± 0.16	0.82± 0.06	311.51± 0.15	98.67± 0.21	280.47± 0.09
CPT4	4.98± 0.21	5.62± 0.12	0.68± 0.21	322.34± 0.09	98.72± 0.13	300.58± 0.14

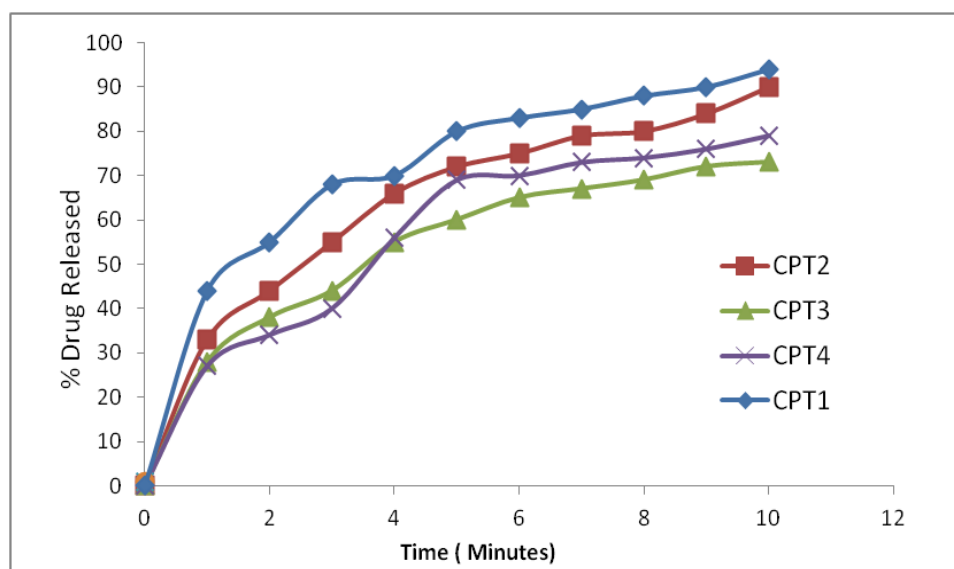


Figure-1: Cumulative percentage drug release of coated tablets of Cilnidipine



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