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RESEARCH ARTICLE

DESIGN AND EVALUATION OF CHRONOTHERAPEUTIC PULSATILE DRUG DELIVERY SYSTEM OF CILNIDIPINE

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Abstract

Objectives: Cilnidipine is the novel calcium antagonist accompanied with L-type and N-type calcium channel blocking function used for the treatment of hypertension. The aim of present work is formulate and evaluate a press coated pulsatile release tablets of Cilnidipine using an admixture of hydrophilic polymers in order to achieve a predetermined lag time for chronopharmacotherapy of Hypertension.
Methods: The pulsatile drug release tablets were prepared by compression coating method. 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.
Results: All formulations have shown good flow properties. The hardness of tablets ranged between 4.93±0.08 to 5.96±0.11 kg/cm^2, percentage friability of tablets ranged between 0.68±0.21 to 0.82±0.06. Maximum drug release was found to be 94.39%.
Conclusion: Study concludes that the prepared pulsatile drug delivery system can be considered as one of the promising formulation technique for delivery of Cilnidipine. Formulation of batch CPT1was found to be optimum.
Keywords: Chronotherapy, circadian variation, hypertension, press coated tablets, pulsatile.

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 body[1]. 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 pattern[2]. 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 amount[3]. 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 release[4].
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 hypertension[5]. 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 effect[6]. 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 (≥135/85 mm Hg) in the morning and controlled levels throughout the day[7]. Heart attacks and stroke usually occur in the morning because of morning hypertension. Between 4:00 AM and noon, the body releases certain hormones

that boost energy and increase morning alertness, but this also results in a sharp increase in blood pressure[8]. 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.

MATERIALS AND METHODS

Cilnidipine was obtained from Swiss pharma ltd, Lagos, Nigeria. Lactose was obtained from Givanas Nigerial Ltd, microcrystalline cellulose was 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

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 machine[9].

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

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 punch[10]. The compositions are as shown in Table 2.

Evaluation of core tablets

Precompressional studies

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[11].

Table 2: Compression coat formula for different Cilnidipine tablet batches.

Ingredients (mg)	Batch Code			
	CPT 1	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

Determination of bulk density and tapped density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 gm 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[12].

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 down[13].

Hausner's Ratio

Hausner's Ratio was determined by the ration of tapped and bulk density[14].

Post-compressional studies:

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 calculated[15].

Weight variation test

Twenty Cilnidipine tablets were selected randomly from each batch and weighed individually to check for weight variation[16].

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/cm^2. Three tablets were randomly picked from each batch and analyzed for hardness. The mean and standard deviation were also calculated[10].

Friability

Twenty Cilnidipine tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were weighed again[10].

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 0.45 µ membrane. The absorbance was measured at 291 nm after suitable dilution[10].

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 (900 ml 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 time.

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±0.5°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[11].

Statistical analysis

Experimental results were expressed as mean±SD. Student's *t*-test and one-way analysis of variance (ANOVA) were applied to check significant differences in drug release from different formulations. Differences were considered to be statistically significant at $p<0.05$.

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.

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

This was further supported by lower compressibility index values. Generally, compressi-bility 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±0.11 kg/cm^2. The formulation CPT1 showed a comparatively high hardness value of 5.96±0.11 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.

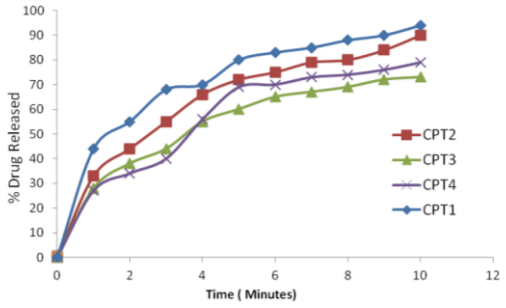

Figure 1: Cumulative percentage drug release of coated tablets of Cilnidipine.

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±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 10 hrs studies.

CONCLUSIONS

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. 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.

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AUTHOR'S CONTRIBUTION

Nweje-Anyalowu PC: writing original draft, methodology. **Anyalogbu EAA:** formal analysis, data curation, conceptualization. **Jim WA:** writing, review and editing, methodology. All the authors approved the finished version of the manuscript.

DATA AVAILABILITY

Data will be made available on request.

CONFLICT OF INTERESTS

None to declare.

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