DESIGN AND EVALUATION OF CHRONOTHERAPEUTIC PULSATILE DRUG DELIVERY SYSTEM OF CILNIDIPINE

Nweje-Anyalowu Paul C, Anyalogbu Ernest AA, White Alalibo Jim

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/cm², 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. 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. 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. 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. 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. 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. 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. 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 pressure. 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 Niger 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.

Table 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 machine.

2. Preparation of press coated pulsatile tablets
The core tablets were 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. The compositions are as shown in Table 2.

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           |

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...
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.

#### 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 0.1N 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.

### 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/cm²) | 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   |

#### 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 be 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±0.11 kg/cm². The formulation CPT1 showed a comparatively high hardness value of 5.96±0.11 kg/cm². 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±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...
ethyelcellulose, 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.

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.

AUTHOR’S CONTRIBUTION
The manuscript was carried out, written, and approved in collaboration with all authors.

CONFLICT OF INTERESTS
There are no conflicts of interest.

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