FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF CELECOXIB

P. Sai Priyanka*, V. Hemalatha, P. Pravin Sri Kumar, M. Ranga Lakshmi Naidu

Department of Pharmacy, St. Mary’s Group of Institutions Guntur, Chebrolu (M), Guntur (dt), Andhra Pradesh, India-522212.

ABSTRACT
The Aim of the present work is to formulate and evaluate an oral pulsatile drug delivery system to achieve time release of celecoxib, based on Chronopharmaceutical approach as NSAIDS. Pulsatile delivery system is capable of delivering drug when and where it required most. Time-delayed tablets, designed to release drug after a predictable lag time, are intended for oral chronotherapy. The basic design consists of a core tablets prepared by wet granulation method. The tablets were coated with an inner swellable layer containing HPMC K100M, guar gum, xanthan gum. The prepared pulsatile tablets were evaluated for the drug content, thickness and in-vitro release profile, etc. In-vitro release profiles of pulsatile device during six hours studies were found to have very good sustaining efficacy. During the first five hours it shows minimum drug release and at the end of six hours immediate release was observed. Increasing the level of the rupturable layer increased mechanical strength and retarded the water uptake and thus prolonged the lag time. Stability studies proved that coating of tablets seems to decrease the effect of temperature and moisture on the degradation of celecoxib. The programmable pulsatile release has been achieved from tablet over a 7-8 hr period, consistent with the demands of chronotherapeutic drug delivery.

KEYWORDS: Pulsatile Drug Delivery; Celecoxib, Sodium, Starch Glycollate, Lactose, Talc, Magnesium Stearate, Crosspovidone, Croscarmellose Sodium, HPMC K100M.
INTRODUCTION
New global trends in drug discovery and development in this century, the pharmaceutical industry is caught between pressure to keep prices down and the increasing cost of successful drug discovery and development. In the form of an NDDS, an existing drug molecule can “get a new life” thereby increasing its market value and competitiveness and extending patent life.

Among modified-release oral dosage forms, increasing interest has currently turned to systems designed to achieve time specific (delayed, pulsatile) and site-specific delivery of drugs. In particular, systems for delayed release are meant to deliver the active principle after a programmed time period following administration. These systems constitute a relatively new class of devices the importance of which is especially connected with the recent advances in chronopharmacology. It is by now well-known that the symptomatology of a large number of pathologies as well as the pharmacokinetics and pharmacodynamics of several drugs follow temporal rhythms, often resulting in circadian variations. Therefore, the possibility of exploiting delayed release to perform chronotherapy. The is quite appealing for those diseases, the symptoms of which occur mainly at night time or in the early morning, such as bronchial asthma, angina pectoris and rheumatoid arthritis. The delay in the onset of release has so far mainly been achieved through osmotic mechanisms, hydrophilic or hydrophobic layers, coating a drug-loaded core and swellable or erodible plugs sealing a drug containing insoluble capsule body.[20] Delivery systems with a pulsatile pattern are receiving increasing interest for the development of dosage forms, because conventional systems with a continuous release are not ideal. Most conventional oral controlled release drug delivery systems release the drug with constant or variable release rates. A pulsatile release profile is characterized by a time period of no release (lag time).

Fig.1 Release mechanism of pulsatile drug delivery system.
Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms and to reduce numbers of colon and rectum polyps in patients with familial adenomatous polyposis. It is marketed by Pfizer under the brand name Celebrex. In some countries, it is branded Celebra. Celecoxib is available by prescription in capsule form.

**MATERIALS AND METHODS**

Celecoxib, HPMCK 100 M obtained as gift sample from Gen Pharma International Pvt Ltd, Pune India, all other ingredients used was of analytical grade.

**DRUG CHARACTERIZAION**

**UV Spectroscopy**

100mg of Celecoxib was accurately weighed and transferred into 100ml volumetric flask. It was dissolved and diluted to volume with 0.1N Hcl to give stock solution containing 1000µg/ml. The standard stock solution was then serially diluted with 0.1N Hcl to get 2 to 10µg/ml of Celecoxib. The absorbances of the solution were measured against 0.1N Hcl as blank at 252 nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

**PREFORMULATION STUDIES**

It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination, solubility and compatibility studies.

**Preparation of Celecoxib granules**

For the batch size of 100 tablets, Celecoxib was taken and mixed with mannitol and other ingredients in glass mortar and pestle and mixed well. Binder solution was added to that mixture to form a cohesive mass and passed through sieve No. 12 and 22. Wet granules were collected and dried at 60°C for one hour. 3% HPMC 50 cps in Distilled water was found to be suitable to formulate granules and tablets of Celecoxib since it gave desirable hardness and friability to the formulated tablets.

**Characterization of Celecoxib granules formulated with HPMC**

The prepared granules were evaluated for different flow properties which include angle of repose, bulk density, tapped density, compressibility index, Hausner’s ratio and drug content.
The drug content was evaluated by an UV spectrophotometric method based on the measurement of absorbance at 252 nm.

**Formulation of tablets of Celecoxib:**
Granules formulated were weighed for practical yield and the same was recorded. These granules were mixed with 1% magnesium Stearate and 1% purified talc mixed with 10% fines and subjected to compression. Compression of tablets was done in rotary compression tablet machine using 16.4x8mm flat oval shape punch. The prepared tablet of each batch was evaluated for the tablet properties.

**Table .1 Composition of Compression Coated Tablets.**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>p1f3</th>
<th>p2f3</th>
<th>p3f3</th>
<th>p4f3</th>
<th>p5f3</th>
<th>p6f3</th>
<th>p7f3</th>
<th>p8f3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Guar gum</td>
<td>400</td>
<td></td>
<td>200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xanthu gum</td>
<td>400</td>
<td></td>
<td></td>
<td>200</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hpmc k100m</td>
<td></td>
<td>400</td>
<td></td>
<td>200</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ethyl Cellulose</td>
<td></td>
<td></td>
<td>400</td>
<td></td>
<td>200</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Evaluation of Tablet Properties**
Tablets were subjected to evaluation of properties including drug content uniformity, weight variation, tablet hardness, friability and thickness and in-vitro drug release with different media.

**Evaluation of Pulsatile Drug Delivery Systems**

**Characteristics of coated tablets of Celecoxib**
Characteristics of tablets of Celecoxib such as hardness and disintegration test were conducted. 3 tablets were taken and hardness of formulations was determined by using Monsanto hardness tester. Average of three determinations was noted down. 6 tablets were taken in Electrolab USP Disintegration test apparatus and disintegration time of tablets was determined using pH 6.8 buffer.

Thickness of coated Celecoxib tablet formulations was determined by using digital Vernier calipers. 3 tablets of each type of coated formulation were determined for thickness and average thickness of the formulation was determined. Similarly the thickness of the coating on the formulation was determined by deducting the thickness of core tablets from thickness of the coated formulation. A successful Pulsatile drug delivery system is one that remains intact in the physiological environment of stomach and small intestine for up to six hours.
releasing no or minimum amount of drug, but completely releases the drug after six hours.

**In-vitro Dissolution methods**

In-vitro dissolution testing is important in the development of solid dosage forms. It provides decisive information on formulation selection, the critical processing variables. In order to provide this information, dissolution testing should be conducted in physiochemical and hydrodynamically defined conditions to simulate the environment that the dosage form encounters in the GI tract. Conventional dissolution testing proposed in USP appears unable to discriminate drug mechanisms. For in-vitro evaluation of Pulsatile drug delivery systems, the ideal dissolution testing should closely mimic the in-vivo conditions with regard to pH, bacteria, types of enzymes, enzymatic activity, fluid volume and mixing intensity. Apparently, such dissolution specifications will be very difficult, if possible at all, to be standardized and validated. Nonetheless, several dissolution methodologies were reported in the literature for the testing of ChrDDS. Dissolution testing of Pulsatile delivery systems with the conventional paddle method at 50 rpm and 37±0.5°C has usually been conducted in different buffers for different periods of time to simulate the GI tract pH and transit time that the Pulsatile delivery system might encounter in-vivo. The ability of the coats/carriers to remain intact in the physiological environment of the stomach and small intestine is generally assessed by conducting drug release studies in 0.1 N Hcl buffer for 2 hours (mean gastric emptying time) and in pH 6.8 phosphate buffer for remaining hours (mean small intestinal transit time) using USP dissolution rate test apparatus. The samples were withdrawn at regular intervals and analyzed by UV spectrophometer (Shimadzu UV/Vis 1800) for the presence of the drug. Dissolution tests were performed in triplicate. Despite the simplicity and convenience, conventional dissolution testing primarily provides essential information on the processing specifications of a Pulsatile drug delivery system rather than on the validity of the system design.

**Effect of outer polymer concentration and water uptake performance**

The % water uptake capacity of tablets was determined in the containers filled with 100 ml of pH 1.2 buffer placed in a biological shaker at 37°C. Speed of shaker was adjusted to 75 rpm. Tablets were removed from containers at predetermined regular intervals, blotted with tissue paper, weighed and again placed in medium till the outer coating of tablet started to rupture. The % water uptake was calculated using the formula.

\[
\% \text{ Water uptake} = \left( \frac{W_t - W_o}{W_o} \right) \times 100.
\]
Where $W_t$ is weight of wet tablet at time $t$ and $W_0$ is weight of dry tablet.

**Stability Studies**

The formulation was selected for the study and formulation was packed in amber-colored bottles tightly plugged with cotton and capped. They were exposed to 40°C temp and 75% RH for 30 days. At regular intervals, the tablets were taken in 100 ml of pH 6.8 buffer and were shaken for 1 hr. The resultant solutions were filtered, properly diluted and estimated spectrophotometrically by keeping pH 6.8 buffer as blank. % drug remained undecomposed was checked for both core and coated tablets.

**Drug Release Kinetic Data**

To investigate the possible mechanisms of Celecoxib release from the prepared tablets, the drug release data were fitted to various models such as Higuchi, Zero-order, First-order, Hixson Crowell and Korsmeyer Peppas kinetics. Model fitting was carried out using PCP DISSO.v 2.08 Software.

![Graphs showing drug release kinetics](image-url)
Fig 2 – A – Zero order kinetics of f3, A1-First order kinetics of f3, B- Zero order kinetics of P1F3, B1-First order kinetics of P1f3, C- Higuchi curve of P1f3, C1- Peppas curve of P1f3.

Table 2: Cumulative percent drug release of core Celecoxib tablets of different formulations. (F1 to F6).

<table>
<thead>
<tr>
<th>Time</th>
<th>f1</th>
<th>f2</th>
<th>f3</th>
<th>f4</th>
<th>f5</th>
<th>f6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>40.2</td>
<td>58.3</td>
<td>64.25</td>
<td>17.2</td>
<td>29.1</td>
<td>37.24</td>
</tr>
<tr>
<td>10</td>
<td>47.9</td>
<td>74.2</td>
<td>85.91</td>
<td>25.3</td>
<td>35.23</td>
<td>46.5</td>
</tr>
<tr>
<td>15</td>
<td>50.2</td>
<td>84.82</td>
<td>101.2</td>
<td>36.4</td>
<td>40.96</td>
<td>59.99</td>
</tr>
<tr>
<td>20</td>
<td>66.3</td>
<td>88.9</td>
<td>49.2</td>
<td>59.8</td>
<td>64.96</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>74.8</td>
<td>95.3</td>
<td>59.7</td>
<td>72.3</td>
<td>79.65</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>86.1</td>
<td>99.24</td>
<td>70.82</td>
<td>81.8</td>
<td>85.36</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>92.34</td>
<td>83.96</td>
<td>90.98</td>
<td>97.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>98.53</td>
<td>97.57</td>
<td>99.89</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 3: Cumulative percentage drug release of core formulation F1 - F3.
RESULTS AND DISCUSSION

Drug characterization

From calibration curve UV absorption maximum of drug was found at 255 nm. According to calibration curve correlation coefficient was found to be 0.297 (Phosphate Buffer), 0.187 (pH 1.2), 0.185 (pH 7.4), 0.188 (pH 6.8). Calibration curve obeyed beer's law in the range of 2-10 μg/ml.

FT-IR spectroscopy

FT-IR spectra of Celecoxib shown peaks at 3857 cm⁻¹, 3737 cm⁻¹, 2920 cm⁻¹, 1606 cm⁻¹, 1526 cm⁻¹, 1389 cm⁻¹. These spectra match with standard drug.

Evaluation of Celecoxib Granules formulated with HPMCK 100M

The angle of repose for the formulated blend was carried out and the results were given. It can be concluded that all the formulation blends angle of repose was found to be in the range 28.43±.005 to 33.36±.004. Hence the entire formulation blends was found to possess good flow property. The drug content was found in the range of ±8.5% (acceptable limit), the thickness 2.5 mm and the hardness of the tablet was found between 3 to 4 kg/cm² indicating good mechanical resistance of the tablets and parameters were found well within the specified limit for uncoated tablets. The loss on friability was less than 1% the total weight of the tablet. The drug content varied from 84.63 – 99.21%. The wetting time varied from 13.5 – 40sec (F-6 and F-1 respectively). The water absorption ratio varied from 53.88 – 238.2 (F-1 and F-6 respectively). The Invitro disintegration time (DT) of the tablets was found to be 69 sec maximum. Tablets containing 5% sodium starch glycolate (F-3) showed disintegration time 42sec. While other formulation showed around 42-69 sec.
**In-vitro release studies**

*In-vitro* drug release profiles from formulation (F6) were found to have very good sustaining efficacy. During the dissolution studies, it was observed that, the enteric coat of the cellulose acetate phthalate was intact for 2 hours in pH 1.2, but dissolved in intestinal pH, which also dissolved in pH 7.4 phosphate buffer and then the exposed polymer plug which absorbed the surrounding fluid, swelled and released the drug through the swollen matrix. After complete wetting of the plug, it formed a soft mass, which was then easily ejected out of the Tablet core; releasing the particles into simulated colonic fluid (pH 6.8 phosphate buffer). With all the formulations, there was no drug release in pH 1.2, thus indicating the efficiency of 5% CAP for enteric coating very slight release was observed in pH 7.4 phosphate buffers.

![In vitro Dissolution study](image)

**Fig 5 - In vitro Dissolution study.**

**CONCLUSION**

The present study was carried out to develop colon target drug delivery of Celecoxib. The main aim of this study was to target drug release for colon to maintain the chrono pharmacological anti-Inflammatory activity. The results obtained from the above study of revealed the following conclusions. The FTIR studies indicated that, there was no interaction between polymer and drug. The result for micromeritic properties of granules showed good flow property for physical mixture and the drug content of all formulation. On the basis of drug content, *in-vitro* release, F6 was selected as better formulation designing pulsatile device. During the dissolution studies, it was observed that, the enteric coat of the cellulose acetate phthalate was intact for 2h in pH 1.2, but dissolved in intestinal pH, which also dissolved in pH 6.8 and then the exposed polymer plug absorbed the surrounding fluid. After complete wetting of the plug, it formed a soft mass, which was then easily ejected out of the
Tablet core. Releasing the minor quantity of granules into colonic fluid (pH 7.4) and other released in pH 6.8 buffer solutions. Statistical data showed that the drug release from the formulation follows Korsmeyer-Peppas model. From the present study it can be concluded that optimized F6 batch of Celecoxib could be delivered drug in colon targeted system for the Anti inflammatory & Analgesic activity.

REFERENCES
3. Filippatos TD, Derdemezis CS, Elisaf MS. Department of Internal Medicine, School of Medicine, University of Loannina Greece. Available from: articles\Diet for hyperlipidemia.mht.
4. Scott MG. Atherogenic dyslipidemia associated with metabolic syndrome and Insulin resistance., 8(1).