Development and evaluation of pulsatile drug delivery system of flurbiprofen

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ABSTRACT

Flurbiprofen an oral colon specific, pulsatile device to achieve time and/or site specific release was formulated. The basic design consists of an insoluble hard gelatin capsule body, filled with eudragit microsphere of Flurbiprofen and sealed with a hydrogel plug. The entire device was enteric coated, so that the variability in gastric emptying time can be overcome and a colon-specific release can be achieved. Flurbiprofen microsphere was prepared by using ratio of Drug: Eudragit L-100: Eudragit S-100 (1:1:2). Different hydrogel polymers were used as plugs (Guar gum, HPMC, Sodium alginate ) to maintain a suitable lag period and it was found that the drug release was controlled by the proportion of polymers used. In vitro release studies of pulsatile device revealed that, increasing the hydrophilic polymer content resulted in delayed release of Flurbiprofen from microsphere. Programmable pulsatile, colon-specific release has been achieved from a capsule device over a 2–15h period, consistent with the demands of chronotherapeutic drug delivery.

Keyword's: Pulsatile, Colon-specific, Chronotherapeutics, Rheumatoid arthritis, Flurbiprofen

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INTRODUCTION

Among modified-release oral dosage forms, increasing interest has currently turned to systems designed to achieve times specific (delayed, pulsatile) and site-specific delivery of drugs. These systems constitute a relatively new class of devices the importance of which is especially connected with the recent advances in chronopharmacology [1]. In the last decade numerous studies in animals as well as clinical studies have provided convincing evidence, that the pharmacokinetics and/or the drug’s effects-side effects can be modified by the circadian time and/or the timing of drug application within 24 h of a day [2,3]. On the other hand, colon-specific drug delivery systems (CDDS) have been developing as one of the site-specific drug delivery systems. Along with many applications in local and systemic delivery of drugs the CDDS would also be advantageous when a delay in absorption is desirable from a therapeutic point of view as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythm, such as rheumatoid arthritis, angina and nocturnal asthma [4,5]. In case of rheumatoid arthritis, peak symptoms occur early in the morning due to the imbalance between anti-inflammatory effect by cortisol and proinflammatory effects exerted by melatonin [6]. So, by developing the pulsatile device for specific colonic delivery, plasma peak is obtained at an optimal time, number of doses per day can be reduced; saturable first pass metabolism and tolerance development can also be avoided [7].

The necessity and advantage of CDDS have been well recognized and reviewed recently. There were currently few strategies to achieve colonic specificity such as bacterially triggered pressure controlled pH and time dependent CDDS [8].

Recent studies with sensitive and reliable equipment contradict the traditional view and provide evidence of a decrease in pH at the gastrointestinal region between the ileum and the colon. Apparently the colon has a lower pH value (6.5) than that of the small intestine (7.0–7.8) [9]. Based on the concept that a formulation on leaving the stomach arrives at the ileocaecal junction in about 6 h after administration and difference in pH throughout GIT, a time and pH dependent pulsatile device proposed for colonic targeting was designed, for achieving the selective delivery of drugs to colon, which is chronopharmaceutical approach for the better treatment of rheumatoid arthritis.

The designed capsule device consists of a non-disintegrating capsule body and a soluble cap. The microencapsulated drug formulation prepared by using pH sensitive methacrylic acid copolymers (Eudragit L-100 and S-100) as coat and Flurbiprofen as core material, is filled within the capsule body and separated from the water-soluble cap by a hydrogel plug. The entire capsule was enteric coated to prevent variable gastric emptying. The enteric coating prevents disintegration of the soluble cap in the gastric fluid. On reaching the small intestine, the capsule will lose its enteric coating and the water-soluble hydrogel polymer plug inside the capsule swells to create a lag phase that equals the small intestinal transit time. This plug ejects on swelling and releases the microencapsulated drug from the capsule in the colon. Further, the controlled release of Flurbiprofen was achieved for up to 24 h as it was microencapsulated in the pH sensitive polymers [10].

Flurbiprofen [1,1 – biphenyl] – 4-acetic, 2-fluro-alpha-methyl, is an important analgesic and non-steroidal anti-inflammatory drug (NSAID) also with anti-pyretic properties whose mechanism of action is the inhibition of prostaglandin synthesis. It is used in the therapy of rheumatoid disorders. Flurbiprofen is rapidly eliminated from the blood, it’s plasma elimination half-life is 3-6 hours and in order to maintain therapeutic plasma levels. The drug must be administered approximately 150-200mg daily by oral individual dosage [11].

So with the proposed device a new lease of life to an existing drug molecule can be achieved.

MATERIALS AND METHODS

Material

Flurbiprofen was obtained from FDC Pharmaceutical Ltd. (India) pH sensitive methacrylic acid co-polymers (Eudragit® L-100 and S-100) were supplied as gifts by Degussa India Pvt. Ltd., Mumbai (India).
Hydroxypropylmethylcellulose-K4M (HPMC) was obtained from Ozone international Mumbai (India). Guar gum and sodium alginate were supplied from S.D. Fine Chem. Ltd., Mumbai. Cellulose acetate phthalate (CAP) were supplied from Sisco Research Laboratory Pvt. Ltd. Mumbai (India). Span 80 were supplied from Ioba Chemical India. Ethanol were supplied from Jiangsu Huaxi International Trade Co. Ltd. (Made IN China), Hard gelatin capsules, Heavy liquid paraffin, Acetone, petroleum ether, Dibutylphthalate, acetone, petroleum ether was obtained from S.D. fine Chem. Ltd., Mumbai (India). All other chemicals and reagent used in this study were of analytical grade.

Preparation of cross-linked gelatin capsules

Twenty-five milliliters of 15% (v/v) formaldehyde was taken into desiccator and a pinch of potassium permanganate was added to it, to generate formalin vapors. The wire mesh containing the empty bodies of the 00 size hard gelatin (about 100 in number) capsule was then exposed to formaldehyde vapors. The caps were not exposed leaving them water-soluble. The desiccator was tightly closed. The reaction was carried out for 12 h after which the bodies were removed and dried at 50°C for 30 min to ensure completion of reaction between gelatin and formaldehyde vapors. The bodies were then dried at room temperature to facilitate removal of residual formaldehyde. These capsule bodies were capped with untreated caps and stored in a polythene bag.

Test for formaldehyde treated empty capsule bodies

Various physical tests such as, identification attributes, visual defects, dimension changes, solubility studies were carried out.

Qualitative chemical test for free formaldehyde

Standard formaldehyde solution used is formaldehyde solution (0.002, w/v) and sample solution is formaldehyde treated bodies (about 25 in number) were cut into small pieces and taken into a beaker containing distilled water. This was stirred for 1 h with a magnetic stirrer, to solubilize the free formaldehyde. The solution was then filtered into a 50ml volumetric flask, washed with distilled water and volume was made up to 50 ml with the washings. In brief, to 1ml of sample solution, 9ml of water was added. One milliliter of resulting solution was taken into a test tube and mixed with 4ml of water and 5ml of acetone reagent. The test tube was warmed in a water bath at 40°C and allowed to stand for 40 min. The solution was not more intensely colored than a reference solution prepared at the same time and in the same manner using 1ml of standard solution in place of the sample solution. The comparison should be made by examining tubes down their vertical axis.

Formulation of pulsatile drug delivery system

The Microspheres were prepared by using ratio of Drug: Eudragit L-100: Eudragit S-100 (1:1:2). The microspheres equivalent to 150 mg of Flurbiprofen were accurately weighed and filled into the treated bodies by hand filling. The capsules containing the microsphere were then plugged with different amounts (20, 30 and 40 mg) of various polymers, i.e., guar gum, hydroxylpropylmethylcellulose and sodium alginate. The joint of the capsule body and cap was sealed with a small amount of the 5% ethyl cellulose ethanolic solution. The sealed capsules were completely coated by dip coating method with 5% w/w CAP in 8:2 (v/v) mixture of acetone: ethanol, plasticized with dibutylphthalate (0.75%), to prevent variable gastric emptying. Coating was repeated until an 8-12% increase in weight is obtained. % weight gain of the capsules before and after coating was determined. Composition for modified pulsatile device on the basis of design summary is given in Table 1

Evaluation of designed pulsatile capsule

Weight variation
Ten capsules were selected randomly from each batch and weighed individually for weight variation. The test requirements are met if none of the individual weights are less than 90% or more than 110% of the average.

### Table 1: Composition for modified pulsatile device on the basis of design summary

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Wt.of empty body (mg*)</th>
<th>Wt.of micro capsule (mg)</th>
<th>Polymer used</th>
<th>Wt.of polymer used (mg)</th>
<th>Total weight with cap (mg)</th>
<th>Wt. after CAP coating (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-1</td>
<td>68.8</td>
<td>355</td>
<td>Guar gum</td>
<td>20</td>
<td>443.8</td>
<td>454.7</td>
</tr>
<tr>
<td>F-2</td>
<td>67.9</td>
<td>355</td>
<td>Guar gum</td>
<td>30</td>
<td>452.9</td>
<td>462</td>
</tr>
<tr>
<td>F-3</td>
<td>68.5</td>
<td>355</td>
<td>Guar gum</td>
<td>40</td>
<td>463.5</td>
<td>470.18</td>
</tr>
<tr>
<td>F-4</td>
<td>67.5</td>
<td>355</td>
<td>HPMC</td>
<td>20</td>
<td>442.5</td>
<td>451.34</td>
</tr>
<tr>
<td>F-5</td>
<td>67.4</td>
<td>355</td>
<td>HPMC</td>
<td>30</td>
<td>452.4</td>
<td>460.8</td>
</tr>
<tr>
<td>F-6</td>
<td>68.5</td>
<td>355</td>
<td>HPMC</td>
<td>40</td>
<td>463.5</td>
<td>473.25</td>
</tr>
<tr>
<td>F-7</td>
<td>68.0</td>
<td>355</td>
<td>Sod. Alg.</td>
<td>20</td>
<td>443.0</td>
<td>454</td>
</tr>
<tr>
<td>F-8</td>
<td>67.7</td>
<td>355</td>
<td>Sod. Alg.</td>
<td>30</td>
<td>452.7</td>
<td>462.35</td>
</tr>
<tr>
<td>F-9</td>
<td>67.6</td>
<td>355</td>
<td>Sod. Alg.</td>
<td>40</td>
<td>462.6</td>
<td>471.95</td>
</tr>
</tbody>
</table>

HPMC: Hydroxy Propyl Methylcellulose; Sod.Alg: Sodium Alginate, * Microcapsule equivalent to 150 mg of drug used.

In vitro release profile of pulsatile capsule [9, 10, 12]

Dissolution studies were carried out by using USP XXIII dissolution test apparatus (Basket) method. Capsules were placed in a basket so that the capsule should be immersed completely in dissolution media but not float. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used referred to as sequential pH change method. When performing experiments, the pH 1.2 medium was first used for 2 h (since the average gastric emptying time is 2 h), then removed and the fresh pH 7.4 phosphate buffer saline (PBS) was added. After 3 h (average small intestinal transit time is 3 h), the medium was removed and fresh pH 6.8 dissolution medium was added for subsequent hours. Nine hundred milliliters of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at 37±0.5 °C. Capsules were tied to paddle with a cotton thread in each dissolution vessel to prevent floating. Five milliliters of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 247 nm, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times.

### RESULTS AND DISCUSSION

As indicated in introduction, the aim of the work described here was to design a new pulsatile, colonic drug delivery device, for the better treatment of nocturnal arthritis. The pulsatile capsule designed here combines two approaches previously attempted: pH-sensitive delivery and time dependent delivery. The system was fabricated into two steps: first, Flurbiprofen was entrapped within pH dependent methacrylic acid copolymers (Eudragit L-100 and S-100 soluble at pH above 6 and 7, respectively); second, microsphere were filled in non-disintegrating capsule body, and sealed with hydrogel plug and the entire capsule was coated with cellulose acetate phthalate for the enteric coating.

#### Formaldehyde treatment of hard gelatin capsule

Formalin treatment has been employed to modify the solubility of the gelatin capsules. Exposure to formalin vapors results in an unpredictable decrease in solubility of gelatin owing to the cross linkage of the amino groups in the gelatin molecular chain with aldehyde groups of formaldehyde by Schiff’s base condensation. In about 100 capsule bodies treated with formaldehyde, about ten were found to be shrunk or distorted. Capsule of ‘00’ size showed a significant decrease in length and diameter after treatment. The solubility tests were carried out for...
normal capsules and formaldehyde treated capsules for 24 h. It was observed that in all the case of normal capsules, both cap and body dissolved within 15 min where as in formaldehyde treated capsules, only the cap dissolved within 15 min, while the capsule body remained intact for about 24 h and hence indicates the suitability for colon targeting. The formaldehyde capsules were tested for the presence of free formaldehyde. The sample solution was not more intensely colored than the standard solution inferring that less than 20 µg of free formaldehyde per 25 capsules, taken for test.

**Evaluation of modified pulsatile capsule**

*In vitro* release profiles of pulsatile device during 15 h studies were found to have very good sustaining efficacy. The *in vitro* release profile for formulations F1–F3 (Fig.1), F4–F6 (Fig.2) and F7–F9 (Fig.3). This contains guar gum, HPMC and sodium alginate respectively as hydrogel plugs at different proportions. During dissolution studies, it was observed that, the enteric coat of the cellulose acetate phthalate was intact for 2 h in pH 1.2, but dissolved in intestinal pH, leaving the soluble cap of capsule, which also dissolved in pH 7.4, then the exposed polymer plug 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 capsule body releasing the eudragit microsphere into simulated colonic fluid (pH 6.8 phosphate buffers). With all the formulations, there was absolutely no drug release in pH 1.2, thus indicating the efficiency of 5% CAP for enteric coating.

**Formulations with guar gum as hydrogel plug**

With formulations F1 (20 mg), F2 (30 mg), at the end of 5th there was 6.05% and 2.77% cumulative drug release was found. In case of F1 and F2 it was observed that polymer concentration was sufficient to retard the drug release in small intestinal fluid and the plug ejected out in colonic fluid, releasing the entire drug in colonic pH, in a controlled manner. At the end of 15 h, 74.61% and 69.43% of drug release was found in F1 and F2, respectively. With F3, a decrease in expelling power of plug was observed which might be due to inadequate wetting of the polymer. It was observed that plug ejected after 6 h and at the end of 15 h 62.59% of drug release was observed.

**Formulation with HPMC as hydrogel plug**

With formulation F4 (20 mg), F5 (30 mg), at the end of 5th hour 5.99% and 4.61% of drug was released respectively and at the end of 15th hour F4 formulation had released 76.46% of drug, whereas F5 formulation released 71.71% of drug up to 15 h in controlled manner. In case of F6 (40 mg), hydrogel plug ejected out in...
between 6th and 8th hour, indicating decrease in expelling power of plug. At the end of 15th hour 59.79% of drug was released.

![Graph](image)

**Fig. 2: In vitro drug release profile of formulation F₄ to F₆**

**Formulations with sodium alginate as hydrogel plug**

With formulations F₇ (20 mg), F₈ (30 mg) and F₉ (40 mg), at the end of 5th hour around 9.303%, 6.087%, 4.436% of drug release was observed respectively. F₇ released 82.85% of drug within 15 h where as F₈ and F₉ released 70.25% and 77.36% of drug at the end of 15th hour. From all the above observations, it was found that the order of sustaining capacity of polymer is, guar gum > HPMC > sodium alginate. The hydrophilic polymers like guar gum, HPMC, and sodium alginate can be used as hydrogels to delay the drug release until the formulation reaches the colon and thereafter the drug is released in the colon. The release of drug from modified pulsatile capsule was found to be proportional to the concentration of the polymer in HPMC and sodium alginate, where as with guar gum there is no such relation. With the formulations containing 20 and 30 mg of guar gum there is no significant difference in controlling release of the drug.

![Graph](image)

**Fig. 3: In vitro drug release profile of formulation F₇ to F₉**

**CONCLUSION**

The present study demonstrates that the Flurbiprofen microsphere could be successfully colon targeted by design of time and pH dependent modified chronopharmaceutical formulation. In conclusion, pulsatile drug release over a period of 2–15 h, consistent with the requirements for chronopharmaceutical drug delivery was achieved from insoluble gelatin capsules, in which microencapsulated Flurbiprofen was sealed by means of a suitable hydrogel plug. Thus the designed device can be considered as one of the promising formulation technique.
for preparing colon-specific drug delivery systems and hence in chronotherapeutic management of by opening a “new lease of life” to an existing drug molecule.

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