



Development of pulsatile release of Aceclofenac tablets with swelling and rupturable layers of ethyl cellulose

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4th Dec 2012
Received in revised form:
18th Dec 2012
Accepted:
20th Dec 2012
Available online:
15th Jan 2013



Online ISSN 2249-622X
<http://www.jbiopharm.com>

ABSTRACT

The objective of this study was to develop and evaluate of Aceclofenac tablets with swelling and rupturable layers of ethyl cellulose. A tablet system consisting Intended for treatment of early morning stiffness and symptomatic relief from pain in patients with rheumatoid arthritis with a distinct predetermined lag time of 6 h. Cores containing Aceclofenac as model drug were prepared by direct compression of different Sodium starch glycolate level CT-1 to CT-4) 8 %, 4%, 2% & without disintegrant and were then coated sequentially with an inner swelling layer containing a superdisintegrant (croscarmellose sodium) and an outer rupturable layer of ethylcellulose. Seven formulations were prepared and formulation F2 possessed good lag time 6 hr and showed pulsatile drug delivery pattern the tablets *In-vitro* evaluation tests. Results of this study indicated that by using ethyl cellulose are suitable to optimize pulsatile drug release formulation of Aceclofenac.

Keywords: Rupturable coating Pulsatile delivery, Aceclofenac.

1. INTRODUCTION

Pulsatile drug delivery systems are gaining a lot of interest now days. These systems are designed according to the circadian rhythm of the body. These systems deliver the drug at specific time as per the pathophysiological need of the disease, resulting in improved patient compliance and therapeutic efficacy. Which is meant as the liberation of drugs following programmed lag phases, has drawn increasing interest, especially in view of emerging chronotherapeutic approaches. Pulsatile drug delivery shows rhythms like rheumatoid arthritis, cardiovascular diseases, asthma, peptic ulcer, allergic rhinitis.

The concept of chronotherapeutics originates from the finding of the major disease conditions such as asthma, cardiac disorders, allergic rhinitis, and arthritis following circadian example of symptom outburst. Chronotherapeutics delivery system have been developed to provide the best treatment regimens which revolve around the objective of assuring maximum concentration of the drug at the time of symptom onset.^[2,3,4,5,6]

Nowadays, concept of chronopharmaceutics has emerged, wherein, research is devoted to the design and evaluation of drug delivery systems that release a therapeutic agent at a rhythm that ideally matches the biological requirement of a given disease therapy. Future of drug delivery must meet the challenge of future medicine^[7]

Aceclofenac, a nonsteroidal anti-inflammatory drug, is used for the symptomatic relief of pain and joint stiffness in patients suffering from rheumatoid arthritis, which is characterized by diurnal variation in circulating levels of proinflammatory cytokines, interleukin-6 and/or tumor necrosis factor- α . Due to this diurnal variation, many symptoms and signs of active rheumatoid arthritis are manifested in the morning^[8] on oral administration at bed-time, releases aceclofenac after a desired lag time of about 6 hr which corresponds with peak levels of proinflammatory mediators. The current study illustrates the formulation, characterization and optimization of a

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Aceclofenac tablets with swelling and rupturable layers of ethyl cellulose. The system is involved of cores coated with two layers of swelling and rupturable coatings was prepared and evaluated as pulsatile drug delivery system.

Method

Preparation of Aceclofenac tablets with swelling and rupturable layers of ethyl cellulose.

Cores containing Aceclofenac as model drug were prepared by direct compression of different Sodium starch glycolate level CT-1 to CT-4) 8 %, 4%, 2% & without disintegrant.

A. Preparation of core tablets (CT):

All ingredients of core tablet given in **Error! Reference source not found.**No 1 were weighed and passed through 30 mesh standard sieve. Resultant powder was mixed thoroughly in mortar and lubricated with magnesium stearate (1 % w/w). A 200 mg powder was weighed and transferred manually in to die and compressed by using 8 mm diameter SC punch tooling.

B. Preparation of rupturable coating by using swelling and rupturable layers of ethyl cellulose.

Preparation coating solution:

1. Coating of inner swelling layer:

Coating of inner swelling layer is prepared by dispersion of croscarmellose sodium (Ac-Di-Sol) and PVP K 30 by in ethanol (95%) 4 % W/W is prepared. And stir solution for 30 min. Coating of swelling layer is done 4 % of tablet weight.

2. Coating of rupturable layer:

Weigh half quantity of Ethanol (95%): Dichloromethane and add Ethylcellulose (20 CPS) and stir the solution for 15 min. Take remain half quantity of Ethanol (95%): Dichloromethane and add Triethyl citrate as and stir solution. Add Titanium dioxide and disperse it add Talc and stii solution. Mix both steps and mix solution stir solution for 30 min till it gets uniform suspension.Coating process was completed with continuous stirring.

Coating of rupturable layer is done at various concentration F1 (5 %), F2 (10%), F3 (12.5%), F4 (13.5 %), F5(15%), F6 (17.5%), and F7(20%) of tablet weight gain.

Evaluation of Tablet Characteristics:

Physicochemical properties of tablets

Weight variation:

Twenty tablets were selected at random and weighed individually. The average weight of 20 tablets was calculated. Individual weights of the tablets were compared with the average weight.

Hardness:

Tablet hardness has been defined as the force required breaking a tablet in a diametric compression test. A tablet was placed between two anvils of hardness tester, force was applied to the anvils, and the crushing strength that

causes the tablet to break was recorded in N

Friability:

Tablets require certain amount of strength or hardness and resistance to withstand mechanical shock of handling in manufacturing, packaging, and shipping. A pre-weighed sample (20 tablets) were placed in the friabilator, and operated for 100 revolutions, then again weighed the tablets and % friability was calculated using the formula.

$$F = \left(1 - \frac{W_0}{W} \right) \times 100$$

Where

W_0 – Weight of tablet before test

W – Weight of tablet after test

Drugs content:

To evaluate a tablet potential for efficacy, the amount of drug per tablet needs to be monitored from tablet to tablet, and batch to batch. To perform the test, 10 tablets were crushed using mortar pestle. Quantity equivalent to 100 mg of drug was dissolved in 100 ml phosphate buffer pH 6.8, filtered and diluted up to 50µg/ml, and analyzed spectrophotometrically at 274.2nm. The concentration of drug was determined using standard calibration curve.

| Sr No | Formulation | CT 1 | CT 2 | CT 3 | CT 4 |
|-------|---------------------------|-----------|-----------|-----------|-----------|
| | | mg/tablet | mg/tablet | mg/tablet | mg/tablet |
| 1. | Aceclofenac | 100.00 | 100.00 | 100.00 | 100.00 |
| 2. | MCC (Avicel pH102) | 40.00 | 44.00 | 46.00 | 48.00 |
| 3. | Dicalcium phosphate (DCP) | 40.00 | 44.00 | 46.00 | 48.00 |
| 4. | Sodium starch glycolate | 16.00 | 8.00 | 4.00 | - |
| 5. | Sunset yellow iron oxide | 2.00 | 2.00 | 2.00 | 2.00 |
| 6. | Magnesium stearate | 2.00 | 2.00 | 2.00 | 2.00 |

F= Formulation code, CT1= Core tablet 1 with Sodium starch glycolate 8%, CT2= Core tablet 2 with Sodium starch glycolate 4%, CT3= Core tablet 3 with Sodium starch glycolate 2%, CT4= Core tablet 4 with Sodium starch glycolate without disintegrant

Table 1 : Effect of Sodium starch glycolate level on drug release profile from uncoated Tablet (CT-1-CT-4) 8 %,4%,2% & without disintegrant

In vitro Dissolution Study:

The in vitro dissolution test was performed using USP type II dissolution test apparatus. The drug release study was carried out in phosphate buffer pH 6.8 900 ml of dissolution media, maintained at 37±0.5°C and agitated at

50 rpm. Periodically 5 ml samples were withdrawn and filtered through whatman filter paper and samples were replaced by its equivalent volume of dissolution media. The concentration of Aceclofenac was measured by spectrophotometrically at 274.2 nm for 6.8 media.

| F | Weight Variation (mg) n=20 | Thickness (mm) n=10 | Hardness (N) n=10 | Friability (%) | Drug Content (%) n=3 |
|----|----------------------------|---------------------|-------------------|----------------|----------------------|
| CT | 200.10±1.24 | 3.20±0.1 | 80 N ± | 0.21 | 99.58±1.65 |
| CT | 200.15±1.11 | 3.20±0.1 | 80N ± | 0.11 | 100.25±1.98 |
| CT | 200.24±1.27 | 3.20±0.1 | 80N ± 9 | 0.25 | 99.98±1.56 |
| CT | 200.24±1.19 | 3.20±0.1 | 80 N ± | 0.15 | 100.58±2.15 |

Table 2: Physicochemical evaluation of core tablets (CT)

Results and discussion:

Evaluation of Tablet characteristics

Physicochemical properties of tablet:

Tables are evaluated for Weight variation, thickness.

hardness, friability and drug content

A. Results of physicochemical evaluation of core tablets (CT) are given in **Error! Reference source not found..**

| Time (min) | % Cumulative Drug Release | | | |
|------------|---------------------------|-------|-------|-------|
| | CT-1 | CT-2 | CT-3 | CT-4 |
| 5 | 72.4 | 46.5 | 20.2 | 5.25 |
| 10 | 99.5 | 62.7 | 44.2 | 17.58 |
| 15 | 101.2 | 84.1 | 80.5 | 30.22 |
| 30 | 100.1 | 100.5 | 100.1 | 79.0 |
| 45 | 99.6 | 99.3 | 98.7 | 100.7 |
| 60 | 98.4 | 98.6 | 98.2 | 99.1 |

Table 3 : Effect of Sodium starch glycolate level on Drug Release Profile from Uncoated Tablet (CT-1-CT-4) 8 %, 4%, 2% & without disintegrant. in phosphate buffer pH6.8 of different core tablets formulations.

| Time (min) | % Drug Release | | | | | | |
|------------|----------------|-------------|-------------|-----------|------------|------------|------------|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 |
| 15 | 100.52 ±1.25 | 0 | 0 | 0 | 0 | 0 | 0 |
| 30 | 99.82±1.47 | 99.89 ±1.36 | 0 | 0 | 0 | 0 | 0 |
| 60 | | 101.35±1.3 | 98.52 ±1.68 | 0 | 0 | 0 | 0 |
| 120 | | | 99.89±1.26 | 0 | 0 | 0 | 0 |
| 180 | | | | 100.8±1.6 | 0 | 0 | 0 |
| 240 | | | | 99.79±2.2 | 0 | 0 | |
| 300 | | | | | 0 | 0 | |
| 360 | | | | | 98.98±1.28 | 0 | |
| 420 | | | | | 101.25±2.1 | 100.1±1.78 | |
| 480 | | | | | 0 | 101.22±1.6 | 101.2±1.29 |
| 540 | | | | | 0 | | 100.5±1.35 |

Table 4: % Cumulative release of aceclofenac for in phosphate buffer pH6.8 of different formulations. (F1 to F7)

In vitro Dissolution Study:**A. Dissolution of core tablets (CT)**

In vitro dissolution test was carried out in phosphate buffer pH 6.8 for 60 min. Results of in vitro dissolution test presented in Table No 3. In order to perform different release kinetics; depending upon different release mechanism involved, effect of Sodium starch glycolate level on drug release profile from uncoated tablet (Formulations CT1 to CT4) were determined. As amount of Sodium starch glycolate level decrease from formulations CT-1 to CT-4; the formulation containing highest amount of Sodium starch glycolate (CT-1) showed fast disintegration and fast release because of swellable disintegrant present in it. As amount of swellable disintegrant decrease amount of drug release decreased. Without disintegrate Sodium starch glycolate level in formulation CT-4 showing decrease in disintegrant property. As shown in figure1 significant change in release profile CT1 shows drug release initially faster compare to CT -4 which without disintegrant. CT1 is selected for coating using swelling and rupturable layers of ethyl cellulose.

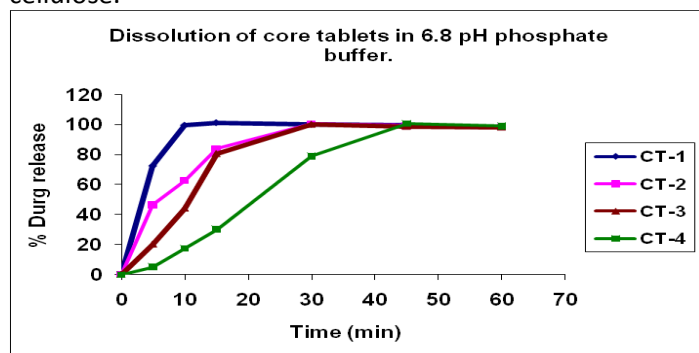


Figure 1: Dissolution of aceclofenac core tablet formulation with various concentration of disintegrant Sodium starch glycolate 8% (CT-1), 4% (CT-2), 2% (CT-3) & without disintegrant (CT-4)

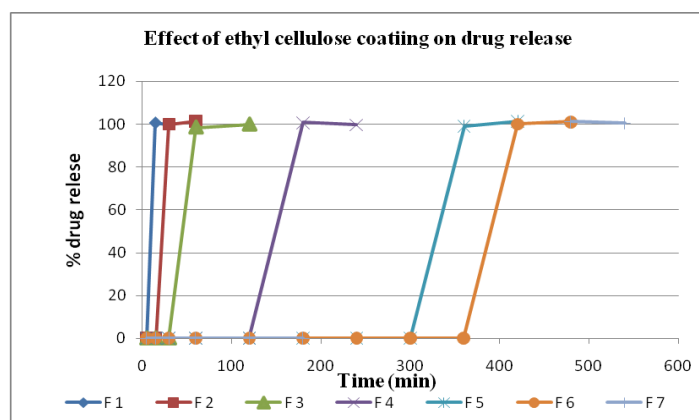


Figure 2: Effect of ethyl cellulose on drug release.

B. Dissolution of aceclofenac by using swelling and rupturable layers of ethyl cellulose.

When the core tablet of Aceclofenac coated with of inner swelling layer of croscarmellose sodium (Ac-Di-Sol).and outer layer by Coating of rupturable layer is done at

various concentration of ethyl cellulose F1 (5 %), F2 (10%), F3 (12.5%), F4 (13.5 %), F5 (15%), F6 (17.5%), and F7 (20%). By rupturable polymer (EC) lag time increases with increasing of EC in formulation F1 to F7. It was observed that as concentration of ethyl cellulose increases lag time also increases. It may due to hydrophobic nature of ethyl cellulose.



Figure No 3: Side view of bust release of dug from rupturable coating. After erosion of ethyl cellulose medium get contacted with inner swelling layer of croscarmellose sodium (Ac-Di-Sol) bust effect on coating layer give rapid drug release.

The order of the time lag changed according to increasing concentration of ethyl cellulose F 1(5 %)-15 min, F2 (10%) 30 min, F 3 (12.5%)-60 min, F4 (13.5 %)-16 min, F5 (15%)-360 min, F6 (17.5%)-420 min, and F 7 (20%)-480 min. Seven formulations were prepared and formulation F5 possessed good lag time 6 hr and showed pulsatile drug delivery pattern. The lag time and drug release profile of Aceclofenac from rupturable layer coated tablets using increasing concentration of ethyl cellulose are given in table No 5 and illustrated in figure No 2

Conclusion:

The objective of this work was to develop and evaluate of Aceclofenac tablets with swelling and rupturable layers of ethyl cellulose. When the core tablet of Aceclofenac coated with of inner swelling layer of croscarmellose sodium (Ac-Di-Sol).and outer layer by Coating of rupturable layer is done at various concentration of ethyl cellulose F1 (5 %), F2 (10%), F3 (12.5%), F4 (13.5 %), F5 (15%), F6 (17.5%), and F7 (20%). By rupturable polymer (EC) lag time increases with increasing of EC in formulation F1 to F7. It was observed that as concentration of ethyl cellulose increases lag time also increases. It may due to hydrophobic nature of ethyl cellulose.

It is possible to obtain a time-lag of 4.0 to 8.0 hrs with different core composition with different release kinetics. Tablet of F5 formulation is best formulation gives pulsatile release pattern with initial 6hr lag time and then burst release.

Acknowledgement

Authors are thankful to Ajanta pharma ltd for the gift samples of Aceclfenac and Dr. Ved Prakash Patil Pharmacy College. Aurangabad for their help.

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Conflict of Interest: None Declared