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DEVELOPMENT AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF ACECLOFENAC SODIUM

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Keywords:

Pulse release tablets, Aceclofenac Sodium, rheumatoid arthritis, compression coating method, lag time

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ABSTRACT

The ability to deliver therapeutic agents to the patients at the right site of action and in right amount has been a matter of interest recently and thus a pulsatile release formulation is prepared. A pulse is designed in such a way that a complete and rapid action is achieved after the completetion of lag time. The main objective of this study was to design and develop pulsatile drug intended for treatment of early morning stiffness and symptomatic relief from pain in patients with rheumatoid arthritis. Aceclofenac sodium was chosen as the model drug for study. The pulsatile release tablets developed consisted of an inner layer of rapidly disintegrating core tablet containing active ingredient and superdisintegrant, while outer compression coated barrier layer comprised of different polymers in varied proportions. Compression coating of optimized core tablets was done by using different grades of two polymers i.e. HPMC K4M & Ethyl Cellulose in varying concentration. Six formulations were prepared and evaluated for weight variation test, thickness, hardness, friability, lag time and dissolution study. An increase in lag time was observed with the increasing concentration of ethyl cellulose. Formulation C5 containing HPMC K4M & EC (20:80) was found to provide maximum lag time of 5hrs and thus, enteric coated with 3% CAP (cellulose acetate phthalate) solution, so as to increase the lag time and minimize the variability in gastric region. The CAP coated formulation showed lag time of 7 hrs and 98% drug release.

INTRODUCTION

Chronopharmaceutics is a branch devoted to design and evaluation of drug delivery system that release the bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy. It deals with the study of three types of biorhythms affecting human body. Ultradian, which are cycles shorter than a day (for example, the milliseconds it takes for a neuron to fire or a 90 minute sleep cycle), circadian, which last about 24 hours (such as sleeping and waking patterns) and infradian, referring to cycles longer than 24 hours (for example, monthly menstruation). Certain diseases, such as arthritis, hypercholesterolemia, asthma, duodenal ulcer, cancer, cardiovascular disease are dependent on circadian rhythms.[1] The symptoms of such diseases became worse during the midnight or in the early morning, so the timing of drug administration and nature of the drug delivery system need careful consideration. By tuning drug delivery to circadian patterns of diseases, maximum therapeutic benefit from drug can be achieved and side effects can be reduced [2]. In such diseases a continuous delivery of drug is not desirable rather release of drug after a certain lag time is required for their effective management. Such a release pattern is known as "Pulsatile release". The main focus of pulsatile drug delivery is to release drugs on a specific pre-programmed pattern i.e. at appropriate time and at appropriate site of action. Pulsatile drug delivery is gaining increasing attention as it offers more sophisticated and better approach over the traditional sustained release and conventional drug delivery systems.[3]

Rheumatoid arthritis (RA) is an autoimmune disease that results in a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks flexible (synovial) joints. It can be a disabling and painful condition, which can lead to substantial loss of functioning and mobility if not adequately treated. The process involves an inflammatory response of the capsule around the joints (synovium) secondary to swelling (turgescence) of synovial cells, excess synovial fluid, and the development of fibrous tissue (pannus) in the synovium. The pathology of the disease process often leads to the destruction of articular cartilage and ankylosis (fusion) of the joints.

Thus, taking into consideration the pharmacokinetics as well as objective of chronotherapy, an attempt has been made to design and evaluate pulsatile drug delivery system of Aceclofenac Sodium which when administered at bedtime will deliver the drug during early morning hours when the stiffness in the joints is maximum.

MATERIALS AND METHOD

Materials: Aceclofenac Sodium was obtained as gift sample from Crescent Therapeutics Ltd., Baddi, India. Cross Carmellose Sodium, Sodium Starch Glycolate, Cross Povidone, MCCP, HPMC E5, HPMC K4M, Ethyl Cellulose & Cellulose Acetate Pthalate was obtained from Arion Health Care Ltd., Baddi, India. All other chemicals were of pharmaceutical grade.

1.1 FORMULATION OF COMPRESSION COATED TABLETS OF ACECLOFENAC SODIUM

The pulsatile drug release tablets of Aceclofenac Sodium were prepared by compression coating method in two stages: initially core tablets, containing the active ingredient and superdisintegrant were prepared and evaluated. During second stage core tablets were coated with an erodible outer barrier coating layer of polymer to obtain the necessary lag time before drug release.

Preparation of Core Tablets

Twelve different formulations (F1 – F12) of core tablets comprsing Aceclofenac Sodium were formulated using three super disintegrants in varying concentration (2%, 3%, 4% & 5%) with the excipients such as Microcrystalline Cellulose (PH-102), Sodium Starch Glycolate, Cross Carmellose Sodium, Crosspovidone, Talcum, Magnesium stearate. API (#30), MCC PH-102 (#30), Superdisintergrants (#40) were sifted through the desired sieve and was blended for 10 minutes followed by addition of Talc (#40) and Magnesium stearate (#40). The mixture was dry blended for 5 minutes and was evaluated for various pre-compression parameters like bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio. After evaluation of powder blend, the tablets were compressed with a tabletting machine having 6.8 mm flat punches set. Composition of coating layer for various formulations is shown in Table 1.

TABLE 1: FORMULATION COMPOSITION OF ACECLOFENAC SODIUM CORE TABLETS

Ingredients Used	Quantity Per Formulation (in mg)											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Aceclofenac Sodium	100	100	100	100	100	100	100	100	100	100	100	100
Cross Carmellose Sodium	1.2	1.8	2.4	3.0	-	-	-	-	-	-	-	-
Sodium Starch Glycolate	-	-	-	-	1.2	1.8	2.4	3.0	-	-	-	-
Cross Povidone	-	-	-	-	-	-	-	-	1.2	1.8	2.4	3.0
Microcrystalline Cellulose (PH-102)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Talcum (2%)	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Magnesium (2%)	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Net Weight (in mg)	160	160	160	160	160	160	160	160	160	160	160	160

Evaluation of core tablets

The core tablets were evaluated for weight variation test, thickness, hardness, friability, disintegration time and *in-vitro* dissolution study and results are shown in the table 2.

TABLE 2: RESULTS FOR EVALUATION PARAMETERS OF CORE TABLETS

Formulation	Weight Variation(mg)	Hardness (kg/cm^2)	Friability (%)	Disintegration Time (sec)	Thickness (mm)	Content Uniformity(%)
F1	160.8 ± 1.641	5.34 ± 0.115	0.224 ± 0.003	99.34 ± 0.058	2.80 ± 0.006	98.36 ± 0.037
F2	161.3 ± 1.444	5.67 ± 0.057	0.235 ± 0.003	85.44 ± 0.045	2.80 ± 0.006	98.42 ± 0.046
F3	161.2 ± 1.141	5.78 ± 0.057	0.222 ± 0.001	69.34 ± 0.030	2.79 ± 0.006	98.44 ± 0.035
F4	162.7 ± 7.041	5.37 ± 0.057	0.234 ± 0.004	48.57 ± 0.026	2.80 ± 0.006	98.74 ± 0.050
F5	160.9 ± 1.242	5.34 ± 0.057	0.235 ± 0.002	74.73 ± 0.041	2.80 ± 0.006	98.40 ± 0.032
F6	161.0 ± 1.489	5.87 ± 0.057	0.226 ± 0.001	58.59 ± 0.05	2.79 ± 0.006	98.74 ± 0.051
F7	161.6 ± 1.667	5.50 ± 0.057	0.213 ± 0.003	33.47 ± 0.020	2.79 ± 0.011	99.02 ± 0.047
F8	161.84 ± 1.724	5.34 ± 0.103	0.232 ± 0.001	10.72 ± 0.040	2.80 ±0.006	99.05 ± 0.020
F9	161.34 ± 1.182	5.54 ± 0.057	0.244 ± 0.003	98.26 ± 0.010	2.80 ± 0.006	98.44 ± 0.036
F10	161.04 ± 1.403	5.37 ± 0.057	0.245 ± 0.003	76.37 ± 0.039	2.79 ± 0.006	98.64 ± 0.035
F11	161.34 ± 1.268	5.37 ± 0.057	0.375 ± 0.001	59.16 ± 0.039	2.80 ± 0.006	98.74 ± 0.050
F12	161.24 ±1.446	5.27 ± 0.057	0.385 ± 0.003	31.46 ± 0.061	2.40 ± 0.006	98.43 ± 0.047

*Values expressed as Mean ± S.D (n=3)

Compression Coating and CAP Solution Coating of Core Tablets

On the basis of results of the evaluation parameters of core tablets, the F8 formulation containing 5 % SSG as superdisintegrant was found to show least disintegration time and better integrity among all formulations; hence it was selected for compression coating. The compression coating was done to evaluate the barrier properties of HPMC and ethyl cellulose to obtain the desired lag time before drug release. Six formulations (C1-C6) using varied ratio of ethyl cellulose (EC) & HPMC K4M polymers were prepared. [25-28] The composition of coating layer for various formulations is shown in Table 3.

TABLE 3: COMPOSITION OF COATING BARRIER LAYER

Materials used in Blend	Mixed Blend formulation					
	C1	**C2**	**C3**	**C4**	**C5**	**C6**
HPMC K4M	100:0	80:20	60:40	40:60	20:80	0:100
Ethyl Cellulose						
PVP 30	5%					
Talcum	2%					
Magnesium Stearate	2%					

*Weight of blend used for compression coating is 400:160 mg (Mixed Blend: Core Tablet)

1.2 EVALUATION OF COMPRESSION COATED TABLETS

The compression coated tablets were evaluated for following parameters and the results are shown in the table 4.

1. Weight variation Test

The weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit.

2. Thickness

The thickness of tablets was determined by using screw gauge and the standard deviation was calculated. The data of thickness is shown in table 4.

3. Hardness Test

The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 3 tablets were chosen randomly and tested for hardness. The average hardness of 4 determinations was recorded.

4. Friability Test

Ten tablets were weighed and placed in the Roche Friabilator and apparatus was rotated at 25 rpm for 4 min. After revolution the tablets were dusted and weighed. The friability is given by the formula:

$$\mathbf{F = (1\text{-}Wo/W) \times 100}$$

Where Wo is the weight of tablets before the test and W is the weight of the tablet after the test. [10]

5. Lag Time Determination by Rupture Test

The lag time of pulsatile release tablets is defined at the time when the outer coating starts to rupture. It was determined visually by using USP dissolution testing apparatus II (900ml buffer 37.0± 0.5 °C, 50 rpm). Initially tablets were subjected to dissolution test in HCl buffer pH 1.2 for 2 h and after that the medium was changed to phosphate buffer pH 7.4. The time at which the outer coating layer starts to rupture was noted. [9, 10]

6. *In vitro* Drug Release

In vitro drug release of Aceclofenac sodium from core tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml of phosphate buffer (pH 7.4) at 37 ± 0.5 ^{0}C. The speed of rotation of paddle was set at 100 rpm. At a predetermined time interval; 5 ml samples were withdrawn, and was filtered through

Whatman filter paper. Absorption of solution was checked by UV spectrophotometer at 275 nm and drug release was determined.

TABLE 4: RESULTS FOR EVALUATION PARAMETERS OF ACECLOFENAC SODIUM COMPRESSION COATED TABLETS

Formulation	Weight Variation (n = 3)	Hardness In kg/cm^2	Thickness in mm	Lag Time (in mins)
C1	460.8 ± 1.641	5.56 ± 0.115	4.70 ± 0.006	131.50 ± 4.59
C2	461.3 ± 1.444	5.58 ± 0.057	4.70 ± 0.006	165.16 ± 3.54
C3	462.2 ± 1.141	5.58 ± 0.057	4.69 ± 0.006	216.16 ± 4.11
C4	462.7 ± 7.041	5.55 ± 0.057	4.70 ± 0.006	289.83 ± 4.11
C5	461.9 ± 1.242	5.54 ± 0.057	4.70 ± 0.006	323.33 ± 4.92
C6	461 ± 1.489	5.57 ± 0.057	4.69 ± 0.006	271.16 ± 6.17

*Values expressed as Mean ± S.D (n=3)

Since, formulation C5 containing 80:20 ratio of EC & HPMC K4M showed maximum lag time and % drug release of 98.12 % so, it was further enteric coated with 3% CAP solution to bypass stomach and prolong the lag time to desired 7 hrs period for the delivery of Aceclofenac Sodium at a pulse in early mornings (after 7 hours of administration).

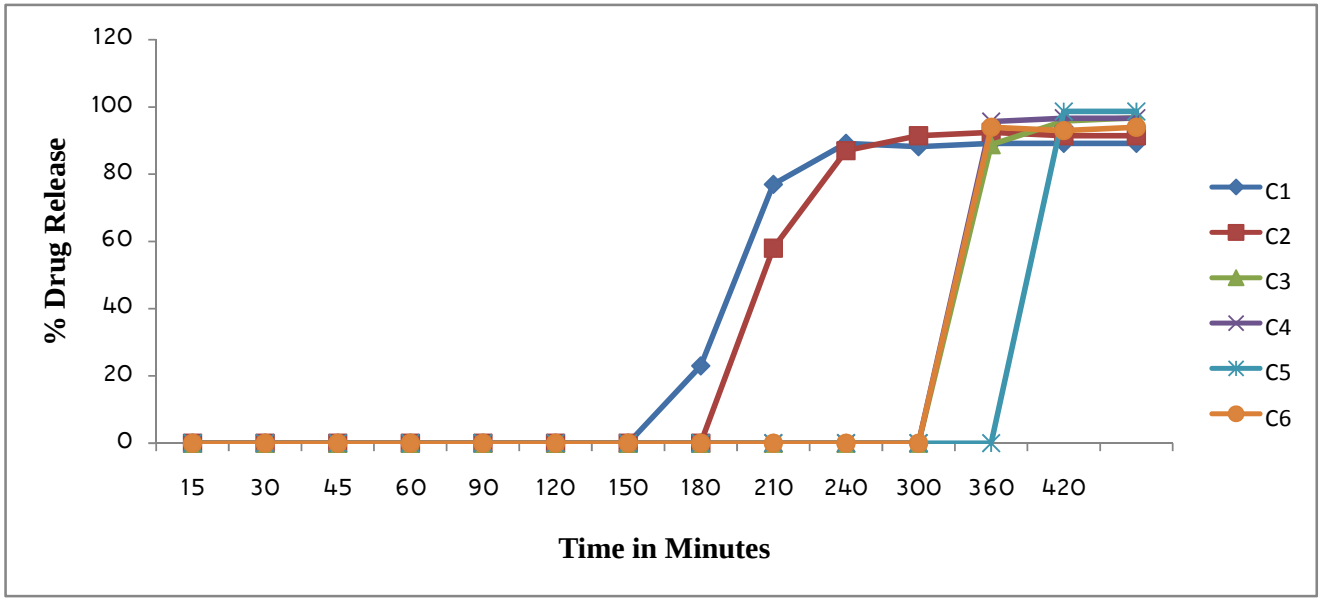

FIGURE 1: GRAPH SHOWING *IN-VITRO* DRUG RELEASE OF ACECLOFENAC SODIUM COMPRESSION COATED TABLETS (C1-C6)

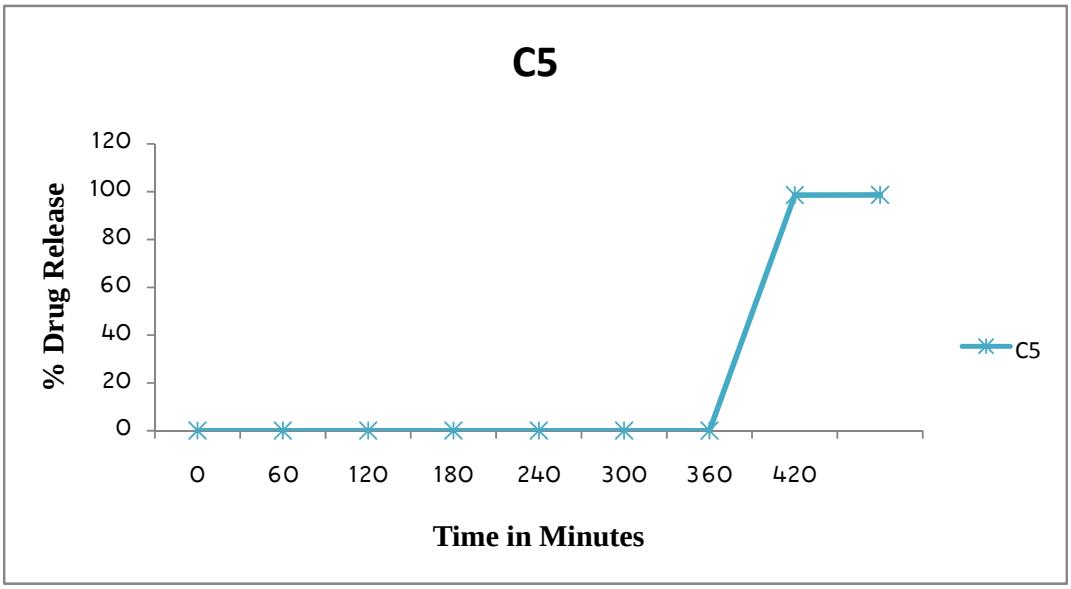

FIGURE 2: GRAPH SHOWING *IN-VITRO* DRUG RELEASE (C5) OF ACECLOFENAC SODIUM CAP SOLUTION COATED TABLETS

STABILITY STUDY

Stability Study was carried out at 40^{o}C temp and 75% RH for 60 days. The CAP coated C5 formulation was packed in bottle slightly plugged with cotton and capped and percent drug content was checked at regular time intervals. The results obtained were in the required limits and there is no change in colour or physical appearance of tablets.

TABLE 7: STABILITY STUDY DATA OF CAP COATED C5 FORMULATION

Time (days)	Accelerated Conditions (40˚C/ 75% RH)	
	Physical appearance	Drug content
0	+	99.07±0.23
7	+	99.05±0.15
15	+	99.42±0.45
21	+	99.10±0.09
30	+	98.82±0.32
38	+	98.74±0.07
45	+	98.63±0.04
54	+	98.54±0.07
60	+	98.52±0.09

*Values expressed as Mean ± S.D (n=3)

Result: No change seen in physical appearance.

RESULTS AND DISCUSSION

In the present study, an attempt was made to design pulsatile drug delivery system of Aceclofenac Sodium for the effective treatment of Rheumatoid Arthritis. Peak symptoms are observed in the early morning. If pulsatile release tablets of Aceclofenac Sodium taken at bedtime, the chronotherapeutic system would release the drug after a desired lag time and morning stiffness & pain restricted to minimum providing relief in Rheumatoid Arthritis. 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 Aceclofenac Sodium were prepared by using Sodium starch glycolate as a superdisintegrant in concentration 5% by direct compression technique. Avicel PH-102 was used as diluent and Magnesium Stearate and Talcum were added to improve the flow properties of blend. To obtain desired lag time before drug release, the core tablets were coated with varied ratio of HPMC K4M & EC polymers to achieve barrier properties by compression coating technique. PVP 30 was added to coating composition to improve the stability and adhesion properties of the coating layer. The compression coated tablets were evaluated for weight variation, thickness, hardness, friability, drug content and lag time. The weight variation of tablets of all the formulations (C1-C6) ranged between 460.68±1.641 to 462.7±7.041. The hardness of tablets of all the formulations ranged between 5.54±0.057 to 5.58±0.057 kg/cm^2. Lag time of all the formulations was found between 131.50±4.59 to 323.33±4.92. It was observed that the formulation containing high ratio of HPMC showed lesser lag time that may be due to the hydrophilic nature of HPMC. When the combination of HPMC and the Ethyl cellulose was used, HPMC hydrated upon contact with dissolution medium and formed swollen compact with ethyl cellulose. The Hydrophobicity of the ethyl cellulose retarded the rapid dissolution/hydration of HPMC therefore dissolution medium could not disintegrate the tablet outer coating layer but the coating eroded slowly. As the concentration of ethyl cellulose was increased, the lag time also increased upto certain level. Among all the formulations, C5 formulation containing 80:20 ratio of EC & HPMC K4M showed maximum lag time of 323.16±4.92 minutes (approx. 5 hrs).

The *in-vitro* dissolution test was done to observe the drug release profile of all the formulations. Percentage drug released ranged between 89.2 - 98.12 % for all the formulations. A zero drug release period was observed initially followed by a sigmoidal drug release pattern characteristic of the pulsatile drug delivery systems. Since, formulation C5 showed maximum lag time and % drug release of 98.12 % so, it was further enteric coated with 3% CAP solution to bypass stomach and prolong the lag time to desired 7 hrs period for the delivery of Aceclofenac Sodium at a pulse in

early mornings (after 7 hours of administration). From the *in-vitro* drug release study of the CAP coated C5 formulation, it was observed that with these formulations, there was absolutely no drug release in simulated gastric fluid (acidic pH 1.2) for 2 hours. CAP gives zero release in acidic media for the first two hours and the dissolution was then continued in pH 7.4 phosphate buffer and here the lag time of around 7hrs was observed after which the polymeric coat ruptured and immediate drug release took place amounting to 98% of total drug realeased. From stability studies, it was observed that there were no significant changes in physical properties and drug content of core and coated tablets, and therefore the formulations are quite stable. A satisfactory attempt was made to develop pulsatile system of Aceclofenac Sodium and evaluated it.

CONCLUSION

Since, the aim of this study was to explore the feasibility of time dependent pulsatile drug delivery system of Aceclofenac Sodium for the effective management of Rheumatoid Arthritis. The rational design of chronotherapeutic drug delivery system of Aceclofenac Sodium was successfully prepared which provided desired lag time for time controlled pulsatile release of Aceclofenac Sodium useful for chronopharmaceutics of Rheumatoid Arthritis. The results of in vitro dissolution tests indicated that amount of polymer in the formulation affects the drug release rate. The release of the drug was sharp and complete after the lag time, which is necessary for any pulsatile drug delivery system. Thus, Pulsatile tablets of Aceclofenac Sodium would deliver the drug according to the need of the patient for control of morning stiffness & pain in joints at early mornings and would be useful for effective mnagement of Rheumatoid Arthritis.

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