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DEVELOPMENT AND EVALUATION OF FLOATING PULSATILE RELEASE TABLET OF ACECLOFENAC

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Abstract

The objective of this study was to develop and evaluate a floating tablet pulsatile drug delivery system intended for treatment of early morning stiffness and symptomatic relief from pain in patients with rheumatoid arthritis. Aceclofenac as a model drug by using various proportion of polymers such as HPMC K4 M and Ethyl celulose. Eight formulations were prepared and formulation F8 possessed good floating property with total floating time 470 and showed pulsatile drug delivery pattern the tablets were also evaluated for its hardness, friability and other *In- vitro* evaluation tests. All parameters complied with IP limits. Results of this study indicated that the combinations of hydrophilic polymers with hydrophobic polymers are suitable to optimize pulsatile drug release formulation of aceclofenac.

Keywords: chronotherapy, pulsatile delivery, floating tablet, aceclofenac.

Introduction:

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. Chronotherapeutic 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.[1,2,3,4,5]

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[6]

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.18 on oral administration at bed-time, releases aceclofenac after a desired lag time of about 420 minutes which corresponds with peak levels of proinflammatory mediators. The current study illustrates the formulation, characterization,and optimization of a trilayer for aceclofenac. The system is based on floating layer,drug layer and polymer layer.

Materials and Methods

Materials

Aceclofenac, was a kind gift sample from Ajanta pharma mumbai , Pune. Hydroxypropyl methylcellulose (HPMC K4M) and ethyl celulose from Colorcon Asia Ltd, Goa .other solvents and reagents used were of analytical grade.

Drug solubility study

Drug solubility studies focus on drug-solvent system that could occur during the delivery of a drug candidate.[i] Drug solubility study was performed by taking an excess quantity of aceclofenac and physical mixture of aceclofenac with excipients in 10 ml of different solutions. Then prepared solutions were kept in a shaking water bath for 24 h with 100 agitations/ min at room temperature. Then solution was passed through a whatmann filter paper and the amount of the drug dissolved was analyzed spectrophotometrically after suitable dilutions.Solubility of aceclofenac, in different solution media in Distilled Water, 0.1 N HCl, Phosphate buffer pH 6.8, Phosphate buffer pH 7.4

Formulation development

Formulation development study was carried out for the preparation of floating pulsatile release tablet, by using direct compression method.

Preparation of triple layer tablets

All ingredients of each layer shown in Table was weighed properly and passed through a 30 mesh standard sieve. The ingredients of first layer, second layer and third layer were mixed separately in mortar and lubricated with magnesium stearate (1% w/w). Powder mixture of first layer was transferred manually into the die, and then powder mixture of second layer was transferred over the first layer, finally after addition of the third layer in to the die, the total die content was compressed with 12 mm diameter flat faced punch tooling.

Table 1. Composition of triple layer tablet formulations.

F	Layer	SBC	CA	MCC pH102	DCP	EC	HPMC K4 M	MS	Aceclofenac
F1	I	10	2	50	111	50	-	2	-
	II	-	-	40	58	-	-	2	100
	III	-	-	40	83	-	100	2	-
F2	I	20	3	40	110	50	-	2	
	II	-	-	40	58	-	-	2	100
	III	-	-	40	83	-	100	2	
F3	I	30	4	40	99	50	-	2	
	II	-	-	40	58	-	-	2	100
	III	-	-	40	83	-	100	2	
F4	I	40	4	35	94	50	-	2	-
	II	-	-	40	58	-	-	2	100
	III	-	-	40	83	-	100	2	-
F5	I	40	4	35	69	75	-	2	-
	II	-	-	40	58	-	-	2	100
	III	-	-	40	83	-	100	2	-
F6	I	40	4	35	44	100	-	2	-
	II	-	-	40	58	-	-	2	100
	III	-	-	40	83	-	100	2	-
F7	I	40	4	35	18.5	125	-	2.5	-
	II	-	-	40	58	-	-	2	100
	III	40	4	40	14	-	125	2	-
F8	I	40	4	30	13.5	-	125	2.5	
	II	-	-	40	58	-	-	2	100
	III	40	4	40	14	-	125	2	-

F= Formulation code, SBC= Sodium bicarbonate, CA= Citric acid, MCC= Microcrystalline cellulose, DCP= Dicalcium phosphate, EC=Ethyl cellulose, HPMC K4M= Hydroxypropyl methylcellulose, MS=Magnesium stearate.

For the development of floating pulsatile release tablet triple layer tablet was prepared. Formulated triple layer tablet

was composed of three layers, top layer containing hydrophobic polymer (ethyl cellulose) dispersed with various percentage of gas generating agents, middle layer contains active ingredient (Aceclofenac) with other additives and bottom layer composed of hydrophilic polymer (HPMC K4M).

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[ii].

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 [iii]. **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[iii].

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

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[iv].

Buoyancy determination:

The buoyancy test of triple layer tablet and FPRT was studied by placing them in 500 ml beaker containing 0.1 N HCl, then tablet from same batches were placed in dissolution test apparatus containing 0.1N HCl, maintained at 37±0.5◦C and agitated at 100 rpm. The floating onset time (time period between placing tablet in the medium and buoyancy beginning) and floating duration of tablet was determined by visual observation..

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,

Result and discussion:

Drug solubility study

The available literature on solubility profile of aceclofenac indicated that the drug is freely soluble in acetone, methanol and practically insoluble in water. The results of aceclofenac solubility in various media and effect of different excipients are shown in **Error! Reference source not found.** and **Error! Reference source not found.**.

The solubility of aceclofenac in water was very less. Aceclofenac showed pH dependent solubility. At lower pH, the solubility was less and as the pH was raised from acidic to 6.8 the solubility drastically improved. Further increasing pH from 6.8 to 7.4 the solubility again decreased. Effect of excipients like DCP, MCC, MS does not affect the solubility of Aceclofenac, but further addition of HPMC, Sodium bicarbonate, and citric acid slightly increased the solubility, but no considerable change was found.

Table 1. Solubility of Aceclofenac in different solution media.

Medium	**Solubility (mg/ml)**
Distilled Water	0.085±0.001
0.1 N HCl	0.007±0.001
Phosphate buffer pH 6.8	13.183±0.554
Phosphate buffer pH 7.4	7.531±0.400

All values are expressed as mean ± SD, n=3

Evaluation of Tablet characteristics

Initially tablet was characterized for floating ability and result of floating ability provided in Table 2.

Table 22. Floating ability of various triple layer tablet formulation.

F	**Floating onset time (min)**	**Floating duration (min)**	**Integrity**
F1	not float	not float	Broken
F2	not float	not float	Broken
F3	not float	not float	Broken
F4	18	30	Separate into layers
F5	6 -8	45	Separate into layers
F6	<3	45	Separate into layers
F7	<3	90	Separate into layers
F8	<1	470	Intact

F= Formulation code.

Formulations from F1 to F3 get dispersed immediately in the medium without floating; this was due to the lower percentage of gas generating agent and polymer. Then formulation from F5 to F7 was formulated with higher percentage of gas generating agents and polymer. Then tablets float, but floating lag time was higher with short period of floating and tablet gets separated into layers.

During the process of layer separation it was observed that hydrophobic layer get separate initially and hydrophilic layer attached as such to middle layer. Hence it concluded that hydrophobic layer unable to make bonding with the middle layer. From this it decided that top and bottom layer should be of hydrophilic polymer to avoid the problem of layer separation.

Then F8 formulation was prepared by replacing Ethyl Cellulose with HPMC K4M. F8 formulation shows optimum floating lag time and duration. But during initial 8 h study in 0.1N HCl shows that open surface of middle layer get exposed to dissolution medium. Due to this medium exposure middle layer get erode slowly and this fails to show pulsatile release.

From all this study it concluded that, polymer coating to the surrounding surface of middle layer was necessary to avoid the contact of dissolution media.

Physicochemical properties of tablet

The results of physicochemical evaluation of tablets are given in **Error! Reference source not found.**. The tablets formulation F8 was found uniform with respect to thickness (3.50 - 3.56 mm), diameter (12 mm) and hardness (5.4 - 7.2 kg/cm^2). The friability (0.40 – 0.73%) and weight variation test complies as per I. P. limits. Good and uniform drug content (>98%) was observed within the batches.

Buoyancy determination

In vitro buoyancy study was studied, initially floating lag time and floating duration of tablet was determined simply by placing tablet in 500 ml beaker containing 0.1 N HCl. Observed floating lag time for F8, was 42, second and floating duration was >1320 min.

Initially dissolution test was performed on F8 formulation in 0.1 N HCl for initial 480 min then followed by phosphate buffer pH 6.8 for 180 min. % cumulative drug release of F8 formulation at the end of 660 min was 71.34%.

In vitro Dissolution Study:

It was observe that initial 480 min no drug release .After lag time 480 min drug release was observed in in phosphate buffer pH6.8.

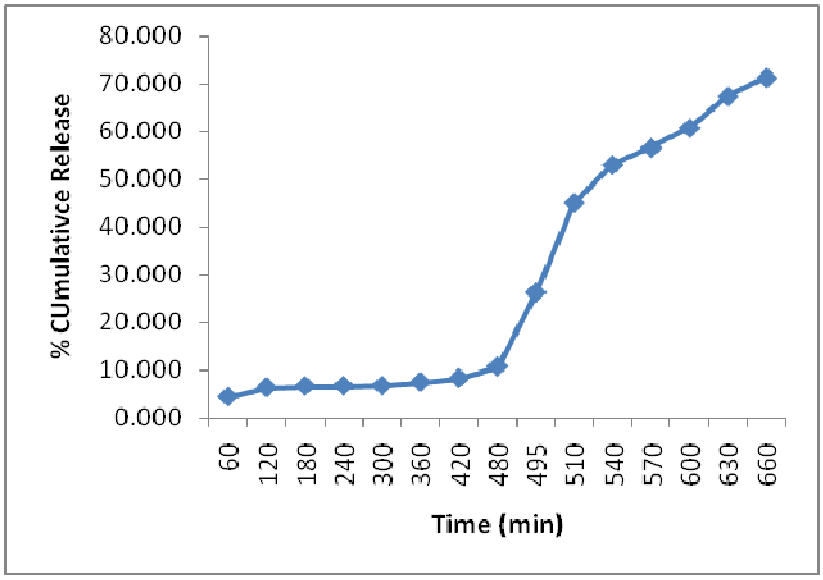

Figure 1: In vitro release profile of Aceclofenac from triple layer floating tablet F8 Formulation in phosphate buffer pH6.8.

Conclusion:

Floating pulsatile drug delivery system intended for chronopharmacotherapy is widely used for the disease which shows circadian variation. Aceclofenac is most suitable candidate for rheumatoid arthritis, osteoarthritis, pain and inflammatory conditions.

The objective of this work was to develop and evaluate a floating-pulsatile drug delivery system using hydrophilic polymer for aceclofenac and to evaluate buoyancy and drug release pattern. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having the lag phase followed by a burst release.

Triple layer tablet was prepared using hydrophilic polymer as bottom layer and hydrophobic polymer as top layer. Initially, F1 to F4 batches were prepared and evaluated for floating characteristics. All four batches show unable to float. After that F5 to F8 batches were prepared and evaluated for floating characteristics. Tablet of F8 formulation float for required period and other tablets get separate into layers. But Tablet of F8 formulation unable to give pulsatile release pattern.

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