

**FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF ZAFIRLUKAST**

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Received on: 23-05-2017; Revised on: 02-06-2017; Accepted on: 24-06-2017

ABSTRACT

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 direct compression method. The tablets were coated with an inner swellable layer containing sodium alginate & ethyl cellulose. The prepared pulsatile tablets were evaluated for the drug content, thickness and *in-vitro* release profile, etc. *In-vitro* release profile 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 Zafirlukast. The programmable pulsatile release has been achieved from table to vera 7-8 hr period, consistent with the demands of chrono therapeutic drug delivery.

Keywords: PDDS, Zafirlukast, Ftir.

INTRODUCTION

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 or ChrDDS, an existing drug molecule can "get a new life" thereby increasing its market value and competitiveness and extending patent life.

Among modified-release or dosage forms, increasing interest has currently turned to systems designed to achieve time specific (delayed, pulsative) 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 & pharmacodynamics of several drugs follow temporal rhythms, often resulting in circadian variations. Therefore, the possibility of exploiting delayed release to perform

Chronotherapy 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.

Delivery systems with a pulsatile pattern are

receiving increasing interest for the development of dosageforms, 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 (lagtime) followed by a rapid and complete release.

MATERIALS AND METHODS

Materials: Zafirlukast donated by M/s. Micro Labs Ltd., Pondicherry. Crosspovidone, Croscarmellose sodium, Sodium starch glycolate were purchased from Narmada chemicals, sodium alginate and other excipients were procured from spectrum pharma research solutions, Hyderabad.

Formulation of Compressed Tablets of Zafirlukast

The methodology adopted includes:

- 1) Preparation of core tablets of Zafirlukast.
- 2) Coating of the core tablets

Formulation of core tablet of Zafirlukast: The inner core tablets were prepared by using direct compression method as per the developed formulation table which was shown above. Accurately weighed amounts of Zafirlukast, MCC, sodium starch glycolate, Croscarmellose sodium, Crosspovidone, and Talc were dry blended for about 15min followed by addition of magnesium stearate. The mixture was then further blended for 10 min. Now the resultant powder blend was manually compressed using punching machine and finally the core tablet was obtained.

Formulation of coated tablets of Zafirlukast: The optimized core tablets were coated with coating ingredients like Sodium alginate, Ethyl cellulose. Now accurately weighed amount of barrier layer material was transferred into a 16mm die then the core tablet was placed manually at the center. The remaining amount of the barrier layer material was added into the die and compressed. 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.

EVALUATION OF FORMULATIONS:

1. Compatibility Studies

Compatibility with excipients was confirmed by FTIR studies. The pure drug and polymers were subjected to FTIR studies. In the present study, the potassium bromide disc (pellet) method was employed.

Preparation of Standard Calibration Curve of Zafirlukast in 6.8 PH BUFFER

10mg of Zafirlukast was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 6.8 phosphate buffer to give stock solution containing 1000µg/ml. The standard stock solution was then serially diluted with 6.8 phosphate buffer to get 2 to 10µg/ml of Zafirlukast. The absorbance of the solution were measured against 6.8 phosphate buffer as blank at 230nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Evaluation of Preformulation parameters

- i. Angle of repose.
- ii. Determination of Bulk Density and Tapped Density
- iii. Hausner's Ratio
- iv. Compressibility index (Carr's Index)

2. Evaluation of Tablet Properties

1. Weight variation: The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is 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. Tablet hardness: The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm². 3 tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded.

3. Friability: 20 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded.

4. Tablet thickness: Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten tablets of each formulation.

5. Content Uniformity: The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 200 mg was weighed accurately and dissolved in 100ml of buffer used. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatman's filter paper No.41.

Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured at 230 nm. The concentration of the drug was computed from the standard curve of the Zafirlukast in 6.8 phosphate buffer.

6. Disintegration time: Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in Electrolab USP disintegration test apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top, and held against a 10 mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 litre beaker containing 6.8 phosphate buffer solution at $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$ such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

7. In-vitro Dissolution time: In-vitro dissolution study of core and coated tablets of Zafirlukast was carried out using Electrolab TDT-08L USP dissolution test apparatus. The details are given as below:

Procedure: Tablet was introduced into the basket of the Electrolab TDT-08L USP dissolution test apparatus and the apparatus was set in motion, 5 ml of sample was withdrawn for half an hour at 5 min intervals. Samples withdrawn were analyzed by UV spectrophotometer for presence of drug using buffer solution as blank.

Evaluation of Pulsatile Drug Delivery Systems:

1. Characteristics of coated tablets of Zafirlukast

Characteristics of tablets of Zafirlukast 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 Zafirlukast 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.

2. In-vitro Dissolution methods:

Dissolution testing of pulsatile delivery systems with the conventional paddle method at 50 rpm and $37 \pm 0.5^{\circ}\text{C}$ 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 0.1N HCL 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 spectrophotometer (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.

3. Stability Studies:

In the present study optimized formulation was selected for the study and formulations were 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.

RESULTS AND DISCUSSION

Determination of Zafirlukast λ -max: Determination of Zafirlukast λ -max was done in 6.8 ph buffer for accurate quantitative assessment of drug dissolution rate. The Zafirlukast peak value is 230.

The linearity was found to be in the range of 2-12 $\mu\text{g/ml}$ in 6.8 ph buffer. The regression value was closer to 1 indicating the method obeyed Beer-lamberts' law.

The solubility studies were conducted in various buffers we can say that 6.8ph buffer has more solubility when compared to other buffer solutions.

FTIR STUDIES: It indicates that the drug was intact and has not reacted with the excipients used in the formulation and hence they are compatible. Hence, it can be concluded that the drug is in free-state and can release easily from the polymeric

network in the free form.

Pre-compression parameters of core tablet of Zafirlukast:

Pre-compression parameters were conducted for all formulations blend and were found to be satisfactory. Bulk density was found in the range 0.461- 0.602 g/sqcm and tapped density in the range of 0.440- 0.523g/sqcm. Using these two density factors Hausner's ratio and compressibility index was calculated. The powder blend of all formulations had Hausner's ratio was between 1.11 – 1.16 which indicates better flow property and compressibility index between 10.57 to 15.20 which indicates fair flow ability property. The fair flow ability property of the powder blend was also evidenced with angle of repose between 25.14 – 29.97 which is below 40 indicating good flow ability.

Post compression parameters of core tablets: The percentage weight variations for all formulations were given. All the formulated (F1 to F9) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits. The weights of all the tablets were found to be uniform with low standard deviation values.

Hardness test: The measured hardness of tablets of all the formulations ranged between 3-4 kg/cm². This ensures good handling characteristics of all batches.

Disintegration test for core tablets: It was found between 30 – 82 seconds ensuring that all the cores of different formulations were rapid disintegrating type.

Friability Test: The % friability was less than 1 % in all the formulations ensuring that the tablets were mechanically stable.

Evaluation of Physical Parameters of compressed tablets of Zafirlukast:

Weight Variation Test: The percentage weight variations for all formulations were given. All the formulated (C1F6 to C6F6) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits. The weights of all the tablets were found to be uniform with low standard deviation values.

Hardness test: The measured hardness of tablets of all the formulations ranged between 5.08 – 5.28 kg/cm². This ensures good handling characteristics of all batches.

Thickness: The measured thickness of tablets of all the formulations ranged between 4.72 - 4.88mm. This ensures good handling characteristics of all batches.

Friability Test: The % friability was less than 1 % in all the formulations ensuring that the tablets were mechanically stable. The percentage of drug content for core tablets was found to be between 91.22% - 98.82%. It complies with official specifications.

The percentage of drug content for press coated tablets were found to be between 94.28% - 99.86%. It complies with official specifications.

From the *In vitro* dissolution data of the core tablets it was concluded that the drug release was found to be maximum at 30mins in F9 formulation containing crosspovidone(9mg).

whereas the press coated tablets the maximum drug release was found to be in formulation C6F9 showing 98.89% of drug release at the end of 8hrs.

ACCELERATED STABILITY STUDIES:

Stability studies proved that the formulation is quite stable and drug content was affected to a lesser extent in case of the core tablet, while in case of coated formulations no change was observed. So it can be concluded that coating of tablets seems to decrease the effect of temperature and moisture on the degradation of Zafirlukast.

CONCLUSION

A satisfactory attempt was made to develop pulsatile system of Zafirlukast and evaluated it. From the reproducible results obtained from the executed experiments it can be concluded that: On the basis of drug content, *in-vitro* release studies and its kinetic data F9 of core tablet and C6F9 of coated tablet were selected as optimized formulations for designing Pulsatile device.

Therefore the study proved that coated Zafirlukast can be successfully used as a time dependent modified Chronopharmaceutical formulation. Stability studies proved that the formulation is quite stable and drug content was affected to a lesser extent in case of the core tablet, while in case of coated formulations no change was observed. So it can be concluded that coating of tablets seems to decrease the effect of temperature and moisture on the degradation of Zafirlukast. Finally from the above results we can conclude that pulsatile drug delivery system of Zafirlukast can be formulated using above mentioned polymers.

Table 1: FORMULATION TABLE OF CORE TABLETS:

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zafirlukast	10	10	10	10	10	10	10	10	10
Sodiumstarch glycolate	3	6	9	--	--	--	--	--	--
Croscarmellose sodium	--	--	--	3	6	9	--	--	--
Crosspovidone	--	--	--	--	--	--	3	6	9
Mannitol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Mg.stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2

Table 2: Composition of compression coated tablets

Formulation	C1F6	C2F6	C3F6	C4F6	C5F6	C6F6
Core	100	100	100	100	100	100
Sodium alginate	400		200	150	250	275
Ethyl cellulose		400	200	250	150	125
Total weight	500	500	500	500	500	500

Table:3 In-Vitro Release Profile of formulations (F1-F9):-

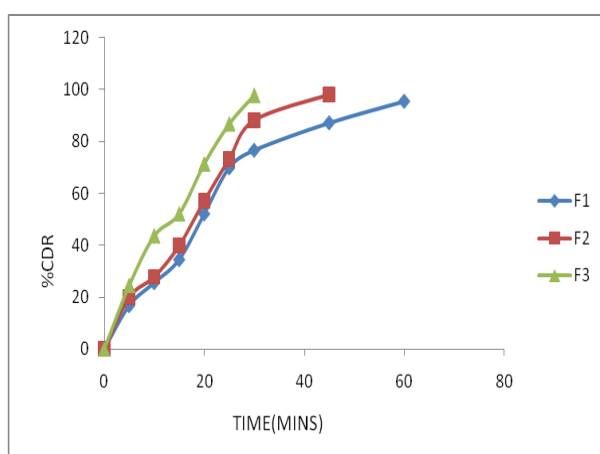
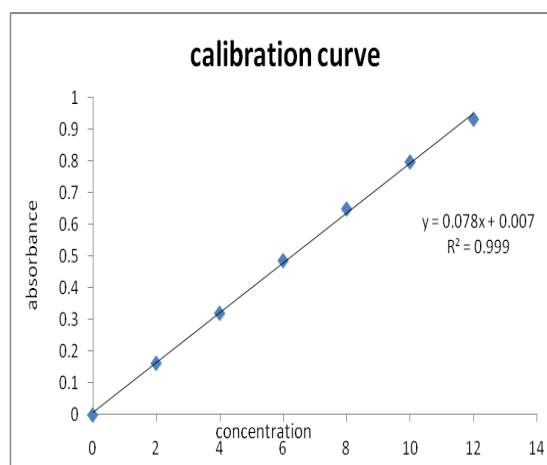
TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	16.78	19.96	24.47	24.59	28.88	36.40	40.11	46.26	49.13
10	25.57	27.78	43.56	32.48	34.60	48.26	54.74	59.69	62.22
15	34.49	39.90	52.02	41.79	48.98	59.36	63.60	66.78	79.65
20	52.11	57.15	71.19	52.80	67.54	74.20	75.09	79.04	84.14
25	69.90	73.30	86.62	65.60	74.59	82.47	82.97	87.23	91.10
30	76.65	88.20	97.59	76.79	82.80	98.66	87.58	92.41	99.45
45	87.19	98.16		82.63	96.19		93.30	98.91	
60	95.50			96.77			99.78		

Table- 4: Cumulative% drug release of coated different formulation (C1F9 to C6F9)

Time(HRS)	C1F9	C2F9	C3F9	C4F9	C5F9	C6F9
0	0	0	0	0	0	0
1	0.52	0.72	0.46	0.52	0.89	0.27
2	0.61	0.96	0.72	1.27	1.36	0.61
3	2.07	39.72	3.67	5.66	4.47	0.86
4	4.18	79.94	8.72	10.22	9.98	1.92
5	19.62	95.62	26.61	21.38	28.6	12.36
6	32.38	--	48.84	36.41	42.48	22.46
7	44.49	--	66.39	67.58	72.14	88.97
8	74.18	--	97.92	82.24	86.19	98.89
9	84.22	--	--	97.59	99.01	--
10	95.42	--	--	--	--	--

Table-5:in-vitro drug release mechanism of best core formulation (F9)

Batch	Zero Order	First Order
Code	r^2	r^2
F9	0.843	0.742

**Fig-1: Cumulative percentage drug release of core formulation F1-F3****Fig-2: Calibration curve**

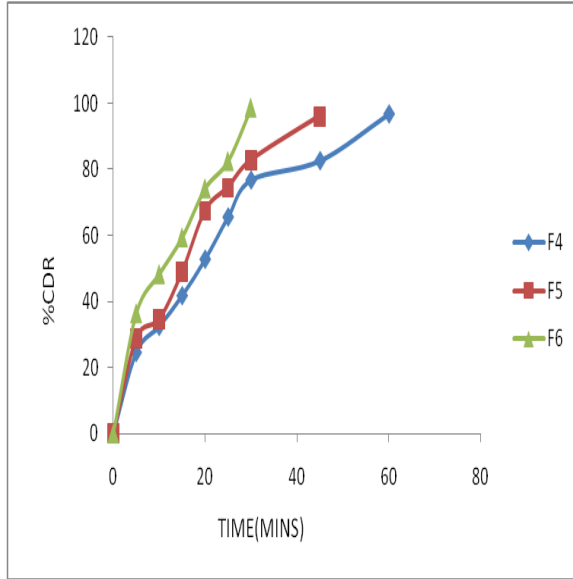


Fig-3: Cumulative percentage drug Release of core formulation F4 -F6

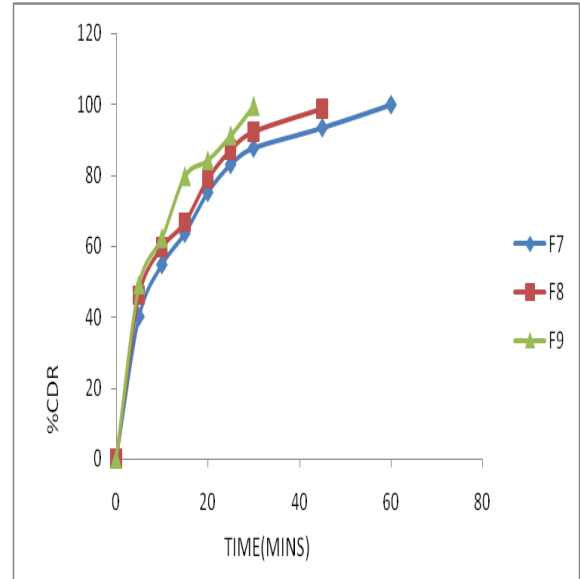


Fig-4: Cumulative percentage drug release of core formulation F7-F9

DRUG RELEASE KINETICS MECHANISMS: FOR BEST FORMULATION (F9)

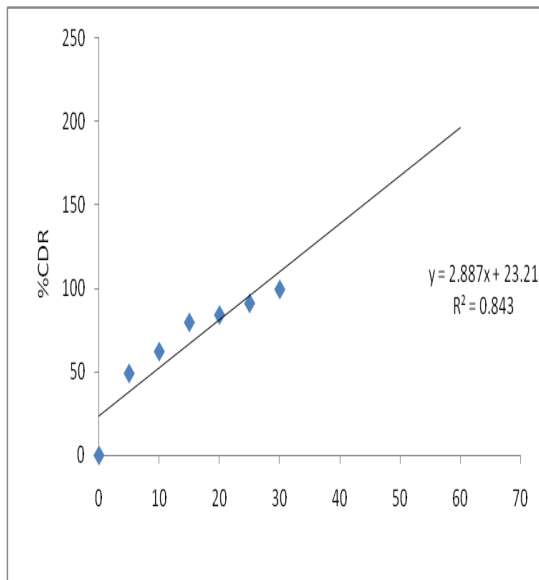


Fig-5: ZERO ORDER RELEASE KINETICS FOR F9

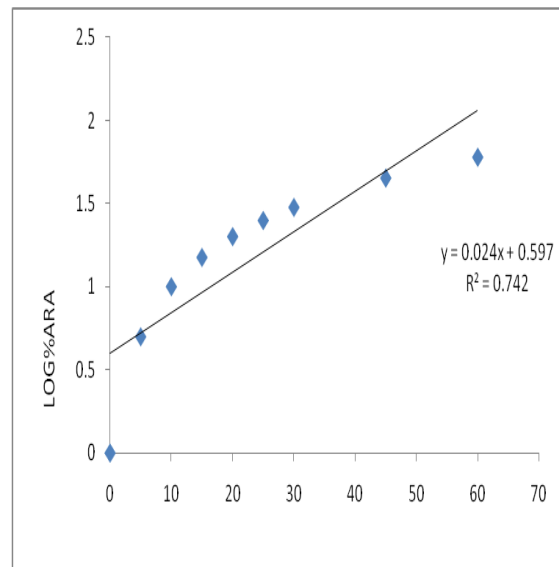


Fig-5: FIRST ORDER RELEASE KINETICS FOR F9

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