International Journal of Pharma Sciences
Vol. 7, No. 6 (2017): 1887-1891
Research Article
Open Access

ISSN: 2320-6810

Formulation and Evaluation of Pulsatile Drug Delivery System of Zafirlukast

Shaik Mehraaj* and B. Rama

Department of Pharmaceutical Technology, Mallareddy Institute of Pharmaceutical sciences, JNTU Hyderabad, Telangana.

* Corresponding author: Shaik Mehraaj, e-mail: info.mehraaj@gmail.com

Received: 09 November 2017 Accepted: 21 November 2017 Online: 02 December 2017

ABSTRACT

Aim of the present work was to formulate and evaluate an oral pulsatile drug delivery system to achieve time release of zafirlukast based on Chronopharmaceutical approach for the treatment of asthma. 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 Xanthan gum, & Guar gum, Hpmc K4M, HPMC K15M. The prepared pulsatile tablets were evaluated for the drug content, thickness and in-vitro release profile, etc. In-vitro release profiles 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 tablet over a 7-8 hr period, consistent with the demands of chronotherapeutic drug delivery.

Keywords: Zafirlukast, pulsatile drug delivery, xanthan gum, guar gum hpmc & stability studies.

1. 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 oral 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 dosage forms, 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 (lag time) followed by a rapid and complete release.

2. MATERIALS AND METHODS

2.1 Materials

Zafirlukast donated by M/s. Micro Labs Ltd., Pondicherry. lycoat, SSG,Ludiflash were purchased from Narmada chemicals, and other excipients were procured from spectrum pharma research solutions, Hyderabad.

2.2 Formulation of Compressed Tablets of Zafirlukast

The methodology adopted includes:

2.2.1 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, lycoat, SSG, ludiflash, 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.

2.2.2 Formulation of coated tablets of Zafirlukast

The optimized core tablets were coated with coating ingredients like Xanthan gum, Guar gum. 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.

2.3 Evaluation of Formulations

2.3.1 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.

2.3.2 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 was measured against 6.8 phosphate buffer as blank at 238nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

2.4 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)

2.5 Evaluation of Tablet Properties

2.5.1 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.

2.5.2 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.

2.5.3 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.

2.5.4 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.

2.5.5 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 un dissolved matter was removed by filtration through Whattman's filter paper No.41. Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured at 238 nm. The concentration of the drug was computed from the standard curve of the Zafirlukast in 6.8 phosphate buffer.

2.5.6 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°C ± 1°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.

2.5.7 In vitro Dissolution time:

In-vitro dissolution study of core and coated tablets of Zafirlukast was carried out using Lab India DS 8000 USP dissolution test apparatus. The details are given as below:

Procedure

Tablet was introduced into the basket of the Lab India DS 8000 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 a analyzed by UV spectrophotometer for presence of drug using buffer solution as blank.

2.6 Evaluation of Pulsatile Drug Delivery Systems

2.6.1 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.

2.6.2 In-vitro Dissolution methods

Dissolution testing of pulsatile delivery systems with the conventional paddle method at 50 rpm and 37±0.5°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 spectrophometer (PG Instruments T60) for the presence of the drug. Dissolution tests were performed.

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.

2.6.3 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 40oC 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 dilutedand estimated spectrophotometrically by keeping pH 6.8 buffer as blank. % drug remained undecomposed was checked for both core and coated tablets

3. RESULTS AND DISCUSSION

3.1 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 238. The linearity was found to be in the range of 2-12 µg/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 6.8 ph buffer has more solubility when compared to other buffer solutions.

3.2 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.

3.3 Precompression parameters of core tablet of Zafirlukast

Pre-compression parameters were conducted for all formulations blend and were found to be satisfactory. The angle of repose of different formulations was ≤ 30.68 which indicates that material had good flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.42g/cm^3 to 0.52g/cm^3.Tapped density was found between 0.48g/cm^3 to 0.60g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 11.53-15.518 and Hausner's ratio from 1.12-1.18 which reveals that the blends have good flow character.

3.4 Post compression parameters of core tablets

3.4.1 Weight Variation Test

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.

3.4.2 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.

3.4.3 Disintegration test for core tablets

It was found between 30 – 86 seconds ensuring that all the cores of different formulations were rapid disintegrating type.

3.4.4 Friability Test

The % friability was less than 0.77 % in all the formulations ensuring that the tablets were mechanically stable.

3.5 Evaluation of Physical Parameters of compressed tablets of Zafirlukast:

3.5.1 Weight Variation Test

The percentage weight variations for all formulations were given. All the formulated (Z1F9 to Z8F9) 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.

3.5.2 Hardness test

The measured hardness of tablets of all the formulations ranged between 5.12 – 5.36 kg/cm2. This ensures good handling characteristics of all batches.

3.5.3 Thickness

The measured thickness of tablets of all the formulations ranged between 4.65 - 4.85mm. This ensures good handling characteristics of all batches.

3.5.4 Friability Test

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

The percentage of drug content of core tablets for F1 to F9 was found to be between 90.23% - 98.86%. It complies with official specifications. The percentage of drug content of press coated tablets for Z1F9 to Z8F9 was found to be between 93.30% - 99.71%. It complies with official specifications. From the drug release kinetics of the core tablet it was concluded that the formulation F9 containing ludiflash 12mg shows maximum drug release at the end of 30mins and it follows first order drug release. From the drug release kinetics of the press coated tablet it was concluded that the formulation Z3F9 maintains lag phase for 5 hours and the drug release was bursted at the end of 8hours. It follows first order release and follows super case II transport mechanism. 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.

Table 1: Formulation of Core Tablets.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zafirlukast	10	10	10	10	10	10	10	10	10
lycoat	5	7.5	12.5	--	--	--	--	--	--
SSG	--	--	--	5	7.5	12.5	--	--	--
Ludiflash	--	--	--	--	--	--	5	7.5	12.5
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Mg.stearate	4	4	4	4	4	4	4	4	4
Talc	2	2	2	2	2	2	2	2	2
Total wt	100	100	100	100	100	100	100	100	100

Table 2: Composition of compression coated tablets.

Formulation	Z1F9	Z2F9	Z3F9	Z4F9	Z5F9	Z6F9	Z7F9	Z8F9
Core	100	100	100	100	100	100	100	100
Xanthan gum	200	250	175	225	-	-	-	-
Guar gum	200	150	225	175	-	-	-	-
HPMC K 4M	-	-	-	-	200	250	175	225
HPMC K 15M	-	-	-	-	200	150	225	175
Total weight	500	500	500	500	500	500	500	500

Table 3: Cumulative percent drug release of core Zafirlukast tablets of different formulations (F1 to 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	22.59	28.88	34.40	40.11	43.26	47.13
10	25.57	27.78	33.56	30.48	36.60	42.26	52.74	59.69	62.22
15	34.49	39.90	42.02	41.79	49.98	53.36	63.60	66.78	70.65
20	52.11	57.15	61.19	50.80	65.54	72.20	75.09	79.04	84.14
25	69.90	73.30	76.62	61.60	79.59	84.47	82.97	87.23	91.10
30	76.65	82.20	85.59	72.79	88.80	96.66	87.58	92.41	99.45

45	87.19	91.16	97.40	84.63	97.19	93.30	98.91	
60	95.50	98.07		92.77		99.78		

Table 4: Cumulative % drug release of coated different formulation (Z1F9 to Z8F9)

Time(hrs)	Z1F9	Z2F9	Z3F9	Z4F9	Z5F9	Z6F9	Z7F9	Z8F9
0	0	0	0	0	0	0	0	0
1	0.54	0.41	0.22	0.51	0.89	0.55	0.28	0.41
2	0.63	0.97	0.64	0.77	1.36	1.23	0.56	0.77
3	2.03	1.75	0.84	3.69	4.47	5.60	2.81	3.69
4	4.12	2.98	1.97	8.79	9.98	10.23	9.24	8.79
5	19.65	13.69	13.36	26.65	26.6	21.36	26.65	26.65
6	32.30	38.79	74.46	48.87	47.48	34.45	48.87	48.87
7	44.47	52.65	85.97	66.30	69.14	66.54	66.30	66.30
8	74.12	68.78	98.89	87.90	87.19	80.21	87.90	87.90
9	84.20	79.96	--	99.02	95.24	96.54	99.86	92.64
10	98.46	92.64	--	--	100.01	98.26		96.22

4. CONCLUSION

An 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-vitr*o release studies and its kinetic data F9 of core tablet and Z3F9 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 timedependentmodified Chronopharmaceutical formulation.

5. REFERENCES

1. Sangita V. Timing is everything. (Cited 17 november 2009) http://www.pharmaquality.com/Feature.7ahtm.
2. Robert W, Thomas P. Drug therapy for hypercholestemia and Dyslipidemia.In: Goodmen and Gilmans. The pharmacological basis of therapeutics. 10th ed. 2003: McGraw- hill. Medical publishing division p. 971-972.
3. Filippatos TD, Derdemezis CS, Elisaf MS. Department of Internal Medicine, School of Medicine, University of Loannina Greece. Available from: articles\Diet for hyperlipidemia.mht.
4. Scott MG. Atherogenic dyslipidemia associated with metabolic syndrome and Insulin resistance. vol 8. Suppl 1.
5. Bi-Botti CY. Chronopharmaceutics: Gimmick or clinically relevant approach to drug delivery- A Review. J Control Rel. 2004 Aug; 98(3):337-353.
6. Jain NK. Controlled and novel drug delivery. 1 st Ed. New Delhi: CBS Publishers; 2002.
7. Bussemer T, Otto I, Bodmeier R. Pulsatile drug delivery systems. Crit Rev TherDrug Carrier Syst. 2001;18(5):433-58. Review.
8. Gothaskar AV, Joshi AM, Joshi NH. Pulsatile drug delivery system-A review. Drug Del Tech. 2004 June; 4(5).
9. Anal AK. Time-Controlled Pulsatile Delivery Systems for Bioactive Compounds. Recent Patents on Drug Delivery & Formulation. 2006 Dec; 1:73-79.
10. Bjorn Lemmer. The clinical relevance of chronopharmacology in therapeutics. Pharmacological Research. 1996; 33(2):107-115.
11. Sharagil L, Pony S. applied Bio-pharmaceutics and Pharmacokinetics. 5th ed. Singapur ; 2005: p. 481-2.
12. Peep Veski. Chronopharmaceutical Drug Delivery. Institute of pharmacy. University of Tartu, Estonia.
13. Libo Yang, James SC, Joseph AF. Colon specific drug delivery: new approaches and in vitro/in vivo evaluation-Review. I J Pharm. 2002; 253:1-15.
14. Shivakumar HG, Pramod KTM, Kashappa GD. Pulsatile drug delivery systems. Indian J Pharm Educ. 2003 July-Sept; 37(3):125-128.
15. Sarasija S, Stutie P. Chronotherapeutics: Emerging role of biorhythms in optimizing drug therapy. Indian J Phrm Sci. 2005 March-April; 67(2):135-140.

*****