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Original Article

FORMULATION DEVELOPMENT AND EVALUATION OF CHRONOMODULATED DRUG DELIVERY SYSTEM BY ZAFIRLUKAST

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ABSTRACT

Objective: The main objective of the present study was to formulate and evaluate a time-controlled single-unit oral pulsatile drug delivery system containing Zafirlukast for the prevention of nocturnal asthma attacks. To provide time-scheduled drug release for Asthma disease. It is used for preventing asthmatic attacks at early morning. Pulsatile release dosage form is increasing patient compliance by reducing the dosing frequency, especially in the early morning.

Methods: Core tablets were prepared by incorporating different concentrations of natural and synthetic super disintegrants. Drug-containing core tablets (ZC1-ZC15) with different compositions of natural super disintegrants (Plantago ovata seed powder, Locust bean gum) synthetic super disintegrants (Sodium starch glycolate (SSG), Cross carmellose sodium (CCS), Crospovidone (CP)) were prepared by direct compression technique. The core tablets were subjected to pre-formulation, physicochemical and *In vitro* drug release studies. The fast disintegrating core tablet formulation was selected and press-coated tablets (P1-P11) were prepared with different compositions of hydrophobic polymers Eudragit RS100, Eudragit RL 100, Ethylcellulose and hydrophilic polymers Hydroxypropyl methylcellulose K4M, K100M. The optimized formulation was selected and quantified based on *in vitro* drug release profile in simulated gastric and intestinal fluids.

Results: The pre and post-compression parameters of tablets were also found to be within limits. Formulation ZC5 with 16 mg of Locust bean gum showed the least disintegrating time, i.e., 22.13 sec, and was selected as the best immediate release core tablet. The press-coated tablet formulation P8 having 62.5 mg Eudragit RS100 and 62.5 mg of HPMC K4M in ratio 1:1 over the core tablet ZC5 showed rapid and drug release nearly after 4 h lag time and 98.86 % up to 12 h. Accelerated stability studies of the optimized formulation P8 indicated no significant difference in release profile after 3 mo.

Conclusion: The *in vitro* dissolution study showed that lag time before drug release was highly affected by the coating amount level and nature of coating polymer used. Time-controlled pulsatile release tablets can be prepared using press-coating techniques.

Keywords: Pulsatile formulation, Zafirlukast, Chronomodulated drug delivery system, Compression coated tablets

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INTRODUCTION

The time-controlled and pulsatile release is increasingly being considered as desirable modes of drug delivery [1-3]. A pulsatile drug delivery system (PDDS) can be defined as a system where the drug is released suddenly after a well-defined lag time according to the circadian rhythm of the disease [4, 5]. PDDS can be classified according to the pulse-regulation of drug release into three main classes; time-controlled pulsatile release (single or multiple unit system), internal stimuli-induced release, and external stimuli-induced pulsatile release systems [4, 6]. PDDS can also be classified according to the dosage form into three main types; capsules, pellets, and tablets. The tablet system consists of two different core tablets, containing the active ingredient, the outer top cover layer of a soluble polymer, and insoluble polymer [4, 7]. The release of some drugs is preferred in pulses. A single dosage form provides an initial dose of the drug followed by one release-free interval, after which a second dose of the drug is released, which is followed by an additional release-free interval and pulse of drug release [8].

Depending upon the physiological and physiopathological changes of circadian rhythmicity, nocturnal symptoms and overnight decrements in lung functions are a common part of the asthma clinical syndrome [9]. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. The dip is particularly pronounced in people with asthma, because bronchoconstriction and exacerbation of symptoms vary in a circadian fashion, a sharp increase in asthmatic attacks during early morning hours. For such conditions a drug delivery system administered at bedtime, but releasing the drug during morning hours, would be an ideal one [10].

The main objective of the study was to develop a time-controlled release formulation based on a press coat technique using rate-controlling natural (hydrophilic) polymers and synthetic (hydrophobic) polymers and Zafirlukast as a model drug. The intention was to maintain lag time 3-4 h. As the symptoms of asthma are experienced in the early morning hours. The incorporation of the drug as an immediate release formulation in the core is proposed to provide the drug to the patient at the right time of asthmatic risk. The release is expected as a burst, i. e at once pulsatile drug delivery of Zafirlukast after a lag time [11-13]. The rationale for the development of an appropriate formulation is to provide the drug at the right time, i.e. early morning. The formulation has a rapid-release core tablet of Zafirlukast with super disintegrants [14].

MATERIALS AND METHODS

Materials

Zafirlukast was Provided by Sura Labs, Dilsukhnagar. Plantago ovata seed powder was Purchased from the local market. Sodium starch glycolate Purchased from SD Fine Chemicals, Mumbai. Crospovidone, Locust bean gum, and Croscarmellose sodium were Purchased from R. K. Enterprises, Ghaziabad. Eudragit RS100 was Purchased from Evonik Industries, Mumbai, Maharashtra. Eudragit RL 100 was Purchased from Evonik Industries, Mumbai, Maharashtra. Ethylcellulose was Purchased from CDH chemicals, New Delhi, India. HPMC K4M and HPMC K100M were Purchased from Colorcon Asia Pvt. Ltd., Goa. Mannitol, Mg Stearate, Talc, and PVP K 30 were purchased from SD Fine Chemicals. Mumbai, Maharashtra. Aerosil was purchased from Reachem labs, New Delhi, India. MCC was purchased from Sigma Chemicals, Bangalore, India.

Methods

Formulation development of tablets

Formulation of core tablets by direct compression

The inner core tablets were prepared by using the direct compression method [15] as shown in the table. Powder mixtures zafirlukast, Plantago ovata seed powder, Locust bean gum, Sodium starch glycolate, Crospovidone, CCS, talc ingredients were blended for 20 min followed by the addition of Magnesium stearate. The mixtures were then further blended for 10 min [16]., 50 mg of resultant powder blend was manually compressed using, Lab press Limited, India with a 6 mm punch and die to obtain the core tablet (table).

Formulation of a mixed blend for the barrier layer

The various formulation compositions containing Ethyl Cellulose, Eudragit RS100, Eudragit RL 100, HPMC K4M, HPMC K100, magnesium stearate, talc, and microcrystalline cellulose. Different compositions were weighed processed using the wet granulation Technique and used as a press coating material to prepare press-coated pulsatile tablets respectively by wet granulation Technique (table).

Preparation of press-coated tablets

The core tablets were press-coated with 300 mg of the mixed blend as given in Table. 200 mg of barrier layer material was weighed and transferred into a 10 mm die then the core tablet was placed manually at the center and compressed by using Lab press Limited, India [17].

Optimization of core tablets

For optimization of core tablets, various formulations were prepared as noted in a table.

Table 1: Formulation development of core tablets

Ingredients (mg)	ZC1	ZC2	ZC3	ZC4	ZC5	ZC6	ZC7	ZC8	ZC9	ZC10	ZC11	ZC12	ZC13	ZC14	ZC15
Core tablet formulation blend															
Zafirlukast	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Plantago ovata seed powder	8	16	24	-	-	-	-	-	-	-	-	-	-	-	-
Locust bean gum	-	-	-	8	16	24	-	-	-	-	-	-	-	-	-
Sodium starch glycolate (SSG)	-	-	-	-	-	-	8	16	24	-	-	-	-	-	-
Cross carmellose sodium (CCS)	-	-	-	-	-	-	-	-	-	8	16	24	-	-	-
Crospovidone (CP)	-	-	-	-	-	-	-	-	-	-	-	-	8	16	24
Aerosil	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Sodium stearyl fumerate (SSF)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Mannitol	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
Total Weight	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150

Table 2: Formulations for press coated blend

Ingredients (mg)	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11
Optimized formulation core tablets (Total weight-150 mg)	ZC*	ZC*	ZC*	ZC*	ZC*	ZC*	ZC*	ZC*	ZC*	ZC*	ZC*
Coated formulation blend											
Ethyl Cellulose	62.5	-	-	-	-	62.5	-	-	62.5	-	-
Eudragit RL 100	-	62.5	-	-	-	-	62.5	-	-	62.5	-
Eudragit RS100	-	-	62.5	-	-	-	-	62.5	-	-	62.5
HPMC K4M	-	-	-	62.5	-	62.5	62.5	62.5	-	-	-
HPMC K100M	-	-	-	-	62.5	-	-	-	62.5	62.5	62.5
PVP K30	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
IPA (Iso Propyl Alcohol)	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
Mg. Stearate	4	4	4	4	4	4	4	4	4	4	4
Talc	2	2	2	2	2	2	2	2	2	2	2
MCC	125	125	125	125	125	62.5	62.5	62.5	62.5	62.5	62.5
Total weight of Press coated blend	200	200	200	200	200	200	200	200	200	200	200
Total weight of Press coated tablet	350	350	350	350	350	350	350	350	350	350	350

*ZC optimized core formulation

Formulation of press coated blend

These ingredients are used in the preparation of different chronomodulated drug delivery system formulation grannules.

Evaluations

Post compression parameters of core and press coated tablets

The tablets after punching of every batch were evaluated for in-process and finished product quality control tests i.e. thickness, weight uniformity test, hardness, friability, drug content, and *in vitro* drug release studies [18].

Hardness

The prepared tablets were subjected to a hardness test. It was carried out by using Monsanto, Mumbai, India, and expressed in Kg/cm^2 [19].

Thickness

The prepared tablets were subjected to a thickness test. It was carried out by using the vernier caliper Mitutoyo, Japan [20] and expressed in millimeters.

Friability test

The friability was determined using the friability test apparatus Labindia, Mumbai, India, and expressed in percentage (%). 20 tablets from each batch were weighed separately (W initial) and placed in the friabilator, which was then operated for 100 revolutions at 25 rpm [21]. The tablets were reweighed (W final) and the percentage friability was calculated for each batch by using the following formula [22].

$$Friability = [(W1 - W2)/W1] * 100$$

Where,

W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Weight variation test

Twenty tablets were selected at random from the lot, weighed individually and the average weight was determined [23]. The percent deviation of each tablet's weight against the average weight was calculated. The test requirements are met if not more than two of the individual weights deviate from the average weight by more than 5%.

Drug content

The Zafirlukast tablets were tested for their drug content. Ten tablets were finely powdered [24]. The required quantities of the powder equivalent to 20 mg of Zafirlukast were accurately weighed and transferred to a 100-mL of volumetric flask [25]. The flask was filled with buffer and mixed thoroughly. The solution was made up of Volume and filtered. Dilute 1 ml of the resulting solution to 100 ml with media and measure the absorbance of the resulting solution at the maximum at 238 nm using a UV spectrophotometer (Labindia, Mumbai, India). The linearity equation obtained from the calibration curve as described previously was used for the estimation of Zafirlukast in the tablets formulations.

Disintegration time of core tablets

A disintegration test was carried out using the tablet disintegration test apparatus specified in Indian pharmacopeia. pH 6.8 phosphate buffer at 37±2 °C was used as the disintegration media and the time in second taken for complete disintegration of the tablet with no palpable mass remaining on the screen was measured in seconds [26].

***In vitro* drug release study of pulsatile zafirlukast tablets**

***In vitro* drug release of Zafirlukast core tablets**

In vitro dissolution studies were carried out using the USP XXIII Type II (paddle method) apparatus. pH 6.8 phosphate buffer was used as a dissolution medium. Release pattern was studied visually by taking a sample of 5 ml at specific time intervals. Also, the sample was analyzed at 238 nm for 6.8 phosphate buffer using a UV spectrophotometer [27].

***In vitro* drug release study of coated tablets**

900 ml 0f 0.1 HCL was placed in a vessel and the USP apparatus–II (Paddle Method) was assembled. The medium was allowed to equilibrate to the temp of 37 °c+0.5 °c. Tablet was placed in the vessel and apparatus was operated for 2 h and then the media 0.1 N HCL were removed and pH 6.8, 7.4 phosphate buffer was added process was continued up to 12 h at 50 rpm. A definite time interval was withdrawn 5 ml of sample, filtered, and again 5 ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at respective wavelengths using UV-spectrophotometer [28].

Application of release rate kinetics to dissolution data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first-order, Higuchi, and Korsmeyer-Peppas release model [29, 30].

Zero-order release rate kinetics

To study the release kinetics, the release rate data are fitted to the following equation.

$$F = K0t$$

Where, 'F' is the drug release at time 't', and 'K0' is the zero-order release rate constant. The plot of % drug release versus time is linear.

First-order release rate kinetics

The release rate data are fitted to the following equation.

$$Log(100 - F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives the first-order release.

Higuchi release model

To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = kt1/2$$

Where 'k' is the Higuchi constant.

In the Higuchi model, a plot of % drug release versus the square root of time is linear.

Korsmeyer and peppas release model

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to the Korsmeyer-Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$Mt/M\alpha = Ktn$$

Where, Mt/M∝ is a fraction of drug released at a time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in the case of Fickian diffusion, n = 0.5; for zero-order release (case II transport), n=1; and for super case II transport, n>1. In this model, a plot of log (Mt/M∞) versus log (time) is linear [31].

Stability studies

For the determination of stability of prepared different formulations, accelerated stability studies were carried out on optimized formulation. Tablets were stored according to ICH guidelines at 40±2 °C/75±5% RH for three months by storing the samples in (Lab-care, Mumbai) stability chamber. After completion of the required duration time, the sample was withdrawn and tested for different tests such as hardness, drug content, and *in vitro* drug release [32].

***In vivo* studies-pharmacokinetic studies**

To investigate the peak plasma concentration pharmacokinetic studies were carried out. The *In vivo* studies were conducted on Wistar male rats weighing 250-300 gm. They were housed in polypropylene cages and had free access to food and water. The dose of zafirlukast was calculated as per the bodyweight of animals and developed tablets were formulated considering the calculated dose. The animal protocol was approved by the Institutional Animals Ethical Committee. The optimized pulsatile tablets were administered orally. Blood samples were collected for over 24 h according to a predetermined sample collection schedule. Various pharmacokinetic parameters like C_{max}, T_{max}, AUC were determined [33].

RESULTS AND DISCUSSION

In the present work, Zafirlukast is an Anti-inflammatory, leukotriene receptor antagonist (LTRAs) drug used in the treatment of asthma and prevent asthma attacks [34]. An attempt has been made to improve the bioavailability Present is in the form of a chronomodulated drug delivery system to provide a controlled release for a prolonged period of time.

Preformulation studies

Table 3: Physical properties of drug

S. No.	Parameter	Drug zafirlukast
1.	Colour	White
2.	Odour	Odourless
3.	Taste	tasteless
4.	Appearance	Amorphous powder

Melting point

Table 4: Melting point determination of drug

Drug name	Reported melting point	Observed melting point
Zafirlukast	138 to 140 °C	139-141 °C

The melting point was determined by the capillary tube method and it was found to be 139-141 °C Zafirlukast by taking the averages of 3 consecutive readings. This value is the same as that of the literature citation shown in table.

Solubility studies

Table 5: Solubility studies of drug

Medium	Ratio (drug: solvent) for zafirlukast	mg/100 ml
Water	1:4	Insoluble
Methanol	1:3	Slightly soluble
0.1N HCL	1:5	Slightly soluble
Phosphate buffer pH(6.8)	1:3	Slightly soluble

The solubility of Zafirlukast was determined in different solvent systems. The maximum solubility was found in 0.1N HCL and water.

FTIR

Drug-excipient compatibility

Table 6: Peaks observed in pure drug and optimized formulation

Functional groups	Wavenumber in cm^{-1}	Pure drug	Optimized formulation
C-H Bending	2960-2850	2952.26	2952.62
C=C Stretch	990	990.86	990.84
C=O Stretching	1730-1700	1723.63	1723.41
C-H Stretch	2960-2850	2870.87	2871.14
O-H Stretching	3600-3200 or3650	3544.94	3542.83
N-H Stretch	3700-3500	3544.94	3542.83
Benzene ring	1660-2000	1696.65	1696.50
C-O	1210-1320	1225.70	1225.52
Aromatic C-H stretch	3020-3000	3010.50	3010.91
SO_2	1374	1368.48	1368.16

From the above table, it was showed no interactions between drug and excipients. Both API and excipients compatibility with each other.

Differential scanning calorimetry (DSC)

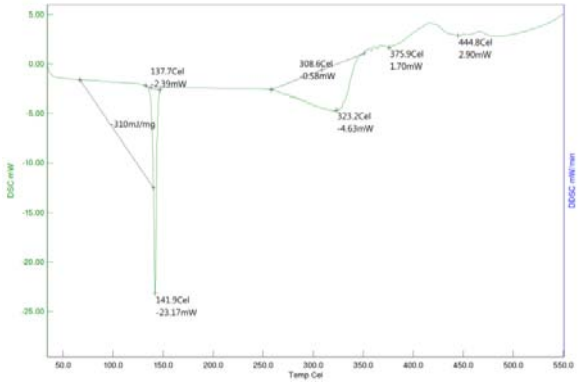

Fig. 1: DSC graph of zafirlukast pure drug

The DSC spectrum of pure Zafirlukast showed a sharp endothermic peak at 141.9 °C and it was the melting point of the drug. The mixture of Zafirlukast and polymers shows doesn't change the thermal behavior of the sharp endothermic peak of the drug at 138.0 °C. It indicated that there was no interaction between the drug and polymers. These results revealed that the drug was stable at higher temperatures and neither drug decomposition nor drug-excipients interactions occurred in the prepared chronomodulated drug delivery system [35].

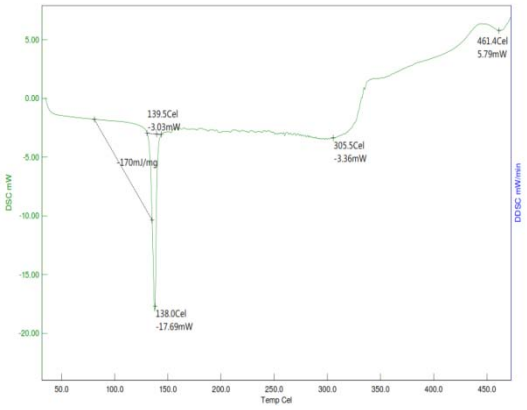

Fig. 2: DSC graph of zafirlukast optimized formulation

Calibration curve

Graphs of Zafirlukast were taken in 0.1 N HCL, phosphate buffer pH 6.8, 7.4.

Table 7: Calibration curve data for zafirlukast

Concentrations [µg/ml]	Absorbance in 0.1N HCL at 235 nm	Absorbance in phosphate buffer pH 6.8 at 239 nm	Phosphate buffer pH 7.4 at 239 nm
0	0	0	0
5	0.114	0.185	0.183
10	0.225	0.358	0.388
15	0.312	0.598	0.595
20	0.411	0.784	0.801
25	0.513	0.989	0.959

The standard graph of Zafirlukast showed good linearity, which indicates that it obeys the "Beer-Lamberts" law [36].

Preformulation parameters of powder blend for core tablets

Table 8: Pre-formulation parameters of blend

Formulation code	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio
ZC1	23.98±1.2	0.549±0.01	0.626±0.01	12.30±0.13	1.140±0.02
ZC2	28.72±2.5	0.335±0.03	0.470±0.05	28.72±0.12	1.401±0.01
ZC3	21.12±2.5	0.409±0.02	0.531±0.06	22.97±0.13	1.298±0.06
ZC4	26.89±0.5	0.681±0.03	0.887±0.05	23.22±0.18	0.980±0.01
ZC5	24.19±0.5	0.547±0.06	0.624±0.04	12.33±0.11	1.140±0.03
ZC6	26.6±0.6	0.555±0.03	0.714±0.07	22.22±0.21	1.280±0.06
ZC7	22.67±0.8	0.395±0.01	0.475±0.01	20.25±0.17	1.202±0.03
ZC8	26.02±0.8	0.267±0.03	0.307±0.03	13.33±0.18	1.150±0.06
ZC9	27.67±1.0	0.429±0.03	0.546±0.05	23.93±0.19	1.272±0.03
ZC10	26.02±1.2	0.267±0.01	0.307±0.08	13.33±0.12	1.150±0.01
ZC11	24.70±0.4	0.519±0.04	0.683±0.08	13.46±0.13	1.315±0.03
ZC12	25.81±0.8	0.393±0.06	0.453±0.09	13.24±0.14	1.150±0.02
ZC13	25.31±2.2	0.330±0.07	0.380±0.05	13.15±0.15	1.152±0.04
ZC14	24.70±1.4	0.462±0.09	0.591±0.06	21.82±0.13	1.279±0.06
ZC15	26.31±1.2	0.232±0.05	0.273±0.07	15.52±0.12	1.181±0.01

Each value represents the mean±SD (n=3)

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.232±0.05 to 0.681±0.03 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.273±0.07 to 0.683±0.08 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 28.72±2.5 which shows that the powder has good flow properties. All the formulations have shown the Hausner's ratio ranging between 0 to 1.401±0.01 indicating the powder has good flow properties [37].

Quality control parameters for tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, Drug content, and drug release studies were performed for core tablets.

Table 9: *In vitro* quality control parameters for core tablets

Formulation codes	Average weight (mg)	Hardness (Kg/cm²)	Friability (% loss)	Thickness (mm)	Drug content (%)
ZC1	150.5±1	4.5±0.8	0.52	3.5±0.01	99.76±0.44
ZC2	150.4±2	4.0±0.6	0.54	3.3±0.05	97.45±0.75
ZC3	149.6±1	4.4±0.5	0.51	3.1±0.03	98.34±0.92
ZC4	149.6±2	4.5±0.4	0.55	3.4±0.04	99.87±0.72
ZC5	151.4±2	4.4±0.6	0.56	3.2±0.07	99.14±0.37
ZC6	150.7±2	4.2±0.1	0.45	3.4±0.05	97.56±0.25
ZC7	148.95±1	4.2±0.3	0.45	3.1±0.03	98.3±0.49
ZC8	149.15±1	4.7±0.2	0.54	3.2±0.04	99.3±0.33
ZC9	150.26±2	4.2±0.3	0.55	3.3±0.02	98.2±0.47
ZC10	150.36±2	4.0±0.6	0.56	3.5±0.05	99.2±0.65
ZC11	149.25±3	4.2±0.1	0.48	3.1±0.06	99.3±0.55
ZC12	148.26±1	4.1±0.5	0.45	3.2±0.07	97.2±0.45
ZC13	150.5±1	4.3±0.2	0.51	3.3±0.09	102.3±1.50
ZC14	150.63±1	4.4±0.7	0.52	3.3±0.04	103.5±1.00
ZC15	151.85±1	4.5±0.2	0.53	3.4±0.05	103.0±0.92

Each value represents the mean±SD (n=3)

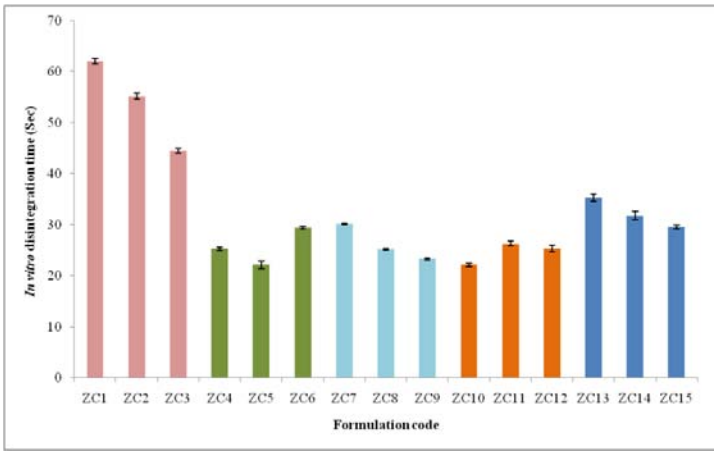

Fig. 3: *In vitro* disintegration time graph of core tablets, each value represents the mean±SD (n=3)

The disintegration time of the tablets was determined as per the Indian Pharmacopoeia monograph. The test was carried out using the Tablet disintegration apparatus. For ZC5 formulation was found to be 22.13±0.72 seconds very less disintegration time compared to other formulation. ZC5 formulation contained 16 mg natural super disintegrant locust bean gum because of the appreciable capability of locust bean gum to increase water penetration due to wicking action which increases porosity thus lowers disintegration time [38].

***In vitro* drug release studies**

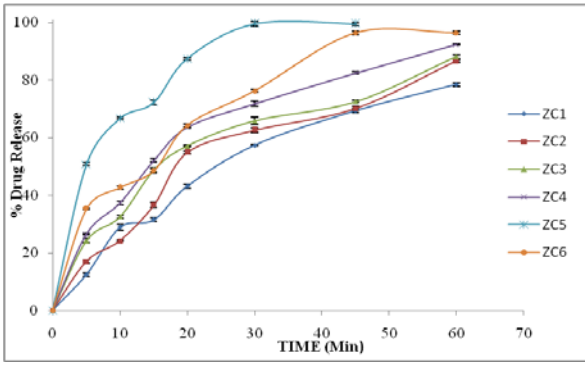

Fig. 4: Dissolution graph of core tablets using natural super disintegrants i.e., Plantago ovata seed powder, locust bean gum, each value represents the mean±SD (n=3)

Core tablets of Zafirlukast were prepared by direct compression technique using two different classes of super-disintegrants, i.e., Naturals class (Locust bean gum, Plantago ovata seed powder) and synthetic class (SSG, CCS, CP). Overall formulation ZC5 containing Locust bean gum at 16 mg disintegrated rapidly to release the drug. The formulations ZC5 were selected for dissolution studies based on their better and satisfactory evaluation studies parameter [39]. From the result, it was concluded that formulation ZC5 are found to be stable and retained their original properties.

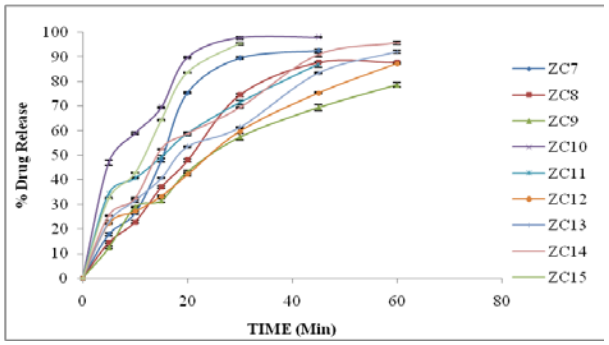

Fig. 5: Dissolution data of core tablets by using Synthetic super disintegrants i.e., Sodium starch glycolate (SSG), Crospovidone (CP), Cross carmellose sodium (CCS), each value represents the mean±SD (n=3)

The formulations ZC5, ZC10 showed more than 50% of drug release within 10 min and almost 98% of the drug release in 30 min. The rapid drug dissolution might be due to the easy breakdown of the particle by super disintegrant action [40]. ZC5 containing 16 mg Locust bean gum and ZC10 containing 8 mg Cross carmellose sodium (CCS) amount. From *in vitro* dissolution data, it was observed the maximum % of Zafirlukast released in 30 min. It was also observed that the change in concentration of both the super disintegrants Locust bean gum and croscarmellose sodium had a significant effect on the dissolution profile of Zafirlukast core tablets.

The excellent *in vitro* release profile is probably the solubility enhancement properties of Locust bean gum. At a stable hardness of tableting, the disintegration time is measured, it is found that the batch ZC5 shows minimum disintegration time (22.13 min), this is attributes to the Locust bean gum capacity of depicting Swelling and Wicking both mechanism simultaneously. It accommodates a helping hand in obtaining burst release of the drug [41]. ZC5 also showed a better dissolution profile and complied with all other parameters with less variation in results and hence was selected as the optimized core tablet formulation.

Table 10: *In vitro* quality control parameters for coated tablets

Formulation code	Average weight (mg)	Hardness (kg/cm²)	Friability (% loss)	Thickness (mm)	Drug content (%)
P1	349.25±0.61	5.9±0.15	0.35	4.99±0.03	99.45±0.55
P2	350.65±0.80	5.5±0.20	0.29	4.89±0.06	99.86±0.33
P3	350.89±0.65	5.8±0.55	0.51	4.68±0.05	99.73±0.45
P4	350.77±0.55	5.3±0.50	0.48	4.90±0.06	99.92±0.64
P5	348.99±0.75	5.2±0.22	0.63	4.19±0.07	99.65±0.12
P6	350.12±0.71	5.1±0.56	0.81	4.72±0.08	99.55±0.23
P7	347.35±0.80	5.3±0.23	0.15	4.39±0.07	98.42±0.37
P8	348.46±0.82	5.8±0.12	0.43	4.57±0.05	99.85±0.49
P9	349.14±1.01	5.1±0.27	0.57	4.38±0.04	99.12±0.57
P10	350.32±0.64	5.0±0.45	0.43	4.29±0.03	98.42±0.62
P11	352.47±0.71	5.94±0.37	0.37	4.35±0.01	99.65±0.19

Each value represents the mean±SD (n=3), All the parameters for press coated tablets such as weight variation, friability, hardness, thickness, drug content were found to be within limits.

In vitro dissolution of the matrix, Zafirlukast coated tablets containing HPMC of various viscosities. The Prepared tablets did not disintegrate, however, a gel layer was formed on the surface of the tablet due to swelling of HPMC in presence of water. Here the concentration of each type of HPMC (K4M and K100M) was kept at 62.5 mg. Formulations containing HPMC K100M showed delayed release as compared to others. HPMC K100M tablets exhibited a significant effect on drug release, it is due to more viscosity and high molecular weight of HPMC K100M in addition to its slower rate of erosion and more swelling. HPMC (K4M and K100M) with hydrophobic polymers like Ethyl cellulose (EC), Eudragit RS100, and Eudragit RL100 for the drug release was retarded with HPMC K4 M in the concentration of 1:1 (Hydrophobic polymer: hydrophilic polymer) up to 97.88% drug released in 12 h. The overall drug release is affected by the rate of water uptake and diffusion rate of the drug through the swollen gel being formed. This gel increases the diffusion path length of the drug. Its viscous nature also affects the diffusion coefficient of the drug [42]. As a result, a reduction in the drug release rate is obtained. Drug release from HPMC matrices showed that the viscosity of polymer plays important role in the retardation of drug release as

HPMC K100M>HPMC K4M

Drug release studies were observed in the case of Ethylcellulose and combination with various viscosity grades of HPMC like K4M and K100M. But hydrophobic and hydrophilic polymer ratio 1:1 for all

the formulations. EC was incorporated in the hydrophilic matrix; the matrix could release the drug retarded more up to 12 h only. Incorporation of EC was found to control the drug release to some extent, which could be attributed to the decreased penetration of the solvent molecules, in the presence of hydrophobic polymer leading to decreased diffusion of the drug from the matrix.

Hydrophobic polymers, which are capable of forming insoluble or skeleton matrices, have been widely used for controlling the release of drugs due to their inertness and drug embedding ability [43]. Liquid penetration into the matrix is a rate-controlling step in such systems unless channeling agents are used, for Example: Eudragit RS100 and Eudragit RL 100.

Eudragits (polymethyl methacrylates) are extensively used as release controlling agents. The drug release was slow down in Eudragit RS100 than in Eudragit RL100 due to 5% of functional quaternary ammonium groups present in Eudragit RS 100 and it was low permeability and pH-independent but in the case of Eudragit RL 100 presence of 10% of functional quaternary ammonium groups, high permeability and pH-independent.

During the dissolution process, it was observed that the hydrophilic polymer in the tablets resulted in a reduction in the drug release rate, all the tablets showed swelling the extent of swelling increased.

Drug release from hydrophobic matrices showed that the type of polymers plays an important role.

Retardation of drug release was in the order of

EC>Eudragit RS 100>Eudragit RL 100

Finally concluded that the P8 formulation containing Eudragit RS 100 and HPMC K4M in combination, was the best. This formulation was retarding the drug release 98.86% up to desired period (12 h).

Release kinetics

Data of *in vitro* release studies of formulations that were showing better drug release were fit into different equations to explain the release kinetics of Zafirlukast release from press coated tablets (P8). The data were fitted into various kinetic models such as Zero, First-order kinetics, Higuchi, Korsmeyer Peppas mechanisms, and the results were shown in the below figures.

Table 11: Dissolution data of press coated tablets using hydrophilic, hydrophobic polymers and combination

Time (min)	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
30(0.5h)	0.00±0.00	0.00±0.00	0.00±0.00	33.42±0.69	21.80±0.10	0.56±0.02	0.12±0.09	0.34±0.06	0.46±0.01	0.31±0.08	0.14±0.06
60(1 h)	0.00±0.00	0.00±0.00	0.00±0.00	41.86±0.37	30.92±0.45	0.77±0.08	0.35±0.08	0.61±0.02	0.95±0.07	0.55±0.15	0.22±0.11
120(2 h)	5.81±0.31	10.89±0.65	0.00±0.00	50.33±0.81	36.84±0.88	1.21±0.39	0.51±0.05	2.34±0.15	1.41±0.10	0.82±0.23	0.58±0.12
180(3 h)	12.34±0.40	22.31±0.39	22.14±0.81	63.49±0.14	39.28±0.65	3.46±0.36	0.62±0.22	4.73±0.88	4.45±0.11	1.36±0.77	1.12±0.21
240(4 h)	17.87±0.34	35.35±0.67	26.43±0.41	73.81±0.84	48.39±0.44	39.54±0.10	0.78±0.35	37.48±0.75	24.75±0.39	1.81±0.43	3.65±0.24
300(5 h)	22.89±0.37	47.26±0.59	38.18±0.65	85.44±0.71	55.83±0.69	43.15±0.60	1.95±1.0	44.85±0.45	42.27±0.55	5.45±0.45	7.34±0.27
360(6 h)	31.83±0.12	58.18±0.14	42.27±0.73	96.65±0.31	65.66±0.48	49.89±0.84	46.34±0.06	52.44±0.33	48.54±0.80	43.90±0.36	12.16±0.29
420(7 h)	39.35±0.92	63.48±0.79	48.54±0.14		85.72±0.54	52.77±0.98	99.48±1.2	63.19±0.45	51.74±0.98	65.32±0.82	50.65±0.33
480(8 h)	46.95±0.14	77.34±0.52	53.78±0.43		94.80±0.21	58.04±0.44		74.55±0.06	55.68±0.58	98.45±1.01	98.54±0.39
540(9 h)	51.89±0.10	89.89±0.91	55.68±0.15			61.04±0.40		83.62±0.40	62.14±0.51		
600(10 h)	65.34±0.34	89.92±0.50	67.35±0.61			68.22±0.93		87.69±0.71	67.35±0.92		
660(11 h)	76.62±0.58		73.62±0.46			81.09±0.13		92.34±0.89	76.43±0.55		
720(12 h)	89.32±0.26		86.43±0.91			89.03±0.20		98.86±0.56	83.28±0.29		

Each value represents the mean±SD (n=3)

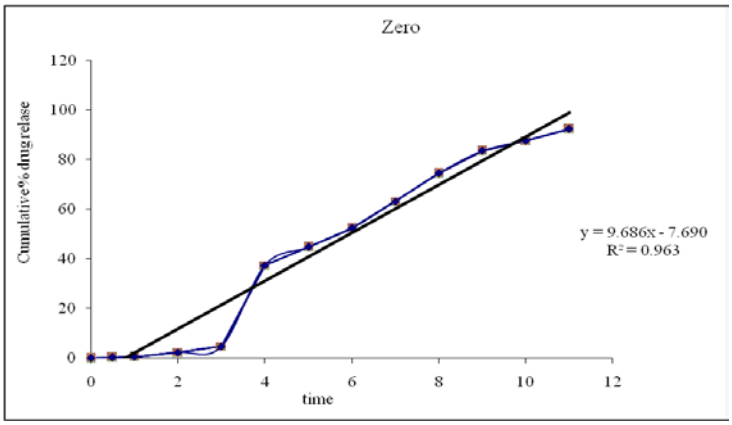

Fig. 6: Zero-order plot of optimized formulation

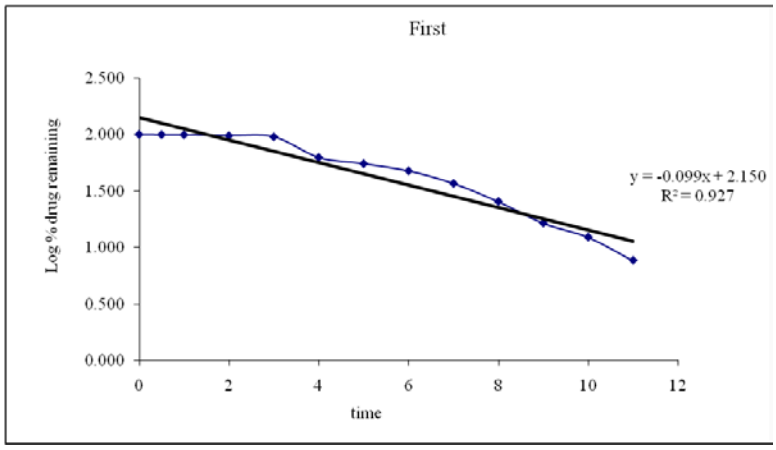

Fig. 7: First-order plot of optimized formulation

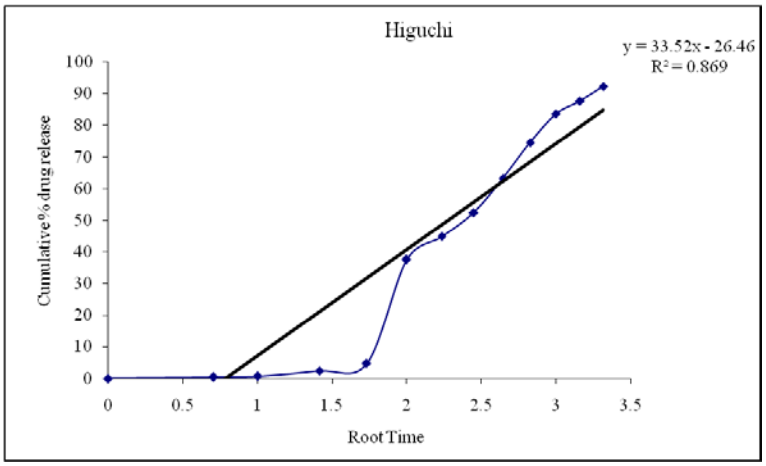

Fig. 8: Higuchi plot of optimized formulation

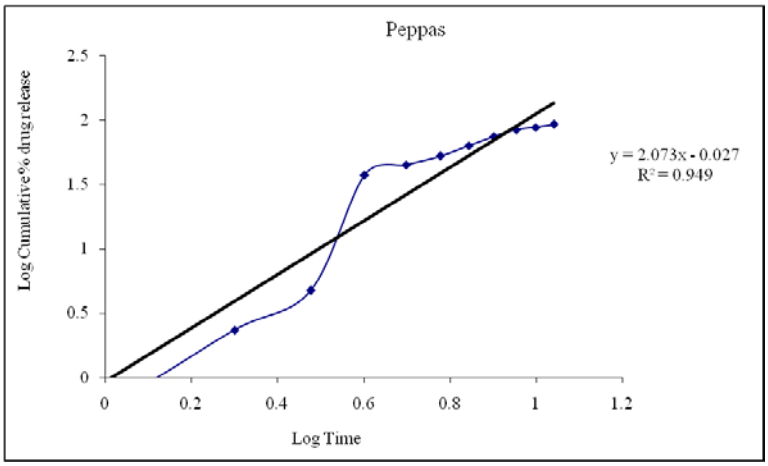

Fig. 9: Koresmeyer-peppas plot of optimized formulation

Based on all studies P8 formulation was found to be better when compared with all other formulations. This formulation was following a Zero-order mechanism with a regression value of 0.963. The kinetics of zero-order release describes the release of drugs slowly and always constant over time. Increased drug concentration is directly proportional to time [44].

Accelerated stability studies

The stability study of the optimized Zafirlukast pulsatile tablets (P8) was carried out according to ICH guidelines at 40±2 °C/75±5% RH for three months by storing the samples in (Lab-care, Mumbai) stability chamber [45]. The results from stability studies are shown in the figure.

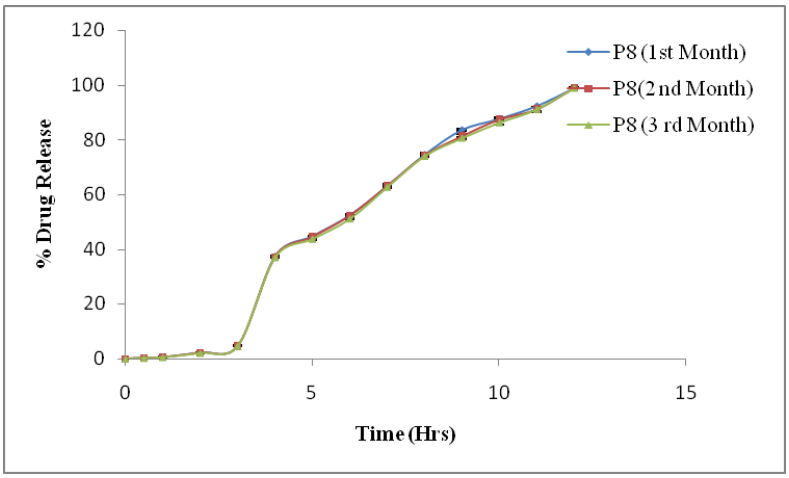

Fig. 10: Stability dissolution profile of optimized Zafirlukast pulsatile tablets (P8) for 1st, 2ndand 3rd months, Each value represents the mean±SD (n=3)

Table 12: Most satisfactory formulation during stability studies for optimized formulation

Time period (month)	Drug content (%)
1	99.85±0.09
2	99.85±0.07
3	99.84±0.10

Each value represents the mean±SD (n=3)

There was no major change in the various physicochemical parameters evaluated drug content, *in vitro* drug release pattern at the various sampling points. There was no statistically significant difference between the initial values and the results obtained during stability studies.

Zafirlukast pulsatile tablets showed no significant change in the physical appearance, percent drug content, *In vitro*, drug release studies were determined at 1st Month, 2nd month, 3 rd Month which showed no significant change at room temperature and instability chamber at 40±1 °C and 75 % relative humidity this indicates that optimized formulations were stable [46].

***In vivo* studies-pharmacokinetic studies**

All the pharmacokinetics parameters are displayed in Table. Meantime to reach peak drug concentration (Tmax) was 1.58 h, while the mean maximum drug concentration (Cmax) was 503.1 ng/ml. The values for Cmax, Tmax, AUC were found to be comparable indicating that their rapid and transient release of a certain amount of drug within a short period immediately after a predetermined off-release period patterns were similar.

Table 13: Pharmacokinetic parameters of optimized formulation

S. No.	Parameter	Zafirlukast optimized pulsatile tablets
1	C_{max}	503.1 ng/ml (±0.21)
2	T_{max} (hr)	1.58 h (±0.57)
3	AUC	1342.8 ng/l·h (±1.29)

CONCLUSION

The pulsatile drug delivery system was developed successfully using the press coating technique. The present investigation revealed that the coating of the core tablet with 62.5 mg of Eudragit RS100 and 80 mg HPMC K4M and 62.5 mg HPMC K4M provided desired lag time required for chronotherapy of Asthma. The optimized formulation showed 4 h of pulsatile release lag time, and more drug release up to 12 h of time. *In vitro* drug release study showed 98.86 % drug release in 12 h. Optimized formulation (P8) showed good stability at accelerated stability conditions. From the experimental findings, it can be concluded that pulsatile tablets of Zafirlukast can give efficient therapy by reducing dose and dosing frequency and provide chronotherapy for effective management of morning the surge of Asthma. Finally, it may be concluded that a pulsatile drug delivery system offers a valuable dosage form treatment of Asthma.

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AUTHORS CONTRIBUTIONS

N. Shiva Krishna has generated the research plan, prepared and revised the manuscript. Dr. B. Jayanthi and A. Madhukarhave given guidance and supervision to carry out this study.

CONFLICT OF INTERESTS

None

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