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RESEARCH ARTICLE OPEN ACCESS

FORMULATION DEVELOPMENT AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF ZAFIRLUKAST TABLETS

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ABSTRACT

The objective of the study to formulate and evaluate ofpulsatile drug delivery containing Zafirlukastfor the treatment of asthama which is used to deliver the drug atspecific time as per pathophysiological need of the disease and improvementof therapeutic efficacy and patient compliance. Zafirlukastin the core tablet was formulated with different concentration of superdisintegrants and microcrystalline cellulose, an outer shell tablet which is formulated with different weight ratios of polymers HPMC K100M, Eudragit RSPO and Xanthan gum.The effects of the formulation of core tablet and outer shell of press coated tablets; on drug release and the lag time were investigated.The formulation was optimized based on acceptable tablet properties and *in vitro* drug release.The release profile of press coated tablet exhibited a lag time dependent upon the amount of polymers in compression coating. The optimized batch F3 gave a lag time of 2 h and drug release of 99.31% of Zafirlukastrespectively. Based on the results programmable pulsatilerelease has been achieved by formulation F3 which meet the demand ofChrono therapeutic objective of asthama.

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INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance. [1,2,3] The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zeroorder release is not desired. The release of the drug as a pulse after a lag time (an interval of no drug release) has to be designed in such a way that a complete and rapid drug release follows the lag time. Pulsatile release is also useful for the targeting of the drug irritating the stomach or degradable therein, as well for drugs developing biological tolerance or with an extensive firstpass metabolism. Conventional controlled release drug delivery systems are based on single or multiple-unit reservoir or matrix systems, which are designed to provide constant or nearly constant drug levels over an extended period of time.[4,5] The temporal rhythms of body functions have been shown to affect not only the severity of a number of diseases but also the pharmacokinetics and pharmacodynamics of most bioactive compounds in use. Accordingly, chronotherapeutic treatments, tailored to supply the patient with the appropriate dose of the required drug at the perfect time, are gaining an increasing interest. Many diseases follow a welldefined circadian pattern such as hypertension, allergic rhinitis, osteoarthritis, rheumatoid arthritis, nocturnal asthma, angina pectoris and peptic ulcer.[6,7] Pulsatile drug delivery system (PDDS) can be defined as a system where drug is released suddenly after a well-defined lag time according to the circadian rhythm of the disease. PDDS can be classified according to the pulseregulation of drug release into three main classes; time-controlled pulsatile release (single or multiple unit system), internal stimuliinduced release and external stimuli-induced pulsatile release systems. PDDS can also be classified according to the dosage form into three main types; capsules, pellets and tablets among which the 'core-in-cup' tablet system. The core-in-cup tablet system consists of three different parts: a core tablet, containing the active ingredient, an impermeable outer shell and a top cover plug layer of a soluble polymer.[8] In the field of oral delivery, besides a widespread use of pro-longed-release dosage forms increasing interest has been focused on the development of formulations able to release active pharmaceutical ingredients after programmed lag times or to specific regions of the gastrointestinal (GI) tract. The timedependent

approach, in particular, is based on the relatively constant small intestinal transit time (SITT; 3 ± 1 h standard error) of dosage forms.[9] On the contrary, the duration of gastric residence of solid dosage forms, which depends on their size and density as well as fasted or fed conditions of subjects, is unpredictable; hence, by the application of an outer gastro resistant layer, which dissolves only after the dosage form is emptied from the stomach, the influence of variable gastric emptying can be overcome. Subsequently, a lag phase imparted to the drugcontaining core allows the system to reach delay duration comparable to SITT. Among time-based devices, a platform for delayed and site-specific release of drugs in the form of a reservoir system, named Chronotopic, has already been developed. Such device is based on single- or multiple-unit drug cores (tablets, capsules, pellets) coated with a functional layer composed of swellable/erodible polymers (Namely, hydroxypropyl methylcellulose, HPMC) of few hundred microns of thickness applied by different techniques (press-coating, spraycoating and powder layering). When intended for time-based drug delivery, an outer enteric film is subsequently applied. Once the device is emptied from the stomach, the enteric coating dissolves and the HPMC-based layer delays the contact of the biological fluids with the core, allowing the release of the drug only after a programmed period of time. The effectiveness of the Chronotopic™ system, its flexibility in terms of duration of the lag phase, both in vitro and in vivo, as well as the possibility of scaling up the manufacturing process has been demonstrated.

A step forward in the development of the Chronotopic™ system was represented by a capsular device (Chronocap™) that combined the release functionality of the polymeric coating with the ability to convey a variety of drug preparations (solid, semi-solid, liquid), thus bringing about both technical and regulatory advantages. [10-12] Pulsatile delivery is generally intended as a release of the active ingredient that is delayed for a programmable period of time to meet particular chronotherapeutic needs and, in the case of oral administration, also target distal intestinal regions, such as the colon. Most oral pulsatile delivery platforms consist in coated formulations wherein the applied polymer serves as the release-controlling agent. When exposed to aqueous media, the coating initially performs as a protective barrier and, subsequently, undergoes a timely failure based on diverse mechanisms depending on its physico-chemical and formulation characteristics. Indeed, it may be ruptured because of the gradual expansion of the core, swell and/or erode due to the glassyrubbery polymer transition or become permeable thus allowing the drug molecules to diffuse outwards. Otherwise, when the coating is a\ semi permeable membrane provided with one or more orifices, the drug is released through the latter as a result of an osmotic water influx. The vast majority of pulsatile delivery systems described so far have been prepared by spray-coating, which offers important versatility and feasibility advantages over other techniques such as pressand dip-coating. [13,14]

Pulsatile delivery systems are non-conventional dosage forms designed to release the active ingredient after a lag phase of programmable duration thereby allowing a chronotherapeutic effect to be attained. Most current pulsatile delivery systems are typically time-controlled in that the onset of release is prompted by inherent mechanisms irrespective of the differing conditions they may encounter in the outer environment. Among them, formulations intended for the oral route are of particular interest in the case of chronic pathologies with circadian symptoms that have a high likelihood of recurring in the night or early morning hours, such as cardiovascular disease, bronchial asthma, rheumatoid arthritis and sleep disorders. Indeed, medications able to provide an appropriate delay phase prior to drug release, administered at bedtime, could selectively cover the especially critical period during which the disease state tends to worsen with no need for waking up the patient for drug intake. In addition, oral pulsatile delivery devices, particularly when able to yield multi-pulse release profiles, may serve in place of prolonged-release systems with drugs that are subject to a strong first-pass metabolism or develop pharmacological tolerance and, in the specific case of antibiotics, would limit the growth of resistant bacterial strains by Circumventing defensive dormancy and affecting a larger number of micro-organisms in the division phase. Moreover, it has recently been suggested that the use of pulsatile release dosage forms could prevent detrimental interactions between co-administered drugs from occurring within the gastrointestinal (GI) tract. Although the earliest pulsatile delivery formulations were devised as multi-layer tablets partially enclosed in an impermeable shell, a timed liberation of orally-administered bioactive compounds is currently achieved mainly by the application of a functional polymeric coating to a drug-containing core. The core may either be a single- or a multiple-unit dosage form, the latter enabling improved reproducibility in the GI transit and absorption consistency. The performance of the coating strictly depends on the relevant physico-chemical nature and is started on exposure to the aqueous biological fluids (solvent activation).[15]

Chronobiology and chronopharmacotherapy of disease: Chronotherapy is co-ordination of biological rhythms and medical treatment. Chronotherapeutic is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. It is becoming increasingly more evident that the specific time that patients take their medication may be even more significant than was recognized in the past. In chronopharmacotherapy drug administration is synchronized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient. Chronotherapy coordinates drug delivery with human biological rhythms and holds huge promise in areas of pain management and treatment of asthma, heart disease and cancer. The coordination of medical treatment and drug delivery with such biological clocks and rhythms is termed chronotherapy. Chronotherapeutics, or delivery of medication in concentrations that vary according to physiological need at different times during the dosing period, is a relatively new practice in clinical medicine and thus many physicians are unfamiliar with this intriguing area of medicine. It is important that physicians understand the advantages of chronotherapy so that they can make well-informed decisions on which therapeutic strategies are best for their patientstraditional ones or chronotherapies.[15]

The goal of chronotherapeutics is to synchronize the timing of treatment with the intrinsic timing of illness. Theoretically, optimum therapy is more likely to result when the right amount of drug is delivered to the correct target organ at the most appropriate time. In contrast, many side effects can be minimized if a drug is not given when it is not needed. Unlike homeostatic formulations, which provide relatively constant plasma drug levels over 24 hours, chronotherapeutic formulations may use various release mechanisms. e.g., time-delay coatings (Covera-HSTM), osmotic pump mechanisms (COER-24TM), and matrix systems (GeminexTM), that provide for varying levels throughout the major objective of chronotherapy in the treatment of several diseases is to deliver the drug in higher concentrations during the time of greatest need according to the circadian onset of the disease or syndrome. The chronotherapy of a medication may be accomplished by the judicious timing of conventionally formulated tablets and capsules. In most cases, however, special drug delivery technology must be relied upon to synchronize drug concentrations to rhythms in disease activity.[16,17]

Advantages of pulsatile delivery

- Extended daytime or night time activity.
- Reduced side effects
- Dosage frequency.
- Reduction in dose size.
- Improved patient compliance.
- Lower daily cost to patient due to fever dosage units are required
- Drug adapts to suit circadian rhythms of body functions or diseases.
- Drug targeting to specific sites like colon.
- Protection of mucosa from irritating drugs.
- Drug loss is prevented by extensive first pass metabolism.

Table 1. Formulations forpress coated tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
HPMC K100M	20	40	60	-	-	-	-	-	-
Eudragit RSPO	-	-	-	20	40	60	-	-	-
Xanthan gum	-	-	-	-	-	-	20	40	60
PVP K30	8	8	8	8	8	8	8	8	8
Magnesium Stearate	6	6	6	6	6	6	6	6	6
Microcrystalline cellulose	61	41	21	61	41	21	61	41	21
Talc	5	5	5	5	5	5	5	5	5
Total weight	100	100	100	100	100	100	100	100	100

Drawbacks of pulsatile delivery

- Lack of manufacturing reproducibility andefficacy
- Large number of process variables.
- Multiple formulation steps.
- Higher cost of production.
- Need of advanced technology.
- Trained/skilled personal needed formanufacturing.[18]

MATERIALS

ZafirlukastPurchased from Aurabindopharama Ltd. Hyderabad., Provided by Sura Labs, Dilsukhnagar.Croscarmellose sodium Maruthi Chemicals Ltd. (Ahmedabad). HPMC K100M S.D. Fine chemicals limited (Hyderabad) Eudragit RSPO SD Fine Chemicals, MumbaiXanthan gum ATOZ Pharmaceuticals, Chennai.PVP K30 FMC Biopolymers. Magnesium Stearate Central Drug House Pvt. Ltd., New Delhi. Microcrystalline cellulose Trishul reagents and chemicals, Chennai. Talc ZIM Laboratories Ltd, Nagpur.

METHODOLOGY

Analytical method development

Preparation of calibration curve in 0.1N HCL: 10mg of Zafirlukast pure drug was dissolved in 10 ml of methanol (stock solution 1). 1ml of solution was taken and makes up with10 ml of 0.1N HCL (100µg/ml) stock-2. From this 1ml was taken and make up with 10 ml of 0.1N HCL (10µg/ml) stock-3. The above stock-II solution was subsequently diluted with 0.1N HCL to obtain series of dilutions containing and 2,4,6,8 and 10µg/ml of solution. The absorbance of the above dilutions was measured at 239 nm for 0.1 N HCL by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2)which determined by least-square linear regression analysis. The Same procedure repeated in pH 6.8 phosphate buffer.

Formulation development of Tablets

Formulation of core tablets by direct compression: The inner core tablets were prepared byusing direct compression method as shown in the Table 7.1. Powder mixtures of Zafirlukast, Croscarmellose sodium, PVPK 30,Talc and Microcrystalline cellulose ingredients were dry blended for 20 min. followed by addition of Magnesium stearate. The mixtures were then further blended for 10 min., 50 mg of resultant powder blend was manually compressedusing, Lab pressLimited, India with a 5 mm punch and die to obtainthe core tablet.

Formulation of mixed blend for barrier layer: The various formulation compositions containing HPMC K100M,Eudragit RSPO,Xanthan gum, Talc and Microcrystalline Cellulose.Different compositions were weighed dryblended at about 10 min and used as press coatingmaterial to prepare press-coatedpulsatile tablets respectively by directcompression method.

Preparation of press-coated tablets: The core tablets were press-coated with100 mg of mixed blend as given inTable.No 7.2. 100 mg of barrier layer materialwas weighed and transferred into a 7mmdie then the core tablet was placedmanually at the center. The remainingof the barrier layer materiel wasadded into the die and compressed by using Lab press Limited, India. All the quantities were in mg

RESULTS AND DISCUSSION

Table 2. Calibration data of Zafirlukast in 0.1N HCL

Concentration [µg/ml]	Absorbance
0	0
2	0.125
4	0.243
6	0.352
8	0.485
10	0.591

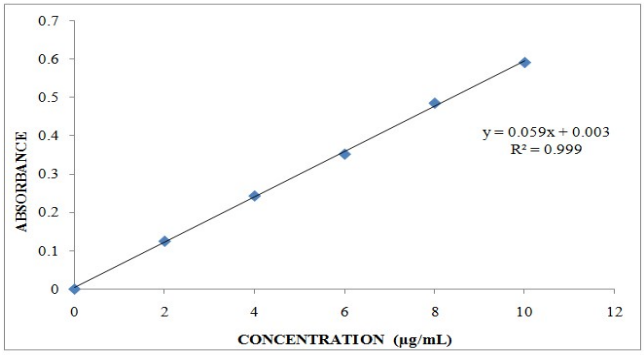

Fig. 1. Standard graph of Zafirlukast in 0.1N HCL

Table 3. Calibration data of Zafirlukast in pH6.8 phosphate buffer

Conc [µg/ml]	Abs
0	0
2	0.188
4	0.351
6	0.512
8	0.671
10	0.832

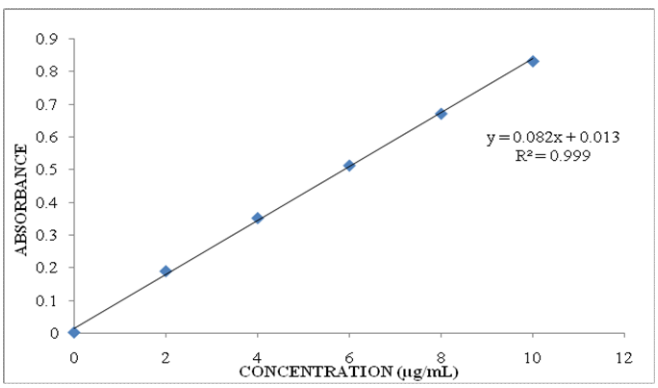

Fig. 2. Standard graph of Zafirlukast in pH 6.8 phosphate buffer

Table 4. Pre compression Parameters of Zafirlukast coated Tablets

Formulation code	Angle of repose (°) *	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	27.08	0.664	0.823	19.32	1.07
F2	32.15	0.652	0.807	19.21	0.98
F3	37.39	0.662	0.901	26.53	0.95
F4	31.47	0.667	0.907	26.46	0.99
F5	31.09	0.624	0.801	22.10	1.10
F6	28.12	0.648	0.862	24.82	0.91
F7	26.89	0.681	0.887	23.22	0.98
F8	25.9	0.651	0.817	20.32	1.13
F9	24.70	0.672	0.826	18.64	1.18

Quality control parameters for tablets:

Table 5. Post compression parameters of Coated tablet

Formulation code	Average weight (mg)	Hardness (kg/cm^2)	Thickness	Friability (%loss)	Drug content (%)	Disintegration time (sec)
F1	149.71	5.1	5.15	0.41	98.73	56
F2	150.01	5.6	5.36	0.68	96.82	43
F3	149.36	4.7	5.18	0.39	97.15	20
F4	148.93	5.0	5.79	0.72	99.57	63
F5	147.89	4.5	5.60	0.28	95.89	48
F6	148.24	4.8	5.31	0.75	98.14	61
F7	149.12	5.3	5.12	0.49	97.43	50
F8	147.67	5.7	5.93	0.62	96.21	41
F9	149.96	4.6	5.74	0.50	99.59	28

***In Vitro* Drug Release Studies**

Table 6. Cumulative % drug release of Coated

TIME (MIN)	% OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	0
2	10.71	13.96	15.38	8.50	10.32	19.02	08.21	10.34	13.59
3	15.82	23.61	28.26	16.15	18.19	25.10	19.59	28.92	23.86
4	28.10	31.53	36.16	21.23	29.65	37.28	23.46	36.47	32.12
5	40.59	43.82	41.97	35.68	41.27	50.55	62.93	52.40	43.18
6	63.62	81.19	87.75	68.28	71.54	86.13	71.14	68.98	53.89
7	76.58	90.24	94.14	76.93	78.15	90.82	87.10	73.12	72.26
8	82.14	95.26	99.31	89.12	87.03	96.14	96.45	91.75	89.97

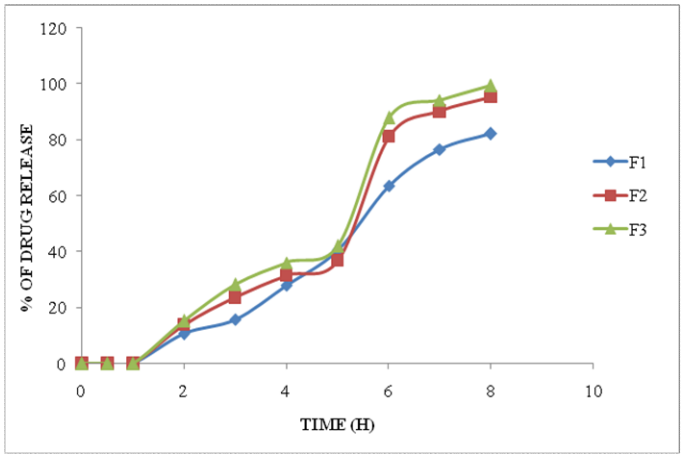

Fig. 3. Cumulative % drug release study of Zafirlukast pulsatile tablets (F1, F2 & F3)

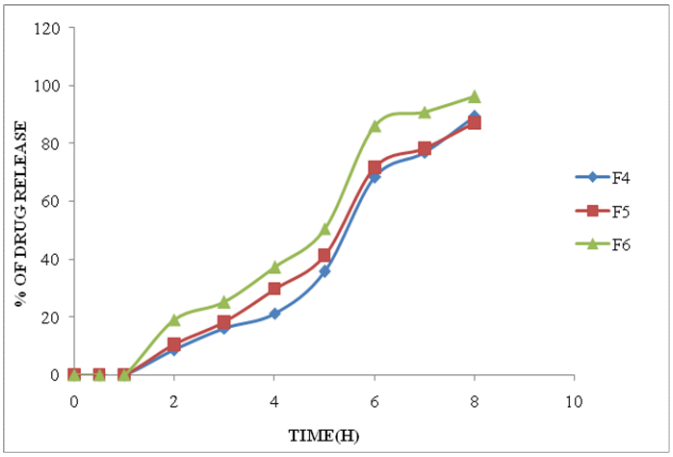

Fig. 4. Cumulative % drug release study of Zafirlukast pulsatile tablets (F4, F5 & F6)

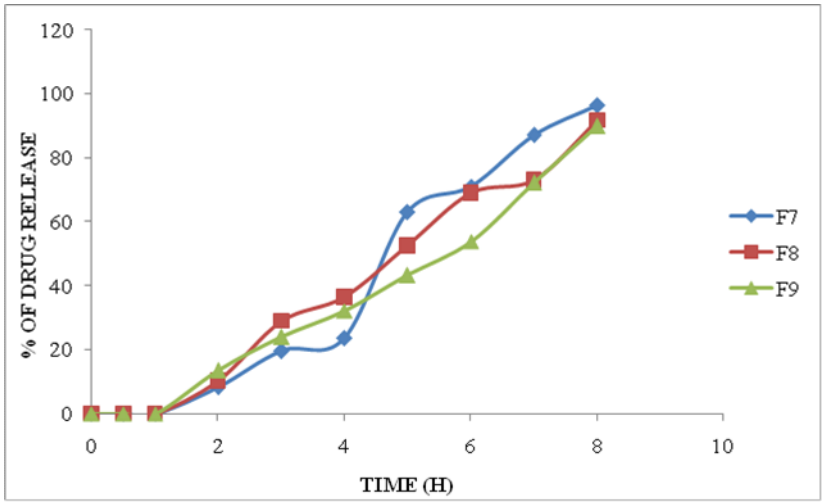

Fig. 5. Cumulative % drug release study of Zafirlukast pulsatile tablets (F7, F8 & F9)

Table 7. Release kinetics data for optimized formulation

Cumulative (%) release q	Time (t)	Root (t)	Log (%) release	Log (t)	Log (%) remain	Release rate (cumulative % release / t)	1/cum% release	Peppas log q/100	% drug remaining	Q01/3	Qt1/3	Q01/3-qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
0	0.5	0.707	#NUM!	-0.301	2.000	0.000	#DIV/0!	#NUM!	100	4.642	4.642	0.000
0	1	1.000	#NUM!	0.000	2.000	0.000	#DIV/0!	#NUM!	100	4.642	4.642	0.000
15.38	2	1.414	1.187	0.301	1.927	7.690	0.0650	-0.813	84.62	4.642	4.390	0.251
28.26	3	1.732	1.451	0.477	1.856	9.420	0.0354	-0.549	71.74	4.642	4.155	0.486
36.16	4	2.000	1.558	0.602	1.805	9.040	0.0277	-0.442	63.84	4.642	3.997	0.645
41.97	5	2.236	1.623	0.699	1.764	8.394	0.0238	-0.377	58.03	4.642	3.872	0.770
87.75	6	2.449	1.943	0.778	1.088	14.625	0.0114	-0.057	12.25	4.642	2.305	2.336
94.14	7	2.646	1.974	0.845	0.768	13.449	0.0106	-0.026	5.86	4.642	1.803	2.839
99.31	8	2.828	1.997	0.903	-0.161	12.414	0.0101	-0.003	0.69	4.642	0.884	3.758

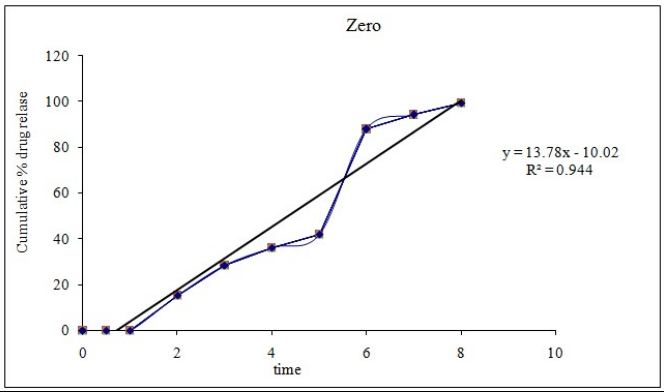

Figure 6. Graph of zero order kinetics

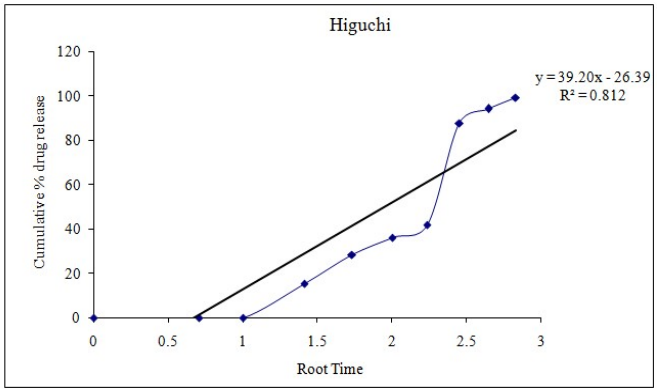

Figure 7. Graph of higuchi release kinetics

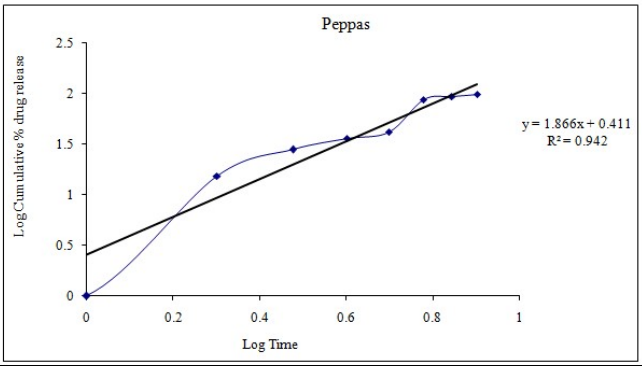

Figure 8. Graph of peppas release kinetics

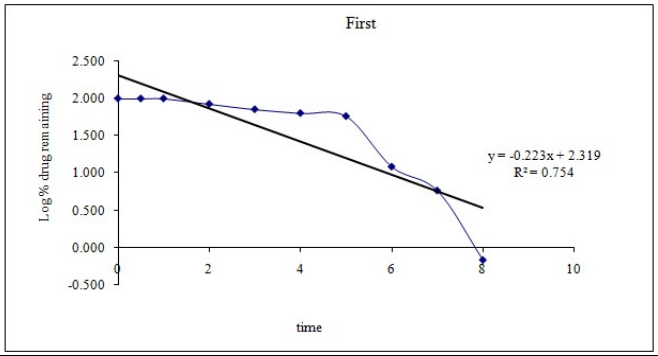

Figure 9. Graph of first order releases kinetics

Drug – Excipient compatibility studies

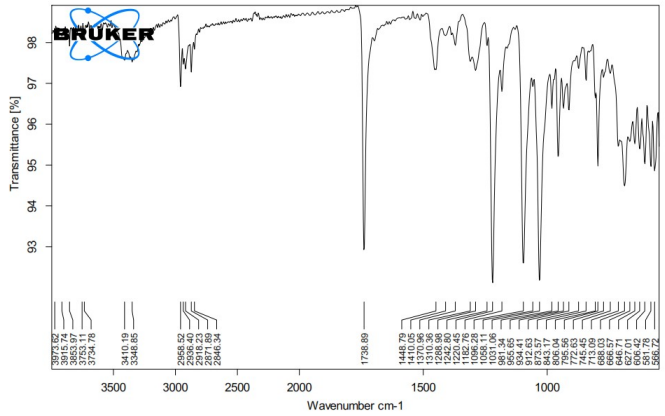

Fig. 10. FTIR spectra of Zafirlukast pure drug

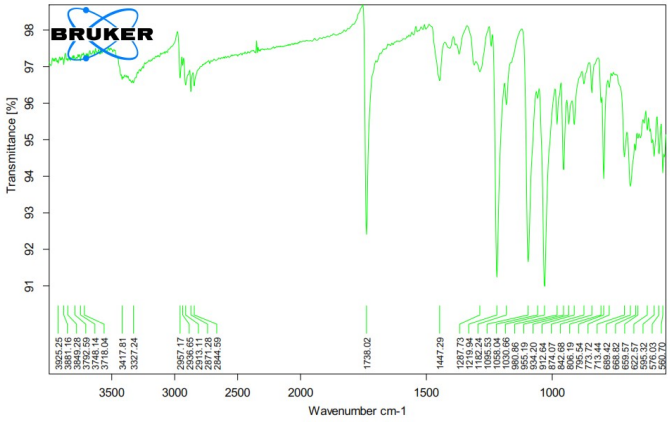

Fig. 11. FTIR spectra of optimized Formula

CONCLUSION

Over the past decades, there has been a growing appreciation on theimportance of circadian rhythms on GI tract physiology and to diseasestates. In the present study, an effort is made to formulate and evaluatetime-controlled single unit pulsatile tablets of Zafirlukast. Theimmediate drug releasing core tablets were formulated and press coated for intentionally delaying the drug release from therapeuticpoint of view in the treatment of asthama, where peaksymptoms are observed in the early morning. The results from FTIR spectroscopy revealed that the drug andpolymers used were satisfactorily compatible. In the present study an attemptwas made to develop pulsatile drug delivery systemof Zafirlukastto overcome thedosing requirement of conventional tablets. Direct compression method was applied for formulationof core tablet by using excipients such as MCC, Croscarmellose sodium and PVP K30 as bindingagent. Core tablets coated with HPMC K100M, Eudragit RSPO and Xanthan gum polymers was found to besatisfactory with respect to the required lag time (it has a lag time of 2 h) The core tablet were evaluated pre and post compression parameters the all results are found in acceptable limits and the core tablet evaluated disintegration test the tablet is disintegrated in very less time 20 sec. So F3 formulation was selected for press coating and enteric coating formulations.

The compression coated tablets were further evaluated for weight variation test, thickness, hardness, friability, swelling studies and dissolution study all results are found to be acceptable limits. Among All Formulations F3 was showed maximum % drug release 99.31 % at 8 hours. Hence F3 Formulation was considered as optimized Formulation. Time-controlled pulsatilerelease tablets of Zafirlukast with a lag time of nearly 2 h weresuccessfully prepared to treat the asthamasymptoms.

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