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

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ABSTRACT

The aim of this study was to explore the feasibility of time dependent pulsatile drug delivery system of Zafirlukast, is to blocks the action of the cysteinyl leukotrienes on theCysLT1receptors, thus reducing constriction of the airways, build-up of mucus in the lungs and inflammation of the breathing passages. A satisfactory attempt was made to develop pulsatile system of Zafirlukast and evaluated it. From the reproducible results obtained from the executed trails of core and press coated tablets it can be concluded that drug like Zafirlukast and excipients like MCC, Lycoat, SSG, Ludiflash, and Talc were used to prepare pulsatile formulation. Prepared pulsatile drug delivery systems were evaluated for hardness, friability, weight variation, drug content uniformity, drug-polymer interaction, *invitro* drug release. Various formulations prepared, formulationF6 were selected as optimized formulations.

Keywords: Zafirlukast, Ludiflash, Lycoat, Sodium starch glycolate and MCC.

INTRODUCTION

Controlled drug delivery systems have acquired a center stage in the area of pharmaceutical research and development sector. Such systems offer temporal and /orspatial control over the release of drug and grant a new lease of life to a drug molecule in terms of patentability. Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for obvious advantages of oral route of drug administration[1-3]. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuation, reduction in dose of drug, reduced dosage frequency, avoidance of side effects and improved patient compliance. In such systems the drug release commences as soon as the dosage form is administered as in the case of conventional dosage forms. However, there are certain conditions, which demand release of drug after a lagtime[4-6].Such a release pattern known as pulsatile release.

Traditionally, drug delivery has meant getting a simple chemical absorbed predictably from the gut or from site of injection. A second-generation drug delivery goal has been the perfection of continuous, constant rate (zero order) delivery of bioactive agents. However, living organisms are not “zero order” in their requirement or response to drugs. They are predictable resonating dynamic systems, which require different amounts of drugs at predictably different times within the circadian cycle in order tomaximizedesiredandminimizeundesireddrugeffects[7-9].Duetoadvancesinchronobiology, chronopharmacology and global market constraints, the traditional goal of pharmaceutics (eg. design drug delivery system with a constant release rate) is becoming obsolete. However, the major bottleneck in the development of drug delivery systems that match circadian rhythms (chrono pharmaceutical drug delivery systems: Chr DDS) may be the availability of appropriate technology. The diseases currently targeted for chrono pharmaceutical formulation or those for which there are enoughscientificbackgroundstojustifyChrDDScomparedtotheconventional drug administration approach. These include

asthma, arthritis, duodenal ulcer, cancer, diabetics, cardiovascular diseases, hypercholesterolemia, ulcer and neurologicaldisorder[10-13].

MATERIALS AND METHODS

Zafirlukast were procured from B.M.R Chemicals, Hyderabad. Ludiflash Lycoat, Sodium starch glycolate, Microcrystalline cellulose, HPMCK 200 M and talc were procured from S.D. Fine Chemical Ltd, Mumbai and Loba Chemie Pvt. Ltd, Mumbai.

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 tablets 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.

Formulation of coating of the core tablets of Zafirlukast

The optimized core tablets were coated with coating ingredients like HPMC K200M and ethyl cellulose. Now accurately weighed amount of barrier layer material was transferred into a 12 mm 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 12mm flat oval shape punch. The prepared tablet of each batch was evaluated for the tablet properties.

Flow properties

Angle of repose

Angle of repose is determined as the maximum angle possible between the surface of the pile of the powder and horizontal plane. Fixed funnel method was used to determine the angle of repose of powder or granules.

Bulk density

Weighed amount of the powder blend was taken and transferred to a measuring cylinder. Bulk volume of the blend is noted as per the reading on the measuring cylinder.

Tapped density

Tapped density is determined by the weighed quantity of powder blend is poured into the graduated cylinder, which is then tapped for 100 taps.

Compressibility Index

Compressibility index is important to measure the tendency of powder formulation. It indicates the flow properties of the blend. Low percentage of compressibility index indicates free flowing powder, whereas high compressibility index indicates poor flowing powder. (Table 3 and Table 4).

InVitro Dissolution Studies

From the *invitro* drug release studies of Apremilast controlled release tablets using Xanthangum, Ethylcellulose, Sodium CMC in three different polymer ratios using MCC as a filler and PVPK30asbinder. Among the all 9 trails, F1-F3 trails were formulated using Ethyl cellulose in three different ratios like 6%, 12% and 18%, the drug release was decreased with increase in the polymer concentration. F1 formulation containing 6% of Ethyl cellulose shows 89.09% of drug release at the end of 24 hours, while F2 formulation containing 12% of Ethyl cellulose shows 90.28% of drug release at the end of 24 hours, whereas F6 formulation containing 18% of Ethylcellulose shows 94.15% of drug release at the end of 24 hours. So, further formulations were prepared using Xanthangum. Then F4-F6 trails were formulated using Xanthan gum in four different ratios like 6%, 12%,18% and 24%. F4 formulation containing 6% of Xanthan gum shows 95.57% of drug release at the end of 24 hours, while F5 formulation containing 12% of Xanthan gum shows 97.82%of drug release at the end of 24hours, whereas F6 formulation containing 18% of Xanthan gum shows 99.86% of drug release at the end of 16 hours. Further formulations were prepared using Sodium CMC. The *invitro* release profiles were shown in Figure 1.

FT-IR STUDIES

The IR spectrum of pure drug was found to be similar to the standard spectrum of Zafirlukast. The spectrum of Zafirlukast shows the following functional groups at their frequencies. From the spectra of Zafirlukast, combination of Zafirlukast

with polymers, it was observed that all characteristic peaks of Zafirlukast were not altered and present without alteration in the combination spectrum, thus indicating compatibility of the drug and polymers. FT-IR spectra of Zafirlukast, and optimized formulation are shown in Figure 2and 3 respectively.

RESULTS AND DISCUSSION

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 0.42±0.04g/cm^3 to 0.52±0.06g/cm^3.Tapped density was found between 0.48±0.01 g/cm^3 to 0.60±0.03 g/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±0.26-15.51±0.94 and Hausner's ratio from 1.12±0.02-1.18±0.05 which reveals that the blends have good flow character. Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 3-4 kg/cm^2. All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of the tablet weight. Friability values were found to be less than1% in all the formulations F1-F6 and considered to be satisfactory ensuring that all the formulations are mechanically stable. The drug content value for all the formulations (F1–F6) was found to be in the range of 85-98%. From the *invitro*drug release in studies itwas observed that the formulations containing ludiflas has a super disintegrant in different concentrations like 3 and 6 %, reveals that the increased in the superdisintegrant concentration decreases the drug release time and the F6 formulation containing ludiflash 6 % concentration shows maximum amount of drug release (99.45%) at the end of 30 mins. Whereas formulations containing lycoat as a super disintegrant in differentconcentrationslike3and 6 %, reveals that the increased in the super disintegrant concentration decreases the drug release time and the F2 formulation containing lycoat with 6 % concentartion shows maximum amount of drug release (98.81%) attheendof45mins. Whereas formulations containing SSG as a superdisintegrant in different concentrations like 3and 6 % reveals that the increased in the superdisintegrant concentration decreases the drug release time and the F4 formulation containing SSG with 6 % concentartion shows maximum amount of drug release (98.42%)at the end of 45mins. So,F6 formulation containing 6%concentration of ludiflash shows maximum release within 30mins. So that it is chosen as optimized formulation. Dissolution study was carried out to measure the release rate of drug from prepared Press coated formulation using USP I dissolution apparatus at 37^{0}C using 2 different dissolution media of pH1.2, pH 6.8 phosphate buffers in order to mimic *invivo* GIT conditions. Initially first 2hrs of dissolution was conducted in pH 1.2 buffer, followed by 10 hrs of dissolution study in pH 6.8phosphatebuffer. All the 4 formulations of Zafirlukast Press coated were subjected to dissolution studies.

CONCLUSION

The aim of this study was to explore the feasibility of time specific pulsatile drug delivery system of Zafirlukast to treat asthma, often used in conjunction with an inhaled steroid and/or long-acting bronchodilator. From the results obtained from executed experiments it can be concluded that, the preformulation studies like pH, solubility and UV-analysis of Zafirlukast, were compiling with BP standards. The FT-IR Spectra revealed that, there was no interaction between polymer and drug. The drug content of coated core tablet was obtained as 92.46- 98.10 and *invitro* evaluation of optimized coated core tab was obtained as 98.56%.

Table 1: Formulation Table of zafirlukast Core Tablets

Ingredients	F1	F2	F3	F4	F5	F6
Zafirlukast	10	10	10	10	10	10
Lycoat	3	6	--	--	--	--
SSG	--	--	3	6	--	--
Ludiflash	--	--	--	--	3	6
MCC	81	78	81	78	81	78
Mg.stearate	3	3	3	3	3	3
Talc	3	3	3	3	3	3
Totalwt(mg)	100	100	100	100	100	100

Table 2: Composition of compression coated tablets of Zafirlukast

Formulation	C1F6	C2F6	C3F6	C4F6
Core	100	100	100	100
HPMCK200M	100	--	50	100
Ethyl cellulose	--	100	100	150
Core:coating polymer(ratio)	1:1	1:1	1:0.5:1	1:1:1.5
Total weight (mg)	200	200	250	350

Table 3: Flow properties of powder blend

FC	Derived properties		Flow properties		
	Bulk density (mean±SD)	**Tapped density (mean±SD)**	**Angle of Repose (mean±SD)**	**Carr'sindex (mean±SD)**	**Hausner's ratio (mean±SD)**
F1	0.48±0.01	0.56±0.015	26.38±0.30	14.28±0.02	1.16±0.06
F2	0.46±0.01	0.52±0.02	27.42±0.39	11.53±0.26	1.13±0.03
F3	0.42±0.04	0.48±0.01	24.02±0.68	12.58±0.08	1.14±0.05
F4	0.46±0.02	0.54±0.15	26.26±0.96	14.81±0.28	1.12±0.02
F5	0.52±0.06	0.60±0.03	30.68±0.73	13.33±0.86	1.17±0.04
F6	0.49±0.24	0.58±0.06	29.26±0.36	15.51±0.94	1.18±0.05

Table 4: Characterization Zafirlukast Tablets

FC	Post compression parameters of core tablet					
	Avg.Wt(mg)	**Hard-ness(kg/cm^2)**	**Thickness(mm)**	**Friability(%)**	**Disintegration time(secs)**	**Drug content**
F1	99.12±0.04	3.34±0.40	2.52±0.32	0.23±0.42	86±0.48	86.02±0.15
F2	98.97±0.52	3.12±0.02	2.36±0.18	0.41±0.26	63±0.26	89.23±0.79
F3	97.56±0.36	3.30±0.10	2.48±0.36	0.77±0.18	47±0.84	93.30±0.26
F4	98.56±0.48	3.20±0.06	2.50±0.48	0.54±0.04	29±0.22	94.22±0.33
F5	99.23±0.36	3.33±0.14	2.54±0.29	0.63±0.54	75±0.69	88.56±0.45
F6	99.78±0.04	3.45±0.24	2.38±0.54	0.70±0.26	69±0.52	98.69±0.98

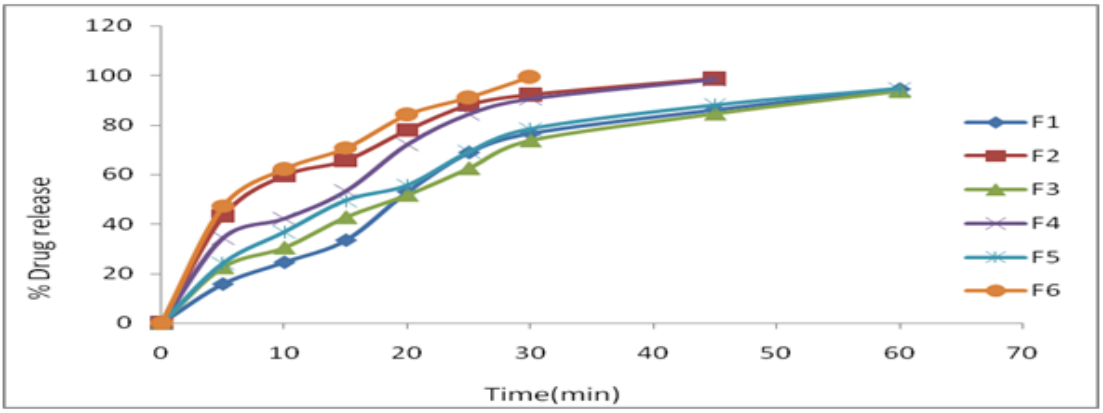

Fig. 1: *Invitro* dissolution data of formulations

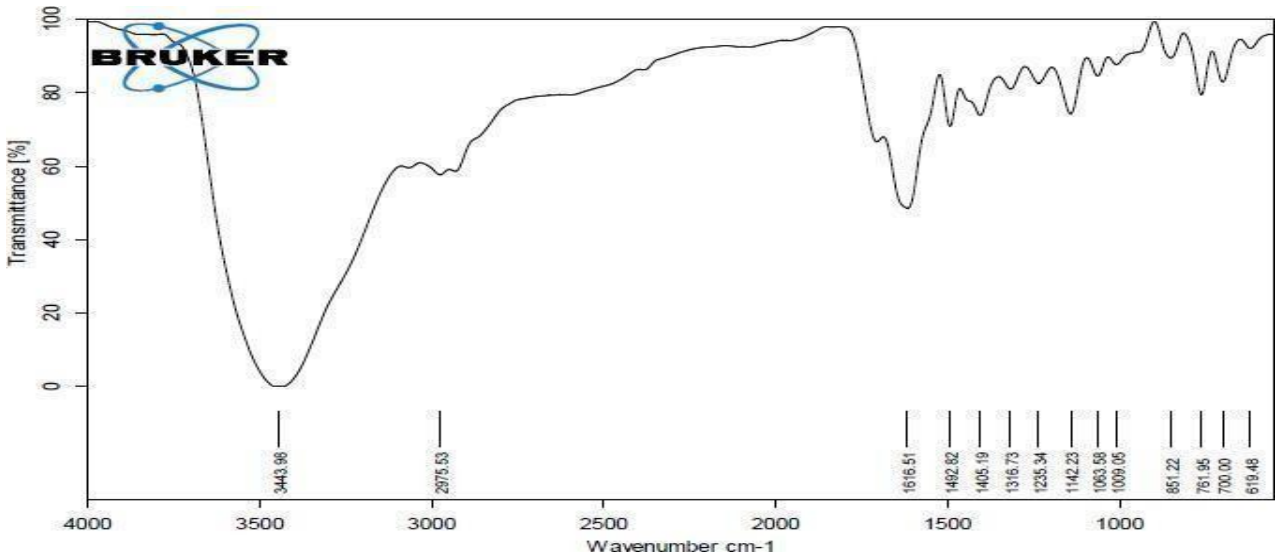

Fig. 2: FT-IR spectrum of Zafirlukast

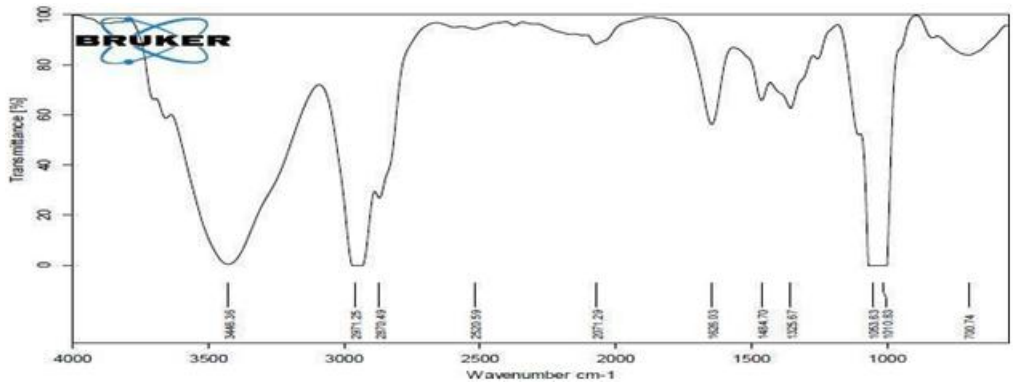

Fig. 3: FT-IR spectrum of optimized formulation

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