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Design, Development and Optimization of Zafirlukast Press Coat Tablets for Pulsatile Drug Delivery

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Abstract

The Aim of study design and developed of press coated tablets of Zafirlukast. The drug and excipients compatibility was studied by DSC and FTIR studies. The prepared tablets were evaluated f or physicochemical properties and *in vitro* drug release patterns. FTIR and DSC studies revealed that there was no chemical interaction between drug and polymers used. The prepared tablets passed all physicochemical tests. The *in vitro* drug release pattern indicated that type of polymer and its concentration had marked influence on the drug release form tablets. The result of stability studies for the optimized formulation indicated that the formulation was stable even after stressed storage conditions.
Keywords: Zafirlukast, HPMC K100M, Press Coat tablets, pulsatile

Contents

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1. Introduction

Pulsatile drug delivery system is the type of drug delivery system, where the delivery device is competent of releasing drug later than determined time-delay that is lag time known as palatial drug delivery system [1]. In exacting nearby is great deal of significance in how chronotherapy preserve relax help patients suffering starting allergic rhinitis, rheumatoid arthritis, moreover associated disorders asthma cancer cardio vascular diseases and peptic ulcer disease. The function of circadian rhythms in the pathogenesis with treatment of asthma indicates that air way resistance increase with time at night in asthmatic patients [2].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) polymer and synthetic (hydrophobic) polymer and Zafirlukast as a model drug. The intention was to maintain lag time 4-6 h. As the symptoms of asthma are experienced in the early morning hours. The incorporation of 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 [2-4].

2. Materials and Method

Materials:

Zafirlukast was a gift sample from Chandra Labs, Hyderabad, Microcrystalline cellulose was procured from Degussa India Pvt. Ltd., Mumbai. Crospovidone, Sodium starch glycolate,, Croscarmellose sodium, Magnesium stearate and Sodium lauryl sulphate were procured from S.D. Fine Chemicals, Mumbai. HPMC K100M, Guar gum, Ethyl cellulose were procured were procured from Sisco Research Labs, Mumbai. Double distilled water was used whenever required.

Table 1: Composition of core tablets

Ingredients (mg)	Formulations					
	F 1	**F2**	**F 3**	**F 4**	**F5**	**F6**
Zafirlukast	10	10	10	10	10	10
Croscarmellose Sodium	7.5	-	-	11.5	-	-
Sodium Starch Glycolate	-	7.5	-	-	11.5	-
Crospovidone	-	-	7.5	-	-	11.5
Magnesium stearate	3	3	3	3	3	3
Micro crystalline cellulose	126.5	126.5	126.5	122.5	122.5	122.5
Sodium lauryl sulphate	3	3	3	3	3	3
Total weight	150	150	150	150	150	150

Table 2: Composition of Press coat tablets

Press coated polymers (mg)	**P1 1:1**	**P2 1:3**	**P3 3:1**	**P4 1:1**	**P5 3:1**	**P6 1:3**
HPMC K100M	150	75	225	-	-	-
Ethyl Cellulose	150	225	75	150	225	75
Guar gum	-	-	-	150	75	225
Total weight	300	300	300	300	300	300

Compatibility Studies shows spectrums:

Pure drug FTIR spectrum:

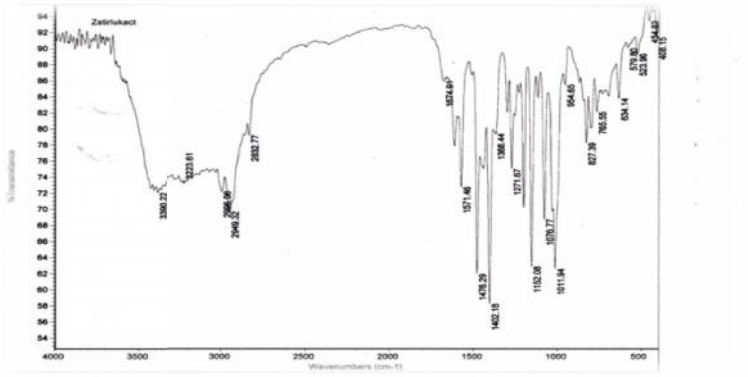


Figure 1: FTIR Spectrum shows pure drug Zafirlukast

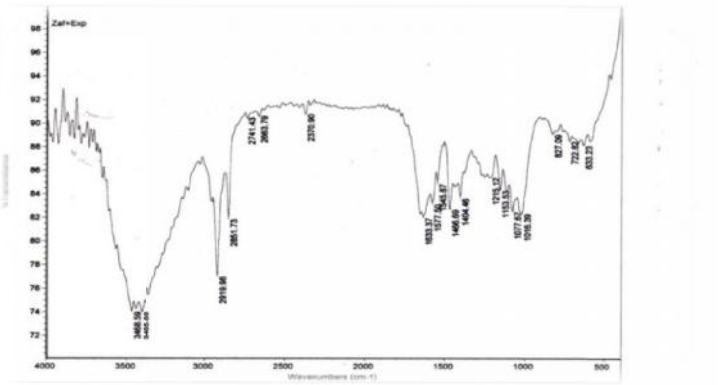


Figure 2: FTIR Spectrum shows Zafirlukast and Optimized formulation

DSC Thermo grams: Pure drug

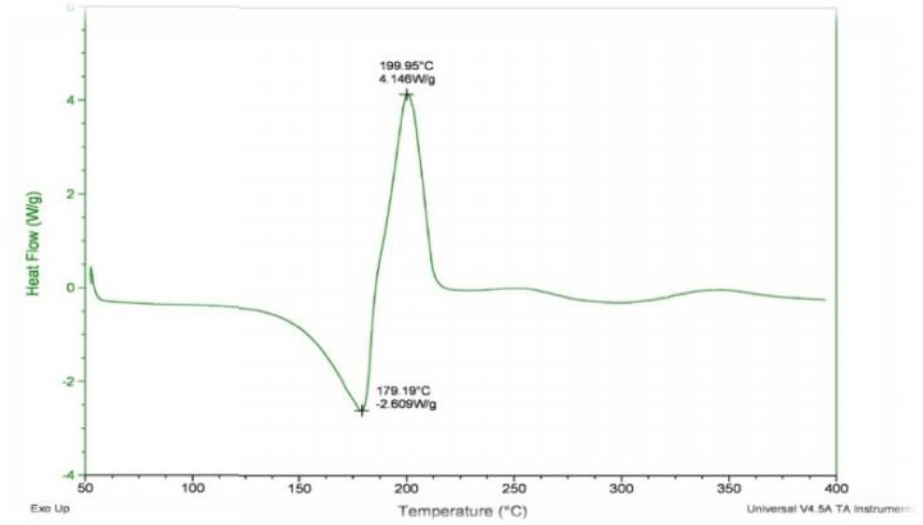


Figure 3: DSC Thermo gram of Pure drug Zafirlukast

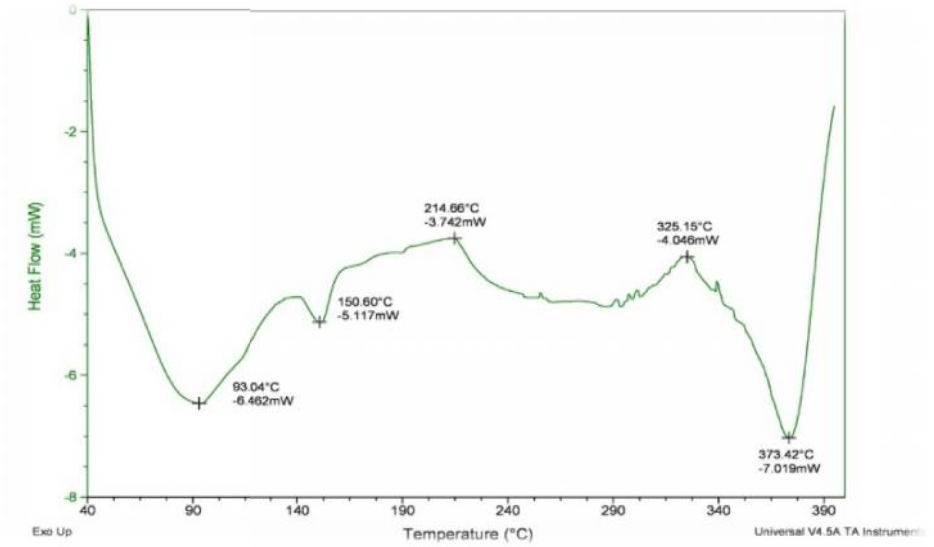


Figure 4: DSC Thermo gram of optimized formulation Press coat tablets

Pre compression parameters:

Powder blends used for preparing core tablets were evaluated for angles of repose, bulk density, tapped density, Hausner's ratio, Carr's index and the results are shown in table. The values for angle of repose, Hausner's ratio, and compressibility index were found to be in good correlation, indicating that all formulations possess good flow property and compressibility [5-8].

Table 3: Pre-compression parameters for formulation batches

Formulation	Bulk density(g/ml)	Tapped density(g/ml)	Carr's Index (%)	Hausner's ratio	Angle of repose (θ)	Flow property
F1	0.45±0.045	0.50±0.07	12.23±0.6	1.11±0.04	25.58±0.15	Very good
F2	0.44±0.044	0.50±0.09	12.58±0.8	1.13±0.08	24.44±0.11	Very good
F3	0.45±0.045	0.52±0.04	15.19±0.1	1.15±0.06	24.36±0.13	Very good
F4	0.44±0.044	0.52±0.01	15.48±0.6	1.18±0.08	26.52±0.19	Very good
F5	0.45±0.045	0.51±0.04	13.48±0.8	1.13±0.09	26.32±0.19	Very good
F6	0.51±0.045	0.59±0.04	14.48±0.8	1.15±0.09	24.69±0.19	Very good

Formulation of core tablets by direct compression:

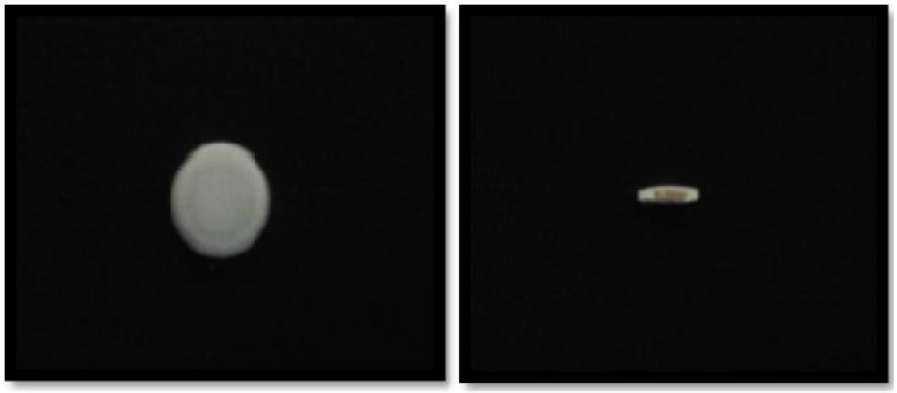
The inner core tablets were prepared by using direct compression method. As shown in Table powder mixtures of Zafirlukast, microcrystalline cellulose (MCC, Avicel PH-102), Croscarmellose sodium (Ac-Di-Sol) ,SSG, cross Povidone, SLS ingredients were dry blended for 20 min. Followed by addition of Magnesium Stearate. The mixtures were then further blended for 10 min., 150mg of resultant powder blend was manually compressed using hydraulic press at a pressure of 1 ton, with a 8mm punch and die to obtain the core tablet [9].

Formulation of mixed blend for barrier layer:

The various formulation compositions containing HPMC K100M, Ethyl cellulose and Guar gum. Different compositions were weighed dry blended at about 10 min. and used as press-coating material to prepare press-coated pulsatile tablets respectively by direct compression method [10-12].

Preparation of press-coated tablets:

The core tablets were press-coated with 300mg of mixed blend/granules as given in Table. 150mg of barrier layer material was weighed and transferred into a 12mm die then the core tablet was placed manually at the center. The remaining 150mg of the barrier layer materiel was added into the die and compressed at a pressure of 5 tons for 3min using hydraulic press [10-12].



a. b.

Figure 5: (a). Press coated tablet,(b).Longitudinal transfer section.

Post compression parameters:

Disintegration time:

To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 liter beaker containing sodium lauryl sulphate 2% at 37°C ± 1°C such that the tablet remains 2.5cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted [10-12].

***In vitro* Dissolution method for core tablets:**

Dissolution rate studies of Zafirlukast from all formulations were performed using dissolution rate testing apparatus with paddle type II according to USP. The dissolution fluid was 900ml in 0.2%w/v aqueous solution sodium lauryl sulphate. The test was performed at a speed of 50rpm and at a temperature of 37±0.5°C. Samples of dissolution medium (5ml) were withdrawn through a filter of 0.45µm at different time intervals, suitably diluted and assayed for Zafirlukast by measuring absorbance at242nm. The dissolution experiments were conducted in triplicate. [10-12]

***In vitro* Dissolution methods for press-coated tablets:**

In vitro Dissolution studies of Pulsatile delivery systems was done with the conventional paddle method of press coated tablets were performed at 37 ± 0.5 °C using 0.2% w/v aqueous solution sodium lauryl sulphate in USP II paddle method at 50 rpm. 5 ml of filtered aliquot was manually withdrawn at pre-determined time intervals and replaced with 5 ml of fresh 0.2% sodium lauryl sulphate solution maintained at the same temperature. The samples were analyzed at242nm using a UV spectrophotometer. The lag time and percentage release was determined of the eachformulation.

Drug content observed:

The Zafirlukast amorphous form of was tested for drug content and it was found that the drug was within the compendia limits 99%w/w. All the coated tablets were uniform in drug content.

Swelling index for press coated tablets:

The tablets were weighed and placed in petri dish containing 10ml of Distilled water. At specified time intervals, remove the tablets and bottled with tissue paper to remove excess water and weighed [10-12].

$$\text{Swelling index (\%)} = [Ws\text{-}Wd/Wd]\ 100$$

Where Ws is Weight of swollen tablet at time 't' and Wd is the weight

3. Results and Discussion

FTIR studies were carried with a view to evaluate the in situ drug and Excipients compatibility. The IR spectra of pure Zafirlukast and Zafirlukast with different Excipients. Pure Zafirlukast showed characteristic IR absorption bands at 1011.94 cm^{-1} indicating the presence of C-N group, 1152.08 cm^{-1} indicates the presence of C-O-C group in aromatic ring, 1402.18cm^{-1} indicates the presence of C-F group, 1476.29 cm^{-1} indicates the presence C=N group, 1674.91cm-1 indicates the presence of stretching of C=O group, 2949.32 cm^{-1} indicates the presence of bending of N-H group, 3390.22cm^{-1} indicates the presence -OH group. From the result, these prominent peaks of drug were also present in the IR spectra of physical mixtures of drug with various Excipients. Thus, revealing compatibility of the selected drug with Excipients.

Differential scanning calorimetry was used to characterize the Zafirlukast optimized formulation Excipients. The DSC thermo grams were shown in figure 3. The DSC thermo gram of Zafirlukast exothermic peak at179.19°C,-2.609 w/g and endothermic peak at 199.2°C, 4.146 w/g corresponding to its melting point.DSC thermo grams of Zafirlukast optimized formulation prepared by base line calibration method showed slight shift in peaks which indicates interaction between Zafirlukast press coat tablets. An absorption maximum (λ_{max}) of Zafirlukast was found to be at 242nm.Standard Calibration Curve for Zafirlukast.

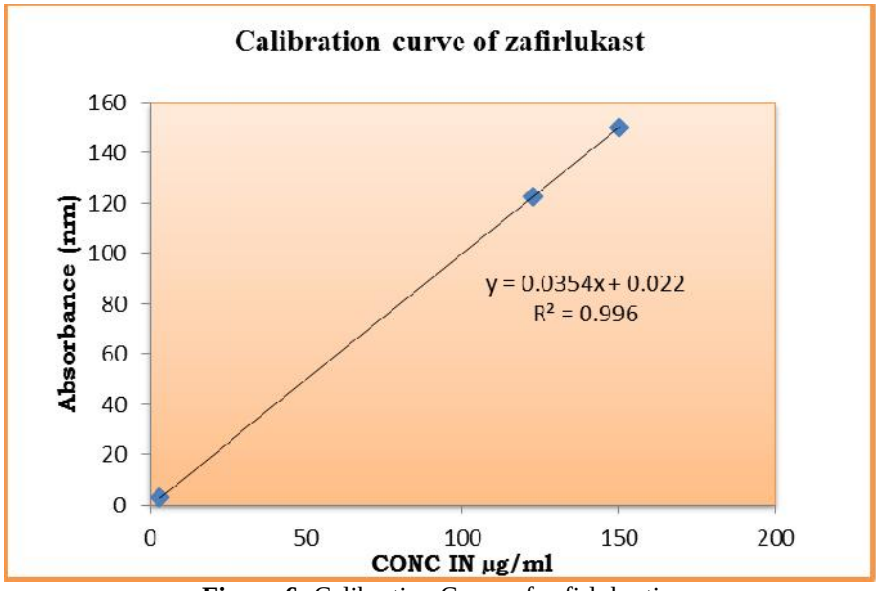


Figure 6: Calibration Curve of zafirlukastin

Table 5: Post Compression Physical Evaluation Parameters for Core Tablets

Physical parameter	F1	F2	F3	F4	F5	F6
Weight(mg)	150	152	150	149	152	150
Hardness (Kg/cm^2)	4.6	4.8	4.8	4.9	4.3	4.7
Thickness (mm)	2.4	2.45	2.61	2.46	2.44	2.49
Friability (%)	0.4	0.55	0.62	0.54	0.62	0.57
Disintegration time (min)	2.0	3.0	1.2	2.0	3.0	1.0

Table 6: Dissolution studies for CORE tablets

Time (min)	Core Tablets for Cumulative % Drug Release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	12.7	10.2	24.6	14.5	17.8	35.5
10	27.9	24.7	45.1	30.6	29.1	49.2
15	35.8	31.2	52.4	41.1	35.2	58.6
30	46.2	40.1	69.9	50.9	56.6	74.3
45	68.6	62.4	74.7	73.5	69.8	86.3
60	80.2	76.8	82.8	88.3	80.0	97.2

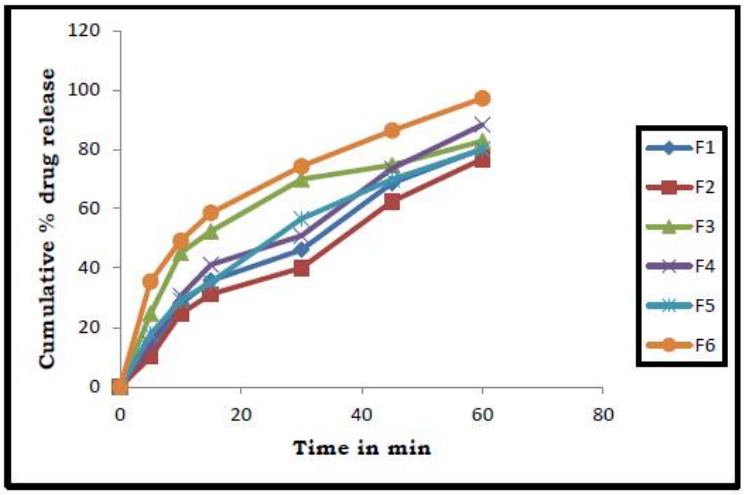


Figure 7: Dissolution graph for core formulations F1-F6

Table 7: Post compression Evaluation Parameters for Press Coated Tablets

Physical Parameter	P1F6	P2F6	P3F6	P4F6	P5F6	P6F6
Weight (mg)	452	451	453	450	450	452
Hardness (Kg/cm^2)	7.5	7.7	7.8	7.2	7.6	7.4
Thickness (mm)	2.5	2.6	2.4	2.4	2.5	2.3
Friability (%)	0.56	0.55	0.62	0.54	0.62	0.56
Swelling index (%)	81	84	85	92	98	88
Drug content (%)	87	82	86	81	98	84

Table 8: Dissolution data for press coated tablets

Time (h)	Coated Tablets Formulation for Cumulative % Drug Release					
	P1F6	P2F6	P3F6	P4F6	P5F6	P6F6
0	0	0	0	0	0	0
1	1.2	0.31	1.6	0.8	0.3	0.1
2	3.0	1.3	2.0	1.1	1.2	1.5
3	10.8	4.0	5.2	3.6	4.7	3.8
4	21.3	10.3	18.3	4.3	8.8	4.2
5	80.6	85.2	86.4	7.4	10.4	7.7
6	98.7	97.3	97.0	11.3	17.3	9.4
7	--	--	--	20.8	88.6	12.8
8	--	--	--	85.2	98.8	86.6

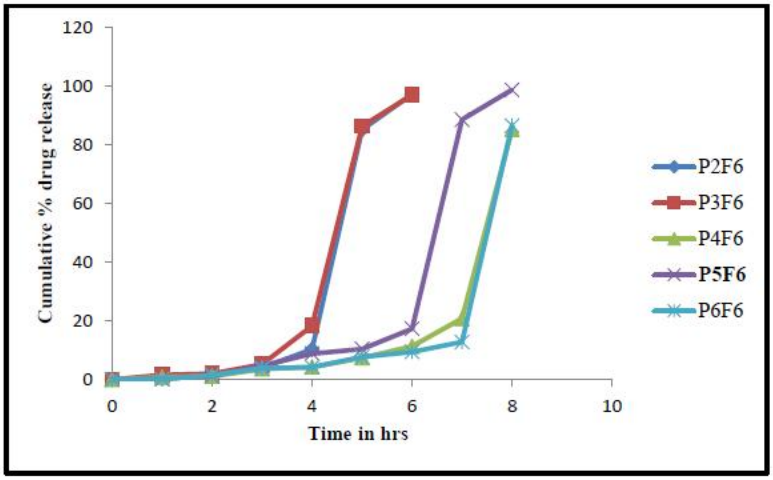


Figure 8: Dissolution graphs for press coated tablets of formulations

Figure 9: (a).1st hour (b) 2nd hour(c) 6th hour

From the above core formulations **P5F6** was selected for press coat by using different polymers like, Ethyl cellulose, and Guar gum in different ratios among which 1part of Guar gum and Ethyl cellulose 1 part of was optimized based on the lag time (10.4% in 5 hours) and percent of drug release and also further evaluated [9-11].

Table 9: Stablility studies

Cumulative %drug release during 8h			
Sampling interval	**25^{0}C/60%RH**	**30^{0}C/65%RH**	**40^{0}C/75%RH**
0 Days	99.9	99.9	99.5
30Days	98.8	99.8	99.4
60 Days	97.2	98.4	98.8
90 Days	97.3	97.6	97.3

Percent Stability studies of the formulation P5F6 of Zafirlukast press coated were carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at 25^{o}C/60%RH, 30 ^{o}C/65% RH and 40 ^{o}C/75% R H for 90 days. There was no significant change in the physical property and per cent of drug release was within the limits±4 during 8hour during the stability period [13].

4. Conclusion

From the above experimental results it can be concluded that, formulated tablets gave satisfactory results for various physicochemical parameters like hardness, friability, thickness, weight variation, drug content, and swelling index. Among all the core tablet formulations F6 was selected based on drug release within a given period of time. *In vitro* release rate studies showed that the maximum drug release was observed in P3F6 and P5F6 formulations was optimized based on less amount of drug release during lag time. Guar gum and ethyl cellulose (1:3) ratios have predominant effect on the lag time, while also shows significant effect on drug release.

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