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In vitro Characterization of Press Coated Zafirlukast Chrono Formulation

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Abstract
The aim of the study was to develop press coated time release tablets of Zafirlukast, to achieve the time controlled disintegrating or rupturing function with a distinct predetermined lag time and produce sustained drug delivery released to suite the chrono therapeutics of the disease i. e ,asthma. The core tablets were prepared by using compression coating technique with two novel disintegrants i.e ludiflash, lycoat in different concentrations after doing the post compression parameters analysis & drug release F12 was optimized and then coated with a PH sensitive polymers such HPMC K200M and Ethyl cellulose mixture of it respectively. Fourier transform infra-red (FTIR) spectrometry, Differential scanning calorimetry (DSC), were applied to investigate the drug-excipients compatibility of the formulation and the studies revealed no chemical interactions between drug and polymers used. Stability studies also were performed for 3 months at 40ºC and 55ºC at 75% RH as per ICH guidelines for optimized formulation and it was found to be stable. The effect of formulation composition on the barrier layer comprising both polymers, excipients on the lag time of drug release was investigated. It was observed that when compared with all other formulations developed, formulation C4F12 shows great ideal in pulsatile drug delivery and compared with marketed product. The release data from the formulation was found to fit in peppas model with R2 of 0.983.

Keywords
Chrono therapeutics, Ethyl cellulose, HPMC K200M, ludiflash, lycoat and Zafirlukast.

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INTRODUCTION [1-5]
Chronotherapeutic refers to a clinical practice of synchronizing drug delivery in a manner consistent with the body's circadian rhythm including disease states to produce maximum health benefits and minimum side effects. It is recognized that episodes of Asthma, angina pectoris, asymptomatic ischemia, acute coronary syndromes, sudden death, ventricular ectopic activity, and stroke all exhibit an increased incidence in the late night and in early morning (4:00 am to 6:00 am).[1-3]
A release pattern of drug is not suitable in certain disease condition. At that time, release profile of a delivery system characterized by lag time. In other words, the drug should not release during its initial period of administration, followed by a rapid and complete release (pulse release) of drug that is called pulsatile drug delivery system. [4]
Zafirlukast is a selective and competitive receptor antagonist of leukotriene D4 and E4 (LTD4 and LTE4), components of slow reacting substance of anaphylaxis (SRSA). Cysteinyl leukotriene production and receptor occupation have been correlated with the pathophysiology of asthma, including airway edema, smooth muscle constriction, and altered cellular activity associated with the inflammatory

process, which contribute to the signs and symptoms of asthma. Patients with asthma were found in one study to be 25-100 times more sensitive to the broncho constricting activity of inhaled LTD4 than non-asthmatic subjects

Zafirlukast pulsatile drug delivery tablets are developed to increase the absorption and bioavailability of the drug after a certain lag time period thereby if the concentration of polymer increase the lag time is also increase so the drug will release based on the circadian rhythm of the body at right amount, thereby bioavailability was increase.

MATERIALS AND METHODS

Materials: Zafirlukast, ludiflash and lycoat was purchased from B.M.R Pharmaceuticals &chemicals, Hyderabad and remaining all chemicals were laboratory chemicals.

Raw Material Analysis

Flow Properties of Zafirlukast: Raw Zafirlukast is testes for flow properties i.e. Bulk density, true density, Carr's index, Hausners ratio & angle of repose to check the compressibility of powder. Results were shown in table no-3.[6]

UV spectrum of Zafirlukast:

Zafirlukast crude powder analyzed with UV spectroscopic at the range of 200-400 cm-1 and maximum absorption **(λ_{max})** was determined. results were shown in Fig No1.

Solubility studies:

Saturation solubility was determined by the shake-flask method. Plain Zafirlukast in excess quantity were placed in glass-stopper flasks containing 10 ml of distilled water, pH1.2, pH6.8, pH7.4 respectively. The samples were placed in a mechanical shaker at 37 °C and 100 rpm until equilibrium was achieved (24 h). The aliquots were filtered through Whatman No. 41 filter paper. The filtrates were diluted appropriately in distilled water and assayed spectrophotometric ally at 246 nm. Results were shown in table no-4 &fig no-2 [7]

Standard Calibration curve:

25mg of Zafirlukast was weighed and transferred to a volumetric flask containing 2 ml of methanol solvent. This was sonicated for 5 min to dissolve it and the solution obtained was diluted to 100 ml with Phosphate buffer pH1.2. 10ml of this standard preparation was transferred to another volumetric flask and then diluted to 100 ml with buffer. From these suitable dilutions were made to get concentration of 2,4,6,8,10 µg/ml. Absorbance of these solutions was measured spectrophotometrically at 246 nm. The same procedure was followed with Phosphate buffer pH 6.8 and 7.4 and the absorbance was measured spectro photo metrically. Results were tabulated in table no 6,7&8.[8-10]

Drug-excipient compatibility studies:

The compatibility between drug and polymers was evaluated using Infrared spectroscopy (IR). Physical mixtures of Zafirlukast and formulation were prepared. The IR shows that all peaks are present in Zafirlukast spectra are present in the physical mixture. The results were shown in figure no- 3 and 4.

Formulation of core tablets:

As per Table No -1, all excipients are blended and punched with 6mm punch.

Table No -1 Formulation of Core Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Zafirlukast	10	10	10	10	10	10	10	10	10	10	10	10
Lycoat	2	4	6	8	--	--	--	--	--	--	--	--
SSG	--	--	--		2	4	6	8	--	--	--	--
Ludiflash	--	--	--	--	--	--	--	--	2	4	6	8
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Mg.stearate	3	3	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Total wt(mg)	100	100	100	100	100	100	100	100	100	100	100	100

COATING OF THE CORE TABLET BY COMPRESSION COATING METHOD

Precise amounts of the pH resistant polymers were correctly blended and measured, half a weighted polymer was applied to the dietary cavity, and the center tablet was placed on the remaining half of the coated polymers.[12]

Table no-2: Composition of compression coated tablets

Formulation	C1F12	C2F12	C3F12	C4F12	C5F12	C6F12
Core (wt in mg)	100	100	100	100	100	100
HPMC K200M	250	--	175	100	150	75
Ethyl cellulose	--	250	75	150	100	175
Total weight (wt in mg)	350	350	350	350	350	350

Evaluation of tablets (core & coated) [12-16]:
All the evaluation test (Hardness Test, Thickness Of Coated Tablet, Weight Variation, Friability, Disintegration Test, *In vitro* drug release test) for core and coated tablets as per the standard procedures from book. Three measurements were taken and reported on average. The result was shown in Table no 8&10.

Drug Content[14]:
Randomly 10 tablets were weighed and powered. The powder equivalent to 100mg was weighed accurately and transferred to 100ml of volumetric flask then dissolved with 5ml of methanol and sonicated for 5 min. The Volume was then made up to 100ml with phosphate buffer pH 7.4. Above solution was filtered through whatman paper and absorbance was measured at246 nm. The results were shown in Table no 8&10.

***In- Vitro* Dissolution Studies Of Compressed Coated Tablets[17]** :
Dissolution test of coated tablet of Fluvastatin was performed by using pH1.2, 6.8 and 7.4 phosphate buffers for 10 hrs, 2hrs in pH-1.2 (HCL) followed by 3hrs in 6.8 pH and 5 hrs. In pH-7.4, The Dissolution study was carried out at 37^0C and 50 rpm by using USP type II apparatus. 1ml sample were withdrawn from dissolution medium at every 1 hr up to 10hr and diluted to 10ml with respective pH medium, the absorbance was measured by using UV spectroscopy at 246 nm. The withdrawn sample was immediately replaced by equal volume of fresh buffer. The dissolution data obtained were plotted as percentage drug release versus time. The result was shown in Table no.11.

Swelling Index[16-17]:
In containers loaded with 10 ml pH 1.2 and pH 7.4 Phosphate buffers, the percentage swelling strength of tablets was determined. Tablets have been withdrawn from containers, weighted and again weighed in the medium at fixed intervals, lined with tissue paper, until the external surface of the tablet has begun to break. The% swelling was calculated using the formula. The result was shown in Table no-12.

% swelling = ((Wt -Wo)/Wo) ×100
Wt = weight of wet tablet at time Wo = weight of dry tablet.

Rupture Test[18]:
The breakage test was performed with USP paddle 2 system on closed tablets. The other criteria here were similar with the in-vitro process of dissolution. The rupture time was carried out in pH 1.2 6.8 and 7.4. The time at which the outer coating layer starts to rupture is called as lag time. The sample for this was ruptured. The results are shown in table no -13.

***In-Vitro* Comparative Study[19]**
The dissolution study was carried out for C4F12 and **ZUVAIR** for 10 hours using USP paddle type 2 dissolution apparatus in 0.1N HCL (pH 1.2) (900 ml) was placed in dissolution flask and allowed to obtain temperature at 37±0.5°C and 50 rpm for first 2 hr followed by 3 hr in 6.8 pH and 7.4 pH phosphate buffer. A 1ml samples were collected from each vessel at every 1hr up to 10 hr and diluted to 10ml with respective pH medium. The absorbance was measured by using UV spectroscopy at 292nm. The retired specimen was replaced immediately with a fresh buffer counterpart. The data obtained for dissolution was compared to time in a percentage of medicines released. The result was shown in table no14& figure no 5.

KINETIC RELEASE[20]:
Drug release kinetics found to be good for all formulations out of 6 formulation data of formulation **C4F12**was best explained by Higuchi equation, as the plot showed highest linearity (*r2* = 0.656), followed by zero order equation (*r2* = 0.862). As the drug release was best fitted in Higuchi kinetics, indicating that the rate of drug release is diffusion. The result was shown in Table No.15 and Fig No 6

RESULTS AND DISCUSSION

Flow Properties of Zafirlukast:

Table No-3 Flow Properties Of Zafirlukast

Angle of Repose	29.48±0.32
Bulk density	0.55±0.24
Tapped density	0.68±0.10
Carr's index	19.11±0.08
Hausner's ratio	1.23±0.24

From the flow properties of pure Zafirlukast it was observed that Zafirlukast have fair flow property.

UV spectrum of Zafirlukast:

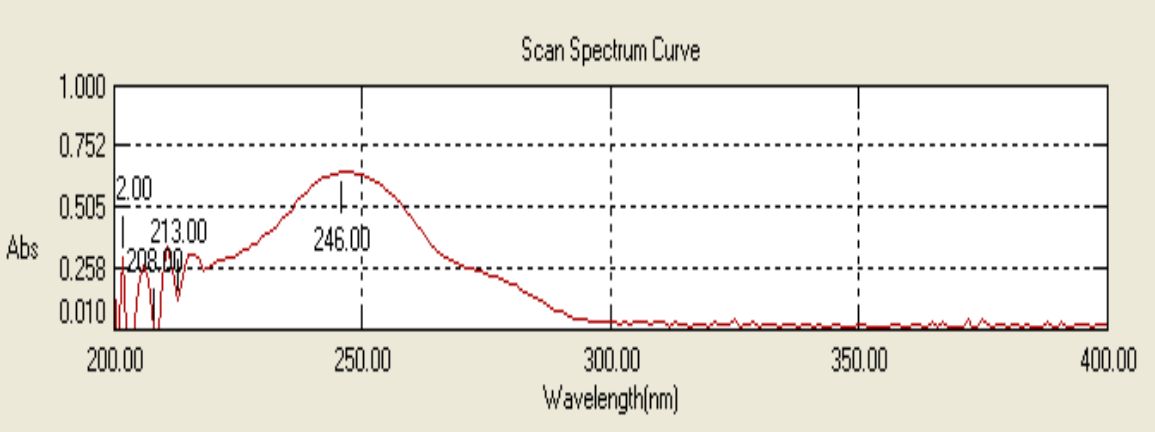

Fig No-1: UV Spectra of Zafirlukast At 246nm

In UV spectroscopy crude drug sample shown the maximum absorption peak at 246 nm which shows that the sample of Zafirlukast is pure.

Solubility studies:

Table no-4 Solubility studies of Zafirlukast:

Solvents	Solubility(mg/ml)
0.1N HCL	0.318±0.10
6.8pH Buffer	0.802±0.04
4.5pH Buffer	0.522±0.16
7.4pH Buffer	0.602±0.22

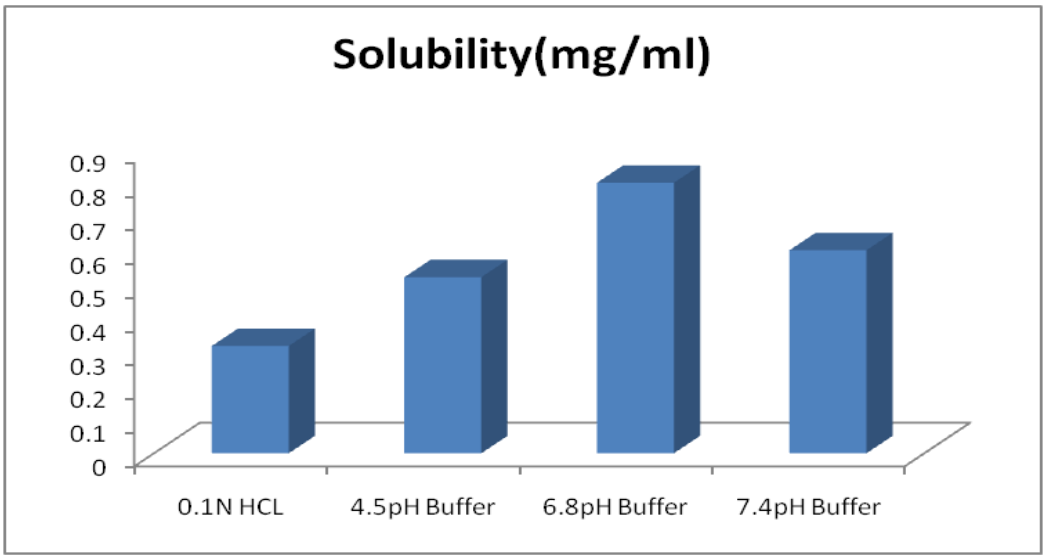

Fig No-2 Solubility Studies Of Zafirlukast

From the solubility studies it was observed that the Zafirlukast have higher solubility in 6.8pH buffer than the other buffers.

Standard Calibration curve:

Table No -5 Standard Calibration Curve of Zafirlukast in 0.1N HCl

S. No	Concentration(µg/ml)	Absorbance
1	0	0
2	5	0.032±0.18
3	10	0.102±0.32
4	15	0.197±0.04
5	20	0.278±0.18
6	25	0.322±0.30
7	30	0.408±0.02

Table No-6: Standard calibration curve of Zafirlukast in 6.8pH buffer

S. No	Concentration(µg/ml)	Absorbance
1	0	0
2	5	0.121±0.10
3	10	0.288±0.24
4	15	0.434±0.16
5	20	0.587±0.22
6	25	0.752±0.58
7	30	0.904±0.14

Table no-7: Standard calibration curve of Zafirlukastin7.4pH buffer:

S. No	Concentration(µg/ml)	Absorbance
1	0	0
2	5	0.092±0.04
3	10	0.202±0.29
4	15	0.311±0.58
5	20	0.421±0.94
6	25	0.524±0.22
7	30	0.621±0.36

FT-IR SPECTRUM:

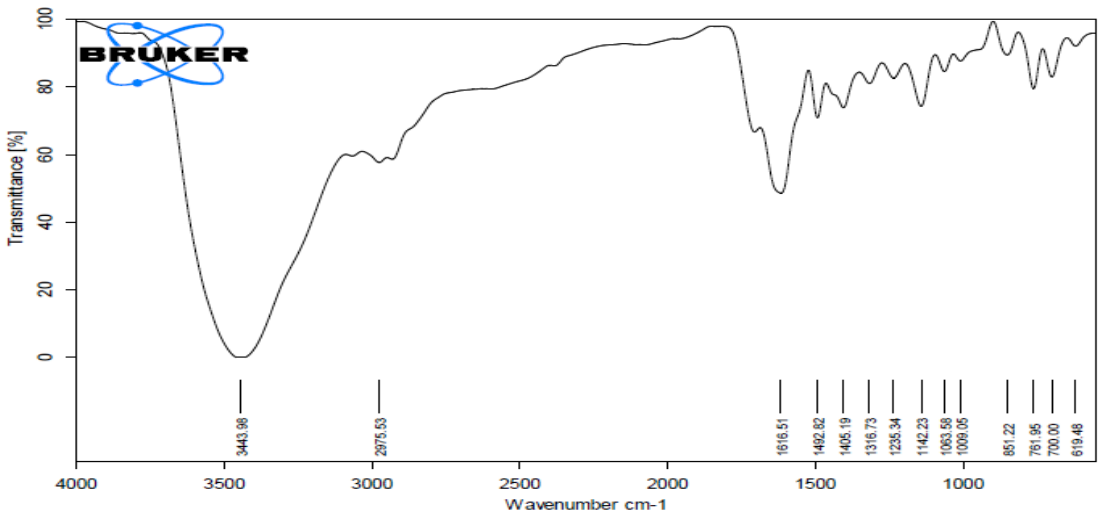

Fig no -3 FTIR Spectrum of Zafirlukast pure

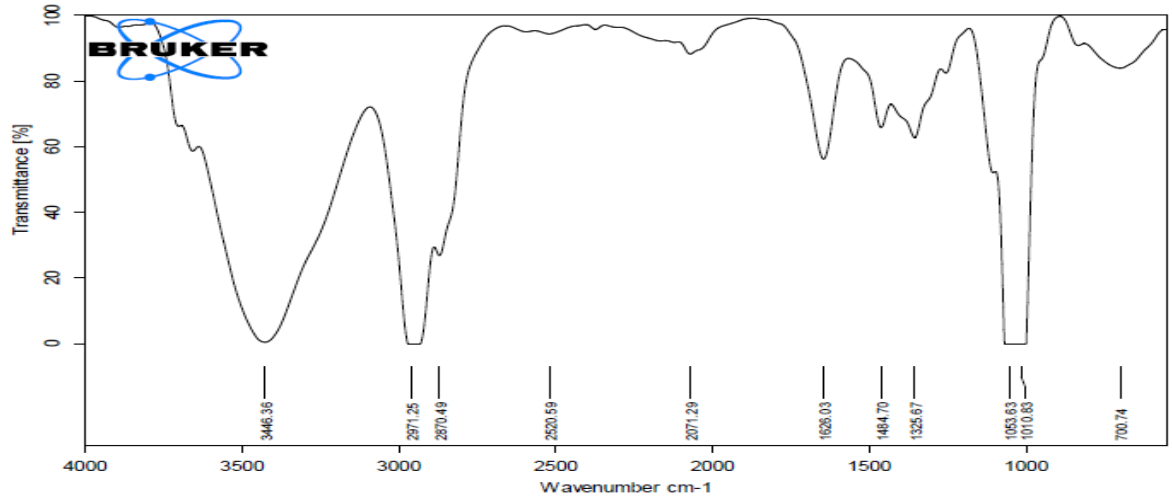

Fig no-4 FTIR Spectra of Zafirlukast optimized formulation

FTIR spectroscopy was used to study the possible interactions between Zafirlukast and the polymer. All major peaks of Zafirlukast were observed at wave numbers 3443.31 cm-1 (free O–H stretching vibrations); 2971.230 and 2877 cm-1 (C–H stretching vibrations); and 1616.5 cm-1 (stretching vibration of ester and lactone carbonyl functional groups);1316,1235 and 1063 cm-1(C-O stretching of esters and anhydrides) were retained in physical mixtures with Zafirlukast , which clearly indicate that no interaction exists between pure drug and polymer. IR studies indicated no interaction between drug and polymers.

Evaluation of tablets (core & coated)

Table No -8 Evaluation of Core Tablet

FC	Post compression parameters of core tablet					
	Avg. Wt (mg)	Hardness (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	85.69±0.98
F7	98.89±0.24	3.36±0.22	2.68±0.76	0.19±0.32	51±0.46	90.41±0.77
F8	98.55±0.56	3.55±0.12	2.52±0.62	0.35±0.10	33±0.24	92.59±0.44
F9	99.41±0.32	4.02±0.36	2.50±0.10	0.48±0.04	50±0.42	88.86±0.32
F10	99.52±0.08	4.12±0.04	2.48±0.12	0.39±0.58	41±0.48	90.22±0.48
F11	98.56±0.12	3.98±0.22	2.46±0.28	0.18±0.16	34±0.22	94.26±0.16
F12	98.24±0.64	4.20±0.18	2.54±0.54	0.33±0.28	26±0.04	96.52±0.20

Table no-9: Cumulative percent drug release of core Zafirlukast tablets of different formulations (F1toF12)

Time (mins)	F1	F2	F3	F4	F5	F6	F 7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	**0**
5	16.78	19.96	24.47	43.26	22.59	28.88	40.11	34.40	24.16	27.13	43.26	**47.13**
	±0.40	±0.48	±0.54	±0.34	±0.48	±0.68	±0.14	±0.54	±0.20	±0.48	±0.58	**±0.42**
10	25.57	27.78	33.56	59.69	30.48	36.60	52.74	42.26	36.78	41.22	59.69	**62.22**
	±0.12	±0.16	±0.10	±0.22	±0.14	±0.42	±0.36	±0.22	±0.04	±0.26	±0.24	**±0.08**
15	34.49	39.90	42.02	66.78	41.79	49.98	63.60	53.36	49.52	50.65	66.78	**70.65**
	±0.33	±0.40	±0.25	±0.18	±0.12	±0.12	±0.58	±0.34	±0.16	±0.29	±0.36	**±0.20**
20	52.11	57.15	61.19	79.04	50.80	54.29	75.09	72.20	54.62	64.14	79.04	**84.14**
	±0.22	±0.29	±0.34	±0.29	±0.10	±0.38	±0.10	±0.16	±0.28	±0.38	±0.08	**±0.16**
25	69.90	73.30	76.62	87.23	61.60	65.54	82.97	84.47	69.10	71.10	87.23	**91.10**
	±0.18	±0.34	±0.12	±0.34	±0.28	±0.56	±0.25	±0.28	±0.72	±0.56	±0.19	**±0.28**
30	76.65	82.20	85.59	92.41	72.79	79.59	87.58	90.66	77.32	82.45	92.41	**99.45**
	±0.01	±0.16	±0.58	±0.58	±0.04	±0.08	±0.02	±0.14	±0.06	±0.41	±0.32	**±0.46**
45	87.19	91.16	97.40	98.91	84.63	88.80	93.30	98.52	86.91	90.52	98.91	
	±0.28	±0.22	±0.16	±0.16	±0.16	±0.10	±0.12	±0.22	±0.14	±0.22	±0.50	
60	95.50	98.07			92.77	97.19	99.78		92.58	96.10		
	±0.16	±0.54			±0.58	±0.19	±0.36		±0.2	±0.36		

All the formulation F1-F12 was evaluated for post compression parameters such as weight variation, thickness, hardness, friability, drug content, disintegration, *in-vitro* dissolution, swelling studies, rupture studies, acid uptake studies etc. The weights of all the tablets were found to be uniform with low standard deviation values. The measured hardness of tablets for all the formulations was ranged between 3.34 to 4.20 kg / cm^2. The % friability for all the formulations was found to be 0.18-0.71%. The values of drug content were found to be 86.02-96.52. The values of disintegration were found to be 26 to 86 sec.

Based on % drug release compare to all formulations F12 was shown **99.45±0.46** at 30 min so F12 is optimized for further process.

Table no-10: Evaluation of compressed coated tablets

Formula	Avg. wt (mean± SD, mg)	Hardness (mean± SD)	Friability (%)	Thickness	Drug content (%)
C1F12	351.30±0.11	6.08±0.52	0.89±0.36	5.72±0.14	92.46±0.12
C2F12	349.56±0.20	6.28±0.10	0.78±0.22	4.88±0.36	98.10±0.36
C3F12	350.66±0.59	6.16±0.36	0.65±0.58	4.59±0.18	96.08±0.58
C4F12	351.98±0.45	6.20±0.02	0.26±0.10	4.72±0.38	94.12±0.12
C5F12	350.79±0.03	6.23±0.51	0.78±0.26	4.79±0.52	97.56±0.58
C6F12	351.80±0.30	6.22±0.10	0.96±0.18	4.76±0.68	96.48±0.22

All the formulation C1F12-C6F12 were evaluated for post compression parameters such as weight variation, thickness, hardness, friability, drug content, disintegration, *in-vitro* dissolution, The weights of all the tablets were found to be uniform with low standard deviation values. The measured hardness of tablets for all the formulations was ranged between 6.08 to 6.28 kg / cm^2. The % friability for all the formulations was found to be 0.26-0.96%. The values of drug content were found to be 92.46-98.10%w/v.

Table no-11: Cumulative percent drug release of coated tablets

Time(hrs)	C1F12	C2F12	C3F12	C4F12	C5F12	C6F12
0	0	0	0	**0**	0	0
1	0.54±0.28	0.22±0.54	0.41±0.52	**0.05±0.32**	0.89±0.28	0.51±0.01
2	0.63±0.64	0.64±0.63	0.97±0.32	**0. 23±0.16**	1.36±0.36	0.77±0.38
3	2.03±0.04	0.84±0.22	1.75±0.18	**1.60±0.28**	4.47±0.20	3.69±0.58
4	4.12±0.15	1.97±0.08	2.98±0.54	**4.23±0.04**	9.98±0.48	8.79±0.32
5	19.65±0.36	13.36±0.16	13.69±0.26	**9.36±0.68**	26.6±0.26	12.65±0.10
6	32.30±0.58	74.46±0.24	38.79±0.38	**34.45±0.12**	47.48±0.10	48.87±0.25
7	44.47±0.72	85.97±0.04	52.65±0.76	**66.54±0.30**	69.14±0.48	66.30±0.16
8	64.12±0.05	98.89±0.08	68.78±0.18	**80.21±0.10**	77.19±0.10	87.90±0.28
9	79.20±0.32		79.96±0.52	**96.54±0.52**	85.24±0.58	99.02±0.14
10	82.46±0.14		92.64±0.48	**98.26±0.08**	90.01±0.69	

All 6 formulations were evaluated for percentage drug release in PH 1.2,6.8&7.4 buffers the values were tabulated. After 5 hr. of lag time drug release is stated for all 6 formulations in PH 7.4 Phosphate buffer based on data C4F12 shown good release i. e 98.26±0.08 at 10th hour**.**

Swelling Index:

Table No -12 Swelling Index

Time (hr)	C1F12	C2F12	C3F12	C4F12	C5F12	C6F12
0	0	0	0	0	0	0
1	142±0.21	98±0.86	149±0.15	96±0.01	108±0.23	146±0.14
2	152±0.54	112±0.58	164±0.16	118±0.23	114±0.21	168±0.25
3	164±0.21	120±0.21	202±0.23	124±0.25	126±0.52	196±0.22
4	189±0.56	136±0.56	228±0.52	182±0.96	148±0.41	214±0.15
5	221±0.32	159±0.74	242±0.48	258±0.74	172±0.45	232±0.02
6	226±0.21	172±0.84	206±0.96	226±0.85	158±0.89	184±0.14
7	251±0.58	186±0.56	194±0.25	184±0.41	122±0.65	162±0.56
8	264±0.01	188±0.23	188±0.23	92±0.56	105±0.21	139±0.52
9	279±0.45	-	146±0.02	76±0.03	98±0.02	114±0.23

The swelling studies of pulsatile tablet during 9hrs studies were found to have very good sustaining efficacy. The percentage swelling at the end of 5th hour of formulation, C4F12was found to be 258±0.74. So, increase in the concentration of polymer will decrease the % water uptake capacity and increase the Lag-time.

Rupture test:

Table no-13 Rupture test

Formulation	Time (hrs)
C1F12	4.2±0.32
C2F12	5.0±0.52
C3F12	6.3±0.63
C4F12	6.0±0.14
C5F12	5.2±0.50
C6F12	5.15±0.8

All 6 formulations are subjected to rupture test, the rupture test was carried out using USP paddle 2 apparatus at 37°c, the time at which the outer polymer coating starts to rupture is called as rupture time. The rupture time of formulations was found to be in a range between 4.2 to 6.3hr.

Comparison of optimized formulation of Zafirlukast& marketed formulation:

Table No-14 Comparison of Optimized Formulation of Zafirlukast & Marketed Formulation

Time(hrs)	C4F12	ZUVAIR
0	0	0
1	0.05	99.63
2	0.23	
3	1.6	
4	4.23	
5	9.36	
6	34.45	
7	66.54	
8	80.21	
9	96.54	
10	98.26	

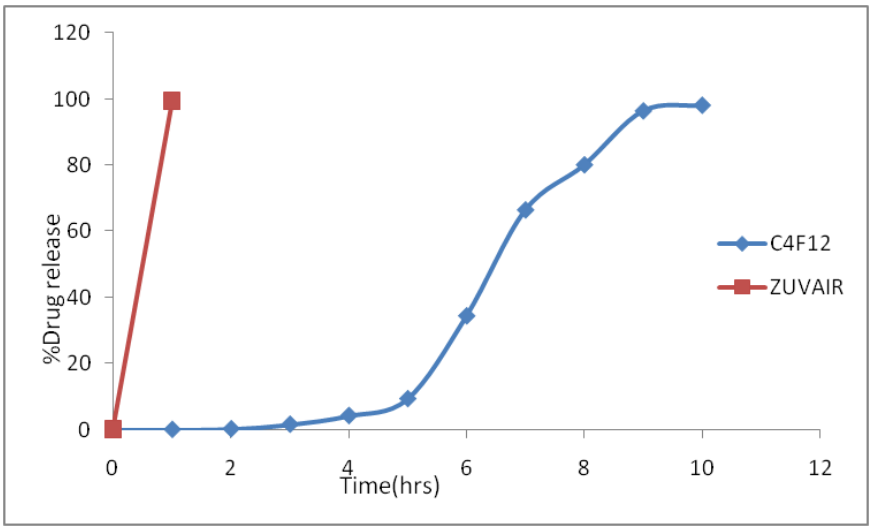

Fig No-5 Comparison of Optimized Formulation of Zafirlukast& Marketed Formulation

The comparative study was done for best formulation **C4F12** and marketed product and **ZUVAIR**. At the end of 10 hr study the formulation **C4F12** shows 98.26 % of drug release. The marketed product **ZUVAIR** shows 99.63% of drug release at the end of 1hr.

DRUG RELEASE KINETICS

Table No-15 Drug Release Kinetics

Formulation code(zafirlukast)	Zero order	first order	Higuchi model	korsmeyer-Peppas	
	r2	r2	r2	r2	N
C1F12	0.898	0.764	0.694	0.9	2.309
C2F12	0.764	0.631	0.545	0.787	2.681
C3F12	0.923	0.765	0.681	0.897	2.363
C4F12	0.862	0.65	0.656	0.875	2.973
C5F12	0.924	0.869	0.746	0.954	2.214
C6F12	0.853	0.62	0.637	0.922	2.419

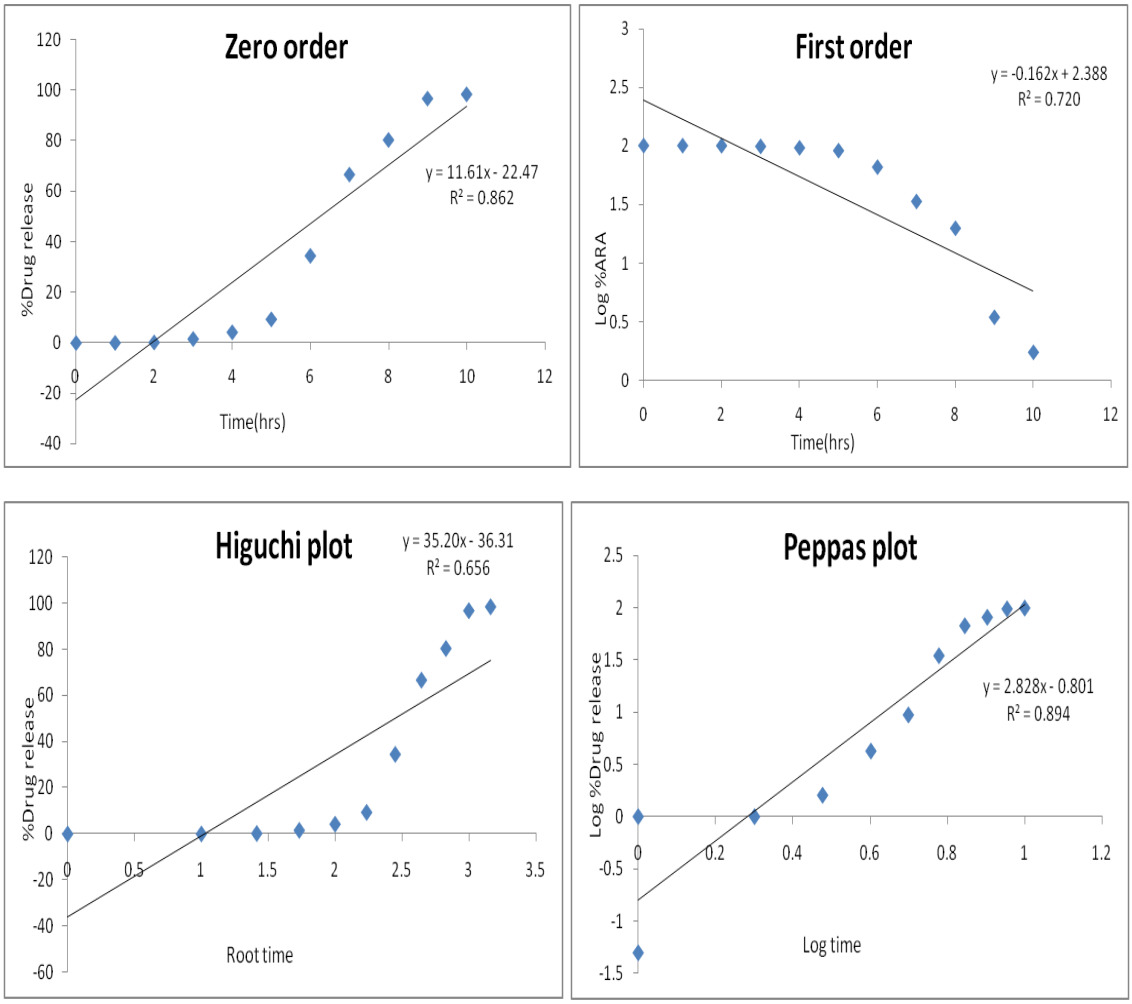

Fig no-6 Drug release kinetics of optimized batch

Drug release data of formulation C4F12 was best explained by Higuchi equation, as the plot showed highest linearity (r^2 = 0.694), followed by zero order equation (r^2 = 0.924). As the drug release was best fitted in Higuchi kinetics, indicating that the rate of drug release is diffusion the Drug release was best fitted in zero order, indicating that the rate of drug release is concentration in dependent. Further the mechanism of drug release was found by Korsmeyer-Peppas equation, the diffusion exponent "n" was between 2.3-2.9, which appears to indicate the mechanism is non-Fickian diffusion. And indicates that the drug release was controlled by more than one process both diffusion and dissolution.

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