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Invitro charecterization of press coated zafirlukast chrono formulation

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ABSTRACT

The present study was carried out on Pulsatile drug delivery system for Zafirlukast tablets. For this study drug wavelength and calibration curve were determined in 0.1N HCL and pH 6.8 phosphate buffer. Core and coated blends were studied for pre compression parameters such as bulk density, tapped density, carrs index, hausners ratio and angle of repose. Those were found to be within limits. Core and coated tablets were taken for post compression studies such as weight variation, thickness, hardness, friability, drug content were found to be within limits. From the dissolution data of core tablets F2 formulation was considered as optimised formulation. After coating the tablet again dissolution studies were carried out. From those studies P3 formulation was considered as optimised formulation which retards the drug release upto 8 hrs.

Keywords: Zafirlukast, Pulsatile drug delivery system

INTRODUCTION

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.

CLASSIFICATION OF CHRONOPHARMACEUTICAL DRUG DELIVERY SYSTEM

Pre-Programmed Delivery System

Time controlled pulsatile drug delivery system

Principally, timed pulsatile delivery system is capable of providing one or more rapid release pulses at predetermined lag times or at specific sites, results in better absorption with effective plasma concentration-time profile for a therapeutic agent. Due to potential limitations of the dosage

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form size, and/or polymeric materials and their compositions, a few orally applicable pulsatile release systems are going for approach[2].

Capsular structure based system

The pharmaceutical capsular dosage form that releases its drug content at either at predetermined time or at a specific site (e.g., colon) in the gastrointestinal tract e.g., PULSINCAP. The drug formulation consists of insoluble capsular body, swellable and degradable plugs which made up of approved substances such as hydrophilic polymers, lipids and bioactive molecules.

System based on rupturable coating

This is a reservoir-type time-controlled pulsatile release system consists of water insoluble but water permeable polymeric barrier which surrounded to the drug core subject.

A time dependent pulsed release system of salbutamol sulfate in nocturnal asthma consisting of an effervescent core surrounded by consecutive layers of swelling and rupturable polymers was prepared and evaluated. This system prepared by direct compression method using different ratios of microcrystalline cellulose and effervescent agent and then coated sequentially with an inner swelling layer containing a hydrocolloid, hydroxypropyl methylcellulose E5 and an outer rupturable layer having Eudragit RL / RS (1:1).

Site specific pulsatile drug delivery system

Generally, the aim of site specific and receptor release system refers to targeting of the drug directly to a certain biological location that means the drug must release at targeted site with sufficient amount to maintain peak plasma concentration for the desired time period.

pH targeted drug delivery

Induced targeted drug delivery is a targeting method that does not depend on changes in the luminal pH of the GIT, but on the pH change within the dosage form itself. Basically stomach and small intestine is the part of GIT but significant variations in the pH with values ranging from approximately 1.2 in the stomach to 6.6 in the proximal small intestine and a peak of about 7.5 in the distal small intestine followed by a sharp decline in colon where the luminal pH is below 7. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, hydroxyl propyl methylcellulose phthalates, sodium carboxy methyl cellulose etc. are utilized for enteric coating to avoid the degradation of drug in upper GIT and attain drug release at specific part of intestine (according to solubility of polymer at particular pH and specific site of intestine) after a predetermined lag time. In conclusion, pulsatile drug release over a period of 3-12 hr is consistent with the requirements for chronopharmaceutical drug delivery. The results of serum study in New Zealand rabbits showed that the developed formulation provided a significant lag phase of 5 hr[2].

Chemically induced pulsatile drug delivery system

Inflammation induced pulsatile drug delivery system

Any physical or chemical stress like-injury, fracture etc. which acts as a stimulus in the case of inflammation due to hydroxyl radicals produced from inflammation responsive cells. Yui et al., (1992), designed and prepared stimuli based inflammation responsive chronotropic system which responded to hydroxyl radicals and degraded in a limited manner. Basically with the system utilized hyaluronic acid (HA) which is specifically hydrolyzed by hyaluronidase or free radicals that present at inflammatory site. Degradation of HA via the hyaluronidase is very low in a normal state of health. Hence it became possible to treat patient with inflammatory diseases like rheumatoid arthritis, NSAIDS incorporated into hyaluronic acid gels as a new implantable drug delivery sys

Externally stimulated pulsatile drug delivery systems

This kind of open-loop system is not self regulated. But for deliver the drug in pulse manner another way in which drug release in programmed pattern can be the external regulated system. This system is magnetically stimulated, ultrasonically modulated, photo stimulated[2]

MATERIALS &METHODOLOGY

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone, r = Radius of the cone base

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3 The bulk density was calculated using the formula:

$\text{Bulk Density} = M / V_o$

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$\text{Tap} = M / V$

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Formulation development of Tablets

Formulation of core tablets by direct compression

The inner core tablets were prepared by using direct compression method as shown in the table. Powder mixtures zafirlukast, CCS, SSG, talc, ingredients were blended for 20 min. followed by addition of Magnesium Stearate. The mixtures were then further blended for 10 min., 50mg of resultant powder blend was manually compressed using , Lab press Limited, India with a 6mm punch and die to obtain the core tablet. (Table no 1).

Formulation of mixed blend for barrier layer

The various formulation compositions containing Ethyl Cellulose , HPMC K 100, magnesium stearte, talc and microcrystalline cellulose. 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. (Table no 2)

Preparation of press-coated tablets

The core tablets were press-coated with 300 mg of mixed blend as given in Table6.3. 150 mg of barrier layer material was weighed and transferred into a 10mm die then the core tablet was placed manually at the center. The remaining 150 mg of the barrier layer materiel was added into the die and compressed by using Lab press Limited, India

Table no 1 : Formulation development of core tablets

S.NO	MATERIALS	F1	F2	F3	F4	F5	F6
1	Zafirlukast	20	20	20	20	20	20
2	CCS	5	10	15	--	--	--
3	Sodium starch glycolate	--	--	--	5	10	15
4	Talc	2	2	2	2	2	2
5	Mg.sterate	2	2	2	2	2	2
6	MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
7	TOTAL WT	100	100	100	100	100	100

Table no 2: Formulations for press coated blend

S.NO	MATERIALS	P1	P2	P3
1	HPMC K 100	250	--	125
2	Ethyl cellulose	--	250	125
3	Magnesium stearate	4	4	4
4	Talc	4	4	4
5	Microcrystalline cellulose	Q.S	Q.S	Q.S
6	TOTAL WEIGHT	300	300	300

EVALUTIONS

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.

Hardness

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

Thickness

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

Friability test

The friability was determined using friability test apparatus Labindia, Mumbai, India and expressed in percentage (%). 10 tablets from each batch were weighed separately ($W_{initial}$) and placed in the friabilator, which was then operated for 100 revolutions at 25 rpm. The tablets were reweighed (W_{final}) and the percentage friability was calculated for each batch by using the following formula.

Friability = [(W1-W2) / W] × 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. The percent deviation of each tablets 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. The required quantities of the powder equivalent to 20 mg of Zafirlukast were accurately weighed and transferred to a 100-mL of volumetric flask. The flask was filled with buffer and mixed thoroughly. The solution was made up to 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 UV spectrophotometer (Labindia, Mumbai, India). The linearity equation obtained from calibration curve as described previously was use for estimation of Zafirlukast in the tablets formulations.

Disintegration time of core tablets

Disintegration test was carried out using the tablet disintegration test apparatus specified in Indian pharmacopoeia. pH 6.8 phosphate buffer at 37 ± 0.5 ºC 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.

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 USP XXIII Type II (paddle method) apparatus. pH 6.8 phosphate buffer was used as dissolution medium. Release pattern was studied visually by taking sample of 5 mL at the specific time intervals. Also the sample was analyzed at

238nm for 6.8 phosphate buffer using a UV spectrophotometer.

In vitro drug release study of coated tablets

900ml 0f 0.1 HCL was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCL were removed and pH 6.8 phosphate buffer was added process was continued up to 8 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at respective wavelength using UV-spectrophotometer.

RESULTS AND DISCUSSION

Standard graph of Zafirlukast in pH 6.8 phosphate buffer (238)

Zafirlukast showed maximum absorbance in phosphate buffer (pH 6.8) at 238 nm. The solution obeyed Beer-Lambert's law for concentration range of 5 to 25 µg / mL with regression coefficient of 0.998. Standard curve of prepared Zafirlukast in phosphate buffer pH 6.8 is shown below.

Table no 3:Calibration data of Zafirlukast in pH 6.8 phosphate buffer

Conc [µg/ml]	Abs
0	0
5	0.165
10	0.342
15	0.505
20	0.664
25	0.812

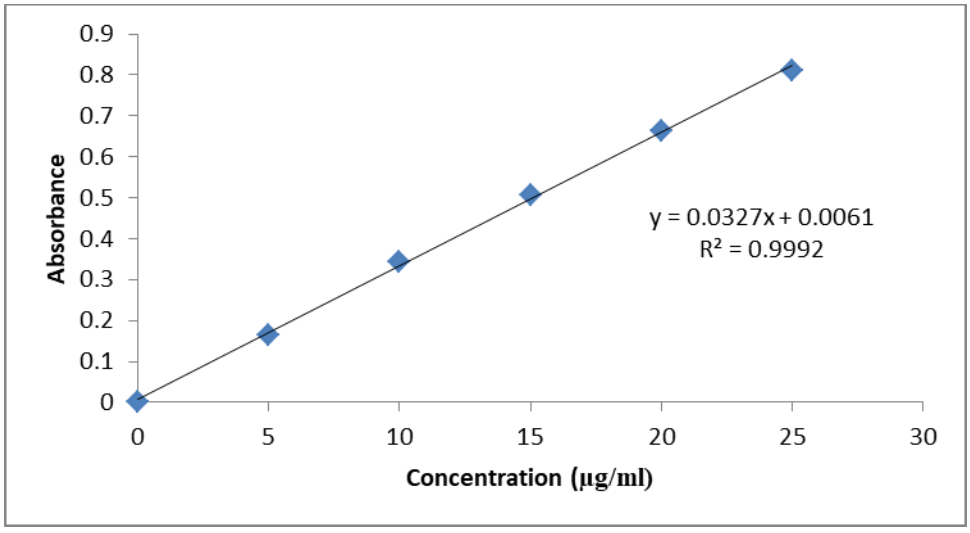

Fig no 1-Standard Graph of Zafirlukast in pH 6.8 phosphate buffer

FT-IR (Fourier Transform Infrared Spectrophotometry

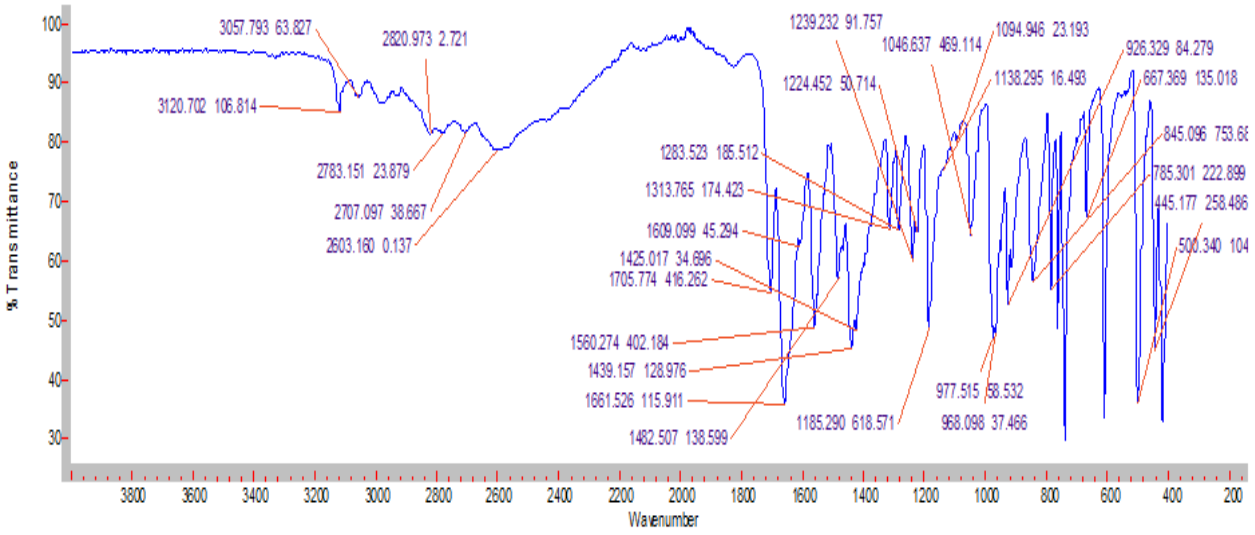

Fig no 2 :FTIR spectra of Zafirlukast pure drug

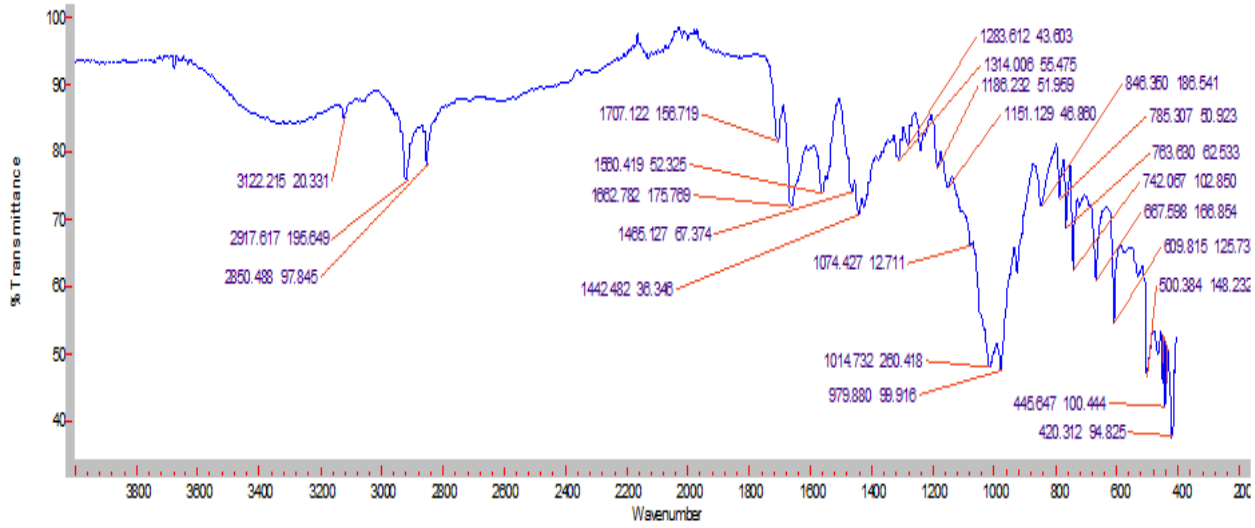

Fig no 3- FTIR spectra of optimized formula

EVALUATION STUDIES

Table no 4: Pre compression parameters of Zafirlukast core tablets

Formulation code	Angle of repose (^{0})	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	26.01±0.02	0.51±0.01	0.56±0.015	16.21±0.015	1.09±0.015
F2	28.8±0.24	0.55±0.015	0.63±0.011	16.87±0.01	1.14±0.01
F3	27.74±1.55	0.56±0.015	0.68±0.01	17.1±0.01	1.21±0.04
F4	26.33±0.01	0.55±0.015	0.65±0.01	17.67±0.01	1.18±0.005
F5	28.24±1.084	0.56±0.015	0.68±0.0057	16.92±0.015	1.21±0.04
F6	25.12±0.015	0.54±0.0057	0.61±0.01	17.65±0.015	1.12±0.01

Table no 5: Post compression parameters of Core tablet

Formulation code	Average Weight (mg)	Hardness(kg/cm2)	Thickness	Friability (%loss)	Drug content (%)
F1	102.5±0.1	2.7±0.1	2.13±0.001	0.55±0.1	98.76±0.005
F2	95.4±0.1	2.6±0.1	2.05±0.15	0.62±0.057	99.45±0.01
F3	103.6±0.057	3.0±0.1	2.19±0.01	0.63±0.057	98.34±0.005
F4	99.6±0.1	2.8±0.15	2.16±0.015	0.54±0.1	99.87±0.01
F5	96.4±0.58	2.6±0.1	3.0±0.05	0.56±0.057	99.14±0.01
F6	105.7±1.06	2.0±0.11	2.19±0.01	0.58±0.11	97.56±0.01

In Vitro Drug Release Studies of Zafirlukast core tablet

Table no 6: Dissolution data of Zafirlukast core tablets prepared with CCS in different concentrations

Time (min)	F1	F2	F3
0	0	0	0
5	16.31	24.51	17.12
10	30.78	49.63	36.48
15	59.74	73.24	60.36
30	70.96	98.74	81.63
45	85.47		96.45
60	96.54		

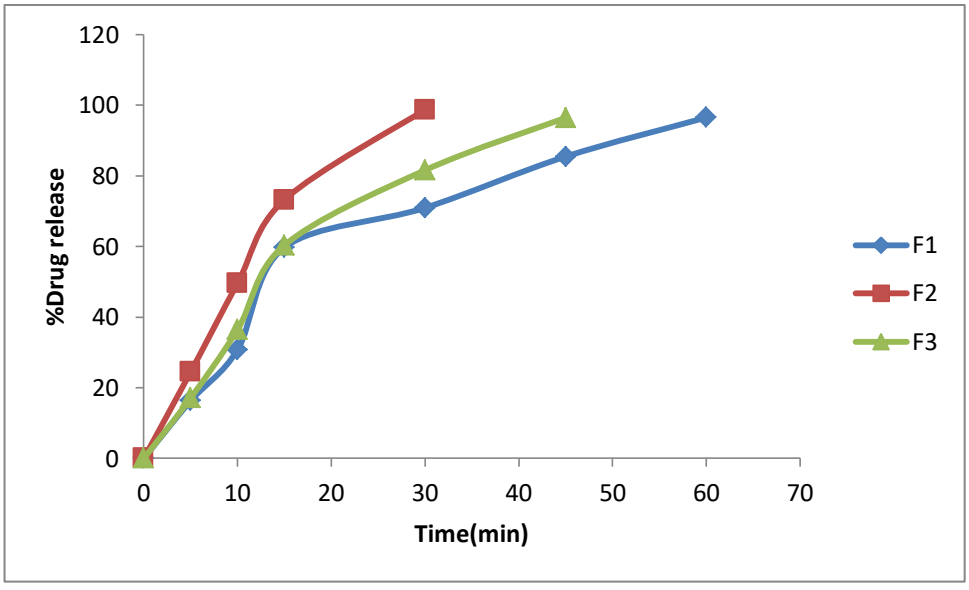

Fig no 4: Dissolution profile of Zafirlukast core tablets (F1, F2, F3 formulation)

Table no 7: Dissolution data of Zafirlukast core tablets prepared with SSG in different concentrations

Time (min)	F4	F5	F6
0	0	0	0
5	12.48	19.42	20.45
10	24.69	39.15	40.78
15	48.65	57.12	64.32
30	60.14	76.56	85.15
45	72.14	88.45	98.15
60	85.21	98.45	

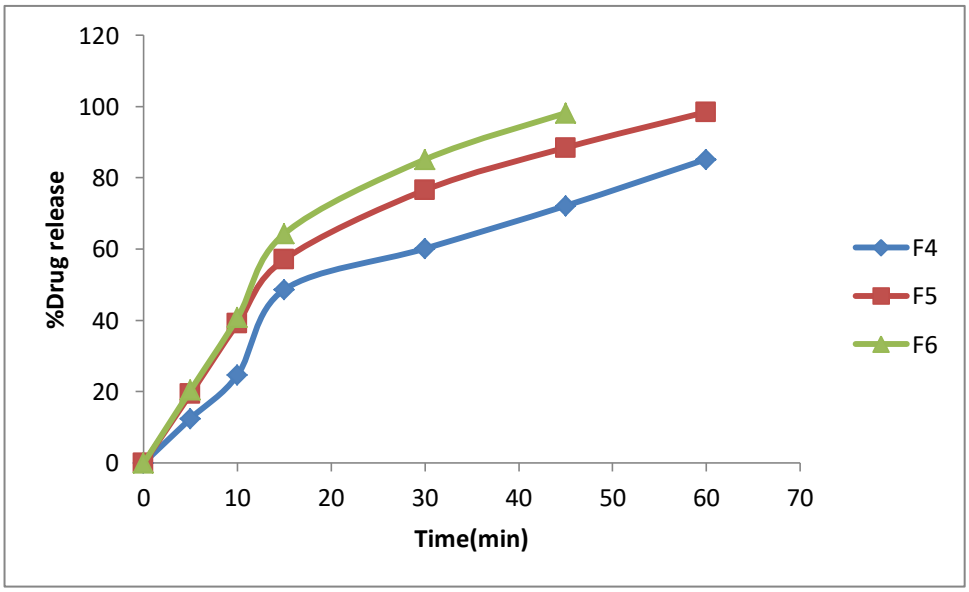

Fig no 5: Dissolution profile of Zafirlukast core tablets (F4, F5, F6 formulation)

Formulations prepared with CCS and SSG .Among all formulations formulation F2 containing cros carmellose sodium was shown maximum drug release at 30 min 98.74%. Hence F2 formulation was concluded as optimised formulation

Table no 8: Dissolution data of Zafirlukast coated tablets prepared with HPMC K 100, Ethyl cellulose

Time (hr)	P1	P2	P3
0	0	0	0
0.5	0.04±0.57	0.4±0.5	0.01 ±0.15
1	0.6±0.65	1.0±0.12	0.36±0.11
2	1.0±0.11	3.0±0.21	0.98±0.13
3	4.0±0.34	7.0±0.65	1.52±0.21
4	40.51±0.57	52.71±0.22	2.97±0.31

5	70.14±0.15	96.55±0.18	8.35±0.45
6	98.45±0.21		61.44±0.15
7			75.86±0.57
8			96.47±0.18

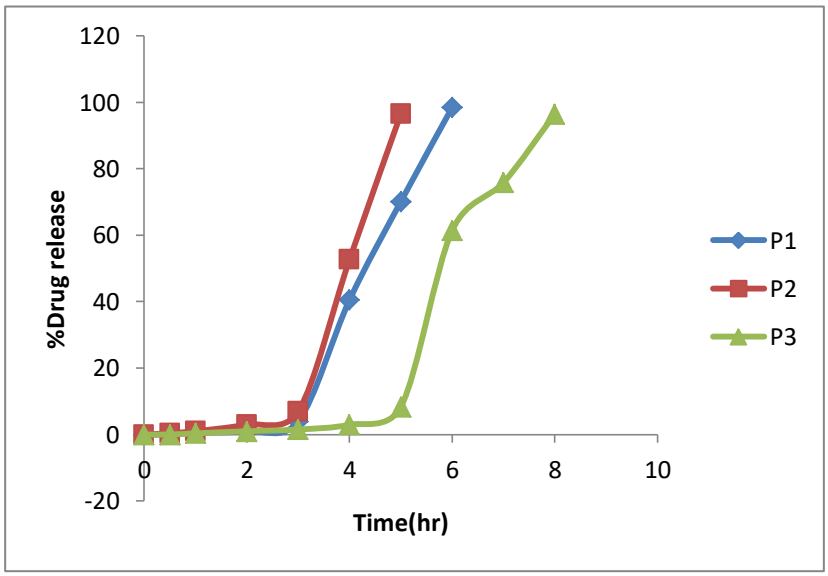

Fig : Dissolution profile of zafirlukast coated tablets (P1,P2,P3).

CONCLUSION

The present study was carried out on Pulsatile drug delivery system for Zafirlukast tablets. For this study drug wavelength and calibration curve were determined in 0.1N HCl and pH 6.8 phosphate buffer. For preparation of Core tablet CCS, SSG were used as superdisintegrants. Core blend was studied for pre compression parameters such as bulk density, tapped density, carrs index, hausners ratio and angle of repose. Those were found to be within limits. These core tablets were also studied for post compression studies such as weight variation, thickness, hardness, friability, drug content were found to be within limits.

From the dissolution data of core tablets F2 formulation which contain 10 mg of croscarmellose sodium were considered as optimised formulation. After optimising the core tablet, Coating blend was prepared with HPMC K 100M and Ethylcellulose. Those coating blend was also taken for pre compression studies such as bulk density, tapped density, carrs index, hausners ratio and angle of repose. Those were found to be within limits.

After completion of press coating to core tablets, those tablets were evaluated for hardness, thickness, weight variation, friability, drug content and dissolution. From the dissolution data of coated tablets, P3 formulation containing combination of HPMC K 100M and Ethylcellulose were retarded the drug release up to 8 hrs. Hence it was considered as optimised formulation.

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