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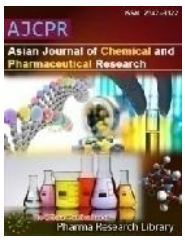

Research Article **Open Access**

Design and *In-Vitro* Evaluation of Enteric Coated Pulsatile drug delivery system of Zileuton Tablets

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A B S T R A C T

In the present research work pulsatile drug delivery system of Zileuton tablets were formulated by employing compression coating technology. Initially the core tablets were prepared by using various concentrations of super disintegrates, the formulated core tablets were coated with the polymers by using compression coating technology. All the core and press coated tablet formulations were subjected to various physical and chemical evaluation tests for core and press coated tablets. The thickness, hardness and weight variation shown by all the tablet formulations were found within the official pharmacopoeial limits. In vitro release of Zileuton of core tablet formulations F1-F12, F4 showed faster drug release after 15 min. Faster drug release can be correlated with the high disintegration and friability observed in this study. The enteric-coated formulations C1, C3, and C4 showed maximum drug release after 4 hour. C2 formulation showed slow release about 10.64% in around 8 hour. C5 and C6 showed maximum drug release after 7th hr. Time dependent pulsatile drug delivery system has been achieved from tablet of formulation C5 and C6 with 102.79% and 100.21%.

Keywords: Zileuton, Super disintegrates, Ethyl cellulose, Pulsatile tablets.

A R T I C L E I N F O

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1. Introduction

In recent years, a major goal for the drug delivery research is turned towards the development of efficacious drug delivery systems with already existing active ingredients in case of new drug discovery. Many of pharmaceutical therapeutic agents are mostly effective when made available at constant rates or near to absorption sites. Much effort has been going on to develop sophisticated drug delivery systems such as osmotic devices for oral application. Oral drug delivery system is more favored on popular controlled drug delivery system in pharmaceutical research and development (R & D) business due to increase in awareness of medical and pharmaceutical community about the importance of safe and effective use of drug. This system aims to maintain plasma drug concentration within the therapeutic window for long period of time.

Traditionally, it is becoming increasingly more evident with the specific time that patients have to take their medication may be even more significant than was recognized in the past. The tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24-hr period, may be changing as researcher's report that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms. In the human body systems such as cardiovascular, pulmonary, hepatic and renal systems show variation in their function throughout a typical day. They are naturally followed by the internal body clocks and are controlled by the sleep wake cycle. This system focused on controlled or sustained release of drug of which has such advantages of nearly constant level of drug at site of administration, minimizing peak - valley fluctuation of drug concentration in body and avoidance of adverse effect. A reduction in dose, dosage frequency and patient efficacy and compliance by this delivery system also expected. 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. This system aims to deliver a drug via the oral route at a rate different than constant i.e., zero order release. The lag time is the time interval between the dosage forms is placed into the aqueous environment and drug get to release from its dosage form after rupturing or eroding outer layer. The lag time between 0.5 hr to 4 hr is desire for upper region of gastrointestinal tract and more than 4hr for lower portion of small intestine. Chronopharmaceutics consist of two words chronobiology and pharmaceutics, chronobiology is the study of biological rhythms and their mechanisms. Mainly mechanical rhythms in our body are:

- Circadian - this word comes from Latin word "circa" means about and "dies" means day and oscillation completed in 24 hr
- Ultradian - oscillation of shorter duration (more than one cycle per 24 hr).
- Infradian - oscillations that are longer than 24 hr (less than one cycle per day)

Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 hr and regulate many body functions like- metabolism, sleep pattern, hormone production etc. PDDS are widely important in such wide spread disease, which is mentioned below

a. Chronopharmacotherapy of diseases which shows circadian rhythms in their patho-physiology Confidential. Extended day time or night time activity. Avoiding the first pass metabolism e.g., protein and peptides
b. Biological tolerance **(**transdermal nitroglycerin)
c. For targetting specific site in intestine (colon)
d. For time programmed administration of hormone and drugs. Gastric irritation or drug instability in gastric fluid
e. For drugs having the short half life
f. Lower daily cost to patient due to fewer dosage units are required in therapy
g. Reduction in dose size and dosage frequency and also side effects

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. Environmental factors like pH or enzymes present in the intestinal tract and also transit time control the release of a site-controlled system where as the drug release from time-controlled systems is controlled primarily by the delivery system and not by the environment. Over the past two decades, the major challenge for scientist is to target the drugs especially to the colonic region of GIT. Previously colon was considered as a innocuous organ that responsible for the water absorption, electrolytes and stool storage but it's accepted as important site for the delivery of drugs.

2. Materials and Methods

Materials:

Zileuton, Sodium starch glycolate, Cross caramellose sodium, Cross povidone, Talc, Magnesium Sterate, different grades of Eudragit polymers, Ethyl Cellulose.

Methodology

Analytical method development:

Determination of absorption maxima:

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

Preparation calibration curve:

100 mg of Zileuton pure drug was dissolved in 100 ml of water(stock solution) 10 ml of solution was taken and make up with 100 ml of water (100 µg/ml).from this 10 ml was taken and make up with 100 ml of water (10 µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 2,4,6,8,10,20,30,40,50, 60,70,80,90 and 100 µg/ml of Zileuton per ml of solution.

The absorbance of the above dilutions was measured at 231 nm 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 procedure was repeated with required buffers.

Pre-formulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

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.

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 of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting.

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.

Formulation development of Tablets:

Preparation of Zileuton core tablets formulations

Tablets of Zileuton were made by direct compression method. All ingredients were weighted accurately and mix well in mortar-pastle for 15 min. microcrystalline cellulose was used as direct compressing agent. Croscarmellose sodium, sodium starch glycolate and crospovidone were used in different compositions as disintegrating / swelling agents for various formulations. Talc and magnesium stearate were used as lubricant. Tablets were made in mini press tablet machine (Ridhi Pharma Machinery Pvt. Ltd. Ahmedabad, India) in concave punch (Diameter 8 mm).

Compression coating of Zileuton core tablets

Components of the coat were mixed for 10 minutes. Die filling, core centralization and machine operation were undertaken using by a standardized manual process. Half of the powder mass for one tablet coat was weighed into a die. A lower coating layer was consolidated and the core centered on an even bed. The remaining powder was then added to the die and compressed in to tablets using single punch tablet machine in concave punch (Diameter 10 mm).

Evaluations

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 hardness tester (Labtech, AVI-PH-4522, India) and expressed in Kg/cm2.

Thickness

The prepared tablets were subjected to thickness test. It was carried out by using the validated digital electronic vernier caliper (Sealey professional tools, Model No: AK962EV. V2, UK) and expressed in millimeter.

Friability test

The friability was determined using friability test apparatus (Ketan, Koshish Industries, Bombay, India, Model No: SS153) and expressed in percentage (%). 10 tablets from each batch were weighed separately (Winitial) and placed in the friabilator, which was then operated for 100 revolutions at 25 rpm. The tablets were reweighed (Wfinal) and the percentage friability was calculated for each batch by using the following formula.

$$(\%)F = \frac{Winitial - Wfinal}{Winitial} \times 100$$

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% and none deviates more than 10%.

Disintegration time of Zileuton core tablets

Disintegration test was carried out using the tablet disintegration test apparatus (Servewell Instruments pvt. Ltd., Electrolab ED-2L, India) specified in indian pharmacopoeia. Distilled water 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 Zileuton tablets**

***In-vitro* drug release of Zileuton core tablets**

In vitro dissolution studies were carried out using USP XXIII Type II (paddle method) apparatus. Distilled water 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 271 nm using a UV spectrophotometer.

Determination of lag time (t^{10}) of pulsatile tablets

In vitro dissolution studies were carried out using USP XXIII Type II (paddle method) apparatus. The dissolution profile shows lag time with the coated formulations (C1-C6). The intention of the study was to develop a tablet which will be protected from gastric environment and will release the drug rapidly in the intestine after administration. Therefore, above formulations showed various in lag time with respect to their coating level. The lag time was determined while performing the dissolution test. When performing the experiment, 0.1N HCl medium was used for 2 hr (since the average gastric emptying time is 2 hr). Then removed and fresh phosphate buffer (pH 7.4) was added for subsequent 3 hours.). Finally, replace the 7.4 buffer solution with phosphate buffer (pH 6.8) for subsequent hours in 900 ml of dissolution medium was used at each time and stirred at 50 rpm at 37 ± 0.5 °C. 5 mL of dissolution media was withdraw at predetermined time interval and fresh dissolution media was replaced. The withdrawn samples were analyzed at 271 nm using a UV spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics:

To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

$$F = K_o t$$

Where, 'F' is the drug release at time 't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$Log (100-F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

F = k t1/2

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t/ M_\infty = K t^n$$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent

Hixson-Crowell release model:

$$(100-Q_t)^{1/3} = 100^{1/3} – K_{HC}.t$$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

3. Results and discussion

Present study was done on pulsatile tablets with different formulations C1 to C6. Formulations had weight ratio of polymers like Ethyl cellulose, Eudragit S100, Povidone k30 and Eudragit L100 along with various excipients. Ethyl cellulose is an insoluble, Eudragit S-100 and Eudragit L-100 as enteric coating polymer. Eudragit L-100 and Eudragit S-100 suppressed drug release in the stomach due to poor uptake of drug in GI tract or destruction of the drug by acid fluid in the stomach. Eudragit L-100 and Eudragit S-100 dissolved at pH above 6 was selected to be the coating material to fit the mentioned purpose. Aim of the formulation was to get effect of drug in early morning asthma like disease. This section gives detailed description of the results and discussion on pulsatile Zileuton tablets.

Pre-formulation Studies

Determination of λ max of Zileuton

The λ max of Zileuton was estimated by carrying out UV scan between the wavelength 200 to 400 nm which gave a highest peak at 271 nm and the same was selected for Zileuton. Standardization method for estimation of Zileuton Standard curves of Zileuton were prepared in 0.1N HCl, phosphate buffer (Ph 7.4) and phosphate buffer (pH 6.8). Standard graph of Zileuton in 0.1N HCl Zileuton showed maximum absorbance in 0.1N HCl at 271 nm. The solution obeyed Beer-Lambert's law for concentration range of 1 µg / mL to 10 µg / mL with regression coefficient of 0.999. Standard curve of Zileuton prepared in 0.1N HCl.

Table 4: Calibration data of Zileuton in 0.1N HCl

S.No.	ID	Conc [mg/l]	Abs
1	Standard 1	0.0000	0.000
2	Standard 2	1.0000	0.074
3	Standard 3	2.0000	0.135
4	Standard 4	3.0000	0.199
5	Standard 5	4.0000	0.244
6	Standard 6	5.0000	0.307
7	Standard 7	6.0000	0.370
8	Standard 8	7.0000	0.426
9	Standard 9	8.0000	0.485
10	Standard 10	9.0000	0.553
11	Standard 11	10.0000	0.618

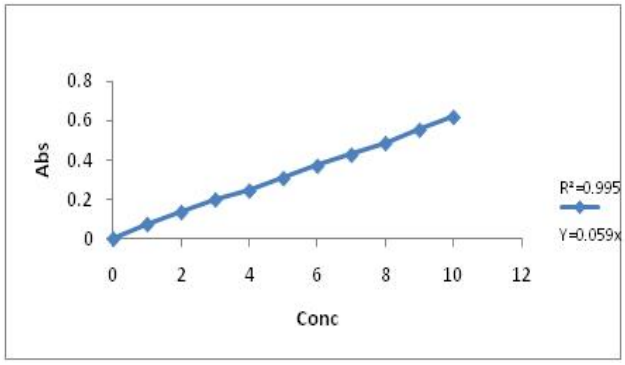

Figure 1: Standard Graph of Zileuton in 0.1N HCl

Standard graph of Zileuton in phosphate buffer (pH 7.4): Zileuton showed maximum absorbance in 7.4 phosphate buffer at 271nm. The solution obeyed Beer-Lamberts law for concentration range of 1 g/ml to 10 g/ml with regression coefficient of 0.997. Standard curve of Zileuton prepared in pH 7.4 is shown below in Table and

Table 5: Calibration data of Zileuton in pH 7.4 phosphate buffer

S.No.	ID	Conc [mg/l]	Abs
1	Standard1	0.0000	0.000
2	Standard2	1.0000	0.059
3	Standard3	2.0000	0.122
4	Standard4	3.0000	0.189
5	Standard5	4.0000	0.243
6	Standard7	5.0000	0.283
7	Standard8	6.0000	0.370
8	Standard9	7.0000	0.389
9	Standard10	8.0000	0.449
10	Standard11	9.0000	0.525

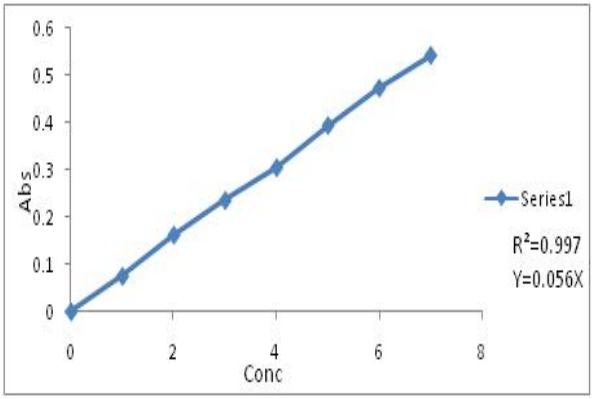

Figure 2: Standard Graph of Zileuton in pH 7.4 phosphate buffer

Standard graph of Zileuton in phosphate buffer (pH 6.8): Zileuton showed maximum absorbance in phosphate buffer (pH 6.8) at 271 nm. The solution obeyed Beer-Lambert's law for concentration range of 1 to 10 µg / mL with regression coefficient of 0.991. Standard curve of Zileuton prepared in phosphate buffer pH 6.8 is shown below.

Table 6: Calibration data of Zileuton in pH 6.8 phosphate buffer

Sl. No.	ID	Conc [mg/l]	Abs
1	Standard1	0.0000	0.000
2	Standard2	1.0000	0.075
3	Standard3	2.0000	0.162
4	Standard4	3.0000	0.235
5	Standard5	4.0000	0.304
6	Standard6	5.0000	0.393
7	Standard7	6.0000	0.472
8	Standard8	7.0000	0.541
9	Standard9	8.0000	0.575
10	Standard10	9.0000	0.651
11	Standard11	10.0000	0.655

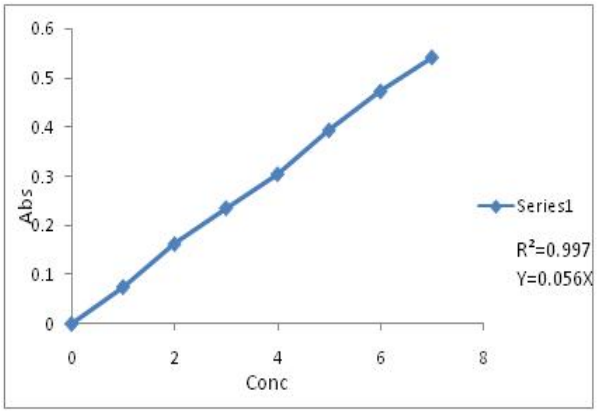

Figure 3: Standard Graph of Zileuton in pH 6.8 phosphate buffer

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.07 to 0.58±0.06 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18, which show that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

***In-vitro* quality control parameters for tablets**

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In-Vitro* Drug Release Studies of Theophyllne core tablet:** *In vitro* dissolution studies of Zileuton core tablets were performed using USP XXIII Type II rotating paddle dissolution apparatus by using phosphate buffer (pH 6.8) as a dissolution medium. From formulation F1-F12 Zileuton core tablets, F4 showed faster drug release after 15 mins than the other formulations. Faster drug release can be correlated with the high disintegration and friability observed in this study. So, F4 Zileuton core tablet formulation was selected as best formulation for further press coating and enteric coating formulations.

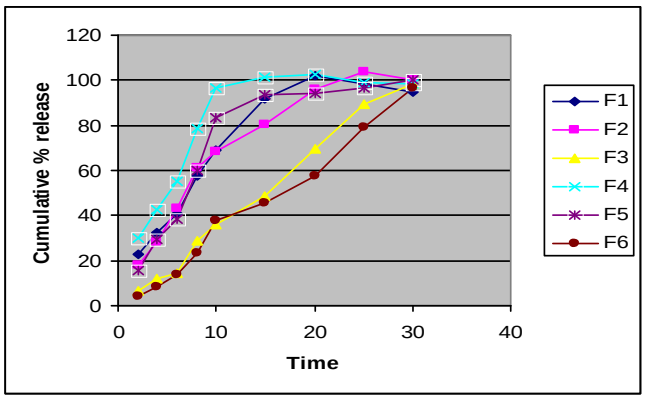

Figure 4: Cumulative % *drug* released of Zileuton core tablets

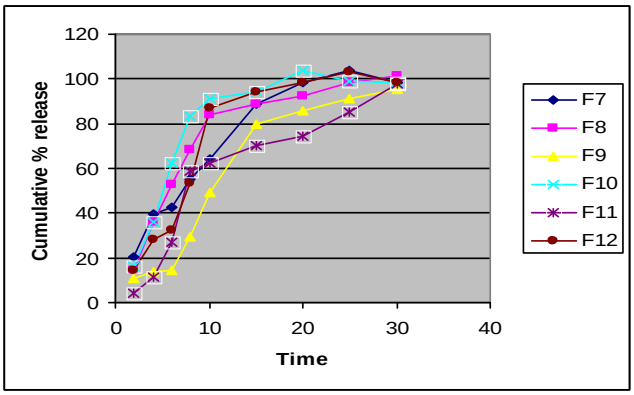

Figure 5: Cumulative % drug released of Zileuton core tablets

Post compression parameter for compression coated tablets: All the formulations showed almost uniform size, shape and appearance. The physico-chemical properties of all the formulations (C1-C6). Thickness ranged between 6.36 ± 0.19 and 6.72 ± 0.18 mm and weight ranged between 498 ± 0.16 and 504 ± 0.18 mg. The friability ranged from 0.4 ± 0.18 to 0.7 ± 0.16 % and hardness lies between 6.34 ± 0.14 and 6.92 ± 0.12 Kg/cm 2. Friability is less than 1% which indicated that tablets good mechanical resistance. The drug content ranged between 97.96 ± 0.28 and 102.62 ± 0.18 mg in different formulations, showed favorable drug loading efficiency. An ultraviolet (UV) spectrophotometric method was used for the determination of drug content.

***In vitro* drug release study of Zileuton pulsatile tablets**

Based on the above characters formulation F4 was selected as best formulation and press coated and enteric coated to find out the changes in the release rate of the Zileuton from enteric coated tablets. This enteric coat has enabled us to achieve definite non release lag phase for 5 hours. The formulations C1, C3, and C4 showed maximum drug release after 4th hour.. C2 showed slow release of drug only 10% after 8 hours. F5 and F6 showed maximum drug release after 7th hr. Time dependent pulsatile drug delivery system has been achieved from tablet of formulation C5 and C6 with 102.79% and 100.21% drug release which meets demand of chronotherapeautic drug delivery. The formulations containing Eudragit L-100, Ethylecellulose, Eudragit S-100 and Ethylcellulose in 1:1 ratio was found to be optimum as enteric coating polymers. The data were shown below.

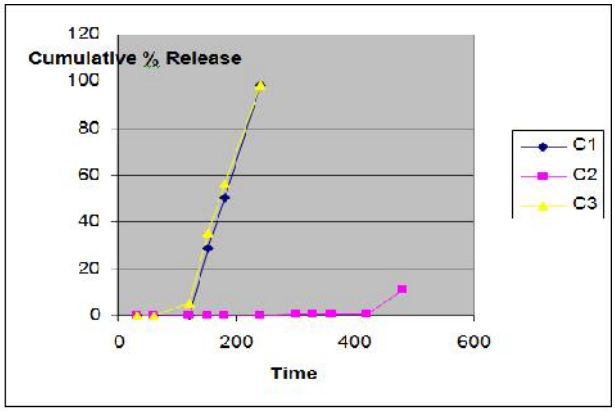

Figure 6: Cumulative % release study of Zileuton pulsatile tablet

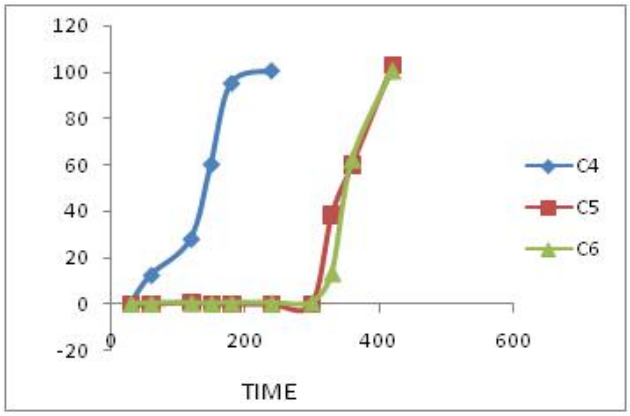

Figure 7: Cumulative % release study of Zileuton pulsatile tablets

Table 1: Formulation for preparation Zileuton core tablets

S.No.	Ingredients	F1	F2	F3	F4	F5	F6
1	Zileuton	100mg	100 mg	100 mg	100 mg	100 mg	100 mg
2	SSG	13.2 mg	-	-	17.6 mg	-	-
3	CCS	-	13.2 mg	-	-	17.6 mg	-
4	Crosspovidone	-	-	13.2 mg	-	-	17.6 mg
5	Talc	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg
7	Magnesium stearate	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg
8	MCC	96.8 mg	96.8 mg	96.8 mg	92.4 mg	92.4 mg	92.4 mg

Table 2: Formulation for preparation Zileuton core tablets

S.No.	Ingredients	F7	F8	F9	F10	F11	F12
1	Zileuton	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
2	SSG	22 mg	-	-	6.6 mg	-	6.6 mg
3	CCS	-	22 mg	-	6.6 mg	6.6 mg	-
4	Crosspovidone	-	-	22 mg	-	6.6 mg	6.6 mg
5	Talc	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg
7	Magnesium stearate	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg
8	MCC	88 mg	88 mg	88 mg	96.8 mg	96.8 mg	96.8 mg

Table 3: Composition of coat over Zileuton core tablet (330mg)

S.No	Ingredients	C1	C2	C3	C4	C5	C6
1	Eudragit L-100	100 mg	-	200 mg	200 mg	150 mg	-
2	Eudragit S-100	200 mg	100 mg	-	100 mg	-	150 mg
3	Ethylecellulose	-	200 mg	100 mg	-	150 mg	150 mg
4	Povidone K 30	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg

Table 7: Pre compression Parameters Of Zileuton Core Tablets

Formulation code	Angle of repose (o) *	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	26.01	0.49±0.07	0.57±0.01	16.21±0.06	0.86±0.06
F2	24.8	0.56±0.06	0.62±0.05	16.87±0.05	0.98±0.05
F3	22.74	0.52±0.03	0.68±0.07	17.11±0.01	0.64±0.03
F4	25.33	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04
F5	26.24	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
F6	26.12	0.56±0.05	0.66±0.06	17.65±0.09	1.06±0.09
F7	27.08	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03
F8	25.12	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09
F9	25.45	0.54±0.08	0.62±0.03	17.54±0.09	1.17±0.02
F10	27.08	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03
F11	25.12	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09
F12	25.45	0.54±0.08	0.62±0.03	17.54±0.09	1.17±0.02

Table 8: Post compression parameters of Core tablet:

Formulation codes	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	300.5	4.1	0.52	2.8	99.76
F2	295.4	4.2	0.54	2.9	99.45
F3	298.6	4.2	0.51	2.9	99.34
F4	299.6	4.1	0.55	2.9	99.87
F5	299.4	4.2	0.56	2.7	99.14
F6	298.7	4.2	0.45	2.5	98.56
F7	300.3	4.1	0.51	2.6	98.42
F8	299.2	4.3	0.49	2.7	99.65
F9	301.3	4.1	0.55	2.6	99.12
F10	298.6	4.2	0.51	2.9	99.34
F11	299.6	4.1	0.55	2.9	99.87
F12	299.4	4.2	0.56	2.7	99.14

Table 9: Cumulative % drug release of Zileuton core tablets

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
2	22.64	18.24	6.47	30.17	15.62	4.45	20.34	14.30	10.56	16.27	4.31	14.57
4	32.48	28.09	11.97	42.44	29.17	8.17	39.42	36.25	13.74	35.83	11.2	28.37
6	40.85	43.15	14.47	54.94	38.24	13.63	42.52	53.04	14.57	62.14	26.95	32.39
8	57.52	61.28	28.65	78.70	60.21	23.36	55.25	68.18	29.16	83.42	58.92	53.18
10	69.25	68.42	35.83	96.73	83.60	37.84	64.23	84.01	49.02	91.48	62.21	87.26
15	92.03	80.36	48.31	101.38	93.75	45.44	88.88	88.59	79.85	94.32	69.95	94.04
20	102.13	95.76	69.67	102.89	94.32	57.62	98.39	92.46	85.58	103.93	74.68	98.20
25	98.29	103.64	89.53	98.98	96.62	79.42	103.53	98.46	91.42	99.06	85.29	103.07
30	94.90	100.34	98.17	98.67	99.92	96.62	98.39	101.64	95.17	98.48	97.91	98.54

Table 10: Post compression parameters of compression coated tablets

Formulation	Thickness	Hardness	Friability	Weight	Drug content
C1	6.45 0.22	6.45 ± 0.16	0.5 ± 0.14	504 ± 0.18	99.32 ± 0.24
C2	6.67 0.18	6.72 ± 0.24	0.6 ± 0.18	502 ± 0.24	98.82 ± 0.18
C3	6.36 0.19	6.34 ± 0.14	0.6 ± 0.11	499 ± 0.22	99.72 ± 0.32
C4	6.42 0.28	6.74 ± 0.11	0.7 ± 0.16	503 ± 0.19	101.16 ± 0.16
C5	6.72 0.18	6.82 ± 0.19	0.4 ± 0.19	502 ± 0.26	102.62 ± 0.18
C6	6.52 0.20	6.92 ± 0.12	0.5 ± 0.12	500 ± 0.20	99.42 ± 0.21

Table 11

S.No	Time (min)	C1	C2	C3	C4	C5	C6
1	30	0.12	0.10	0.14	0.28	0.13	0.13
2	60	0.14	0.12	0.20	12.56	0.17	0.28
3	120	0.25	0.21	5.43	28.18	0.95	0.35
4	150	28.54	0.14	35.68	60.30	0.12	0.30
5	180	50.34	0.28	56.32	95.17	0.23	0.38
6	240	98.37	0.30	98.62	100.61	0.22	0.39
7	300	-	0.31	-	-	0.15	0.59
8	330	-	0.34	-	-	38.50	13.30
9	360	-	0.48	-	-	60.06	62.12
10	420	-	0.68	-	-	102.79	100.21
11	480	-	10.64	-	-	-	-

4. Conclusion

Pulsatile drug delivery system is characterized by a lag time that is interval of no drug release followed by rapid drug release. It is useful in body functions that follow circadian, Drugs have extensive first pass metabolism, biological tolerance and interact with other drugs. A pulsatile dosage form taken at bedtime with a programmed start of drug release in the early morning hours, can prevent a sharp increase in the incidence of asthmatic attacks during the early morning hours (nocturnal asthma), a time when the risk of asthmatic attacks is the greatest. In the present study, an attempt was made to design and characterize pulsatile drug delivery system in order to release the drug after 5-6 hr in the intestine, and intentionally delaying the drug absorption from therapeutic point of view in the treatment of nocturnal asthma, where peak symptoms are observed in the early morning. Standard plots of Zileuton in 0.1N HCl, phosphate buffer (pH 7.4) and phosphate buffer (pH 6.8) were prepared by UV Spectrophotometry which showed good correlation coefficient (R^2) values. The drug-polymer interaction studies were performed by FTIR Spectrophotometry and it was found that there was no interaction between the drug and various polymers used in the formulation. The coated tablets were prepared by direct compression method. The pulsatile tablet of Zileuton tablets are composed of three components, a drug containing core tablet (rapid release function), the press coated with swellable hydrophobic polymer (SSG, CCS, CP and MCC) and hydrophobic polymer (ethyl cellulose) alone and / or in different weight ratio. An enteric coating layer (Eudragit L-100 and Eudragit S-100) for acid resistance function. The tablet does not release the drug in the stomach due to the acid resistance of the outer enteric coating layer. After gastric emptying, the enteric coating layer dissolves and the intestinal fluid begins to slowly erode the press coated polymer layer.

The formulation mixtures of powders for core tablets (F1-F12) prior to the compression step have been evaluated for pre-compression parameters namely angle of repose, bulk density, tapped density and Carr's Index for the flow ability nature was determined. All the formulation mixtures showed good to excellent compressibility. All the core and press coated tablet formulations were subjected to various physical and chemical evaluation tests for core and press coated tablets. The thickness, hardness and weight variation shown by all the tablet formulations were found within the official pharmacopoeial limits. All the formulations showed favourable drug loading with uniformity of drug content in the tablets and disintegration time. Based on the friability and disintegration time, formulation A1 was selected as best formulation and press coated and enteric coated for further evaluations studies. All the formulations of press-coated tablets showed almost uniform size, shape and appearance. The physico-chemical properties of all the formulations (C1-C6) like thickness, friability, hardness and drug content ranged lies within pharmacopoeia limits. *In-vitro* release of Zileuton of core tablet formulations F1-F12, F4 showed faster drug release after 15 mins. Faster drug release can be correlated with the high disintegration and friability observed in this study. The enteric-coated formulations C1, C3, and C4 showed maximum drug release after 4 hour. C2 formulation showed slow release about 10.64% in around 8 hour. C5 and C6 showed maximum drug release after 7th hr. Time dependent pulsatile drug delivery system has been achieved from tablet of formulation C5 and C6 with 102.79% and

100.21%. .50%, drug release which meet demand of chrono therapeautic drug delivery. Formulation of time release pulsatile Zileuton tablets which breaks after 5-6 hr was studied. Ethylcellulose was used in combination with Eudragit S-100 and Eudragit L-100 as a result upon contact with dissolution medium. The pulsatile Zileuton tablets did not release the drug in acidic environment(0.1N HCl) due to protective polymer coating and released the drug after pre-determined time period of 6-7 hours in phosphate buffer (pH 6.8). In accordance with chronotherapeutic model for nocturnal asthma, symptoms typically occur between midnight and especially around 4 am to 6 am because of increased airway responsiveness and worsening of lung function. Thus this study attempts to design and evaluate a chronomodulated drug delivery system of Zileuton, a bronchodilator for the treatment of asthma. To achieve this, Zileuton core tablets were coated with composition of hydrophobic and hydrophilic polymers and were further coated with an enteric coating polymer (Eudragit L-100 and Eudragit S-100). This coat has enabled us to achieve definite non-release lag phase. The pulsatile tablets were designed to prevent drug release in stomach and release drug rapidly after predetermined lag time in the intestinal tract when pH is above 6. The intention is that the formulation should be administered in the evening at 22:00 in treating diseases in which symptoms are experienced in the early morning hours (4:00 to 06:00). The system was found to be satisfactory in terms of release of the drug after a predetermined lag time when the greatest need of drug in early morning to treat the disease. One of the promising formulation demanded for pulsatile drug delivery system with specific lag time 5 hours hence with the existing drug molecule, the chronotherapeutic management of asthma has opening a “new lease of life”.

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