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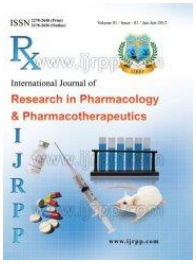

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Research article ***Open Access***

Development of novel gastroretentive mucoadhesive pulsetile tablets for zileuton

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ABSTARCT

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 30% concentrations of super disintegrates, the formulated core tablets were coated with the polymers (Ethyl cellulose, EudragitL-100, EudragitS-100) by using compression coating technology. All the core and press coated tablet formulations were subjected to various physical and chemical evaluation tests.. The drug delivery system was designed to deliver the drug at such a time when it could be most needful to patient of nocturnal asthma. The thickness, hardness and weight variation shown by all the tablet formulations were found within the official pharmacopoeial limits. In vitro release of Zileuton core tablet formulations F1 (Drug, SSG, Talc, Magnesium stearate, MCC pH 102) 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, showed maximum drug release after 4 hour. Time dependent pulsatile drug delivery system has been achieved from tablet of formulation C3, C6 and C9 with 95.5%, 94.76% and 97.48 % respectively.

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

INTRODUCTION

Over recent years, controlled release combination products have become increasingly popular within the pharmaceutical industry. In the body under physiological conditions, many vital functions are regulated by transient release of bioactive substances at a specific time and site. Over the last 30 years the pharmaceutical market has been demonstrated increasing preferably for controlled and targeted drug delivery system. However, there are certain conditions for which certain release pattern is not suitable. Such condition that leads to the requirements of a time programmed therapeutic systems, which are capable of releasing drug after pre-determined time delay and maintains constant drug levels throughout the day. Thus, to mimic the function of living systems and in view of emerging chronotherapeutic approaches, pulsatile delivery,

which is meant to release a drug following programmed lag phase, has attracted increasing interest in recent years. A pulsatile-release profile is characterized by a time period of no release (lag time) followed by a rapid and complete drug release [1-5]**.**

However, pulsatile delivery is desirable for drugs acting locally or having an absorption window in the gastro-intestinal tract or for drugs with an extensive first pass metabolism, e.g. β-blockers or for drugs, which develop biological tolerance, where the constant presence of the drug at the site of action diminishes the therapeutic effect, or for with special pharmacokinetic features designed according to the circadian rhythm of human [6].

Pulsatile drug delivery systems are generally classified into time-controlled and site-specific delivery systems. The release from the first group is primarily controlled by the system, while the release from the second group is primarily controlled by the biological environment in the gastro-intestinal tract such as pH or enzymes [7, 8]. Most pulsatile drug delivery systems are reservoir devices covered with a barrier coating. The barrier can dissolve, erode or rupture during/after a certain lag time, after which the drug is released rapidly from the inner reservoir core. The rupturing of the barriers are induced by an expanding core upon water penetration through the barrier coating. The expansion can be caused by effervescent excipients or swelling agents [9-10].

The proposed system consists of a core tablet coated with two layers, an inner swelling layer and an outer rupturable coating [11]. The swelling layer is composed of Sodium starch glycolate, a super-disintegrant and Microcrystalline cellulose was used as direct compressing agent, Talc and magnesium stearate were used as lubricant.,while the rupturable coating is an Eudragit L-100 film [12].

MATERIALS

Zileuton, Croscarmellose sodium, Talc, Magnesium stearate, Micro Crystalline Cellulose, Eudragit L-100, Eudragit S- 100, Ethyl Cellulose, HCL are gifted by Sura Laboratories Hyderabad.

METHOD

Preparation of Zileuton core tablets formulations

Tablets of Zileuton were made by direct compression method as shown in **Table** All ingredients were weighted accurately and mix well in mortar-pastle for 15 min. Tablets were made in labpress tablet machine. A 8-mm punch and die set were used to obtain tablets of mass 150 mg (containing 20 mg of drug) and crushing strength of 80 N. The friability of the tablets was measured as per USP specifications and found to be less than 0.05%.

Table1. : Formulation for preparation Zileuton core tablets

Sl.No.	INGREDIENTS	F1	F2	F3
1	Zileuton	10mg	10 mg	10 mg
2	SSG	10 mg	20mg	30 mg
3	Talc	1mg	1 mg	1 mg
4	Magnesium stearate	1 mg	1 mg	1 mg
5	MCC	qs	qs	qs

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 10mm).

Table 2: Composition of coat over Zileuton core tablet

INGREDIENTS	C1	C2	C3	C4	C5	C6	C7	C8	C9
Eudragit L-100	50	100	150	-					
Eudragit S-100	-	-	-	50	100	150	-	-	-
Ethylecellulose	-	-	-	-	-	-	50	100	150
Mag. Stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
MCC PH 102	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s

RESULTS AND DISCUSSION

Preformulation studies

Drugs Polymer Interaction Study by FTIR spectrophotometer

In order to investigate the possible interaction between drug and selected polymers, FTIR studies were carried out. IR spectrum for pure drug and physical mixture of drug- polymers were obtained and analyzed for principle peaks The studies suggest that there is no incompatibility between drug and polymer.

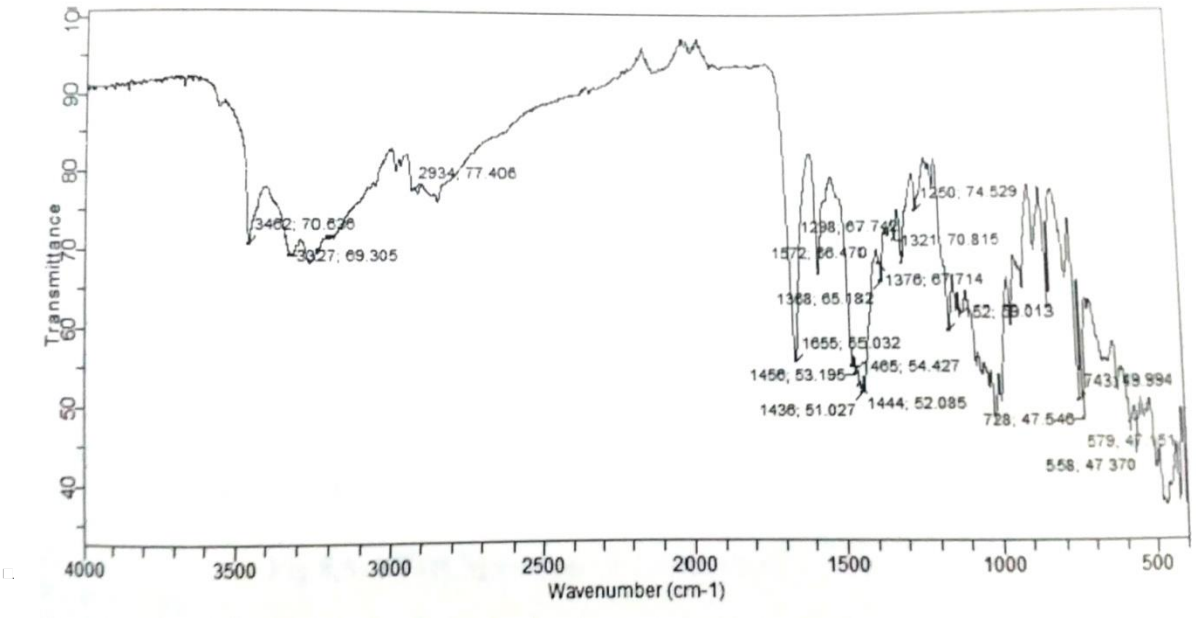

Fig 1: FTIR Spectrum of Zileuton pure drug

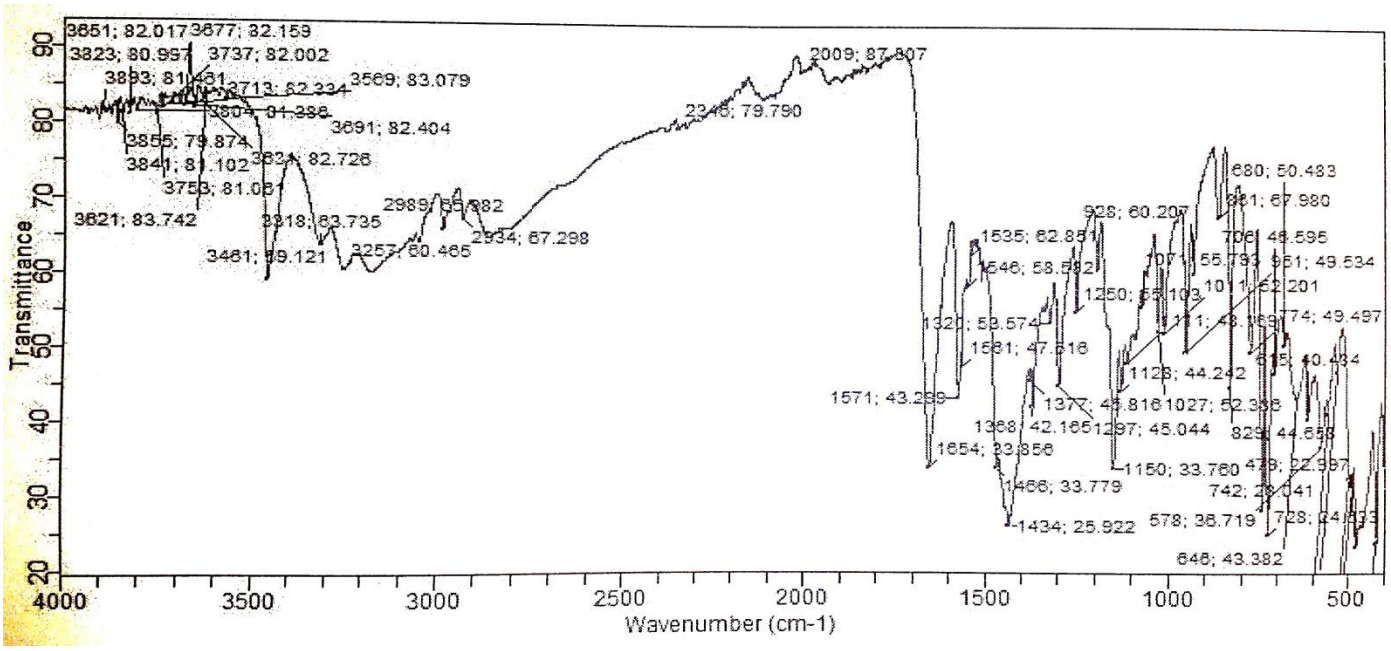

Fig 2: FTIR spectrum of Optimized formulation

Pre compression parameters of Zileuton coating tablets

Table 3: Pre compression Parameters of Zileuton Coated Tablets

Formulation code	Angle of repose (^{0}) *	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
C1	26.01	0.46	0.55	16.66	1.19
C2	24.8	0.56	0.62	16.87	1.10
C3	22.74	0.52	0.65	17.11	1.25
C4	25.33	0.54	0.65	16.92	1.20
C5	26.24	0.53	0.65	18.46	1.22
C6	26.12	0.54	0.67	17.91	1.24
C7	27.08	0.56	0.67	16.41	1.19
C8	25.12	0.48	0.58	17.24	1.20
C9	25.45	0.53	0.65	18.46	1.22

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 0.46 to 0.56 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.55 to 0.67 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.25 indicating the powder has good flow properties.

Post compression parameters of coated tablet

Table 4: Invitro quality control parameters for tablets

Formulation code	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
C1	700.5	4.1	0.62	4.8	96.76
C2	695.4	4.4	0.63	4.9	95.45
C3	698.6	4.2	0.45	4.9	100.34
C4	699.6	4.5	0.74	4.9	97.87
C5	699.4	4.2	0.56	4.7	95.14
C6	698.7	4.4	0.50	4.5	94.56
C7	700.3	4.5	0.61	4.6	99.42
C8	699.2	4.2	0.53	4.7	109.65
C9	701.3	4.0	0.58	4.6	96.12

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 Zileuton 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 that formulation showed faster drug release after 15 mins. So, that Zileuton core tablet formulation was selected as best formulation for further press coating and enteric coating formulations. *In vitro* drug release profiles of all Zileuton core tablets were shown in **Table 4** and **Figure**3**.**

Table 4: Invitro drug release

Time (min)	F1
2	32.64
4	45.48
6	60.85
8	77.52
10	89.25
15	100.03
20	102.13

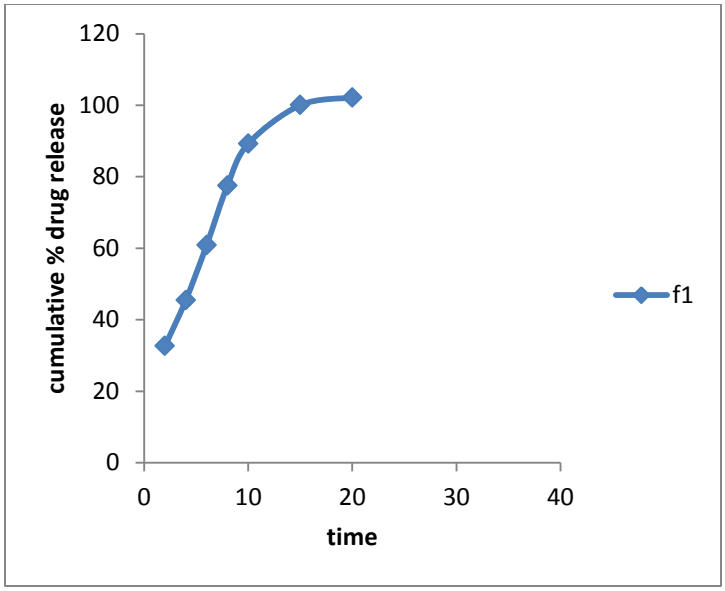

Fig 3: Cumulative % *drug* released of Zileuton core tablets

In vitro drug release study of Zileuton pulsatile tablets

Based on the above characters formulation F1 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, and C4 showed maximum drug release after 4th hour. Time dependent pulsatile drug delivery system has been achieved from tablet of formulation C3, C6 and C9 with 95.45%, 94.76% and 97.48% drug release up to 12 hours. Which meets demand of chronotherapeautic drug delivery. The formulations containing ethylcellulose Eudragit L-100 and Eudragit S-100 was found to be optimum as enteric coating polymers. The data were shown below.

Table 5: Cumulative % drug release of zileuton pulasatile tablets

Time(min)	C1	C2	C3	C4	C5	C6	C7	C8	C9
0.5	0.14	0.13	0.10	0.28	0.12	0.10	0.19	0.16	0.12
1	0.18	0.19	0.20	12.56	0.19	0.17	0.65	0.54	0.50
2	0.25	0.21	5.43	28.18	1.95	1.35	1.95	1.84	1.54
3	28.54	25.29	15.68	50.30	10.12	9.30	5.39	14.74	19.74
4	50.34	30.18	24.32	85.17	21.23	20.38	13.73	20.38	25.38
5	98.37	41.72	30.62	90.61	30.22	28.39	27.37	38.48	36.48
6		51.31	39.57	99.76	39.15	35.59	41.38	47.48	45.48
7		60.34	44.20		43.50	40.30	63.83	50.29	52.29
8		72.48	50.02		49.06	52.12	80.29	61.27	66.27
9		88.68	61.25		55.79	64.21	96.38	79.38	71.38
10		100.64	77.30		75.34	74.86		86.39	78.39
11			84.92		94.25	80.67		96.28	86.28
12			95.45			94.76			97.48

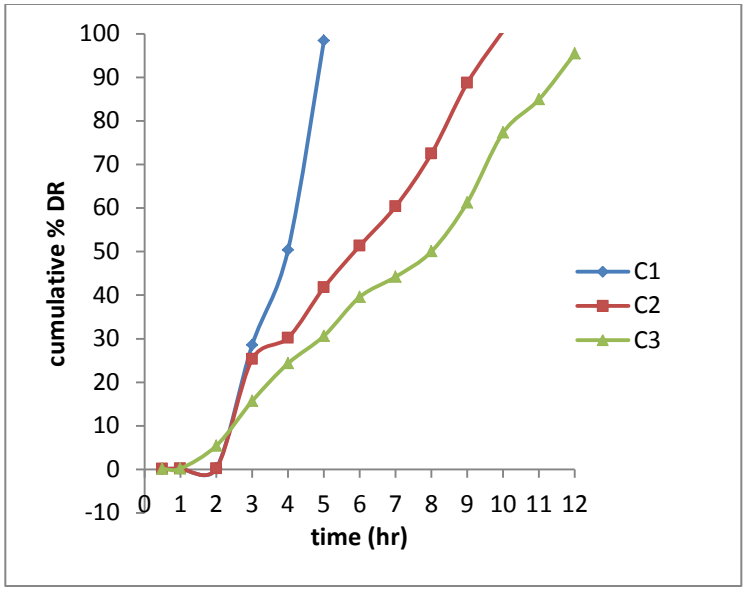

Fig: 4: ***Cumulative %*** **release study of Zileuton pulsatile tablets with eudragit L-100 (C1-C3)**

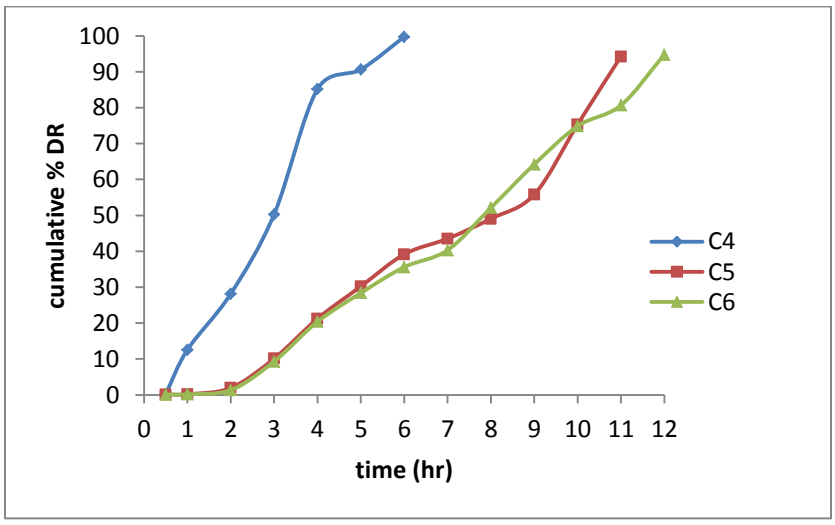

Fig: 5: ***Cumulative %*** **release study of Zileuton pulsatile tablets with eudragit s-100 (C4-C6)**

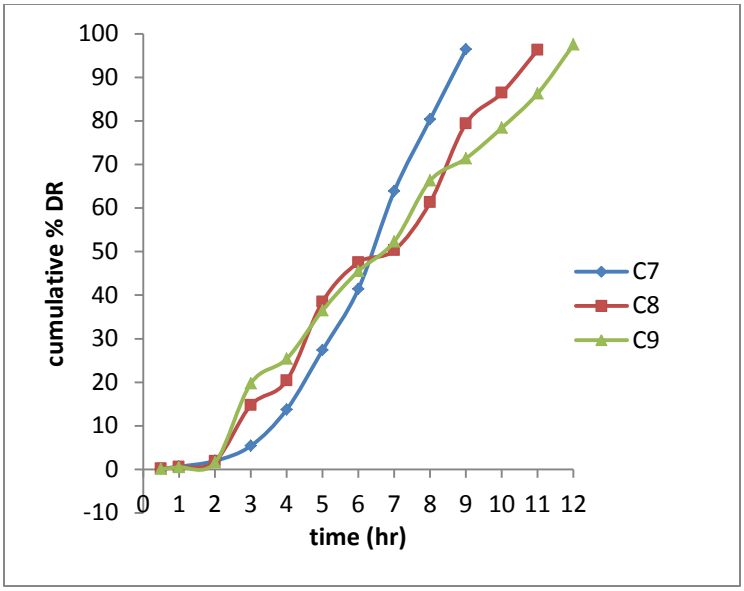

Fig: 6: *Cumulative %* release study of Zileuton pulsatile tablets with ethylcellulose (C7-C9)

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.

Table 6: Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG (%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
0.12	**0.5**	0.707	-0.921	-0.301	1.999	0.240	8.3333	-2.921	99.88	4.642	4.640	0.002
0.5	**1**	1.000	-0.301	0.000	1.998	0.500	2.0000	-2.301	99.5	4.642	4.634	0.008
1.54	**2**	1.414	0.188	0.301	1.993	0.770	0.6494	-1.812	98.46	4.642	4.618	0.024
19.74	**3**	1.732	1.295	0.477	1.904	6.580	0.0507	-0.705	80.26	4.642	4.314	0.328
25.38	**4**	2.000	1.404	0.602	1.873	6.345	0.0394	-0.596	74.62	4.642	4.210	0.432
36.48	**5**	2.236	1.562	0.699	1.803	7.296	0.0274	-0.43	63.52	4.642	3.990	0.652

								8				
45.48	**6**	2.449	1.658	0.778	1.737	7.580	0.0220	-0.342	54.52	4.642	3.792	0.850
52.29	**7**	2.646	1.718	0.845	1.679	7.470	0.0191	-0.282	47.71	4.642	3.627	1.015
66.27	**8**	2.828	1.821	0.903	1.528	8.284	0.0151	-0.179	33.73	4.642	3.231	1.411
71.38	**9**	3.000	1.854	0.954	1.457	7.931	0.0140	-0.146	28.62	4.642	3.059	1.583
78.39	**10**	3.162	1.894	1.000	1.335	7.839	0.0128	-0.106	21.61	4.642	2.785	1.856
86.28	**11**	3.317	1.936	1.041	1.137	7.844	0.0116	-0.064	13.72	4.642	2.394	2.248
97.48	**12**	3.464	1.989	1.000	0.401	8.123	0.0103	-0.011	2.52	4.642	1.361	3.281

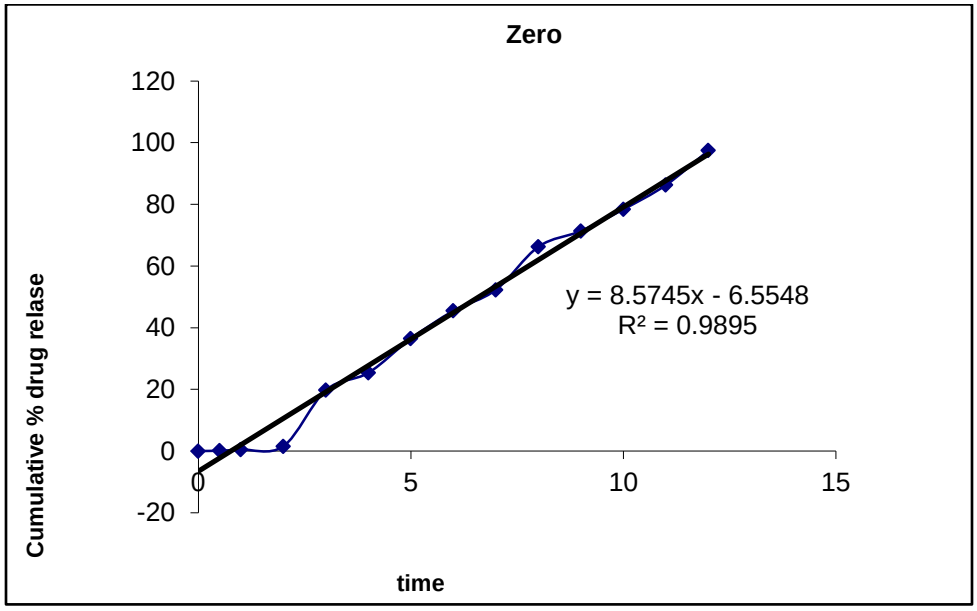

Fig 7 : Zero order release kinetics graph

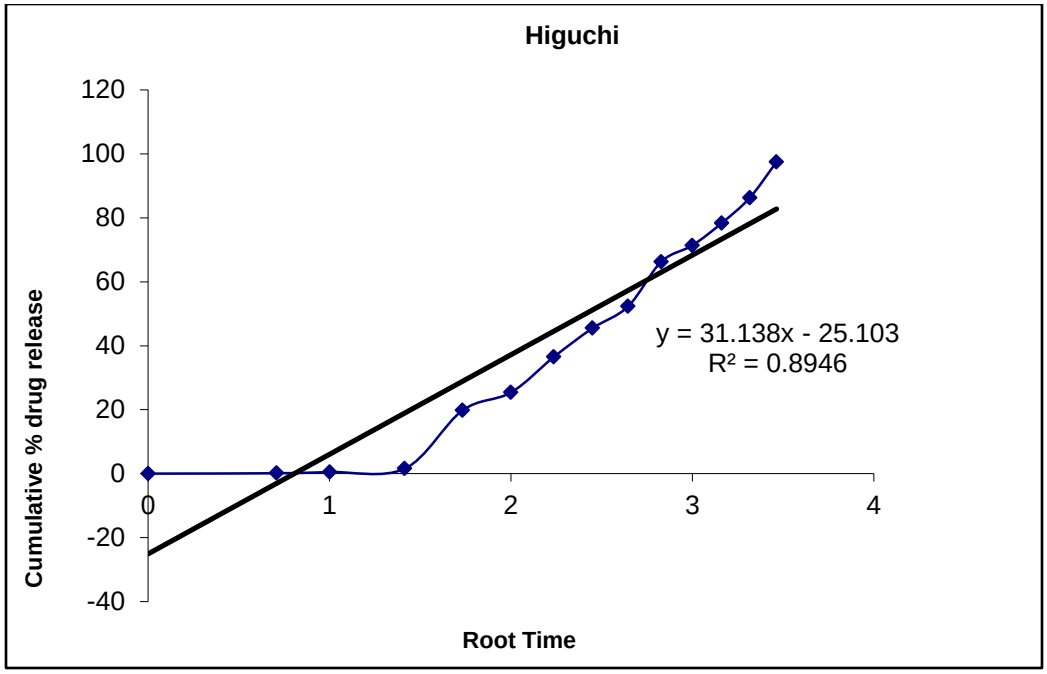

Fig 8 : Higuchi release kinetics graph

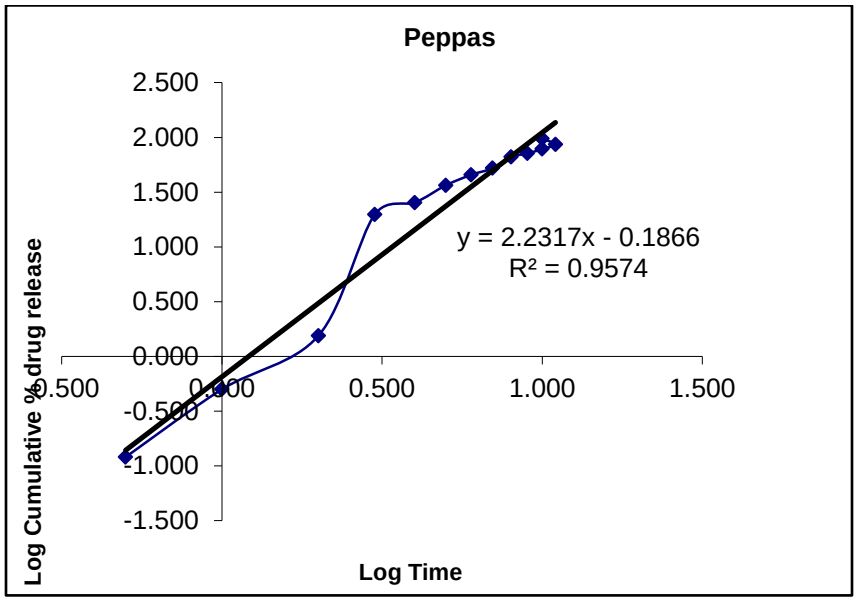

Fig 9: Kars mayer peppas graph

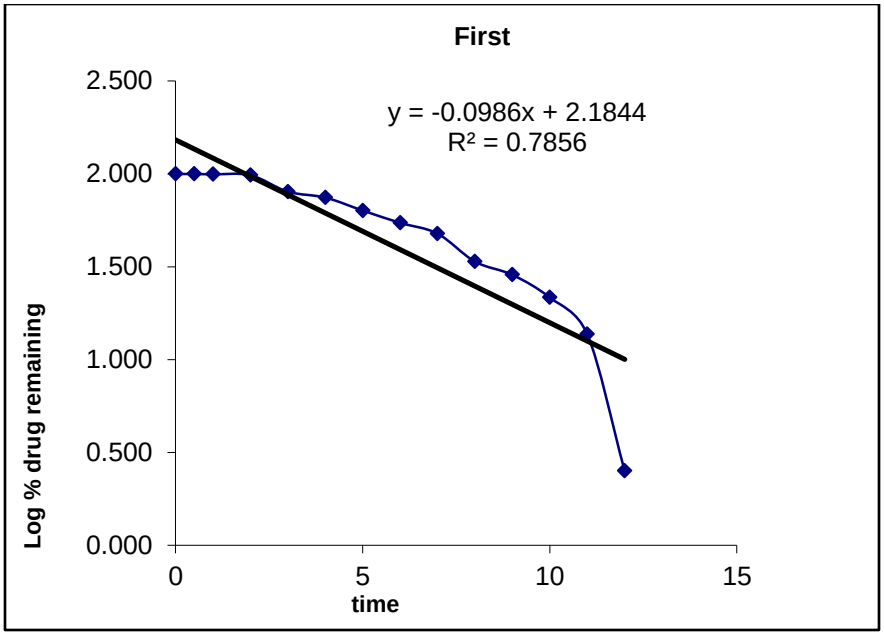

Fig 10: First order release kinetics graph

From the above graphs it was evident that the formulation F6 was followed Zero order release kinetics.

SUMMARY

Chronotherapy is an approach that fulfills the criteria of drug delivery at a specific time as per the pathophysiological need of the disease, to improve patient compliance. Development of Zileuton pulsatile drug delivery is one of the alternative routes of administration to effect and provide delayed release of drug. The formulation was prepared by direct compression method using various polymers.

The formulated press coated tablets were evaluated for different parameters such as drug excipient comparability studies, weight variation, thickness, hardness, content uniformity. *In vitro* drug release. *In vitro* drug release studies performed in 0.1N HCl and phosphate buffer pH 6.8 for 12hrs in standard dissolution apparatus the data was subjected to zero order, first order, zero and first diffusion models. The following conclusions can be drawn from the results of various experiments.

- FTIR studies concluded that there was no interaction between drug and excipients.
- The physic-chemical properties of all the formulations prepared with different polymers like eudragit L100, eudragit S100 and ethyl cellulose showed within limits.

Properties and from the results, it was concluded that the in vitro drug release of the optimized formulations is suitable for pulsatile drug delivery.

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 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 one components, a drug containing core tablet (rapid release function), the press coated with swellable hydrophobic polymer (ccs) and Ethyl cellulose, Eudragit S-100, Eudragit L-100 as 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 coating tablets (C1-C9) 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 flowability 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 F1 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-C9) like thickness, friability, hardness and drug content ranged lies within pharmacopoeia limits.

In vitro release of Zileuton of core tablet formulations F1 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 and C3, showed maximum drug release after 4 hour.

Time dependent pulsatile drug delivery system has been achieved from tablet of formulation C3, C6 and C9 with 95.5%, 94.76% and 97.48%%. .50%, drug release which meet demand of chronotherapeautic drug delivery. Formulation of time release pulsatile Zileuton tablets which breaks after 5-6 hr was studied. 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 (ethylcellulose 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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