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Research Article

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Design and *In-vitro* Evaluation of Enteric Coated Pulsatile Drug Delivery System of Zileuton Tablets

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Abstract 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 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 pharmacopoeias limits. *In-vitro* release of Zileuton of core tablet formulations F1 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 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, Enteric coated, Pulsatile tablets.

Introduction

Now a days, a major goal for the drug delivery research is turned towards the development of In 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 near 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 [1]. 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 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. [2, 5, 6, 11]

Materials and Methods

Materials:

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

Methodology

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 228 nm and the same was selected for Zileuton.

Standardization method for estimation of Zileuton

Standard curves of Zileuton were prepared in 0.1N HCl, and phosphate buffer (pH 6.8).

Standard graph of Zileuton in 0.1N HCl

Zileuton showed maximum absorbance in 0.1N HCl at 228 nm. The solution obeyed Beer-Lambert's law for concentration range of 2 µg / ml to 10 µg / ml with regression coefficient of 0.9957. Standard curve of Zileuton prepared in 0.1N HCl is shown below in Table 1 and Figure1.

Standard graph of Zileuton in phosphate buffer (pH 6.8)

Zileuton showed maximum absorbance in phosphate buffer (pH 6.8) at 228 nm. The solution obeyed Beer-Lambert's law for concentration range of 1 to 10 µg/ml with regression coefficient of 0.9966. Standard curve of Zileuton prepared in phosphate buffer pH 6.8 is shown Table 2 & Figure 2.

Formulation development of Tablets:

Preparation of Zileuton core tablets formulations

Tablets of Zileuton were made by direct compression method as shown in **Table 3.** All ingredients were weighted accurately and mix well in mortar-pestle for 15 min. Microcrystalline cellulose was used as direct compressing agent. Sodium starch glycolate was used in different compositions as disintegrating / swelling agents for various formulations. Talc and magnesium stearate were used as lubricant. Tablets were made in labpress tablet machine.

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). All ingredients weight were in mg.

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. The F1 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 5** and **Figure**.**3**.

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 Figure 4,5,6 & Table 6**.**

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

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.[3,4,7,10]

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 and expressed in Kg/cm^2.

Thickness

The prepared tablets were subjected to thickness test. It was carried out by using the validated digital electronic vernier caliper and expressed in millimeter.

Friability test

The friability was determined using friability test apparatus 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.

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 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.

Results and Discussion

Table 1: Calibration data of Zileuton in 0.1N HCl

Concentration (µg/ml)	Absorbance
0	0
2	0.14
4	0.249
6	0.388
8	0.517
10	0.68

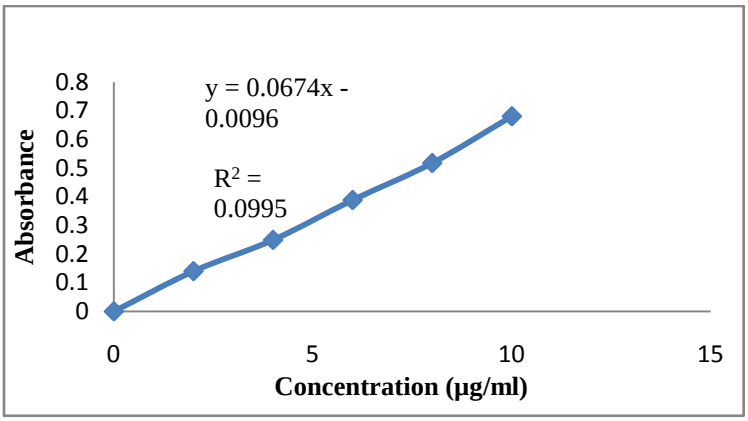

Figure 1: Standard Graph of Zileuton in 0.1N HCl

Table 2: Calibration data of Zileuton in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
2	0.236
4	0.431
6	0.612
8	0.805
10	1.051

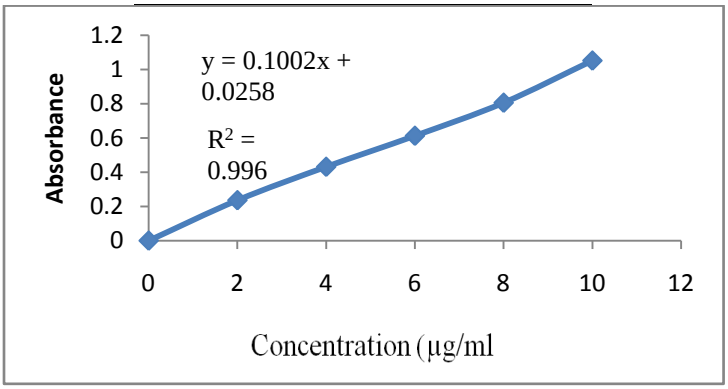

Figure 2: Standard Graph of Zileuton in pH 6.8 phosphate buffer

Table 3: Formulation for preparation Zileuton core tablets

S. 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

Table 4: Cumulative % drug release of Zileuton core tablets

Time (min)	F1
0	0
2	32.64
4	45.48
6	60.85
8	77.52
10	89.25
15	100.03
20	102.13

Table 5: Cumulative % drug release of Zileuton core 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

Table 6: Composition of coat over Zileuton core tablet (300mg)

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

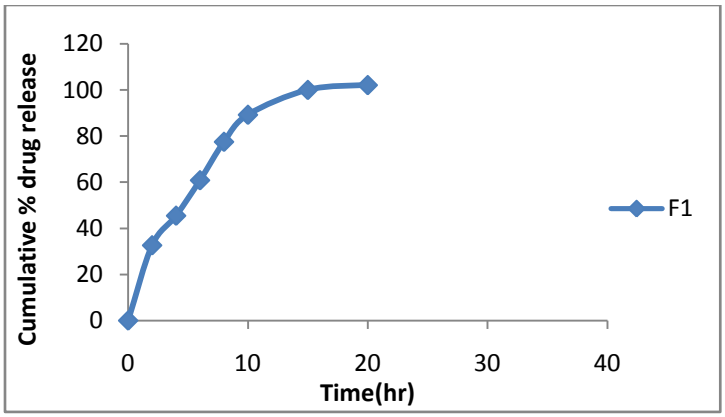

Figure 3: Cumulative % drug released of Zileuton core tablets

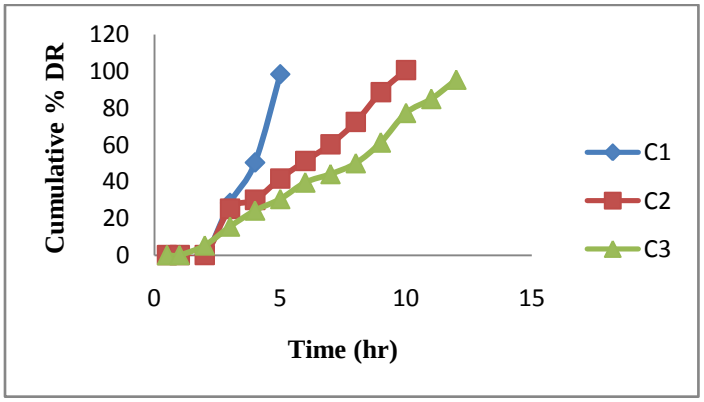

Figure 4: Cumulative % release study of Zileuton pulsatile tablets with eudragit L-100 (C1-C3)

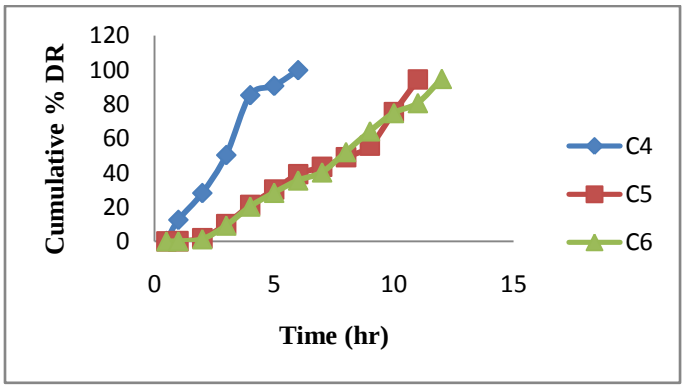

Figure 5: Cumulative % release study of Zileuton pulsatile tablets with eudragit s-100 (C4-C6)

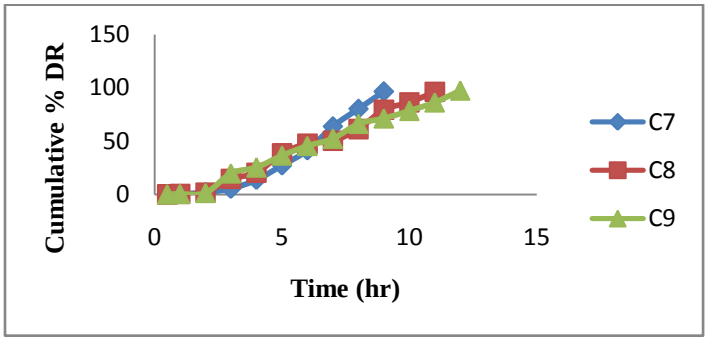

Figure 6: Cumulative % release study of Zileuton pulsatile tablets with ethyl cellulose (C7-C9)

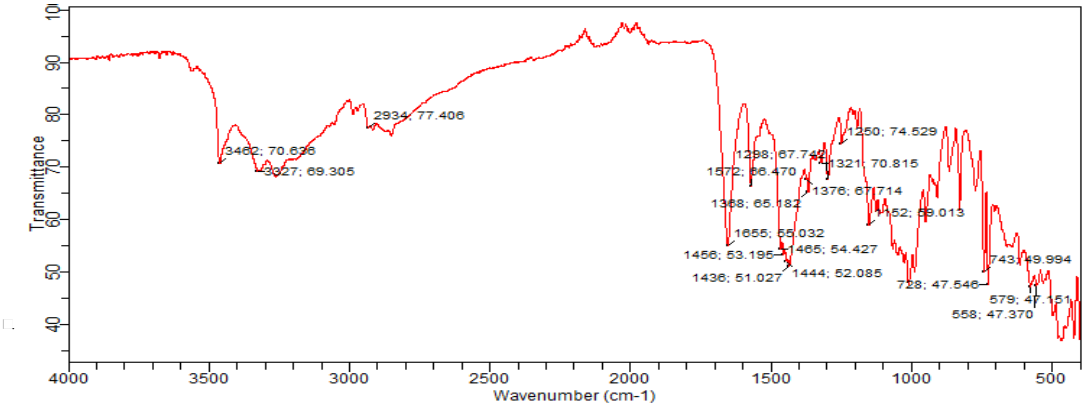

Figure 7: FTIR Spectrum of Zileuton pure drug

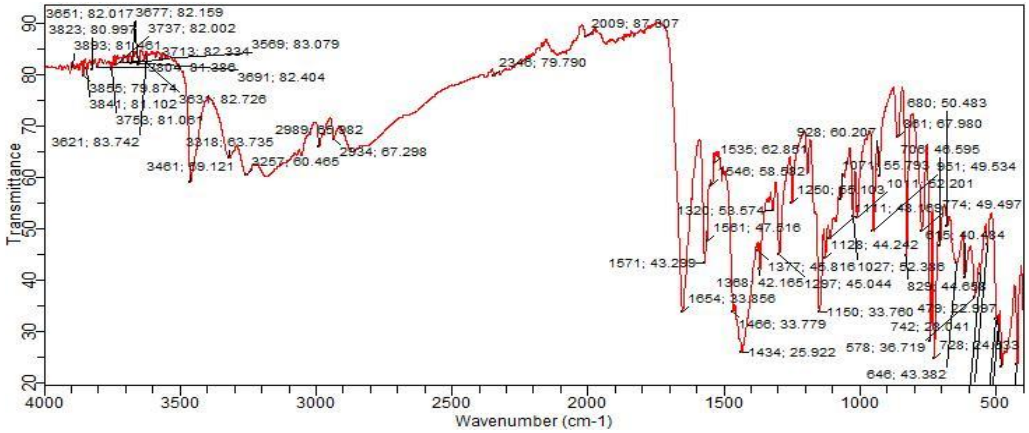

Figure 8: FTIR spectrum of Optimized formulation

Pre compression parameters of Zileuton coating tablets

Table 7: Pre compression Parameters of Zileuton Coated Tablets

Formulation code	Angle of repose (θ) *	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/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 0.55 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 show 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 8: *In-vitro* quality control parameters for tablets

Formulation code	Weight variation(mg)	Hardness (kg/cm^2)	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.

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 could be drawn from the results of various experiments FTIR studies concluded that there was no interaction between drug and excipients. The physico-

chemical properties of all the formulations prepared with different polymers like eudragit L100, eudragit S100 and ethylcellulose 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 etylcellulose, eudragit s-100, eudragit L100 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 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.

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