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Formulation and evaluation of enteric coated time release press coated tablets of theophylline for chronopharmacotherapy

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ABSTRACT

The aim of the investigation was to develop a novel oral pulsatile drug delivery system based on enteric coated time-release press coated (ETP) tablet. Tablet containing mainly three layers; a theophylline core tablet by direct compression, outer shell by different weight ratio of hydrophobic polymer of ethylcellulose (EC) and hydrophilic excipients such as low-substituted hydroxy propylcellulose (L-HPC) or hydroxypropyl methylcellulose (HPMC) and top layer of enteric coated polymer like Eudragit L-100. The effect of the formulation of an outer shell comprising both hydrophobic polymer and hydrophilic excipients on the lag time of drug release was investigated. The drug delivery system was designed to deliver the drug at such a time when it could be most needful to patient during nocturnal asthma. The time-release function should work more efficiently in the small intestine as compared the stomach. In the small intestine drug carrier will be delivered to the target side and drug release will begin at a predetermined time point after gastric emptying. The release profile tablet exhibited a time period without drug release (time lag) followed by a rapid and complete release phase, in which the outer shell ruptured. Dissolution studies were carried out in simulated gastric, intestinal fluid with 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8), respectively. The optimized formulation complied with the ICH stability testing guidelines.

Key words: Nocturnal asthma, Low-substituted hydroxy propylcellulose, Ethylcellulose, Hydroxy propyl methylcellulose, Eudragit L-100, Pulsatile drug delivery.

INTRODUCTION

In recent year, 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 [1]. 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 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 [2].

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 hour

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 [3].

However, a release pattern of drug is not suitable in certain disease condition. At that time release profile of a delivery system characterised by lag time. In other words, the drug should not release during its initial period of administration, followed by a rapid and complete release (pulse release) of drug that is called pulsatile drug delivery system [4]. This system aims to deliver a drug via the oral route at a rate different than constant i.e., zero order release [5-10]. The lag time is the time interval between the dosage form 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 hour to 4 hour is desire for upper region of gastrointestinal tract and more than 4 hours for lower portion of small intestine [11]. Pulsatile drug delivery capable of releasing its drug content at either a predetermined time or at a specific site in the gastrointestinal tract.

Nocturnal and morning wheeze are common symptoms of patients with asthma. These patients have overnight decreases in peak expiratory flow rate or forced expiratory volume in one second. Because of this bronchoconstriction they can't sleep well and become more hypoxaemic during the night. Although regular inhaled treatment reduces the overnight fall in peak flow rates in those patients who have taken their treatment as required. Still some patients complain of nocturnal symptoms despite adequate inhaled treatment. As a result of this the therapeutic effect of theophylline has been studied which can improve nocturnal symptoms and the morning decrease in peak flow rates in patients [12].

Theophylline (dimethylxanthine) is methylated xanthine class of drug used in therapy for respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma. It is a nonselective phosphodiesterase inhibitor, also a bronchodilator, which enhance the respiratory muscle function and mucociliary clearance. The aim of the present work was to develop a time controlled release formulation of theophylline based on a enteric coated time release press-coated technique for nocturnal asthma.

MATERIALS AND METHODS

Materials

The drug theophylline,, microcrystalline cellulose, citric acid, sodium bicarbonate, ethylcellulose (Ethocel), low-substituted hydroxyl propylcellulose (L-HPC) were obtained as gift samples from Cipla Pharma, Mumbai, India. Cross-carmellose sodium, magnesium stearate, talc was purchased from Signet Chemical Corporation, Mumbai, India. Hydroxy propyl methylcellulose (K4M & K100M) and Eudragit L-100 were obtained from Fine Chem Industries, Mumbai, India.

Methods

Formulation of pulsatile tablets

The inner core tablets were prepared by using direct compression method as shown in **Table 1.** Powder mixtures of theophylline, microcrystalline cellulose (MCC, Avicel PH-102), citric acid, sodium bicarbonate and cross-carmellose sodium (Ac-Di-Sol) were dry powder for 20 min, followed by addition of magnesium stearate and talc as lubricant. The mixtures were then further blended for 10 min., 300 mg of resultant powder blend was manually compressed using hydraulic press (Riddhi Pharma Machinery Ltd., Model No: RDB4-10, Ahmedabad, India) at a pressure of 1 ton, with 8mm punch and die to obtain the core tablet. From the four formulations A1, A2, A3, A4, the formulation A1 is selected as best formulation and press coated with the various compositions containing HPMC-K4M, HPMC-K100M, Ethylcellulose and L-HPC with their compositions (**Table 2**). The formulations C1, C2, C3, C4, C5, C6, C7, C8, C9, different compositions were weighed dry blended at about 10 min and used as press-coating material to prepare press-coated pulsatile tablets, C1-C9, respectively by direct compression method. Further the above formulations were enteric coated with Eudragit L-100 in acetone (6% w/v) and the formulations were renamed as F1, F2, F3, F4, F5, F6, F7, F8, F9.

Table 1: Formulations of core tablets of theophylline

Ingredient	Formulation Code			
	A1	**A2**	**A3**	**A4**
Theophylline	100	100	100	100
Lactose	45	45	-	45
Microcrystalline cellulose	95	95	95	50
Starch	-	45	45	45
Sodium carbonate : citric acid (1 :1)	45	-	45	45
Cross carmellose sodium	09	09	09	09
Magnesium stearate	03	03	03	03
Talc	03	03	03	03
Total (mg)	**300**	**300**	**300**	**300**

Table 2: Composition for press coating

Ingredient	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**
HPMC K4M	200	-	-	-	50	-	50	-	50
HPMC K100M	-	200	-	-	-	50	50	-	50
L- HPC	-	-	200	-	-	-	-	50	50
EC	-	-	-	200	150	150	100	150	50
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total weight of press coated tablet -500 mg									

EVALUATIONS

Flow Properties of powder blend

The flow properties of powder blend were characterized in terms of angle of repose, compressibility index and Hausner ratio. Angle of repose was performed using funnel method [13] by keeping a funnel vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom was closed and 2 gm of powder was filled in the funnel. Then the funnel was opened to releases the powder on the paper to form a smooth conical heap. The radius of the heap (r) and the height of the heap (h) were measured. The $\tan^{-1}$ of the height of the pile / radius of its base gave the angle of repose. Bulk density (ρb) and tapped densities (ρt) were determined and thereby hausner ratio (H_R) and compressibility index were calculated according to the following equations.

$$Compressibility\ index\ = \frac{\rho\ tapped - \rho\ bulk}{\rho\ tapped} \times 100$$

$$Hausner\ ratio = \frac{\rho\ tapped}{\rho\ bulk}$$

Hardness, Thickness, Weight variation, Disintegration time and Drug content of core tablets and press coated tablets

Hardness of the tablets was tested using a Monsanto hardness tester (Labtech, AVI-PH-4522, India). Thickness was determined by electronic vernier caliper (Sealey professional tools, Model No: AK962EV.V2, UK). Friability of the tablets was determined in a friability test apparatus (Ketan, Koshish Industries, Bombay, India, Model No: SS153). Disintegration time of the tablets was determined using a tablet disintegration test apparatus (Servewell Instruments pvt. Ltd., Electrolab ED-2L, India) using distilled water as fluid. For drug content (without entric coating) the tablets was estimated by the spectrophotometrically at 272 nm (Shimadzu 1800, Japan).

In vitro drug release of core tablets

In vitro dissolution studies were carried out using USP Type II (paddle method) apparatus (Electrolab TDT-08L, India). Distilled water was used as dissolution medium. Release pattern was studied by taking sample of 5 mL at the specific time intervals and analyzed at 272 nm using a UV spectrophotometer (Shimadzu 1800, Japan).

In vitro drug release of enteric coated tablets

In vitro dissolution studies were carried out using USP XXIII Type II (paddle method) apparatus (Electrolab TDT-08L, India). In order to simulate the pH changes along with the gastro intestinal tract (GIT), dissolution media with 0.1 N HCl and phosphate buffer (pH 6.8) were sequentially used. When performing the experiment, 0.1 N HCl medium was used for 2 h (since the average gastric emptying time is 2 h). Then removed and fresh phosphate buffer (pH 6.8) was added for subsequent hours. 900 mL of the dissolution medium was used at each time and stirred at 50

rpm at 37 ± 0.5 ºC. 5 mL of dissolution media was withdraw at predetermined time interval and fresh dissolution media was replaced. The withdrawn samples were analyzed at 272 nm using a UV spectrophotometer.

Determination of lag time (t^{10}) for enteric coated tablets

The dissolution profile shows lag time with the enteric coated formulations (F1-F9). The intention of the study was to develop a pulsatile 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.

Stability Studies

The stability studies were carried out of the most satisfactory formulation as per ICH guidelines to assess the drug and formulation stability. The most satisfactory formulation sealed in aluminum packaging and kept in humidity chamber maintained at 30 ± 2 ºC, 65 ± 5% RH and at 40 ± 2 ºC, 75 ± 5% for two months [14]. At the end of studies, samples were analyzed for the post-compression parameters like hardness, drug content and lag time.

RESULTS AND DISCUSSION

The pulsatile drug delivery system consisted of inner core tablet containing drug reservoir and outer coating layer with various composition of water insoluble polymer ethylcellulose and water soluble polymer L-HPC and HPMC. Various core tablets of theophylline is prepared (A1-A4) from which, the formulation A1 is selected as best core tablet due to its disintegration time and further press coating and enteric coating.

ETP tablets are composed of three components, a drug containing core tablet (rapid release function), the press coated with swellable hydrophobic polymer layer of hydroxy propylcellulose layer and hydrophobic ethyl cellulose and Eudragit L-100 as an enteric coating layer 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 rapidly dissolved and the intestinal fluid begins to slowly erode the press coated polymer layer. When the erosion front reaches the core tablet, rapid drug release occurs since the erosion process takes a long time as there is no drug release period (lag phase) after gastric emptying. The mechanism of producing a lag time of this formulation was based upon the hydration of outer barrier layer and / or water penetration through outer barrier layer. Ethylcellulose was used in combination with L-HPC as a result of solubility of L-HPC upon contact with dissolution medium, L-HPC hydrated and form compact with ethylcellulose. The hydrophobicity of ethylcellulose retards the hydration of L-HPC. Therefore dissolution medium did not penetrate but the coating eroded slowly.

Flow Properties of blend

The blend prepared for core tablets was evaluated for their flow properties **(Table 3).** Bulk density varied between of 0.33 ± 0.021 to 0.37 ± 0.018 gm / cm^3 and tapped density lies between 0.37 ± 0.020 to 0.44 ± 0.017 gm/cm^3. Carr's index was found to be 12.2 ± 0.36 to 17.4 ± 0.21% and hausner ratio ranged from 1.13 ± 0.020 to 1.20 ± 0.017 for powers of different formulations. Angle of repose ranged between 27.7 ± 0.14 and 30.5 ± 0.18. These values indicated that the prepared powers exhibited good to fair flow properties.

Table 3: Flow Properties of powder

Formulation code	Bulk density (gm / cm^3)	Tapped density (gm / cm^3)	Carr's index (%)	Hausner ratio (%)	Angle of repose (θ)
A1	0.35± 0.015	0.40 ± 0.012	12.5 ± 0.28	1.14 ± 0.012	27.7 ± 0.14
A2	0.33 ±0.021	0.37 ±0.020	12.2 ± 0.36	1.13 ± 0.020	29.7 ± 0.28
A3	0.37 ± 0.018	0.44 ±0.017	14.77 ± 0.24	1.17 ± 0.022	30.4 ± 0.16
A4	0.36 ± 0.012	0.43 ± 0.014	17.4 ± 0.21	1.20 ± 0.017	30.5 ±0.18

Mean ±SD, n = 3

Hardness, Thickness, Weight variation, Disintegration Time and Drug content of core tablets

The physico-chemical properties of all the formulations (A1 - A4) are shown in **Table 4.** The hardness for different formulations was lies between 4.5 ± 0.052 and 4.6 ± 0.032 Kg/cm^2 and it indicating that all the formulation is having satisfactory mechanical strength. The average weight of the core tablets varied 299 ± 0.20 mg and 301 ± 0.12 mg, and thickness ranged between 5.46 ± 0.023 and 5.52 ± 0.018 mm for different formulations which are well within the desirable limit and indicating uniform in mass and thickness. The friability ranged from 0.52 ± 0.014 to

0.74 ± 0.012% for different formulations and it was below 1%, which represents good mechanical resistance of the tablets. The drug content ranged between 98.96 ± 0.16 and 99.82 ± 0.21 mg in different formulations, showed favorable drug loading efficiency. Based on the friability, formulation A1 was selected as best formulation and press coated and enteric coated for further evaluations studies like physico-chemical properties and *in vitro* drug release studies.

Table 4: Post compression parameter of theophylline core tablet

Formulation Code	Hardness (Kg / cm^2)	Thickness (mm)	Friability (%)	Disintegration Time (sec)	Weight Variation (%)	Drug Content (%)
A1	4.5 ± 0.057	5.50 ± 0.011	0.52 ± 0.014	58 ± 0.4	299 ± 0.24	99.82 ± 0.21
A2	4.6 ± 0.028	5.46 ± 0.023	0.74 ± 0.012	180 ± 0.2	301 ± 0.12	98.96 ± 0.16
A3	4.5 ± 0.052	5.52 ± 0.018	0.68 ± 0.017	157 ± 0.2	300 ± 0.16	99.24 ± 0.21
A4	4.6 ± 0.032	5.56 ± 0.021	0.62 ± 0.013	181 ± 0.3	299 ± 0.20	99.42 ± 0.22

Mean ±SD, n = 3

Hardness, Thickness, Friability, Weight variation and Drug content of press coated tablets

All the formulations showed almost uniform size, shape and appearance. The physico-chemical properties of all the formulations (C1-C9) are shown in **Table 5**. 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. The drug content ranged between 97.96 ± 0.28 and 101.16 ± 0.16 mg, in different formulations, showed favorable drug loading efficiency.

Table 5: Post-compression parameters of press coated tablets

Formulation Code	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight Variation (mg)	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	100.62 ± 0.18
C6	6.52 ± 0.20	6.92 ± 0.12	0.5 ± 0.12	500 ± 0.20	99.42 ± 0.21
C7	6.42 ± 0.16	6.52 ± 0.20	0.5 ± 0.19	498 ± 0.16	97.96 ± 0.28
C8	6.49 ± 0.24	6.84 ± 0.14	0.4 ± 0.18	500 ± 0.23	99.58 ± 0.12
C9	6.64 ± 0.21	6.68 ± 0.17	0.5 ± 0.24	501 ± 0.21	99.34 ± 0.25

Mean ±SD, n = 3

***In vitro* drug release of core tablets and enteric coated tablets**

In vitro release of theophylline from core and enteric coated tablets is shown in **Fig. 1 & 2**. From formulation A1, A2, A3 and A4 (core tablets), A1 showed faster drug release after 9 mins. Faster drug release can be correlated with the high disintegration and friability observed in this study. Based on the above characters formulation, A1 was selected as best formulation and press coated and enteric coated to find out the changes in the release rate of the theophylline from enteric coated tablets. The formulations F1, F2, F3, F4 and F7 showed maximum drug release after 12^{th}, 10^{th}, 5^{th}, 6^{th} and 9^{th} hr respectively. F6 and F8 showed maximum drug release after 7^{th} hr and F5 and F9 shoed after 8^{th} hr. Time dependent pulsatile drug delivery system has been achieved from tablet of formulation F8 with 99.50%, drug release which meet demand of chronotherapeautic drug delivery. The formulation F8 containing L-HPC (50 mg) and EC (150 mg) for press coating with 6 % w/v Eudragit L-100 was found to be optimum as enteric coating polymer.

Lag time (t^{10}) for enteric coated tablets

The dissolution profile of all 9 batches shows increase in the lag time with respect to their polymers. The aim 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 5-6 hours of administration. So the above batches showed increase in lag time from 173 ± 2.64 to 579 ± 4.04 min with respect to their composition coating level. Data are show shown in **Figure 3.**

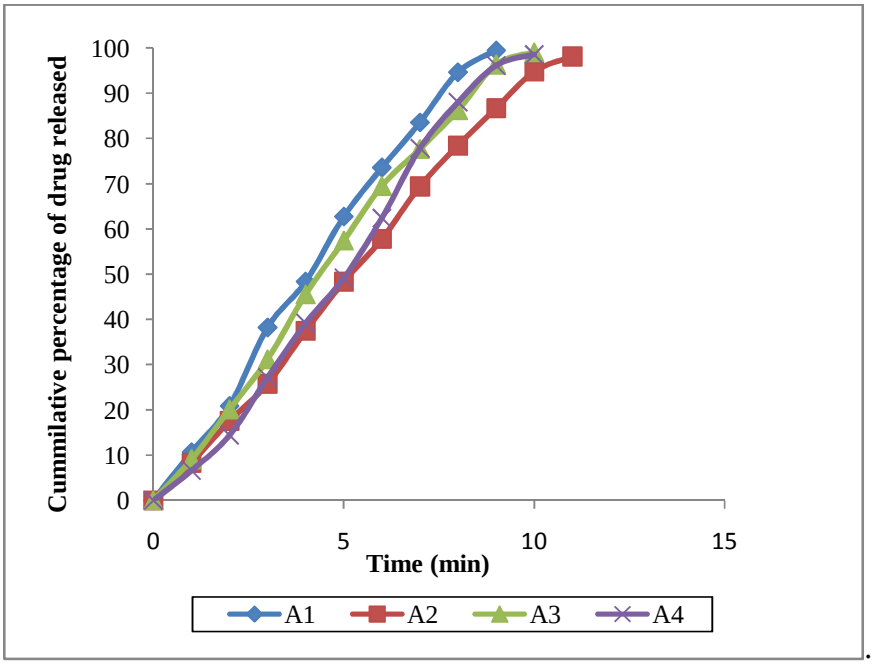

Fig 1. *In vitro* drug released form core tablets

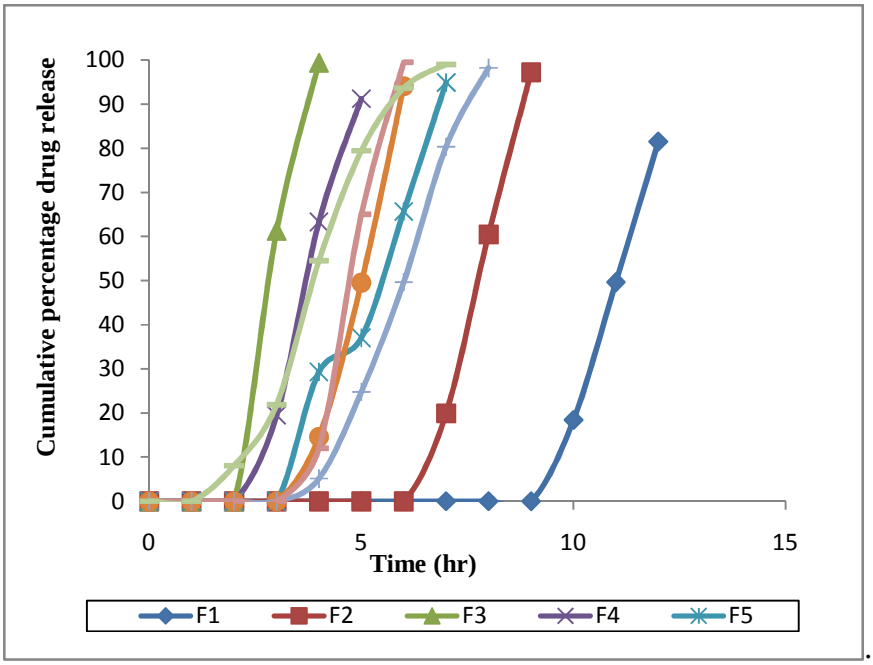

Fig 2. *In vitro* drug released form enteric coated tablets

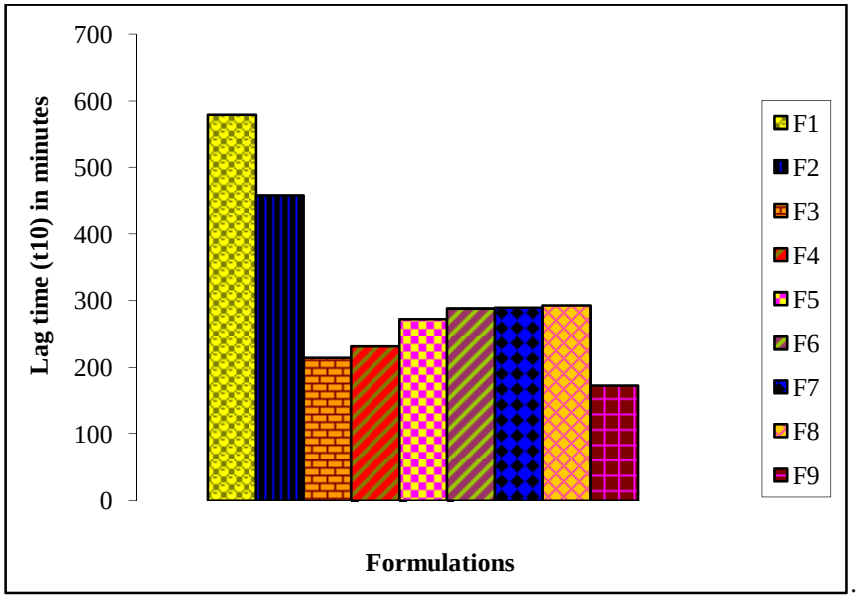

Fig 3. Lag time of enteric coated tablets

Stability studies

Stability studies of selected formulation F8 were performed at temperature of 30 ± 2ºC, 65 ± 5% RH and at 40 ± 2 ºC, 75 ± 5% RH for two months. The changes in the appearance, drug content and lag time of the stored tablets were investigated at the end of 1 and 2 month intervals. Stability studies revealed that there was no significant change in hardness, drug content and lag time of the all formulations. No color changes or an unexpected change in the texture was observed. The drug content was found to be in the range of 96.82 ± 0.44 mg to 98.94 ± 0.38 mg. The results of stability studies indicated that the formulations were physically and chemically stable during the test period. The data of stability study is shown in **Table 6**.

Table 6: Evaluation parameters of most satisfactory formulation F8 during stability studies

Time (Days)		Hardness (kg/cm^2)	Drug content (%)	Lag time (min)
0		6.84 ± 0.14	99.58 ± 0.12	293 ± 2.64
30	At 30 ± 2 °C, 65 ± 5% RH	6.5 ± 0.54	98.94 ± 0.38	291 ± 3.18
	At 40 ± 2 °C, 75 ± 5% RH	6.4 ± 0.26	98.07 ± 0.22	291 ± 4.82
60	At 30 ± 2 °C, 65 ± 5% RH	6.4 ± 0.24	97.35 ± 0.18	288 ± 1.92
	At 40 ±2 °C 75 ± 5% RH	6.3 ± 0.38	96.82 ± 0.44	286 ± 2.71

Mean ±SD, n = 3

CONCLUSION

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 theophylline, a bronchodilator for the treatment of asthma. To achieve this, theophylline core tablets were coated with composition of hydrophobic and hydrophilic polymers and were further coated with an enteric coating polymer (Eudragit L-100). This coat has enabled us to achieve definite non-release lag phase. The pulsatile ETP 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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