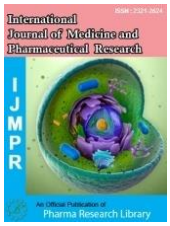

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Formulation and Evaluation of Chronomodulated Theophylline Pulsatile Capsule

Mohan Vikas P[1]*, Chandu Babu Rao[2]
*[1]Research Scholar Acharya Nagarjuna University, Guntur
[2]Pridarshini Institute of Pharmaceutical Sciences, Guntur

A B S T R A C T
Nocturnal asthma is a variable exacerbation of the underlying asthma condition associated with increases in symptoms, need for medication, airway responsiveness, and/or worsening of lung function. Theophylline medications exhibit a shorter T max and a greater C max when they are ingested in the evening (at time night) than morning. Indeed the bioavailability of theophylline preparation was found to show a threefold increase when dosed in the evening (at time night) as opposed to the morning. Administration time differences in drug kinetics occur in both children and adults. The exact mechanisms of the administration time dependent differences in theophylline kinetics are unknown. In accordance with the chronomodulated therapy of asthma, the lag time criterion of 5 hours was satisfied by tablet plug containing 16% of HPMC K100LV(Batch C5). The in-vivo lag time was 4 h. In-vitro lag time of 5.1 h could be due to less shear under in-vitro conditions, as compared to shear of peristalsis in the intestine.

Keywords: Theophylline, Chronomodulated, Asthma, Bioavailability

A R T I C L E I N F O

***Corresponding Author**
Mohan Vikas P
Research Scholar
Acharya Nagarjuna University,
Guntur, Andhra Pradesh

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Contents

1. Introduction

Nocturnal asthma

The worsening of asthma at night commonly referred to as nocturnal asthma (NA). Nocturnal asthma is a variable exacerbation of the underlying asthma condition associated with increases in symptoms, need for medication, airway responsiveness, and/or worsening of lung function. These changes are related to sleep and/or circadian events.[1] The mechanism of nocturnal asthma is intimately related to circadian rhythm which influences inflammatory cells and mediators, hormone levels and cholinergic tone. A brief overview of nocturnal asthma is shown in Figure[1]. There are many complex interactions that produce the nocturnal worsening of asthma. Not only does lung function decrease at night, but bronchial hyper reactivity increases from day to night. These changes have been related to the normally occurring circadian changes in cortisol levels at night. The decrement in cortisol may lead to down regulation of the β2 adrenergic receptors. In nocturnal asthma patients there appears to be significantly expressed genetic polymorphism (Gly16) that is linked to down regulation of the β2 receptors.[2,3,4]

Chronokinetics of theophylline

Chronokinetics refers to administration time (with reference to biological rhythms) differences in the absorption, distribution, metabolism, elimination, and even bioavailability of medications. Theophylline

medications exhibit a shorter T_{max} and a greater C_{max} when they are ingested in the evening (at time night) than morning. Indeed the bioavailability of theophylline preparation was found to show a threefold increase when dosed in the evening (at time night) as opposed to the morning (Fig 2). Administration time differences in drug kinetics occur in both children and adults. The exact mechanisms of the administration time dependent differences in theophylline kinetics are unknown.

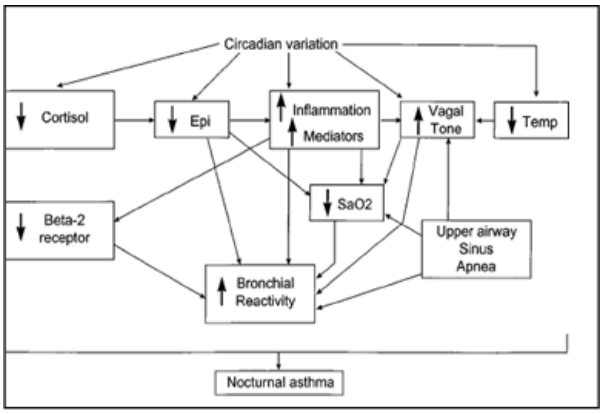

Figure No. 1: Potential mechanisms that contribute to the worsening of asthma at night. Epi = Epinephrine; temp = temperature

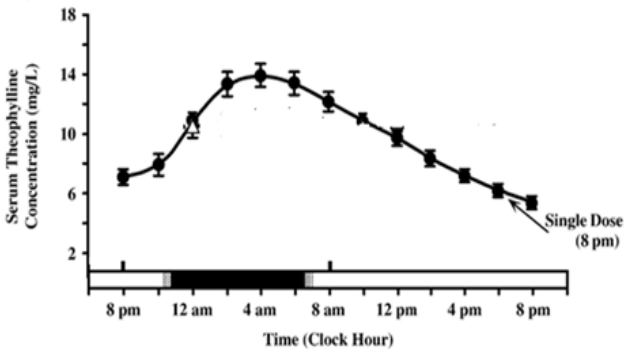

Figure No. 2: Pharmacokinetics of once a day evening preparations of theophylline

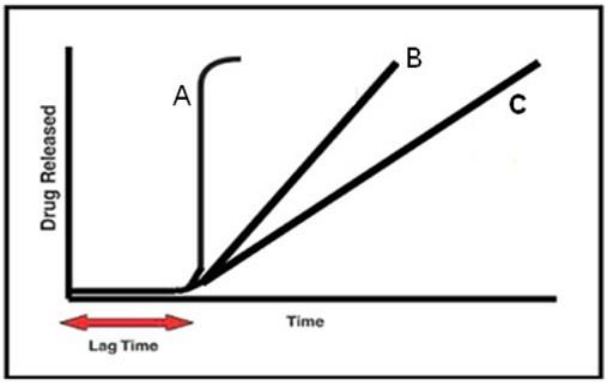

Figure No. 3: Drug release profile of pulsatile drug delivery system A: Ideal sigmoidal release after lag time, B & C: Delayed release after initial lag time

The oral controlled release system maintains the drug concentration in the therapeutic window for a prolonged period of time, thereby ensuring sustained therapeutic action. However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. Pulsed drug release (Fig 3) is defined as the rapid and transient release of a drug after a predetermined off release period.[5]

2. Methodology

Theophylline (100 mg) was dissolved in pH 1.2 buffer6 and volume was made up to 100 ml in volumetric flask. Ten ml of this solution was diluted to 100 ml with pH 1.2 buffer to get 100µg/ml stock solution. From this stock solution, aliquots of 2, 4, 6, 8, 10, 12, 14, 16 and 18 ml were pipetted out and made up to 100 ml in order to get concentration ranging from 2- 18µg/ml. The absorbance of the solution was measured at 271 nm (λmax of theophylline) by UV spectrophotometry.7, 8

Standard calibration curve of theophylline in phosphate buffer pH 6.8

Theophylline (100 mg) was dissolved in phosphate buffer8 pH 6.8 and volume was made up to 100 ml in volumetric flask. Ten ml of this solution was diluted to 100 ml with phosphate buffer pH 6.8 to get 100 µg/ml stock solution. From this stock solution, aliquots of 2, 4, 6, 8 and 10 ml were pipetted out and volume was made up to 100 ml in order to get concentration ranging from 2-10 µg/ml. The absorbance of the solution was measured at 272 nm (λ max of theophylline) by UV spectrophotometer. [9,10]

Theophylline (100 mg) was dissolved in water and volume was made up to 100 ml in volumetric flask. 25 ml of this solution was diluted to 50 ml with water to get 500 µg/ml stock solution. From this stock solution, aliquots of 0.5, 2.5, 5, 10 and 20 ml were pipetted out and volume was made up to 50 ml in order to get concentration ranging from 5 –250 µg/ml.

An internal standard (caffeine) stock solution was prepared in acetonitrile. Caffeine 50 mg was dissolved in acetonitrile and volume was made up to 50 ml in volumetric flask. 5 ml of this solution was diluted to 50 ml with acetonitrile to get 100 µg/ml stock solution. From this stock solution 2.5 ml was pipetted out and volume was made up to 50 ml in order to get 5 µg /ml (working internal standard solution).

Formulation of theophylline pulsatile capsule system

Formaldehyde (15% v/v in water) was taken into desiccators and pinch of potassium permanganate was added to it, to generate formalin vapors. The body and the cap of the hard gelatin capsules (size 0) were separated. The capsule bodies was placed on the wire mesh and exposed to formaldehyde vapors for six hours at room temperature, after which the capsules bodies were removed and dried at 50oC for 12 hours in hot air oven. Afterwards the capsule body and the untreated soluble cap were stored in desiccators for further use. In order to identify proper plug material, two different viscosity grades of polymer hydroxypropyl methylcellulose were evaluated. The erodible tablet plugs (150 mg) of pure material (HPMC K100LV and K4M) as well as polymer and spray dried

lactose ratio 1:1 were prepared by direct compression method and subjected to erosion studies. Based on these erosion studies HPMC K100LV was chosen for preparation of erodible tablet plug material.

Direct compression method was used to prepare the erodible tablet plug. The compositions of different erodible tablet plugs used were as shown in Table 2. The plug ingredients (HPMC and spray dried lactose) were mixed for 10 minutes. Magnesium stearate was added to the previous mixture and further blended for 5 minutes and compressed using single punch tablet machine. The diameter of the tablet plug was 7 mm. The tablets plugs were subjected to various evaluation tests such as hardness, friability and weight variation.

The impermeable capsule body was filled with drug and excipient mixture (Table 2). Theophylline (100 mg) and lactose, the filler (200 mg) was passed through a 100 mesh sieve, followed by hand filling of the mixture into the capsule bodies (Fill weight 300 mg). To investigate the influence of effervescent agent on drug release, lactose was partly replaced by 10 or 30 mg (batch A2 & A3; Table 4.1) mixture of sodium bicarbonate and citric acid (1:1 ratio) and subjected to dissolution studies. (Based on dissolution studies, 30 mg of effervescent blend was added in capsule contents). Pulsed release capsule device was assembled by filling the mixture of drug, filler and effervescent agent at the bottom of impermeable capsule body. Further an erodible HPMC K100LV/spray dried lactose tablet plug was inserted into the mouth of the impermeable capsule body to fit snuggly. Finally the soluble capsule cap was placed over the impermeable capsule body. The composition of different pulsatile capsule device is shown in Table 2.

Characterization of erodible tablet plug

Determination of erosion rate of the tablet plug

The time required for complete erosion of the tablet plug (plug weight 150 mg) was determined with a disintegration tester.

Weight variation test

To study weight variation 20 tablets were weighed separately using a Sartorius electronic balance and the test was performed according to the IP procedures.

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Hardness of core tablets was determined using a Monsanto type hardness tester. It is expressed in kg/cm2. The tablets were randomly picked from each batch and analyzed for hardness.

Friability test

Friability was evaluated as the percentage weight loss of 20 tablets tumbled in a friabilator for 100 revolutions. The tablets were then dedusted and the loss in weight caused by fracture or abrasion was recorded as the percentage friability. Friability was determined by following equation.

$$\text{Friability} = \frac{\text{Initial weight–Final weight}}{\text{Initial weight}} \times 100$$

Evaluation of pulsatile capsule device

Dissolution studies of pulsatile capsule device

The dissolution study of pulsatile capsule was carried out using USP I basket apparatus. The capsule was placed in the basket and the speed was adjusted at 50 rpm. The temperature was maintained at 37± 0.5 °C. First 900 ml of buffer pH 1.2 was used as dissolution medium up to 2 hours. There after the dissolution medium was replaced by phosphate buffer (pH 6.8) and the dissolution test was continued in the new medium**.** Aliquots of the dissolution medium were removed at 1 hr intervals and amount of theophylline released was estimated by spectrophotometer at a wavelength of 272 nm. The lag time (t_{10}) was defined as intersection point on the time axis when 10% of the drug contained was released.[5]

3. Results and Discussion

Drug excipient interaction studies

The DSC thermograms of theophylline and mixture of theophylline and excipients are shown in Figure 4 & 5.

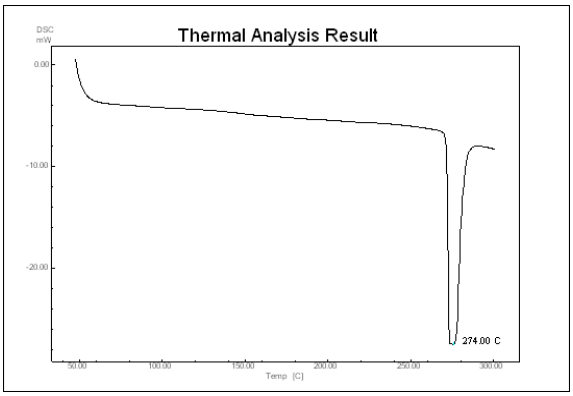

Figure No. 4: DSC thermogram of theophylline

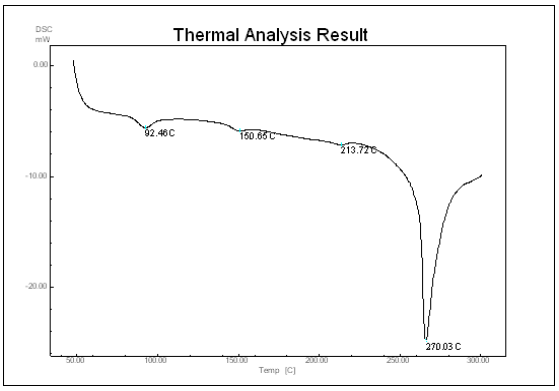

Figure No. 5: DSC thermogram of drug excipient mixture

The drug exhibited a sharp melting endotherm at 274oC (as per European Pharmacopoeia melting point range of theophylline is 270-274°C). No significant change in the melting endotherm of the drug in the mixture of theophylline and excipients was observed. From this it can be inferred that there exists no interaction between the drug and excipients.

The FTIR spectra of pure theophylline and its physical mixture with other excipients are shown in Figure 6 & 7.

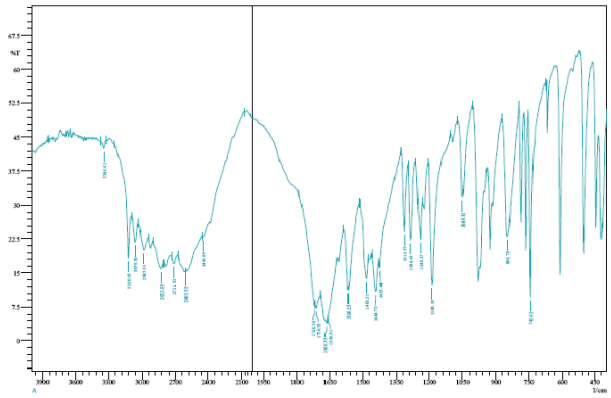

Figure No. 6: FTIR spectra of theophylline

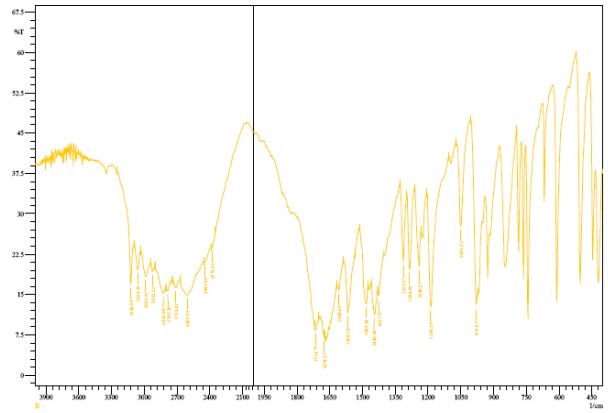

Figure No. 7: FTIR spectra of drug excipient mixture

Pure theophylline showed major peaks at 3335 cm-1 (OH stretch), 3057 cm–1 (aromatic CH stretch), 2974 cm–1 (methyl asymmetric stretch), 1608 & 1485 cm–1 (aromatic ring stretch), 1380 cm-1 (t-butyl symmetric bend), 1068 cm-1 (secondary alcohol stretch). The results revealed no considerable changes in the above mentioned IR peaks of theophylline in the drug excipient mixture when compared to pure drug, thereby indicating the absence of any interaction.

Gelatin is readily soluble in biological fluids at body temperature. Formalin treatment has been employed to modify the solubility of the gelatin capsules. Exposure of formalin vapors' results in decrease in solubility of gelatin which due to the cross linkage of the amino groups in the gelatin molecular chain with aldehyde groups of formaldehyde by Schiff's base condensation.

The treated capsules were subjected to disintegration test. The results revealed that all the six capsule caps disintegrated and solubilized within 25 minutes in the disintegration test of empty capsules, while the formaldehyde treated body of the capsule remained intact for more than 10 h. Thus drug will be released from a limited surface area of open end of the hard gelatin capsule body, which indicates the suitability for pulsed release dosage form.

The results of the physicochemical characterization of various erodible tablet plugs are shown in Table 4.

Effect of Capsule Content on Drug Release

The results of the effect of addition of effervescent agents to the capsule contents are shown in Figure 8

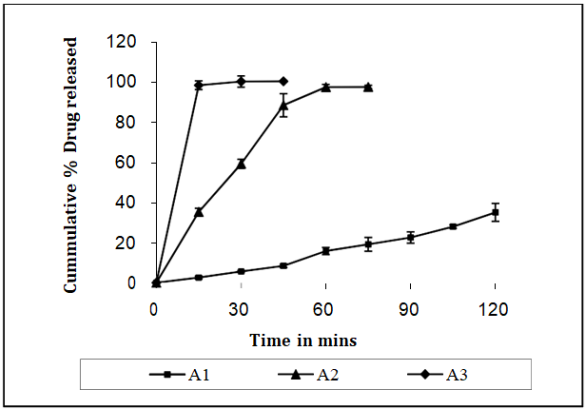

Figure No. 8: Effect of effervescent agent on drug release from capsules without tablet plug.

To achieve pulsatile release, the drug should be released rapidly once the capsule contents are exposed to the medium. Addition of 30 mg effervescent agents to capsule contents (batch A3) resulted in complete drug release within 10 min. The drug released increased with increasing concentration of effervescent agents. The results concluded that extent of lag time prior to the drug release is primarily controlled by the rate of erosion of tablet plug; the subsequent drug release phase will be determined by the composition of capsule content. Therefore in all further studies 30 mg of effervescent agents was added to capsule contents.

Selection of proper erodible tablet plug material /erosion properties of tablet plug material. The results of the erosion profiles of different erodible tablet plug material are shown in Table 4.3 and Figure 9.

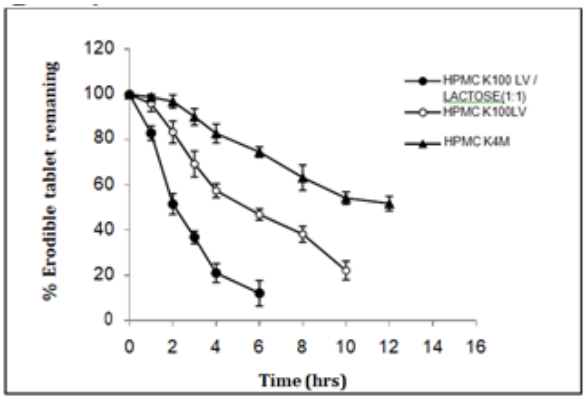

Figure No. 9: Erosion properties of different tablet plug material

In order to identify proper plug material, two different viscosity grades of polymer hydroxypropyl methylcellulose (HPMC K100LV and K4M) were evaluated. Depending on the viscosity of HPMC, the polymer matrix degrades at different rates by erosion/dissolution of the polymer. To control and to increase the erosion rate, water soluble filler

lactose was added to the hydrophilic tablet plug. The higher viscosity grade HPMC K4M swelled28, but eroded too slowly to be suitable choice for pulsatile system. The low viscosity grade (K100LV) did not form stronger gel29 and eroded faster as compared to higher viscosity grade. Considering the fact that exposed area (erosion area) of the tablet plug positioned within the capsule body is limited to one side than the surface area of free plugs in disintegration test, therefore low viscosity grade HPMC K100LV was selected for further study.

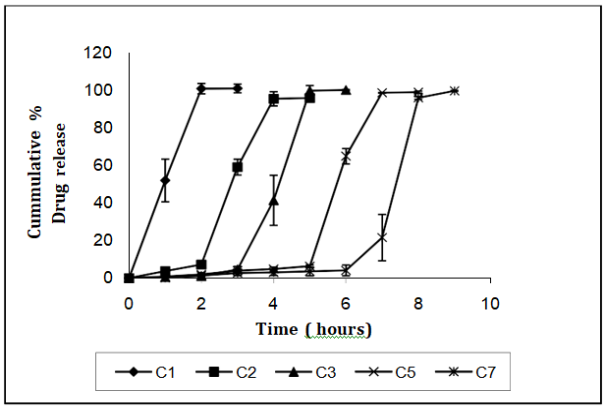

Figure No. 10: In-vitro release profiles of various pulsatile capsule devices

After evaluating the plug material and the capsule content separately, the complete pulsatile drug delivery system was investigated next. It consisted of formaldehyde treated capsule body containing theophylline, lactose the filler mixed with 30 mg of effervescent agents and erodible tablet plug having different composition.

The release profiles revealed pulsatile characteristics. The lag time (t10) for the formulations C1, C2, C3, C5 and C7 was 0.2 h, 2 h, 3.2 h, 5.1 h and 6.35 h respectively (fig 4.9). Increasing the concentration of HPMC K100LV in tablet plug resulted in increase in lag time. In accordance with the chronomodulated therapy of asthma, the lag time criterion of 5 hours was satisfied by formulation C5 (containing 16% of HPMC K100LV). The results of the effect of erodible tablet weight on lag time is shown in Figure 11

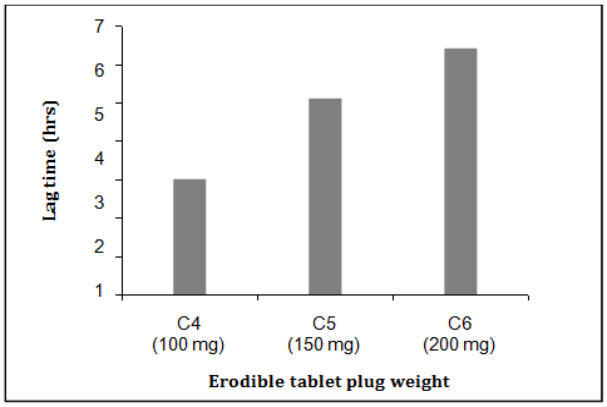

Figure No 11: Influence of tablet plug weight on lag time

Maintaining the same composition of erodible tablet, plugs of different weights such as 100, 150 and 200 mg (batch C4, C5 & C6) were evaluated for lag time. A good correlation was observed between them. Increasing tablet plug weight seemed to prolong lag time since the time required to complete the dissolution or erosion of the tablet plug would be longer. This suggested that the lag time could also be adjusted by changing the plug weight.

Table 1: Materials used in the present investigation

Materials	Procured
Theophylline	Cipla Ltd Mumbai
Eudragit L	Cipla Ltd Mumbai
Starch1500	Cipla Ltd Mumbai
HPMC K100LV	Coloron Asia Ltd, Goa
HPMC K4M	Coloron Asia Ltd, Goa
Ethyl cellulose (Ethocel 10)	Coloron Asia Ltd, Goa
Ethyl cellulose (Ethocel 45)	Coloron Asia Ltd, Goa
Ethyl cellulose (Ethocel 100)	Coloron Asia Ltd, Goa
Hydroxy propyl cellulose-L (HPC-L)	Coloron Asia Ltd, Goa

Table 2 : Composition of different pulsatile capsule device

Batch code	Capsule fill composition (capsule contents)				% Composition of different Erodible tablet plug			
	Wt of drug (mg)	Lactose (mg)	Amount of effervescent blend (mg)	Totalfill Wt (mg)	HPMC K100LV(%)	Spray dried Lactose (%)	Mg. stearate (%)	weightof tablet plug (mg)
A1	100	200	-	300	-	-	-	-
A2	100	190	10	300	-	-	-	-
A3	100	170	30	300	-	-	-	-
C1	100	170	30	300	4	95	1	150
C2	100	170	30	300	8	91	1	150
C3	100	170	30	300	12	87	1	150

C4	100	170	30	300	16	83	1	100
C5	100	170	30	300	16	83	1	150
C6	100	170	30	300	16	83	1	200
C7	100	170	30	300	20	79	1	150

Table 3: HPLC conditions for plasma samples	
Column	Luna C_{18} (ODS) column (4.6 × 250mm, 5µm).
Internal standard used	Caffeine
Mobile phase	Methanol and Water (30:70, v/v)
Flow rate	1.2 ml/ min.
An UV detector set at	271 nm.

Table 3: Calibration data of theophylline in pH 1.2 buffer		
Sr. No.	**Concentration (µg / ml)**	**Average Absorbance at 271 nm**
1	2	0.114
2	4	0.232
3	6	0.312
4	8	0.422
5	10	0.531
6	12	0.625
7	14	0.719
8	16	0.833
9	18	0.937

Table 4: Physicochemical characterization of various erodible tablet plugs			
Batch code	Hardness Kg/cm^2	Friability (%)	Weight variation (%)
C1	4.1±0.28	0.82	± 2.3
C2	5.0±0.5	0.76	± 1.1
C3	5.2±0.76	0.53	± 3.0
C5	5.1±0.5	0.19	± 2.0
C7	4.8±0.76	0.14	± 1.5

Table 5: Erosion profiles of different erodible tablet plug material

Time(hrs)	**% Erodible tablet remaining**		
	HPMC K100 LV / LACTOSE(1:1)	**HPMC K100LV**	**HPMC K4M**
0	100	100	100
1	82.93	95.97	98.87
2	51.51	83.35	96.92
3	36.69	69.24	90.15
4	20.97	57.49	82.73
5	11.80	46.82	74.51
6		38.17	63.20
8		22.04	54.13
10			51.74
12			

Table 6: In-vitro release study of various pulsatile capsule device							
Time (Hours)	**Cumulative % drug release**						
	Batch code						
	C1	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**
1	52.15	3.71	0.5	0.25	0.79	0.20	0.3

2	101.17	7.23	1.08	3.68	1.96	2.25	1.37
3	101.29	59.28	4.64	5.12	3.91	3.58	2.68
4		95.74	41.53	37.39	4.83	4.64	3.05
5		96.12	100.07	96.81	6.40	5.93	3.58
6			100.43	97.04	65.12	7.34	4.12
7					98.96	15.62	21.67
8					99.32	79.45	96.24
9						99.02	99.96
10						100.57	

4. Conclusion

In accordance with the chronomodulated therapy of asthma, the lag time criterion of 5 hours was satisfied by tablet plug containing 16% of HPMC K100LV(Batch C5). The in-vivo lag time was 4 h. In-vitro lag time of 5.1 h could be due to less shear under in-vitro conditions, as compared to shear of peristalsis in the intestine.

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