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Formulation and Evaluation of Timed Delayed Capsule Device for Chronotherapeutic Delivery of Terbutaline Sulphate

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ABSTRACT

The aim of the present study was to develop timed delayed capsule device of terbutaline sulphate intended for chronotherapy. A time delayed capsule was prepared by sealing the drug tablet and the expulsion excipient inside the insoluble hard gelatin capsule body with erodible tablet plug. The erodible tablets were prepared by direct compression. Influence of formulation factors such as type of plug material, different plug composition, erodible tablet weight and hardness was investigated to characterize the lag time (t_{10}). The results indicated that drug release from the time delayed capsule exhibited an initial lag period, followed by a stage of rapid drug release. Erodible tablet plugs prepared using higher molecular weight of polyethylene oxide resulted in longer lag times. A good correlation was observed between erodible tablet weight and lag time. In accordance with the chronomodulated therapy of asthma the lag time criterion of 5hrs was satisfied by formulation containing 90mg of WSR N-10 (low molecular weight polyethylene oxide) in the erodible tablet plug.

KEYWORDS: chronotherapy, delayed released, lag time

INTRODUCTION

A time delayed release profile is characterized by a lag time followed by rapid and complete drug release[1].Several approaches to delay drug release exists. Some systems contain a drug reservoir, surrounded by a barrier which either erodes or dissolves[2,3] or ruptures[4,5]. With eroding or dissolving systems, a potential problem is the retardation and therefore not immediate drug release after the loss of the barrier function or a premature release seen in particular with highly water soluble drugs. Capsular-shaped systems are more independent from the nature of the content[6] and system consists of an insoluble capsule body with swellable[7] or erodible tablet plugs[8] have been reported.

Based on chronopharmacology, many common clinical diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer and hypertension display significant circadian variation in onset or exacerbation of symptoms[9,10]. A review of the chronobiology of asthma highlighted that airway resistance, bronchoconstriction, exacerbation of symptoms and worsening of lung function, increase progressively at night. It has been reported that risk of asthma attacks is l00 fold greater during the night time hours (around 2.00 am) than during other times of day, an observation which has nicely been confirmed in modern epidemiologic studies in asthmatic patient[11,12].

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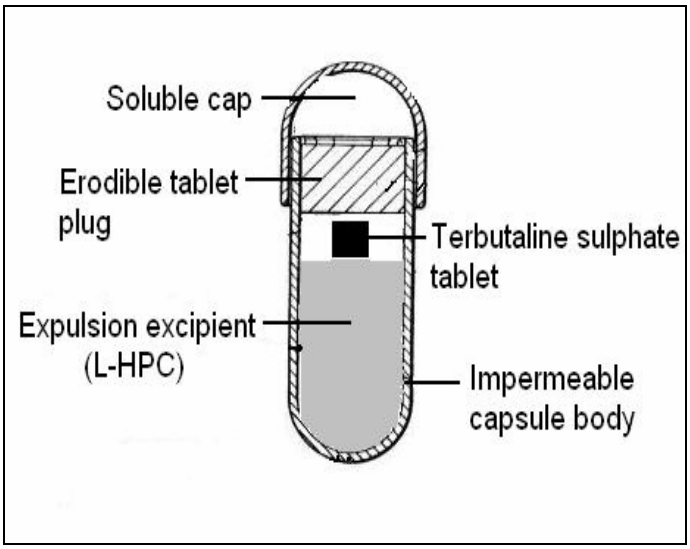
Terbutaline sulphate, a potent β2 receptor stimulant and has been effective for preventing time related occurrence of asthma[13].In the light of the chronobiologic and chronopathologic findings, this study attempts to design and evaluate time delayed capsule of terbutaline sulphate, consisting of insoluble hard gelatin capsule body, which contains the drug tablet and is closed by an erodible tablet plug (Figure 1). It was aimed to have a lag time of five hours i.e., the system is taken at bed time and expected to release the drug after a period of 5h (around 2.00 am) when the asthma attacks are more prevalent. The lag time (t_{10}) was defined as intersection point on the time axis when 10% of the drug contained was released. Effect of various formulations parameters such as type of plug material, different plug composition, plug weight and plug hardness was investigated to characterize the lag time.

Figure 1: Assembly of timed delayed capsule device



MATERIALS AND METHODS

Materials

Terbutaline sulphate was obtained as gift sample from Sehat Pharma Ltd, Himatnagar. Three different molecular weights of polyethylene oxide (PEO) WSR N-10(MW 100,000), PEO WSR N-80(MW 200,000), and PEO WSR N-750 (MW 300,000) were obtained as gift sample from Coloron Asia Ltd. Avicel (microcrystalline cellulose pH102) and spray dried lactose were obtained as gift sample from Cipla Ltd, Mumbai. Low substituted hydroxypropylcellulose (HPC-L) was obtained as gift sample from Nippon Soda Japan. Sodium starch glycolate (SSG), magnesium stearate, and talc were purchased from S. D. Fine chemicals Ltd. Mumbai. All other chemicals were laboratory grade.

Methods

Drug excipient compatibility studies

Infrared spectra were taken by using KBr pellet technique using a Shimadzu FTIR 8300 Spectrophotometer (Shimadzu, Tokyo, Japan) in the wavelength region of 4000 to 400 cm−1. The procedure consisted of dispersing a sample (pure drug or mixture of drug and excipients or only excipients) in KBr and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained.

Preparation of impermeable/insoluble capsule body

The body and the cap of the hard gelatin capsules (size 0) were separated. Capsule bodies was exposed to formaldehyde vapors for six hours at room temperature and dried at 50 ^{o}C for 12 hours in

hot air oven[14]. Afterwards the capsule body and the untreated soluble cap were stored in desiccators for further use. The efficacy of the treated capsules was checked by a disintegration (Model Electrolab-ED2, Mumbai) test[15].

Preparation of terbutaline sulphate tablets

Terbutaline sulphate tablets (5mg/tablet) were prepared by direct compression method having the following composition: Terbutaline sulphate 6.25%, Avicel 88.75%, SSG 2%, talc 1%, and magnesium stearate 2%. All the ingredients except magnesium stearate were dry blended for 10 min. Magnesium stearate was added and then further blended for additional 5 minutes. The resultant mixture was tableted to 80mg using 5mm flat-faced punches using a rotary tablet machine (Cadmach Machinery, India). The tablets were evaluated for the different physicochemical parameters such as hardness, friability, weight variation, drug content and disintegration time.

Preparation of erodible tablet plug

Direct compression method was used to prepare the erodible tablet plug. The compositions of different the erodible tablet plugs used were as shown in Table 1. The plug ingredients (PEO and spray dried lactose) were mixed for 10 minutes. Magnesium stearate (1%) was added to the previous mixture and further blended for 5 minutes and compressed using single punch tablet machine. (Cadmach, Machines Ltd Ahmedabad, India).The diameter of the tablet plug was 7mm and the weight was varied between 110-190mg.

Table 1: Composition of different erodible tablet plugs

Batch code	WSR N10	WSR N80	WSR N750	Lactose	Magnesium stearate	Total weight
A1	30	-	-	118.5	1.5	150
A2	-	30	-	118.5	1.5	150
A3	-	-	30	118.5	1.5	150
A4	-	25.5	-	123	1.5	150
A5	-	-	25.5	123	1.5	150
A6	45	-	-	103.5	1.5	150
A7	60	-	-	88.5	1.5	150
A8	75	-	-	73.5	1.5	150
A9	90	-	-	58.5	1.5	150
A10	105	-	-	43.5	1.5	150

Note: All the quantities expressed in milligrams.

Time delayed capsule assembly

Assembly of delayed release capsule device proceeded as follows (Figure 1); L-HPC (150 mg) was weighed into the bottom of impermeable capsule body and lightly compacted. Terbutaline sulphate tablet was placed onto the compacted L-HPC layer. An erodible tablet plug was inserted into the mouth of the capsule so that upper surface of the erodible tablet flushed with the open end of the

capsule body. The erodible tablet plug fitted snuggly with the wall of the capsule. Finally the soluble capsule cap was placed over the impermeable capsule body.

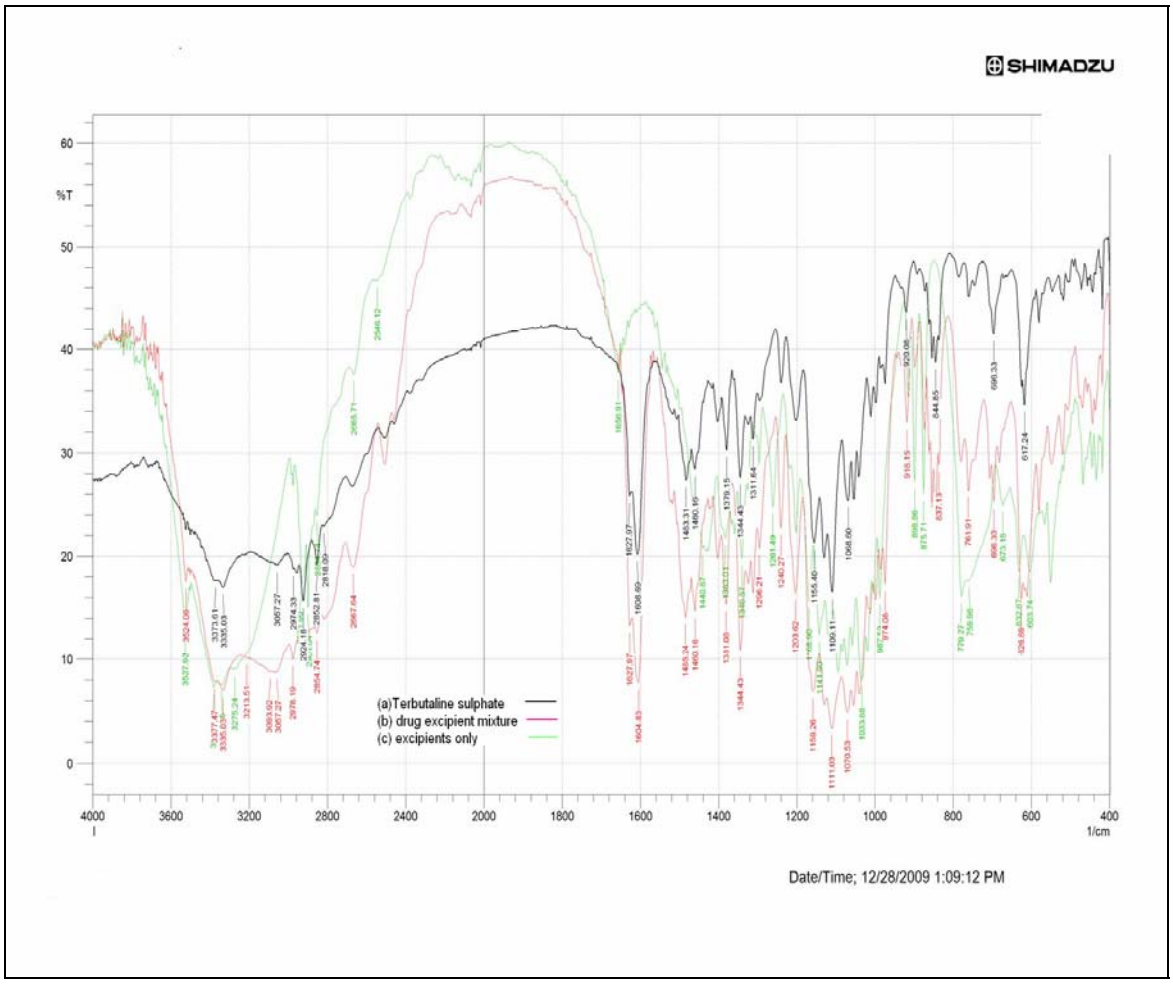
Dissolution studies of time delayed capsule device

The dissolution study of time delayed capsule was carried out using USP Type II apparatus (model VDA-6D, Veego Ltd Mumbai) at 37 ± 0.5 ^{o}C and paddle speed of 50rpm. First 900ml 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 different time intervals and amount of terbutaline sulphate released was estimated by spectrophotometrically[16]. Each dissolution data point represents the mean of at least three individual trials in Figures 3-6.

RESULTS AND DISCUSSION

Drug excipient interaction studies

Figure 2: (a) Terbutaline sulphate alone. (b) Drug–excipient mixture. **(c)** Excipient mixture alone



The FTIR spectra of pure terbutaline sulphate and its physical mixture with other excipients and only excipient are shown in Figure 2. Pure terbutaline sulphate showed major peaks at 3335cm^{-1}(OH stretch), 3057cm^{-1}(aromatic CH stretch), 2974cm^{-1}(methyl asymmetric stretch), 1608&1485cm^{-1}(aromatic ring stretch), 1380(t-butyl symmetric bend), 1068cm^{-1}(secondary alcohol stretch. The results revealed no considerable changes in the IR peak of terbutaline sulphate in the prepared formulation when compared to pure drug, thereby indicating the absence of any interaction.

Physicochemical Characterization of terbutaline sulphate tablets

Terbutaline sulphate tablets were prepared by direct compression method. For direct compression of materials, it is required to possess good flow and compacting properties. Therefore tablet powder blend was studied for angle of repose, Carr's index and Hausner ratio. Values for angle of repose 20–30° generally indicate good flow property. A Hausner ratio of less than 1.25 and Carr's index of 12–16 indicate good flow. The angle of repose, Carr's index and Hausner ratio was found to be 27.64±0.8°, 15.55±1.2%, and 1.18 ±0.01 respectively. The average weight of the tablets was 80±4mg. Hardness, friability, drug content and disintegration time of terbutaline sulphate tablets was 3.50±0.19 kg/cm^2, 0.65%, 98.4±3.3% and 2minutes respectively.

Formaldehyde treatment of hard gelatin capsule

Gelatin is readily soluble in biological fluids at body temperature. Formaldehyde and heat treatment was employed to modify the solubility of the hard gelatin capsule. 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 tests of empty capsules, while the formaldehyde treated body of the capsule remained intact for more than 12 hrs. Thus drug will be released from a limited surface area of open end of the hard gelatin capsule body, which indicates the suitability for timed delayed released dosage form.

Physicochemical Characterization of erodible tablet plug

Different erodible tablet plugs were also prepared by direct compression method. The results of micromeritic properties are presented in Table 2.Tablet plugs were studied for hardness, friability and weight variation. The average weight of the tablet plugs was found to be 150±3.5mg respectively. The friability of all the tablets was below 1%.

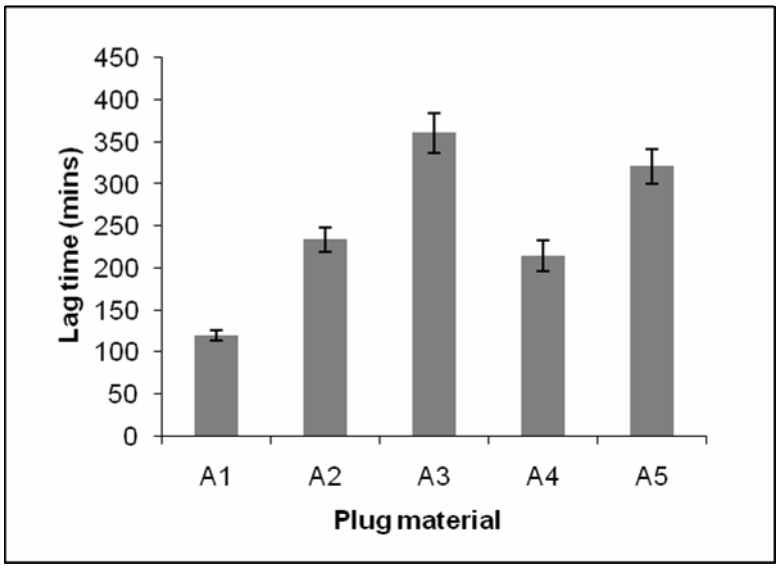
Table 2: Physicochemical characterization and micromeritics properties of various erodible tablet plugs

Batch code	Angle of repose	Carr's index	Hausner ratio	Hardness Kg/cm^2	Friability (%)	Weight variation (%)
A1	20.05±1.3	12.50±0.25	1.14±0.010	4.1±0.28	0.82	± 2.3
A2	23.64±1.7	11.11±1.06	1.12±0.015	5.0±0.5	0.76	± 1.1
A3	24.03±1.4	14.70±0.32	1.17±0.020	5.6±0.76	0.53	± 3.0
A4	22.96±0.6	12.72±1.2	1.14±0.005	4.8±0.5	0.22	± 2.2
A5	25.43±0.8	13.55±0.51	1.15±0.015	5.1±0.5	0.19	± 2.0
A6	17.34±1.5	15.06±0.9	1.17±0.005	4.8±0.76	0.14	± 1.5
A7	21.21±1.2	15.6±0.23	1.21±0.036	5.0±0.5	0.21	± 3.5
A8	19.30±1.6	14.80±1.03	1.18±0.020	5.3±0.28	0.34	± 2.7
A9	23.35±1.3	16.28±0.73	1.20±0.025	5.6±0.28	0.27	± 2.5
A10	24.46±0.4	17.18±0.53	1.22±0.010	5.8±0.5	0.39	± 3.0

Effect of different tablet plug material on lag time

In order to identify proper plug material, the lag times of delayed release capsule with different erodible tablet plug materials were investigated. The water soluble polymer polyethylene oxide appeared attractive as erodible plug materials because of their frequent use in hydrophilic matrix tablets. Three different molecular weights of polyethylene oxide(PEO), (WSR N-10, WSR N-80, and WSR N-750) were evaluated. The results are shown in Figure 3. When comparing three different molecular weight of PEO within this study it was found that capsules prepared using higher molecular weight polyethylene oxide resulted in longer lag times. Depending on the molecular weight of PEO, the polymer matrix degrades at different rates by erosion/dissolution of the polymer[17]. Further the system with PEO WSR N-10 was less sensitive to the amount of PEO in the erodible plug, which might be important from a manufacturing point of view. This could be very advantageous, because a deviation of the amount of PEO in the plug would result in only relatively small changes in lag time and consequently reproducible drug release profiles, with rapid and complete drug release. Therefore WSR N-10 was selected for further study as a plug material for the preparation of the erodible tablet plug.

Figure 3: Effect of different tablet plug material on lag time of timed delayed capsule device

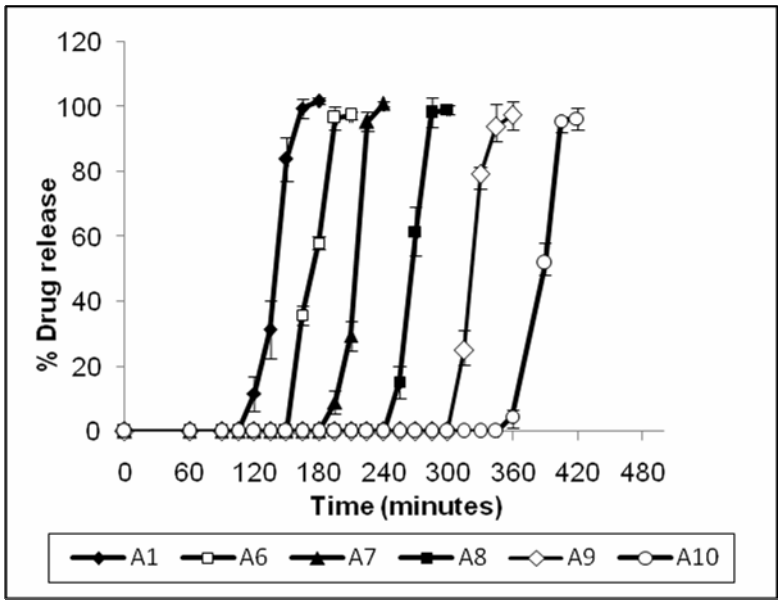


Effect of WSR N-10 content in erodible tablet plug

Dissolution profiles of timed delayed capsule device containing different content of WSR N-10 in the erodible tablets are shown in Figure 4.The lag time (t_{10}) for the formulations A1, A6, A7, A8, A9 and A10 was 120mins, 153mins, 195mins, 252mins, 307mins and 351mins respectively. The release profiles revealed time delayed released characteristics. Increasing the concentration of PEO WSR N-10 in tablet plug resulted in increase in lag time.

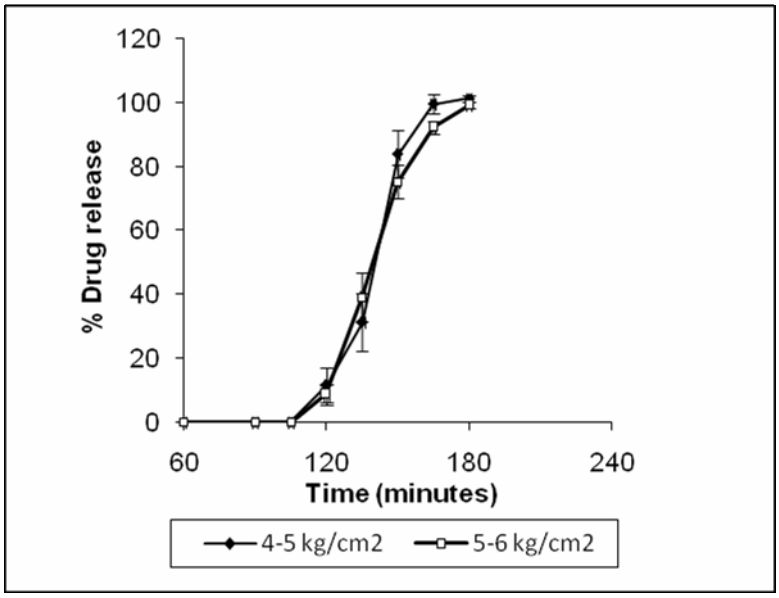
Visual observation during the dissolution process revealed the detachment of gelled plumes from the erodible tablet surface. Eventually, at a point at which only the smallest of gel layers remained, water ingress then followed leading to expansion of the expulsion excipient (L-HPC) and pushes the terbutaline sulphate tablet towards the open end of the hard gelatin capsule body. L-HPC has previously been shown to have excellent expansion potential for application such as pulsatile capsule device[18] and enables complete drug expulsion from Pulsincap formulation[19] and was successfully employed as an expulsion system in these studies. In accordance with the chronomodulated therapy of asthma, the lag time criterion of 5 hours was satisfied by formulation A11.

Figure 4: Effect of WSR N-10 content in the erodible tablet plug on drug release of timed delayed capsule device



Effect of tablet plug hardness on drug release

Figure 5: Effect of tablet plug hardness on drug release (Batch A1)



To study the effect of tablet hardness on drug release, erodible tablet hardness (Batch A1) varied between 4-6 kg/cm^2.The results are shown in Figure 5. The similarity factor (f_2) was used to evaluate the drug release.

$$f_2 = 50 \times \mathrm{Log}\{[1 \frac{1}{n}\sum_{j=1}^{n} W_j \ |R_j - T_j|^2]^{-0.5} \times 100\}$$

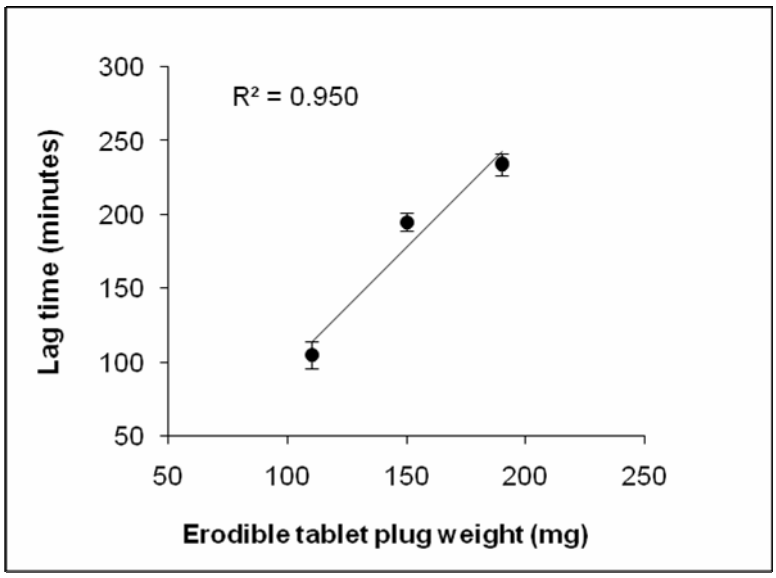
Where R_j and T_j are the average percentage of drug released from the three test tablets and three reference tablets at each point time j and n are the number of time points tested. Two curves are thought to be statistically similar if the f_2 value was above 50. The similarity factor of dissolution curve for different tablet hardness was 68.04. The results concluded that tablet hardness within the

range of 4-6kg/cm^2 did not significantly influence the drug release.

Effect of erodible tablet plug weight on lag time

Maintaining the same composition of erodible tablet (Batch A7), plugs of different weights such as 110, 150 and 190mg were evaluated for lag time. The relationship between plug weight and lag time is shown in Figure 6. A good correlation was observed between them (r^2=0.950). 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**.**

Figure 6: Influence of the Erodible Plug Weight on the Lag Time (Batch A7)



CONCLUSION

A timed delayed capsule device for chronotherapeutic delivery of terbutaline sulphate was successfully developed. In accordance with the chronomodulated therapy of asthma, the lag time criterion of 5 hours was satisfied by formulation A11. The dosage form can be taken at bed time and will release the contents in the early morning hours when asthma attacks are more prevalent.

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