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Short Communication

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Pulsatile Drug Delivery for the Treatment of Nocturnal Asthma: a Chronopharmaceutical Approach

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SUMMARY. **The objective of the present study was to develop and evaluate a pulsatile system of theophylline based on chronopharmaceutical considerations. The basic design consists of an impermeable capsule body, which contains the drug and is closed by an erodible tablet plug. The body portion of the hard gelatin capsules was cross-linked by the combined effect of formaldehyde and heat treatment. The formulation variables such as type of plug material, capsule content, different plug composition, plug weight and plug hardness was investigated to characterize the lag time (t10).The results indicated that drug release from the pulsatile capsule exhibited an initial lag period, followed by a stage of rapid drug release. For the complete and rapid drug release from the capsule body, 15% of effervescent agent had to be included in the capsule content. The lag time criterion of 5 hrs was satisfied by the tablet plug containing 16%HPMC K100LV. A good correlation was observed between erodible tablet weight and lag time.**

INTRODUCTION

Recently pulsatile systems are gaining a lot of interest and attention, as they deliver the drug at the right site of action at right time and in right amount, thus providing spatial and temporal delivery and increasing patient compliance. A pulsatile release profile is characterized by a lag time followed by rapid and complete drug release, which is useful for the treatment of certain diseases which exhibit circadian rhythm such as asthma, gastric ulcer, hypertension, ischemic heart disease and arthritis [1,2]. For this purpose, several technologies have been described which include pulsatile implants [3], pulsatile microspheres [4], time clock system [5], osmotic systems [6], compression coated tablets [7] and floating pulsatile beads systems [8].

A review of the chronobiology of asthma highlighted that airway resistance, bronchoconstriction, exacerbation of symptoms and worsening of lung function, increase progressively at night [9,10]. It has been reported that risk of asthma attacks is l00 fold greater during the night time h (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].

In the light of the chronobiologic and chronopathologic findings, this study attempts to design and evaluate chronomodulated pulsatile drug delivery system consisting of impermeable capsule body, which contains the drug and is closed by an erodible tablet plug. It was aimed to have a lag time of five h i.e., the system is taken at bed time and expected to release the drug after a period of 5 h (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, capsule content (effervescent agent), different plug composition, plug weight and plug hardness was investigated to characterize the lag time.

KEY WORDS: Chronotherapy, Lag time, Pulsatile capsule.

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MATERIALS AND METHODS

Materials

Theophylline was obtained as gift sample from Cipla Ltd, Mumbai. Two viscosity grades of Hydroxypropylmethylcellulose, HPMC K100LV and HPMC K4M cps were obtained as gift sample from Coloron Asia Ltd. Lactose, magnesium stearate, sodium bicarbonate and citric acid were purchased from S. D. Fine chemicals Ltd. Mumbai. All other chemicals were laboratory grade.

Preparation of impermeable 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 h at room temperature and dried at 50 °C for 12 h in hot air oven. 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 disintegration (Model Electrolab-ED2, Mumbai) test [13].

Filling of capsule bodies

The impermeable capsule body was filled with drug and excipient mixture. 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 5 or 15% of a mixture of sodium bicarbonate and citric acid (1:1 ratio).

Preparation of erodible tablet plug

Direct compression method was used to prepare the erodible tablet plug. The formulations containing 4, 8, 12, 16, 20 and 50% HPMC K100LV were prepared by weighing 4, 8, 12, 16, 20 and 50 g of HPMC K100LV and adding lactose to 99 g. Each formulation was mixed for 10 min, followed by addition of 1 gm of magnesium stearate to each blend. The resultant blends were mixed for 5 min and directly compressed into tablets using single punch tablet machine. (Cadmach Machines Ltd Ahmedabad, India) The diameter of the tablet plug was 8 mm and the weight and hardness (Monsanto hardness tester) were varied between 100-200mg and 5-7 kg/cm^2.

Determination of erosion rate

The time required for complete erosion of the tablet plug (plug weight 150 mg) was determined with a disintegration tester.(900ml pH 1.2 buffer for 2 h, thereafter pH 6.8 phosphate buffer, 37 °C,(n = 3)

Pulsatile capsule assembly

Assembly of pulsed release capsule device proceeded as follows (Fig. 1), drug and filler mixed with 15% of effervescent agent was filled at the bottom of impermeable capsule body. An erodible HPMC K100LV/lactose 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.

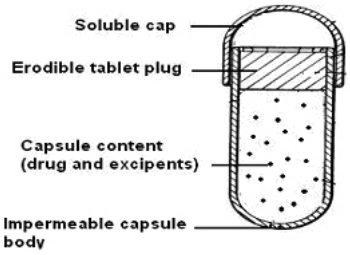

Figure 1. Assembly of pulsed release capsule device.

Dissolution studies of pulsatile capsule device

The dissolution study of pulsatile capsule was carried out using USP I basket apparatus, model VDA-6D (Veego Ltd). 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 h. 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 h intervals and amount of theophylline released was estimated by spectrophotometer (Shimadzu UV1700 pharmaspec) at a wavelength of 272 nm. Each dissolution data point represents the mean of at least three individual trials in Figures 2-5.

RESULT AND DISCUSSION

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 [14,15]. The treated cap-

sules were subjected to disintegration test. The results revealed that all the six capsule caps disintegrated and solubilized within 25 min in the disintegration tests of empty capsules, while the formaldehyde treated body of the capsule remained intact for more than 12 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.

Effect of capsule content on drug release

To achieve pulsatile release, the drug should be released rapidly once the capsule contents are exposed to the medium. The effect of addition of effervescent agents to the capsule contents is shown in Figure 2. The addition of 15% effervescent agents resulted in complete drug release within 10min. 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.

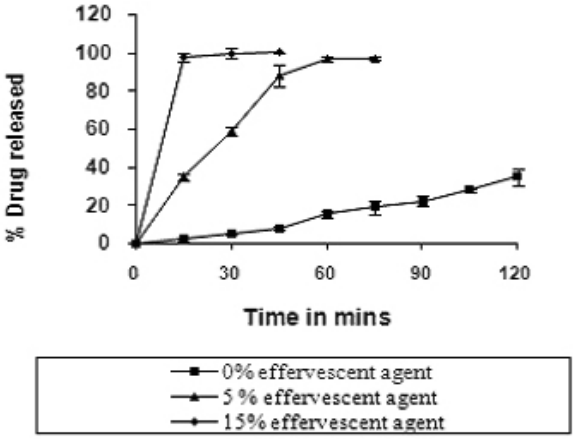

Figure 2. Effect of effervescent agent on drug release from capsules without tablet plug.

Effect of different plug composition on drug release

In order to identify proper plug material, two different viscosity grades of HPMC (K100LV and K4M) were evaluated. To control and to increase the erosion rate, water soluble filler lactose was added to the hydrophilic tablet plug. The time required for complete erosion of HPMC K4M: lactose (1:1) tablet plug was more than 8 hrs and for HPMC K100LV: lactose (1:1) was in between 3.5 to 4 h. The higher viscosity grade HPMC K4M swelled, but eroded too slowly to be suitable choice for pulsatile system. The low viscosity grade (K100LV) did not form stronger gel 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.

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 15% of effervescent agents and erodible tablet plug having different composition. The effect of different plug composition on theophylline release is shown in Figure 3. The release profiles revealed pulsatile characteristics. The lag time (t10) for the formulations containing 4, 8, 12, 16 and 20% of HPMC K100LV in tablet plug was 0.2 h, 2 h, 3.2 h, 5.1 h and 6.35 h, respectively. 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 h was satisfied by formulation containing 16% of HPMC K100LV.

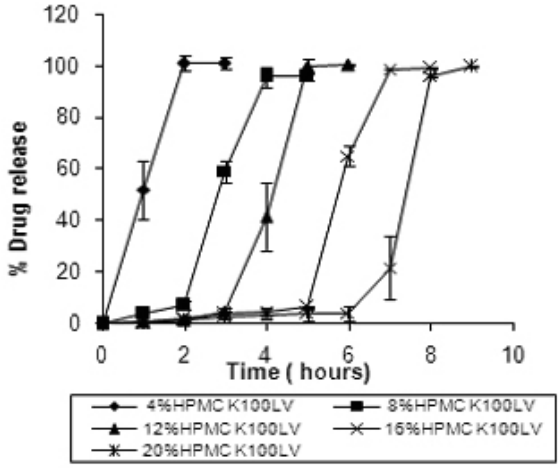

Figure 3. Effect of different plug composition on pulsatile release of theophylline (plug weight 150 mg).

Effect of tablet plug hardness on drug release

To study the effect of tablet hardness on drug release, the erodible tablet hardness was varied between 5-7 kg/cm^2. The results are

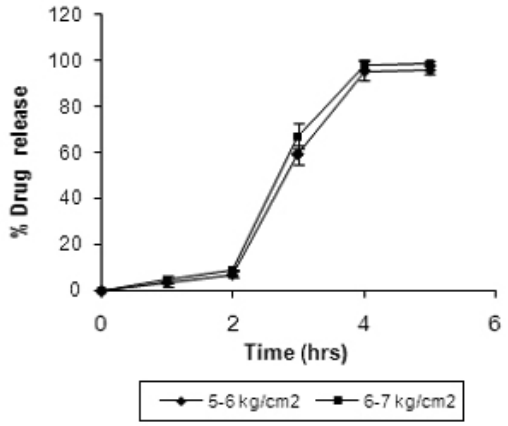

Figure 4. Effect of tablet hardness on drug release (composition of tablet plug 8% HPMC K100LV).

shown in Figure 4. Within the range of 5-7 kg/cm², drug release profiles remained relatively unchanged. The results concluded that tablet hardness did not influence the drug release within the ranges studied.

Effect of tablet plug weight on lag time

Maintaining the same composition of erodible tablet (16% HPMC K100LV), plugs of different weights such as 100, 150 and 200mg were evaluated for lag time. The relationship between plug weight and lag time is shown in Figure 5. A good correlation was observed between them. (r^2 = 0.9899). 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.

CONCLUSION

A chronomodulated pulsatile drug delivery system of theophylline was successfully developed. In accordance with the chronomodulated therapy of asthma, the lag time criterion of 5 h was satisfied by formulation containing 16% of HPMC K100LV. The dosage form can be taken at bed time and will release the contents in the early morning h when asthma attacks are more prevalent.

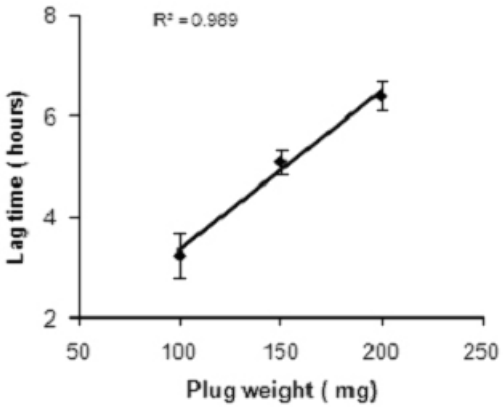

Figure 5. Influence of tablet plug weight on lag time.

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