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Research Article

FORMULATION AND EVALUATION OF CHRONOPHARMACEUTICAL DRUG DELIVERY OF THEOPHYLLINE FOR NOCTURNAL ASTHMA

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ABSTRACT

The objective of this study was to develop and evaluate a pulsatile drug delivery system based on impermeable capsule body filled with theophylline pellets and sealed with erodible polymer plug placed in the opening of capsule body. Erodible plugs were prepared by direct compression followed by placing the pellets in the capsule by congealing directly a meltable plug material directly within the capsule opening. The theophylline pellets were prepared in four batches with PVP K30, water as binder solution and evaluated for the surface morphology, particle size, drug content and in- vitro release profile and from the obtained results; one best formulation was selected for further fabrication of pulsatile capsule. Different hydrogel polymers were used as plugs, to maintain a suitable lag period and it was found that the drug release was controlled by the proportion of polymers used. The lag time prior to pulsatile drug release correlated well with erosion properties of the plugs and, besides the composition of the plug, could be controlled by the thickness of the plug. Programmable pulsatile release has been achieved from a capsule device over a 2–36 hr period, consistent with the requirement of chronopharmaceutical drug delivery.

Keywords: Chronopharmaceutical, Theophylline, Pulsatile release, Hydrogel, Pellets, Nocturnal Asthma

INTRODUCTION

Drug delivery systems can be designed to release the drug over time in a linear (reservoir systems), non-linear (matrix systems) or in a pulsatile fashion [1, 2]. With pulsatile systems, the drug is released rapidly within a short period of time after a specified lag time with no or little drug being released [3,4]. Pulsatile drug delivery system is capable of providing one or more rapid release pulses at predetermined lag times which results in better absorption of the active solute, and thereby provides more effective plasma concentration-time profile. Most pulsatile delivery systems are reservoir devices covered with a barrier coating. The barrier can dissolve, erode or rupture during/after a certain period of time, after which the drug is released rapidly from the inner reservoir core. The time-controlled explosion system (TES) has four layered structure. The drug is layered on an inner core, followed by a swellable layer (hydroxypropyl cellulose) and an insoluble polymeric top layer (ethyl cellulose). Upon water ingress, the swellable layer expands resulting in the rupturing of the outer coating followed by rapid drug release [5, 6].

For several drugs or therapies, a pulsatile release profile, where the drug is released completely after a defined lag time, is advantageous [7, 8]: for drugs which develop biological tolerance, for drugs with an extensive first pass metabolism, for drugs targeted to a specific site in the intestinal tract, e.g. to the colon, protecting the drug from degradation and for the adaptation of drug needs to circadian rhythms of body functions or diseases [9, 10]. With eroding or dissolving systems, a potential problem is the retardation and therefore there is no immediate drug release after the loss of the barrier function [11] or a premature release, seen in particular with highly water-soluble drugs[12,13]. Capsular-shaped systems are more independent from the nature of the content, for example, the Pulsincap system [14, 15], which consists of an insoluble capsule body and a swellable plug. Several single unit pulsatile dosage forms with capsular design have been developed. The Pulsincap systems consists of a water impermeable capsule half, filled with the drug formulation [16].The capsule half is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution media or gastrointestinal fluids, the plug swells and is ejected from the capsule after a specific time interval, followed by rapid release of capsule contents [17].

The objective of the present study was to develop and evaluate an alternative pulsatile drug delivery system consisting of a drug-containing impermeable gelatin capsule, a swelling layer and an insoluble polymeric coating, which used only approved excipients and was prepared by standard pharmaceutical procedures. The lag time was controlled by the hydration/expansion of the swelling layer and subsequent complete rupturing of the polymer coating, allowing a fast drug release.

MATERIALS AND METHODS

Materials

The following chemicals were obtained from commercial suppliers and used as received, Theophylline (Cipla, Bangalore, India), Sugar spheres, Sugar powder and Aerosil (R A Chem pharma Pvt. Ltd., Hyderabad), PVP K30 (Dr Reddy's Pvt. Ltd., Hyderabad), Crosspovidone XL-10 (International Specialty Inc, Hyderabad),Ethyl cellulose, Lactose, Formaldehyde solution(Bharat Institute of Technology-Pharmacy, Hyderabad), Xanthan gum and Veegum (Al-ameen College of Pharmacy, Bangalore), Gum Kondagogu and Karayagum (AP Girijan Cooperative Society) ,Hard gelatin capsules, Tween 80 (AP Pharma distributors, Hyderabad), Dichloromethane, High density polyethylene, Phosphate buffer saline, Polydimethylsiloxane, Isopropyl alcohol (S D Fine Chemicals ltd, India).

Methods

Preparation of theophylline pellets

The composition formulas of theophylline (TPH) pellets were given in **[Table No: 01]**. Theophylline was pulverized and drug excipients (mixture of theophylline, aerosil and sugar powder) were passed through a 120 mesh screen. Then the above drug and excipients mixture were blended for 15 minutes in a double cone blender (Sreenex machines Pvt ltd,Hyderabad). PVPK-30 was added in water and stirred well still to get a clear solution. Basic core sugar pellets were transferred into coating pan (Bectochem Consultants & Engineers Pvt., Ltd, Hyderabad). Theophylline blend was added slowly by spraying the binder. The pellets are then dried in a tray drier at about 45^0 C-55^0 C to attain the moisture content less than 2.5%. The dried pellets are sized on a sifter to remove agglomerates, broken pellets and fine powder. After checking the weight of the pellets and noting down the yield they are packed in a high density polyethylene container lined with double polythene bags, labelled and securely tied.

Filling of capsule bodies

The drug and excipients were sieved (315 µm), blended in a Turbula-mixer (IISC, Bangalore) for 15 mins. The bodies and caps of formaldehyde treated hard gelatine capsules were separated manually. Pellets equivalent to 150 mg of theophylline were accurately weighed and filled into the treated bodies by hand filling. The capsules containing the pellets were then plugged with various polymers, i.e., Xanthan gum, Veegum, Gum Kondagogu, Karaya gum, Karaya gum, Crosspovidone XL-10, etc.

Preparation of compressed and meltable plugs

The powder was sieved through a 315 µm sieve and blended in a Turbula-mixer for 15 mins (if the plug consisted of two or more components). The plugs were prepared by direct compression method with a single punch press with varying compression pressures. A suspension of magnesium stearate in isopropyl alcohol was used as an external lubricant to avoid sticking of the tablets to the punches. The diameter of the compressed plugs was 6 mm, the weight was 300 mg and the hardness were 40, 80 and 120 N i.e., each polymer weighed 300mg was directly compressed with 3 different compression pressures. In order to determine the erosion properties of the meltable plugs, they were prepared by melting and pouring the melt into a mold (height: 13-14 mm, diameter: 11mm). Glycerine was used to lubricate the mould. Tween 80 was poured into petridish and investigated for erosion.

Preparation of cross-linked gelatin capsules

Twenty-five milliliters of 15% (v/v) formaldehyde was taken into desiccator and a pinch of potassium permanganate was added to it, to generate formalin vapors. The wire mesh containing the empty bodies of the 100 mg capacity hard gelatin (about 100 in number) capsule was then exposed to formaldehyde vapors. The caps were not exposed leaving them water-soluble. The dessicator was tightly closed. The reaction was carried out for 12 hrs after which the bodies were removed and dried at 50 ⁰C for 30 min to ensure completion of reaction between gelatin and formaldehyde vapors. The bodies were then dried at room temperature to facilitate removal of residual formaldehyde. These capsule bodies were capped with untreated caps and stored in a polythene bag.

Preparation of the complete system

The various compressed and meltable plugs (300mg) of Xanthan gum, Cross-linked poly vinyl pyrrolidine and Carrageen or Veegum etc with dip coating and without dip coating with different compression pressures were placed by hand on top of the pellets in the open end of capsule. Then the cap is replaced. The meltable plug materials were molten and filled with a pipette on top of capsule content. The capsules were completely coated by dip coating method with 5% ethyl cellulose ethanolic solution.

Drug excipient compatibility studies

Compatibility studies were performed using FTIR (Fourier Transformer Infra-Red) spectrophotometer (Shimadzu, Japan). The FTIR spectrum of pure drug and physical mixture of drug and excipients were studied. The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum.

Determination of drug content in pellets

In a 100 ml volumetric flask, 25 mg of crushed microcapsules were taken, and volume was made up to mark with pH 6.8. The flask was shaken for 12 hrs using an orbital shaker incubator. Then the solution was filtered and from the filtrate appropriate dilutions were made and absorbance was measured at 272 nm by using UV absorption spectroscopy.

Determination of particle size and external morphology

Determination of average particle size of theophylline pellets was carried out by optical microscopy Scanning Electron Microphotography (SEM) studies was carried out by using JEOL JSM T-330 'A' Scanning microscope (Japan). Dry pellets were placed on an electron microscope brass stub and coated with gold in an ion sputter. Picture of microcapsules were taken by random scanning of the stub.

Determination of drug content

In a 100 ml volumetric flask, 25 mg of crushed microcapsules were taken, and volume was made up to mark with pH6.8. The flask was shaken for 12 h using an orbital shaker incubator (Schimadzu, Japan). Then the solution was filtered and from the filtrate appropriate dilutions were made and absorbance was measured at 272 nm by using UV absorption spectroscopy.

Determination of the time of erosion of the plugs

The time for complete erosion of the plugs (compressed plugs) was determined with a disintegration testing apparatus (Cintex Industrial Corporation, Dadar, Mumbai), (900 ml pH 6.8 phosphate buffer USP XXIII, 37±0.5⁰C).

Determination of swelling index of plugs

The plugs prepared with varying compression pressures were tested for swelling index using disintegration apparatus (900 ml pH 7.4 phosphate buffer USP XXIII, 37±0.5 ⁰C). Xanthan gum polymer was taken as model polymer in order to determine swelling rate.

Determination of in vitro release studies of theophylline pellets

In vitro dissolution profile of each formulation was determined by employing USP XXIII rotating basket method (900 ml of pH 6.8-phosphate buffer, 100 rpm, 37 ±0.5 ⁰C). Microcapsules equivalent to 100 mg of TPH were filled into dialysis bags (12,000 molecular cutoffs) and loaded into the basket of the dissolution apparatus. Five milliliters of the sample was withdrawn from the dissolution media at suitable time intervals and the same amount was replaced with fresh buffer. The absorbance of the filtrate was determined at wavelength of 272 nm by using spectrophotometer (Shimadzu UV-1601, Japan), against pH 6.8 as blank. The amount of drug present in the filtrate was then determined from the calibration curve and cumulative percent of drug release was calculated.

Evaluation of thickness of designed pulsatile capsule

The thickness of the Ethyl cellulose coating was measured using screw gauge and was expressed in mm. 10 capsules were selected randomly from each batch and weighed individually for weight variation. The test requirements are met if none of the individual weights are less than 90% or more than 110% of the average.

In vitro release profile of pulsatile capsule

Dissolution studies were carried out by using USP XXIII dissolution test apparatus (paddle method). Capsules were tied to paddle with a cotton thread so that the capsule should be immersed completely in dissolution media but not float [18-21]. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used referred to as sequential pH change method [22-26]. When performing experiments, the pH 1.2 medium was first used for 2 hrs (since the average gastric emptying time is 2 hrs), then removed and the fresh pH 7.4 phosphate buffer saline (PBS) was added. After 3 hrs (average small intestinal transit time is 3 hrs), the medium was removed and fresh pH 6.8 dissolution medium was added for subsequent hours. Nine hundred milliliters of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at 37±0.5 ⁰C. Capsules were tied to paddle with a cotton thread in each dissolution vessel to prevent floating. Five milliliters of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 272 nm, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times.

Stability studies

Stability studies as per ICH guidelines were carried out for optimised formulation from each polymer batch were selected. This includes storage at both normal and exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same

rate as when originally formulated. Stability samples are stored at accelerated stability studies: 40±2°C/75±5% RH, intermediate stability studies: 30±2°C/65±5% RH, long term stability studies: 25±2°C/60±5% RH. The selected formulations were stored at above mentioned conditions for a period of three months. At weekly intervals, formulations were observed for any physical changes during the period of storage. At the end of third month the formulations were analysed for the analysed for the drug content and dissolution profiles.

RESULTS AND DISCUSSION

A pulsatile capsule shaped delivery system was developed, whereby the pulsatile drug release occurred after erosion of the plug material rather than after ejection of an impact plug. The hard gelatin capsule shell was made impermeable by formaldehyde treatment, exposure to formalin vapors results in an unpredictable decrease in solubility of gelatin owing to the cross linkage of the amino groups in the gelatin molecular chain with aldehyde groups of formaldehyde by Schiff's base condensation[27]. The effect of various parameters of the plug (type of material, thickness and hardness) and the capsule content (type of excipient, effervescent agents) were investigated in order to characterize the lag time prior to drug release and the drug release profiles of the capsules. The plugs were formed by direct compression method with a single punch press with varying compression pressures, the meltable plugs were prepared by melting and pouring the melt into a mould. Theophylline pellets were prepared by direct compression method followed by placing the pellets in the capsule body by hand filling and placing the plug on the capsule opening or by pouring a melt of plug material onto the capsule content followed by congealing the melt into a plug, which closed the capsule. A tight fit between the plug and the impermeable capsule was very important in order to prevent water penetration to the capsule content and drug release prior to complete erosion of the plug material. In order to identify proper plug materials, they were tested for swelling index using disintegration apparatus the results of which are shown in **[Figure no 1]**. Polymer plugs compressed with 120 N pressure showed maximum swelling time i.e., >60 min on the other hand plugs with 60 N pressure showed least time nearly 10 min for swelling. The plugs having compression pressure 80 N were swelled within 28 min and plugs having compression pressure of 100 N displayed optimum swelling time i.e., nearly 30 min. Hence 80 N compression pressure was fixed as constant for further compression of plugs for formulating the entire system. The water soluble polymers like hydroxypropyl methyl cellulose (HPMC) and polyethylene oxide (PEO) appeared attractive as erodible plug materials .The formation of an erodible plug by congealing of a melt within the capsule body was obtained with melt method. The meltable material then eroded by dissolution/emulsification. Like with HPMC plugs, the erosion time of PEO plugs decreased with decreasing molecular weight. The extent of lag time prior to the drug release is primarily controlled by the rate of erosion of plug material; the subsequent drug release phase will be determined by the composition of the capsule content [28- 30]. The FTIR spectra of pure drug and physical mixture of drug and excipients were determined respectively. It was found that the principle peaks of theophylline are intact in the formulations. Drug-excipients interactions were not observed as shown in **[Figure No. 2]**. This indicates that the drug was compatible with the formulation components. The percentage drug content in second batch (TP2) was found to be highest i.e., 99.3% and in the fourth batch (TP4) the percentage drug content was the least i.e., only 89%. In TP1 and TP3 it was found to 93.6% and 95.9% respectively. Hence TP2 batch was selected for the fabrication of pulsatile drug delivery system. The SEM photograph of second batch (TP2) was taken to determine the particle size and surface morphology of pellets as shown in **[Figure No. 3].** On the basis of percentage drug content formulation TP-2 was selected as better formulation for designing pulsatile device. The release profile of theophylline pellets obtained was shown in **[Table No. 2]** and it was observed that more than 98% of the drug was released within 1 h. In vitro release profiles were found to have very good sustaining efficacy. After coating thickness of the plug was increased up to 2-3mm all the designed pulsatile capsules were found to be in the limit of weight variation test. The formulation of Xanthum gum (300 mg) showed a lag time of about 8 h while the lag time of Xanthum gum (200 mg) was decreased to 6 hours because of less amount of polymer in the plug on the other hand lag time of Xanthum gum (150 mg) was further decreased to 4 hrs this might be probably due to the effect of high content of filler and less amount of polymer in the plug. The 2.5 % ethyl cellulose (EC) coating on plugs showed an increase in lag time about 2 hrs. Crosspovidone XL-10 as hydrogel plug formulations released the drug immediately, no lag time was observed, on the other hand 2 hrs lag time was observed for few formulations i.e., at the end of 2nd hr 76.2%, 97.5% . The lag time achieved with the formulations using Karaya gum polymer was 12 hrs, other formulations of karaya gum (200, 150 mg) ejected the plugs well before 12 hrs, this might probably due to the effect of lactose as it enhances the absorption of media, while the 2.5% EC coated plug remarkably achieved a lag time of 28 hrs. The 5% EC coated plug formulation made of karaya gum polymer plug displayed highest lag time of 36 hrs. Formulations containing gum kondagogu as hydrogel plug showed not much lag time as the plugs ejected well below 2 hrs, this was due to rapid absorption of dissolution medium by lactose present in plugs. Formulations containing veegum as hydrogel plug showed not much lag time as the plugs ejected out well before 2 hrs, as the polymer alone itself was very rapidly swelling the effect of filler was not observed. On the basis of in-vitro dissolution studies it was found that in all cases the plugs which were placed 3 mm above the body surface, the plug ejected 2- 4 hrs earlier decreasing the lag time. It was clearly observed that, in all the cases where the plug was placed 3 mm below the surface level of capsule body, showed a delay of lag time ranging from 2- 12 hrs. There were no physical changes found during the entire storage period. The percentage drug content after three months in formulations was found to be between 99.2- 99.0%.

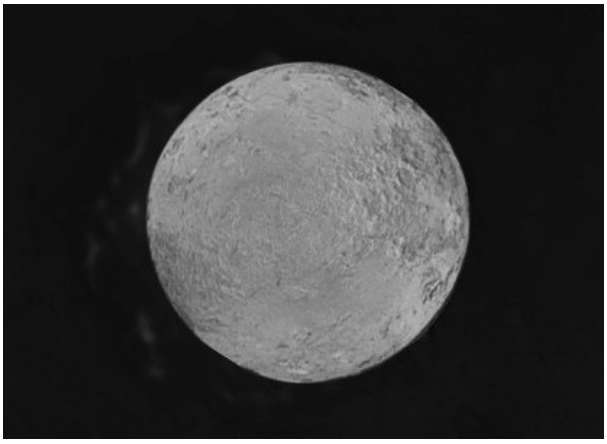

Fig. 1: Comparison of swelling rates of various polymer plugs

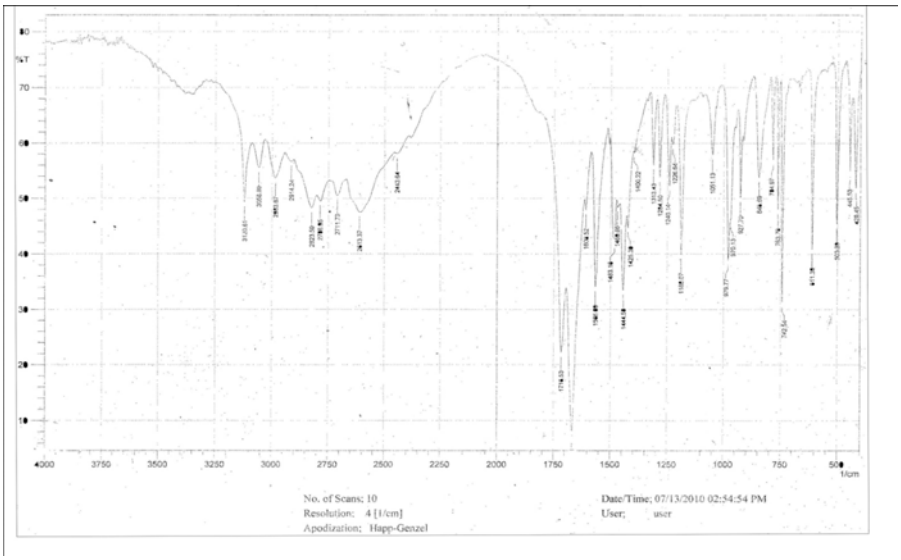

Fig. 2: Scanning electron microphotograph of cross-section batch (TP2) theophylline pellet

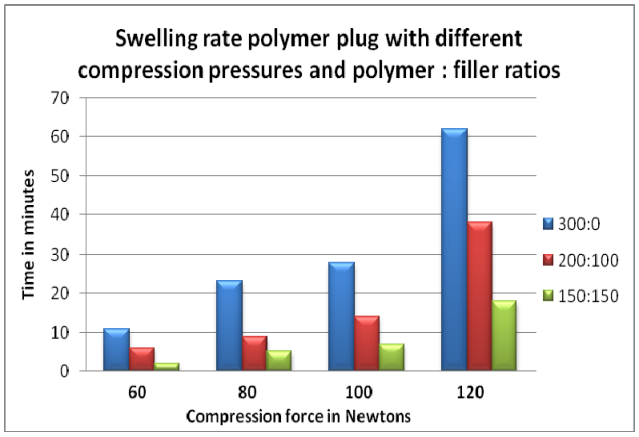

Fig. 3: FTIR spectrum of theophylline combined with excipients

Table 1: Composition formula of theophylline pellets and their quantities as per percentage w/w

Ingredients	TP1	TP2	TP3	TP4
Theophylline	60	60	60	60
Sugar spheres (#24 - #30)	27.50	27.50	27.50	27.50
Aerosil	0.5	1	1.5	2
Sugar powder	2.50	2.50	2.50	2.50
Binder solution				
PVP K30	4.5	4.0	3.5	3
Water	Q.S	Q.S	Q.S	Q.S

Table 2: Dissolution profile of Theophylline pellets Note: Star mark (*) indicates average of three determinations

Time (min)	Absorbance*	Concentration µg/ml	Dilution factor(ml)	Cumulative percentage drug release
0	0	0	10	0
15	0.242	3.966667	10	23.8
30	0.536	8.783333	10	52.7
45	0.802	13.15	10	78.9
60	0.912	15.45	10	98.1
75	0.954	15.85	10	99.3

CONCLUSION

In conclusion, pulsatile drug release was achieved with an impermeable hard gelatin capsular device and erodible plug. The lag time could be adjusted over a broad range by varying the amount and composition of the plug, outer coating layer and amount of swelling layer.

List of abbreviations

Abbreviations	Expanded terminology
PDDS	Pulsatile drug delivery systems
HPMC	Hydroxypropylmethyl cellulose
EC	Ethyl cellulose
SEM	Scanning electron microscopy
DCM	Dichloromethane
CP XL-10	Crosspovidone XL-10
XG	Xanthan gum
KG	Karaya gum
GKG	Gum Kondagogu
VG	Veegum
PVP K30	Polyvinyl pyrrolidone K30
HDEP	High density polyethylene
N	Newton
PBS	Phosphate buffer saline
FTIR	Fourier Transform Infrared Spectroscopy
RH	Relative humidity
CPR	Cumulative percentage release

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