Research Article

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Design, prepare and evaluation of terbutaline tablets for chrono modulated pulsatile drug delivery system

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ABSTRACT

Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. Pulsatile drug delivery system for Terbutaline was formulated initially as core tablets followed by formulation of pulsatile tablets using press-coated technology. Core tablets were formulated. The core tablets were then compressed into pulsatile tablets using various concentrations of polymers. Core tablets were evaluated and based on the dissolution studies trial F1 was optimized as it shows lower disintegration time and faster drug release. Then the pulsatile tablets were evaluated for various tests and drug release studies were conducted for pH 7.4 buffer. Pulsatile tablets were formulated utilizing press coated technology and the combination of polymers provided required lag time with satisfactory dissolution profile.

Keywords: Terbutaline sulphate, Polymers, FTIR studies, Direct compression technique, Core tablets, Drug release studies.

INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Terbutaline is a selective β-2 adrenoceptor agonist. At therapeutic doses it acts on the β-2 Adrenoreceptors of bronchial muscle, with little or no action on the β-2 adrenoreceptors of the heart. [1] It is suitable for the management and prevention of attack of asthma. Terbutaline is incompletely absorbed from the GIT and also subject to extensive first pass metabolism by sulphate conjugation in the liver and possibly by the gut wall. However due to short biological half life and low bioavailability of the drug high frequency dosing is necessary for the effective therapy. [2] The core serves as reservoir, and the release controlling layers protect the core from the environment e.g., water, acidic pH and enzymes until the drug is released after a predetermined lag phase. [3] The coatings can erode/dissolve, rupture or alter their permeability at the required time. Asthma is a disorder that causes the airways of the lungs to swell and

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narrow, leading to wheezing, shortness of breath, chest tightness, and coughing. [4] The coughing often occurs at night or early in the morning. An inflammation to the airways makes them swollen and very sensitive. This study attempts to design and evaluate a chronomodulated drug delivery system of terbutaline sulphate, a selective β_2 receptor blocker for the treatment of nocturnal asthma. [5] It was aimed to have a lag time of six hours i.e., the system is taken at the bed time and expected to release the drug after a period of 6 h i.e., at 4.00 am when the asthma attacks are more prevalent. Such time-controlled pulsatile delivery can be achieved mainly with drug containing cores, which are covered with release controlling layers. [6] The core serves as reservoir, and the release controlling layers protect the core from the environment e.g., water, acidic pH and enzymes until the drug is released after a predetermined lag phase. [7, 8] The coatings can erode/dissolve, rupture or alter their permeability at the required time. Single unit rupturable pulsatile drug delivery system was chosen as the model system over erodible pulsatile drug delivery system or Pulsincap and PORT systems because of ease of manufacturing, better reproducibility of the lag time and rapid drug release after a lag time. [9]

MATERIALS AND METHODS

Terbutaline sulphate was collected as a gift sample from Hetero labs, Hyderabad and various excipients like eudragit, ethylcellulose and hydroxyl propyl methyl ellulose were purchased from AR chemicals, Hyderabad.

METHODOLOGY [10, 11]

Compatibility studies of drug and polymers

In the formulation of Terbutaline sulphate tablet formation , API and Excipient may interact as they are in close communication with each other, which could lead to the instability of drug. FT-IR spectroscopy was employed to ascertain the compatibility between Terbutaline sulphate and the selected polymers. The pure drug and drug with excipients were scanned separately.

Formulation table

Table-1: Formulation development of terbutaline tablets

S.no.	Ingredients	F1	F2	F3	F4
1	Terbutaline sulphate	8	8	8	8
2	Lactose	77	77	77	77
3	Mcc	10	10	10	10
4	Magnesium stearate	3	3	3	3
5	Talc	2	2	2	2
6	Total wt	100	100	100	100

Preparation of core tablets by Direct compression method [12, 13]

Different matrix embedded formulations of Terbutaline sulphate were prepared by direct compression method using varying proportion of polymers either alone or in combination. The ingredients were passed through a 40 mesh sieve. Calculated amount of the drug, polymers and filler (MCC) was mixed thoroughly. Magnesium stearate was added as lubricant; the appropriate amount of the mixture was weighed and then compressed using a an Ten station rotary press at a constant compression force equipped with a 6-mm flat-faced punches at a compression force required to produce tablets of about 5–6 kg/cm^2 hardness. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristics.

Formulatio no pulsatile tablets

Table-2: Formulation of pulsatile tablets

Ingredients	F1	F2	F3	F4
Core tablet	100	100	100	100
HPMC K100M	100	-	-	50
Ethylcellulose	-	100	-	50
Eudragit	-	-	100	-

Formulation of Pulsatile Tablets by Press Coated Technology. The core tablets were compressed using polymer blend which has composition of HPMC K100 M and ethylcellulose, Eudragit in different concentrations. Half of the coating polymer material was placed in the die cavity, then the core tablet was carefully sited in the centre of the die and cavity was filled on the top with the other half of the coating polymer material. Then the tablet was compressed using Rimek tablet machine, with 8 mm punch.

EVALUATION STUDIES

Pre compression parameters [14-16]

Bulk Density

Bulk density is defined as the mass of powder divided by bulk volume.

It is calculated using the following equation:

Bulk density = weight of sample taken /volume noted

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured. Then the cylinder was dropped at 2-second intervals onto a hard wooden surface three times, from a height of one inch. The volume was recorded and the bulk density was calculated.

Tap density

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured. Then the surface was carefully smoothed and the volume was measured. Tap density was calculated by measuring final volume (V_f) after 50 taps on wooden surface from 6 inch height and was expressed in g/cm^3.

Bulk density = W/V_o

Tapped density = W/V_f

Where,

V_o = initial volume

V_f = final volume.

Compressibility index

The are Compressibility index and Hausner ratio measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inte rparticle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility index and Hausner ratio.

The compressibility index and Hausner ratio may be calculated using measured values for bulk density (ρ_{bulk}) and tapped density (ρ_{tapped}) as follows:

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

$$\text{Hausner ratio} = \frac{\rho_{tapped}}{\rho_{bulk}}$$

Angle of repose

The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose.

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$\tan\theta = h/r$

$\theta = \tan^{-1} h/r$

Where

h = height of pile

r = radius of the base of the pile

θ = angle of repose

Post compression parameters [17-19]

Weight variation

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more then two of the individual tablet weight deviate from the average weight by more than the percentage.

Table-3: Percentage deviation allowed under weight variation

Percentage deviation allowed under weight variation test.	
Average weight of tablet (X mg)	PERCENTAGE DEVIATION
130 mg or less	10
130mg to 324 mg	7.5
more than 324 mg	5

Thickness

Twenty tablets were randomly selected form each batch and there thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets were determined.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not loose more than 1% of their weight.

The percentage friability was measured using the formula,

$\% F = \{1-(Wo/W)\} \times 100$

Where,

% F = friability in percentage

Wo = Initial weight of tablet

W = weight of tablets after revolution

Content Uniformity

The tablets were tested for their drug content. Tablets were finely powdered required quantities of the powder equivalent to 100 mg of powder sample were accurately weighed and transferred to a 100ml of volumetric flask. The flask was filled with Phosphate buffer (pH 6.8) solution and mixed thoroughly. The solution was made up to volume and filtered. Dilute 1ml of the resulting solution to 10 ml with Phosphate buffer (pH 6.8) and measure the absorbance of the resulting solution at the λmax using a UV spectrophotometer.

In Vitro Disintegration Test

The disintegration time of tablets was determined by using Disintegration test apparatus (scientific). Tablets were placed in disintegration test assembly and disc was placed on tablets in each glass tube of assembly. The assembly was dipped in a vessel containing 900 ml distilled water at 37°C. The time for disappearance of tablet

residue above mesh was noted as disintegration time.

In- Vitro Release study

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 50 rpm. The dissolution medium consisted of 900 ml of Standard buffer pH 7.4 period of time. Temperature maintained at 37±5.The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 5 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask, and make the volume with buffer. The diluted samples were assayed against reagent blank.

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile.

The prepared pulsatile tablets of Terbutaline sulphate were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2^{o}c and refrigerator 2-8^{o}c for a period of 30 days.

RESULTS AND DISCUSSION

Drug - excipient compatibility studies (FT-IR)

The compatibility between the drug and the selected lipid and other excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-lipid mixture, which confirmed the absence of any chemical interaction between the drug, lipid and other chemicals.

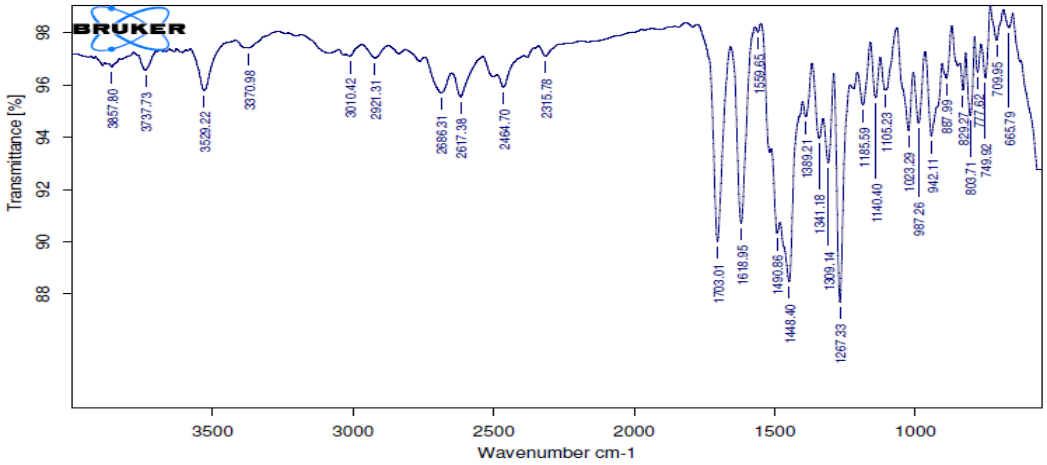

Fig-1: FT-IR Sample for Terbutaline

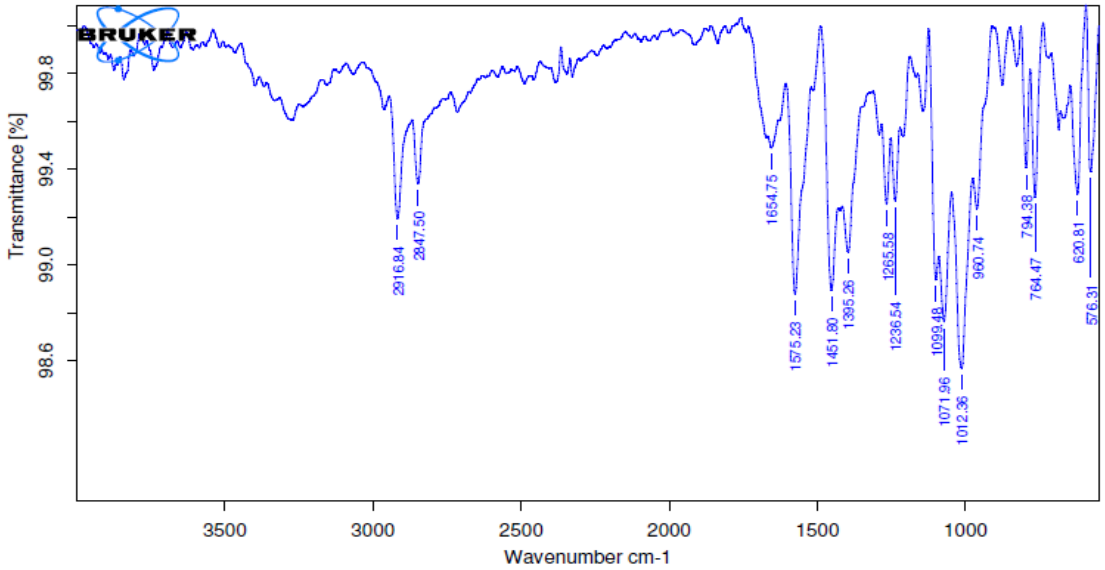

Fig-2: FT-IR Sample for drug and excipients

EVALUATION STUDIES

Pre compression parameters

Bulk Density

The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.426 to 0.442.

Tapped density

The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.538 to 0.553.

Angle of repose

The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 29 to31^0

Compressibility index

Compressibility index was carried out, it found between 10% to 20.81% indicating the powder blend have the required flow property for compression.

Table-4: Precompression parameters of Blend

F. NO	Bulk density	Tapped density	Compressibility index	Hausner ratio	Angle of repose(0)
F1	0.431	0.542	20.47	1.25	30
F2	0.442	0.553	20.07	1.25	29
F3	0.426	0.538	20.81	1.26	31
F4	0.435	0.549	20.76	1.26	29

Post compression parameters

Weight variation

All the formulated (F1 to F4) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness

Mean thickness (n=3) were uniform in F1 to F4 formulations and were found to be in the range of 4.05 mm to 4.16 mm.

Hardness

The measured hardness of tablets of each batch ranged between 6 to 7 kg/cm^2. This ensures good handling characteristics of all batches.

Friability

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity

The percentage of drug content for F1 to F4 was found to be between 94.78% to 93.86% of Terbutaline, it complies with official specifications.

Table-5: Evaluation parameters of core tablets of each batch

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drugcontent (%)	Disintegration time(sec)
F1	100	3.21	5.45	0.21	98.19	58
F2	99	3.19	5.53	0.19	97.86	57
F3	100	3.16	5.60	0.26	95.21	60
F4	99	3.22	5.48	0.24	94.78	61

Table-6: Evaluation parameters of Press coated tablets of Terbutaline

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drugcontent (%)	Disintegration time(sec)
F1	200	4.10	6.09	0.40	93.86	60.15
F2	199	4.16	6.22	0.38	90.35	65.13
F3	199	4.05	6.24	0.32	89.40	63.26
F4	200	4.11	6.26	0.38	88.15	70.15

Dissolution studies

All the four formulation of prepared tablets of Terbutaline were subjected to in vitro release studies these studies were carried out using dissolution apparatus.

Table-7: Dissolution Profile of all formulations

Time (hrs.)	F_1	F_2	F_3	F_4
0	0	0	0	0
1	19.56	18.92	17.58	19.21
2	25.84	24.25	23.79	25.81
3	35.86	32.15	31.21	42.52
4	49.87	48.57	45.89	50.16
5	58.93	55.15	54.16	58.46
6	68.75	65.89	64.25	68.15
7	80.18	76.25	72.31	74.16
8	91.26	90.26	89.26	80.12

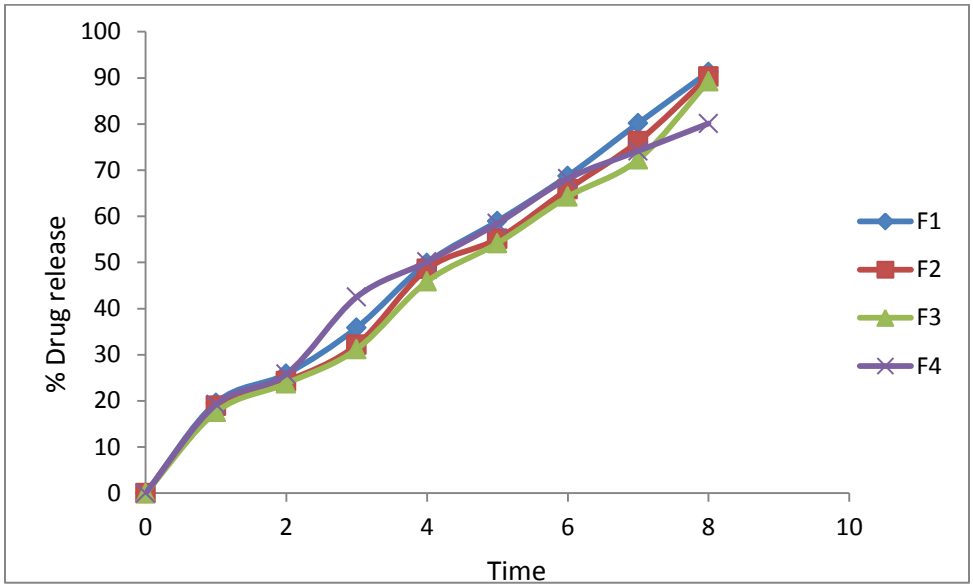

Fig-3: Drug release studies of all formulations

Lag Time Determination by Rupture Test

The time taken for the outer coating to rupture is defined as the lag time of the pulsatile tablet. It was determined by using the USP II paddle dissolution apparatus. Initially 900 ml of 6.8 phosphate buffer was taken as media and was carried for 8 hrs at 37.0 ± 0.5°C, 50 rpm. The time at which the outer coating layer starts to rupture was noted and considered as the lag time.

Table-8: Evaluation of Lagtime

Formulation	Time (min)
F1	101
F2	112
F3	220
F4	252

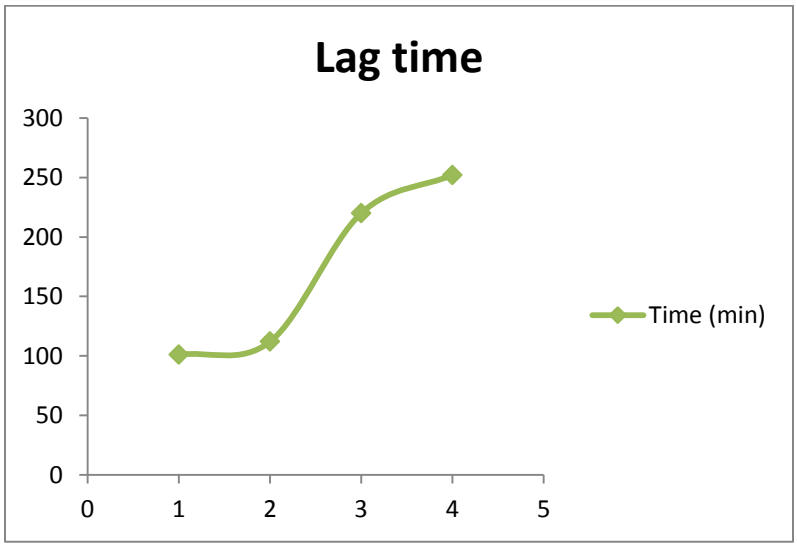

Fig-4: Log time of all the formulations

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-1 after 30 days. Parameters quantified at various time intervals were shown;

Table-9: Stability studies of optimized formulation

F. Code	Time (min)	Initial	1st Month	Limits as per Specifications
F1	**25^0C/60%RH**	91.26	90.99	**Not less than**
	% Release			**85 %**
F1	**30^0C/75% RH**	91.26	90.85	**Not less than**
	% Release			**85 %**
F1	**40^0C/75% RH**	91.26	90.58	**Not less than**
	% Release			**85 %**

CONCLUSION

In this study pulsatile tablets were prepared, which consist of two parts, the core tablet and its outer polymeric part. Core tablets of Terbutaline were formulated by conducting different trials. Tablets were formulated by using direct compression technique. Core tablets were press coated using various polymers. In-vitro release study of formulations F2 F3 and F 4 showed a release slowly to some polymers are used such as ethyl cellulose and eudragit. Formulation F2, F3 and F4 showed a slow release than F1 but the optimum level of sustained release effect was be observed in the formulation F1 containing hydroxyl propyl methyl cellulose. The trial F1 was optimized which contains hydroxyl propyl methyl cellulose as polymer, because as it shows good dissolution profile. In the initial trial F1 only HPMC was used as the polymer, in both the layers but the lag time was satisfactory as it released the drug in the initial time points itself the probable reason may be due to hydrophilic nature of HPMC it may provide the required lag time, Due to presence of polymers it provided the lag time of about 5hours which may be due to the pH dependent nature of the polymers which predominantly ruptures at higher pH. A drug delivery system with a lag time of around 5 hours and pulsatile properties was successfully developed. The aim of the study was to develop a pulsatile drug delivery system of Terbutaline for the management of Asthma. The Chrono therapeutic drug delivery system of Terbutaline was prepared which provided desired lag time thus it can be taken at bedtime such that the drug will be released in the morning hours i.e. at the time of symptoms and useful for chronopharmaceutics of Asthma. The results indicated that amount of polymer in the formulation affects the drug release rate. The drug release was high-pitched and full after the lag time, which is mandatory for a pulsatile drug delivery system. Thus, the formulated pulsatile tablets will deliver the drug permitting to the need of the patient so as to give the highest therapeutic benefit of treatment.

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