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FORMULATION AND EVALUATION OF CHRONOTHERAPEUTIC TIMED RELEASE TABLETS OF TERBUTALINE FOR NOCTURNAL ASTHMA

Priyanka M.* and Grace Rathnam

Department of Pharmaceutics, C. L. Baid Metha College of Pharmacy, Thoraipakkam, Chennai- 600 097, India.

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***Corresponding Author**
Priyanka M.
Department of Pharmaceutics, C. L. Baid Metha College of Pharmacy, Thoraipakkam, Chennai-600 097, India.

ABSTRACT

The study was carried out to develop and assess press-coated tablets for chronotherapeutic (pulsatile) delivery of terbutaline sulfate for the therapy of nocturnal asthma. The event of asthma is most elevated in the early morning hours and is alluded to as "morning dip". A formulation that can deliver the drug in a specific concentration just before the asthmatic attack could effectively control the disease. The dosage form consisted of a tablet inside a tablet which was prepared by direct compression method. The core tablet contained 5 mg terbutaline sulfate for immediate release. The core tablets were press coated with various grades of a swellable polymer HPMC (HPMC K100M, HPMC K4M, and HPMC 15 cps) to achieve a lag time of 6.5 hours. Precompression and post-compression studies for the formulations were carried out. Using Box-Behnken design from Design Expert® 12; Stat-Ease Inc the optimized formulation was obtained. The results of the preformulation studies were satisfactory. No interaction was observed between terbutaline and polymers by Fourier transform infrared spectroscopy. Tablets formulated using the optimized formulas were evaluated for lag time, swelling index, and *in-vitro* dissolution. The developed formulation successfully released the initial dose after 6.5 hours. Due to optimization by Box-Behnken Design, there was no notable change observed between the predicted and the observed actual responses of the optimized formula. Rather than the morning dose, the evening dose could be more effective for the treatment of nocturnal asthma by chronotherapy with terbutaline sulfate. This dosage form can adequately control nocturnal asthma.

KEYWORDS Box-Behnken design, chronotherapy, nocturnal asthma, press coated tablet, terbutaline sulfate, pulsatile drug delivery system.

INTRODUCTION

Asthma is a chronic inflammatory disease causing narrowing of the airways to the lungs. Chronic inflammation is associated with hyper-responsiveness of the airway, airflow obstruction within the lungs leading to recurring symptoms of cough, wheezing, dyspnea (shortness of breath), and chest tightness. Out of all the symptoms, sleep-related worsening of asthma is the common of all, where as other symptoms are usually treatable either immediately or with proper asthmatic treatment.[1,2] The occurrence of respiratory arrests and asthmatic deaths are often during the night. Such findings may be associated with higher bronchial responsiveness which has been illustrated to occur in asthmatics (patients) at night. It is well known that during the daytime, increased bronchial responsiveness is related to producing airway inflammation. For example, on exposure to ozone or antigen challenge in humans, increased activity of bronchial and inflammatory cells in the broncho-alveolar lavage fluid is observed. Since nocturnal asthma is related to an increased bronchial reactivity, it is hypothesized that the inflammatory cells in the broncho-alveolar lavage would be increased during the night.[3,4]

Terbutaline is a selective β-2 adrenergic receptor agonist (stimulator) which is used for the treatment of asthma and diseases of the airways. It acts, on β-2 adrenoceptors of the bronchial muscle, with little or no action on the β-2 adrenoceptors of the heart at therapeutic doses. On inhaling the drug its selectivity is further increased**.** Terbutaline sulfate is appropriate for the management and prevention of asthmatic attacks. The oral absorption of terbutaline sulfate is only 33-50% from the gastrointestinal tract of the entire administered dose out of which 60 % of the drug undergoes the first-pass metabolism by the liver.[5] The drug also undergoes gut wall metabolism.[6] Only 15 % of the bioavailability of the entire administered dose is achieved due to these factors.[7] Further, the drug is also having a short half-life of 3-4 hrs requiring frequent administration.[8] A vital metabolite of terbutaline is the sulfate conjugate which allows urinary excretion to be the primary route of elimination. 15 mg per day is the maximum dose of terbutaline sulfate with a dose frequency of is 4-5 times a day. Terbutaline sulfate is taken twice a day as a sustained-release formulation, maintaining the drug level in the body by preventing asthmatic (nocturnal asthma) attacks during the night and early mornings.[9] Since chronomodulated drug delivery systems have advantages of better exertion

of drugs (API) with shorter half-life with extensive first-pass metabolism consequently by providing better therapeutic outcomes, these systems are utilized for the delivery of terbutaline sulfate for the treatment of nocturnal asthma.

The disorders which depend upon the circadian rhythm (biological clock) like asthma, arthritis, diabetes mellitus, and cardiovascular disorders need chrono-modulated drug delivery systems which are time and rate-controlled systems that release the active pharmaceutical ingredient in fixed time and rate after a predetermined lag time. In some diseases, the changes of the hormonal levels depend upon the circadian rhythm**.** The bronchial constriction is severe at night; rheumatic pain occurs in the early hours of the morning, and abdominal pain is most severe at night due to ulcers.[10] The pulsating system releases the drug at a pre-programmed time in a preplanned pattern at an appropriate location without affecting gastrointestinal factors.[11] Chronobiology is a combination of two words, chrono meaning time and biology meaning study of life. Chrono modulated drug delivery doesn't follow zero-order release.[12] Due to enhanced patient compliance pulsatile drug delivery systems are becoming well-known.[13] The current study is aimed to formulate and evaluate press-coated tablets of terbutaline sulfate for the treatment of nocturnal asthma involving the preparation of core tablets (immediate release) and press coating of core tablets to be released at a predetermined time (lag time).

The drug release from the chronotherapeutic drug delivery system ought to be in such a way that at a predetermined lag time rapid release from the system should follow the lag time.[13,14] Since the drug release is independent of the environment these systems are called time-controlled drug delivery systems.

MATERIALS AND METHODS

Materials

Terbutaline sulfate was obtained as a gift from Fourrts (India) Laboratories Pvt. Ltd. (Chennai, India). Lactose (Fonterra Excipients GmbH & Co, Germany), microcrystalline cellulose BP (Cyclogel 102) and microcrystalline cellulose BP (PH 112) (Gujarat Microwax, Ahmedabad, India), sodium starch glycolate (SSG), crospovidone USP and croscarmellose sodium BP (Loba Chemie Pvt. Ltd, India); povidone K 30 (Nanhang Indl. Co, China); HPMC IP (Grade 15), HPMC K100M (Methocel) BP and HPMC K4M (Colorcon Asia Pvt Ltd, Singapore), magnesium stearate (Loba Chemie Pvt. Ltd, India), pea-green supra (Ajantha Chemical Industries) and brilliant blue (Global Chemicals Ltd, India) supra were

used. Analytical grade ingredients and reagents were used.

Methods

Stock solution (1000 µg/ml) of terbutaline sulfate was prepared and from this sample of concentrations, 10-100 µg/ml were prepared. The absorbances of prepared solutions of terbutaline sulfate were measured at 276 nm in a UV-Visible spectrophotometer against distilled water as blank. Concentration versus absorbance values was plotted.

Drug Excipients Compatibility Studies by FTIR

The FTIR spectrum of terbutaline sulfate, HPMC K100M, HPMC K4M, HPMC 15cps, and physical mixtures was recorded using Perkin Elmer Spectrum Two with IR resolution software. Drug and different polymers were taken in a 1:1 ratio. Accurately weighed drug and polymers mixed, resulting physical mixtures were analyzed in an FTIR spectrophotometer, scanned over the range of 4000 to 400 cm^{-1}.

Formulation of Immediate Release Core Tablet

The immediate-release core tablets were prepared using binder solution by the wet granulation method. The core tablets were prepared based on the compositions as shown in Table 1. Terbutaline sulfate (#100) along with lactose (#60) and microcrystalline cellulose (MCC) (#40) were weighed separately and sifted. Sift-charged dry mix was then put together in a polyethylene bag and mixed for 10 minutes.

Table 1: Composition of terbutaline sulfate core tablet.

Ingredients	Quantity per tablet (mg)		
	C1	C2	C3
Terbutaline Sulfate	5	5	5
Lactose	77.5	77.5	77.5
Microcrystalline cellulose	10	10	10
Povidone K30	2	2	2
Sodium Starch Glycolate	2.5	-	2.5
Crospovidone	2.5	2.5	-
Croscarmellose Sodium	-	2.5	2.5
Magnesium Stearate	0.5	0.5	0.5
Brilliant Blue	0.001	0.001	0.001
Pea Green	0.001	0.001	0.001

The binder solution was prepared by dissolving Povidone K30 in hot water and FDA approved colorant (Brilliant blue and Pea-green Supra) was added. The binder solution was poured over a dry mix and was mixed. The granules were then kept for drying at 60^{o}C for 30

minutes. The granules were passed through #30 and LOD was checked. Superdisintegrants (Sodium starch glycolate, Crospovidone, and Croscarmellose sodium) as per the composition were then added to the granules for all three batches. Magnesium stearate was finally added to the granules and mixed for 5 minutes in the polyethylene bag. The granules were then compressed into tablets of 100 mg using a 6.35 mm round flat bevel punch of D tooling.

Characterization of core granules

Core granules were evaluated for angle of repose, bulk density, tapped density, compressibility index (Carr's index), and Hausner's ratio.

Evaluation of immediate release core tablets

Weight variation test

20 tablets were selected randomly, weighed together and individually in a single pan electronic balance and the average weight was calculated. The uniformity of the tablet was determined according to I.P specifications.

Thickness

10 tablets were checked from each of the formulations for determining the thickness. ±5% may be allowed depending on the size of the tablet.

Hardness

The hardness of the tablets was measured using Tablet Hardness Tester C-DHT 200. The hardness is measured in terms of kg/cm². 10 tablets were chosen randomly and tested for hardness. The average hardness of 10 determinations was recorded.

Friability

10 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. The tablets were then removed from the friabilator, dusted off the fines, and again weighed and the weight was recorded. Percentage friability was calculated using the formula.

$$\% \text{ Friability} = \frac{\text{Initial weight of tablets } (W_1) - \text{Final weight of tablets } (W_2)}{\text{Initial weight of the tablets } (W_1)} \times 100$$

Drug Content (Assay)[15]

Exactly 20 tablets were taken, weighed, and powdered using mortar and pestle. Accurately a quantity of the powder containing about 5 mg of terbutaline sulfate was weighed and

transferred to a 50ml volumetric flask. 30 ml of 0.01 M hydrochloric acid was added and shaken for 10 minutes. The volume was diluted with 0.01 M hydrochloric acid and filtered, rejecting the first 5 ml of the filtrate. To 5.0 ml of filtrate, 35 ml of a tris buffer solution was added. 1.0 ml of a freshly prepared 2.0 percent w/v solution of 4-aminoantipyrine was added, mixed and 1.0 ml of a freshly prepared 8.0 percent w/v solution of potassium ferricyanide was added with vigorous swirling and sufficient of the buffer solution was added to produce 50.0 ml. Exactly 75 seconds after the addition of the potassium ferricyanide solution the absorbance of the resulting solution was measured at 550 nm, using water as the blank.

Disintegration Time

A disintegration test was carried out for the immediate release of core tablets. One tablet each was placed in each of six tubes of the basket of the disintegration apparatus. The apparatus was operated using purified water, maintained at 37 ± 0.5^{o}C as the immersion fluid. The time at which the tablet completely disintegrated was noted.

***In-vitro* Dissolution studies**

In–vitro dissolution studies of pulsatile delivery systems were done with the conventional paddle method of core tablets at 37^{o}C ± 0.5°C using purified water in the USP II paddle method at 100 rpm. 5 ml of filtered aliquot was manually withdrawn at pre-determined time intervals and replaced with 5 ml of purified water maintained at the same temperature. The absorbance was measured at 276 nm.

Experimental Design

Experimental runs were designed by Design Expert 12.0 [Stat Ease. Inc.] Software following Box-Behnken Design (BBD) method. BBD was applied for examining three variables (factors) at two levels with a minimum of 15 runs. The two levels of factor X1 HPMC K100M in press coating at a concentration of 20% and 40%, two-level of factor X2 HPMC K4M in press coating at a concentration of 5% and 20%, and two levels of factor X3 HPMC 15cps in press coating at a concentration of 5% and 20%. The responses studied were drug release, lag time, and swelling index.

The number of experiments (N) required for the development of BBD is defined as.

$N = 2k (k - 1) + Co,$

Where, k is the factors in the design and Co are the central point in the design.

Since there are three factors, three levels, and three center points, the number of runs

according to the above equation is N = 2 × 3(3 – 1) + 3 = 15 runs.

15 fixed-dose combination tablet formulations were prepared to employ selected combinations of the three factors i.e., X1, X2, and X3 as per BBD and evaluated to find out the significance of combined effects of X1, X2, and X3 to select the best combination and the ratio required to achieve the desired delayed/prolonged and immediate release of drug from the dosage form.

The model is of the following form.

Y = b0 + b1 X1 + b3 X2 + b3 X3 + b4 X1 X2 + b5 X1 X3 + b6 X2 X3 + b7 X1 2 + b8 X2 2 + b9 X3 2 + E,

Where, Y is the selected response,

b0 –b9 are the regression coefficients,

X1, X2, and X3 are the factors studied, and

E is an error term.

Table 2: Factors and factor levels investigated in Box-Behnken experimental design.

Independent factors	Unit	Levels	
		Low	High
X1 = Amount of HPMC K100M for press coat	%	20	40
X2 = Amount of HPMC K4M for press coat	%	5	20
X3 = Amount of HPMC 15cps for press coat	%	5	20
Responses (Dependent factors)			
Y1 = Percentage cumulative Terbutaline release after 8 hr	%		
Y2 = Lag time at which drug release must occur	hr		
Y3 = Swelling index of the Tablet after 8 hr	%		

Formulation of press coated tablet

The coat blend was prepared by dry mixing all the excipients. Lactose (#60), MCC 112 (#40), HPMC K100M (#60), HPMC K4M (#60), HPMC 15cps (#60) were separately weighed and sifted. Sift-charged excipients were put one by one in the polyethylene bag for mixing. Lactose and MCC 112 were mixed for 10 minutes. Then polymers along with Povidone K30 were added and mixed for 15 minutes. Finally, magnesium stearate was added and mixed for 5 minutes. The blend was prepared for direct compression.

The press-coated tablets were prepared by the direct compression method. Formulations were made into two parts, the inner layer (containing immediate release core tablet) and the outer layer (containing polymer blend). Core tablets were compressed with punches and die of size 6.35 mm round flat-faced beveled D tooling punch. The outer layer was prepared with the

punches and dies of size 11.9 mm round shallow concave (SC) punch of D tooling. Immediate release core tablets (100 mg) were placed on dies filled with half of the outer layer (250 mg) and the final compression was made after filling the second half of the outer layer (250 mg) with a total of 500 mg.

Table 3: Composition of press coating.

Formulations	Lactose	MCC 112	HPMC K100M	HPMC K4M	HPMC 15 cps	Povidone K30	Magnesium Stearate
F1	148.75	148.5	100	25	62.5	10	5
F2	107.5	107.5	100	100	62.5	15	7.5
F3	147.5	147.5	100	62.5	25	10	7.5
F4	106.25	106.25	100	52.5	100	15	10
F5	102.5	102.5	150	25	100	10	10
F6	101.25	101.25	150	62.5	62.5	15	7.5
F7	102.5	102.5	150	100	25	10	10
F8	63.75	63.75	150	100	100	15	7.5
F9	103.75	103.75	150	62.5	62.5	10	7.5
F10	102.5	102.5	150	62.5	62.5	15	5
F11	140	140	150	25	25	10	10
F12	96.25	96.25	200	25	62.5	15	5
F13	97.5	97.5	200	62.5	25	10	7.5
F14	57.5	57.5	200	62.5	100	15	7.5
F15	58.75	58.75	200	100	62.5	10	10

Evaluation of Press coated tablets

***In-vitro* Dissolution studies**

In–vitro dissolution studies of pulsatile delivery systems were done with the conventional paddle method at 37^{o}C ± 0.5°C using pH 1.2 buffer for the first 2 hours and 6.8 phosphate buffer for the rest of 6 hours in USP II paddle method at 100 rpm. 5 ml of filtered aliquot was manually withdrawn at pre-determined time intervals and replaced with 5 ml of fresh buffer maintained at the same temperature. The samples were then analyzed at 276 nm using a UV spectrophotometer. The lag time and percentage release were determined for each formulation.

Lag time

Lag time is the time before the drug release has started or the time in which less than 10% of the drug has been released. The lag time (hr) for all the 15 formulations was obtained from the in vitro dissolution study of the press-coated tablets.

Swelling index

The initial weight of the tablets (W_1) was noted and placed individually into petridish containing 10 ml of pH 6.8 buffer. The weight of the tablets (W_2) was noted after every hour for 8 hours after wiping out the excess water using filter paper. The swelling index was being calculated using the formula.

$$\text{Swelling index} = \frac{W_2 - W_1}{W_1} \times 100$$ [16]

Stability studies

As per the ICH guidelines, stability studies were carried out for the optimized formulation to assess the drug and formulation stability. The optimized formulation was sealed in aluminum packaging and kept in a humidity chamber maintained at 25°C ± 2°C with 60 ± 5% RH; 30 °C ± 2°C and RH 65% ± 5%; 40 °C ± 2°C, 75 ± 5% for three months. At the end of the studies, samples were analyzed for the post-compression parameters like physical properties and drug content.

RESULTS AND DISCUSSION

The standard calibration curve yields a straight line (regression value of 0.999) which proves linearity and shows that terbutaline sulfate obeys Beer's law at 276 nm in the presented concentration range.

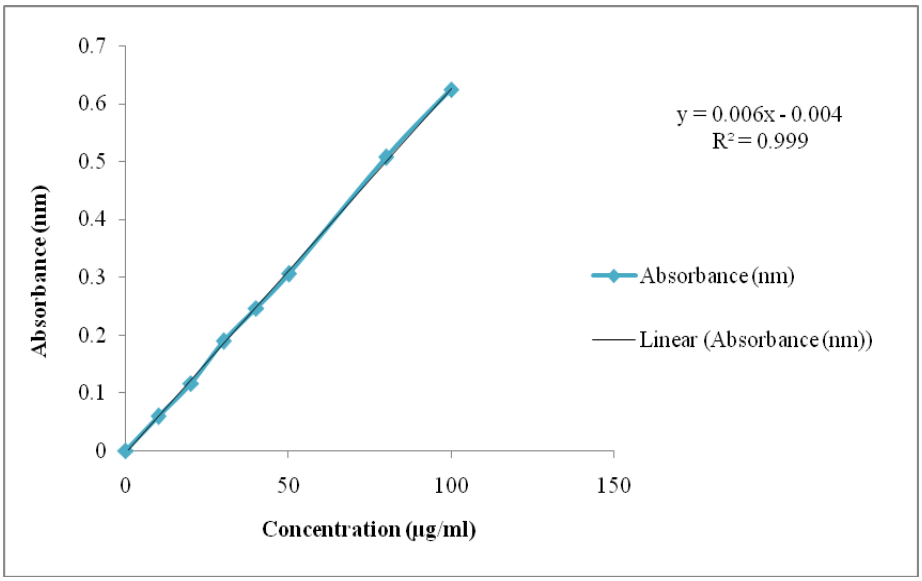


Fig. 1: Calibration curve of Terbutaline sulfate.

The characteristic peaks of terbutaline sulfate observed at 3323.09 cm–1 were for N-H stretching vibrations, 2783.17 cm–1 for O-H stretching, 1609.20 cm–1 for C=C stretching,

1379.40 cm-1 for C-H bending, 1311.62 cm-1 for S=O stretching, and 1107.30 cm-1 for C-O stretching. These peaks were present in all three physical mixture spectra consisting of terbutaline sulfate with varying polymers. All the characteristic peaks of terbutaline sulfate were present in spectra at respective wavelengths, indicating compatibility between drug and polymers (HPMC K10M, HPMC K4M, and HPMC 15cps). It shows that there was no significant change in the chemical integrity of the drug.

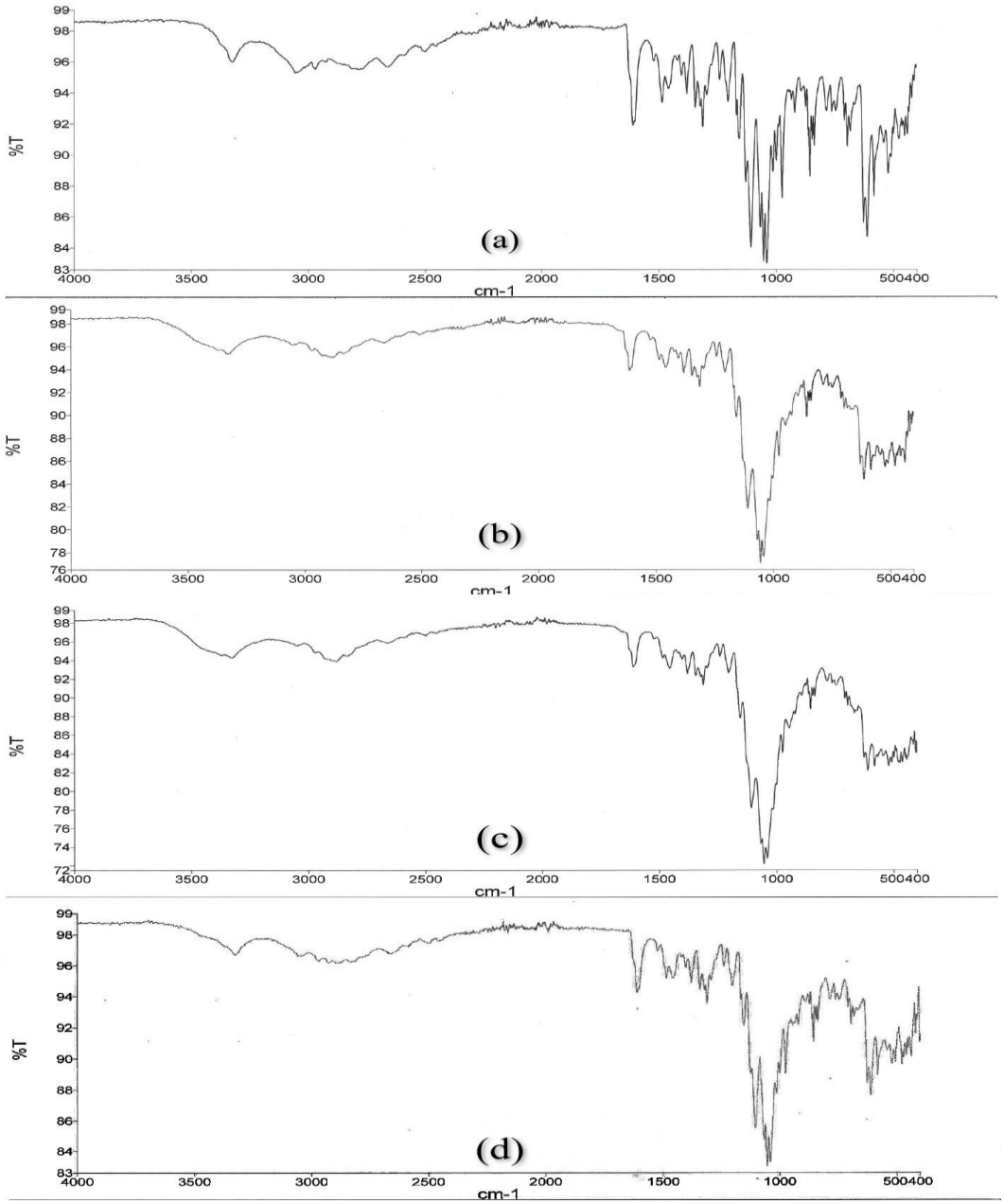


Fig. 2: Combined FTIR spectra for (a) terbutaline sulfate (b) terbutaline sulfate + HPMC K100M (1:1) **(c) terbutaline sulfate + HPMC K4M** (1:1) **(d) terbutaline sulfate + HPMC 15cps** (1:1).

Table 4: FTIR peak positions and vibrations for terbutaline sulfate and its combination with polymers.

Materials	Test wave number (cm^{-1})	Mode of vibrations
Terbutaline sulfate	3323.09	N-H stretching
	2783.17	O-H stretching
	1609.20	C=C stretching
	1456.65	C-H bending
	1379.40	
	1311.62	S=O stretching
	1240.68	C-N stretching
	1107.30	C-O stretching
	1053.03	
Physical Mixture of Terbutaline sulfate and HPMC K100M	3326.54	N-H stretching
	1610.18	C=C stretching
	1379.29	C-H bending
	1311.78	S=O stretching
	1107.22	C-O stretching
	1052.95	
Physical Mixture of Terbutaline sulfate and HPMC K4M	3329.07	N-H stretching
	2883.17	C-H stretching
	1379.26	C-H bending
	1311.93	S=O stretching
	1106.97	C-O stretching
	1053.06	
Physical Mixture of Terbutaline sulfate and HPMC 15 cps	3328.36	N-H stretching
	2887.12	C-H stretching
	1609.81	C=C stretching
	1379.53	C-H bending
	1311.68	S=O stretching
	1107.49	C-O stretching
	1053.09	

The results were obtained for core granules in Table 5 where Hausner's ratio and Carr's index values were within the limits. The angle of repose was excellent which depicts that the formulations have a good flow property.

Table 5: Evaluation of terbutaline core granules.

Core Formulations	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Carr's index (%)	Angle of repose (θ)
C1	0.570±0.01	0.678±0.02	1.19±0.04	15.92±1.20	26.84±2.36
C2	0.546±0.02	0.606±0.02	1.11±0.05	9.90±1.22	26.56±3.12
C3	0.543±0.01	0.632±0.03	1.16±0.02	14.08±1.36	33.82±1.23

The weight of all the tablets was found to be within the range, hardness was constant and % friability of the tablets was also within the acceptable limits. The results obtained were as

shown in Table 6.

Table 6: Evaluation of terbutaline core tablets

Core Formulation	Weight Variation (mg)	Thickness (mm)	Hardness (N)	Disintegration Time (s)	Friability (%)	Assay (%w/w)
C1	101±0.34	2-31±0.2	96±5	133±5	0.09±0.01	98.23±0.1
C2	100±0.27	2.33±0.1	92±4	119±3	0.08±0.02	98.90±0.3
C3	101±0.39	2.32±0.3	78±9	201±4	0.1±0.03	98.76±0.1

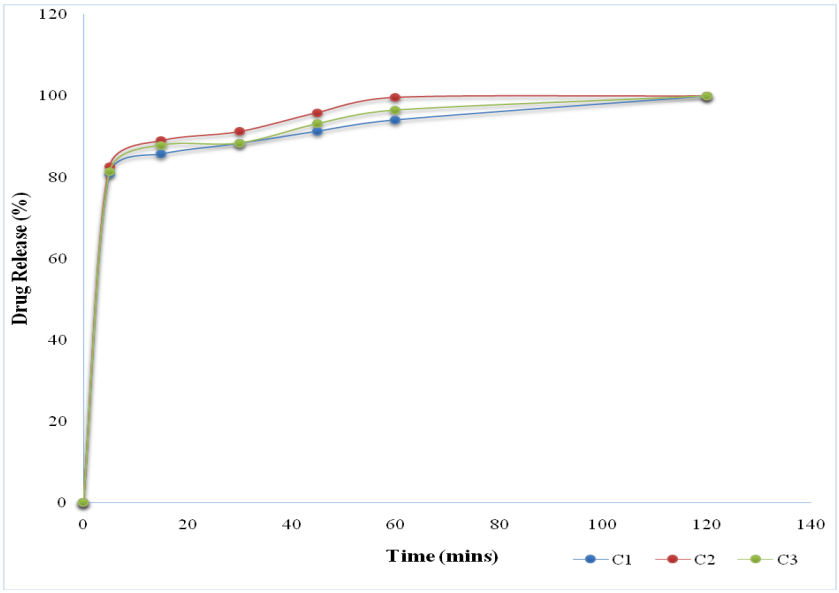


Fig. 3: Comparative *In-vitro* drug release profile of terbutaline sulfate core tablets.

The core tablet shows more than 80 % of drug release within 5 minutes. Upon contact with water, the core tablet swells up and releases the drug. The comparative dissolution study of all the three core formulations was also plotted in Fig. 3. The release of terbutaline sulfate from the core tablet indicates that the drug release rate is directly proportional to the amount and type of disintegrant used in each tablet. The release of terbutaline sulfate from the formulation of C2 was higher than in other formulations.

The formulation C1 contained sodium starch glycolate & crospovidone, the formulation C2 contained crospovidone & croscarmellose sodium, and the formulation C3 contained croscarmellose sodium and sodium starch glycolate as super disintegrants. The C2 formulation showed a faster dissolution profile as compared to the other two formulations i.e., C1 and C3. The core formulation C2 was selected for the further compression coating for the chronotherapeutic delivery of terbutaline sulfate.

Evaluation of press coated tablets

The results of the post-compression parameters performed on the press-coated tablets for batches F1 to F15 are tabulated in Table 7. The weight variation was found to be in the range of 600±0.14 to 601±0.23 mg, the thickness was found to be in the range 4.51±0.25 to 4.83±0.23 mm, and the hardness in the range of 125 to 178 N. The friability and assay values were found to be within the limits.

Table 7: Evaluation of terbutaline sulfate press coated tablets.

Formulations	Weight variation (mg)	Thickness (mm)	Hardness (N)	Friability (%)	Assay (% w/w)	Lag Time (hr)	Swelling Index (%)
F1	601±0.23	4.81±0.21	150±5	0.11±0.01	99.98±0.01	3	153
F2	600±1.01	4.82±0.23	153±4	0.14±0.01	100.32±0.02	3.5	178
F3	600±1.23	4.52±0.24	164±2	0.1±0.01	99.89±0.12	4.2	159
F4	600±0.54	4.81±0.21	178±4	0.1±0.01	99.56±0.45	4.5	167
F5	600±0.74	4.83±0.23	155±5	0.1±0.01	102.52±0.25	5.5	297
F6	600±0.24	4.82±0.21	145±2	0.1±0.01	98.59±0.28	4	258
F7	600±0.15	4.81±0.23	125±1	0.1±0.01	99.52±0.24	7	300
F8	600±0.36	4.83±0.21	158±6	0.1±0.12	99.75±0.31	6.3	287
F9	600±1.45	4.81±0.21	134±4	0.1±0.01	99.45±0.14	6.6	263
F10	600±0.25	4.82±0.22	142±8	0.1±0.12	99.65±0.25	6.7	275
F11	600±0.14	4.81±0.24	137±7	0.1±0.23	99.63±0.28	6.5	257
F12	600±0.36	4.82±0.23	147±9	0.1±0.01	99.28±0.64	8	309
F13	600±0.57	4.82±0.52	153±7	0.1±0.12	99.47±0.28	8	324
F14	600±0.45	4.51±0.25	173±6	0.1±0.14	99.85±0.52	7.5	331
F15	600±0.68	4.68±0.24	157±4	0.1±0.15	100.34±0.52	7.2	347

The formulations containing a higher concentration of HPMC showed a very high lag time and swelling index. The formulations with moderate concentrations of HPMC showed lag time between 6.3 – 7 hours. The lag time varied from 3 – 8 hrs, which was further optimized to obtain the desired lag time of 6.5 hrs.

The dissolution study was carried out for 8 hours where the first 2 hours were carried out in 0.1N HCl (pH 1.2 buffer) while the rest of 6 hours in pH 6.8 buffer. The formulations F1, F2, F3, F4, F6, F9, F10, and F11 showed a faster release at the 5th hour i.e., 50 % of the drug was released. The formulations F7, F8, F12, F13, F14, and F15 showed a lower release at the 6th hour i.e., <40% indicating poor release whereas the formulation F5 showed a better release profile with a release of 96% at the 7th hour and only 34% release at 6th hour as given in Fig. 4.

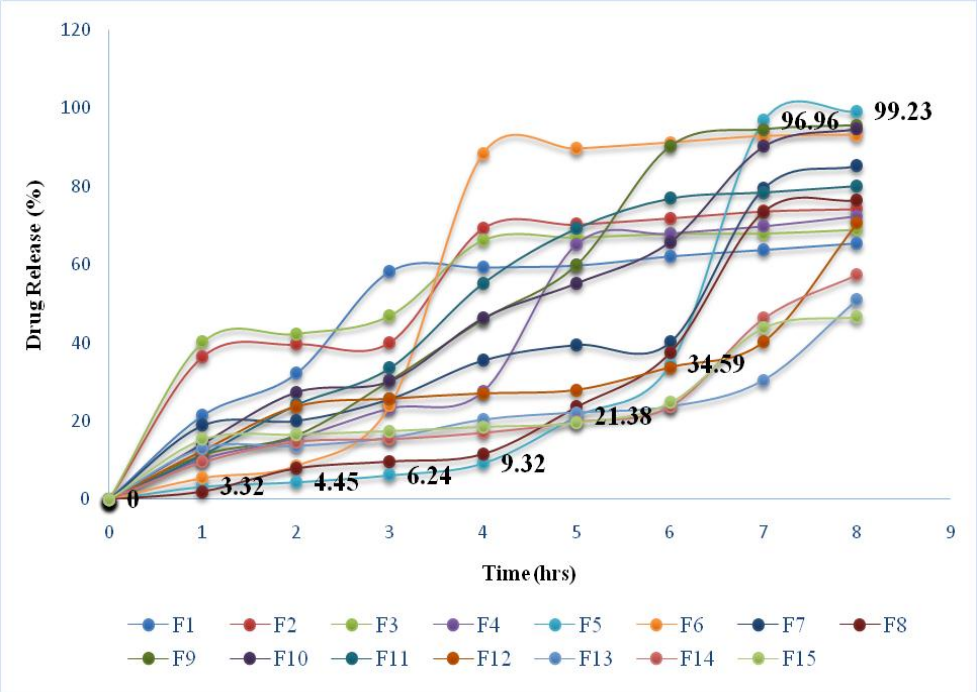


Fig. 4: Comparative In-vitro drug release profile of terbutaline sulfate press coated tablets.

Table 8: Design layout of terbutaline press coated tablets for optimization.

Run	Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3
	A:HPMC K100M	**B: HPMC K4M**	**C: HPMC 15cps**	**Y1: Drug Release**	**Y2: Lag Time**	**Y3: Swelling Index**
	mg	mg	mg	%	hrs	%
1	20	5	12.5	65	2	153
2	20	20	12.5	74	4.5	178
3	20	12.5	5	68	3	159
4	20	12.5	20	72	4.2	167
5	30	5	20	99	6.5	297
6	30	12.5	12.5	93	6.5	258
7	30	20	5	85	8	300
8	30	20	20	76	6.2	287
9	30	12.5	12.5	95	6.7	263
10	30	12.5	12.5	94	6.6	275
11	30	5	5	80	4	257
12	40	5	12.5	70	9	309
13	40	12.5	5	51	10	324
14	40	12.5	20	57	9.5	331
15	40	20	12.5	46	10	347

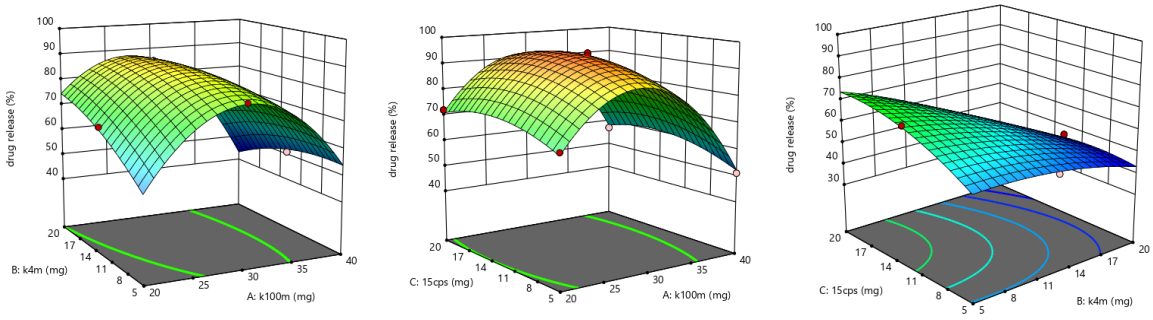


Fig. 5: Response surface plot (three dimensional) showing the effect of HPMC K100M, HPMC K4M, and HPMC 15 cps concentration on; (A) Drug release.

An increase in HPMC K100M concentration decreases the drug release and on increasing HPMC K4M the drug release increase but remains medium to some extent. An increase in the HPMC K100M decreases the drug release, whereas an increase in the concentration of HPMC 15cps increases the drug release as compared to that of HPMC K100M. An increase in the HPMC K4M increases the drug release to some extent, whereas an increase in the concentration of HPMC 15cps increases the drug release as compared to that of HPMC K4M which is evident from Fig. 5.

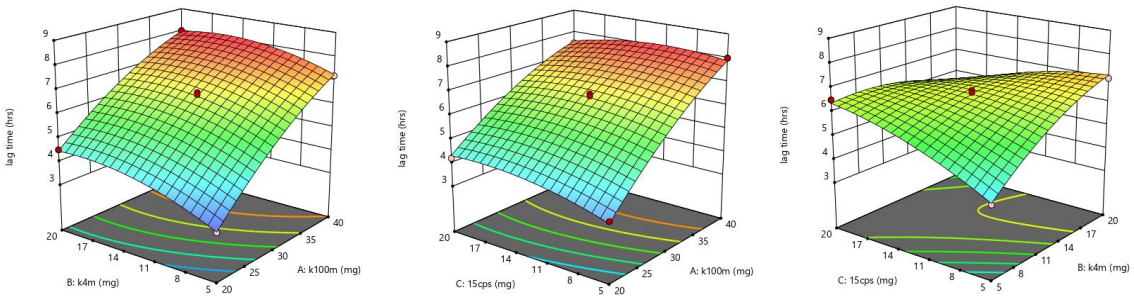


Fig. 6: Response surface plot (three dimensional) showing the effect of HPMC K100M, HPMC K4M, and HPMC 15 cps concentration on; (B) Lag time.

An increase in HPMC K100M concentration increases the lag time and on increasing HPMC K4M the lag time increases to some extent. An increase in the HPMC K100M increases the lag time, whereas an increase in the concentration of HPMC 15cps decreases the lag time to some extent. An increase in the HPMC K4M increases the lag time whereas an increase in the concentration of HPMC 15cps increases the lag time to some extent which is evident from Fig. 6.

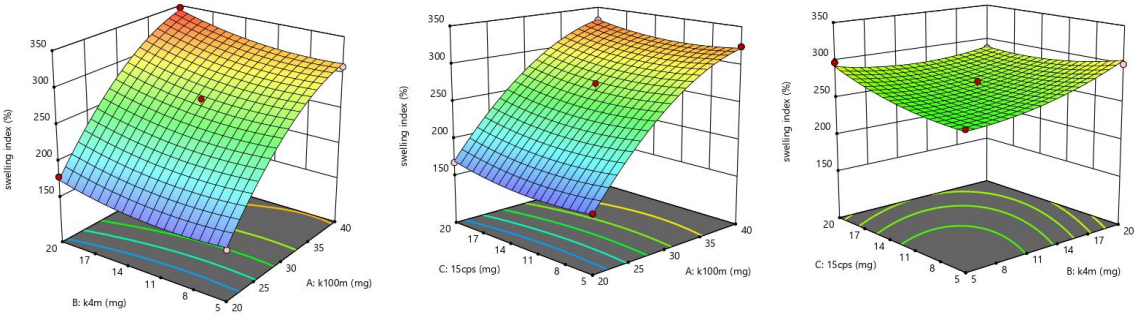


Fig. 7: Response surface plot (three dimensional) showing the effect of HPMC K100M, HPMC K4M, and HPMC 15 cps concentration on; (C) Swelling index.

An increase in HPMC K100M concentration increases the swelling index and on increasing HPMC K4M the swelling index also increases relatively but remains medium to some extent. An increase in the HPMC K100M increases the swelling index, whereas an increase in the concentration of HPMC 15cps increases the swelling index. An increase in the HPMC K4M relatively increases the swelling index whereas an increase in the concentration of HPMC 15cps also increases the swelling index to some extent which is evident from Fig. 7.

Table 9: ANOVA for response surface quadratic model for the responses.

Source	Y1- Drug release		Y2- Lag time		Y3- Swelling index		Interpretation
	F-value	p-value	F-value	p-value	F-value	p-value	
Model	155.08	< 0.0001	119.51	< 0.0001	116.48	< 0.0001	Significant
A-k100m	142.69	< 0.0001	838.08	< 0.0001	937.43	< 0.0001	
B-k4m	51.37	0.0008	64.5	0.0005	20.2	0.0064	
C-15cps	18.87	0.0074	5.02	0.0751	3.87	0.1064	
AB	102.74	0.0002	3.42	0.1237	0.7408	0.4287	
AC	0.3774	0.5659	10.05	0.0248	0.0044	0.9498	
BC	73.96	0.0004	111.63	0.0001	12.31	0.0171	
A^2	987.71	< 0.0001	16.83	0.0093	55.55	0.0007	
B^2	18.31	0.0079	21.25	0.0058	7.42	0.0415	
C^2	40.25	0.0014	11.16	0.0205	5.49	0.0661	
Lack of Fit	3.75	0.2176	0.7115	0.629	0.5786	0.6833	Not significant

Table 10 shows adjusted R^2 for the responses Y1, Y2, and Y3 which is in reasonable agreement with the predicted R^2.

Table 10: Response model and statistical parameters obtained from ANOVA for BBD.

Responses	Adjusted R^2	Predicted R^2	Model P-value	Adequate precision	%CV
Drug release	0.99	0.9503	<0.0001	40.7212	2.17
Lag Time	0.9991	0.9977	0.001	126.8864	1.2
Swelling Index	0.9867	0.959	0.002	30.4076	2.9

Table 11: Polynomial equations.

Polynomial equations	
Drug release (Y_1)	$Y_1 = 94.00 - 6.88A - 4.13B + 2.50C - 8.25AB + 0.5000AC - 7.00BC - 26.62A^2 - 3.62B^2 - 5.38C^2$
Lag Time (Y_2)	$Y_2 = 6.60 + 3.10A + 0.9000B + 0.1750C - 0.3750AB - 0.4250AC - 1.07BC + 0.1375A^2 + 0.3625B^2 - 0.0625C^2$
Swelling Index (Y_3)	$Y_3 = 265.33 + 81.75A + 12.00B + 5.25C + 3.25AB - 0.2500AC - 13.25BC - 29.29A^2 + 10.71B^2 + 9.21C^2$

A mathematical relationship in the form of a polynomial equation for the measured responses was obtained with the statistical software. The equation represents the quantitative effect of variables (X1, X2, and X3) and their interactions on the responses (Y1, Y2, and Y3). Coefficients with more than one-factor term and those with higher-order terms represent interaction terms and quadratic relationships respectively. A positive sign represents a synergistic effect, while a negative sign indicates an antagonistic effect.

Table 12: Point Prediction for press coated tablets.

Point Prediction	Drug release 8 hours (%)	Lag Time (hr)	Swelling Index (%)
Predicted	98.64±1.41	6.379±0.164	292.462±6.54
Observed	101.24±0.23	6.758±0.05	297.54±5.69
% error	2.63	5.94	1.73

% error = (observed value-predicted value)/predicted value x 100

Development of the optimum batch based on the statistical evaluations the software suggested several solutions for compression coating and selected one as the optimal composition. The immediate-release core tablet was press coated with the optimal composition suggested by the software. The predicted lag time was 6.5 hrs. The desirability of optimum formulation was 0.986. When the desirability value is between 0.8 and 1, the formulation quality is regarded to be acceptable and excellent. When this value is <0.63, the formulation quality is regarded as poor.

An optimum and stable formulation has the highest drug release, a lag time of 6.5 hours, and a swelling index of 297%. Using this approach, a set of components was found. A composition of 30.0% of HPMC K100M, 5.0% of HPMC K4M, and 20.0% of HPMC 15cps was predicted that the terbutaline sulfate press coated tablets would have drug release of 101.24%, a lag time of 6.5 hours, and swelling index of 299% respectively.

Table 13: Optimum formulation derived by BBD.

Optimized formulation	HPMC K100M	HPMC K4M	HPMC 15cps	Desirability
	30	5	20	0.986

Table 14: Post Compression report of Optimized Press Coated Tablets.

Formulations	Weight Variation (mg)	Thickness (mm)	Hardness (N)	Friability (%)	Assay (%w/w)
Optimized Formulation	600±0.24	4.83±0.13	160±5	0.1±0.01	100.42±0.55

Table 15: *In - Vitro* release of optimized formulation.

Time (hrs)	Optimized Formulation
1	1.41±1.23
2	2.25±2.12
3	3.63±1.25
4	6.58±1.63
5	11.36±1.24
6	42.36±1.42
7	99.32±1.45
8	101.24±2.31

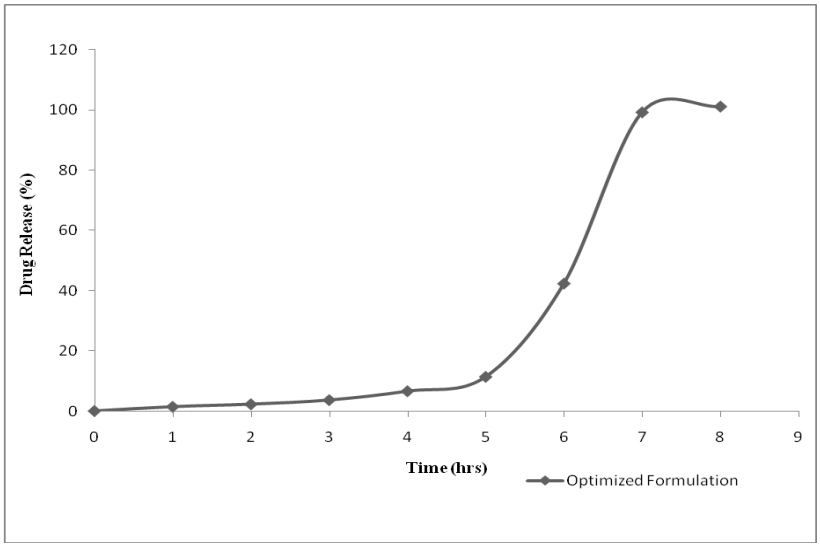


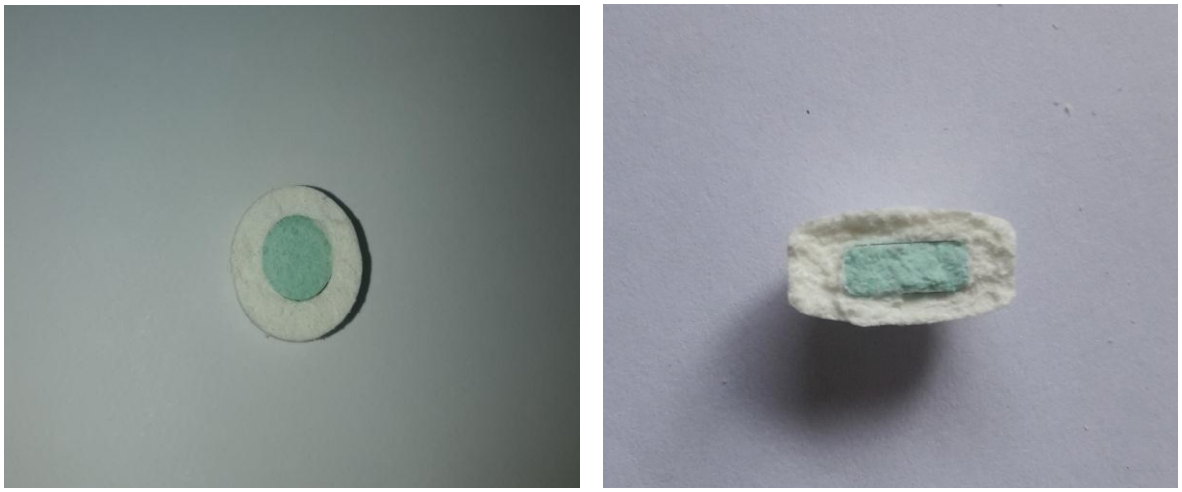
Fig. 8: Dissolution profile of Terbutaline Sulfate Optimized formulation.

Table 16: Lag time and swelling index of optimized terbutaline sulfate press coated tablets.

Formulation	Lag Time (Hrs)	Swelling Index (%)
Optimized formulation	6.5	299

Transverse ad longitudinal section view of optimized press coated tablet

To show the proper alignment of the core tablet at the middle within the press-coated tablet, the core tablet was colored. The tablet was cut using a surgical blade to verify the positioning of the core tablet. Fig. 9 shows the images of these sections which is clear that the core tablet is placed exactly in the center of the press-coated tablet.



(a) **(b)**

Fig 9: Optimized formulation (a) Transverse section and (b) Longitudinal section.

Table 17: Stability testing parameters for optimized press coated formulation.

Storage condition	Appearance	Average weight (mg)	Drug content (%)
Short Term Studies (25°C ± 2 °C & 60 % ± 5 % RH)			
Initial	No change	600±0.25	101.24±1.52
First	No change	600±0.21	101.13±1.96
Third	No change	600±0.02	100.67±1.74
Long Term Studies (30°C ± 2 °C & 65 % ± 5 % RH)			
Initial	No change	600±0.26	102.15±0.58
First	No change	600±0.19	101.25±1.14
Third	No change	600±0.01	100.48±1.24
Accelerated Studies (40°C ± 2 °C & 75 % ± 5 % RH)			
Initial	No change	600±0.24	102.37±0.49
First	No change	600±0.03	101.21±0.76
Third	No change	599±0.56	98.69±1.28

CONCLUSION

Pulsatile release matrix tablets containing sandwiched inner layer of terbutaline sulfate were prepared by direct compression method. Hydrophilic polymers (HPMC K100M, HPMC K4M, and HPMC 15cps) with various concentrations and ratios were developed and evaluated. The formulation C2 containing crospovidone and croscarmellose sodium as

disintegrants followed the desired immediate release hence further press coating was carried out with this core formulation. Using Box-Behnken Design optimization was carried out where 15 press coated formulations with varying polymers were prepared. The optimized formulation obtained using Box-Behnken Design containing 30 % of HPMC K100M, 5 % of HPMC K4M, and 20 % of HPMC 15cps followed the desired release profile for a delayed-release layer with a lag time of 6.5 hours. These tablets had good swelling and delayed release over 8 hours. The optimized formulation was found stable under accelerated conditions for 3 months concerning physical characteristics and drug content.

The study suggested that the morning dose could be more effective for the treatment of nocturnal asthma by chronotherapy with terbutaline sulfate than the evening dose. It is difficult to prefer chronotherapeutic treatment with immediate-release dosage forms if the symptoms of asthma or any disease could occur during the night or early mornings. Hence, treatment with modified-release dosage forms with controlled higher plasma levels during the time of disease occurrence or incidence could be a more successful treatment than with the immediate-release dosage forms**.**

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