Available online on www.ijddt.com
International Journal of Drug Delivery Technology 2017; 7(1); 75-82
doi: 10.25258/ijddt.v7i1.8920
ISSN: 0975 4415

Research Article

Design and Evaluation of Chronotherapeutic Delivery of Terbutaline Sulphate by Pulsincap Technology

Sreejan M*, Krishnaveni V, Sai Padmini K, Satyavathi K, Bhojaraju P, Madhubabu M

Koringa College of Pharmacy, Korangi - 533 461, Tallarevu (M), E. G. Dt., Andhra Pradesh, India.

Received: 30th Dec, 2016; Revised: 11th Feb, 2017; Accepted: 25th Feb, 2017; Available Online: 1st March, 2017

ABSTRACT

The aim of the present research was to develop pulsincap formulation of terbutaline sulphate for chronotherapeutic colon targeted delivery. Formaldehyde treatment was done to increase the disintegration time of capsule body. Hydrogel plug was prepared by combining hydrophilic and hydrophobic polymers to obtain the exact degree of swelling. Based on the disintegration time of the capsule bodies, M3 formulation was selected for preparation of pulsincap. The powder blend was prepared by varying the concentration of sodium starch glycolate and sodium bicarbonate concentration with terbutaline sulphate. The pulsincaps were formulated with the optimized concentration of sodium starch glycolate and sodium bicarbonate sealed with prepared hydrogel plug. FTIR study confirms that there was no incompatibility between terbutaline sulphate and polymers. The drug content was estimated by using pH 7.4 buffer solution and it was found to vary between 97.37 ± 0.67 % to 100.45 ± 0.25 %. The swelling study was carried out by using three different buffer solutions and found in the range of 50.12 ± 0.21 %to 56.75 ± 0.61 %. Formulation F9 was found to have the desired time dependent drug release pattern, and hence was considered as the optimized formulation. From this study, it can be concluded that the pulsincap formulation can serve as a useful technique for time dependent colon targeted delivery of terbutaline sulphate.

Keywords: Terbutaline sulphate, pulsincap, chronotherapeutic, hydrogel plug, swelling index.

INTRODUCTION

Chronotherapeutics is a relatively new practice in clinical medicine that varies according to physiological need at different times during the dosing period[1]. A major objective of chronotherapy in the treatment of several diseases is to deliver the drug in higher concentrations during the time of greatest need according to the circadian onset of the disease or syndrome[2]. The chronotherapy of a medication may be accomplished by the judicious timing of conventionally formulated tablets and capsules[2,3]. In most cases, however, special drug delivery technology must be relied upon to synchronize drug concentrations to rhythms in disease activity[4]. A Pulsatile drug delivery system delivers the drug in rapid and burst manner within a short time period immediately after a programmable lag phase[5,6]. These systems are mainly appropriate for the drugs that are metabolized to pharmacological active compounds, drugs which have long *in-vivo* half lives showing an inherently prolonged duration of action[7], drugs with very short *in-vivo* half life which require a prohibitively large amount of active ingredients in dosage form, drugs which are required in large doses for therapeutic effect and drugs which are required in very low dose[8,9]. Additionally, a delayed burst release can also be utilized for enhancing absorption, reducing side effects, site specific delivery, improving the stability of drug and reduction of dosage forms without affecting the therapeutic effect[10]. Terbutaline sulphate chemically known as 5-[2-(tert-butylamino)-1-hydroxyethyl]benzene-1,3-diol is a relatively selective beta 2-adrenergic bronchodilator[11] that has little or no effect on alpha-adrenergic receptors[12]. Terbutaline sulphate appears to have a greater stimulating effect on beta-receptors of the bronchial, vascular, and uterine smooth muscles (beta 2 receptors) than on the beta-receptors of the heart (beta 1 receptors). This drug relaxes smooth muscle and inhibits uterine contractions, but may also cause some cardio stimulatory effects and CNS stimulation[13].

MATERIALS AND METHODS

Terbutaline sulphate was received as gift sample from RPG Life Sciences Ltd, Mumbai, India. Sodium starch glycolate, Sodium bicarbonate, Vivapur 302, were commercially purchased from S D Fine Chemicals Ltd, Mumbai. Ethyl cellulose, HPMC K100M, guar gum, xantural was procured from Otto Chemicals, Mumbai.

Methods

Drug-Excipient compatibility study by FT-IR

The FT-IR spectra were recorded using an IR spectrophotometer (Bruker- Alpha). The pellets were prepared by mixing with KBr disk method by compressing the powders at 20 psi for 10 min. The prepared pellets were scanned from of 4000- 600 cm^{-1}. FT-IR study was carried on Terbutaline sulphate, physical mixture of terbutaline sulphate and polymers like ethyl cellulose, guar gum, xantural and HPMC K100M & for the best formulation[14].

**Author for Correspondence: manna.sreejan@gmail.com*

Design of Pulsincap

Preparation of cross-linked gelatin capsule

About 100 hard gelatin capsules of size '0' were taken and their bodies were separated from the caps and placed on a wire mesh[15]. The bodies which were placed on a wire mesh were spread as a single layer. 25 ml of 15% v/v of formaldehyde solution was prepared and placed in a desiccator. To this 5 g of potassium permanganate was added. The wire mesh containing the bodies of the capsules was kept on the top of desiccator containing formaldehyde liquid at the bottom in equilibrium with its vapour and immediately the desiccator was tightly closed and sealed. The bodies of capsules were made to react with formaldehyde vapours by exposing them for varying periods of time viz., 3, 6, 9 and 12 h. Then they were removed and kept on a filter paper and dried for 24 h to ensure completion of reaction between gelatin and formaldehyde vapours. Afterwards, the capsules were kept in an open atmosphere to facilitate removal of residual formaldehyde[16]. These capsule bodies were capped with untreated cap and stored in a polythene bag.

Preparation of powder blends for filling into capsules

Accurate amount of drug, sodium starch glycolate, sodium bicarbonate, vivapur 302 and talc were taken as shown in Table No 1. All the ingredients were passed through sieve no 60 and then further mixed with the help of a mortar and pestle for 15 min.

Evaluation tests for crosslinked gelatin capsule shells

Physical test

The prepared formaldehyde treated capsule bodies were studied for stickiness, visual defects and dimensions. Variations in the dimensions (length and diameter) between the formaldehyde treated and untreated capsules were studied by using Vernier callipers.

Chemical test

Qualitative test for free formaldehyde

Standard formaldehyde solution

Dilute a suitable volume of formaldehyde solution with water to give a solution containing 20 µ g/ml of formaldehyde.

Sample solution

25 formaldehyde treated bodies were cut into small pieces and taken into a beaker containing distilled water (40 ml). This was stirred for 1h with a magnetic stirrer, to solubilize the free formaldehyde. The solution was filtered into a 50 ml volumetric flask, washed with distilled water and volume was made up to 50 ml with washings[17].

Procedure

1ml of sample solution was taken in a test tube in which 4 ml of water and 5 ml of acetyl acetone solution were added. The test tube was placed in a water bath at 40°C for 40 min. 1 ml standard formaldehyde solution was taken in a test tube as reference solution and kept in water bath under similar experimental condition. The intensity of the colour of sample solution was visually inspected and compared with the colour intensity of the standard solution.

Disintegration test for the prepared capsule bodies

Disintegration test for prepared formaldehyde treated capsule bodies was carried out by using Hiccon disintegration test apparatus. The capsule bodies were subjected in different buffer solutions, such as pH 1.2, pH 6.8 and pH 7.4 for disintegration test at temperature 37 ± 0.5°C. Formaldehyde treated capsule bodies were joined with untreated caps and was tested for disintegration time. The time taken to disintegrate the capsule bodies were noted down18.

Optimization of sodium starch glycolate and sodium bicarbonate concentration

Seven different formulations were prepared by varying the concentrations of sodium starch glycolate and sodium bicarbonate as given in Table 1. For each formulation, accurately weighed terbutaline sulphate and other excipients were passed through sieve no 60. All the ingredients were mixed uniformly to prepare a homogenous blend. Each formulation was punched as tablet by using tablet compression machine.

Preparation of hydrogel plug

Hydrogel plug was prepared by compressing in tablet punching machine where combinations of polymers in different ratios were used. Ethyl cellulose, guar gum, xantural gum and HPMC K100M were used in different proportions to prepare hydrogel plug. A tight fit between the hydrogel plug and capsule was maintained to prevent the water penetration in to the capsule which can release the drug prior to complete erosion of plug19.

Formulation of pulsincap of terbutaline sulphate

Nine different formulations were prepared by different excipients and polymers in varying ratios as shown in Table 2. Based on disintegration time, the 6 h formaldehyde treated capsule bodies were selected for pulsincap designing. For filling in to capsules, G7 formulation (sodium starch glycolate 8%, sodium bi-carbonate 4%) was selected depending on disintegration time. The hydrogel plug was prepared by using the combination of hydrophobic polymer like ethyl cellulose and natural and semisynthetic hydrophilic polymers like guar gum, xantural gum, HPMC K100M in different ratios. Homogenous mixture of drug and excipients were filled into the 6th h formaldehyde treated capsule body by manual filling method19. The compressed hydrogel plug in the form of a tablet was then placed to close the opening of the capsule body. The hydrogel plug was further covered by a cap. The joint of the treated capsule body and untreated cap was sealed with 5% ethyl cellulose ethanolic solution.

Evaluation of pulsincap dosage forms

Weight variation test

10 capsules were randomly selected from each batch and weighed individually for weight variation test. The test requirements are met if none of the individual weights are less than or more than 110% of the average[20].

Estimation of drug content

Drug content was measured by selecting 10 randomly selected pulsincaps from each formulation. The contents were removed from each pulsincap and 100 mg of powder was weighed accurately and transferred to a volumetric

flask. 10 ml of methanol was added to the volumetric flask to dissolve the terbutaline sulphate and the volume was made up with freshly prepared 7.4 pH phosphate buffer[21]. The resulted solution was filtered through Whatman filter paper and subjected to spectrophotometric (Elico Lab, SL 210) examination to measure the absorbance at 232 nm.

Determination of swelling index of hydrogel plug

Swelling index for the prepared hydrogel plug was determined by measuring the percentage of water uptake by the hydrogel plug. Initially the hydrogel plugs were accurately weighed and placed in 100 ml of 1.2 pH buffer solution for 2 h. Then the same hydrogel plug was removed and kept respectively in 100 ml 6.8 pH buffer solution for 3 h and in 100 ml of pH 7.4 buffer for remaining time. At definite time interval, the plugs were removed and from their respective swelling media and weighed after careful removal of surface water with the help of a filter paper[22]. Swelling index was calculated by using the following formula- Swelling index $= \frac{(S-T)}{T} \times 100$ Where, S = weight of the hydrogel plug after swelling at different time interval, T = initial weight of the hydrogel plug

In-vitro dissolution study

In- vitro drug release study for the prepared pulsincaps was carried out in USP I dissolution apparatus by rotating basket method[23]. In order to stimulate the pH changes along GI tract, three different dissolution media with pH 1.2, 6.8, 7.4 buffers were sequentially used. The temperature of the dissolution media was maintained at 37.4 ± 0.5º C and the speed of rotation of basket was adjusted to 50 rpm. The volume of the dissolution medium was maintained 900 ml for all the experiments. Initially, terbutaline sulphate pulsincaps were placed in basket in each dissolution vessel to prevent floating. Depending on the average gastric emptying time which is 2 h, the simulated gastric fluid was used as a dissolution medium for first 2 h of dissolution. Then the pulsincaps were subjected to simulated intestinal fluid pH 6.8 for next 3 h depending on average intestinal transit time. Then the medium was replaced with freshly prepared buffer solution of pH 7.4 for the remaining time. 5 ml of samples were withdrawn at predetermined time interval and replaced with same volume of similar dissolution medium. Then the samples were filtered and absorbance was measured spectrophotometrically (Elico Lab, SL 210) at λ_{max} 232 nm.

Release kinetics

To determine the release mechanism and kinetics, the result of the *in- vitro* dissolution study of formulated pulsincaps were fitted with various kinetic equations, such as zero-order, first-order, Higuchi's model, Korsmeyer-Peppas model and Hixon- Crowell model[24]. Correlation coefficient (R^2) values were calculated for the linear curves obtained by regression analysis of the above plots.

Zero order kinetics

The zero order describes the systems where the drug release rate is independent of its concentration. A zero order release would be predicted by the following equation, $Q_t - Q_0 = K_0 t$ Where, Q_t = Amount of drug release dissolved in time 't'. Q_o = Initial amount of drug concentration in solution. K_0 = Zero order rate constant. When the data was plotted as cumulative % drug release V_s time, if the plot is linear then data obeys zero order kinetics with slope equal to K_0. This model represents an ideal release profile in order to achieve the prolonged pharmacological action.

First order kinetics

The first order describes the release from system where release rate is concentration dependent. A first order release would be predicted by the following equation $Log\ Q_t = Log\ Q_0 - \frac{K_1 t}{2.303}$ Where, Q_t = Amount of drug released at time 't'. Q_o = Initial amount of drug concentration in solution. K_1t = First order rate constant. When data was plotted as log cumulative % drug remaining V_s time yields a straight line indicating that the release follows first order kinetics. The constant K can be obtained multiplying slope values.

Higuchi's model

Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion. The graph was plotted as % cumulative drug released Vs square root of time. $Q = Kt^{0.5}$ Where, K = Constant reflecting design variable system, t = time in h.

Korsmeyer-Peppas

Korsmeyer *et al*. (1983) derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer- Peppas model. To evaluate the mechanism of drug release, it was further plotted in Peppas equation as log cumulative % of drug released V_s time. $M_t / M_\alpha = Kt^n$

$Log\ M_t / M_\alpha = log\ K + n\ log\ t$

Where, M_t / M_α = fraction of drug released at time t, t = Release time, K = Kinetic constant, n = Diffusional exponent indicative of the mechanism of drug release. This model is used to analyze the release of pharmaceutical polymeric dosage forms depending on 'n' value when the release mechanism is not known or more than one type of release phenomenon was involved. $n \leq 0.43$ symbolize Fickian release, $0.43 < n < 0.85$ symbolize non-Fickian release, and $n \geq 0.85$ indicates a case II transport.

Table 1: Optimization of the formulations at variable drug polymer ratio.

Ingredients	G1	G2	G3	G4	G5	G6	G7
Terbutaline sulphate (mg)	10	10	10	10	10	10	10
Sodium Starch Glycolate (%)	2	2	2	2	4	6	8
Sodium Bicarbonate (%)	1	2	3	4	4	4	4
Talc (%)	2	2	2	2	2	2	2
Vivapur 302 (mg)	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total wt (mg)	150	150	150	150	150	150	150

Table 2: Composition of various formulations of terbutaline sulphate pulsincaps.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Terbutaline sulphate	10	10	10	10	10	10	10	10	10
Sodium starch glycolate	12	12	12	12	12	12	12	12	12
Sodium bicarbonate	6	6	6	6	6	6	6	6	6
Vivapur 302	105	105.5	106	106.5	107	107.5	108	108	108
Talc	3	3	3	3	3	3	3	3	3
Ethyl cellulose	5	4.5	4	3.5	3	2.5	2	2	2
Guar gum	8			9			11		
Xantural		8			9			11	
HPMC K 100M			8			9			11

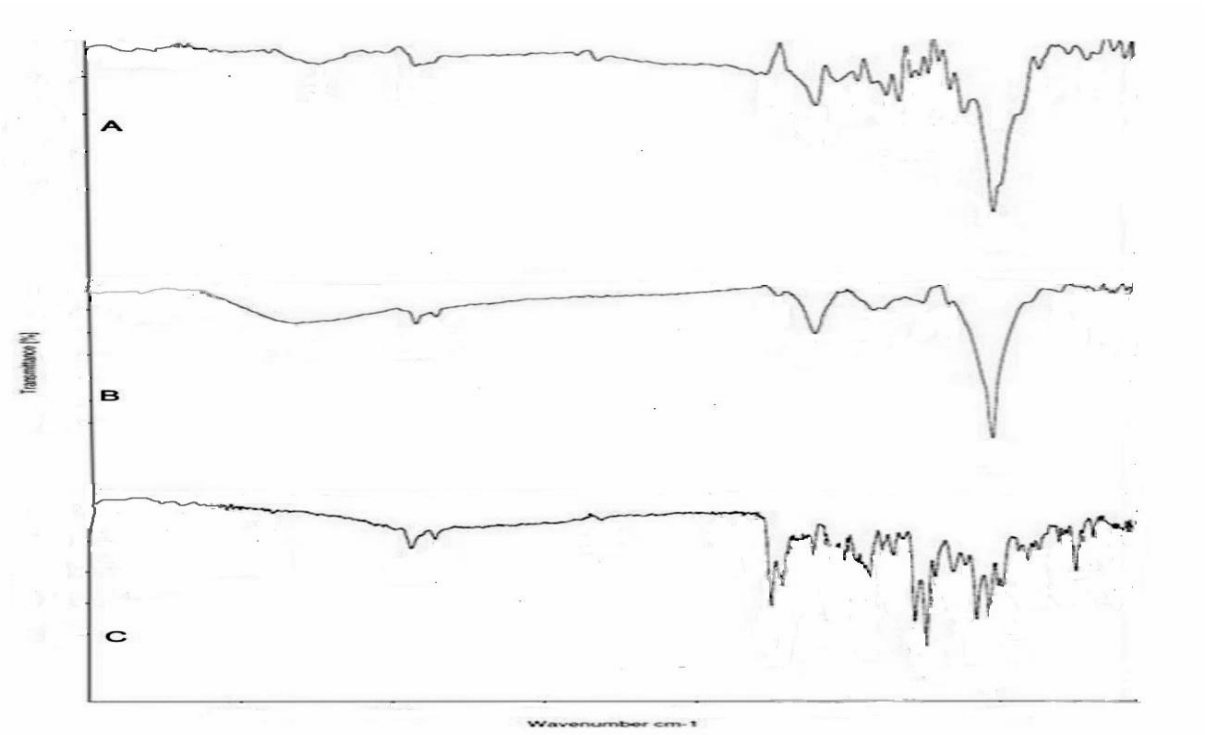

Figure 1: FTIR spectrum of – A - terbutaline sulphate; B – Terbutaline sulphate + vivapur; C – Formulation.

Table 3: Disintegration time for formaldehyde treated capsules.

Formulation Code	Disintegration Time (h)		
	1.2 pH (2 h)	6.8 pH (3 h)	7.4 pH (up to 24 h)
M1 (3rd h)	2	_	_
M2 (6th h)	2	3	3
M3 (9th h)	2	3	7
M4 (12th h)	2	3	19

Hixson-Crowell model

The Hixson-Crowell model describes the release from systems where there is a change in surface area and diameter of particles or tablets. $Q_t^{1/3} - Q_t^{1/3} = K_{HC}$ t Where, Q_t = Remaining amount of drug in the dosage form at time "t". Q_0 = Initial amount of the drug in the tablet. K_{HC} = Rate constant for Hixson-Crowell rate equation.

Stability studies

Stability studies were carried out at 40^0 C temperature and 75% RH for 30 days for all the formulation. All the pulsincap formulations were packed in amber coloured bottles and tightly plugged with cotton and capped. The sample was collected at every 10 days interval and visually inspected for physical appearance like colour, shape and swelling of hydrogel plug. Drug content was also determined after each sample collection[25].

RESULTS AND DISCUSSION

Compatibility study by FT-IR

FT-IR spectrum of pure drug Terbutaline sulphate shows peak at 3446.6 cm^{-1} for presence of amine group (N-H 2º) it is observed in formulation (3413.8 cm^{-1}). The FT-IR spectrum of Terbutaline sulphate showed peaks at 2920 cm^{-1},1602.7 cm^{-1}, 1363.6 cm^{-1}, 1288.4 cm^{-1} for C-H stretching for alkane, C-N 3º stretching for amine group, C=C stretching for aromatic ring, -O- stretching for ether respectively. In formulation FT-IR spectrum showed peaks at 2906.5 cm^{-1}, 1617.3 cm^{-1}, 1365.2 cm^{-1}, 1265.2 cm^{-1} for C-H stretching for alkane, C=C stretching for

Table 4: Swelling index of hydrogel plug for all the formulation.

Code	1st hr	2nd hr	3rd hr	4th hr	5th hr	6th hr	7th hr
F1	15.85±0.23	16.73±0.35	24.73±0.34	26.84±0.10	32.42±0.22	49.99±0.31	50.12±0.21
F2	14.99±0.24	17.94±0.27	25.73±0.32	32.84±0.17	36.97±0.26	48.24±0.25	51.12±0.31
F3	15.75±0.36	17.82±0.43	22.43±0.42	28.88±0.27	32.54±0.43	44.88±0.32	51.98±0.36
F4	17.62±0.45	19.45±0.41	23.56±0.54	26.89±0.32	32.87±0.32	49.72±0.36	52.34±0.46
F5	16.33±0.34	18.56±0.47	22.11±0.14	36.83±0.42	39.75±0.45	48.91±0.56	53.75±0.42
F6	16.52±0.56	17.93±0.56	21.67±0.19	37.82±0.45	48.62±0.49	52.85±0.61	56.02±0.51
F7	15.72±0.51	18.88±0.64	21.78±0.41	38.51±0.54	45.76±0.61	51.13±0.76	54.22±0.49
F8	17.32±0.47	19.36±0.65	24.67±0.28	32.67±0.64	38.51±0.41	50.24±0.91	55.82±0.57
F9	18.12±0.87	21.12±0.55	32.62±0.49	37.72±0.78	42.32±0.79	49.61±0.21	56.75±0.61

Table 5: *In-vitro* dissolution study for terbutaline sulphate pulsincap.

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	5.20±0.93	7.56±1.23	6.70±1.11	4.74±1.08	10.55±1.13	9.47±0.90	9.09±1.09	5.52±1.08	4.15±1.17
2	9.07±1.63	12.44±1.10	14.42±0.99	12.13±0.97	14.58±1.01	16.56±1.20	11.53±0.98	9.15±1.02	6.32±1.94
3	57.57±1.76	50.75±1.12	46.35±1.12	13.77±1.17	15.77±1.06	18.48±1.05	16.67±1.05	17.49±1.04	12.31±1.92
4	83.32±2.21	86.29±1.38	87.22±1.32	16.79±1.16	18.44±1.54	19.62±0.98	23.07±1.06	23.66±1.27	17.60±1.03
5	96.71±2.51	97.94±1.99	97.51±1.82	91.26±1.00	88±1.60	85.62±2.03	27.5±1.96	26.68±1.91	18.25±2.19
6				97.81±0.95	99.21±1,17	96.49±0.92	50.55±2.16	49.48±1.90	19.77±1.90
7							85.56±2.00	86.41±2.06	97.40±2.05
8							97.54±2.07	99.20±2.27	

Table 6: Release kinetics for different pulsincap formulation.

Formulation code	%Drug content (Mean ± S.D.)	Zero order R^2	First order R^2	Higuchi R^2	Korsemeyer-Peppas		Hixon-Crowell R^2
					R^2	n	
F1	98.04±0.43	0.883	0.826	0.735	0.892	0.352	0.890
F2	99.82±0.65	0.897	0.796	0.744	0.856	0.445	0.871
F3	100.22±0.43	0.895	0.802	0.742	0.874	0.433	0.867
F4	98.10±0.23	0.694	0.673	0.551	0.851	0.328	0.704
F5	99.07±0.55	0.716	0.623	0.567	0.733	0.496	0.694
F6	97.37±0.67	0.742	0.677	0.592	0.758	0.497	0.720
F7	100.45±0.25	0.827	0.638	0.675	0.823	0.480	0.732
F8	99.07±0.68	0.819	0.579	0.671	0.898	0.376	0.707
F9	99.35±0.76	0.510	0.394	0.398	0.834	0.297	0.438

aromatic ring, C-N 3º stretching for amine group, -O- stretching for ether respectively. Thus it can be said that Terbutaline sulphate compatible with excipients and no significant changes occurred in drug properties.

Characterization of powder blend

The powder blend was studied for angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio and result for all the parameters were found satisfactory.

Evaluation of formaldehyde treated capsules

Physical tests

Identification attributes

The size '0' capsules chosen were opaque, with white coloured body and red cap. The normal capsule bodies were soft and sticky when touched with wet hand. After formaldehyde treatment, there were no significant changes in the physical appearance of the capsules except the stickiness. The body of capsule was found hard and non-sticking even when touched with wet hand due to treatment with the formaldehyde.

Visual defects

the formaldehyde treated capsules were visually inspected for any kind of defects. Among 100 capsules, 16 capsules were identified to have defects. The defected capsules were found to have shrunk and distortion into different shapes due to complete loss of moisture.

Dimensions

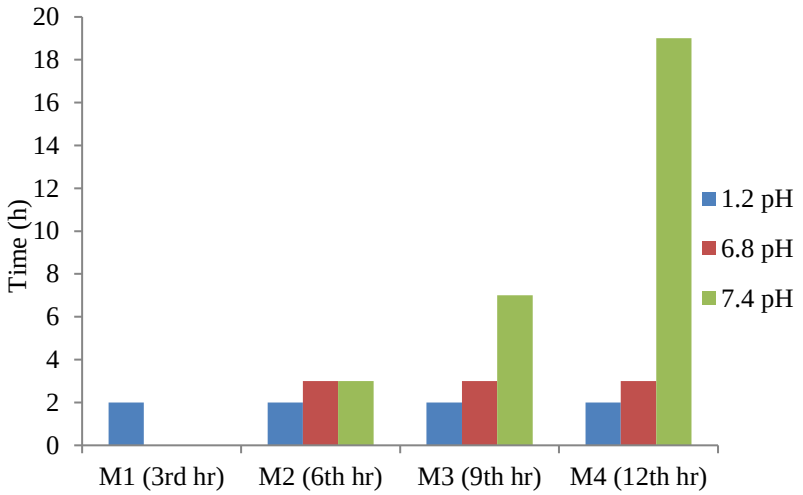

Figure 2: Comparative disintegration time for formaldehyde treated capsules.

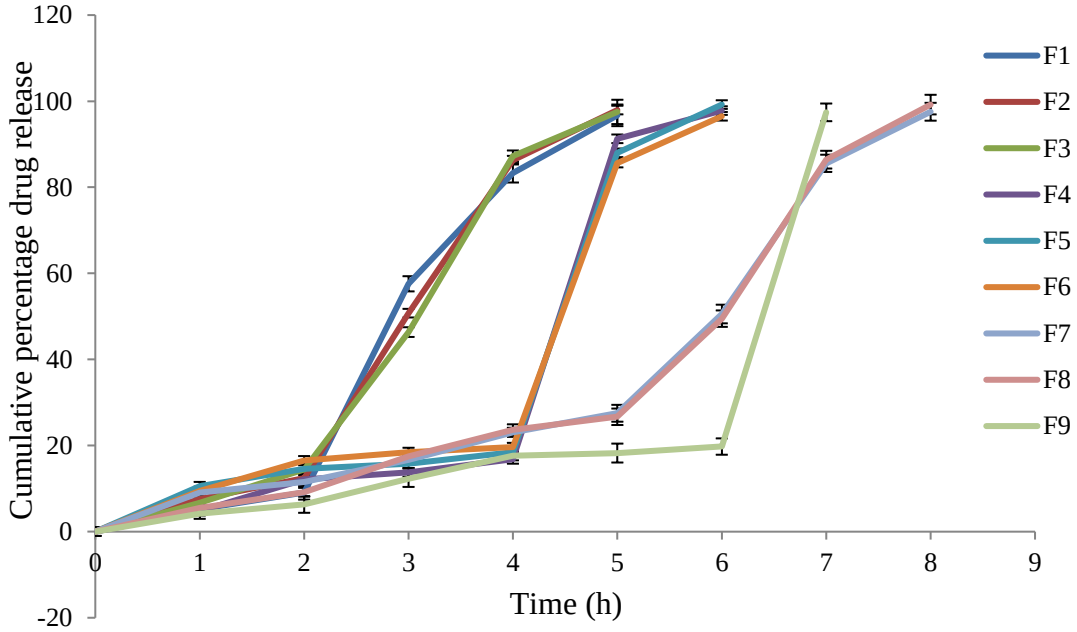

Figure 3: Comparative *in-vitro* dissolution study for all the formulation.

The dimensions of the capsules were examined before and after formaldehyde treatment for separately body and cap portion. The formaldehyde treated '0' size capsules showed significant decrease in length and diameter (data not shown in table). The decrease in capsule dimension is due to shrinkage occurred by formaldehyde treatment.

Qualitative test for free formaldehyde

The formaldehyde treated capsules were tested for the presence of free formaldehyde by comparing colour of sample solution with standard solution. It was found that the sample solution was not more intensity coloured than the standard solution inferring that less than 20µg/ml of free formaldehyde was present in 25 capsule bodies.

Disintegration test for prepared formaldehyde treated capsules

All the formaldehyde capsules were subjected to pH 1.2, 6.8 and 7.4 for 2 h, 3 h and up to 24 h respectively. It was observed that the hardened bodies of capsules which were exposed to formaldehyde vapours for 3 h (M1) got softened and became very sticky masses in 1.2 pH medium after 2 h. The capsule bodies exposed for 6 h, 9 h, 12 h (M2, M3, M4 respectively) to formaldehyde treatment did not disintegrate in 1.2 pH HCl buffer after 2 h of test. Formulation M2, M3 and M4 was disintegrated after 8 h, 12 h and 19 h respectively.

Drug content

The drug content for the prepared pulsincaps of terbutaline sulphate was determined by using pH 7.4 phosphate buffer. The drug content for all the formulation was found within the range of 97.35 ± 0.76 to 100.45 ± 0.25 (data shown in Table 6).

Swelling index

The swelling index for the prepared hydrogel plugs were carried out in three different buffer solutions. After 7 h of study in pH 1.2, 6.8, 7.4 buffers, the swelling index was found to be within the range of 50.12±0.21to 56.75±0.61 as shown in Table 4. The swelling behaviour of hydrogel

Table 7: Stability study for all the formulation.

Formulation	% Drug content (Mean ± S.D.)	Physical Appearance		Swelling index of hydrogel plug (Mean ± S.D.)
		colour	shape	
F1	96.64±0.11	No change	No change	52.24±0.36
F2	98.14±0.15	No change	No change	50.12±0.27
F3	100.22±0.25	No change	No change	51.12±0.48
F4	99.37±0.34	No change	No change	51.72±0.37
F5	100.70±0.41	No change	No change	54.55±0.41
F6	99.37±0.48	No change	No change	57.17±0.27
F7	99.37±0.65	No change	No change	53.58±0.64
F8	98.14±0.69	No change	No change	56.52±0.35
F9	99.37±0.51	No change	No change	56.05±0.59

plug was found maximum in pH 7.4 buffer solution. The least swelling index was found for F1 formulation which contains the highest amount of ethyl cellulose. This phenomenon could happen due to the non swelling nature of ethyl cellulose. The higher concentration of HPMC K 100 M was found to have a positive impact on swelling index of hydrogel plug.

In-vitro drug release studies

All the 9 formulations of Terbutaline sulphate pulsincaps were subjected to dissolution studies by using USP type I dissolution apparatus. A complete release of terbutaline sulphate was observed after 5 h of dissolution for F1, F2 and F3 (96.71 ± 1.514, 97.943 ± 0.990, 97.51 ± 0.822% respectively). Though a restricted swelling is observed after 5 h for F1, F2 and F3 but due to the presence of ethyl cellulose in more concentration in hydrogel plug polymeric erosion takes place which is responsible for sudden burst drug release after 5 h. F4, F5, F6 shows complete release after 6 h of dissolution (97.813 ± 0.957, 99.213 ± 1.173, 96.493 ± 0.925% respectively). Moderate concentration of ethyl cellulose is present in formulation F4, F5 and F6 which results partial erosion of polymeric hydrogel plug. Burst release of terbutaline sulphate is observed at 5^{th} h for F4, F5 and F6. Complete dissolution of drug is observed for F7 and F8 after 8 h of dissolution (97.543±1.072, 99.206±0.277% respectively). Gradual increase in dissolution rate is observed for F7 and F8. F9 shows a sudden burst release of terbutaline sulphate after 6 h of dissolution and a complete release of 97.403±1.050 % is achieved at 7^{th} h. Formulation F9 shows least amount of polymeric erosion of hydrogel plug. The burst release is observed due to removal of hydrogel plug from capsule body after 6 h of swelling. F9 is considered as best formulation considering the time dependent drug release pattern.

Release kinetics

The *in-vitro* drug release data were kinetically evaluated using various different mathematical models like zero order, first order, Higuchi model, Korsemeyer-Peppas and Hixon-Crowell model. The correlation values (R^2) of all the models were determined and the nearer value to 1 was considered as best fit model. F1, F6, F8, F9 were found to follow Korsemeyer- Peppas release kinetics. F2, F3, F5, F7 were following zero order kinetics and F4 was found to follow Hixon-Crowell model. The release exponent was determined for all the formulation and found within 0.297–0.497 indicating a non-Fickian release mechanism.

Stability testing

The results of accelerated stability study showed that there was no significant change in the prepared pulsincap formulation after one month. The physical appearance such as colour, shape was checked after one month and was not found to show any variability. The drug content and swelling index of hydrogel plug was also evaluated after one month and no significant changes were found.

CONCLUSION

The aim of this study was to explore the feasibility of time and pH dependent colon specific, pulsatile drug delivery system of terbutaline sulphate to treat bronchial asthma. The FTIR study confirmed that there was no significant interaction between terbutaline sulphate and polymers. Formaldehyde treated capsules were prepared and with selected capsules pulsincaps of terbutaline sulphate was developed. Hydrogel plugs were prepared with hydrophilic and hydrophobic polymer combination. HPMC K 100M was selected as hydrophilic swellable polymer and ethyl cellulose as an erodible hydrophobic polymer. Swelling behaviour of hydrogel plug was studied in various buffer solution and F9 was found to have highest swelling index due to more concentration of HPMC K 100M. F9 showed 6 h of lag time when subjected to dissolution study. After 6 h of time burst release of terbutaline sulphate is observed due to removal of hydrogel plug from the capsule body. The dissolution data were kinetically analysed for release pattern and it was found that F9 was following Korsemeyer- Peppas kinetics. Stability study confirms that the formulations are stable in elevated temperature and humidity. It can be evidently concluded that pulsincap formulation of terbutaline sulphate is an effective means to treat bronchial asthma.

ACKNOWLEDGEMENT

This work was encouraged by the management of Koringa College of Pharmacy, Korangi, Andhra Pradesh, India.

REFERENCES

1. Sarasija S, Stutie P. Chronotherapeutics: Emerging role of biorhythms in optimizing drug therapy. Indian J. Pharm. Sci 2005; 67(2) 135-140.
2. Prevesh K, Sunil S, Hemendra G, Ajit KY. A review on impact of chronopharmaceutics on the treatment of disease. Int. J. Appl. Pharm 2013; 5(2) 19-25.

3. Lemmer B. Chronopharmacology: time, a key in drug treatment. Ann Biol.Clin. 1994; 52(1) 1-7.
4. A.E. Reinberg, Concepts of circadian chronopharmacology, in: W.J.M. Hrushesky, R. Langer, F. Theeuwes (Eds.), Temporal Control of Drug Delivery, 618, Ann. NY Acad. Sci., 1991, 102–115.
5. Deepika J, Richa R, Vikas J, Praveen B, Ranjit S. Recent technologies in pulsatile drug delivery systems. Biomatter 2011; 1(1): 57–65.
6. Bussemer T, Otto I, Bodmeier R. Pulsatile drug-delivery systems. Crit Rev Ther Drug Carrier Syst. 2001;18: 433–58.
7. Shidhaye SS, Lotlikar VM, Ghule AM, Phutane PK, Kadam VJ. Pulsatile drug delivery systems: an approach for chronotherapeutic diseases. Sys Rev Pharma. 2010;1: 55–61.
8. Ritschel WA, Forusz H. Chronopharmacology: a review of drugs studies, methods find. Exp Clin Pharmacol. 1994; 16:57–75.
9. Reddy RK, Jyothsna MV, Mohamed TS. Saleem, Chetty CMS. Review on: pulsatile drug delivery systems. J Pharm Sci Res. 2009; 1:109–15.
10. Benjamin JB, Geoffrey DM, Carol SL. Basics and recent advances in peptide and protein drug delivery. Ther Deliv. 2013; 4(11): 1443–1467.
11. Paolo M, Giovanni C. Bronchodilating Drugs for Chronic Obstructive Pulmonary Disease: Current Status and Future Trends. J. Med. Chem., 2015**;** *58* (10), 4131–4164.
12. Takahashi HK, Morichika T, Iwagaki H, Yoshino T, Tamura R, Saito S, Mori S, Akagi T, Tanaka N, Nishibori M. Effect of beta 2-adrenergic receptor stimulation on interleukin-18-induced intercellular adhesion molecule-1 expression and cytokine production. Pharmacol Exp Ther. 2003; 304(2):634-642.
13. Ravi G, Padmakar A, Sathe B, Sudesh B. Simultaneous Quantitative Determination of Terbutaline and Theophylline from Drug Product by RP-HPLC Method. Biological Forum – An International Journal 2013; 5(1): 33-41.
14. Manna S, Lakshmi US, Racharla M, Sinha P, Kanthal LK, Kumar SPN. Bioadhesive Hpmc Gel Containing Gelatin Nanoparticles for Intravaginal Delivery of Tenofovir. J App Pharm Sci 2016; 6 (08): 022-029.
15. Srinivas L, Lohithasu D, Madhupriya D, Siddhartha N, Tejaswi N. Formulation and evaluation of ibuprofen pulsincap technique for controlled release. Der Pharmacia Lettre 2013; 5 (1):60-68.
16. Anil KSN, Chitagunta P, Kavitha K. Colonic drug delivery system of trimetazidine hydrochloride for angina pectoris. Int J Pharm Pharm Sci 2011; 3(2): 22-26.
17. Shahi SN, Aziz A, Bhuiyan MA. Design, Formulation and *in vitro* evaluation of sustained release pulsatile capsule of metoprolol tartrate. Int J Pharm Sci Res 2015; 6(7): 2755-61.
18. Bussemer T, Peppas NA, Bodmeier R. Evaluation of the swelling, hydration and rupturing properties of the swelling layer of a rupturable pulsatile drug delivery system. Eur J Pharm Biopharm 2003; 56:261–270.
19. Meena A, Kumar B, Suriya PTNK, Senthamarai R. Development and evaluation of pulsatile drug delivery system of lornoxicam. Int. J. Pharm. World Res 2011; 2(2): 1-15.
20. Abdel NZ, Rowa JA, Abeer AG, Aiman Q, Yara AZ. Weight and content uniformity of lorazepam half-tablets: A study of correlation of a low drug content product. Saudi Pharm J 2013; 21(1): 71–75.
21. Jana S, Manna S, Nayak AK, Sen KK, Basu SK. Carbopol gel containing chitosan- egg albumin nanoparticles for transdermal aceclofenac delivery. Colloids and Surf. B: Biointerfaces 2014; 114, 36-44.
22. Neha N. An updated review on: floating drug delivery system (FDDS). Int J Appl Pharm 2011; 3(1), 1-7.
23. Jagdale SC, Chede SM, Gulwady R, Kuchekar BS, Lokhande PD, Shah TP, Chabukswar AR. Pulsatile multiparticulate drug delivery system of metoprolol succinate. Arch Pharm Res 2011; 24(3):369-376.
24. Suvakanta D, Padala NM, Lilakanta N, Prasanta C. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm Drug Res 2010; 67: 217-223.
25. Cha J, Gilmor T, Lane P, Ranweiler JS. Stability studies in handbook of modern pharmaceutical analysis. Separation Science and Technology. Elsevier, 2001, 459-505.