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FORMULATION, DEVELOPMENT AND EVALUATION OF CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEM FOR THE TREATMENT OF NOCTURNAL ASTHMA BY USING SALBUTAMOL SULPHATE MICROSPHERE

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ABSTRACT

Asthma can show noticeable daily fluctuations. Patients usually have symptoms that appear mainly during sleep, and even when symptoms occur during the day, they usually worsen at night. Deaths from asthma also usually occur at night or in the early morning. The rational of this study is to design and evaluate an oral site-specific, pulsatile drug delivery system containing Salbutamol Sulphate, which can be targeted to colon in a pH and time dependent manner, to modulate the drug level in synchrony with the circadian rhythm of nocturnal asthma. In the present research work, we have attempted to develop a novel dosage form by using a chronopharmaceutical approach. A microsphere dosage form, taken at bed time with a programmed start of drug release early in morning hours, can prevent a sharp increase in the incidence of asthmatic attacks, during the early morning hours (nocturnal asthma), a time when the risk of asthmatic attacks is the greatest.

Keywords: Salbutamol sulphate, Chronotherapeutics, Nocturnal asthma, Microsphere.

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways. Chronic inflammation is associated with airway hyperreactivity (an excessive airway narrowing response to triggers such as allergens and exercise), resulting in recurrent symptoms such as wheezing, dyspnea (shortness of breath), chest tightness, and coughing. Asthma symptoms are wheezing with a high-pitched wheezing sound, especially in children. Absence of wheezing and a normal chest examination do not rule out asthma.

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PATHOPHYSIOLOGY OF ASTHMA

Inflammation of the airways is a major problem in asthma. The first event in asthma appears to be the release of inflammatory mediators (eg histamine, tryptase, leukotrienes, and prostaglandins) caused by exposure to allergens, irritants, cold air, or exercise. Depending on the activity of inflammatory mediators, there are two types of response:

- Early-phase asthmatic response.
- Late-phase asthmatic response.

NOCTURNAL ASTHMA

Asthma can show noticeable daily fluctuations. Patients usually have symptoms that appear mainly during sleep, and even when symptoms occur during the day, they usually worsen at night. Deaths from asthma also usually occur at night or in the early morning. Researchers have recently tried to disrupt sleep in patients with nocturnal asthma but have generally failed to reduce peak expiratory flow at night. Breathing undergoes significant changes during sleep, and these changes have recently been extensively studied. Rapid eye sleep (REM) sleep in humans and normal animals is a period of irregular breathing with brief apnea pauses. Significant fluctuations in airway tone have also been described in REM sleep.

Two studies involving people with asthma, one in adults and the other in children, analyzed sleep variables. Stage 4 sleep is relatively shorter in adults with asthma.

1. Asthma attacks are only documented by a history of dyspnea and are not confirmed by objective measurements of airway obstruction.
2. Adult asthmatics have taken drugs such as supplements containing phenobarbital and oral steroids that can interfere with sleep.
3. Respiratory pattern and oxygen saturation were not checked.
4. Asthmatics were not reassessed when they were no longer having attacks, so it is uncertain whether these findings relate to unstable asthma or asthma alone.

Methods of treatment of nocturnal asthma

- ☐ Prevention
- ☐ Specific immunotherapy
- ☐ Pharmacotherapy

Pharmacotherapy for Nocturnal Asthma

Pharmacological treatment of asthma depends on the frequency and severity of asthma.

Table 1: Commonly drugs used in Nocturnal Asthma

Commonly used drugs in Nocturnal Asthma	Examples
Corticosteroids	Beclomethasone, Budesonide, Prednisolone, Fluticasone, Mometasone
Anticholinergics	Ipratropium bromide, Tiotropium bromide
Short acting Beta 2 Agonists	Salbutamol, Albuterol, Metaproterenol, Pirbuterol, Terbutaline

RESEARCH METHODOLOGY: Formulation of Salbutamol Sulphate Microspheres By Emulsification Technique

Microspheres formulations using Chitosan as polymers were prepared using the emulsification method. A solution of Chitosan (1% w/v) was prepared in glacial acetic acid (1% v/v) solution of drug (1%) was added to their respective solution. This was further added to a continuous phase (which consisted of light liquid paraffin containing Span 80 (0.1ml) as surfactant) under constant stirring (2,000 rpm) using a three blade propeller stirrer to form a w/o emulsion. This procedure was followed by addition of 0.5 ml of Glutaraldehyde (25% v/v) drop wise with stirring at the same speed. Stirring was continued at the same speed for next 5 minutes, and then stirring speed was reduced to different speeds (500 rpm, 1000rpm and 1500rpm).

Glutaraldehyde (0.25 mL) was added twice to the mixture, once after 1 hour and then after 2 hours, respectively, with continuous stirring. Stirring was stopped after 1 hour of the final addition of glutaraldehyde. The microspheres so obtained were separated by centrifugation and washed with petroleum ether to remove liquid paraffin. The microspheres were suspended in 5% w/v sodium bisulphite solution and stirred for 15 min. to remove residual Glutaraldehyde. Final washing was done with distilled water; the microspheres were dried and stored in a vacuum desiccator.

. MICROENCAPSULATION OF THE CHITOSAN MICROCORES

Chitosan microcores (100 or 50 mg) were dispersed in 5 ml of an organic solvent (acetone: ethanol ratio 2:1) in which Eudragit S-100 (500 mg) were previously dissolved to give 5:1 coat / core ratio. This organic phase was then poured into 70 ml of liquid paraffin containing Span 80. The system was maintained under stirring at 1000 rpm at room temperature for 3 h to allow the evaporation of the solvent. Finally, the micro cores were collected, rinsed with *n*-hexane and air dried. All batches are enteric coated.

RESULTS & DISCUSSIONS***IN-VITRO* DRUG RELEASE STUDY OF CHITOSAN MICROSPHERE FORMULATIONS**

The in vitro dissolution study was carried out using method described earlier. The chitosan microspheres equivalent to 5 mg of the drug was introduced into the dissolution jar and the basket was rotated at 100 rpm. At different time intervals, 5 ml samples were withdrawn and analysed spectrophotometrically at 276.6 nm for the drug release. The results are depicted by the following tables and figures.

Table 3: Percentage drug release of microsphere formulations

[CH-8, CH-9, CH-10, CH-12, CH-13, CH-14, CH-15, CH-16]

Time (Hr.)	Media pH	Cumulative Percent Drug Release±S.D.								
		CH-8	CH-9	CH-10	CH-11	CH-12	CH-13	CH-14	CH-15	CH-16
00:00	1.2	0	0	0	0	0	0	0	0	0
00:30	1.2	1.3±0.457	1.4±0.452	1.4±0.584	1.1±0.457	1.2±0.452	1.2±0.475	0.8±0.234	0.9±0.286	1.0±0.341
01:00	1.2	2.6±0.578	2.8±0.547	3.0±0.498	2.4±0.647	2.6±0.872	2.8±0.385	2.1±0.714	2.3±0.624	2.5±0.546
01:30	1.2	5.2±0.875	5.7±0.459	6.1±0.843	4.9±0.955	5.2±0.657	5.3±0.735	4.5±0.842	4.8±0.627	5.0±0.351
02:00	6.8	8.6±0.981	8.9±0.985	9.3±0.872	8.4±0.246	8.7±0.623	8.9±0.981	7.9±0.291	8.2±0.358	8.3±0.412
02:30	6.8	13.8±0.876	17.4±1.254	17.9±0.124	13.5±0.630	17.0±0.245	17.4±0.785	12.9±0.240	16.5±0.531	16.9±0.453
03:00	7.4	25.7±0.758	31.5±1.054	33.1±0.354	25.0±0.861	30.9±0.351	32.5±0.654	28.3±0.358	30.3±0.486	31.8±0.681
03:30	7.4	52.2±1.673	58.4±0.891	61.0±0.451	50.1±0.561	59.8±0.245	59.9±0.348	49.3±0.562	55.0±0.671	57.1±0.714
04:00	7.4	73.8±0.546	81.6±1.256	84.4±0.568	71.1±0.568	80.9±0.356	81.3±0.610	70.0±0.568	77.1±0.356	80.1±0.610
04:30	7.4	87.6±1.836	91.2±0.864	92.4±0.483	84.9±0.856	89.8±0.564	91.1±0.536	82.8±0.246	86.4±0.511	88.3±0.679
05:00	7.4	93.5±0.983	95.4±0.547	94.8±0.578	92.1±0.873	94.8±0.523	94.2±0.864	87.1±0.983	89.9±0.346	90.1±0.801
06:00	7.4	96.6±1.586	97.0±0.546	96.2±0.485	95.1±0.652	96.8±0.451	96.1±0.444	89.6±0.551	90.9±0.849	91.1±0.351
09:00	7.4	98.3±1.586	98.6±1.845	97.1±0.845	96.3±0.561	97.0±0.681	96.3±0.354	90.7±0.377	91.4±0.588	91.6±0.894
12:00	7.4	98.5±0.854	98.7±0.586	97.2±0.457	96.5±0.325	97.2±0.416	96.5±0.892	91.2±0.546	91.6±0.622	91.8±0.833

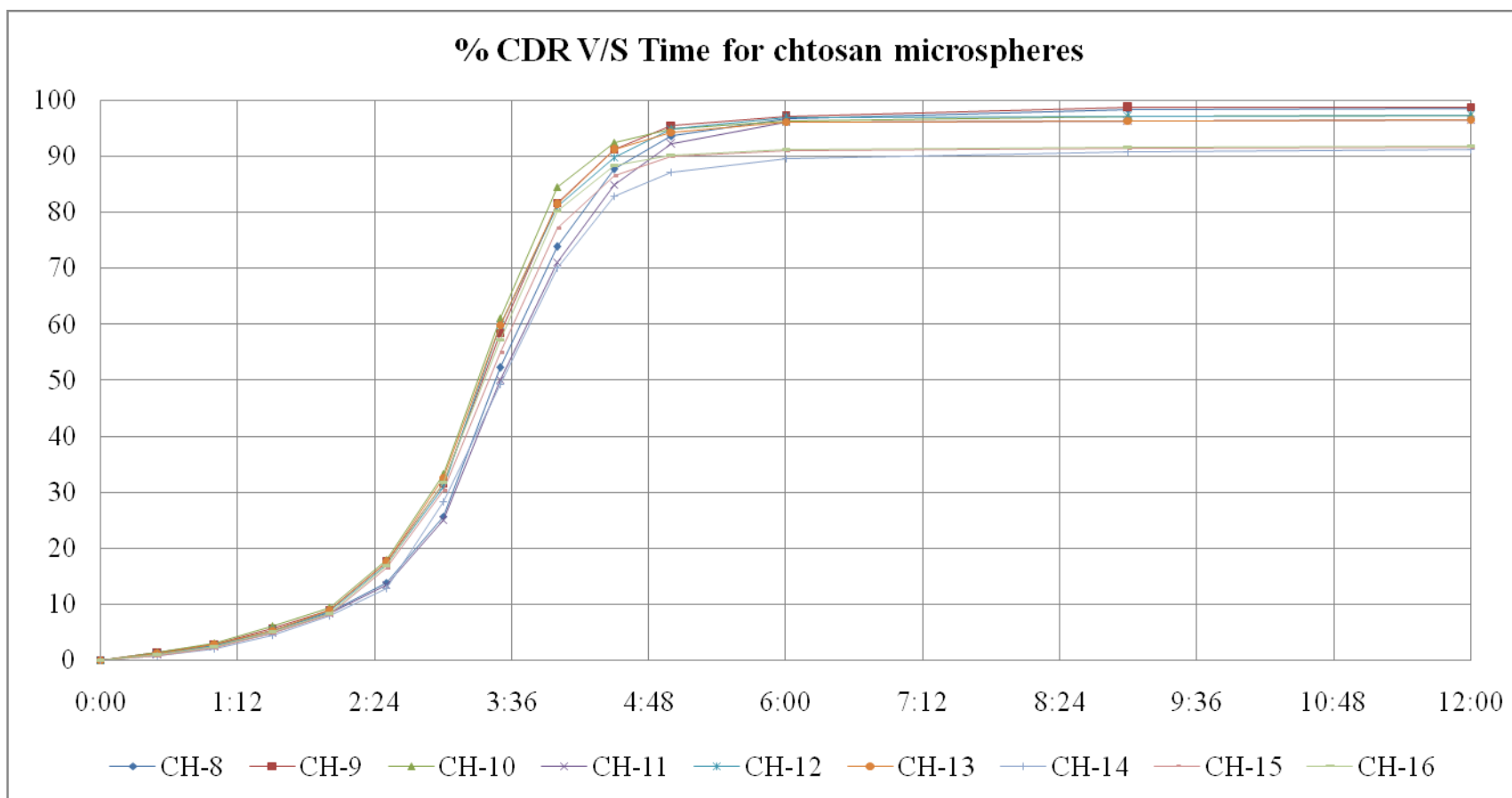


Figure 1 : Percentage Cumulative Drug Release of Microsphere Formulations V/S Time [CH-8, CH-9, CH-10, CH-11, CH-12, CH-13, CH-14, CH-15, CH-16]

In all the formulations, about 70-85 % of the drug was released within 4 hours. Figure 1 and table 3 shows that with increasing drug: polymer ratio % cumulative drug release at required time, decreases but with increasing stirring speed firstly it increases and afterwards decreases. Formulation CH-9 has shown maximum cumulative drug release but its entrapment efficiency and percentage yield is very low as compared to Formulation CH-12 which also showed approximately similar % cumulative drug release. Beside most of the drug is released very early as compared to time required to release the drug so we need to enteric coat the formulation.

Table 4: An overview of the comparative study of different drug release kinetics models, best fit model

Batch Code	Zero Order Release	First Order Release	Higuchi's Release	Korsmeyer-Peppas Release		Hixson Crowell	Best Fit Model
	R ²	R ²	R ²	Slope (n)	R ²		
CH-8	0.7234	0.8710	0.9615	1.8178	0.8996	0.8197	Higuchi's
CH-9	0.7009	0.8582	0.9620	1.8729	0.8916	0.8886	Higuchi's
CH-10	0.6843	0.7940	0.9625	1.7082	0.8886	0.7528	Higuchi's
CH-11	0.7250	0.8157	0.9607	1.8868	0.9031	0.7894	Higuchi's
CH-12	0.6946	0.7984	0.9626	1.9549	0.8907	0.7643	Higuchi's
CH-13	0.6893	0.7820	0.9625	1.9556	0.8901	0.7507	Higuchi's
CH-14	0.7162	0.7919	0.9610	2.0643	0.9007	0.7667	Higuchi's
CH-15	0.6906	0.7513	0.9618	2.0723	0.8927	0.7315	Higuchi's
CH-16	0.6801	0.7371	0.9626	2.0331	0.8887	0.7181	Higuchi's

All the formulations followed zero order, first order, Higuchi and Korsmeyer-Peppas models, though Higuchi was the best fit model. When analysed according to the Peppas model, the release exponent was found to be greater than 1.0. This shows to be due to supercase II transport.

CONCLUSION

- From the optimization study it was found that formulation CH-12 was the best among other formulations but none of these shown the *in vitro* drug release profile required for the chronotherapy of nocturnal asthma.
- These formulations were again coated with Eudragit S100 polymer for delaying the release of the drug according to the chronotherapeutic requirements. From the optimization study it was found that formulation ECH-12 was the optimum for chronotherapeutic drug delivery system.
- From the *in-vitro* release studies of device, it was observed that with all formulation, there was absolutely no drug release in simulated gastric fluid (acidic pH 1.2) for 2 hours. Small amount of drug release was observed in simulated intestinal fluid (pH 6.8 phosphate buffers). Burst effect was found in colonic medium (pH 7.4 phosphate buffers).
- The obtained results showed the capability of the system in delaying drug release for a programmable period of time and the possibility of exploiting such delay to attain colon targeting.
- Effect of Drug: Polymer Ratio and Stirring Speed on Various Responses were studied via 2 D Contour Plots And 3 D Response Surface Methodologies using numerical optimization tool of the DESIGN EXPERT software.

- From these data desirability graphs were plotted and the values of different variables were calculated using above mentioned software. Formulation was prepared according to desirability requirement using values of the variables predicted by software and the actual values of the various responses were compared with the predicted values. Actual values were found to be within limits of the predicted values

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