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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. Thesystem 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 |

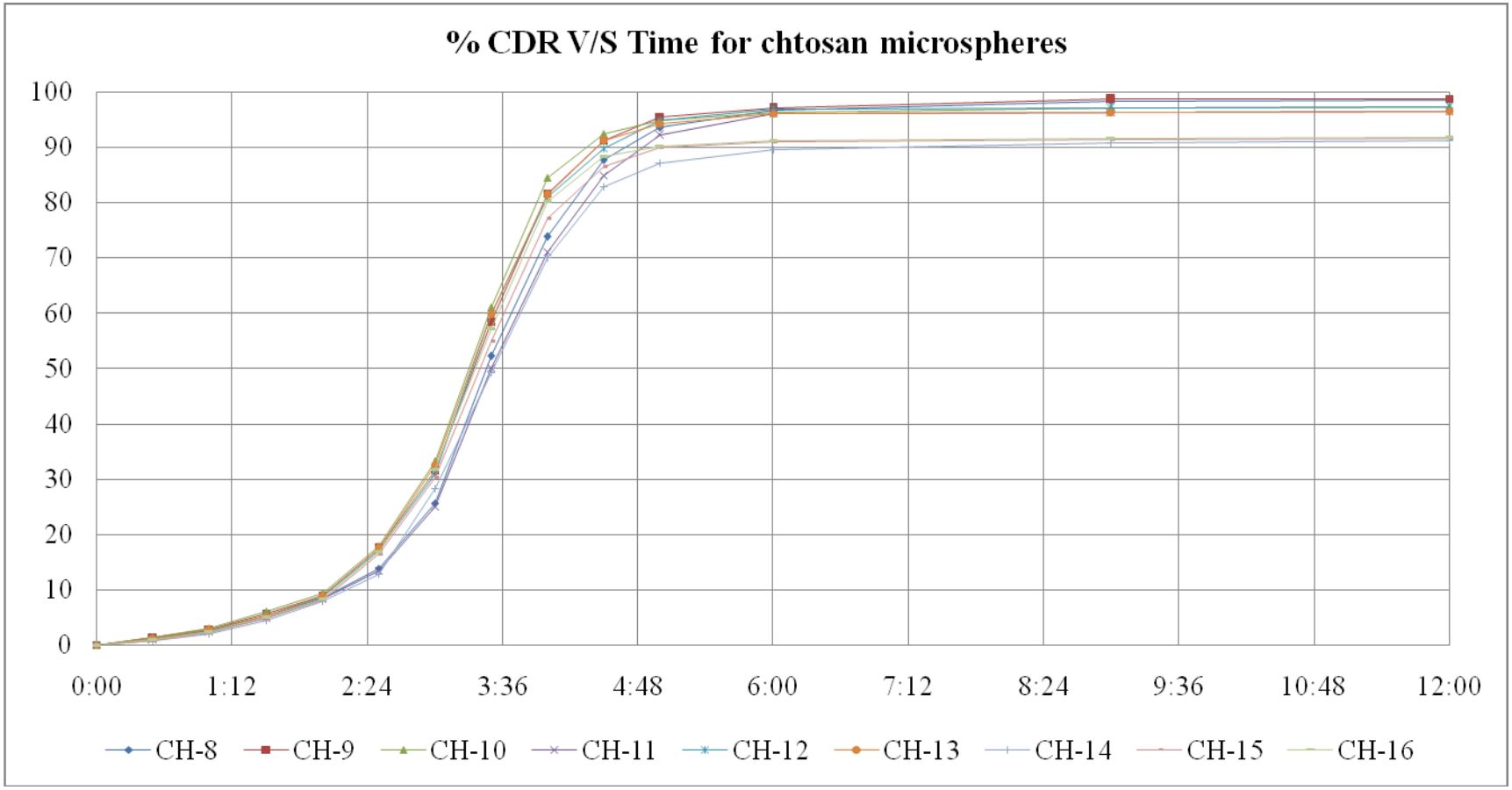


**Figure 1 : Percentage Cumulative Drug Release of Microsphere Formulations V/S Time [CH-8, CH-9, CH-10, CH-11, CH-12, CH-13, CH-14, CH-15, CH-16]**

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. Whenanalysed 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

## REFERENCES


1. Lamberg L., Chronotherapeutics Implications for drug therapy. American pharmacy.1991; NS31 (11):796-799.
2. Maronde E, Stehle JH, The mammalian pineal gland: known facts, unknown facets. Trends Endocrinol. Metab. 2007; 18:142–149.
3. Kalsbeek A, Palm IF, La Fleur SE, Scheer FA, Perreau-Lenz S, Ruiter M, Kreier F, Cailotto C, Buijs RM, SCN outputs and thehypothalamic balance of life. J. Biol. Rhythms.2006; 21:458–469.
4. Smolensky MH, D'Alonzo GE, Medical chronobiology: concepts and applications. Am Rev Respir Dis. 1993; 147(6 Pt. 2):S2-19.
5. Moore JG, Smolensky MH, Biological rhythms in gastrointestinal function and processes: implications for the pathogenesis and treatment of peptic ulcer disease.in: Swabb EA, Szabo S, editors. Ulcer Disease, Investigation and Basis for Therapy. New York: Marcel Dekker Inc.; 1991. 55–85.
6. Reinberg A, New aspect of human chronopharmacology. Arch.Toxicol. 1976; 36:327-339.
7. Stehlin I, a time to heal: chronotherapy tunes into body's rhythms. FDA consumer magazine, April, 1997:215-218.
8. Moore JG, Halberg F, Circadian rhythm of gastric acid secretion inactive duodenal ulcer: chronobiological statistical characteristics and comparison of acid secretory and plasma gastrin patterns in healthy and postvagotom and pyloroplasty patients. Chronobiol. Int.1987; 4:101–110.
9. Bateman JR, Clark SW, Sudden death in asthma. Thorax. 1979; 34:40–44.
10. Cugini P, Di Palma L, Battisti P, Leone G, Materia E, Parenzi A, Romano M, Ferrera U, Moretti M, Ultradian, circadian and infradian periodicity of some cardiovascular emergencies. Am. J. Cardiol. 1990; 66:240–243.
11. Kowanko ICR, Knapp MS, Pownall R, Swannell AJ, Domiciliary self-measurement in rheumatoid arthritis and the demonstration of circadian rhythmicity. Ann. Rheum. Dis. 1982; 41:453–455.
12. Kelmanson IA, Circadian variation of the frequency of sudden infant death syndrome and of sudden death from life-threatening conditions in infants. Chronobiologia. 1991; 18:181–186.
13. Smolensky MH, Reinberg AG, Labrecque, Twenty-four hour pattern in symptom intensity of viral and allergic rhinitis: treatment implications. J. Allergy Clin. Immunol. 1995; 95:1084–1096.
14. Gallerani M, Manfredini R, Ricci L, Grandi E, Cappato R, Calò G, Pareschi PL, Fersini C, Sudden death from pulmonary thromboembolism chronobiological aspects. Eur. Heart J. 1992; 6:305–323.
15. Portaluppi F, Manfredini R, Fersini C, from a static to a dynamic concept of risk: the circadian epidemiology of cardiovascular risk. Chronobiol. Int. 1999; 16:33–50.
16. Wehr TA. Circadian rhythm disturbances in depression and mania.in: Brown FM, Graeber RC, editors. Rhythmic aspects of Behavior. Hillsdale: NJ: Lawrence Erlbaum Associates; 1982. p. 399–428.
17. Folkard S, Glynn CJ, Lloyd JW, Diurnal variation and individual differences in the perception of intractable pain. J. Psychosom. Res. 1976; 20 (4):289–304.

18. Manfredini R, Gallerani M, Salmi R, Calò G, Pasin M, Bigoni M, Fersini C, Circadian variation in the time of onset of acute intestinal bleeding. J. Emerg. Med. 1994; 12:5–9.
19. Skloot GS, Nocturnal asthma. The Mount Sinai Journal of Medicine. 2002; 69 No. (3):140-147.
20. Montplaisir J, Walsh J, Malo JL, Nocturnal asthma: features of attacks, sleep and breathing patterns. Am. Rev. Respir. Dis. 1982; 125:18-22 (1982).

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