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Development and characterization of enteric-coated salbutamol sulphate time release tablets.

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Abstract

In the present study, an attempt was made to develop immediate-release enteric-coated time release tablets of salbutamol sulphate for the treatment of nocturnal asthma. Nocturnal asthma is an asthma phenotype marked by nighttime increases in airway inflammation, airway hyper responsiveness, and expiratory airflow limitation. The occurrence of nocturnal asthma is associated with increased morbidity and inadequate asthma control, and has an important negative impact on quality of life. Formulation of enteric-coated time release tablets with suitable lag time could address the problems associated with asthma. To achieve this goal, immediate release tablets were prepared by direct compression method using superdisintegrants that contribute to the faster disintegration of tablet and thereby improved solubility of the drug. Different disintegrants like cross caramellose sodium, crospovidone and sodium starch glycolate in different concentrations (2.5 – 7.5%w/w) were tried in order to further improve disintegration time. The formulation, which showed best disintegration and dissolution profile, was coated with ethyl cellulose as inner layer and Eudragit S100 as outer enteric-coating polymer which does not dissolve at gastric pH but dissolve at intestinal pH, releasing the drug immediately in the alkaline medium. The optimized enteric-coated formulation E6 containing 2.5%w/w of Eudragit S 100 and 30%w/w of ethyl cellulose as coating system inhibited the release of the drug in 0.1 N HCl, and whereas 99.04% of drug was released in the intestinal medium. Thus, dissolution profiles indicated that E6 tablet may be better alternative in the treatment of nocturnal asthma which overcomes the problems of conventional forms.

Keywords: salbutamol sulphate, ethyl cellulose, pH sensitive polymer, time release, lag time.

Introduction

For centuries, the biological rhythms of the human body and their association to conventional environmental cycles have been studied. It has been reproved by ancient healers that, to be successful, treatment had to be offered with regard for various external and internal cycles. A biological rhythm is a self-sustaining process inside the human body. It is defined as the processes that occur periodically in an organism in conjunction with and often in response to periodic changes in environmental condition [1]. Biological rhythm within a single day is termed as circadian rhythm. Here, the oscillation time is 24 hours. Term Circadian is derived from the Latin term circa meaning “about" and dies which is derived from "a day" [2]. Also, each term indicates an oscillation period of time. The concept of chronotherapeutics is utilized and devoted to the design and evaluation of drug delivery systems that release a therapeutic agent at a rhythm that ideally matches the biological requirements of a given disease therapy. Disease conditions where constant drug levels are not preferred but need a pulse of therapeutic concentration in a periodic manner acts as a push for the development of time drug delivery systems. These systems have a peculiar mechanism of delivering drug rapidly and completely after a “lag time” i.e. a period of no drug release, characterized by a programmed drug release [3]. Asthma is one of the most common ailments with the largest circadian variation [4]. It is a disease of lung airways (bronchi) characterized by hyper-responsiveness to a variety of stimuli [5, 6]. Nocturnal asthma is defined as a variable night time exacerbation of the underlying asthma condition associated with increased airway responsiveness and worsening of lung functions [7]. The lung function (peak expiratory flow rate, FEV1) is usually highest at 4 pm and lowest at 4 am. Generally, asthma attacks are more prevalent in early morning [8]. It is inconvenient for a patient to take medicine at midnight. In this condition, a drug delivery system that can release the drug at a predetermined time to guarantee therapeutic efficacy is a prerequisite. With the advancement of technology in the pharmaceutical field, drug delivery systems that synchronize the drug delivery with the circadian variation in periods of increased risk are highly desirable for management of asthma. Ideal oral

timed drug delivery systems would overcome the problem of administering the drugs frequently.

A time delayed release profile is characterized by a lag time followed by rapid and complete drug release [9].Several approaches to delay drug release exists. The application of an enteric coating to a solid dosage form is a well established approach to prevent drug release in the stomach and allow release in the small intestine. The most commonly used enteric coatings employ pH-dependent polymers which contain carboxylic groups. These remain un-ionized in the low pH environment of the stomach, and become ionized in the higher pH conditions of the small intestine, thus allowing the dissolution of the coating and drug is released in a controlled fashion from polymers. This allows time-controlled drug release when the symptoms of the disease are worse to fatal and ultimately this leads to improved patient compliance [10, 11]. Salbutamol sulphate is β2 receptor agonist widely used as bronchodilator to relieve acute as well as chronic attacks of asthma. Salbutamol sulphate dilates or enlarges the airways by relaxing the muscles surrounding the airways and thereby opens airways [12]. The objective of present study was to develop an enteric coated time release tablet based on chronopharmaceutical approach for the treatment of nocturnal asthma using salbutamol sulphate as a model drug.

Materials and Methods

Materials

Salbutamol sulphate was a gift sample from S.M. Pharmaceuticals, Bengaluru. Eudragit S 100, Ethyl cellulose were obtained as gift samples from Gland Pharma Ltd., Mumbai. Acetones, Polyethylene glycol, Talc were procured from S. D. Fine chemicals Pvt. Ltd, Mumbai. Diethyl Pthalate was gifted from Pellet Pharma, Hyderabad. All other reagents used were of analytical grade.

Methods

Formulation of core tablet

Core tablets containing 5 mg of salbutamol sulphate were prepared by direct compression method. Superdisintegrants such as cross caramellose sodium, crospovidone and sodium starch glycolate were used in varying concentrations (2.5 – 7.5% w/w). The drug, diluents and superdisintegrants were passed through sieve no.40 and mixed together in a plastic container. Magnesium stearate and aerosil passed through sieve no.80 were mixed and blended with above mixture. The mixed blend of excipients was compressed into tablets using 7 mm flat punches on a 10 stationed rotary compression machine. The core tablet formula is given in Table 1.

Table 1: Formulae of core tablets

Ingredients (mg)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Salbutamol sulphate	5	5	5	5	5	5	5	5	5
Cross caramellose sodium	5	10	15	---	---	---	---	---	---
Crospovidone	---	---	---	5	10	15	---	---	---
Sodium starch glycolate	---	---	---	---	---	---	5	10	15
Lactose	70	70	70	70	70	70	70	70	70
Microcrystalline cellulose	115	110	105	115	110	105	115	110	105
Magnesium stearate	3	3	3	3	3	3	3	3	3
Aerosil	2	2	2	2	2	2	2	2	2
Total weight (mg)	200	200	200	200	200	200	200	200	200

Optimization of core tablets

The core tablets were optimized based on the disintegration time and dissolution (in-vitro drug release studies) by using the different superdisintegrants in varying concentrations. The technical details and evaluation relating to core formulation are described in an earlier publication [13]. The optimised formulation F3 from the above batch of tablets was selected for present research work.

Development of enteric coated time release tablets

The optimised core tablet formulation F3 of salbutamol sulphate was first coated with ethyl cellulose (EC), a pH independent polymer as Inner hydrophobic layer and later it was coated with pH dependent polymer Eudragit S 100 (ES 100) as outer layer to protect the drug from disintegrating in stomach and to provide the necessary lag time essential for time delivery. Different levels of

coating of Inner and outer layer for optimized immediate release formulation are shown in Table 2. The inner and outer polymer coats were applied by using conventional pan coating system. The conditions of coating operation are given in Table 3. A schematic diagram of the supposed enteric coated time release tablet is shown in Figure 1.

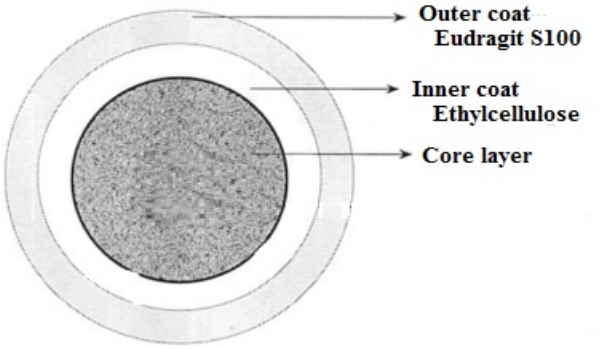


Figure 1: Schematic diagram of enteric coated time release tablet

Table 2: Different concentrations of inner and outer coating layers.

Formulation	Inner layer	Outer layer
	Ethyl cellulose%	Eudragit S 100 %
E1	5.0	2.5
E2	10	2.5
E3	15	2.5
E4	20	2.5
E5	25	2.5
E6	30	2.5
E7	35	2.5

Table 3: Coating conditions for inner and outer polymeric layers.

Apparatus conditions	Inner layer	Outer layer
	Ethyl cellulose	Eudragit S 100
Inlet temp (°C)	50-55	40-45
Exhaust temp (°C)	40-45	30-35
Spray rate (mL/min)	3-5	5
Spray gun distance from tablet bed	10 – 15	10 – 15
Pan Speed(rpm)	25	25

Preparation of Ethyl cellulose inner coating solution and coating of core tablets

The coating solution was prepared by hydrating EC in acetone by overnight storage. This hydrated solution was stirred for 15 mins. Plasticizer Diethylpthalate (% based on dry polymer weight) was added into the polymeric solution and mixed on a magnetic stirrer for another 10 mins. This polymer solution was then sprayed on to the core tablets in a conventional pan coating apparatus. The coating process was repeated till the desired levels of coatings were achieved. Seven different formulations were obtained by coating the tablets at different levels from 5 to 35%w/w (Table 2). The coated tablets were further dried in the coating pan for 15 mins [14].

Preparation of Eudragit S 100 outer coating solution

A homogeneous coating solution of pH sensitive polymer Eudragit S100 was prepared using PEG 400, talc and acetone. 1.25 % w/w PEG 400 was used as plasticizer (% based on dry polymer weight). Talc (2% of polymer weight) was used as a glidant and antitacking agent. The pH sensitive polymer Eudragit S100 was dissolved in acetone on magnetic stirrer, plasticizer was added and stirring continued till sufficient plasticization of the polymer was ensured, in order to get a good, intact and flexible polymeric film. Talc was then added and mixed till a homogenous mixture was obtained [15, 16].

Enteric/outer coating of ethyl cellulose coated core tablets

Enteric coating of ethyl cellulose coated core tablets was performed by pan coating (Cipweka, India). Different ethyl cellulose coated formulations were coated with pH sensitive polymer Eudragit S100 at a coating level of 2.5% as total solid applied. Tablets were placed in the pan and coating solution was sprayed and dried with the help of inlet air. The coating process was repeated till the desired level of coating was achieved. The tablets were further dried in the coating pan for 15 mins.
The % weight gain of enteric coated tablets was calculated using the following equation:

$$\% \text{ weight gain} = (Wt - Wo)/Wo \times 100$$

Where Wt is the weight of the tablet after coating, Wo is the initial weight of tablet [17].

Evaluation of enteric coated time release tablets

The prepared enteric coated time release tablets were evaluated for following properties:

Film thickness

The thickness of ten randomly selected tablets from each batch of coated tablets was individually recorded in mm using a vernier calliper. The mean and standard deviation values were calculated from each value recorded.

Weight variation

The weight variation of the coated tablets was determined by official method as given in IP. The percentage difference in the weight variation for each batch of coated tablets was computed from average tablet weight of each batch. Ten tablets were used for weight variation test.

Drug Content of enteric coated tablets

10 tablets were weighed individually and powdered. Equivalent to one tablet of theoretical drug content was weighed and dispersed in 100 ml of pH 6.8 buffer. The UV absorbance was measured at 276 nm against blank reagent. Test was performed in triplicate and drug content was calculated by using the following formula [18].

$$\text{Drug content(mg)} = \frac{(\text{Absorbance} - \text{Slope} \pm \text{Intercept}) \times \text{Dilution factor}}{1000}$$

Scanning electron microscopy (SEM)

SEM has been extensively used to study the morphology and surface topography of the coated tablets [19]. The optimized enteric coated and uncoated tablets of salbutamol sulphate were tested for scanning electron microscopy to know the surface morphology and uniformity of thickness of the coating layer. The samples to be examined were mounted on the SEM sample stub using a double sided sticking tape. The samples mounted were coated with gold (200 A^0) under reduced pressure (0.001 torr) for 5 mins using an ion sputtering device. The gold coated samples were observed under the SEM and photomicrographs of suitable magnifications were obtained.

Drug – excipient compatibility studies by FT-IR

Drug- excipient interactions play a crucial role with respect to the stability and potency of the drug. FT-IR technique was used to study the physical and chemical interaction between drug and excipients used. The IR spectrum of pure drug, pure polymers ethyl cellulose, Eudragit S100 and Optimized enteric coated formulation were recorded in the stretching frequency range of 400-4000 cm^{-1}. The samples were prepared by KBr (Potassium Bromide) press pellet technique.

Water uptake experiment

The percentage of water uptake by the enteric coated tablets was determined in 100 ml of 0. 1 N HCl as medium filled in containers placed in horizontal shaker at 37ºC. At predetermined time points the tablets were removed from the medium, carefully blotted with tissue paper to remove surface water, weighed and then placed back in the medium up to the time when the coating of the tablet started to rupture. Water uptake was calculated as amount of penetrated water related to dry tablet mass.

% water uptake was calculated as follows:

$$\text{Water uptake (\%)} = (Wt - Wo)/ Wo \times 100$$

Where Wt is weight of wet tablet at time t and Wo weight of dry tablet [20].

Lag time of enteric coated tablets (Rupture test)

The time at which the outer coating layer starts to rupture is defined as the lag time. The intention of the study was to develop enteric coated tablets which remain protected from gastric environment and will release the drug rapidly in the intestine after administration. Providing suitable lag time for the enteric coated tablets would serve the purpose. Hence Lag time was determined, by placing the coated tablets in USP dissolution apparatus II containing 900 ml of 0.1 N HCl for initial 2 hrs and then changing to phosphate buffer of pH 6.8 till the coating ruptures. The media was agitated at 50 rpm and maintained at 37±0.5°C. The time taken for outer coating to rupture was visually monitored and reported as lag time. In addition to the rupture behavior; the enteric coated tablets were photographed by a digital camera [21, 22].

Effect of inner layer concentration on lag time

Core optimized tablet formula F3 was coated with different levels of ethyl cellulose as inner layer to obtain the required lag time. The core tablet F3 was coated with 5, 10, 15, 20, 25, 30 and 35%w/w of ethyl cellulose and obtained formulations were subjected to in vitro dissolution study. Effect of ethyl cellulose layer concentration over lag time and release behavior was observed using a spectrophotometer, as described in the method under in vitro drug release studies.

Disintegration time

The disintegration test for the enteric coated tablets was carried out using USPXXIII (Electrolab, Bangalore, India) disintegration tester. Six enteric coated tablets were placed in each tube of the apparatus; the disintegration test was performed initially in pH 1.2 without the discs for two hours. After 2 hrs, the same tablets were tested for disintegration in mixed pH 6.8 phosphate buffer as medium with the discs. The temperature of the water bath was maintained at 37 ± 5°C throughout the test. The disintegration time for the tablets was recorded in minutes [23].

In-vitro dissolution studies

Dissolution studies of the enteric coated tablets were carried out in triplicate employing USP type-II apparatus (USP XXIII Dissolution Test Apparatus) following conditions that simulate gastrointestinal tract. 0.1N HCl and phosphate buffer of pH 6.8 were used as dissolution medium. The temperature of the dissolution medium was maintained at 37±0.5^{0}C with a stirring speed of 50 rpm. Initially tablets were subjected to dissolution in 0.1N HCl for 2 hrs and after that media were changed to phosphate buffer pH 6.8. The samples were withdrawn at regular intervals of time and analysed for presence of drug by UV spectrophotometer at 276 nm. The concentration of the drug was determined from standard calibration curve. The dissolution data was analysed for knowing

the amount of drug released and percentage cumulative drug released at different time intervals [23].

Drug release kinetics

In order to study the mechanism of drug release from the prepared enteric coated time release tablets, the release data obtained was evaluated using zero-order release kinetics (Eq. 1), first order kinetics (Eq. 2), Higuchi's square root of time equation (Eq. 3) [24] and Korsemeyer and Peppas equation (Eq. 4) [25, 26].

$$M_t = M_0 + k_0 t \quad (1)$$

where M_t is the amount of drug dissolved in time t, M_0 is the initial amount of drug in the solution, k_0 is the zero-order release rate constant and t is the release time,

$$M_t = M_0 e^{-kt} \quad (2)$$

where M_t is the amount of drug dissolved in time t, M_0 is the initial amount of drug in the solution, k is the first-order release rate constant and t is the release time,

$$M_t = k_h\ t \quad (3)$$

Where M_t is the amount of drug dissolved in time t, k_h is the Higuchi dissolution constant and t is the release time,

$$M_t/M = k_s t^n \quad (4)$$

where, M_t and M are the cumulative amount of drug released at time t and infinite time, respectively; k_s is a constant incorporating structural and geometric characteristics of the device, and n is the drug release exponent, indicative of the mechanism of drug release. The values of n assigned to a cylinder are 0.45 for Fickian diffusion (case I) and 0.45 < n < 0.89 for non-Fickian (anomalous) diffusion; and > 0.89 indicates super case II type of release respectively. Case II generally refers to the erosion of the polymeric chain and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release.

Stability studies

The stability studies were carried out for the optimized formulation at 40 °C/75% RH for a period of three months. The sample tablets were wrapped in the laminated aluminum foils and were placed in the accelerated stability chamber at 40° C/75% RH for a period of three months. Sampling was done at a predetermined time intervals. The tablets were evaluated for their general appearance; drug content, lag time and in vitro drug release study [27].

Results and Discussion

The enteric coated time release tablet of salbutamol sulphate developed in the present study was a reservoir device where the tablet core was surrounded by two consecutive layers, a hydrophobic inner layer and an outer rupturable layer. Ethyl cellulose was coated as inner layer to avoid premature drug release in lower pH-media and to increase the lag time because of its reduced wettability, media uptake and erosion properties. Eudragit S 100 which hydrates and swells due to the presence of quaternary ammonium groups was selected as enteric coating polymer. Eudragit S 100 coating was given to the ethyl cellulose coated core tablets to achieve ideal time release tablets for treatment of nocturnal asthma.

Optimization of core tablets

The salbutamol sulphate timed release tablets consisted of inner core tablet containing drug reservoir and outer coating layer with various compositions to provide the suitable lag time. Various core tablets of salbutamol sulphate were prepared (F1-F9). The most important parameter that needs to be optimized in the development of core immediate release tablets is disintegration time of tablets. The disintegration time of the tablets prepared by using superdisintegrants was well within the limits. Cross caramellose sodium provided the immediate and highest release compared to other disintegrants. The In-vitro drug release profile of salbutamol sulphate immediate release tablets revealed that formulation F-3 containing 15 mg of cross carmellose sodium (7.5% of tablet weight) released 98.58% of drug in 12 minutes in pH 6.8 phosphate buffer and was considered as optimized formulation[13]. Hence for further research work, formulation F3 was utilised.

Coating of core tablets

Most of the time release systems contain a drug reservoir, surrounded by a barrier, which erodes/dissolves or ruptures. These barrier technologies used around the active agent are designed to degrade or dissolve after a certain time, and in those that the degradation of the polymer itself induces the release of the active agent. Ethyl cellulose, a pH independent polymer in different percentages from 5 to 35%w/w was applied as barrier coating between the core tablet and enteric coating using pan coating apparatus. This barrier avoids leaching of moisture into tablet core and erodes or dissolves after predetermined lag time. Ethyl cellulose being hydrophobic does not interfere with tablet disintegration and provide the effective barrier from water to achieve the desired lag time required for the time release system. All the ethyl cellulose coated core tablets were pan coated with Eudragit S100 (2.5% w/w) to prevent the drug release in stomach. Eudragit S100 coating dissolves at pH ≥7 and complete release of drug occurs after a suitable lag time in the intestine. The produced coated tablets had no visible defects such as orange peel effect, chipping, tacking or any other physical flaws. The coating system followed was dispersed in the minimum amount of time, and produced acceptable weight gains.

Evaluation of enteric coated time release tablets

Film thickness

The mean thickness of the enteric coated tablets E1 to E7 was found to be 5.79, 5.93, 6.18, 6.33, 6.44, 6.53 and 6.65 mm respectively (Table 4). The thickness of the coated tablets increased with increase in the coat weight applied. The percentage increase in the thickness of tablets was found to be 2.8% - 18.1% for formulations E1- E7 respectively.

Weight variation

The Weight variation results of enteric coated tablets are potrayed in Table 4. The average tablet weight for the coated tablets was in the range of 215.4 to 275 mg. The tablet weight variation was found below 2% for all the batches of coated tablets indicating it was within IP official limit. The percent practical weight gain calculated from the average tablet weight was found to be between 7.7 to 37.5% for all batches of tablets respectively.

The drug content of all the formulations was found to be with-in the official limits. The drug content was found in the range of 5.03 – 5.12 mg respectively (within the acceptable range) for all the formulations (Table 4). The results proved that coating process did not affect the integrity of tablet and no drug loss occurred during the coating process.

Drug Content of enteric coated tablets

Table 4: Characteristics of enteric coated time release tablets.

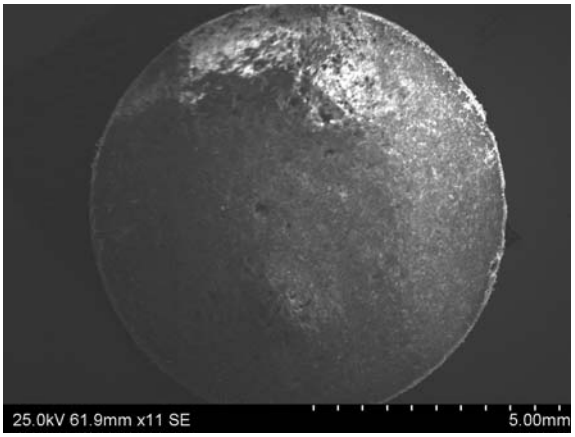
Formulation	Thickness (mm)(Mean±SD, n=10)	Weight variation (mg) (Mean±SD, n=10)	Drug Content (mg)(Mean±SD, n=3)
E1	5.79±0.11	215.4±1.40	5.05±0.05
E2	5.93±0.01	224.6±1.07	5.09±0.03
E3	6.18±0.10	235.2±0.91	5.04±0.10
E4	6.33±0.20	245.3±0.94	5.10±0.13
E5	6.44±0.05	254.9±0.99	5.03±0.06
E6	6.53±0.01	265.0±1.15	5.12±0.11
E7	6.65±0.11	275.0±0.81	5.10±0.10

Scanning electron microscopy

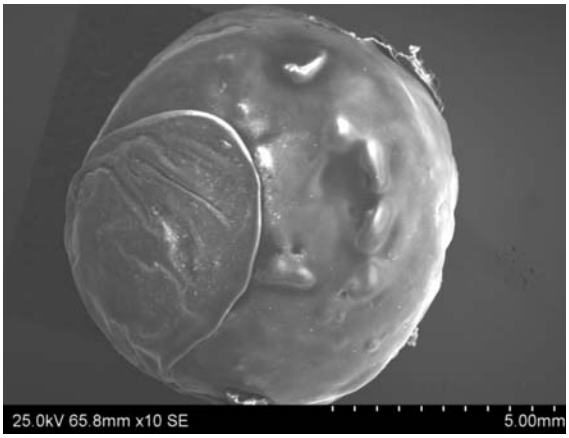
The surface morphology of optimised coated tablet E6 and uncoated tablet as viewed by the scanning electron microscopy are shown in Fig. 2 (a) and (b) respectively. The SEM of uncoated tablet showed a rough, not very smooth surface with pores in it.

The coated surface of E6 was fairly smooth and tight surface free from cracks or pores as visualized under high magnification. The surface view of the coated tablet revealed a distinct continuous and dense coat.

Figure 2: SEM Photomicrographs



a) Surface morphology of uncoated tablet and



b) Surface morphology of optimised enteric coated time release tablet E6.

Drug – excipient compatibility studies by FT-IR

The FT-IR spectra of optimised enteric coated time release tablet E6 is presented in Figure 3. The FT-IR spectra of coated tablets E6 was compared with spectra of pure drug salbutamol sulphate to study the compatibility of drug and polymers or excipients used. The FT-IR spectrum of formulation E6 exihibited the characteristic absorption bands almost in the same pattern as that of pure drug

with negligible difference in the position of the bands. The peaks present in the finger print region are totally in agreement with the peaks of pure drug in the same region. These observations ruled out the possibility of any chemical interaction between the drug salbutamol sulphate and the other polymer or excipients used.

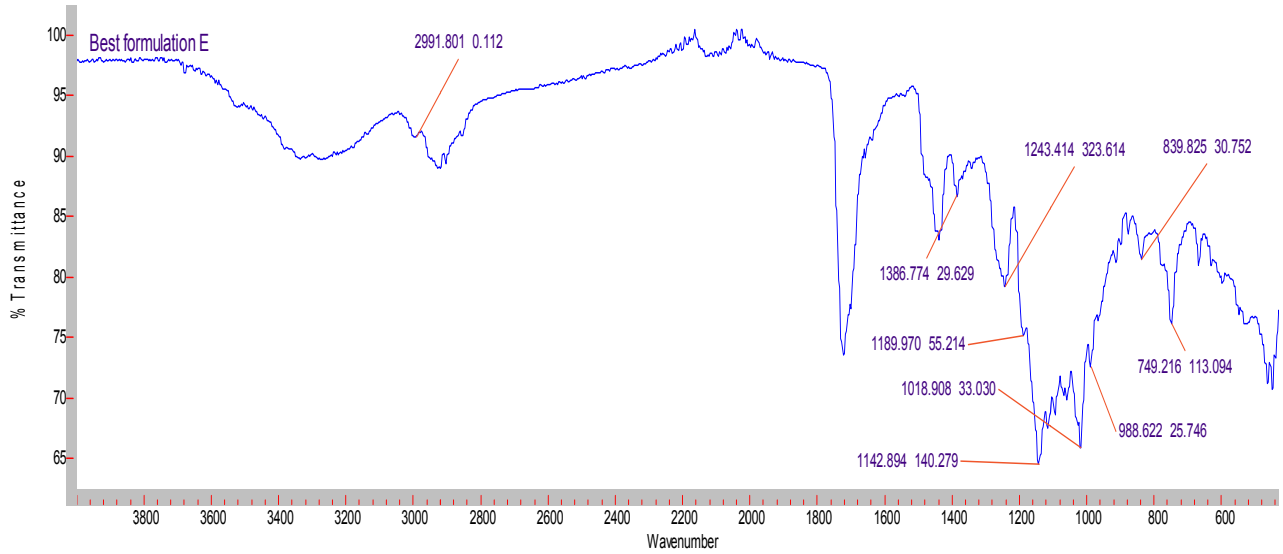


Figure 3: FT-IR spectra of optimised enteric coated time release tablet E6.

Water uptake experiment

Water uptake studies performed for optimised enteric coated tablet E6 revealed that water influx was through the outer semipermeable rupturable coating, which leads to erosion of inner layer. The rupture of outer coating leads to rapid release of the drug after certain lag time. The water uptake capacity and drug release was dependent on outer acrylate polymer coating. It was observed that with slow increase in water uptake the lag time also increased linearly (Figure 4).

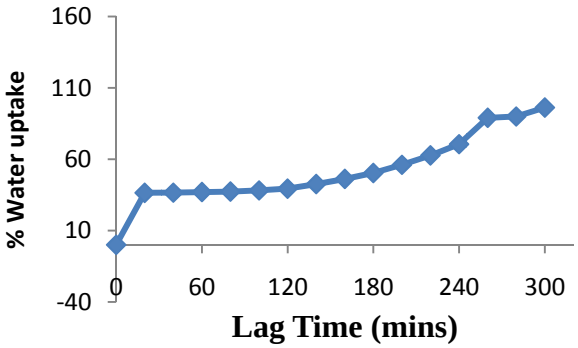


Figure 4: % Water uptake and lag time studies of optimized enteric coated time release tablet E6.

Lag time of enteric coated tablets (Rupture test)

In the present study all the formulations were coated with pH sensitive polymer Eudragit S 100 at 2.5% w/w as outer layer. The lag time or rupture studies indicated that this level of coating was not sufficient to contain the core tablet and the tablet eventually ruptured within 2 hrs as seen with formulations E1 – E3. However with formulations E4 – E5 enhanced lag time essential for time release was noticed which solely explains the role of inner ethyl cellulose layer in providing the lag time. The result is displayed in Figure 5. It is evident from the results that as the ethyl cellulose concentration was increased the lag time also enhanced. The formulations E5 – E7 provide more than two hours of lag time i.e., 140 to 320 mins. The aim of the study was to develop a tablet which will be protected from gastric environment and will release the drug rapidly in the intestine after 3-5 hours of administration. So the above batches showed lag time in the required range with respect to their composition coating level. Figure 6 depicts the rupture behavior of the enteric coated time release tablet at different time intervals.

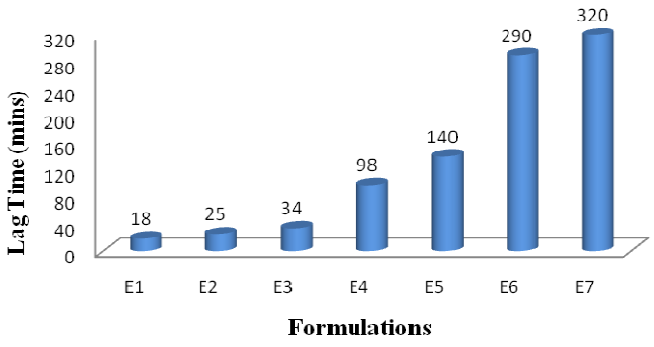


Figure 5: Rupture test (Lag Time) of enteric coated time release tablets.

A (0 hrs) B (4.75 hrs) C (5.25 hrs)

Figure 6: Rupture sequence of enteric coated time release tablets.

Effect of inner layer concentration on lag time

Ethyl cellulose was coated as inner layer at different levels to achieve the required lag time. It was noticed that as the concentration of ethyl cellulose was increased from 5 – 35%w/w the lag time also increased from 18 to 320 mins. Increase in coat thickness also caused resistance to water penetration and coat rupture. As revealed in Fig. 5, with the increase of coat thickness, there was a corresponding increase in the lag time and subsequent drug release. Thus, percent coating mass gain was found to be another crucial parameter in the modulation of lag time and in achieving the desired drug release profile. A plot of percentage ethyl cellulose mass gain against lag time showed a good linear relationship, as shown in Fig. 7 (R^2 = 0.908) indicating the vitality of this factor in lag time modulation.

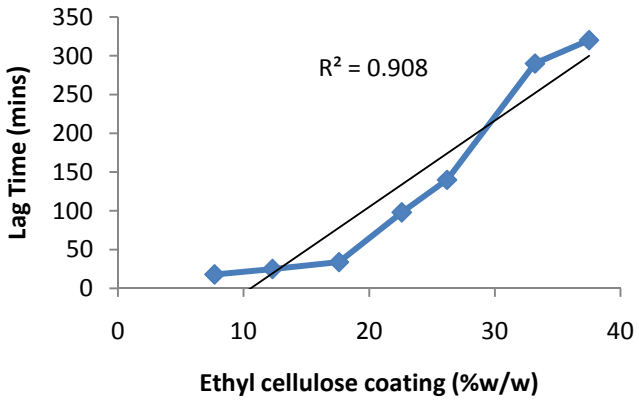


Figure 7: Plot of percent ethyl cellulose mass gain vs. lag time.

Disintegration time

The results of in-vitro disintegration studies are given in Table 5. It was observed that the formulations E1 – E4 disintegrated in 0.1N HCl within 25 mins. The formulations failed the disintegration test in 0.1 N HCl. This indicated that the amount of combination of inner ethyl cellulose (5 – 20%w/w) and outer Eudragit S 100 polymer (2.5%w/w) layer in these formulations was unable to withstand acid media. Hence, three more formulations were prepared (E5 – E7) with greater amount of inner ethyl cellulose coating material (weight gain up to 35%). Table 4 shows the increase in the ethyl cellulose coating (up to 35%w/w) resulted in non disintegration of the tablets in the acid media (0.1 N HCl) during the study period (2 hrs). The observed results are in agreement with the reported literature showing the potential of this polymer combination to prevent disintegration in acidic media. The formulations E 5 – E7 disintegrated between 7 -15 mins when the test was done in mixed phosphate buffer pH 6.8. The results of these formulations indicated that disintegration time in pH 6.8 was found to increase with increase in percent weight gain by tablets. The data also suggested that the disintegration time was independent of the enteric coating weight gain but most likely depends on the inner polymer, in the current experimental condition.

Table 5: Disintegration time of enteric coated time release tablets

Formulation	Disintegration Time in simulated gastric fluid (0.1 N HCl)	Disintegration Time in simulated intestinal fluid (pH 6.8)
E1	Disintegrated in 10 min	-
E2	Disintegrated in12 min	-
E3	Disintegrated in 15 min	-
E4	Disintegrated in 25 min	-
E5	No Disintegration up to 120 min	07 min
E6	No Disintegration up to 120 min	13 min
E7	No Disintegration up to 120 min	15 min

In vitro Dissolution tests

In- vitro drug release studies was carried out for all the seven enteric coated time release formulations in simulated gastric environment (pH 1.2) for 2 hrs and then in simulated intestinal environment of pH 6.8. All formulations released the drug in the range of 84.50 to 99.04% in about 7.25 hrs. Formulations E1, E2, E3 and E4 released 98.60, 96.85, 93.48 and 91.77% of drug at the end of 4.25 hrs (Figure 8). In case of tablets E1- E4 it was evident from the nature of the graph that the outer Eudragit S 100 coating at 2.5%w/w and inner ethyl cellulose coating between 5 – 20%w/w were unable to hold the core tablet from rupturing. This indicated that the lower level of coat polymer weight was insufficient to prevent the premature drug release. In fact the low coat thickness film formed around the core tablet retards drug release but diffusion of drug continues through such a film. The rapid release of drug in initial hours of dissolution study from these tablets suggested need for greater degree of mechanical strength of the coating. From these observations, it could be assumed that the first step in drug release was penetration of water in the core tablet by diffusion through Eudragit film and the rate and amount of water entered was dependent on film thickness. The penetration rate of water accelerated in to the core tablet due to outer polymer chain relaxation. When water reached the core tablet, a visible 'breakdown, of the tablet matrix in to smaller granules was observed due to presence of superdisinterating agent croscarmellose sodium. The weakly held fragments of porous core tablet disaggregated into relatively fine particles under the rotating movement of the paddle. As a result the total water contact area with drug was enhanced and thereby maximum dissolution of drug was noticed. A cronomodulated release profile should be characterized by a lag time followed by rapid and complete drug release. After the desired lag time, the onset of release can be achieved by action of superdisintegrant in the core tablet. To achieve the above objective the formulations E5 – E7 were designed by increasing the coating level of inner layer up to 35%w/w. Formulations E5, E6 and E7 released 98.91, 99.04 and 84.50% of drug in 7.5 hrs. The percent drug released versus time plot of these formulations revealed that they provided the needed lag time for chronomodulated delivery and also resisted the acidic medium up to 2 hrs. These plots also showed that the dissolution rate was inversely proportional to the thickness of the coat applied. As represented in Figure 5 the lag time for E5 – E7 was 2.34, 4.80 and 5.34 hrs respectively. The lag time increased with increase in inner ethyl cellulose coating level due to greater degree of mechanical strength of the thick coating which lowers rupturing. This made the outer acrylic coat more impermeable and drug release was retarded. The water uptake capacity and drug release before the rupture of tablet was dependent on outer acrylate polymer coating and inner ethyl cellulose layer (Figure 4). Slowly as the outer coating solubilized, drug dissolution through it was facilitated. These findings were equally supported by disintegration studies of the enteric coated time release tablets. Furthermore, the pH of the dissolution medium played an important role in dissolution of coating in case of formulations E5 – E7; increasing the pH of dissolution fluid accelerated the dissolution. Consistently faster drug release from coated tablet was observed in simulated intestinal dissolution fluid (pH 6.8) than acidic environment (pH 1.2). The optimum coating level to obtain a suitable lag time and to initiate drug release at the target site (lower small intestine or lleocolon junction), was found with 2.5% (w/w) of Eudragit S 100 and 30% (w/w) of ethyl cellulose polymeric film i.e., formulation E6.

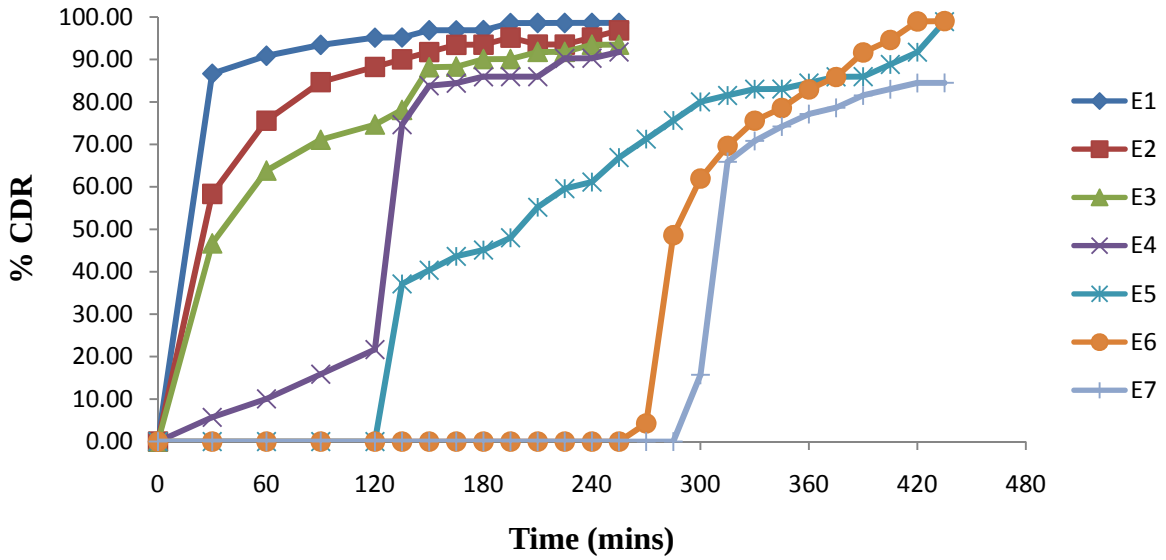


Figure 8: Cumulative percent of drug released versus time profile of enteric coated time release tablets

Drug release kinetics

Values of the coefficient of determination for all the release models obtained for enteric coated time release tablets E1 – E7 are given in Table 6. A comparative study of these values clearly showed that the Korsemeyer and Peppas model was the best-fit model for the batches prepared during the study except E6 and E7. The values of regression in the Korsemeyer and Peppas model (i.e., R^2) were close to unit in all cases excluding E6 and E7. The n values were in the range of 0.06 – 1.5 indicating super case II type of release. The drug release is attributed to the erosion of the outer Eudragit S100 film, which leads to the formation of pores that facilitate drug dissolution due to combination of both diffusion and erosion. The formulations E6 and E7 follow zero order release mechanism due to presence of higher quantity of polymer coat.

Table 6: Comparative release model characteristics of enteric coated time release tablets

Formulation	Zero order	First Order	Higuchi's	Korsemeyer and Peppas
E1	0.40	0.862	0.668	0.984
E2	0.61	0.698	0.854	0.918
E3	0.76	0.823	0.946	0.968
E4	0.84	0.801	0.775	0.888
E5	0.92	0.921	0.877	0.975
E6	0.75	0.442	0.561	0.488
E7	0.68	0.862	0.491	0.453

Stability Studies

The stability studies of optimum formulation E6 done at 40 C/75% RH revealed no change in physical appearance, no significant reduction in the drug content, lag time and drug release of the tablets occurred over a period of three months (Table 7).

Table 7: Stability studies of enteric coated time release tablets at 40 C/75% RH

Formulation	Drug content (mg) (Mean±SD, n=3)	Lag Time (mins)	%Cumulative drug released
E1	4.03±0.01	16	96.40
E2	4.01±0.04	28	94.05
E3	4.00±0.01	30	90.02
E4	4.04±0.10	90	88.24
E5	3.99±0.04	130	95.12
E6	4.00±0.08	275	96.02
E7	4.10±0.02	304	80.30

Conclusion

In accordance with chronotherapeutic model for nocturnal asthma, symptoms typically occur between midnight and especially around 3 am to 6 am because of increased airway responsiveness and worsening of lung function. Thus in this study an attempt was made to design and evaluate a chronomodulated system of salbutamol sulphate, a bronchodilator for the treatment of asthma. To achieve this, salbutamol sulphate core tablets were coated with composition of hydrophobic inner ethyl cellulose and outer enteric Eudragit S-100 polymer. This coating composition i.e., 2.5w/w of Eudragit S-100 and 20 – 35%w/w of ethyl cellulose helped achieve a definite non-release lag phase. The enteric coated time release tablets of salbutamol sulphate designed prevented drug release in stomach and released drug rapidly after predetermined lag time in the intestinal tract when pH was above 6. The intention was to administer the formulation at around 10.00 pm so that after a specified lag time the drug is rapidly available in the early morning hours to treat nocturnal asthma. The formulation E6 with 30%w/w coating of inner ethyl cellulose layer was considered optimized one as it provided 4.8 hrs of lagtime and 99.04% of drug release. Thus the above formulations are worth evaluating for chronotherapeutic treatment of nocturnal asthma.

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