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Research Article
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DESIGN AND EVALUATION OF TIME DEPENDENT COMPRESSION COATED SALBUTAMOL SULFATE (SS) TABLETS

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ABSTRACT

An attempt has made to the design and evaluation of pH and time dependent compressional coated salbutamol sulfate for treatment of Nocturnal asthma. Compressed coated tablets were prepared in two steps, initially Fast dissolving core tablets are prepared using croscarmellose sodium, sodium starch glycolate as super disintegrants by the direct compression method. The prepared core tablets were evaluated for weight variation, hardness, friability, disintegration, drug content and in-vitro dissolution studies. F9 formulation of core tablet releases 85.3% of drug at 15min, selected as a core tablet for compressional coating. In the second step compressional coating is done by using pH dependent polymer Eudragit S100, retarding polymer HPMCK4M in different ratios (1:1, 1:2) F_{a1}-F_{a7} and F_{b1}-F_{b7}. The prepared compression coated tablets were evaluated for weight variation, friability, thickness, hardness, In-vitro drug release and lag time. The results indicate that F_{b5} (HPMCK4M: Eudragit S100 4:6) formulation has mimicking in-vitro drug release behavior is mimicking to the circadian rhythms of nocturnal Asthma.

KEY WORDS

Coated Salbutamol sulfate (ss) tablets, Nocturnal Asthma, Croscarmellose sodium, sodium starch glycolate.

INTRODUCTION:

Chronopharmaceutics is a combination of Chronobiology and pharmaceutics. biological rhythms and their mechanisms are discussed. These biological rhythms are three types circadian, infradian and ultradian. Circadian is a term derived from the Latin word “circa” meaning about and “dies” meaning day. Oscillation of more than one cycle per 24h is called as ultradian, less than one cycle per 24h are known as infradian [1-2]. Chronotherapy is the administration of drugs in accordance with biological rhythms of disease, maximize the safety and minimize the adverse effects [3].

A number of common diseases are affected by Chronobiology. Such diseases include angina, rheumatoid arthritis, allergic rhinitis, hypertension and cancer. Asthma may be the most common disease with the largest circadian variation. The activity of the lung exhibits a circadian rhythm with a maximum around 4 pm and a minimum around 4 a.m. [4]. In asthmatic patients, the intensity of variation in lung function is as much as 50% in a day.

Nocturnal asthma defined as an exacerbation of asthma at night, is associated with increases in symptoms and need for medication, increased airway responsiveness and worsening of lung

function. Nighttime worsening of asthma has been recognized since the 5th century A.D. and is believed to be quite common, affecting a majority of asthmatics.

Control release systems for 12 or 24 hour drug release are not suitable for diseases, which follow a circadian variation. In that condition, there is requirement for time or pulsatile drug delivery system. Pulsatile drug delivery systems are the systems where drug is released suddenly after well-defined lag time or time gap, according to circadian rhythm of disease states [5]. Advantages of pulsatile drug delivery systems: Treatment of diseases which are affected by Chronobiology such as angina, rheumatoid arthritis, cancer, etc. Drugs which undergo extensive first pass metabolism, in case of chronic treatment drug resistance may grow and adverse effects may be seen Nitrates [6-8]. In such condition it is help full. In compression coating the solvent usage can be eliminated, solvent takes more time to evaporate and each time there is a need to add solvent which is time consuming and more about the technical process [9].

The Present study was aimed to study the effect of HPMC4M and Edragit S 100 as release retarding polymer at different concentrations on compressional coated tablets of Salbutamol sulfate. The formulation was designed as an immediate release core tablet by using various super disintegrants such as Croscarmellose sodium, Sodium starch glycolate and gastric retardant coat.

MATERIALS AND METHODS

Materials

Salbutamol sulphate (SS) procured as a gift sample by Vital Therapeutics & Formulation Pvt.Ltd. India. Microcrystalline Cellulose (MCC) purchased from Rolex lab reagent, India, Croscarmellose sodium (CCS), Sodium starch glycolate (SSG), Lactose monohydrate, Hydroxyl-propyl-methyl cellulose K4M (HPMC K4M), purchased from yarrow Chemical Pvt. Ltd. Mumbai, India. All other chemicals used for formulation and analytical purpose were purchased from local manufacturers.

FTIR study

A physical interaction study was carried out between the SS and polymers by scanning between 4000cm^{-1} to 400cm^{-1} (BRUKER, India) individually and in combination to know any unknown interacts if exist.

Preparation of SS core tablet

Accurately weighed SS, lactose monohydrate, CCS, SSG was sifted through sieve no. 60, blended for 20 min in polythene bag, lubricated with magnesium stearate and talc for 5min. Lubricated blend was compressed into tablets by 10 station rotary punching machine in an 8mm die cavity [10]. Compression force was adjusted to 4-5 Kg/cm^2.

Table 1. Composition of SS core tablet per tablet (mg)

Formulation code	F_{a1}	F_{a2}	F_{a3}	F_{a4}	F_{a5}	F_{a6}	F_{a7}	F_{b1}	F_{b2}	F_{b3}	F_{b4}	F_{b5}	F_{b6}	F_{b7}
Eudragit S 100	100	90	80	70	60	50	40	200	180	160	140	120	100	80
HPMC k4M	-	10	20	30	40	50	60	-	20	40	60	80	100	120
MCC	57	57	57	57	57	57	57	104	104	104	104	104	104	104
Talc	3	3	3	3	3	3	3	6	6	6	6	6	6	6

Reparation of SS compression coat tablet

Coat tablet was prepared based on the procedure explained by Priti et.al Variable concentration of HPMCk4M, Eudragit S 100 accurately dispensed, blended in a polythene bag with a binding agent (MCC) and blender (talc). 12mm die cavity filled to half volume with coating material prepared. Optimized formulation of core tablet was placed in the half fill die cavity, finally the die cavity was filled with remaining quantity and compressed to produce the compression coat tablet [11-15].

Table 2. Composition of SS cote tablet (mg)

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
SS	4	4	4	4	4	4	4	4	4
Lactose monohydrate	105.2	100.4	95.6	105.2	100.4	95.6	105.2	100.4	95.6
MCC	40	40	40	40	40	40	40	40	40
CCS	4.8	9.6	14.4	-	-	-	2.4	4.8	7.2
SSG	-	-	-	4.8	9.6	14.4	2.4	4.8	7.2
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3

***In-vitro* evaluation SS core and compression coated tablets**

The prepared tablets were evaluated for weight variation, physical strength (Hardness) using Monsanto apparatus, friability (Electro lab, Mumbai, India), content Uniformity randomly selected five tablets were powdered and 4mg of salbutamol sulphate i.e. 160 mg of powder is weighed and dissolved in known quantity of buffer observed at 276 nm[16].

Lag time:

The lag time of pulsatile release tablets is defined as the time when the outer coating starts to rupture. It was determined visually by using the USP II paddle dissolution apparatus[16].

***In-vitro* dissolution study**

In-vitro dissolution of fast dissolving tablets of Salbutamol sulphate was studied in USP XXIV dissolution apparatus-2,(Lab India, Mumbai, India) initially in 500 ml of 0.1M HCl for 0.1N HCl for 2h followed by phosphate buffer 6.8 for 3hrs finally phosphate buffer 7.4 for 12 h. Sink condition was maintained throughout the experiment. Samples (10ml) were withdrawn at regular intervals of time and pre warmed dissolution medium was replaced 37±0.5°C throughout the experiment. The sample withdrawn at regular intervals of time and analyzed for drug release by measuring the absorbance at 276 nm Calculated cumulative percent drug released was plotted against time [16].

RESULTS AND DISCUSSION

FTIR study SS showed typical stretching vibrations at 3267.43cm^{-1} and 3476.22 cm^{-1} due to NH and OH stretching, due to aromatic stretching and characteristic bands observed at 1616.55 cm^{-1}.

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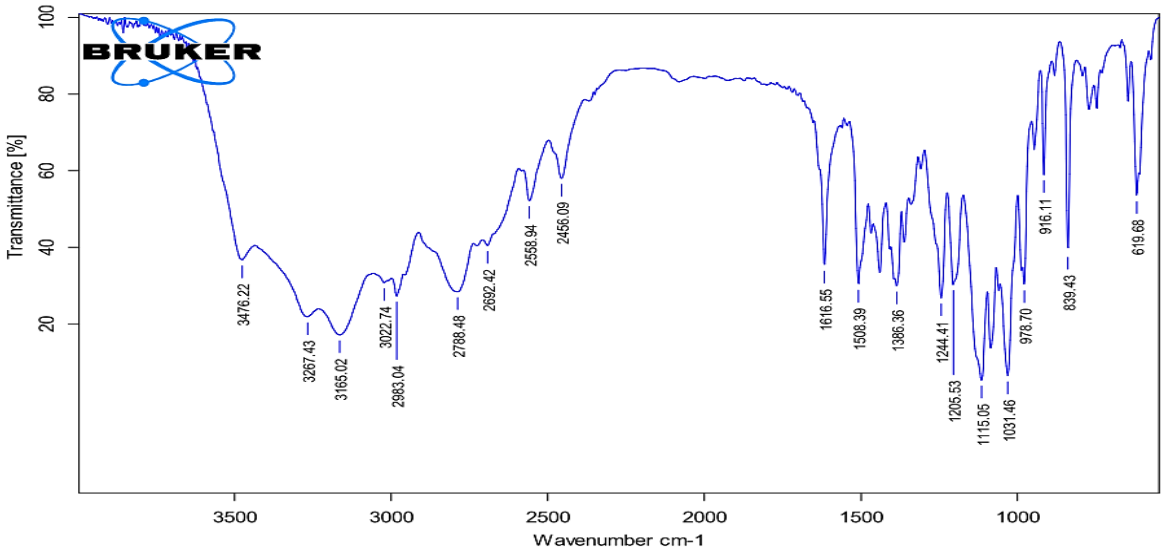

Fig. 1: FT-IR spectrum of Salbutamol sulphate drug.

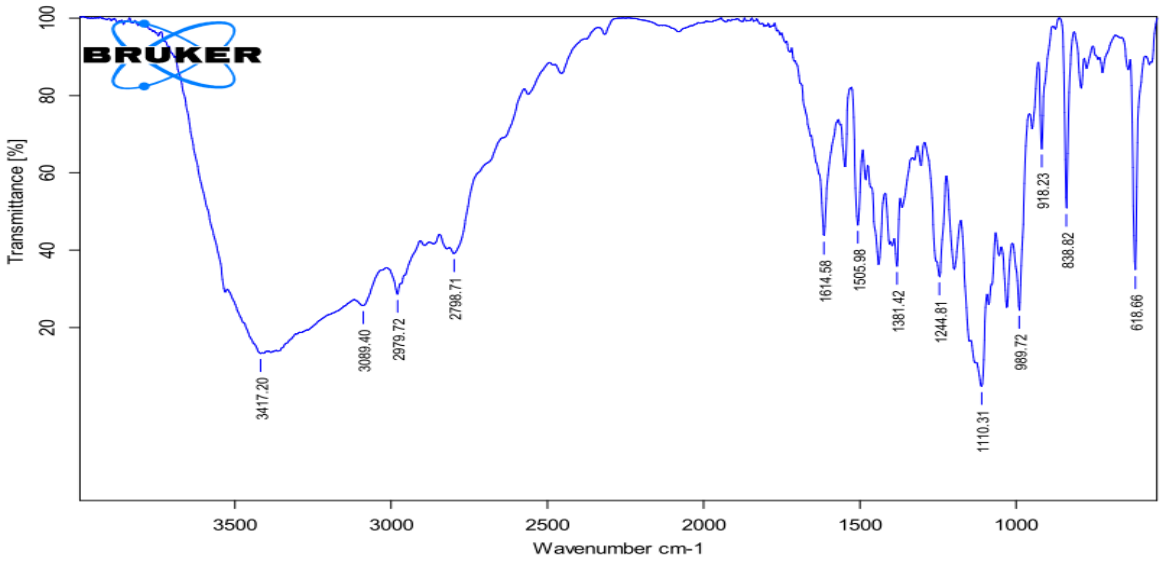

Fig. 2: FTIR graph of Salbutamol sulphate +Croscarmellose sodium.

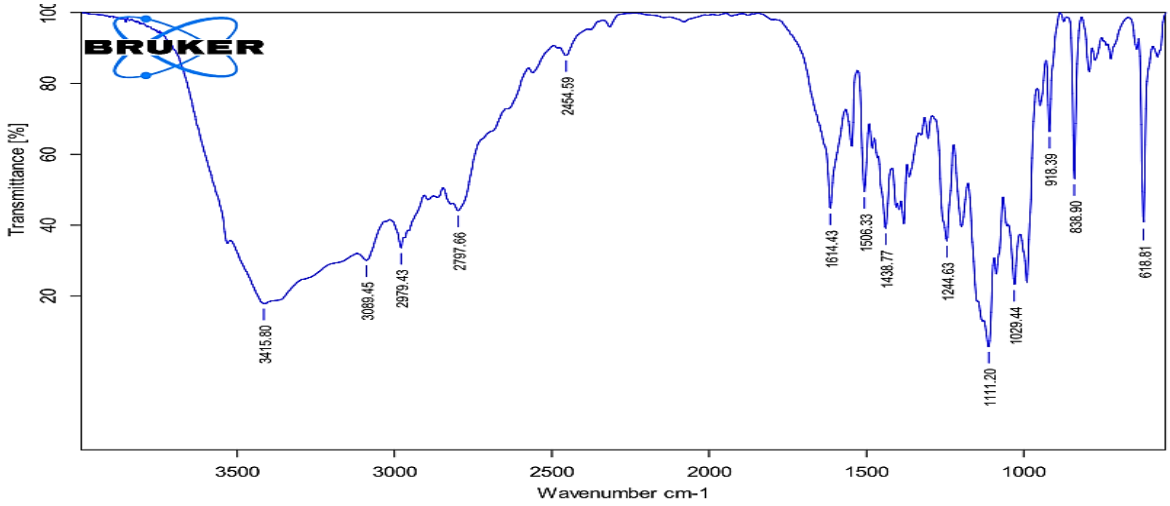

Fig. 3: FTIR graph of Salbutamol sulphate +Sodium starch glycolate.

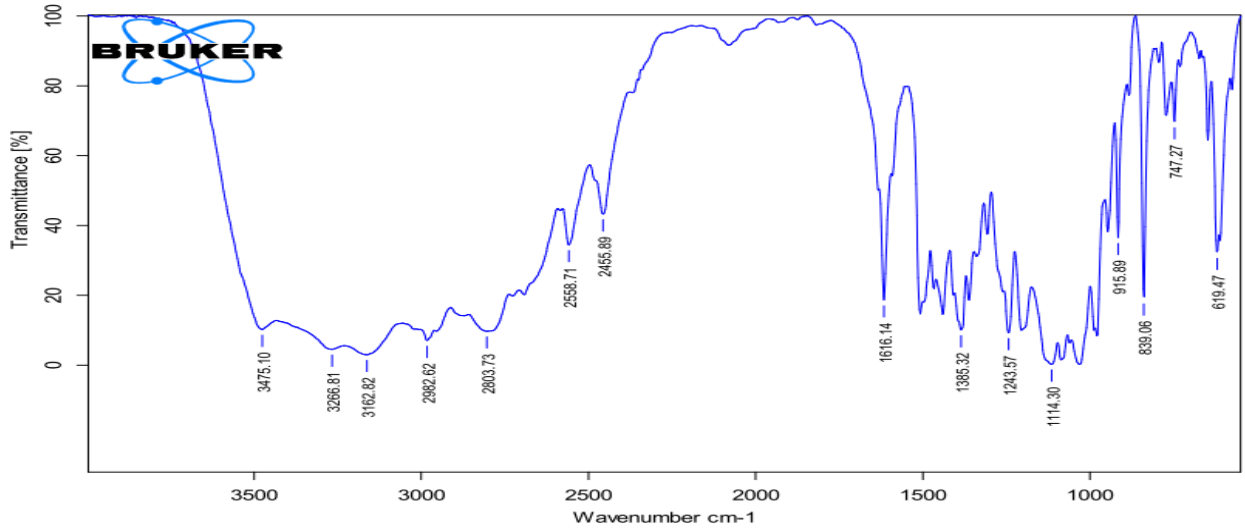

Fig. 4: FTIR spectrum of Salbutamol sulphate +HPMCK4M.

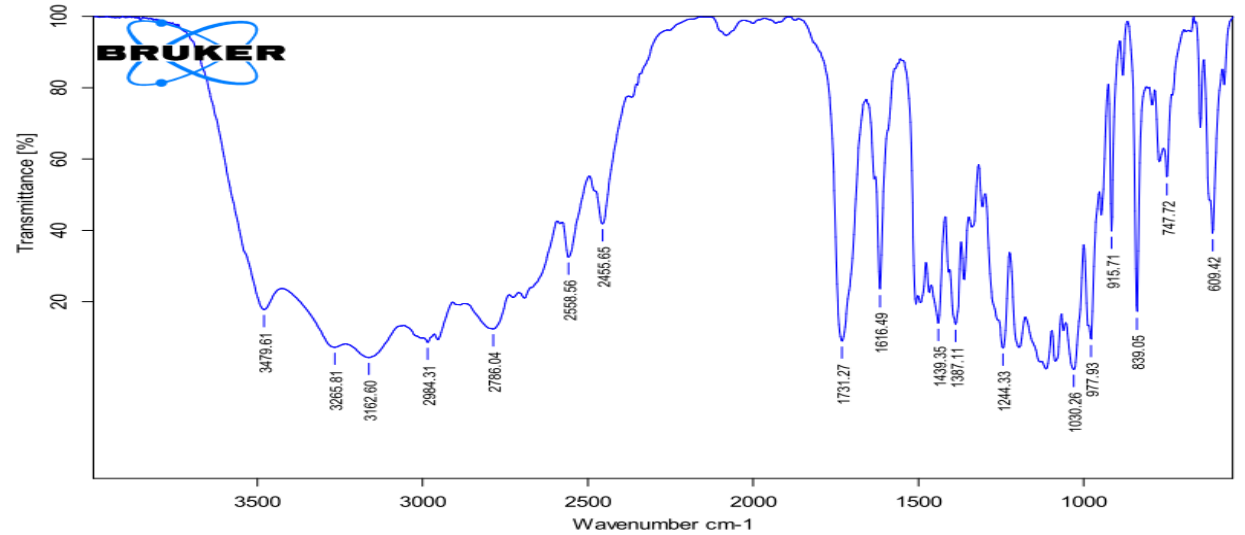

Fig. 5: FTIR spectrum of Salbutamol sulphate +Eudragit S100.

Inlay Tablet dual-retard drug delivery system was prepared by compressing a smaller tablet, forming a core tablet and then surrounded with a powder mixture compressed to produce a bigger tablet and evaluated

***In-vitro* evaluation of SS core tablet**

Fast dissolving core tablet was prepared using variable concentrations (3%,6% &9%) of croscarmellose sodium, sodium starch glycolate by the direct compression method. Pre-compressional studies and angle of repose (25^0.15' ±1.99 to 35^0.21'± 3.53), compressibility index (7.39 ± 1.25% to 14.4 ± 2.12%,), Hausner's ratio (1.08±0.014 to 1.15 ± 0.28),were conducted to the blend of the coat and core tablets proved too good flow properties with compressibility nature. Post compressional studies for the prepared core tablets thicknesses (2.4 ± 0.42mm to 2.8 ± 2.12 mm) and Hardness (4.26±0.15 to 4.7 ±0.1 kg/cm^2), friability less than 1%, drug content (98±0.05% to 103±0.09 %) and Disintegration time (18 ± 0.62 to 44 ± 0.13 Sec). *In-vitro* dissolution studies conducted in 0.1M HCl, 500ml medium

maintained at 35 ± 0.5^{0}C cumulative percentage release at the end of 15 min ranges from (37.8±2.23% to 85.3±2.23%), F9 formulation was isolated for compression coating.

***In-vitro* evaluation of SS coat tablet**

Compression coating was done to the selected F9 core tablet by the direct compression method using Eudragit S100, HPMCK4M as a coating material. Tablets were prepared in variable core: coat (i.e. 1:1 & 1:2), and evaluated for *in-vitro* evaluation studies result indicates Thickness of the tablet ranges from 3.1 ± 0.76 to 4.5 ± 3.21, Avg. weight of the tablet (315.23 ± 2.27 to 484.23 ± 3.21), Hardness (Kg/cm^2) (5.13±0.31 to 6.56±2.12), Friability (%) (0.35 to 0.74), Lag time (min) (4±2.12 to 509± 1.41) and Percentage of drug content (98 ± 0.05 to104 ± 0.1) From the results it was known that the thickness of the tablet has not had a positive effective and it is depending upon the polymer. A lag time of F_{b5} was 6hrs 10mins. It indicates that Eudragit S100 alone coated formulation should have less lag time, while increasing HPMCK4M concentration increases lag time and remaining *in-vitro* parameters are within the limits as per official standards I.P and U.S.P.

***In-vitro* dissolution study of SS core and coated tablet**

In-vitro dissolution studies conducted in 0.1M HCl, of F1-F9 at 15min founded between 37.8±2.23% to 85.3±2.23%, F9 (9% croscarmellose sodium + sodium starch glycolate) with 85.3±2.23% of drug releases at 15min formulation selected as a suitable core for compression coating (fig 3a). Compressed coated tablets evaluated for *in-vitro* drug release at different pH conditions as explained in the procedure (fig 3b). The cumulative percentage of drug release at 1hr in F_{a1}-F_{a3} (71.05±2.24% to 80.54± 4.47%), F_{b1}- F_{b3} (67.09±1.12% to 82.12± 4.48 %). The present main objective of the present formulation is to preprogram to release the maximum amount drug at the 6th hour, F_{a7} (75.65±3.46%), F_{b4} (81.04±0.79%), F_{b5} (16.6±2.23%), Fb_6 (5.06± 1.12%) and F_{b7} (6.65±3.66%). At the end of 6hr F_{b5} formulation releases (79.41± 1.07%), F_{b6}(10.7±0.01%) and F_{b7}(9.12±2.31%) so from the results it was understood HPMCK4M: Eudragit S100 4: 6 was ideal for the present pulsatile system.

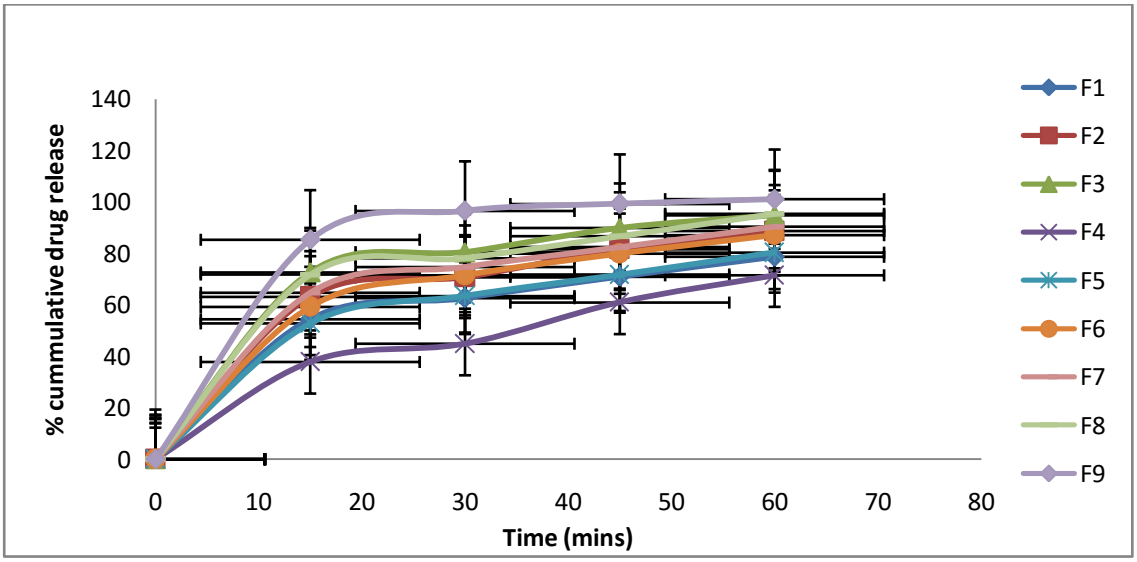

Fig. 6: *In-vitro* drug release study of SS core tablet

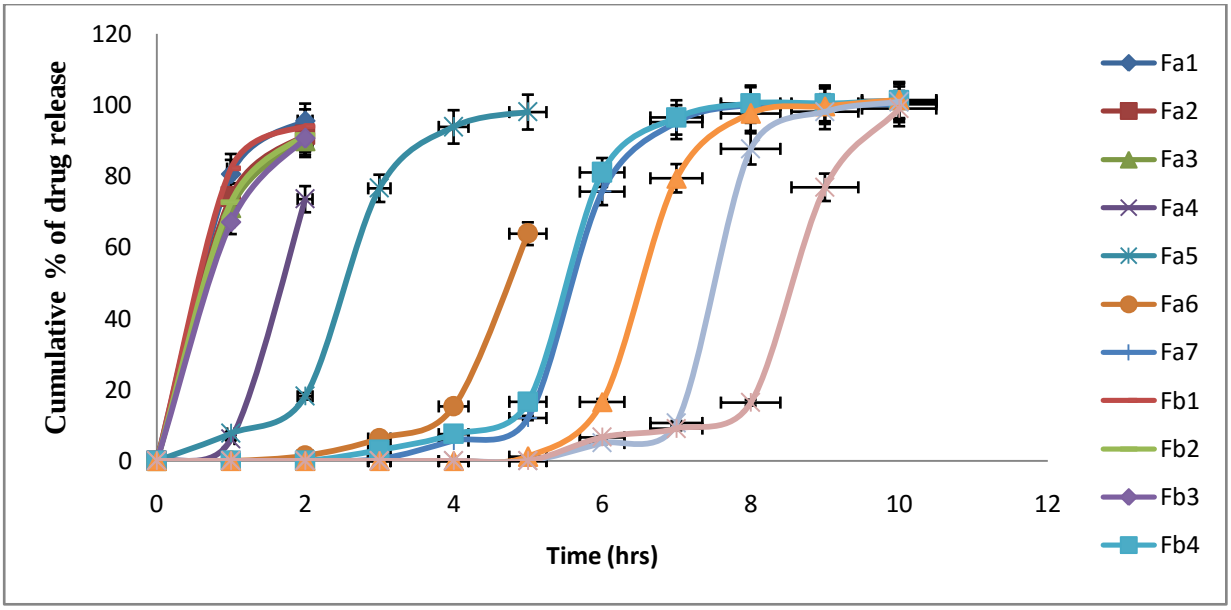

Fig. 7: *In-vitro* drug release study of SS coat tablet

Table 5: Cumulative % of drug release of core tablet.

S.no	Time (min)	F1 (%C.D ±S.D)	F2 (%C.D ±S.D)	F3 (%C.D ±S.D)	F4 (%C.D ±S.D)	F5 (%C.D ±S.D)	F6 (%C.D ±S.D)	F7 (%C.D ±S.D)	F8 (%C.D ±S.D)	F9 (%C.D ±S.D)
1	0	0	0	0	0	0	0	0	0	0
2	15	54.4±1.12	63.1±2.24	72.6±2.24	37.8±2.23	52.8±3.35	59.2±3.35	64.7±2.23	71.8±3.35	85.3±2.23
3	30	62.6±4.45	70.7±2.27	80.5±4.41	44.9±4.51	63.4±3.4	71.5±1.14	74.7±1.14	78.1±3.42	96.5±2.26
4	45	70.9±3.45	81.6±2.30	89.9±4.56	60.9±1.18	71.8±2.32	79.9±2.32	82.5±1.18	86.7±2.42	99.2±1.21
5	60	78.7±3.5	88.7±1.23	94.8±4.74	71.5±1.2	80.3±1.27	87.1±1.18	90.4±3.45	95.4±3.57	101.1±1.0

Table 6: Drug release studies of compressional coated salbutamol sulphate (core: coat 1:1).

Time (hrs.)	Cumulative % of drug release ± S.D						
	F_{a1}	F_{a2}	F_{a3}	F_{a4}	F_{a5}	F_{a6}	F_{a7}
1	80.54± .47	74.21± 4.48	71.05±2.24	6.17±2.24	7.76±2.24	0	0
2	95.59± 1.21	91.52± 2.33	89.87±2.28	73.53±3.31	18.19±1.16	1.55±2.19	0
3	-	-	-	-	76.58±3.89	6.33±4.65	0.64±0.91
4	-	-	-	-	93.83±3.98	15.35±4.69	5.73±1.28
5	-	-	-	-	97.99±2.82	63.84±4.74	12.09±0.04
6	-	-	-	-	-	-	75.65±3.46
7	-	-	-	-	-	-	95.17±2.13
8	-	-	-	-	-	-	99.97±0.06
9	-	-	-	-	-	-	100.09±0.06
10	-	-	-	-	-	-	100.17±0.07

Table 7: Drug release studies of compressional coated SSalbutamol sulphate (core: coat 1:2).

Time (hrs.)	Cumulative % of drug release ± S.D						
	F_{b1}	F_{b2}	F_{b3}	F_{b4}	F_{b5}	F_{b6}	F_{b7}
1	82.12±4.48	72.63±2.24	67.09±1.12	0	0	0	0
2	94.05±3.44	91.48±2.19	90.58±1.13	0	0	0	0
3	-	-	-	3.09±4.36	0	0	0
4	-	-	-	7.57±1.35	0	0	0
5	-	-	-	16.64±3.67	1.25± 0	0	0
6	-	-	-	81.04±0.79	16.6±2.23	5.06±1.12	6.65±3.66
7	-	-	-	96.49±1.23	79.41± 1.07	10.7±0.01	9.12±2.31
8	-	-	-	100.43±0.07	97.58± 2.26	87.66±1.09	16.42±3.46
9	-	-	-	100.44±0.04	99.64±0.32	98.1± 2.23	76.87±1.3
10	-	-	-	101.22±0.99	101.37±0.08	100.84±1.04	98.97±0.91

CONCLUSION

From the present study it could be concluded that the compression coated tablet of SS prepared and from the *in-vitro* dissolution study it was concluded that Fa_5 (understand HPMCK4M: Eudragit S100 4: 6) drug release was to mimic the circadian rhythm of nocturnal asthma, proved to stable and containing the therapeutics quantity of drug. Future *in-vivo* study was planned to carry out to conform its significance.

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