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Formulation and Evaluation of Chrono-Modulated Drug Delivery System for Asthma

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KEYWORDS:

Antiasthmatic drugs, asthma, Time-controlled pulsatile tablet, Time Dependent Delivery, Press-coated tablet, 5 h lag time, Burst release.

ABSTRACT:

This study's main goal was to develop and assess a single-unit time-controlled oral pulsatile medication delivery system that contains antiasthmatic drugs to prevent nocturnal asthma attacks. Time-dependent delivery systems are made to release medication quickly or gradually after a certain amount of time, known as the lag time. Medication and chronotherapeutic formulations can be administered into the colon using these devices, among other uses.

The creation of a time-dependent press-coated tablet was the aim of this project. In order to treat nocturnal asthma, this work aims to develop and evaluate a chronomodulated drug delivery system of antiasthmatic medication, a selective β2 receptor blocker, which is a legitimate and acceptable rationale. This paper aims to give an overview of the main formulation techniques and the reasoning behind delayed-release dosage forms. When a medication is prescribed for the pharmacological treatment of asthma, maintain a lag time of 4-5 hours before drug release and a lag time of 4-5 hours between plasma peak concentration and controlled release. A five-hour lag time was the target. The gadget is utilized before going to bed. and is anticipated to administer the medication five hours later, or about four in the morning, when asthma attacks are most frequent.The direct compression method was used to create drug-containing core tablets with different superdisintegrant compositions, such as sodium starch glycolate, croscarmellose sodium, and crospovidone. Press-coated tablets were produced using hydroxypropyl methylcellulose K4M in a variety of hydrophobic and hydrophilic polymer compositions after the fast-dissolving core tablet formulation was selected.The drug release profile and in vitro lag time in simulated stomach and intestinal fluids were used to select and quantify the coated polymers.The best instant-release core pill was determined to be the crospovidone formulation, which had the quickest dissolving time of 30 minutes. After a five-hour lag, the press-coated tablet formulation with a 350 mg barrier layer covering the core tablet demonstrated rapid and complete drug release. After six months, accelerated stability evaluations of the updated formulation revealed no appreciable changes in the release profile. The in vitro dissolving study showed that the amount and kind of coating polymer utilized had a significant impact on the lag time before drug release. Press-coating techniques can be used to produce time-controlled pulsatile release tablets.

INTRODUCTION:

Chronopharmaceutics is the distribution of medications at a time that corresponds to biological requirements for the treatment or prevention of a certain condition. A chronopharmaceutical device called pulsatile drug delivery systems (PDDS) uses a lag time to release medicine in pre-programmed patterns [3]. Asthma is the most prevalent chronic illness among children. It is a long-lasting inflammatory respiratory illness. Early in the morning, people with nocturnal asthma have a decrease in lung function and an increase in airway resistance. Nighttime symptoms are experienced by two-thirds of asthmatics. The likelihood of having an asthma attack is 100 times higher at night than during the day. At 4 a.m., the forced expiratory volume in one second is reduced [5,6]. Around 4 a.m., histamine levels increased, coinciding with the most severe bronchoconstriction [1]. Circadian variations in adrenaline, cortisol, histamine, AMP, melatonin, vagal tone, body temperature, lower airway secretions, and other factors all contribute to nocturnal bronchoconstriction. Salbutamol is a highly selective, fast-acting β2-adrenoceptor agonist with little adverse effects on the heart. It is used to treat asthma by causing the bronchi to widen quickly by relaxing the smooth muscle of the bronchial tubes [9,10]. Oral salbutamol sulfate tablets (2–8 mg) are efficiently

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absorbed by the GI tract, with a peak plasma concentration of 1-3 hours and an absolute bioavailability of 44% [11]. Salbutamol sulfate, on the other hand, has a high first-pass metabolism and a brief biological half-life (3–4 hours). Hypokalemia may occur from high doses or long-term usage. Salbutamol sulphate formulations with time-controlled pulsatile release dosages can lessen these restrictions [12]. It might not be feasible to treat asthma with rapid-release dosage forms if symptoms are severe at night or in the early morning. When asthmatic episodes are most likely to occur in the early morning, pulsatile-release dosage forms can be administered at night [13]. The benefits of manufacturing simplicity led us to select a single-pulse system. Compress-coated methods reduce the hygroscopic drug salbutamol sulphate's instability when compared to standard pan-coated methods [14,15].

MECHANISM OF DRUG RELEASE FROM PDDS

1. Pulsatic system with a rupturable coating.

For example, Time-controlled Explosion system (TCES).

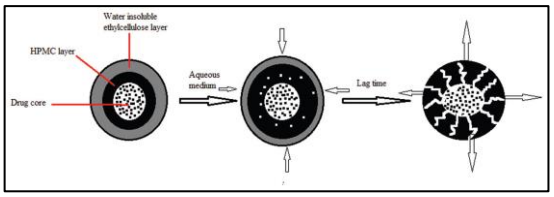

Fig 1: Time-controlled explosion system[1]

2. Osmotic based rupturable coating system.

For example, Permeability controlled system.

3. Pulsatic delivery by a change in membrane permeability.

For example, sigmoidal release system.

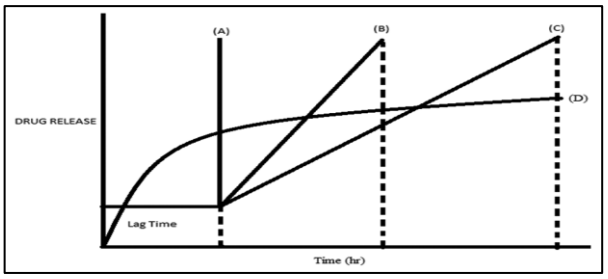

Fig. 2: Schematic representation of different drug delivery systems was (A) sigmoidal release after the lag time, (B) delayed-release after the lag time, (C) sustained-release, (D) extended-release without lag time.[1]

The mechanism of drug release from the PDDSs occurs in the following ways.

1. Diffusion

Water diffuses into the inside of the molecule. Particles interact with watery liquids in the GIT tract and resultant medication arrangements diffuse across the delivery coat to the outside.[1]

2. Erosion[1,2]

Some coatings intended to dissolve steadily with time, bring about the arrival of the medication contained inside the molecule.

3. Osmosis

An osmotic pressing factor can be developed inside the inside of the molecule when water is permitted to enter in specific situations. The medication is constrained out of the molecule into the outside through the covering.[1,2]

A PDDS is characterized as the quick and transient release of a specific amount of drug molecule within a short period immediately after a predetermined off-release period, that is, lag time. These systems are characterized by two release phases. A first phase during which little drug is released, followed by a second phase, during which the drug is released completely within a short period after a lag time. Most PDDSs are repository gadgets coated by a barrier polymeric coating. The coating prevents drug release from the core until the polymeric shell is completely dissolved, eroded, or ruptured during/after a certain lag time. After this, the drug is released rapidly from the inner reservoir core. Pulsatile release tablet formulation generally consists of a rapid release core tablet encased in a barrier layer either formed by presscoating or liquid coating or a combination of both. PDDSs have a peculiar mechanism of delivering the drug rapidly and completely after a lag time, that is, a period of no drug release. Such a release pattern is known as pulsatile release.

To present the idea of chronotherapeutics, it is imperative to characterize the accompanying ideas:

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Chronobiology

Chronobiology is the science worried about the natural system of the diseases as per a period structure. “Chrono” relates to time and “science” relates to the study, or science, of life.

Chronopharmacology

Chronopharmacology is the science worried about the varieties in the pharmacological activities of different medications throughout some times of the day.

Chronopharmacokinetics

Chronopharmacokinetics includes the investigation of transient changes in drug absorption, distribution, metabolism, and excretion. Pharmacokinetic parameters, which are traditionally viewed as consistent on time, are impacted by various two physiological capacities showing circadian beat. Circadian changes in gastric corrosive discharge, GI motility, GI bloodstream, drug-protein restricting, .[2]

Chronotherapy

Coordination of biological rhythms and clinical treatment is called chronotherapy.

Chronotherapeutics

Chronotherapeutics is the order worried about the conveyance of medications as per the inalienable exercises of a disease over a specific period. It is turning out to be progressively more obvious that the particular time that patients take their drug might be much more critical than was perceived in the past.

BENEFIT OF PDDS[1]

There are numerous benefits of the pulsatile measurement structure over regular dose structure.

- Increase the absorption and bioavailability than conventional immediate release or sustained release drugs.
- Site targeting permits the delivery of poorly bioavailable medications that would get destroyed in a higher GIT climate.
- Lessens the dose of the medication without decreasing the therapeutic effect.
- Chronotherapy modified delayed discharge gives an ideal treatment of the disease.
- Lower day-by-day expenses to the patient because fewer dosage units are needed by the patient in treatment.
- Medication adjusts to suit circadian rhythms of the body.

METHODS AND MATERIALS:

MATERIALS

Neuland Laboratories Pvt. Ltd. provided a gift sample of salbutamol sulfate. Pharmacopoeial-grade hydroxypropyl methylcellulose K4M (HPMC K4M), low substituted sodium starch glycolate (SSG), croscarmellose sodium (CCS), crospovidone, polyvinylpyrrolidone K-30, microcrystalline cellulose, magnesium stearate, aerosil 200, and lactose monohydrate. The medication was placed in a fast-disintegrating core and press-coated with an appropriate barrier layer in a revolutionary method called "time-dependent PDDS." The direct compression method was used to create drug-containing core tablets with various superdisintegrate compositions, including SSG, CCS, and crospovidone. Press-coated tablets with various compositions of hydrophobic and hydrophilic polymers, HPMC K4M, ethyl cellulose, and eudragit S100 were made using the fast-disintegrating core tablet formulation. Based on the drug release profile and in vitro lag time in simulated stomach and intestinal fluids, the coated polymers were chosen and measured.

METHODS

basic tablet formulation using direct compression. After 15 minutes of dry mixing, the materials listed in Table 1 aside from magnesium stearate and aerosil-200—were added, and the dry blending process continued for an additional five minutes. A single punch rotary punching machine was used to compress the drug and excipient mixture, resulting in round tablets with a diameter of 9 mm and a weight of 100 mg. An assessment of the core tablet.

Preparation of press-coated tablets:

The produced barrier mixes from T1 to T9 were used to press-coat the core tablets. After weighing half of the barrier layer material, the core tablet was physically

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positioned in the middle. The die was filled with the remaining half of the barrier layer material, which was then squeezed.

Calibration Curve Of Salbutamol Sulphate: From a solution having concentration of 100 µg/ml, parts of 0.2, 0.4, 0.6, 0.8, 1.0, 1.2,1.4, 1.6, 1.8, and 2 ml were pipette out into 10 ml volumetric flasks. The volume was made up to the mark with 0.1N HCL to get the final concentration of 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 µg/ml, respectively. The absorbance of each concentration was measured at 276 nm. A graph of absorbance versus concentration was plotted. It shows the straight line, which means the calibration curve obeys the Beer-Lambert law.[18]

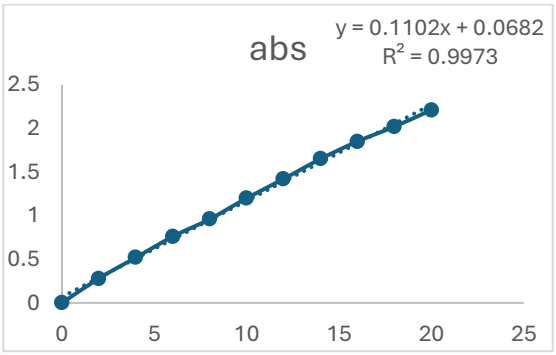

Fig. 1 Calibration Curve of salbutamol sulphate with distilled water

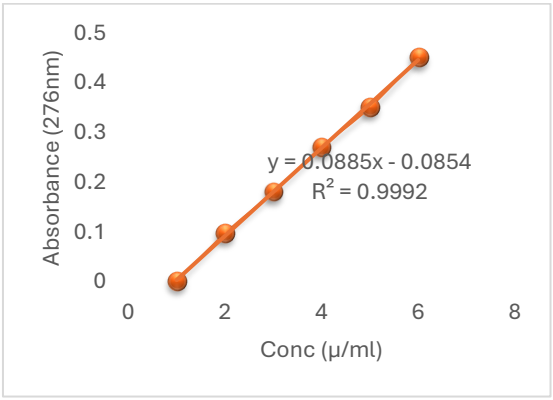

Fig.2 Calibration Curve of Salbutamol sulphate with 0. N HCL

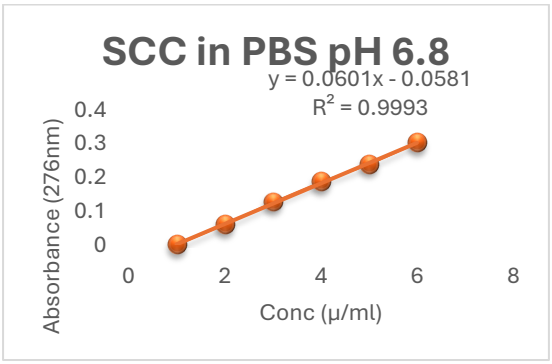

Fig. 3 Calibration Curve of salbutamol sulphate with pH 6.8

The calibration curve of salbutamol sulphate shows the R^2 value, which is equal to 0.999 nearly a straight line, which shows that the study follows Beer's law.

Pre-formulation study

Angle of Repose - The largest angle created between the powder plane and the horizontal surface during rotation is known as the angle of repose. Particle flow characteristics, which may be related to particle packing densities and mechanical configurations, may be ascertained with the use of angle of repose. The powder angle of repose was determined using the fixed funnel and free-standing cone technique. Weighing the grains was done carefully. Next, the height of the funnel was adjusted such that its tip just brushed the top of the granule pile. Granules were allowed to freely pass through the funnel and land on the surfaces. The diameter and angle of repose of the powder cone were measured.[25]

Bulk density may be calculated by putting preserved bulk powder into a graduated measuring cylinder and measuring the volume and weight of the powder. The following formula can be used to compute bulk density.

$$\text{Bulk density} = \frac{\text{Mass of powder}}{\text{Bulk Volume}}$$

Determination of Tapped density - Tapped density can be determined by pouring preserved powder into a graduated measuring cylinder via a large funnel and tapping for 100 times on a wooden plank and measuring the volume and weight of the powder. Tapped density can be calculated by the following formula.

$$\text{Tapped Density} = \frac{\text{Mass of powder}}{\text{Tapped Volume}}$$

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Compressibility Index (or Carr's index (I) – An indirect method of measuring powder flow from bulk densities was developed by Carr. The percentage of compressibility of the powder is a direct measure of the potential powder arch and stability. Carr's index for each formulation prepared was calculated.

Table 1: Evaluation of Micromeritic Properties of Powder Blends for Different Formulation Batches

Formulation batch	bulk density (g/cm^3 ± SD)	tapped density (g/cm^3 ± SD)	Carr's index (% ± SD)	hausner's ratio(± SD)	angel of repose(± SD)
T1	0.56±0.02	0.63±0.02	12.91±1.08	1.13±0.01	24.9±0.38
T2	0.57±0.01	0.66±0.01	12.31±1.04	1.12±0.02	24.23±0.34
T3	0.56±0.01	0.67±0.03	12.80±1.10	1.12±0.01	23.17±0.44
T4	0.58±0.02	0.65±0.02	13.25±0.89	1.14±0.01	23.29±0.38
T5	0.59±0.00	0.63±0.12	12.4±0.96	1.13±0.00	24.76±0.32
T6	0.60±0.02	0.66±0.15	13.2±0.59	1.14±0.01	22.87±0.40
T7	0.54±0.01	0.63±0.05	12.36±0.79	1.15±0.02	24.54±0.39
T8	0.52±0.01	0.66±0.08	12.3±0.82	1.14±0.01	24.47±0.39
T9	0.53±0.01	0.63±0.09	12.34±0.45	1.13±0.00	24.44±0.33

Table 2: Manufacturing formula of the core tablet:

CORE TABLET		Quantity in mg/tablet								
S.N	Ingredients	T1	T2	T3	T4	T5	T6	T7	T8	T9
1	salbutamol Sulphate	4	4	4	4	4	4	4	4	4
2	Microcrystalline cellulose	10	10	10	10	10	10	10	10	10
3	Magnesium stearate	3	3	3	3	3	3	3	3	3
4	Cropovidone	0	0	0	3	6	9	0	0	0
5	Croscarmellose sodium	0	0	0	0	0	0	3	6	9
6	Lactose monohydrate	73	70	67	73	70	67	73	70	67
7	PVP K30	5	5	5	5	5	5	5	5	5
8	Sodium starch glycolate	3	6	9	0	0	0	0	0	0
9	Aerosile-200	2	2	2	2	2	2	2	2	2
	Total Weight(mg)	100	100	100	100	100	100	100	100	100

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IN-VITRO DISSOLUTION PROFILE OF CORE TABLET:

Table 3: %Cumulative Drug Release in Different formulation

Time (hrs)	T1	T2	T3	T4	T5	T6	T7	T8	T9
0	0	0	0	0	0	0	0	0	0
2	6.68±0.26	9.36±0.16	15.59±0.26	18.59±0.34	13.26±0.46	23.26±0.16	12.86±0.06	14.59±0.29	18.68±0.12
5	9.16±0.19	19.49±0.03	29.49±0.25	39.76±0.29	22.35±0.65	41.95±0.19	23.48±0.07	25.59±0.07	29.46±0.26
10	16.43±0.14	39.59±0.21	57.59±0.16	58.69±0.06	36.86±0.39	91.19±0.24	36.36±0.14	41.68±0.21	44.19±0.04
15	21.68±0.28	49.59±0.14	78.48±0.09	83.34±0.35	47.49±0.48	99.56±0.11	52.48±0.29	63.19±0.06	56.68±0.14
20	39.63±0.11	61.19±0.23	86.67±0.21	91.48±0.25	66.68±0.16	99.48±0.16	61.91±0.06	69.69±0.19	79.32±0.04
25	49.43±0.02	72.49±0.16	94.68±0.18	93.86±0.04	81.16±0.32	100.02±0.01	66.82±0.21	72.48±0.13	84.61±0.06
30	58.59±0.09	81.68±0.06	98.49±0.04	98.26±0.03	95.49±0.03	100.03±0.04	72.48±0.09	80.47±0.09	93.49±0.03

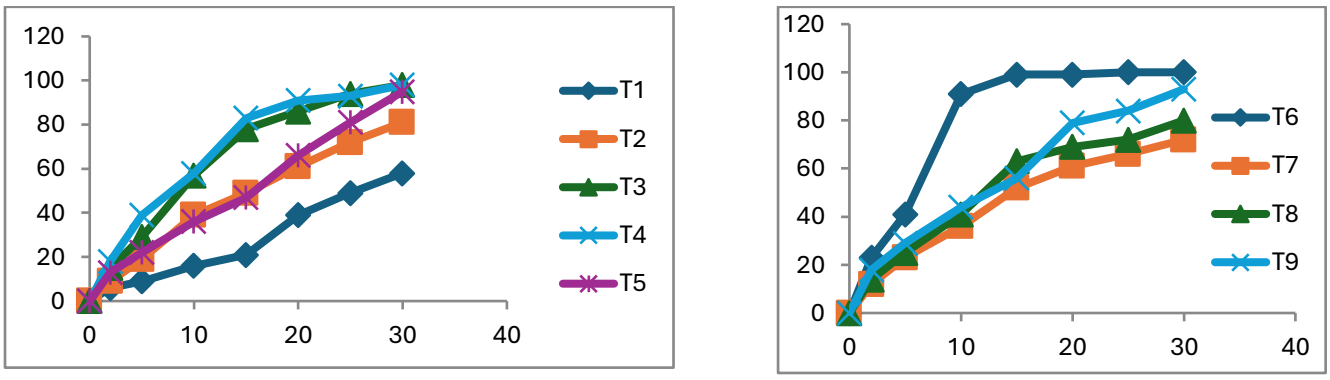

Fig. 4: In vitro drug release profile of F1- F9 formulation

Table 4. Manufacturing formula of barrier layer for press-coated tablets:

Coated Tablet		Quantity in mg/tablet				
S.N	Ingredient	F1	F2	F3	F4	F5
1	Core tablet	100	100	100	100	100
2	Eudragit S100	50	100	150	200	250

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3	HPMC K4M	250	200	150	100	50
4	Ethyl cellulose	50	50	50	50	50
	Total Weight(mg)	450	450	450	450	450

EVALUATION OF TIME DEPENDENT COATED TABLET:

Table 5: Evaluation of Physical Parameters of Tablet Formulation Batches

Formulation batch	Weight variation	Hardness (kg/cm^3)	Thickness(mm)	Friability
F1	448.3±3.87	6.79±0.69	3.86±0.03	0.21±0.02
F2	447.7±2.64	7.46±0.75	3.91±0.02	0.23±0.01
F3	450.8±4.46	9.65±0.43	3.93±0.05	0.26±0.02
F4	451.4±3.76	8.18±0.41	3.87±0.04	0.19±0.03
F5	450.3±3.91	7.78±0.56	3.82±0.03	0.25±0.01

The Average Weight of all time-dependent core tablets within the formulation was found to be uniform. This indicates uniform filling of the die cavity during tablet compression. The Hardness of all-time dependent core tablets was found to be in the range of 3.63±0.23to 3.79±0.9 kg/cm^2. This ensures good mechanical strength. The Thickness of all time-dependent core tablets was found in the range of 1.96±0.04 to 2.02±0.03mm. There were no marked variations in the thickness of all formulations, indicating uniform behaviour of powder throughout the compression process. The Friability of all time-dependent core tablets was found to be in the range 0.21 to 0.26, which indicates good flow ability. The Drug Content of all formulations was found to be between 97.67±0.18 to 99.69±0.33%. The values ensure good uniformity of drug content in the tablet. From the results, it was observed that the lag Time of all formulations was in range 4.33 to 5.56 h.

Drug And Polymer Compatibility Studies:

The FTIR spectrum of the drug was recorded on an infrared spectrophotometer (Shimadzu Affinity-1). The IR spectrum of the drug, polymers, and their physical mixture were recorded in the frequency range of 400-4000 cm^{-1}. The recorded peaks were then noted and matched with the standard FTIR of the drug.

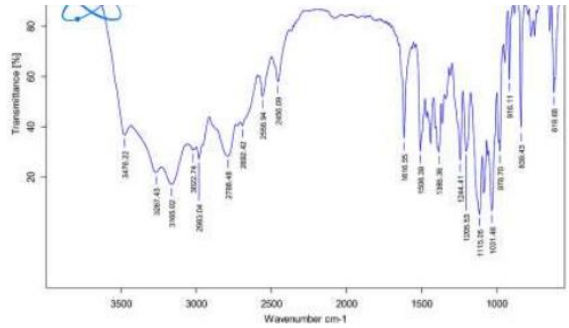

Fig. 5: FT-IR spectrum of Salbutamol sulphate drug

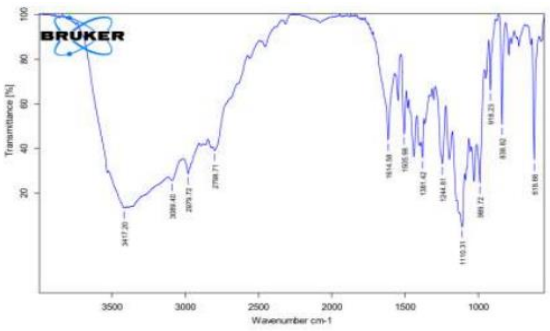

Fig. 6: FTIR graph of Salbutamol sulphate + Croscarmellose sodium

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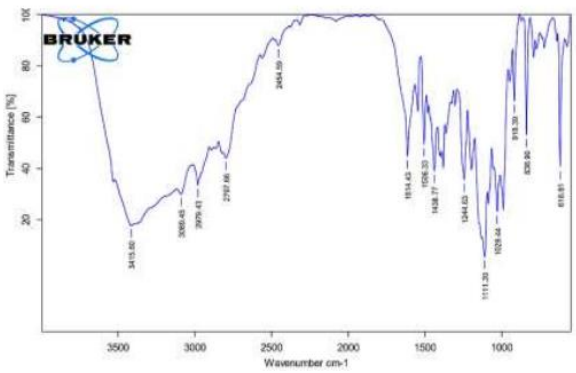

Fig. 7: FTIR graph of Salbutamol sulphate

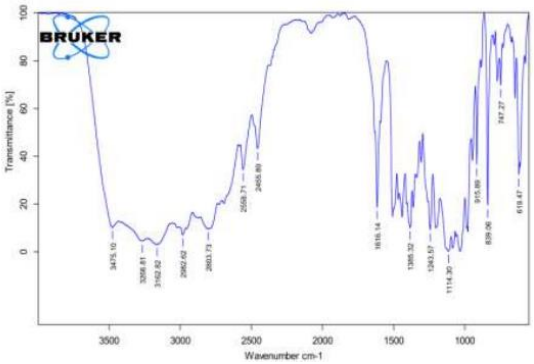

Fig. 8: FTIR spectrum of Salbutamol sulphate +HPMCK4M +Sodium starch glycolate.

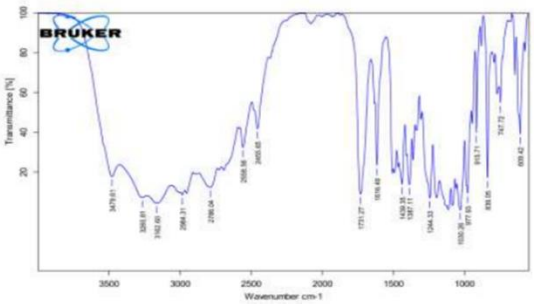

Fig. 9: FTIR spectrum of Salbutamol sulphate Eudragit S100.

Drug–Polymer Compatibility Study (FTIR)

FTIR studies were conducted to evaluate compatibility between salbutamol sulphate and excipients.

FTIR spectra:

- Drug alone
- Drug + CCS
- Drug + SSG
- Drug + HPMC K4M
- Drug+Eudragit 100S

Table 6: FTIR spectra of drug and drug–polymer mixtures

Sample	Observation	Inference
Pure drug	Characteristic peaks intact	Reference
Drug + CCS	No peak shift	Compatible
Drug + SSG	No new peaks	Compatible
Drug + HPMC K4M	No interaction	Compatible
Drug + Eudragit S100	Stable spectrum	Compatible

Observed characteristic peaks of Salbutamol sulphate:

- O–H stretching
- N–H stretching
- C–O stretching
- Aromatic C=C stretching

All characteristic peaks of salbutamol sulphate were retained in physical mixtures without significant shift, disappearance, or formation of new peaks, indicating no chemical interaction between drug and polymers.

The results of the FTIR study show that, the drug was not found to show any interactions with the polymers i.e. Eudragit S100 , Croscarmellose sodium, and HPMC K4M. Hence, we can use the chosen polymers for further study

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Table 7: % swelling index study

TIME (hrs)	F1±SD	F2±SD	F3±SD	F4±SD	F5±SD
0	0±0	0±0	0±0	0±0	0±0
1	5.6±0.659	3.7±0.946	4.8±0.458	4.2±0.486	3.8±0.459
2	12.4±0.349	9.5±0.491	11.4±0.365	9.1±0.963	8.5±0.756
3	28.8±0.465	22.3±0.459	23.7±0.893	17.6±0.489	14.9±0.953
4	39.5±0.683	34.2±0.763	32.6±0.148	25.7±0.256	23.6±0.415
5	54.2±0.861	42±0.369	45.3±0.349	33.9±0.346	29.7±0.563
6	66.3±0.684	56.7±0.159	58.6±0.843	41.4±0.692	38.4±0.489
7	74.2±0.629	66.4±0.986	69.7±0.459	51.6±0.315	47.9±0.256
8	79.5±0.734	70.9±0.146	76.5±0.136	56.8±0.852	54.6±0.864
9	92.7±0.364	74.6±0.356	82.9±0.896	64.9±0.469	61.8±0.789

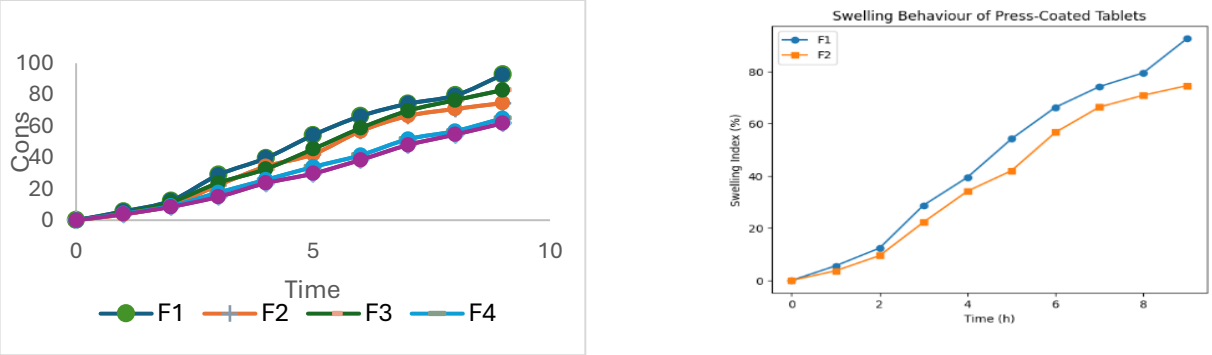

Fig 10. % swelling index

The swelling index increased with time for all formulations. F1 showed higher swelling compared to F2, indicating better hydration and gel formation of HPMC K4M, which contributed to prolonged lag time before drug release.

Table 8: In Vitro Dissolution Profile Of Press Coated Tablet

Dissolutios Media	TIME	Cumulative % Drug Release in Different Trials				
		F1	F2	F3	F4	F5
Simulated gastric fluid (0.1 HCL)	0.5	0	0	0	0	0
	1	0	0	0	0	0
	1.5	0	0	0	0	0
	2	0	0	0	0	0
	2.5	0	0	6.2±0.56	0	0

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Simulated pH 7.4	3	0	0	15.3±0.29	0	0
	3.5	0	3.16±0.36	30.8±0.43	5.3±0.61	3.18±0.35
	4	0	10.15±0.63	46.2±0.32	8.2±0.27	9.17±0.36
	4.5	2.28±0.42	17.3±0.25	58.9±0.16	13.6±0.16	21.9±0.43
	5	3.74±0.36	38.61±0.53	78.3±0.76	19.7±0.31	34.33±0.65
Simulated pH 6.8	5.5	38.8±0.19	56.32±0.41	87.3±0.62	29.8±0.39	47.3±0.16
	6	53.58±0.49	70.2±0.39	91.6±0.54	53.12±0.65	72.56±0.54
	6.25	72.65±0.68	84.2±0.23		68.2±0.46	89.62±0.41
	6.5	86.7±0.76	96.52±0.16		78.33±0.65	96.8±0.62
	6.75	93.09±0.56	99.82±0.35		81.96±0.19	
	7	99.15±0.62				

All values are expressed as mean ± standard deviation, n=3

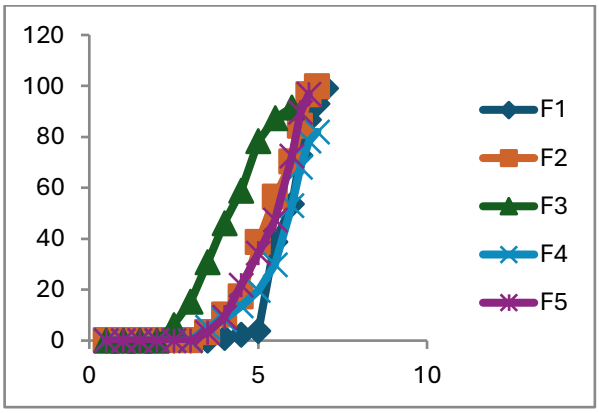

Fig 11. Cumulative % Drug Release in Different Trials

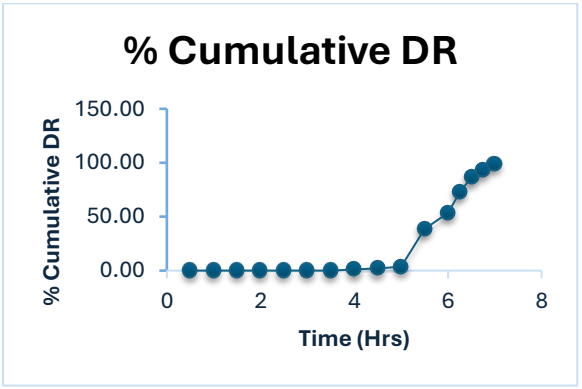

Fig 12. Cumulative % Drug Release in optimize F1batch

Table 9: Lag time and t90% of all batch press- coated tablets

Formulation	F1	F2	F3	F4	F5
Lag time (h)	5.5	4.5	3	3	4.3
t90% (h)	6.90	6.36	6	6.55	6.45

The results obtained in the in vitro drug release study are tabulated. The cumulative percentage of salbutamol sulfate released as a function of time for all the formulations is the optimize batch F1 shown in graph . Coating of tablets with Eudragit S-100 :HPMC K4M :Ethyl cellulose in combination showed the lag time of nearly before the burst effect. From the result, concluded that the combination of Eudragit S-100:HPMC K4M: Ethyl cellulose can be successfully utilized to create a desired release profile similar to the targeted release profile in future studies. From the results, we have seen that press coating gave us more appropriate results as the release of the drug at pH 7.4 was less and the drug release at pH 6.8 was more, i.e, the drug release was more in the colonic region.

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Stability study of the formulation:

Table 10: Drug release profile of formulation F1 for stability study

	days	0 %CDR	7 %CDR	14 %CDR	21 %CDR	28 %CDR
sr .no	time	0	0	0	0	0
1	0	0	0	0	0	0
2	1	0	0	0	0	0
3	2	0	0	0	0	0
4	3	0	0	0	0	0
5	4	0	1.14±0.01	1.13±0.01	1.1±0.02	1.1±0.01
6	4.5	2.32±0.02	2.26±0.01	2.21±0.01	2.15±0.02	2.18±0.02
7	5	3.39 ±0.04	3.35±0.02	3.29±0.03	3.12±0.01	3.11±0.01
8	5.5	38.8±0.01	37.56±0.03	36.33±0.07	35.2±0.03	33.13±0.02
9	6	53.58±0.06	16.8±0.08	51.3±0.04	50.51±0.09	48.19±0.05
10	6.25	72.65±0.21	52.8±0.12	71.6±0.11	69.15±0.8	67.01±0.1
11	6.5	86.7±0.05	73.24±0.14	84.41±0.17	81.15±0.16	78.12±0.19
12	6.75	93.09±0.13	92.12±0.19	91.96±0.19	89.3±0.29	87.2±0.31
13	7	99.15±0.17	97.03±0.23	95.89±0.16	94.96±0.38	94.54±0.21

Table 11: Stability Evaluation of Formulation Over Time (0–4 Weeks) in Terms of % Drug Content, Lag Time, and Appearance

Stability study	% Drug Content	Lag Time (hr)	Apperence
0days	99.15±0.17	5.5	No Change
1week	97.03±0.23	5.5	No Change
2week	95.89±0.16	5.5	No Change
3week	94.96±0.38	5.5	No Change
4week	94.54±0.21	5.5	No Change

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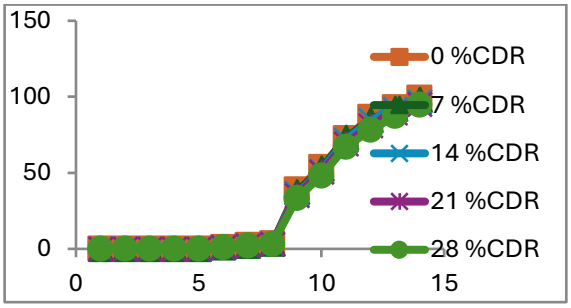

Fig 13: Comparative In Vitro Drug Release Profiles of Formulations Containing Different Concentrations of CDR

It was concluded that F1 had sufficient lag time of 5.5 hours. The greater the lag time, more will be the time take for the dosage form to release the drug.

The selected formulation (F1) was found to be stable upon storage for 4 weeks. No change was observed in the appearance, hardness, and average weight of the tablet. Also, no significant change was observed in the in vitro release of the drug

FACTORIAL DESIGN

The study follows a formulation-variable based factorial optimization approach. The statistical comparison is based on variation of superdisintegrant type and concentration for core tablets, and polymer ratios for press-coated tablets

Table 12 : Schematic representation of factorial formulation design

Factor	Variable	Levels	Response	Statistical Representation
X1	Superdisintegrant type	SSG, CCS, Crospovidone	Disintegration Time	Mean ± SD
X2	Superdisintegrant concentration	3, 6, 9 mg	%Drug Release	Mean ± SD
X3	Polymer ratio	F1–F5	Lag Time	Mean ± SD

Table 13: factorial formulation design.

Formulation	Lag Time (h)	t90% (h)
F1	5.5	6.90
F2	4.5	6.36
F3	3.0	6.00
F4	3.0	6.55
F5	4.3	6.45

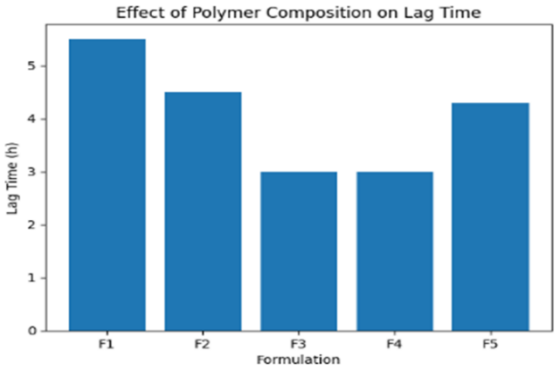

Fig. 14: Influence of Polymer Composition on Lag Time of Different Formulation Batches

This graph shows the influence of polymer composition on lag time of press-coated tablets. Formulation F1 exhibited the highest lag time (5.5 h) due to higher HPMC K4M content, confirming its suitability for chronotherapeutic delivery in nocturnal asthma.

KINETICS

Based on the dissolution profile, the optimized formulation F1 exhibits a pulsatile release pattern with an initial lag time followed by burst release.

Models applied

- Zero-order
- First-order
- Higuchi model
- Korsmeyer–Peppas

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Table 14: Application of Various Kinetic Models to Drug Release Data and Interpretation of Release Mechanism

Kinetic Model	Applicability	Reason	Inference
Zero Order	Not suitable	No continuous release	Rejected
First Order	Not suitable	Non concentration-dependent	Rejected
Higuchi	Not suitable	Not diffusion controlled	Rejected
Korsmeyer–Peppas	Best fit	Swelling & erosion controlled	Super Case II transport

Table 15: Correlation Coefficients (R^2) for Different Drug Release Kinetic Models

Model	R^2 value
Zero order	**0.942**
First order	0.704

The in-vitro drug release data of optimized formulation F1 showed the highest linearity with zero-order and Higuchi models, indicating diffusion-controlled release after a defined lag time, followed by burst release behavior.

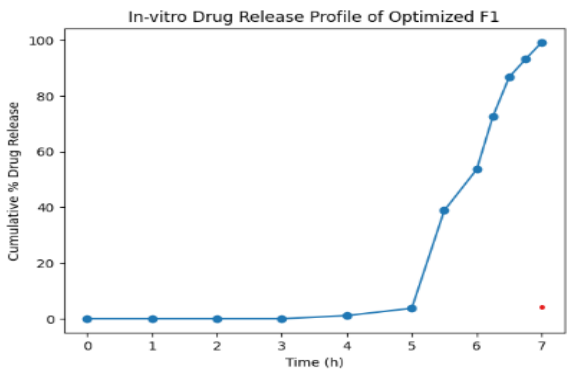

Fig. 15: Cumulative Percentage Drug Release Profile of Optimized Formulation F1 Over Time

The optimized formulation F1 showed negligible drug release up to 5.5 hours followed by rapid burst release, confirming a successful time-dependent pulsatile release profile suitable for early-morning asthma attacks.

CONCLUSION

From the above results, we can conclude that Salbutamol sulphate press-coated (pulsatile) tablet formulations prepared with Edragit, HPMC K4M, Ethyl cellulose showed acceptable properties like friability, weight variation, hardness, etc, and in-vitro drug release, which remained unchanged upon storage for 12 weeks. Eudragit S100 was the most successful coating polymer. Salbutamol sulphate tablets with the formulation code T6 proved to be the formula of choice. While the coating ratio 0.5:2.5:0.5.F1 Batch was selected for coating, using the press coating, a small amount of drug was degraded in the small intestine. But the main site release of the drug in the pH 6.8 (colonic pH) was more drug release as compared to the F2, F3 F4, and F5 Batch coating. So, the optimized formula of coating consisted of F1 Batch coating of tablets. since it showed the highest drug release and lag time. So, Salbutamol sulphate tablets can be used in burst release drug delivery in the treatment of asthma, so as to improve the absorption of drug in colon and also to reduce the dosing frequency of the drug.

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