RESEARCH PAPER

Formulation and Evaluation of Time Dependent Drug Delivery for Asthma

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ABSTRACT

The primary purpose of this study was to design and evaluate a single-unit time-controlled oral pulsatile drug delivery system containing salbutamol sulphate for nocturnal asthma attack prevention. Time-dependent delivery systems are designed to provide a rapid or prolonged release of the medicine after a specified period, referred to as the lag time. These systems can be used for various purposes, including the administration of chronotherapeutic formulations and medication into the colon. The purpose of this work was to create a time-dependent press-coated tablet. This work seeks to create and assess a chronomodulated drug delivery system of antiasthmatic medication, a selective β2 receptor blocker for the treatment of nocturnal asthma, which is a valid and acceptable reasoning. The purpose of this paper is to provide an overview of the rationale for delayed-release dosage forms as well as the primary formulation methodologies. 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 of a medication indicated for the pharmacological treatment of asthma. The goal was to have a five-hour lag time. The device is used at bedtime and is expected to deliver the medicine after 5 hours, or around 4 a.m., when asthma episodes are most common.

Method: Drug-containing core tablets with various superdisintegrant compositions such as sodium starch glycolate, croscarmellose sodium, and crospovidone were made using the direct compression technique. The fast-dissolving core tablet formulation was chosen, and press-coated tablets were manufactured with hydroxypropyl methylcellulose K4M in varied hydrophobic and hydrophilic polymer compositions. The coated polymers were chosen and measured based on in vitro lag time and drug release profile in simulated stomach and intestinal fluids.

Result: The crospovidone formulation had the fastest dissolving time, 0.31 minutes, and was chosen as the best instant-release core tablet. The press-coated tablet formulation with a 350 mg barrier layer over the core tablet exhibited quick and full drug release after a 5-hour lag period. The revised formulation's expedited stability assessments after 6 months found no significant variations in the release profile.

Conclusion: The coating amount and kind of coating polymer used had a substantial influence on the lag time before medicine release, according to the in vitro dissolution study. Time-controlled pulsatile release tablets can be created using press-coating methods.

Keywords: Salbutamol sulfate, asthma, Time-controlled pulsatile tablet, Time Dependent Delivery, Press-coated tablet, 5 h lag time, Burst release

How to cite this article: Quraishi MV, Kumar P. Formulation and Evaluation of Time Dependent Drug Delivery for Asthma. Int J Drug Deliv Technol. 2026;16(22s): 449-461. DOI: 10.25258/ijddt.16.22s.54

Source of support: Nil.

Conflict of interest: None

INTRODUCTION:

The delivery of pharmaceuticals at a time that corresponds to biological requirements for the treatment or prevention of a certain disease is known as chronopharmaceutics. Pulsatile drug delivery systems (PDDS) are a chronopharmaceutical technology in which the medication is released in pre-programmed patterns using a lag time [3]. The most common chronic condition in children is asthma. It's a respiratory inflammatory condition that lasts for years. Nocturnal asthma sufferers experience an increase in airway resistance and a reduction in lung function in the early morning hours. Two-thirds of asthmatics experience symptoms at night. Asthma episodes are 100 times more likely to happen at night than during the day. The forced expiratory volume in one second is lower at 4 a.m. [5,6]. Histamine levels peaked around 4 a.m., at a level that corresponds to the most acute bronchoconstriction [1]. Nocturnal bronchoconstriction is caused by circadian fluctuations in adrenaline, cortisol, histamine, AMP, melatonin, vagal tone, body temperature,

lower airway secretions, and other variables. Salbutamol is a rapidly acting, highly selective β2-adrenoceptor agonist with few cardiac side effects. It is used to treat asthma by relaxing the smooth muscle of the bronchial tubes, allowing the bronchi to dilate promptly [9,10]. The GI tract absorbs Oral Salbutamol Sulfate Tablets (2–8 mg) well, with an absolute bioavailability of 44% and a peak plasma concentration of 1–3 hours [11]. On the other hand, salbutamol sulphate has a short biological half-life (3.8–6 hours) and a high first-pass metabolism. High dosages or prolonged use might result in hypokalemia. These limitations can be reduced by using salbutamol sulphate formulations with time-controlled pulsatile release doses [12].

If asthma symptoms are severe at night or early in the morning, treating asthma with rapid-release dose forms may be impractical. Pulsatile-release dose forms can be given at night, with medication release beginning in the early morning hours when asthmatic episodes are most likely [13].

We chose a single-pulse system because of the advantages of manufacturing simplicity. When compared to normal pan-coated procedures, compress-coated techniques alleviate the instability of salbutamol sulphate (a hygroscopic medication) [14,15].

Asthma[5]

Asthma is a common disease and has a range of severity, from a very mild, occasional wheeze to acute, life-threatening airway closure. It usually presents in childhood and is associated with other features of atopy, such as eczema and high fever.

Etiology

Asthma comprises a range of diseases and has a variety of heterogeneous phenotypes. The recognized factors that are associated with asthma are a genetic predisposition, specifically a personal or family history of atopy (propensity to allergy, usually seen as eczema, hay fever, and asthma).

The overall etiology is complex and still not fully understood, especially when it comes to being able to say which children with pediatric asthma will carry on to have asthma as adults (up to 40% of children have a wheeze, only 1% of adults have asthma), but it is agreed that it is a multifactorial pathology, influenced by both genetics and environmental exposure.[5]

Triggers for asthma include:

- Viral respiratory tract infections
- Exercise
- Gastroesophageal reflux disease
- Chronic sinusitis
- Environmental allergens
- Use of aspirin, beta-blockers
- Tobacco smoke
- Insects, plants, chemical fumes
- Obesity Emotional factors or stress

Epidemiology

Asthma is a common pathology, affecting around 15% to 20% of people in developed countries and around 2% to 4% in less developed countries. It is significantly more common in children. Up to 40% of children will have a wheeze at some point, which, if reversible by beta-2 agonists, is termed asthma, regardless of lung function tests. Asthma is associated with exposure to tobacco smoke and inhaled particulates and is thus more common in groups with these environmental exposures.

Of all the asthma cases, about 66% are diagnosed before the age of 18 years. Almost 50% of children with asthma have a decrease in severity or disappearance of symptoms during early adulthood.[6]

Pathophysiology[5]

Asthma is a condition of acute, fully reversible airway inflammation, often following exposure to an environmental trigger. The pathological process begins with the inhalation of an irritant (e.g., cold air) or an allergen (e.g., pollen), which then, due to bronchial hypersensitivity, leads to airway inflammation and an increase in mucus production.

Airway obstruction occurs due to the combination of:

- Inflammatory cell infiltration.
- Mucus hyper secretion with mucus plug formation.
- Smooth muscle contraction.

Toxicokinetics

The only relevant toxicokinetics in asthma relates to its management as the absorption and systemic side effects of the beta-2 agonists must be monitored. Typically these will be removed from the body in 2 to 4 hours if salbutamol and albuterol, 18 to 24 hours if salmeterol, or 48 to 72

hours if clenbuterol, which is no longer used in the management of asthma.

The side effects of the beta-2 agonists include tachycardia, flushing, sweating, and other signs of sympathetic system overdrive. There is also the chance of iatrogenic hypokalaemia, which must be monitored.

Treatment / Management[5]

Conservative Measures

Measures to take include calming the patient to get them to relax, moving outside or away from the likely source of allergen, and cooling the person. Removing clothing and washing the face and mouth to remove allergens is sometimes done, but it is not evidence-based.

Weight reduction in obese asthmatics leads to improved control.

Allergen immunotherapy remains controversial. Large studies have not shown any significant benefit, and the technique is prohibitively expensive.

Monoclonal antibody therapy is indicated for patients with moderate to severe asthma who have a positive skin test. The treatment can lower IgE levels, which in turn decreases histamine production. However, the cost of the injections is high.[5]

Medical

Medical management includes bronchodilators like beta-2 agonists and muscarinic antagonists (salbutamol and ipratropium bromide respectively) and anti-inflammatories such as inhaled steroids (usually beclometasone but steroids via any route will be helpful).

There are five steps in the management of chronic asthma; treatment is started depending on the severity and then escalated or de-escalated depending on the response to treatment.

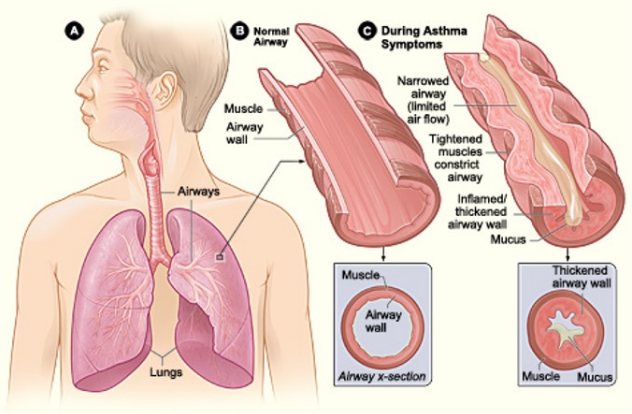


Fig. 1: Schematic Representation of Structural Changes in Airways Under Normal Conditions and During Asthma

Indications for admission

If a patient has received three doses of an inhaled bronchodilator and shows no response, the following factors should be used to determine admission:

The severity of airflow obstruction
Duration of asthma
Response to medications
Adequacy of home support
Any mental illness

Patients with life-threatening asthma are managed with high flow oxygen inhalation, systemic steroids, back to back nebulizations with short-acting beta 2 agonists, and short-acting muscarinic antagonists and intravenous magnesium sulfate. Early involvement of the intensive care team consultation helps to reduce mortality. In the case of near-fatal asthma, early intubation and mechanical ventilation are needed.

Evidence-based Medicine

Many guidelines have been published for the diagnosis and management of asthma, but the most critical feature is patient education. Thenurses are the last professionals to see the patient before discharge from the emergency department or the floors. Similarly, since mostasthmatics are treated as outpatients, pharmacists encounter them regularly. Evidence shows that teaching patients about this disorder and theimportance of compliance are critical for good outcomes. The patient should be taught about monitoring techniques, inhaler use, andmodifying the environment. A social worker should be involved in the care to ensure that the patient has adequate home support and facilities.

Many evidence-based asthma plans are available for the management of asthma and should be handed out to patients. Finally, nurses also plays vital role in school-based asthma education programs that can help improve self-esteem, knowledge, and self-management behaviors. (Level II)

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.

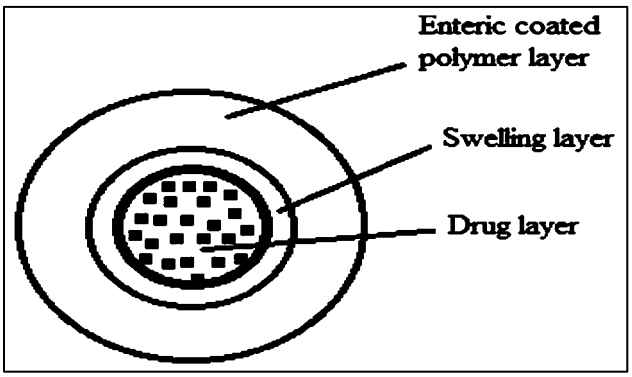


Fig. 2: Schematic Representation of Enteric-Coated Pulsatile Drug Delivery System

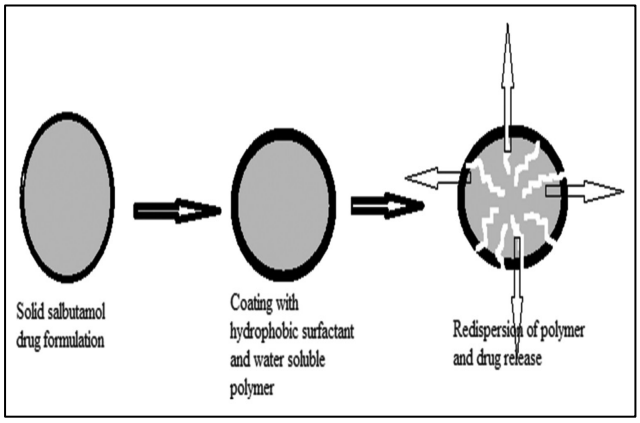


Fig. 3: Mechanism of Drug Release from Polymer-Coated Formulation

Time-controlled explosion system[1]:

1. Pulsatic system with a rupturable coating.
   For example, Time-controlled Explosion system (TCES).
2. Osmotic based rupturable coating system.
   For example, Permeability controlled system.
3. Pulsatic delivery by a change in membrane permeability.

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.

METHODS AND MATERIALS:

MATERIALS

Salbutamol sulfate was obtained as a gift sample from Neuland Laboratories Pvt. Ltd., 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 were of pharmacopoeial grade. A novel technique, "time-dependent PDDS," was designed with the drug contained in fast fast-disintegrating core and press-coated with a suitable barrier layer. Drug-containing core tablets with different compositions of superdisintegrates such as SSG, CCS, and crospovidone were prepared by the direct compression technique. The fast-disintegrating core tablet formulation was selected, and press-coated tablets were prepared with different compositions of hydrophobic and hydrophilic polymers, HPMC K4M, ethyl cellulose, and eudragit S100. The coating polymers were selected and quantified based on in vitro lag time and drug release profile in simulated gastric and intestinal fluids.

METHODS

Formulation of core tablets by direct compression. The ingredients as depicted in Table 1, except magnesium stearate and aerosil-200, were dry blended for 15 min, followed by the addition of quitted ingredients and dry blending for another 5 min. The mixed blend of drug and excipients was compressed using a single punch rotary punching machine to produce round tablets weighing 100 mg with a diameter of 9 mm. Evaluation of the core tablet

Preparation of press-coated tablets:

The core tablets were press-coated with prepared barrier blends as per the mentioned formulas from T1 to T9. Initially, half of the barrier layer material was weighed, and then the core tablet was placed manually at the center. The remaining half of the barrier layer material was added to the die and compressed.

Dissolution rate studies of press-coated tablets:

Dissolution rate studies were performed for all the press-coated tablets using, an eight-stage dissolution rate testing apparatus with a paddle. The dissolution fluid was 900 mL of 0.1 M HCl for 2 h, which was replaced with phosphate buffer pH 6.8. The test was performed at 50 rpm and at a temperature of 37±0.5°C. Samples were withdrawn every ½ h up to 7 h, and the lag times were observed for every batch tablet and The collected samples were analyzed for the drug released by ultraviolet spectrophotometer at 276 nm to know whether the formulations show sigmoidal release[16]

Table 1: 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	8	8	8	8	8	8	8	8	8
2	Microcrystalline cellulose	09	9	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	70	67	67	70	66	63	69	66	63
7	PVP K30	5	5	5	4	5	5	5	5	5
8	Sodium starch glycolate	3	6	5	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

Table 2: 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
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:

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.

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]

PRECOMPRESSION STUDY :

Angle of Repose - On rotation, the angle of repose is the greatest angle formed by the plane of powder with the horizontal surface. Angle of repose is useful in determining particle flow qualities, which may be connected to particle packing densities and mechanical arrangements. The fixed funnel and free-standing cone method was used to calculate the powder angle of repose. The grains were carefully weighed. The funnel's height was then modified such that the funnel's tip just touched the pinnacle of the granule heap. Granules were permitted to flow freely through the funnel onto the surfaces. The powder cone's diameter and angle of repose 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.

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

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 the each formulation prepared was calculated

EVALUATION OF TIME DEPENDENT CORE TABLET:

Dimensions – Control of physical dimensions of the tablets, such as thickness and is essential for consumer acceptance and tablets uniformity. The thickness and diameter of the tablets are carried out using digital Vernier Calliper. Three tablets are used from each batch and the results are expressed in Millimetre (mm).

Weight Variation Test – 20 tablets are selected at random, individually weighed in a single pan electronic balance and the average weight is calculated. As per IP not more than two of individual weights should deviate from average weight by more than 5% and none deviate more than twice that Percentage.[25]

Hardness Test –The tablet was held between a fixed and moving jaw. Scale was adjusted to zero and then load is gradually increased till the tablet started to break. The value of the load at that point gives the hardness of the tablet. Three tablets from each batch are used for the hardness test, and results are expressed in Kg/cm^2 .

Friability Test – Pre-weighed samples of 20 tablets are placed in the friabilator, which is then operated for 100 revolutions (5 min). The tablets are then dusted and reweighted. Compressed tablets that lose less than 0.5 to 1.0% of their weight are generally considered acceptable.

In vitro Study - The lag time capacity of the tablets was determined using the USP Dissolution apparatus II containing 900 ml of simulated gastric fluid. The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the dissolution medium was taken as buoyancy Lag Time, and the after 2hr transfer in buffer 7.4 and 6.8, and calculated lag time capacity of the coated tablet[26,28]

Determination of Drug Content - Ten tablets are weighed and taken in a mortar and crushed to make powder form. A quantity of powder weighing equivalent to 10 mg of the drug is taken in a 100 ml volumetric flask, and 0.1 N HCl is added. The solution is filtered using a membrane filter (0.45µm), and 10 ml of filtrate is taken into a 100 ml volumetric flask and made up to the final volume with buffer pH 6.8. Then its absorbance is measured at 200-400nm using UV UV-Visible spectrometer. Then the amount of total drug present in one tablet is calculated.

IN-VITRO DRUG RELEASE STUDIES: Dissolution characteristics of the formulated press-coated tablets of salbutamol sulphate were carried out using USP Type II (paddle) dissolution test apparatus for 9 hrs. Method - 900 ml of 0.1 N HCl.PH 7.4 and 6.8 were filled in the dissolution vessel, and temperature of the medium is set at 37°C ± 0.5°C. One tablet of different batch is placed in each dissolution vessel, and the rotational speed of the paddle is set at 50 rpm. 5ml of sample is withdrawn at a pre-determined time interval of every one hour for up to 9 hours, and the same volume of fresh medium is replaced immediately. The withdrawn sample is diluted to 10 ml in a volumetric flask and filtered through a 0.45µ membrane filter. The resultant samples are analysed for drug content at 200-400 nm using a UV-Visible spectrophotometer.

DETERMINATION OF SWELLING INDEX: For each formulation batch, one tablet was weighed and placed in a beaker containing 100 mL of media. After each interval, the tablet should be removed from the media and weighed again up to 24 hours, and note down the readings.

STABILITY STUDIES: In the present study, stability studies were carried out at 40°C ± 2°C, 70 ± 5% RH, (24°C ± 2°C ,70% ± 5% RH) and (40°C ± 2°C, 70% ± 5% RH) for a specific time period up to 4 weeks for the optimized formulation. The optimized formulation was analysed for the drug contents study, pH, lag time (hr), and cumulative drug release (%). Experiments were performed in triplicate, and average values are noted. The stability studies data were then recorded.

RESULTS AND DISCUSSION:

EVALUATION OF TIME DEPENDENT PRESS COATED TABLET:

Drug and polymer compatibility studies

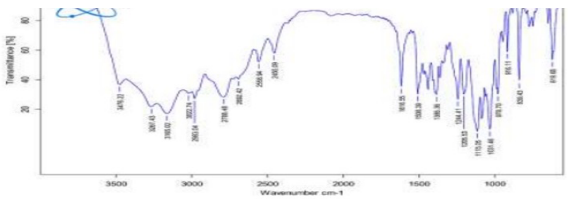


Fig. 3: FT-IR spectrum of Salbutamol sulphate drug

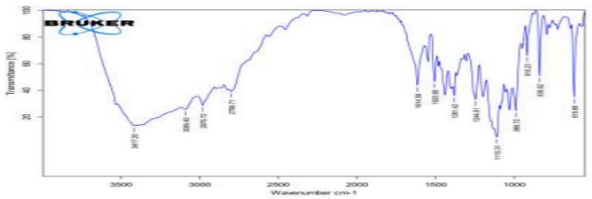


Fig. 4: FTIR graph of Salbutamol sulphate + Croscarmellose sodium

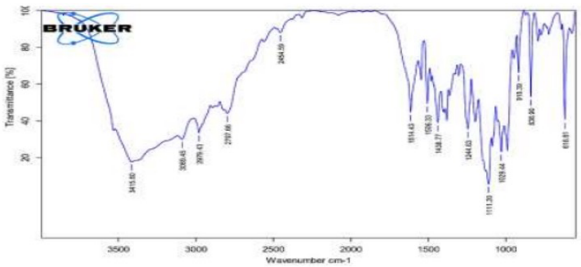


Fig. 5: FTIR graph of Salbutamol sulphate +Sodium starch glycolate.

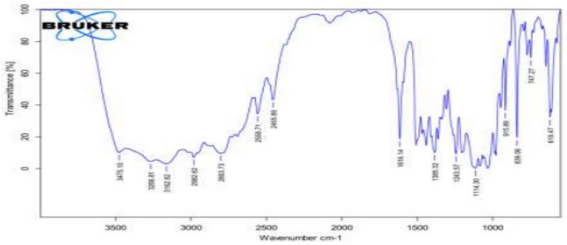


Fig. 6: FTIR spectrum of Salbutamol sulphate +HPMCK4M.

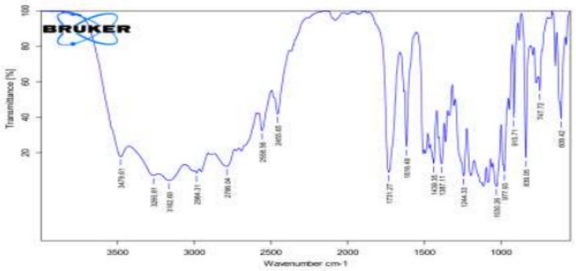
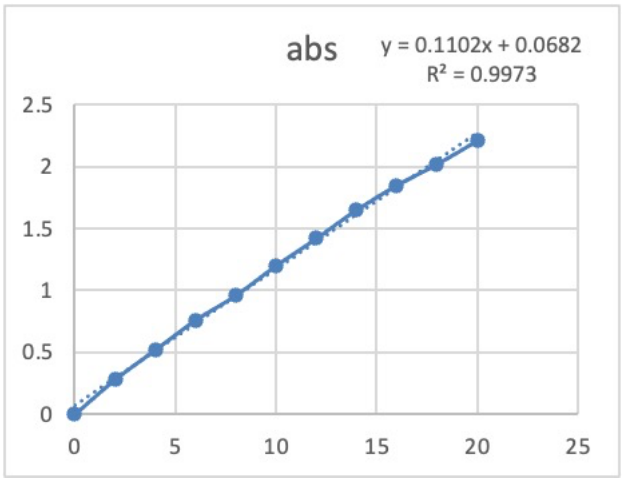


Fig. 7: FTIR spectrum of Salbutamol sulphate Eudragit S100.

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.

Calibration Curve of salbutamol sulphate :



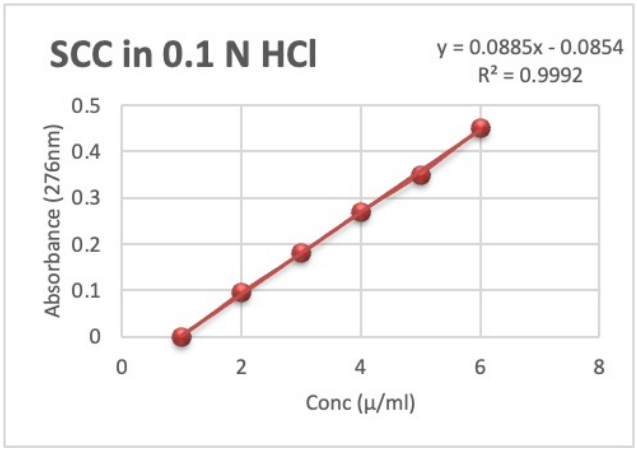


Fig.8 Calibration Curve of salbutamol sulphate with 0. 1N HCL

Fig.9 Calibration Curve of salbutamol sulphate with distilled water

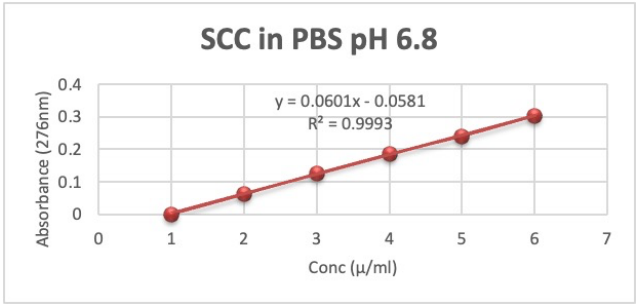


Fig.10 Calibration Curve of salbutamol sulphate with pH 6.8

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.

Table 3: Evaluation of directly compressible of core tablet powder

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 4: Evaluation of formulations of core tablet

Formulation batch	Weight variation (mg)	Hardness (kg/cm^3)	Thickness (mm)	Friability	Drug content	Disintegration Time
T1	101.1±1. 42	3.76±0 .19	1.96 ±0.0 4	0.2 9	98.6 ±0.2 1	12.61 ±0.30
T2	99.7±1.3 9	3.69±0 .16	1.97 ±0.0 8	0.3 1	98.7 ±0.2 3	6.71± 0.79
T3	100.8±1. 43	3.66±0 .18	1.99 ±0.0 3	0.3 5	99.6 ±0.2 4	3.95± 0.39
T4	101.6±1. 34	3.68±0 .11	1.98 ±0.0 8	0.3 2	97.6 7±0. 18	2.19± 0.24
T5	101.9±1. 47	3.74±0 .17	2.01 ±0.0 7	0.3 1	99.5 6±0. 17	2.76± 0.20
T6	99.8±1.5 4	3.79±0 .9	1.99 ±0.0 9	0.3 7	99.2 3±0. 27	1.45± 0.09
T7	99.9±1.4 5	3.73±0 .21	2.02 ±0.0 3	0.3 8	97.9 1±0. 32	1.20± 0.10
T8	100.2±1. 59	3.65±0 .20	1.98 ±0.1 0	0.3 6	99.1 6±0. 29	0.58± 0.06
T9	101.1±1. 41	3.63±0 .23	1.98 ±0.1 1	0.2 8	99.6 9±0. 33	0.35± 0.03

IN-VITRO DISSOLUTION PROFILE OF CORE TABLET

Table 5: % Cumulative Drug Release in Different Trials (T1-T5)

Time (hrs)	T1	T2	T3	T4	T5
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
5	9.16±0. 19	19.49± 0.03	29.49± 0.25	39.76± 0.29	22.35± 0.65
10	16.43± 0.14	39.59± 0.21	57.59± 0.16	58.69± 0.06	36.86± 0.39
15	21.68± 0.28	49.59± 0.14	78.48± 0.09	83.34± 0.35	47.49± 0.48
20	39.63± 0.11	61.19± 0.23	86.67± 0.21	91.48± 0.25	66.68± 0.16
25	49.43± 0.02	72.49± 0.16	94.68± 0.18	93.86± 0.04	81.16± 0.32

30	58.59± 0.09	81.68± 0.06	98.49± 0.04	98.26± 0.03	95.49± 0.03

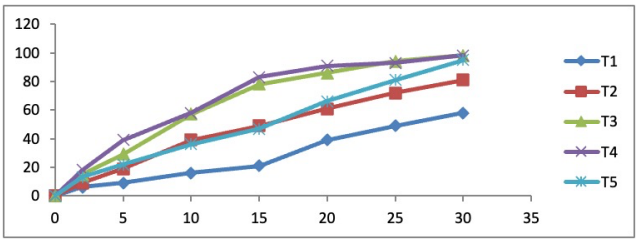


Fig. 11: %Cumulative Drug Release of core tablet

Table 6: % Cumulative Drug Release in Different Trials (T6-T9)

T6	T7	T8	T9
0	0	0	0
23.26±0.16	12.86±0.06	14.59±0.29	18.68±0.12
41.95±0.19	23.48±0.07	25.59±0.07	29.46±0.26
91.19±0.24	36.36±0.14	41.68±0.21	44.19±0.04
99.56±0.11	52.48±0.29	63.19±0.06	56.68±0.14
99.48±0.16	61.91±0.06	69.69±0.19	79.32±0.04
100.02±0.01	66.82±0.21	72.48±0.13	84.61±0.06
100.03±0.04	72.48±0.09	80.47±0.09	93.49±0.03

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

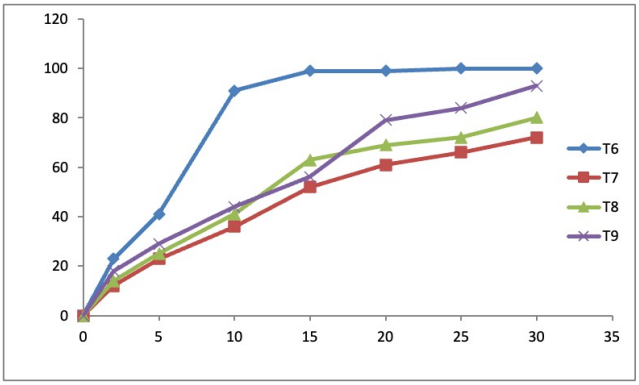


Fig. 12: % Cumulative Drug Release of core tablet

Table 7: Evaluation of press-coated tablet

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

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/cm2. 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 0.28 to 0.38, 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.

%swelling index:

Table 8: swelling index data of press-coated tablet

TIME	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

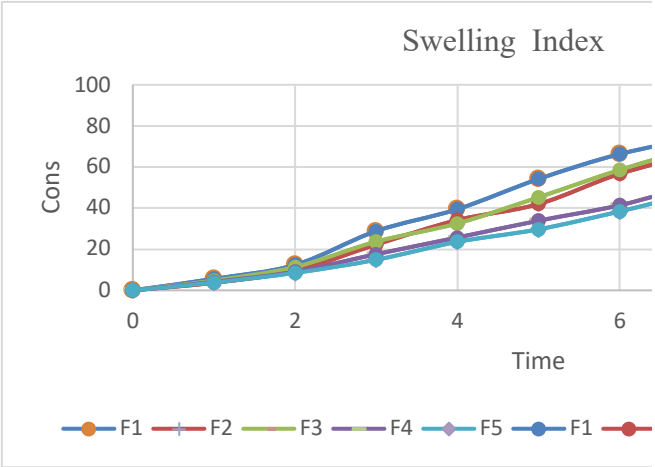


Fig. 13: %swelling index of press coated tablets

Table 9: 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
Simulated pH 7.4	2.5	0	0	6.2±0.56	0	0
	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

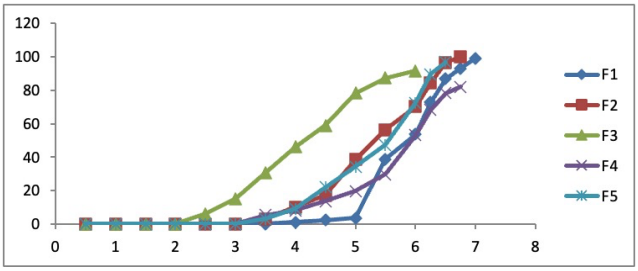


Fig.14. Cumulative % Drug Release in Different Trials

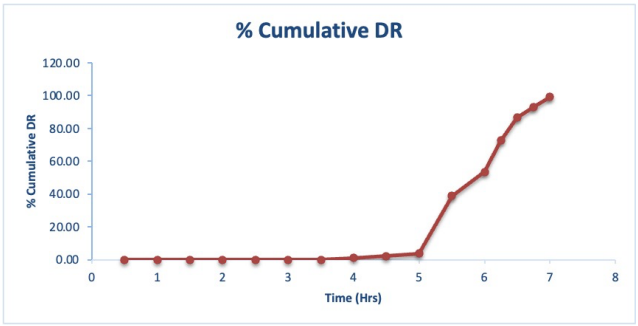


Fig.15 Cumulative % Drug Release in optimize F1batch

Table 10: 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 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.

Stability study of the tablet:

Table 11: Drug release profile of formulation F1 for stability study

	days	0 %CDR	7 %CDR	14 %CDR	21 %CDR	28 %CDR
sr .no	Time (hrs)	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

Fig. 16: Drug release profile of Optimized formula for stability study

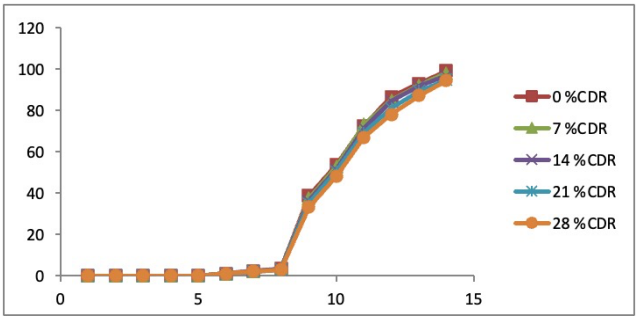


Table 12: Stability Study of Formulation Over Time

Stability study	% Drug Content	Lag Time (hr)	Apperenc e
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

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.

SUMMARY:

An oral press-coated tablet was developed by means of direct compression and to achieve the time-controlled tablet with a distinct predetermined lag time. This press-coated tablet containing salbutamol sulphate in the inner core was formulated with an outer shell by different weight ratios of hydrophobic polymer of ethylcellulose powder and hydrophilic polymer hydroxy propyl methyl cellulose,Eudragit S100 The effect of the formulation of an outer shell comprising both hydrophobic polymer and hydrophilic polymer on the time lag of drug release was investigated. The typical pulsatile profile was shown by tablets prepared by direct compression and wet granulation method. The release profile of the press-coated tablet

exhibited a time period without drug release (time lag) followed by a rapid and complete release phase. In vitro drug release study shows that as hydrophilic polymer increases lag time decrease. Press coated tablets coated by dry mixing and by wet granulation showed variations in lag time. As compared to dry mixed blend method gives less lag time. [4,6,]

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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