ORIGINAL ARTICLE

RB SCIENCE
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JOURNAL OF PHARMACOLOGY AND BIOMEDICINE

Published by RB Science Home Page: www.jpbiomed.com

Development of Chronomodulated drug delivery: Salbutamol Sulphate Compression coated bi-layered core tablet for Nocturnal asthma

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Article History

Received on: 01/08/2024

Revised on: 17/08/2024

Accepted on: 19/08/2024

Published on: 17/09/2024

Keywords

Chronotherapy

Salbutamol

HPMC

Locust bean gum

Nocturnal Asthma

ABSTRACT

The aim of this work was to prepare a bi-layered core tablet of salbutamol sulfate coated with locust bean gum polymer for use as a chronotherapeutic drug delivery system to treat nocturnal asthma attacks. Salbutamol sulfate is intended to be delivered via a pH- and time -dependent chronotherapeutic drug delivery system, and the purpose of this study is to examine how the locust bean gum polymer coating affects drug release from hydroxypropyl methylcellulose matrix. Asthma incidence is highest in the early morning, when it is known as the "morning dip." The disease could be efficiently controlled by a formulation that could deliver the medicine at the proper concentration immediately before the attack. Maintaining the medication release after that point would allow the dosage to be administered once daily. The medication was given as two tablets that were directly compressed together. Salbutamol (4 mg for sustained release and 2 mg for burst release) were present in the core pill. To achieve a time lag of 5 hours for the initial burst release, the core was compression coated with a swellable polymer HPMC and then dip coated with polymer locust bean gum in a 1:1 ratio, a pH independent semipermeable membrane. After five hours, the designed system effectively discharged the first dose, which was then maintained for over twelve hours. For the most part, the drug release afterwards 0 order kinetics. With this dosage, the nighttime asthma would be effectively controlled.

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JOURNAL OF PHARMACOLOGY AND BIOMEDICINE

ISSN No. 2456-8244

Publication Hosted by
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Introduction

The term chrono basically refers to the observation that each metabolic event undergoes rhythmic changes in time. Chronopharmaceutics consist of two words chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanism , whereas pharmaceutics is the science of dosage form design. Chronopharmacology is the science concerned with variations in the pharmacological actions of various drugs in a day. Physiological and biological conditions of the human body vary considerably during a day; results in changes in both disease state and plasma drug concentrations. (1) The circadian clock is an internal body or cellular clock with a rhythmic period of 24 h. The central pacemaker, the suprachiasmatic nucleus (SCN), is the dominant oscillator receiving light/dark signals from the eye, and it controls peripheral clocks throughout the body via various signals (2). Chronotherapeutics is the purposeful delivery of medications in unequal amounts over time. Chronotherapeutics takes into account rhythm determinants in (i) disease pathophysiology (chronopathology), (ii) chronopharmacology (chronokinetics, chronodynamics, chronesthesy, and chronotoxicology) of medications, and (iii) attributes (period, phase, amplitude, and level) of the human circadian time structure to determine the drug-delivery pattern, dose, and administration time to optimize desired and/or minimize adverse effects. (3) ChrDD refers to the method that is widely used to attain the in vivo drug availability to match up with the circadian cycle of the human being to overcome the side effects of the drugs and enhance or optimize the therapeutic effect of the drugs. The circadian rhythms of the human body fluctuate from time to time during the day, as is well-known. So, for the treatment of such diseases, this method is widely used (4). Various technologies to develop chronotherapeutic drug delivery systems have been extensively studied in recent decades. Chronotherapeutic delivery systems may be a single unit or multiple unit systems, mainly include tablet, capsule, advanced osmotic devices and multiparticulate delivery system. These units have the capability of delivering therapeutic agents into the body in a time or position controlled pulsatile release fashion. (5)

Material and Methods

Salbutamol Sulphate was obtained as a gift sample from Alkem laboratories ltd (Haridwar, India). Various grades of HPMC and $PVPK_{30}$ were procured from (central drug house, New Delhi. All other chemicals used were of analytical grade.

Preparation of bi-layered core tablets

An optimal formulation for the core pill was discovered after carrying out multiple experimental procedures. In an effort to establish sustained discharge for about 12 hours, locust bean gum was created. (6) With the previously mentioned formula, 4mg salbutamol was compressed to get a sustained release layer of 50 mg. The excipients were combined in geometric dilutions and were compressed after passing through sieve no. 44. Using a 5mm flat punch on a rotary press, a 50mg mixture was only slightly crushed. To create a bi-layered intact tablet, the second layer of a 10 mg formulation containing 2 mg of the drug was poured over the top of the first layer and lightly squeezed once more. The prepared compressed bi-layered core tablets were further assessed for the various tablet evaluation

criteria, including diameter, thickness, friability, hardness, and weight variation. (7)

Blend of locust bean gum and salbutamol:

A formula for core tablet formulation (bilayer) was tried and the ingredients were mixe (table 1), passed through sieve number 60.

Table 1: Salbutamol and Locust bean powder blend

Outer layer-immediate release	**Present in one tablet in milligrams (approximate values)**		
	F1	F2	F3
Salbutamol sulphate	2	2	2
Mannitol	0.5	1	1.5
Lactose	12.5	12	11.5
Inner layer-sustained release			
Salbutamol sulphate	4	4	4
$PVPK_{30}$	0.25	0.5	0.75
Locust bean gum	40.5	40	40
Talc	0.25	0.5	0.25

Compression coating of the core tablet

Making use of 8mm flat punches in a rotary press, compression coating was applied to the 5mm bi-layered core tablets. The hopper was filled with the coating material, HPMC: lactose combination (140:0/120:20/100:40). At the weight control cam, the die fill weight was changed to 140 mg. After the weight control cam, a specifically made device was positioned so that, when the bottom punch passed over the "device," half of the coating material that had been poured in the die was expelled. On the die table, the expelled coating material was placed aside. The bi-layered core tablet was manually positioned in the die fill's centre once the machine was stopped. After lowering the lower punch, the coating material that had been placed to one side on the die table was added back into the die cavity above the core tablet. After then, the machine was operated to coat the compression-coated tablet evenly throughout. (8,9)

Dip coating of compression coated tablet

After compression coating, a 1:1 polymeric layer of polymer locust bean gum was applied to the tablets. One plasticizer that is utilized is dibutyl phthalate. Acetone was used to dissolve the polymers, yielding 10, 15, and 20% solutions. Throughout the procedure, the coating solution was kept covered on the ice bath to stop the acetone from evaporating and keep the polymer concentration steady. To eliminate any remaining solvent, the dip-coated tablets were initially allowed to air dry before being dried again for an hour at 40 °C in an oven. By varying the amount of dips the tablets took in the coating solution, different coating levels were achieved. Three, four, and two dips were allotted. (10)

Evaluation of Tablets

Tablet prepared after compression with locust bean polymer and salbutamol as active ingredients were subjected to evaluation by following parameters as discussed, General Appearance (Tablet shape, Size, Color, Odor, Taste, Texture), Weight variation, Hardness, Friability, Disintegration time, Uniformity of content, Swelling or Erosion Studies, etc.

General appearance of core bi-layered tablets

Controlling lot-to-lot uniformity, tablet-to-tablet uniformity, and consumer acceptance all depend on a tablet's overall look, identity, and general elegance. General appearance control includes measuring things like size, shape, color, taste, odor, and absence or presence of these things.

Physical properties of core bi-layered tablets

The tablet's percentage friability was ascertained right after upon formulation. With an electronic balance, the weight fluctuation of the twenty pills was achieved in accordance with the instructions specified in I.P. 1996 (11).

A Roche type friabilator operating at 25 rpm for four minutes was used to assess the friability of ten tablets.

A Monsanto hardness tester was used to assess the hardness of ten tablets. Ten tablets were randomly chosen from each formulation batch, and a vernier caliper was used to measure the tablets' thickness.

Uniformity of Drug Content

Compressed bi-layered sustained release tablets were assayed in distilled water to determine the dosage per tablet. In order to conduct this test, 5 tablets were weighed, crushed in a glass mortar, and 200 mg of the resulting powder—equivalent to 8 mg of the drug—was added to a stoppered 100 mL volumetric flask with 100 mL of water before being dissolved. The resultant solution was filtered, and a UV visible spectrophotometer was used to measure absorbance at a maximum wavelength of 277 nm. Salbutamol sulphate milligram per milliliter concentration (Table 3) was derived from drug's standard calibration plot.

Drug-polymer compatibility studies

To investigate the interactions between the drug and polymer, FTIR analysis was performed on Salbutamol Sulphate, HPMC, and mixtures of medicines and polymer. Using a pressure compression machine, 3-5 mg of the sample and 100–150 mg of potassium bromide were ground to create a pellet with a diameter of around 01 mm. The sample pellet was placed inside the Shimadzu FTIR (8400S) compartment and scanned between 4000 and 500 cm-1 in wavelength. (12,13)

Using the DSC-TA system (Perkin Elmer), thermal analysis of the pure drug and a chosen formulation was carried out to examine any incompatibilities with the drug excipients (11). Every sample was placed within a crimped aluminum pan and heated to a temperature of 2000C per minute while traveling through a nitrogen gas atmosphere at a flow rate of 60 milliliters per minute. As a guide, empty aluminum pan was utilized. (14)

Percentage of swelling

A swelling test in phosphate buffer (pH 6.8) was conducted for 24 hours on the best batch of composite bi-layered tablets (figure1 and figure 2). The LBG- PVPK30 Composite cryogel sample was obtained, and it was weighed at different times—1, 2, 3, 4, 5, and 6 hours—after that. Following that, blotting paper was used to clean the sample so that a closer examination of the weight growth could be made. Three duplicates of the experiment were conducted. Nonetheless, the percentage of swelling was determined using the formula below (15):

$$\text{Swelling}\,(\%) = \frac{W_2 - W_1}{W_1} \times 100 \quad \ldots\ldots (1)$$

Where W1 is the initial weight of cryogel and W2 is the final cryogel weight.

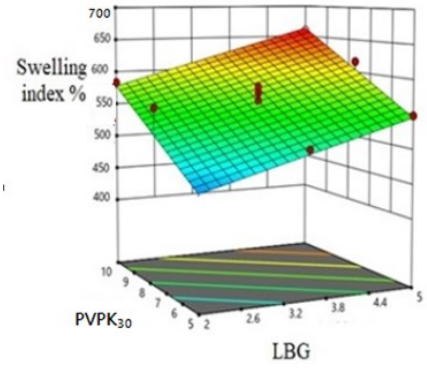

Figure 1. Response surface plots displaying combined impact of concentrations of LBG and PVPK$_{30}$ on swelling index (%)

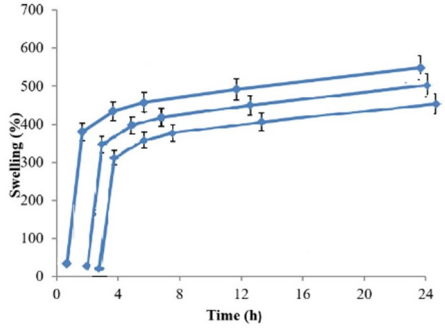

Figure 2. Swelling (%) of compressed bi-layered tablet of LBG-PVPK$_{30}$

Preparation of Standard Calibration Curve in Phosphate Buffer at pH 7.4

Salbutamol's standard curve in phosphate buffer at pH 7.4 was established. The drug salbutamol (10 mg) was first weighed, thoroughly shaken, and then added to phosphate buffer until the desired volume was reached, resulting in a salbutamol stock solution that contained 1000µg/ml. One milliliter of the salbutamol stock solution should be made and put into a 1000 milliliter volumetric flask in order to prepare the dilution. Phosphate buffer was now added to make up the volume. Aliquots were then taken from this solution, and phosphate buffer saline was used to prepare a dilution containing 1µg–10µg of drug per milliliter. This was then made up to a volume of 10 milliliters using the same buffer solution. Following preparation, the solutions were examined with UV spectroscopy to determine the absorbance readings .

In vitro Dissolution study of tablet

Initially, the dissolution was done in 900 ml of 0.1 N HCl with 1% SLS in a USP II apparatus running at 100 rpm for 12 hours. Phosphate buffer (pH 6.8) was added after it, and both were allowed to settle to 37 ± 0.5 °C. Throughout the course of 15 hours, aliquots were taken out at prearranged intervals and subjected to spectrophotometric analysis (16). Together with the graph shown in figure 1, the three formulations displaying the percentage of cumulative drug release (CDR) at various time intervals are listed in Tables 1, 2, and 3 below.

Outer coat rupture test

During the tablet's disintegration trials, pulsatile release tablets were simultaneously visually inspected for rupture. The lag time was determined to be the rupture time. The moment in time at which the outer coating broke because of the underside HPMC layer's enlargement was called the lag time. (17,18)

Dissolution Comparison of Test Product Vs Marketed Product

The finalized bi-layered core tablets (formulation F1, F2, F3) were characterized with respect to drug release rate. Dissolution profile of prepared tablets of salbutamol was comparable to the marketed product VOSPIRE®. The details of release profile of different formulations and marketed product are shown in Table 1, 2, 3, 4.

From Figure 1 and Figure 2, it is clear that the there is no appreciable difference in the drug release rate of all the three bi-layered core tablets and marketed product, hence both Test and Marketed products are comparable to each other. Though, the formulations F1, F2 and F3 are bi-layered and marketed product is a layered matrix, yet they show comparable dissolution profile. However, the rate of dissolution of formulation F1 and marketed product VOSPIRE® 8 mg showed comparable results as VOSPIRE dissolution rate showed 99% drug dissolved in 12 hours and F1 formulation gave 97.5% dissolution rate. Nevertheless, the formulation F1 can be considered to be a better chronotherapeutic formulation as it provides an immediate release followed by sustained release when compared with marketed product VOSPIRE which is extended release drug providing 100% release in 15 hours as similar to the formulation F1 .

Stability Study

An accelerated stability investigation was conducted at 40±2°C and 75±5% relative humidity with the completed formulation. A 60 cc HDPE bottle with a 33 mm child-resistant cap and an induction seal was filled with 50 tablets. During stability, the dissolution rate was investigated. When it came to dissolving, the USP-II (Paddle) suggested dissolution procedure was used, which involved 50 RPM, 900 mL, 0.1NHCl, and 1% SLS in a USP II apparatus running at 100 rpm for 12 hours. Phosphate buffer (pH 6.8) was added after it, and both were allowed to settle to 37 ± 0.5 °C. Throughout the course of 15 hours, aliquots were taken out at prearranged intervals and subjected to spectrophotometric analysis. Hours: 1, 2, 4, 6, 9, & 12. (19, 20).

Results and discussion

General Appearance

Locust bean gum after observing for its general appearance showed the following characteristics as, **Colour:** Off white; **Shape:** circular; **Size:** 5 mm; **Weight:** 60 mg; **Odour:** Odourless; **Texture:** smooth; **Taste:** mildly sweet with

slightly bitter taste of salbutamol.

Evaluation of bi-layered core tablet

The bilayered core tablets were assessed for a number of factors, including hardness, friability, weight fluctuation, thickness, and diameter. It was determined that every parameter was within allowable limits and is listed below in the table 2 as follows:

Table 2: Evaluation of physical properties of core tablet

Formulation Code	Thickness **(mm)**	Weight variation (mg)	Hardness (Kg/cm2)	Friability	(%) Drug content (%)	Diameter
F1	2.23± 0.02	3.05± 0.21	2.9± 0.03	0.81 ± 0.22	100.01 ±1.12	5.03± 0.05
F2	2.19± 0.03	3.15± 0.23	3.2± 0.04	0.84 ± 0.25	99.01± 1.23	5.01± 0.06
F3	2.41± 0.02	3.12± 0.18	3.4± 0.03	0.82 ± 0.34	100.02 ±1.27	5.01± 0.03

Compatibility analysis

The FTIR method is widely used in the analysis of functional groups. The FTIR spectra of LBG and salbutamol sulphate are shown in Fig. 3.

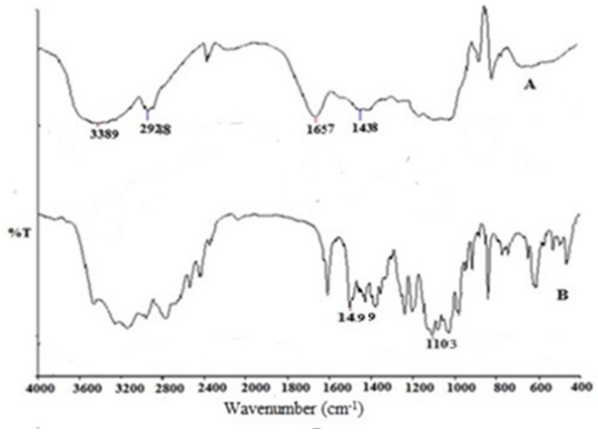

Figure 3. FT-IR spectra of LBG (a), salbutamol sulphate(b)

Differential scanning calorimetry is a useful thermal analytical method for determining the alteration in thermal conductivity with temperature. Thermal evaluation may be used to identify the characteristics of the matrix material in composite materials. In comparison to the separate polymers, the mix typically exhibits an increase in glass transition temperature.

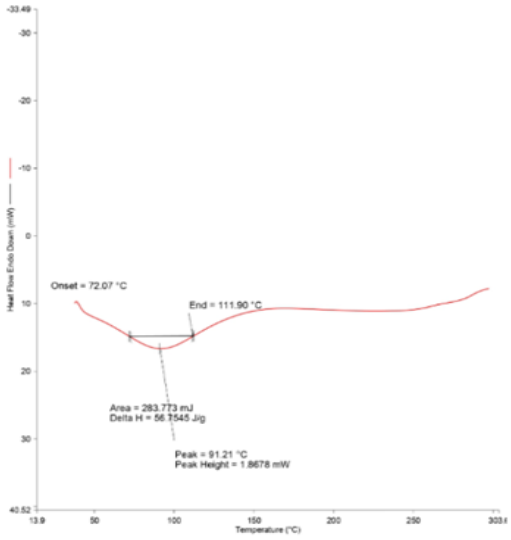

Fig 4(a) DSC thermogram of LBG

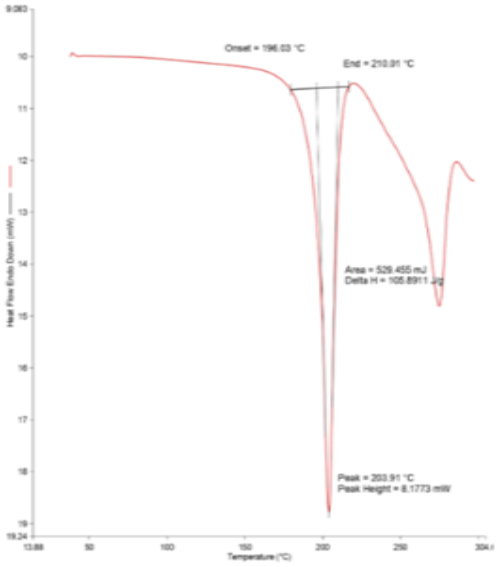

Fig 4(b) DSC thermogram of Salbutamol sulphate

Evaluations of the compression coated batch

The compressed core tablets were then assessed for a number of factors, including hardness, friability, weight fluctuation, thickness, and diameter. It was determined that every pa-

rameter was within allowable limits and is listed in table 3 as follows.

Table 3: Evaluation of compressed core tablets

Formulation Code	Thickness **(mm)**	Weight variation (mg)	Hardness (Kg/cm2)	Friability	(%) Drug content (%)	Diameter (mm)
F1	5.27± 1.03	4.85± 1.12	3.8± 0.3	0.61 ± 0.52	99.89± 1.12	8.04± 0.04
F2	5.31± 1.05	4.77± 1.03	3.9± 0.3	0.64 ± 0.65	98.01± 1.23	8.03± 0.05
F3	5.26± 1.02	4.71± 1.11	3.9± 0.4	0.62 ± 0.54	100.02±1.27	8.01± 0.05

***In vitro* Dissolution Testing**

The three formulations showing % Cumulative drug release (CDR) at different time intervals are listed below in Table 4 along with the graph indicated in figure 5.

Table 4: Release Profile of Formulation F1, F2, F3

Time (hrs)	% Cumulative drug release of **F1**	% Cumulative drug release of **F2**	% Cumulative drug release of **F3**
0	0	0	0
1	2.8±0.34	1.9±0.31	2.3±0.35
3	45.5±0.28	18.2±0.24	16.7±0.29
6	84.3±0.31	48.6±0.35	53.4±0.38
9	94.5±0.33	72.2±0.22	78.9±0.23
12	98.5±0.28	88.6±0.21	92.8±0.18
15	100±0.27	100±0.30	100±0.25

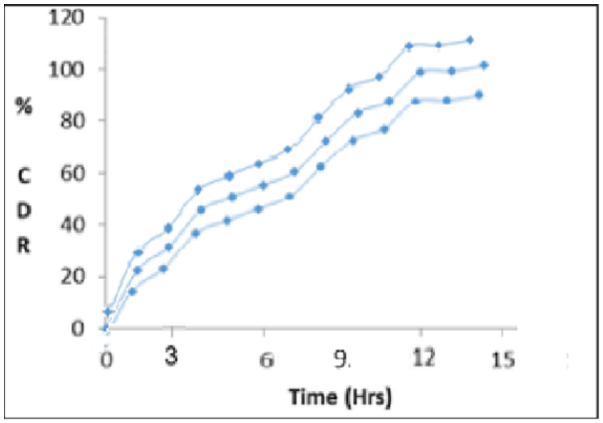

Figure 5: The dissolution profile of three different bi-layered core tablets

Standard Curve of Salbutamol in Phosphate Buffer at pH 7.4

The prepared solutions were then analyzed under UV spectroscopy for obtaining the absorbance readings as shown below in and figure 6.

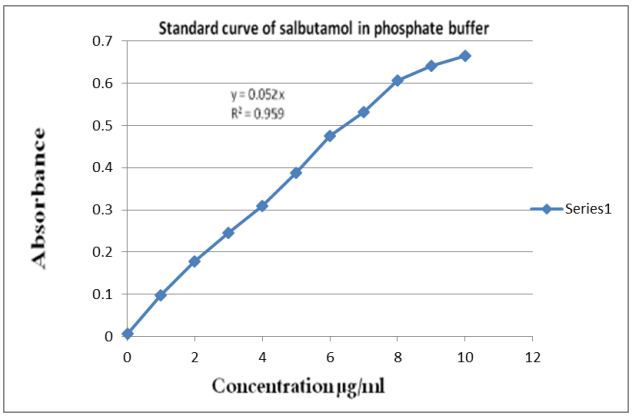

Figure 6: Standard curve of salbutamol in phosphate buffer

Dissolution Comparison of Test Product Vs Marketed Product

the formulation F1 can be considered to be a better chronotherapeutic formulation as it provides an immediate release followed by sustained release when compared with marketed product VOSPIRE which is extended release drug providing 100% release in 15 hours as similar to the formulation F1 (Table 5 and figure 7).

Table 5: Dissolution profile comparison of Test and Standard Vospire

Formulation	**Time in hrs**					
	1	3	6	9	12	15
Vospire (Marketed product)	5.9± 0.27	48.6± 0.2	86.6± 0.29	95.8± 0.17	99±0.20	100± 0.23
Test Formulation F1	2.8± 0.34	45.5± 0.28	84.3± 0.31	94.5± 0.33	98.5± 0.28	100± 0.27

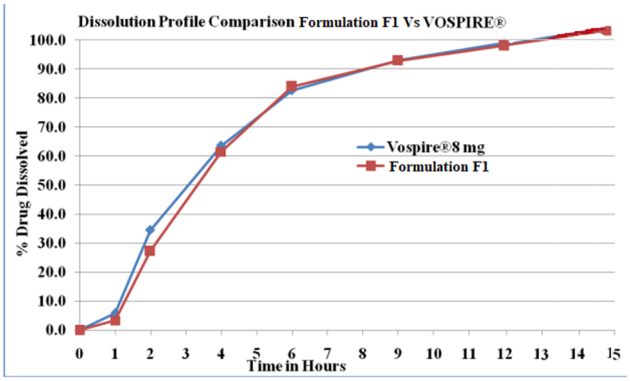

Figure 7: – Dissolution Profile Comparison of bi-layered core tablet formulation F1 Vs Marketed Product (VOSPIRE® 8 mg)

Stability Studies

There were no significant changes in the dissolution parameters even after three months period thereby indicating a stable formulation and there was no change in the different physicochemical parameters of the tablets.

Final tablets of test sample (F1) were subjected to accelerated stability study for a period of three months at different time intervals indicating 3, 6, 9,12, and 15 hours (Table 6).

Table 6. Stability studies of optimum batch formulation

Time in hrs	% drug release			
	Initial	1 month	2 months	3 months
3	20.8± 0.34	21.2± 0.40	21.0± 0.33	20.7± 0.38
6	61.5± 0.28	61.8± 0.43	61.8± 0.43	61.4± 0.32
9	82.3± 0.31	82.0± 0.35	82.4± 0.41	82.4± 0.27
12	97.5± 0.33	97.6± 0.39	97.6± 0.39	97.5± 0.41
15	100.0± 0.27	100.0 ±0.29	100.0± 0.31	100.0 ±0.28

Conclusion

The creation and optimization of a compression -coated tablet for chronotherapeutic drug release was accomplished with success. Two layers made up the 60 mg core tablet: a 10 mg layer for immediate release and a 50 mg layer for extended release. Both layers were created by direct compression. The immediately and extended release properties of the core tablet were assessed and verified. After that, a swellable layer of HPMC: lactose blend was compression coated onto the core tablet using a specialized tool that divided the coating material equally between the top and lower layers. at order to obtain a pH independent semipermeable barrier, the so-coated tablet was additionally dip coated with polymer locust bean gum at a 1:1 ratio. The Box-Behnken design was used to optimize the coat rupture time. After a six-month accelerated stability study carried out in accordance with ICH criteria, stability was determined. If the prescribed dosage form is taken right before bed, it will be released as a first burst of dose in the early morning hours, between three and four in the morning, and the impact will last for ten hours after that. Hence, the "nocturnal asthma" can be adequately managed with this dosage type.

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Cite this article as

Singh N, Kalra N, Singh G, Srivastava SP. Development of chronomodulated drug delivery: salbutamol sulphate compression coated bilayered core tablet for nocturnal asthma. J Pharmacol Biomed. 2024; 8(3): 709-717