An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

DESIGN AND EVALUATION OF TABLET IN CAPSULE DEVICE- PULSATILE DRUG DELIVERY SYSTEM FOR THE TREATMENT OF NOCTURNAL ASTHMA

Subhash Jadav[1]*, Chandramouli Golla[1], Durga Srinivasa Rao.M[2]

[1]Department of Pharmaceutics, Sri Kakatiya Institute of Pharmaceutical Sciences, Unikicherla, Warangal, Telangana-506370

[2]S.Chavan College of Pharmacy, Nellore, Andhra Pradesh, India

***Corresponding author E-mail:** *subhashspips@gmail.com*

ARTICLE INFO

Key Words

Salbutamol Sulphate, Nocturnal asthma, pH dependent drug deliverysytem, Tablet-in-Capsule

ABSTRACT

The present study aimed at preparing a novel time dependent pulsed release system containing 'Tablet-in-Capsule' for the programmed release of Salbutamol Sulphate for the treatment of nocturnal asthma. The core tablets of Salbutamol Sulphate were prepared using wet granulation containing a super disintegrant. Physical characterization of tablets and powder blends used to form the core tablet was undertaken using a range of experimental technique. Eudragit S100 and Eudragit L100were used as pH dependent polymers for coating the core tablet which were filled into the capsule. Dissolution studies of 'Tablet-in-Capsule'device in media with different pH (1.2, 5.5, 6.8 and 7.4) showed that drug release in colon could be modulated by optimizing the concentration of Eudragit L100: Eudragit S100 (1:2). The study showed that, lag time prior to drug release was highly affected by the coating level. The dissolution data reveled that the level of coating and the ratio of polymers are very important to achieve a optimum formulation. The In-vitro release was found to be independent of paddle speed. The gamma scintigraphic study pointed out the capability of the system to release drug in lower parts of GIT after a programmed lag time for nocturnal asthma. Stability study of the formulation indicates no significant difference after a period of one month.

INTRODUCTION:

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance However, there are certain conditions for which such a release pattern is no suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release. Based on the concept that a formulation given once a time daily, a two-pulse drug release system proposed for oral administration can be designed, for achieving the selective delivery of drugs at appropriate time, which is a chrono pharmaceutical approach for the better treatment of disease with circadian rhythms.

This novel system is a so-called "tablets in capsule device." The designed capsule device consists of an impermeable capsule body and a soluble cap. The multi-layered tablets formulation prepared is filled within the capsule body and sealed with the water-soluble cap. A two tablet system in capsule, one of which serves to give first pulse to provide a loading dose and second tablet after a lag time of 4 to 5 hrs gives the second pulse. Both tablets are inserted into an impermeable capsule body with a waters soluble cap. On reaching body fluid, the cap dissolved and the first pulse released, following which the modulating barrier swelling and eroded which cause a lag phase preceding the onset of release of the second pulse. The modulating barrier of the bilayered tablet performs the same role. Lag time can be successfully controlled by adjusting the ratio of barrier materials in the coating(1-5).

Salbutamol sulphate Salbutamol is a selective β2 adreno receptor agonist. At therapeutic doses it acts on the β2 adreno rceptors of bronchial muscle, with little or no action on the β2 adreno receptors of the heart. It is suitable for the management and prevention of attack in asthma, it is Freely soluble in water, slightly soluble in ethanol (95 %) and in ether Very slightly soluble in dichloromethane. Salbutamol has the duration of action of 4 to 6 hours in most patients. As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased on medical advice. The usual effective dose of salbutamol is 4 milligrams three or fourtimes per day. Some patients obtain adequate relief with 2 milligrams salbutamol three or four times daily (6).

In present work formulated Salbutamol Sulphate tablets(1. First pulse dose and 2. Second pulse dose after lag time), determined of physicochemical parameter of prepared granules and tablets, Optimization of best coating ration/concentration of coating polymers for second pulse tablet, *In-vitro* dissolution profile of second pulse release tablet, Filling of tablet i.e. first pulse and second pulse tablet in "0" size capsule. Evaluation of the dosage forms for their physicochemical parameters, drug content, *In-vitro* release rate and *in-vivo* gamma scintigraphic studies.

EXPERMENTAL

MATERIALS

Salbutamol Sulphate was procured from Jayco chemical industries as a gift sample, Eudragit S-100, Eudragit L-100 Hydrochloric acid, Isopropyl alcohol, Acetone, Magnesium stearate,Mannitol, Lactose monohydrate B.P., Micro crystalline cellulose, Polyvinyl pyrrolidone Sodium starch glycolate,Potassium dihydrogen phosphate, Sodium hydroxide pellets, Aerosil, Talcum powder and other chemical and solvents were of analytical grade/IP/equivalent grade and procured from laboratory.

METHODS

Preparation of core tablets:

The core tablets (average weight 70 mg) of Salbutamol Sulphate were prepared by wet granulation technique using PVP-K30 and Starch solution as binders. The composition of core tablets is given in **Table 1.** Lactose was used as a diluent and SSG (2mg) was added to obtain a fast disintegrating tablet.

Pre compressional Studies:

Angle of repose:

The angle of repose of blend was determined by the funnel method. The accurately weight blend was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the blend. The blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\mathbf{Tan\ \theta = h/r}$$

Where, h and r are the height and radius of the powder cone [11]

Bulk density and Tapped Density:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 gm of blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until

no further change in volume was noted. LBD and TDB were calculated using the following equations. LBD= Weight of the Granules/Untapped Volume of the packing TBD=Weight of the Granules/Tapped Volume of the packing.

Compressibility Index:

The Compressibility Index of the blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

Carr's Index (%) = [(TBD-LBD) x100]/TBD

Hausner's Ratio: Hausner's Ratio was determined by Following Equation:

Hausner's Ratio = Tapped Density / Bulk Density

Post-Compressional Studies:

Shape and appearance:

Tablets were examined under a lens for the shape of the tablet, and color was observed by keeping the tablets in light [11].

Uniformity of thickness:

Thickness and diameter of both core tablets and coated tablets were measuredusing a calibrated dial calipers. Three tablets of each formulation were picked randomly and dimensions determined. It is expressed in mm and standard deviation was also calculated [11].

Weight variation test:

To study weight variation To study weight variation 20 tablets of each pulse dose formulation were weighed separately using a Sartorius electronic balance and the test was performed according to the official method [11].

Hardness test:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Hardness of core tablets was determined using a validated dial type hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked from each batch and analyzed for hardness. The mean and standard deviation were also calculated [11].

Friability test: For each pulse dose tablet formulation, the friability of 6 tablets was determined using the Roche friabilator (Camp-bell Electronics, Mumbai, India).

***In-vitro* Disintegration test for first pulse tablet:**

Tablet disintegration was carried by placing one tablet in each tube of the basket and top portion of the each tube was closed with disc and run the apparatus containing pH 1.2 SGF (simulated gastric fluid) maintained at $37\}2^{0C}$ as the immersion liquid. The assembly was raised and lowered between 30 cycles per minute. The time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded. The experiment was carried out in triplicate [10].

Preparation of coating solution:

Coating solution was made using different ratios of material like Eudragit L100 and Eudragit S100. Required quantity of polymers were dissolved in mixture of solvents and stirred on magnetic stirrer to get homogeneous coating solution. Diethyl Phthalate was added in above solution as plasticizer (1%w/v). After getting homogeneous coating solution, coating was done on tablets.

Parameter	**Value**
Inlet Air Temperature	40-45^{0}C
Exhaust Temperature	30-35^{0}C
Bed Temperature	38^{0}C
Atomization (bar)	2
Spray rate (gm/min)	10
Pan RPM	1

Preparation of "Tablet in Capsule" device:

Tablet in capsule device was formed by filling size "0" capsule with two tablets, one of each pulse, i.e., one for first pulse release and other for second pulse release.

Evaluation of "Tablet in Capsule" device:

***In-vitro* drug release studies of device:**

Conducting in vitro drug release studies assessed the **"Tablet in capsule"** device of Salbutamol to release the drug in two pulses with immediate first pulse as loading dose and remaining second pulse after the required lag time. Drug release studies were carried out using a USP XXIII dissolution rate test apparatus (Apparatus2, 100 rpm, 37 °C) for 2 hr in 0.1 M HCl (900 ml) as the average gastric emptying time is about 2 hr[9]

Effect of paddle speed on the lag time and release characteristics:

Devices were subjected to in-vitro dissolution study at different paddle speed (50, 75 and 100 rpm). Other conditions remained as described above. Effect of paddle speed on release behavior and lag time was observed and analyzed using a Spectrophotrometer[6]

***In-vivo* Gamma-Scintigraphic Studies:**

Rabbit was used for scintigraphy study. The radio labeled capsule was administered and then rabbit was immobilized and seated comfortably in the rabbit cage. The rabbit had small sealed source of 0.06MBq ^{99m}T firmly taped to the skin at the position of its shoulder joint and hip joint on the same side, which was depicted as an anatomical reference marker. The source was also used for repositioning when the images were taken. Scinti scans were taken after 30 min, 2 hrs, 4 hrs and after 5.5 hrs [7-8].

Stability study of "Tablet in Capsule" device:

The stability study was carried out at 40°C/75% RH for Stability study of "Tablet in Capsule" device up to 30 days [10].

Drug - excipient Compatibility Studies:

Compatibility studies of pure drug Salbutamol sulphate with polymers and other excipients were carried out prior to the preparation of tablets. I.R spectra of pure drug salbutamol sulphate, and that of with polymers and other ingredients were obtained, which are shown in Figure No.1 to 3**.** All the characteristic peaks of Salbutamol Sulphate were present in spectra thus indicating compatibility between drug and excipients. It shows that there was no significant change in the chemical integrity of the drug.

Analytical Method

The absorbance reading of Salbutamol Sulphate standard solution containing 10 – 100 µg/ml of drug in pH 1.2, phosphate buffer pH 5.5, pH 6.8 and pH 7.4 at the maximum wavelength of 276 nm. Standard calibration curve for salbutamol sulphate with slope, intercept and regression co-efficient. The calculations of drug contents and in-vitro drug release study are based on this standard curve.

EVALUATION OF CORE TABLETS:

Pre compressional parameters:

Granules of all the formulations were subjected for various precompressional evaluations such as angle of repose, bulk and tapped density, compressibility index and Hausner's Ratio. Results of all the pre-compression parameters performed on the granules for batch T1 and T2. The result of angle of repose was found to be 28.36 and 27.36 for batch T1 and T2 respectively. Compressibility index was found to be 13.84 and 13.95 for batch T1 and T2. The results of Hausner's ratios were found to be 1.15 and 1.13 respectively for batch T1 and T2. The results of angle of repose (<30) indicate good flow properties of the powder based on Table No.3. This was further supported by lower compressibility index values. Generally, compressibility index values up to 15% results in good to excellent flow properties.

Post-compressional parameters*:*

All the tablet formulations were subjected for evaluation according to various official specifications and other parameters. Shape, thickness, hardness, friability, weight variation, tablet dosage form assay and *IN VITRO* disintegration time.

Shape and appearance:

Formulations prepared were randomly picked from each batch examined under lens for shape and in presence of light for color. Tablets showed standard concave surfaces with circular shape. Tablets were white in color.

Uniformity of thickness:

Thickness of the tablets was measured using calibrated dial calipers by picking three tablets randomly from all the batches. The results of thickness for tablets are shown in **Table No. 2**. The mean thickness of tablets (n=3) of batch T1 and T2 were 2.8±0.1mm. The standard deviation values indicated that all the formulations were within the range.

Weight variation test:

The weight variation of both the formulations is shown in **Table No.2**. All the tablets passed the weight variation test, i.e., average percentage weight variation was found within the pharmacopoeial limits of ±10%.

Ingredients Quantity	First pulse tablets (mg/tablet)	second pulse tablets (mg/tablet)
Salbutamol sulphate	2.4	4.8
Lactose	35.4	33
Starch (intra granular)	25.2	25.2
Starch (binder solution)	3.5	3.5
PVPK-30	0.5	0.5
Magnesium stearate	1	1
Aerosil	1	1
Sodium Starch Glycolate	1	2
Total weight	**70**	**70**

Table 1: Composition of Salbutamol sulphate tablets

Batch	T1*	T2*
Uniformity of thickness (mm)	2.8 ± 0.1	2.8 ± 0.1
Weight variation	70.15 ± 0.64	70.60 ± 0.64
Hardness (mg)	3.0 ± 0.28	3.5 ± 0.5
Friability (%)	0.56	0.42
% Drug Content	98.17 ± 0.33	98.56±0.30
Disintegration Time	2.5 ± 0.25	4.5 ± 0.25
T1* :- First pulse tablet, T2*:-Second pulsetablet		

Table 2: Post compression parameters

Fig 1: FT-IR Spectra of pure Salbutamol sulphate

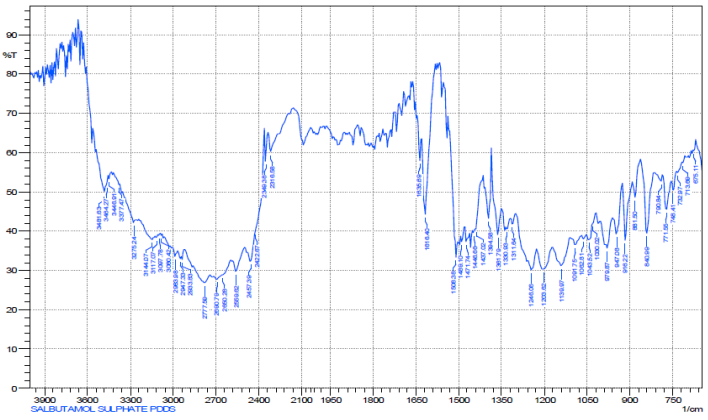

Fig 2: FT-IR Spectra of Salbutamol sulphate + Eudragit L-100

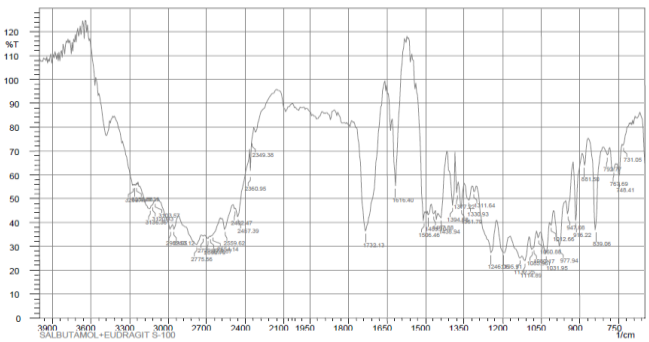

Fig 3: FT-IR Spectra of Salbutamol sulphate + Eudragit 100

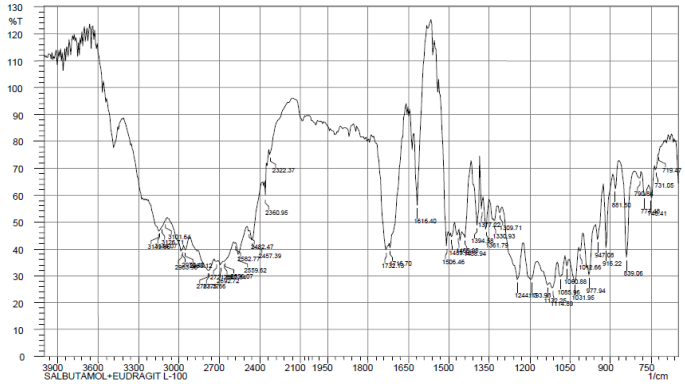

***Fig 4: In-vivo* Gamma-Scintigraphic Studies:**

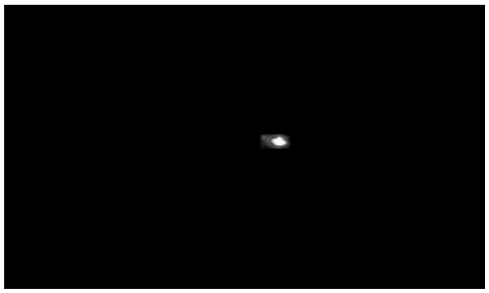

Plate No. 1: Image taken after 30 min

Plate No. 2: Image taken after 2 hrs

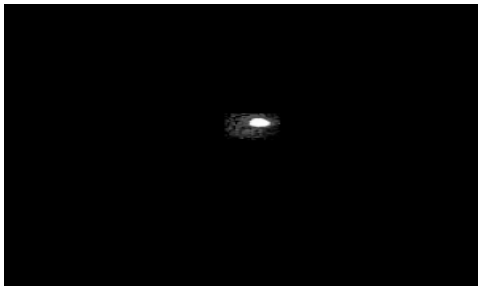

Plate No. 3: Image taken after 4 hrs

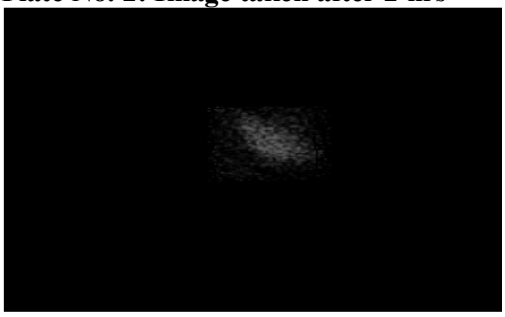

Plate No.4: Image taken after 5.5 hrs

Hardness test: Hardness or crushing strength of the tablets of both the formulation was found to be 3.0±0.28 for batch T1 and 3.5±0.5 for batch T2. The mean hardness test results are tabulated in Table No.2**.** The low standard deviation values indicated that the hardness of all the formulations was almost uniform and the tablets possess good mechanical strength with sufficient hardness.

Friability test: Friability values for batch T1 and T2 were found 0.56 and 0.42% respectively. The obtained results were found to be well within the approved range (<1%) in all the designed formulations. That indicated tablets possess good mechanical strength. The results are tabulated in Table No.2.

***In-vitro* disintegration time of first pulse tablet:** *In- Vitro* disintegration time for T1formulations was found to be 2.5±0.25 minutes. The formulation showed the in–vitro DT within the limit specified in pharmacopoeia.

Evaluation of "Tablet in Capsule" device:

***In-vitro* drug release studies of device:** The 100% drug released from the first pulse tablet within 15 minutes and 87.77% drug released after a completion of lag time. Drug released before lag completion of lag time was found to

be 17.23%. The results obtained in the *in-vitro* drug release study. The cumulative percentage of salbutamol sulpahte released from "Tablet-in – Capsule" device as a function of time. The drug release profile showed sigmoidal release pattern which is considered to be an ideal for the pulsatile drug delivery system.

Effect of paddle speed on the lag time and release characteristics: Drug release from the device, need to be independent of agitational intensity of the release media. In order to verify effect of agitational intensity, the dissolution studies were conducted at three different rpm (75, 100, and 150). Dissolution studies were carried out using USP- Type II dissolution apparatus and release profile is plotted. The cumulative percentages of drug released from the device were found to be 92.74, 94.15 and 95.74% respectively for 50, 75, and 100 rpm. A perusal to Figure no.9 showed there was no drastic change in release profiles. No significant difference in drug release was observed for release study in under different rotational speed. This shows an advantage for the system, as it predicts no change in the performance of the system as increased gastric motility.

In-vivo **Gamma-Scintigraphic Studies:** Gamma Scintigraphy, a noninvasive technique, is a reliable tool for evaluating the *IN-VIVO* performance of dosage form in the different regions of GIT. Plate no. 1 to 4 shows the scinti scans taken on the rabbit during gamma scintigraphic studies.

Stability study of "Stability study of "Tablet in Capsule" device: The stability study was carried out at 40°C/75% RH for Stability study of "Tablet in Capsule" device up to 30 days, The results of accelerated stability study showed that there was no change in the formulation after one month

CONCLUSION: The aim of this study was to explore the feasibility of time and pH dependent colon specific, pulsatile drug delivery system of Salbutamol Sulphate to treat the nocturnal symptoms of asthma. A satisfactory attempt was made to develop new 'Tablet in Capsule' device using pH dependent polymers (Eudragit S100 and Eudragit L100) and evaluated for *IN VITRO* characterization studies.

ACKNOWLEDGEMENTS: Authors thankful to the Management and Principal of the Sri Kakatiya Institute of Pharmaceutical Sciences (SKIPS), Warangal for providing facilities to carry out the research work.

BIBLIOGRAPHY

1. Gothoskar AV, Joshi AM, Joshi NH. Pulsatile drug delivery systems: a review. *Drug Delivery Technology* 2004;4(5):1-11.
2. Shivakumar HG, Pramod kumar TM, Kashppa GD. Pulsatile drug delivery system, Indian J Pham Educ 2003;37(3):125
3. Ishibashi T, Pitcairn GR, Yoshino H, Mizobe M, Wilding IR. Scintigraphic Evaluation of a new capsule-type colon specific drug delivery system in healthy volunteers. *J Pharm Sci*.1998; 87:531-5.
4. Banker GS, Anderson NR. (1987). Tablets. In: Lachman L, Lieberman HA, Kanig JL, ed. The theory and practice of industrial pharmacy. 3rd ed. Mumbai: Varghese Publishing House, 182-4; 296-303:311-2.
5. Sarasija, S, Hota, A. Colon-specific drug delivery systems. *Ind J Pharm Sci* 2000; 62(1):1-8.
6. Qureshi, Chronomodulated drug deleivery sytem of salbutamol sulphate for the treatment of nocturnal asthma. *J Pharm Sci*. 2008; 70:146-9.
7. Mastiholimath VS, Dandagi PM, Jain SS, Gadad AP, Kulkarni AR. Time and pH dependent colon specific colon specific, pulsatile delivery of theophylline for nocturnal asthma. *Int J pharm* 2006; 328:49-56.
8. Ishibashi T. Scintigraphic Evaluation of a new capsule-type colon specific drug delivery system in healthy volunteers. *J Pharm Sci*.1998; 87:531-5.
9. Shivakumara HN, Suresh S, Desai BG. Design and evaluation of minitablet for chronotherapeutic drug delivery of theophylline. *Ind J Pharm Sci*.2007;69(1):73-9
10. Stability studies in overview of ICH guidelines for drug products: Natalie Mc Clure, Matrix Pharmaceutical Inc; 1997