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# Formulation and Evaluation of Press-Coated Pulsatile Tablets of Salbutamol Sulphate

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**Abstract:** Chronopharmacotherapy, the drug regimen based on circadian rhythm is recently gaining much attention worldwide. Various diseases like asthma, hypertension, and arthritis show circadian variation, that demand time scheduled drug release for effective drug action. Treating these diseases with immediate release dosage forms may be impractical if the symptoms of the disease are pronounced during the night or early morning. Even Modified release dosage forms fail to provide effective drug concentration at exact required time. This study attempts to design and evaluate a chronomodulated pulsatile drug delivery system of Salbutamol Sulphate for the treatment of Asthma in early hours of a day. A novel compression coating technique comprising of rapid release core tablet coated with suitable polymers that could delay release of Salbutamol Sulphate was used. Effect of individual polymer and its effect on drug release and lag time were studied. The effect of different weight ratio of combination of permeable polymers and gellable polymer on the drug release behavior of the time controlled tablet formulation. Core

and Coating materials blend were evaluated for flow properties, compressibility index, Hausner's ratio.Tablets were evaluated

for hardness, thickness, friability, weight variation.

**Keywords:** Chronotherapy, Asthma, Press-Coated, Salbutamol Sulphate

**Introduction:** During the past several decades, conventional drug dosage forms have been widely used for treatment of various disorders and disease conditions. In conventional therapy drug is released immediately after medication. So, the drug concentration in the plasma is raised and sometimes it is more than the toxic level.[1] It was in early 1990s that second-generation modified-release drug preparations achieved continuous and constant-rate drug delivery, in which constant or sustained drug release minimizes "peak and valley" levels of drug in the blood, so promoting drug efficacy and reducing adverse effects particularly for potent drugs.

Controlled-release medications deliver continuous treatment, rather than providing relief of symptoms and protection from adverse events solely when necessary, the development of a third-generation of advanced drug delivery systems (DDSs) to optimize and create new innovative DDS which provide a defined dose, at a chosen rate, at a selected time, to a targeted site is now a growing challenge. A chronodelivery system, based on biological rhythms, is a state-of the- art technology for drug delivery. Chronomodulated DDSs not only increase safety and efficacy levels, but also improve overall drug performance.[2, 3]

Diseases, where a constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner acts as a push for the development of "pulsatile drug delivery system". These

systems have a peculiar mechanism of delivering the drug rapidly and completely after a "lag time," i.e., a period of "no drug release." The principle rational for the use of pulsatile release is for the drugs, where a constant drug release, i.e., a zero-order release is not desired.[4]

Homeostatic theory is classical hypothesis that govern design of formulations. This theory is based on the assumption of biological functions that display constancy over time. However, chronobiological studies have established circadian rhythm for almost all body functions, e.g., heart rate, blood pressure, body temperature, plasma concentration of various hormones, gastric pH and renal function. It has become apparent that rhythmic processes are indispensable for the treatment of human diseases. This makes necessary that treatment of diseases like Cardiovascular diseases, Asthma, Sleep disorder, Peptic ulcer, Epilepsy, Hypercholesterolemia, Arthritis etc should occur by a formulation that show synchrony with the severity of symptoms in said diseases.

Asthma is one such disease which demands pulsatile release. With the projected increase in the proportion of the world's urban population from 45% to 59% in 2025, there is likely to be a marked increase in the number of asthmatics worldwide over the next decade. It is estimated that there may be an additional 100 million persons with Asthma by 2025. Many of the deaths are preventable, but occur either due to lack of suboptimal long-term medical care and/or delay in obtaining help during the attack. It has been recognized that asthma is worse in night. One of the earliest observations of a day-night pattern in asthma was made by Aurelianus Caelius in the 5$^{th}$ century A.D. in the 1880s, Slater wrote that "sleep favours asthma……spasm of the bronchial tubes is

prone to occur during the insensibility and lethargy of sleep than during the waking hours". The activity of the lung exhibits a circadian rhythm with a maximum around 4 p.m. and a minimum around 4 a.m. In asthmatic patients, the intensity of variation in lung function is as much as 50% in a day. In Asthma it is necessary to modulate the drug level in synchrony with the circadian rhythm of nocturnal asthma. [5-8]

Salbutamol Sulphate is very highly used in chronic treatment of Asthma. However, it has shortcomings like short half life, high first pass metabolism and high tolerance rate. This makes it necessary to formulate it in Chronomodulated form which exposes the Salbutamol Sulphate when it is actually required.[9]

In the present research project, we have attempted to develop a novel dosage form by using a chronopharmaceutical approach. A pulsatile dosage form, taken at bedtime with a programmed start of drug release in the early morning hours, can prevent a sharp increase in the incidence of asthmatic attacks, during the early morning hours (nocturnal asthma), a time when the risk of asthmatic attacks is the greatest. Core tablets containing Salbutamol Sulphate were press coated using Eudragit RSPO and HPMC K4M in coating layer.

## MATERIALS AND METHODS

### Materials

Salbutamol Sulphate was obtained as a gift sample from Jayco chemicals, Mumbai. Eudragit RSPO was kindly gifted by Evonik Degussa pvt.ltd. HPMC K4M was kindly supplied by Colorcon Asia Pvt.Ltd. Micro Crystalline Cellulose, Croscarmellose Sodium, Sodium Starch Glycolate and Crosspovidone were kindly supplied by Maple biotech Pvt.Ltd. Magnesium Stearate was procured from J.P.fine chemicals. All chemicals used were of analytical grade.

**Methods**

**Pre-Compression Parameters of Core Tablets Coating Material Powder Blend**[12-14]

Coating material powder blend and core tablet powder blend were evaluated for various precompression parameters such as angle of repose, bulk density, tapped bulk density, hausner's ratio and compressibility index.

**Preparation of Core Tablets**[10, 18, 19]

The core tablets containing Salbutamol Sulphate were prepared by using the composition shown in table no.1. All excipients were mixed for 20 min and passed through a 40 mesh size sieve and directly compressed in to 70 mg tablets using 6 mm round flat punches on a rotary tablet machine.

**Preparation of Press Coated Pulsatile Tablets**[10, 18, 19]

The core tablets were press coated with polymer blend. Polymer blend was composed of HPMC K4M and Eudragit RSPO in different concentrations. Half of the coating material was placed in the die cavity, the core tablet was carefully positioned in the centre of the die and cavity was filled with the other half of the coating material. Coating materials was compressed around the core tablet using of 10mm punch. The compositions were as shown in table no. 2.

**Table no.1.** Formula for core tablets.

| Sr. No | Ingredients | Quantity (mg) |
|---|---|---|
| 1 | Salbutamol Sulphate | 4 |
| 2 | Superdisintegrant* | 4.2 |
| 3 | Avicel PH 102 | 60.8 |
| 4 | Magnesium Stearate | 1 |
| Total Weight | | 70 |

**Table no.2.** Selection of Polymer concentration for optimisation

| Batch code | Coating material | % Ratio | Amount in upper and lower layer |
|---|---|---|---|
| $A_1$ | Eudragit RSPO: HPMC K4M | 100:0 | 250 |
| $A_2$ | Eudragit RSPO: HPMC K4M | 90:10 | 250 |
| $A_3$ | Eudragit RSPO: HPMC K4M | 80:20 | 250 |
| $A_4$ | Eudragit RSPO: HPMC K4M | 70:30 | 250 |
| $A_5$ | Eudragit RSPO: HPMC K4M | 60:40 | 250 |
| $A_6$ | Eudragit RSPO: HPMC K4M | 50:50 | 250 |
| $B_1$ | Eudragit RSPO: HPMC K4M | 100:0 | 300 |
| $B_2$ | Eudragit RSPO: HPMC K4M | 90:10 | 300 |
| $B_3$ | Eudragit RSPO: HPMC K4M | 80:20 | 300 |
| $B_4$ | Eudragit RSPO: HPMC K4M | 70:30 | 300 |
| $B_5$ | Eudragit RSPO: HPMC K4M | 60:40 | 300 |
| $B_6$ | Eudragit RSPO: HPMC K4M | 50:50 | 300 |

**Evaluation of Core Tablets**[15-17]

Core tablets and Press Coated Pulsatile Tablets were evaluated for following parameters as per their pharmacopoeial procedures.

**1. Thickness and Diameter test:** It was determined for 10 tablets in each formulation and average was taken. Digital vernier calliper was used for this purpose

**2. Hardness test:** It was determined using Monsanto hardness tester.

**3. Friability test:** Ten tablets were initially weighed and transferred into Roche friabilator. The friabilator was operated at 25 rpm for 4 minutes.

**4. Weight variation test:** Ten tablets were selected randomly from each formulation and weighed individually to check for weight variation

**5. Drug content uniformity:** Twenty tablets were weighed and ground into a fine powder. The powder equivalent to 4 mg of salbutamol sulphate was weighed and extracted in phosphate buffer pH 6.8 (100 ml) and the concentration of drug was determind by measuring absorbance at 225 nm by spectrophotometer.

**6. *In vitro* drug release studies:**

**Core Tablets**

The *in vitro* drug release from core tablets was carried out using USP paddle apparatus at 50 rpm and 37±0.5 ºC. Phosphate buffer (pH 6.8) was used as the dissolution medium. The samples were withdrawn at regular intervals and analyzed by UV spectrophotometer at 225nm for the presence of the drug. Dissolution tests were performed in triplicate.

**Press Coated Pulsatile Tablets**

The *in vitro* drug release from coated tablets was carried out using USP paddle apparatus at 50 rpm. HCl (0.1 N) and phosphate buffer (pH 6.8) were used as the dissolution medium. Initially tablets were subjected to dissolution in 0.1 HCl for 2h and after that media were changed to phosphate buffer (pH 6.8). The samples were withdrawn at regular intervals and analyzed by UV spectrophotometer at 225 nm for the presence of the drug. Dissolution tests were performed in triplicate.

## RESULTS AND DISCUSSION

**Precompression parameters of Core tablets and coated material powder blend**

Core tablets and coated material powder blend were evaluated for angle of repose, bulk density, tapped density, hausner ratio and compressibility index. The values for angle of repose, Hausner ratio and compressibility index were found well within required limits indicating that all formulations possess good flow property

and compressibility. However, in coated material powder blend it was found that though Eudragit RSPO has better flowability than HPMC K4M, it has less compression properties.

**Table no.3.** Pre-Compression Parameters Core Tablets

| Bulk Density gm/cm$^3$ | Tapped Density gm/cm$^3$ | Hausner Ratio | Compressibility Index | Angle of Repose |
|---|---|---|---|---|
| 0.489 ±0.003 | 0.574 ±0.008 | 1.17±0.005 | 14.808 ±0.98 | 32.72 ±0.53 |

**Table no.4.** Pre-Compression Parameters Press Coated Pulsatile Tablets

| Batch code | Bulk Density gm/cm$^3$ | Tapped Density gm/cm$^3$ | Hausner Ratio | Compressib-ility Index | Angle of Repose |
|---|---|---|---|---|---|
| $A_1$ | 0.657 ±0.021 | 0.811 ±0.015 | 1.232±0.027 | 18.981±1.12 | 22.21 ±1.23 |
| $A_2$ | 0.663±0.025 | 0.818±0.019 | 1.233±0.014 | 18.948±0.82 | 25.34±0.98 |
| $A_3$ | 0.672±0.032 | 0.827±0.033 | 1.230±0.039 | 18.742±1.32 | 27.43±1.34 |
| $A_4$ | 0.681±0.043 | 0.836±0.034 | 1.227±0.046 | 18.540±1.43 | 29.13±2.1 |
| $A_5$ | 0.689±0.019 | 0.843±0.026 | 1.223±0.036 | 18.268±0.93 | 31.11±0.86 |
| $A_6$ | 0.696±0.041 | 0.849±0.023 | 1.219±0.028 | 18.021±1.09 | 34.19±0.47 |
| $B_1$ | 0.657 ±0.021 | 0.811 ±0.015 | 1.232±0.027 | 18.981±1.12 | 22.21 ±1.23 |
| $B_2$ | 0.663±0.025 | 0.818±0.019 | 1.233±0.014 | 18.948±0.82 | 25.34±0.98 |
| $B_3$ | 0.672±0.032 | 0.827±0.033 | 1.230±0.039 | 18.742±1.32 | 27.43±1.34 |
| $B_4$ | 0.681±0.043 | 0.836±0.034 | 1.227±0.046 | 18.540±1.43 | 29.13±2.1 |
| $B_5$ | 0.689±0.019 | 0.843±0.026 | 1.223±0.036 | 18.268±0.93 | 31.11±0.86 |
| $B_6$ | 0.696±0.041 | 0.849±0.023 | 1.219±0.028 | 18.021±1.09 | 34.19±0.47 |

**Evaluation of Core Tablets**

Weight variation, diameter, thickness and hardness were found to be within acceptable limit. The friability was also below 1% for all the formulation, which is an indication of good mechanical resistance of the tablet and stability to transportation. The hardness of

core tablets was maintained to be within 3 to 4 kg/cm$^2$ as they are subjected to double compression in step of final coating. Drug content of core tablets was observed to be 99.23±0.25. Drug content uniformity is important parameter which insures that each tablet contains sufficient amount of drug as per stated limits.

**Table no.5.** Evaluation of Core Tablets

| Thickness (mm) | Diameter (mm) | Weight Variation | Hardness (kg/cm$^2$) | Friability (% loss of Weight) | % Drug content |
|---|---|---|---|---|---|
| 2.03±0.03 | 6.03±0.02 | 70.43±0.09 | 3.8±0.2 | 0.389±0.05 | 99.23±0.25 |

**_In vitro_ drug release studies of Core tablets**

It is very important to determine the drug release from core tablet. Dissolution studies were carried out for core and results are as shown in table no.5. It shows 96 % drug release in just 5 minutes. Salbutamol sulphate being highly water soluble releases rapidly.

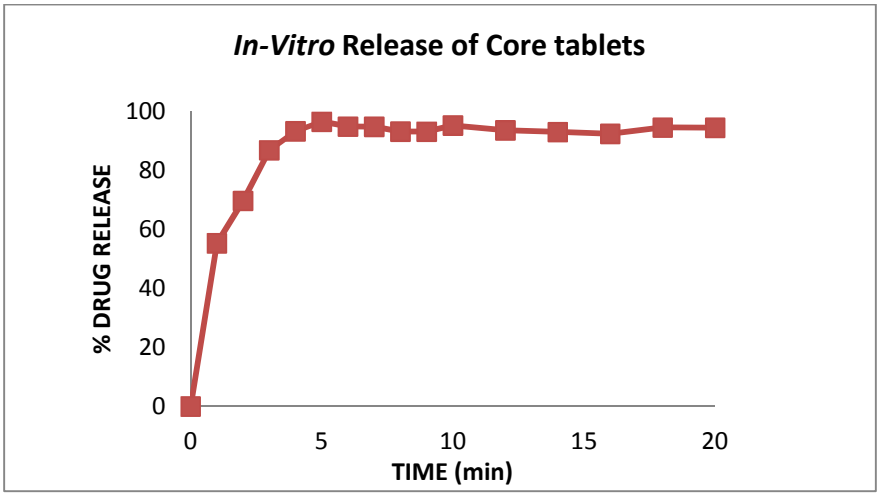


**Figure no.1.** *In vitro* drug release studies of Core tablets

**Evaluation of Press Coated Pulsatile Tablets (PCPT)**

Both thickness and diameter was well within the limits without much variation from mean value. IP states limit of ±5 % for this weight range. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±5 % of the average weight. The weights of all the tablets were found to be uniform with low standard deviation. The hardness of PCPT was maintained to be within 4 to 6 kg/cm$^2$ which is optimum range for normal tablets. The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness. The highest friability among all the 12 formulation was just 0.436%, less than 1% indicating that the friability is within the prescribed limits. The results show that the % drug content uniformity is within the range of 99.47±0.12 to 99.98±0.58. It insures that each tablet contains sufficient amount of drug as per stated limits.

**Table no.6.** Evaluation of Press Coated Pulsatile Tablets (PCPT)

| Batch code | Thickness (mm) | Diameter (mm) | Weight Variation (mg) | Hardn-ess (kg/cm$^2$) | Friability (% loss of Weight) | % Drug content |
|---|---|---|---|---|---|---|
| $A_1$ | 2.43±0.22 | 9.99±0.02 | 319.12±0.14 | 5.2±0.1 | 0.436±0.03 | 99.91±0.21 |
| $A_2$ | 2.38±0.14 | 10.02±0.06 | 322.1±0.09 | 5.3±0.4 | 0.423±0.045 | 99.43±0.10 |
| $A_3$ | 2.36±0.13 | 10.03±0.03 | 318.33±0.11 | 5.6±0.2 | 0.411±0.09 | 99.76±0.27 |
| $A_4$ | 2.4±0.31 | 9.98±0.04 | 321.29±0.12 | 5.8±0.1 | 0.422±0.10 | 99.56±0.41 |
| $A_5$ | 2.42±0.18 | 10.00±0.02 | 318.27±0.22 | 5.4±0.4 | 0.399±0.082 | 99.98±0.58 |
| $A_6$ | 2.38±0.14 | 10.01±0.01 | 320.45±0.31 | 5.8±0.2 | 0.401±0.056 | 99.69±0.54 |
| $B_1$ | 3.0±0.12 | 9.97±0.07 | 368.75±0.64 | 5.7±0.5 | 0.432±0.043 | 99.47±0.12 |
| $B_2$ | 2.9±0.33 | 10.02±0.04 | 372.67±0.24 | 5.4±0.3 | 0.426±0.081 | 99.93±0.62 |
| $B_3$ | 2.95±0.23 | 10.00±0.05 | 369.53±0.19 | 5.3±0.1 | 0.419±0.039 | 99.88±0.25 |

| | | | | | | |
|---|---|---|---|---|---|---|
| $B_4$ | 3.05±0.1 | 10.04±0.06 | 371.19±0.56 | 5.4±0.4 | 0.403±0.043 | 99.86±0.20 |
| $B_5$ | 2.98±0.18 | 10.03±0.01 | 370.36±0.71 | 5.2±0.2 | 0.423±0.029 | 99.61±0.46 |
| $B_6$ | 2.93±0.11 | 10.02±0.06 | 370.93±0.15 | 5.6±0.1 | 0.416±0.035 | 99.78±0.33 |

***In vitro* drug release of Press Coated Pulsatile Tablets (PCPT)**

The studies were performed as per the procedure described earlier. Time required to release 10 % of drug was considered as lag time. It was found that batch $A_1$ to $A_6$ showed different dissolution profile as compared to their counterpart having same % ratio of polymer but increased level of coating. In present study a combination of permeable and gellable / swellable polymer had been used. It was found that batch $A_1$ which comprised only of Eudragit RSPO and total coating of 250 mg showed no significant lag time and burst within first 45 minutes. Eudragit RSPO is a copolymer of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups. The ammonium groups are present as salts and make the polymers permeable. This makes the tablet to burst as the dissolution medium permeates inside and pressure is developed by superdisintegrant present inside the core tablet.[11]

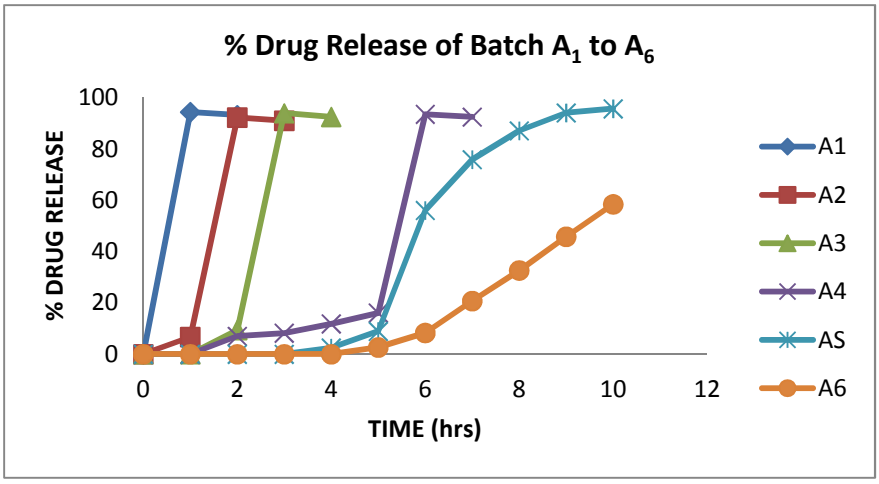

**Figure no.2.** % Drug Release of Batch $A_1$ to $A_6$

Batch $A_4$ comprising of about 30 % HPMC K4M shows 11.82 % drug release in 4 hours. It shows 16.06 % drug release in 5 hours. Tablet bursts at about 310 minutes causing drug to release in 6th hour. Batch $B_4$ with similar composition follows lag time of 6 hrs releasing the drug in late 7th hour. Tablet burst at about 410 minutes. Drug release in this hour was 84.45 % and in subsequent hour it was about 93.94 %. These observations show that increasing concentration of HPMC K4M increases lag time. It may be attributed to swellable and gellable nature of HPMC K4M. Eudragit RSPO is low permeable polymer and leads to bursting of tablets. Salbutamol Sulphate is highly water soluble and hence some amount of it diffuses prior to bursting of tablet.

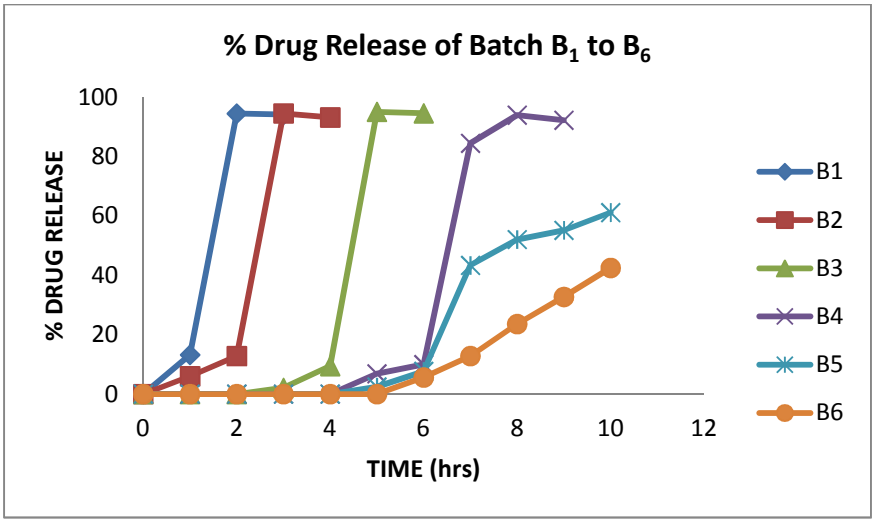


**Figure no.3.** % Drug Release of Batch $B_1$ to $B_6$

Batch $A_5$ and $A_6$ exhibited slightly different results. These batches showed a lag time but the release there-after was not sharp as the tablet didn't burst, instead they swelled and Salbutamol sulphate being water soluble showed release like that in normal delayed release tablets. Similar results were observed in batch $B_5$ and $B_6$. This may be attributed to increased level of HPMC K4M in coating blend. The gel network formed by HPMC K4M is stronger and doesn't burst. The drug being highly water soluble release by mechanism of diffusion. HPMC K4M

may show all its properties of swelling, gelling and erosion together or dependent on concentration used. These properties also depend on other polymer used in the combination.

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