Formulation and Evaluation of Erodible Pulsatile Drug Delivery System of Salbutamol Sulphate for Nocturnal Asthma

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Abstract
Aim of the present work was to formulate and evaluate an oral, pulsatile drug delivery system to achieve time release of Salbutamol sulphate, based on chronopharmaceutical approach for the treatment of nocturnal asthma. An asthmatic attack mainly takes place in the early morning at 4 o’clock. Pulsatile delivery system is an ideal approach for delivering drug when and where it required most. The basic design consists of a core tablets prepared by direct compression method and coating it with an inner swellable layer containing 30 % HPMC E5. The entire device was enteric coated with 5% cellulose acetate phthalate, which overcomes the gastric emptying time. The prepared Pulsatile tablets were evaluated for the drug content, thickness and in-vitro release profile and other parameters. Three optimized formulation was selected and subjected to further studies like effect of inner swelling layer on lag time, effect of outer rupturing layer, effect of paddle speed on drug release etc. In vitro release profiles of pulsatile device during six hours studies were found to have very good sustaining efficacy. During the first four hours there was no drug release and in between 5 to 6 hrs immediate release was observed. Increasing the level of the rupturable layer (CAP) increased mechanical strength and retarded the water uptake and thus prolonged the lag time. The lag time of the pulsatile tablets decreased with increasing amounts HPMC E5 in the inner coating layer. Accelerated stability studies proved that coating of tablets seems to decrease the effect of temperature and moisture on the degradation of Salbutamol sulphate. The time dependent pulsatile release has been achieved from a coated tablet over a 5-6 hrs period, consistent with the demands of chronotherapeutic drug delivery.

Key words: Pulsatile drug delivery, Chronotherapeutics, Circadian rhythm, Nocturnal asthma, Salbutamol sulphate

Introduction
Traditionally, drugs are released in an immediate or extended fashion. However, in recent years, pulsatile drug release systems are gaining lots of interest. A Pulsatile drug release, where the drug is released rapidly after a well defined lag-time, could be advantageous for many drugs or therapies. There are certain

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Volume 3, Issue 3, May - June 2013
http://www.ijpi.org
conditions for which controlled drug delivery system is not 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.

Pulsatile drug delivery is one such system that, by delivering drug at the right time, right place and in right amounts, holds good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension etc. Thus designing of proper Pulsatile drug delivery will enhances the patient compliance, optimum drug delivery to the target site and minimizes the undesired effects\(^1\). A drug should be delivered only when and/or where it is needed at the minimum required dose\(^2\). For the drugs to follow circadian rhythm, like in asthma, a reasonable and an acceptable rationale is a delivery system capable of releasing drugs in a Pulsatile fashion rather than as a continuous delivery at the predetermined time/site following oral administration\(^3,4\).

A time dependent pulsed release system consisting of an effervescent core surrounded by consecutive layers of swelling and rupturable polymers. The principle of time controlled drug delivery systems is that the release of the drug happens according to a predetermined rate so to achieve maximum therapeutic and minimum toxic effect.

Nocturnal asthma is defined as a variable night-time exacerbation of the underlying asthma condition associated with increase in symptoms and need for medication, increased airway responsiveness and/or worsening of lung function. Approximately two-thirds of asthmatics suffer from night-time symptoms. Lung function is usually highest at 4 PM and lowest at 4 AM. The mechanisms of nocturnal asthma are intimately related to circadian rhythms which can be treated by chronotherapy. So for these reason, pulsatile drug delivery system proves better for the treatment of nocturnal asthma.

Salbutamol sulphate is a short-acting, relatively selective \(\beta_2\)-adrenergic bronchodilator used for the relief of bronchospasm in conditions such as asthma and chronic obstructive pulmonary disease\(^5\). The plasma half-life of this drug is 4 to 6 hours. In this research work we have attempted to develop a novel dosage form containing Salbutamol sulphate by using a chronopharmaceutical approach. This dosage form taken at bed time with a programmed start of drug release early in morning hours which 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.

**Materials**

The drug Salbutamol sulphate is obtained as a free gift from Mahendra Pharma, Bangalore, India. Microcrystalline cellulose, citric acid and sodium bicarbonate were procured from Cipla Pharma, Mumbai, India. Magnesium stearate was purchased from Rolex chemicals, Bombay, India. Hydroxy propyl methylcellulose was obtained from Micro labs, Bangalore, India. Cellulose
Acetate phthalate was procured from Central drug house, New Delhi, India. Lactose, tartaric acid and starch were purchased from S.D Fine Chemicals, Mumbai, India.

**Methods**

**Formulation of pulsatile tablet of Salbutamol sulphate**

Direct compression was followed to manufacture the Salbutamol sulphate core tablets. Each core tablet (average weight 200mg) for in vitro drug release studies consisted of Salbutamol sulphate and excipients like microcrystalline cellulose, starch, lactose, magnesium stearate, talc.

First the drug and excipients selected were passed through 60-mesh sieve. Required quantity of drug and excipients were weighed properly and transferred into mortar and the blend was mixed for at least 10 min. After that, magnesium stearate and talc were added to the blend. The tablets were compressed using 6 mm diameter punches in Riddhi pharma machinery Ltd. tablet punching machine to get round concave shaped 200 mg tablets. Formulations of core tablet were shown in Table 1.

**Table 1. Formulation of pulsatile tablet of Salbutamol sulphate**

<table>
<thead>
<tr>
<th>Compositions</th>
<th>Quantity (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Salbutamol sulphate</td>
<td>9.64</td>
</tr>
<tr>
<td>Lactose</td>
<td>90.36</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>60</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>3</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>3</td>
</tr>
<tr>
<td>Citric acid</td>
<td>-</td>
</tr>
<tr>
<td>Tartaric acid</td>
<td>-</td>
</tr>
<tr>
<td>Starch</td>
<td>30</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2</td>
</tr>
<tr>
<td>Talc</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
</tr>
</tbody>
</table>

Compression coating of Salbutamol sulphate core tablets

The Salbutamol sulphate core tablets were compression coated with different concentration of HPMC E5 coating material. The different concentration of HPMC E5 like 10%, 20%, 30% and 40% is selected as an inner swelling coating layer to retard the drug release. Half quantity of the coating material was placed in the die cavity; the core tablet was carefully positioned in the center of the die.
cavity and was filled with other half of the coating material. The coating material was compressed around the core using 8 mm round, concave punches.

Dip coating of compressed coated tablet

The outer polymeric layer consisting of cellulose acetate phthalate (CAP) dispersed in acetone using propylene glycol as a plasticizer. The compositions of coating solution are shown in Table 2. The outer polymeric layer was incorporated by dip coating method. Selected polymer solution was prepared and the tablets were dipped in the coating solution and simultaneously dried with the help of hot air. The coated tablets were then dried in hot air oven at 40 °C until the coat is dry. Then dried tablets were weighed and re-coated in the same procedure until expected weight gain was obtained by deep coating. For the CAP coating, coating procedure carried out until the tablets resist disintegration in pH 1.2 buffers for minimum period of two hrs. CAP gives zero release in acidic media for first two hours.

Table-2 Composition of CAP coating solution

<table>
<thead>
<tr>
<th>Composition</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose acetate phthalate</td>
<td>5%</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>0.1%</td>
</tr>
<tr>
<td>Acetone</td>
<td>100 mL</td>
</tr>
</tbody>
</table>

Evaluations

Flow Properties of powder blend

The flow properties of powder blend were characterized in terms of angle of repose, compressibility index (Ic) and Hausner ratio. Angle of repose was performed using funnel method by keeping a funnel vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom was closed and 2 gm of powder was filled in the funnel. Then the funnel was opened to releases the powder on the paper to form a smooth conical heap. The radius of the heap (r) and the height of the heap (h) were measured. The \( \tan^{-1} \) of the height of the pile / radius of its base gave the angle of repose. Bulk density (\( \rho_b \)) and tapped densities (\( \rho_t \)) were determined and thereby hausner ratio (\( H_R \)) and compressibility index were calculated according to the following equations.

\[
I_c = \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \times 100
\]

\[
Hausner \ ratio = \frac{\rho_{tapped}}{\rho_{bulk}}
\]

Post-compression parameters

Weight variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of twenty tablets were calculated. The batch passes the test for weight variation if not more than two of the individual weight of tablet deviate from the average weight by more than the % deviation according to standard limit.

Hardness

The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of Kg/cm². Three tablets were chosen randomly and tested for hardness.
The average hardness of 3 determinations was recorded.

**Friability**

Twenty tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded.

\[
\text{Friability} = \{1 - (W_t/W)\} \times 100
\]

Where, \( F \) = Friability in percentage, 

\( W \) = Initial weight of tablets, 

\( W_t \) = Weight of tablets after friability

**Thickness**

Thickness of the tablet is important for uniformity of tablet size. Thicknesses of the tablet were measured using digital vernier calipers. It was determined by checking the thickness of ten tablets from each formulation.

**Content uniformity**

Randomly ten tablets were weighed and powdered. The powder equivalent to 50 mg was weighed accurately and dissolved in 100 mL of phosphate buffer pH 6.8. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatman No.1 filter paper. Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured at 275.8 nm. The concentration of the drug was computed from the standard curve of the Salbutamol sulphate in phosphate buffer (pH 6.8).

**Disintegration time**

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in Electrolab USP disintegration test apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top, and held against a 10 mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of tablet, one tablet was placed in each tube and the basket rack was positioned in a 1 litre beaker containing phosphate buffer solution (pH 6.8) at 37 °C ± 1 °C such that the tablet remains 2.5 cm below the surface of liquid. The time taken for the complete disintegration of the tablets was noted.

**Effect of inner swelling layer on lag time of compression coated tablet**

Core tablets were coated with different coating concentration of HPMC E5 as inner swelling layer and subjected to dissolution study as described in method\(^6\). Effect of swelling layer concentration over lag time and release behavior was observed using a spectrophotometer in phosphate buffer pH 6.8.

**Dip coating of compressed coated tablet\(^{12}\)**

The outer polymeric layer consisting of cellulose acetate phthalate (CAP) dispersed in acetone using propylene glycol as a plasticizer. The composition of coating solution is shown in Table 3. The outer polymeric layer was incorporated by dip coating method. Selected polymer solution was prepared and the tablets were dipped in the coating solution and simultaneously dried with the help of hot air. The coated tablets were then dried in hot air oven at 40 °C until the coat is dry. Then dried tablets were weighed and
re-coated in the same procedure until expected weight gain was obtained by deep coating. For the CAP coating, coating procedure carried out until the tablets resist disintegration in pH 1.2 buffers for minimum period of two hrs. CAP gives zero release in acidic media for first two hours.

Table- 3 Composition of CAP coating solution

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<tr>
<td>Cellulose acetate phthalate</td>
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</tr>
<tr>
<td>Propylene glycol</td>
<td>0.1%</td>
</tr>
<tr>
<td>Acetone</td>
<td>100 ml</td>
</tr>
</tbody>
</table>

In vitro dissolution for optimized formulation

In-vitro dissolution study of core tablet of Salbutamol sulphate was carried out using Electrolab TDT-08L USP dissolution test apparatus. Tablet was introduced into the dissolution jar of the Electrolab TDT-08L USP dissolution paddle test apparatus and the apparatus was set in motion. 2 hrs study was carried out in 0.1 N HCl (pH 1.2) followed by dissolution in phosphate buffer solution (pH 6.8) up to 4-5 hours at 50 RPM. 1 mL samples was withdrawn and analyzed by UV spectrophotometer after suitable dilution and withdrawn volume was replaced by fresh buffer solution.

Accelerated stability studies for the optimized formulation

Stability studies were carried out as per ICH guidelines, at 40 ± 2 ºC/75 ± 5% RH.

Stability studies were carried out using stability chamber. The temperature and relative humidity values selected at 40 ± 2 ºC/75 ± 5% RH for a period of 2 months. The samples were packed in a HDPE container and analyzed for the parameter like appearance, weight variation, hardness and drug content parameters.

RESULTS AND DISCUSSION

Flow properties of blend

The evaluation of powder blend for Salbutamol sulphate core tablet like Bulk density, Tapped density, Carr's index, Hausner's ratio and Angle of repose are shown in Table 4. The loose bulk density and tapped bulk density for all formulations varied in range of 0.529±0.006 gm/mL to 0.581±0.013 gm/mL and 0.644±0.008 gm/mL to 0.725±0.017 gm/mL respectively. The value obtained lies within the acceptable range and with no significant difference found between loose density and tapped density. This result helps in calculating the % compressibility of the powder. Carr's index was found to be between 13.56±1.936% and 21.82±0.098% indicating the powder blend have fair flow property for compression. Hausner’s ratio was found to be in a range 1.15±0.025 of 1.29±0.016 which shows that powder blend have good compressibility. It can be concluded that all the formulation blends angle of repose was found to be 28.65 to 31.20 º. Hence the entire formulation blends was found to possess good flow property.
Table 4 Pre-compression parameters of Salbutamol sulphate core tablet

<table>
<thead>
<tr>
<th>Formula No</th>
<th>Bulk Density* (gm/cm³)</th>
<th>Tapped Density* (gm/cm³)</th>
<th>Carr’s Index* (%)</th>
<th>Hausner Ratio*</th>
<th>Angle of Repose* (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.563±0.010</td>
<td>0.667±0.009</td>
<td>15.59±2.696</td>
<td>1.18±0.037</td>
<td>31.20±1.205</td>
</tr>
<tr>
<td>F2</td>
<td>0.548±0.010</td>
<td>0.663±0.007</td>
<td>17.34±1.075</td>
<td>1.20±0.015</td>
<td>28.65±1.491</td>
</tr>
<tr>
<td>F3</td>
<td>0.567±0.007</td>
<td>0.656±0.005</td>
<td>13.56±1.936</td>
<td>1.15±0.025</td>
<td>30.48±0.693</td>
</tr>
<tr>
<td>F4</td>
<td>0.534±0.007</td>
<td>0.644±0.008</td>
<td>17.08±1.628</td>
<td>1.20±0.023</td>
<td>29.62±0.856</td>
</tr>
<tr>
<td>F5</td>
<td>0.563±0.008</td>
<td>0.684±0.006</td>
<td>17.69±1.777</td>
<td>1.21±0.026</td>
<td>29.74±1.336</td>
</tr>
<tr>
<td>F6</td>
<td>0.574±0.007</td>
<td>0.703±0.010</td>
<td>18.34±2.112</td>
<td>1.22±0.031</td>
<td>30.19±1.120</td>
</tr>
<tr>
<td>F7</td>
<td>0.551±0.004</td>
<td>0.714±0.006</td>
<td>21.82±0.098</td>
<td>1.29±0.016</td>
<td>30.74±1.037</td>
</tr>
<tr>
<td>F8</td>
<td>0.529±0.006</td>
<td>0.665±0.007</td>
<td>20.45±0.259</td>
<td>1.25±0.004</td>
<td>29.93±1.063</td>
</tr>
<tr>
<td>F9</td>
<td>0.581±0.013</td>
<td>0.725±0.017</td>
<td>19.86±0.746</td>
<td>1.24±0.014</td>
<td>30.48±1.086</td>
</tr>
</tbody>
</table>

*Mean ± S.D., n=3

Weight variation, hardness, friability, disintegration, drug content and disintegration time of core tablet of Salbutamol sulphate

The post compression parameters of Salbutamol sulphate core tablet is shown in Table 5.

All the formulated (F1 to F9) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits. Weights of tablets were lies between 191.28±3.49 mg to 205.12±5.89 mg. The weights of all the tablets were found to be uniform with low standard deviation values. The measured hardness of tablets of all the formulations ranged between 3.1±0.22 to 3.4±0.41 Kg/cm². This ensures good handling characteristics of all batches. The thickness of the tablets from each formulation was measured using digital vernier caliper by picking three tablets randomly. The mean values were found to be in range 3.64±0.033 mm to 3.87±0.013 mm. It was found between 22±1.527 to 74±2.746 seconds. Based on disintegration time, it ensures that all the formulations were suited for time release pulsatile drug delivery system. The % friability was less than 0.5% in all the formulations ensuring that the tablets were mechanically stable. The percentage of drug content for F1 to F9 was found to be between 97.36% and 99.77%. It complies with official specifications. The disintegration time was varied between 22±1.527 and 53±2.081. Among all the formulations, three formulations F2, F6
and F8 were selected as the best depending upon the physicochemical evaluations and compression coated with 30% HPMC E5 coating material.

Table-5 physicochemical parameters of Salbutamol sulphate core tablet

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Weight variation* (mg)</th>
<th>Thickness** (mm)</th>
<th>Hardness* (kg/cm²)</th>
<th>Friability* (%)</th>
<th>Drug Content*** (%)</th>
<th>Disintegration time*** (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>196.81±5.74</td>
<td>3.87±0.013</td>
<td>3.3±0.27</td>
<td>0.394</td>
<td>98.11</td>
<td>46±1.154</td>
</tr>
<tr>
<td>F2</td>
<td>201.99±7.45</td>
<td>3.85±0.016</td>
<td>3.1±0.22</td>
<td>0.400</td>
<td>99.13</td>
<td>38±0.577</td>
</tr>
<tr>
<td>F3</td>
<td>196.53±4.11</td>
<td>3.74±0.018</td>
<td>3.2±0.27</td>
<td>0.417</td>
<td>98.94</td>
<td>53±2.081</td>
</tr>
<tr>
<td>F4</td>
<td>194.71±5.50</td>
<td>3.69±0.018</td>
<td>3.4±0.41</td>
<td>0.422</td>
<td>98.27</td>
<td>49±2.645</td>
</tr>
<tr>
<td>F5</td>
<td>191.28±3.49</td>
<td>3.64±0.033</td>
<td>3.3±0.27</td>
<td>0.345</td>
<td>99.68</td>
<td>42±2.081</td>
</tr>
<tr>
<td>F6</td>
<td>204.33±7.57</td>
<td>3.69±0.026</td>
<td>3.1±0.22</td>
<td>0.363</td>
<td>99.77</td>
<td>22±1.527</td>
</tr>
<tr>
<td>F7</td>
<td>195.43±6.85</td>
<td>3.81±0.004</td>
<td>3.4±0.41</td>
<td>0.355</td>
<td>98.10</td>
<td>39±3.214</td>
</tr>
<tr>
<td>F8</td>
<td>202.43±7.55</td>
<td>3.87±0.007</td>
<td>3.4±0.22</td>
<td>0.360</td>
<td>99.73</td>
<td>25±2.516</td>
</tr>
<tr>
<td>F9</td>
<td>205.12±5.89</td>
<td>3.78±0.014</td>
<td>3.3±0.39</td>
<td>0.483</td>
<td>97.36</td>
<td>74±2.746</td>
</tr>
</tbody>
</table>

*Mean ± S.D., n=5, **Mean ± S.D., n=10, ***Mean ± S.D., n=3

Compression coated Salbutamol sulphate tablets

The Salbutamol sulphate core tablets were compression coated with 30% HPMC E5 coating material as an inner swelling coating layer to retard the drug release. Half quantity of the coating material was placed in the die cavity; the core tablet was carefully positioned in the center of the die cavity and was filled with other half of the coating material. The coating material was compressed around the core using 8 mm round, concave punches.

Effect of inner swelling layer on the lag time

Core tablets were coated with different coating level of HPMC E5 like 10%, 20%, 30% and 40% as inner swelling layer and subjected to dissolution study in phosphate buffer pH 6.8 as described in method. The effect of inner swelling layer (HPMC E5) on formulation F2, F6 and F8 is shown in Figure 1(a), (b) and (c).
Figure 1(a). Effect of inner swelling layer (HPMC E5) on formulation F2

Figure 1(b). Effect of inner swelling layer (HPMC E5) on formulation F6

Figure 1(c). Effect of inner swelling layer (HPMC E5) on formulation F8
Evaluation of Dip Coated tablets of Salbutamol sulphate

Tablets of Salbutamol sulphate (200 mg) were coated with HPMC E5 by direct compression method and followed by dip coating with CAP and subjected to evaluation studies such as weight variation, hardness, and thickness. All the formulated tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits. The weights of all the tablets were found to be 280.57, 281.42 and 281.61 mg for formulation F2, F6 and F8 respectively with low standard deviation values. The measured hardness of coated tablets of selected three formulations F2, F6 and F8 were 6.6±0.11, 6.8±0.05 and 6.6±0.05 Kg/cm² respectively. This ensures good handling characteristics of all formulations. The measured thicknesses of coated tablets of optimized formulation were found to be 5.6±0.047, 5.6±0.015 and 5.5±0.036 mm respectively. This ensures uniform coating to all three batches.

In vitro drug release profile of optimized formulation

The in vitro drug release profile of optimized formulation F2, F6 and F8 is shown in Figure 2. The all selected formulations give release of the drug within 5 to 6 hrs. Means after 5 hr only it shows the release and in between 5 to 6 hrs it gives maximum release.

![Figure 2 In vitro drug release profile of formulations F2, F6 and F8](image)

All the three formulations of prepared coated tablets of Salbutamol sulphate were subjected to in-vitro release studies. These studies were carried out using USP dissolution apparatus type-II, and 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) as dissolution media. During dissolution studies, it was observed that, the enteric coat of the cellulose acetate phthalate was intact for 2 hours in 0.1 N HCl (pH 1.2), but dissolved in intestinal pH, leaving the insoluble coat of HPMC.
E5(30%), which is swell and form pores. Through these pores water penetrates inside the membrane. Then water penetrated inside the core tablet which contained sodium bicarbonate in their core which generated carbon dioxide, which resulted in building up of pressure inside the core and helped in early rupturing of the outer polymeric layer of HPMC E5(30%). The presence of an osmotic agent helped in drawing water towards the tablet which resulted in rupturing of outer coating layer in phosphate buffers (pH 6.8).

With all the formulations, there was no drug release in 0.1 N HCl (pH 1.2), thus indicating the efficiency of 5% CAP for enteric coating. In case of formulation F2, it contains 2.5% Sodium bicarbonate and 2.5% Sodium chloride. At the end of 6\textsuperscript{th} hour the cumulative drug release was found to be 92.01%. So, it ensures that the drug release is going to be increase which might be due to increase in pressure inside coated layer. Formulation F6 and F8 contain 2.5% citric acid and 2.5% tartaric acid respectively. These formulations also contain 2.5% sodium bicarbonate. Here in F6 and F8 cumulative drug release was found to be 98.66 and 95.59 respectively at 6\textsuperscript{th} hour. So as the content of tartaric acid and citric acid increased with sodium bicarbonate, pressure inside the coated layer increased which rupture the layer which leads to increase the cumulative percent drug release. Tartaric acid is retarding drug release as compared to citric acid.

**Accelerated stability studies**

The stability studies were carried out on formulation F6 as per ICH Guidelines in stability chamber. The stability studies results of prepared tablets formulation F6 were carried out at 40 °C with 75% RH. There were no significant changes in their physical appearance, average weight of tablets and hardness. It was observed that the initial drug content and the drug contents of the samples analyzed after 30 and 60 days of storage were similar. Hence, it can be concluded from the results that the developed tablets were stable and retain their pharmaceutical properties over a period of two month.

**Conclusion**

In conclusion, Pulsatile drug release over a period of 5-6 hrs was achieved, in which core tablet of Salbutamol sulphate was coated first by 30% HPMC E5 layer then by 5% CAP coating solution. Thus Pulsatile drug delivery system can be considered as one of the promising formulation technique for chronotherapeutic management of nocturnal asthma. Therefore the study proved that coated Salbutamol Sulphate can be successfully used as a time dependent modified chronopharmaceutical formulation.

**References**

3. Yoshida R, Sakai K, Okano T,


