Effect of polymers in release rate of Metoprolol succinate in Pulsatile release tablets

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Abstract
The objective of the present investigation was to develop and evaluate an oral pulsatile drug delivery system. The design of the system consisted of a rapid release tableted core and a controlled release tableted coat. The core layer consists of Metoprolol Succinate and coating layer consists of Benecil K 200M, HPMCK 100 M and Eudragit RSPO. The compatibility of Metoprolol Succinate with polymers used was performed by FTIR studies. The prepared tablets passed the pre compression and post compression evaluation characteristics. An in vitro dissolution study of the prepared tablet was conducted initially for 2 h in simulated 0.1 N HCl and after that medium was changed to acetate buffer pH 4.5 for 4h finally in phosphate buffer pH 6.8. The in vitro data was further treated with mathematically to know the rate of release. The study concluded the F6 formulation showed compliance with circadian rhythm.

Keywords: Metoprolol Succinate, Pulsatile tablets, Benecil K 200M, HPMCK 100 M

Introduction
Oral dosage forms are promising, safe and convenient drug delivery systems since past few decades. The controlled release drug delivery systems with reservoir or matrix systems release the active drug for extended period of time [1]. Chronopharmaceutics, the drug delivery 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. Results of several epidemiological studies have demonstrated the elevated risk of different pathologies during a 24 h cycle. Blood pressure which rises notably just before waking up is usually responsible for attacks. New technology based on pulsatile release control was developed to satisfy this requirement [2]. Metoprolol tartarate is selective β adrenoreceptor blocking agent used to treat hypertension, angina and heart attack [3]. The aim of the present work is to develop pulsatile drug delivery system tablets using core and
coating layers. The core layer consists of Metoprolol Succinate and coating layer consists of Benecil K 200M, HPMCK 100 M and Eudragit RSPO.

![Diagrammatic representation of Core in cup tablet drug delivery system](image)

**Fig.1 Diagrammatic representation of Core in cup tablet drug delivery system**

### Materials and Methods

**Materials**

Metoprolol succinate (MS) was a gift sample from Mylan Pharmaceuticals Pvt Ltd., Hyderabad. Benecil K 200M, HPMCK 100 M and Eudragit RSPO were procured from standard chemicals, Hyderabad, India. PVP K 30, Micro crystalline Cellulose, Aerosil, Magnesium stearate and Talc were procured from Serin Formulations Pvt. Ltd, Hyderabad, India. All reagents used were of analytical reagent grade. Double distilled water was used whenever required.

**Preparation of Metoprolol Core in Cup tablets**

*Preparation of Metoprolol Core Tablet*

The core tablets of Metoprolol succinate (MS) were prepared by direct compression technique. MS, Micro crystalline cellulose, PVP K 30, Magnesium stearate, Aerosil and Talc were mixed with each other according to the geometric method. Rapid release core tablets were prepared by compressing all the ingredients using 6 mm flat faced punch and die cavity on a single station rotary tablet punching machine [4-6].

**Preparation of Compression Coated Tablets**

The core tablets were compression coated with different weight ratios (w/w) of Benecel K200M, HPMC K100 M mixtures. Half of the total quantity of coating powder blend was filled in die cavity to make a powder bed at the bottom. The previously compressed tablet using 6 mm flat faced punches placed in the center on the above powder blend. The remaining equivalent powder was filled in the die, and the content was compressed using a flat faced punch, 9 mm in diameter and punched in a single station punching machine [4-6].

### Table 1. Composition of Core Tablet

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol Succinate</td>
<td>23.75</td>
</tr>
<tr>
<td>Micro crystalline Cellulose</td>
<td>25</td>
</tr>
<tr>
<td>PVP K 30</td>
<td>15</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.25</td>
</tr>
<tr>
<td>Aerosil</td>
<td>0.5</td>
</tr>
<tr>
<td>Talc</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>66</strong></td>
</tr>
</tbody>
</table>

### Table 2. Composition of Coating layer

<table>
<thead>
<tr>
<th>Ingredients (g)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benecil K 200M</td>
<td>2.5</td>
<td>5</td>
<td>7.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPMCK100 M</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.5</td>
<td>5</td>
<td>7.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Eudragit RSPO</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.5</td>
<td>5</td>
<td>7.5</td>
</tr>
<tr>
<td>MCC</td>
<td>7.3</td>
<td>4.8</td>
<td>2.3</td>
<td>7.3</td>
<td>4.8</td>
<td>2.3</td>
<td>7.3</td>
<td>4.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Mg stearate</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Total weight</strong></td>
<td><strong>10</strong></td>
<td><strong>10</strong></td>
<td><strong>10</strong></td>
<td><strong>10</strong></td>
<td><strong>10</strong></td>
<td><strong>10</strong></td>
<td><strong>10</strong></td>
<td><strong>10</strong></td>
<td><strong>10</strong></td>
</tr>
</tbody>
</table>
Evaluation
Compatibility studies
Fourier Transform Infrared Spectroscopic (FTIR) analysis
The prepared MS pulsatile tablets were evaluated for compatibility between drug and excipients using Fourier transform infrared spectrophotometer (Perkin Elmer, spectrum-100, Japan) using the KBr disk method. The scanning range was 500 to 4000 cm\(^{-1}\) and the resolution was 1 cm\(^{-1}\). This spectral analysis was employed to check the compatibility of drugs with the polymers used.

Pre-compression parameters
Angle of repose
Angle of repose was determined by using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height (h), was obtained. Diameter of heap, (D), was measured. The angle of repose (θ) was calculated by the following equation [7-9].

\[ \theta = \tan^{-1}\left(\frac{h}{r}\right) \]

Where,
θ is the angle of repose, h is the height in cm and r is the radius.

Bulk Density
Apparent bulk density was determined by pouring pre sieved drug excipient blend into a graduated cylinder and measuring the volume and weight “as it is”. It is expressed in g/ml and is given by the following equation [7-9].

\[ D_b = \frac{M}{V_0} \]

Where,
M is the mass of powder and \(V_0\) is the Bulk volume of the powder

Tapped density
It was determined by placing a graduated cylinder, containing a known mass of drug- excipient blend, on mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by the following equation [7-9].

\[ D_t = \frac{M}{V_t} \]

Where,
M is the mass of powder and \(V_t\) is the tapped volume of the powder.

Carr’s Index (\(I_C\)):
It is expressed in percentage and is expressed by the following equation [7-9].

\[ I_C = \frac{D_t - D_b}{D_t} \]

Where,
\(D_t\) is the tapped density of the powder and \(D_b\) is the bulk density of the powder.

Hausner’s ratio (\(H_R\))
It is expressed in percentage and is expressed by the following equation [7-9].

\[ H_R = \frac{D_t}{D_b} \]

Where,
\(D_t\) is the tapped density of the powder and \(D_b\) is the bulk density of the powder.

Post Compression Parameters
Post compression parameters evaluated are thickness, hardness, friability, weight variation of the tablets. Further the tablets are subjected to the following evaluation parameters [8-10].

Drug Content Estimation
Five tablets are taken and crushed, drug equivalent to 100 mg is placed in a stoppered 100 ml conical flask and drug is extracted with 25 ml of phosphate buffer pH 6.8 and filtered into 100 ml volumetric flask through Whatman No.1 filter paper (Mean pore diameter 1.5 µm) and volume is made up to 100 ml. Aliquots of the solution are filtered and analyzed for drug content by measuring the absorbance at 222 nm.

Rupture Test
The lag time of pulsatile release tablets is defined as the time when the outer polymer layer coating starts to rupture. This was determined visually by using USP II paddle dissolution apparatus [11-15].

In vitro Dissolution Studies of the Coated Tablets
Drug release studies of coated tablets were carried out using USP XXIII dissolution test apparatus I. Initially tablets were placed in 900 ml of 0.1 N HCl for 2 h followed by pH 4.5 acetate buffer for 2 h and 6.8 pH phosphate buffer for 6 h maintained at 37±0.5 0c, 50 rpm. Aliquots of 5 ml were collected manually at predetermined intervals.
replacing with temperature maintained fresh buffer to maintain sink condition and analysed for drug content using a UV-visible spectrophotometer at \(\lambda\) max of 222 nm by using Lab India DS 8000 Dissolution Apparatus.

**Accelerated Stability studies**

A short term accelerated stability studies were performed for the best formulation by storing the tablets at 40°C/75% RH over a 3 months period according to ICH guidelines. At regular intervals for the period of three months, the tablets were examined for any physical characteristics, drug content and *in vitro* drug release [16].

**Results and Discussions**

**Fourier Transform Infrared Spectroscopic (FTIR) analysis**

FTIR spectrum (Fig.2) of MS (in KBr) showed a characteristic absorption peaks, bands and stretching, which were found in FTIR spectrum of MS and polymer blends and final formulation blends (Fig. 3, 4 and 5). It can be inferred that drug and the polymer do not exhibit significant chemical interaction and therefore, are compatible with each other.

![FTIR spectrum of Metoprolol succinate pure drug](image1)

**Fig 2. FTIR spectrum of Metoprolol succinate pure drug**

![FTIR spectrum of Metoprolol succinate with PVP K 30](image2)

**Fig 3. FTIR spectrum of Metoprolol succinate with PVP K 30**
The angles of repose (θ) for the blend of various formulations F1 to F9 was ranged from 26±0.23 to 29±0.25, indicating that the studied blends have excellent flow property. The values of loose bulk density and tapped bulk

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**Table 3. Pre compression parameters of formulation blend (core tablet blend)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle of Repose (θ)</td>
<td>28.25±0.13</td>
<td>27.02.25</td>
<td>27.10.20</td>
<td>26.10.23</td>
<td>26.10.45</td>
<td>28.10.25</td>
<td>29.10.20</td>
<td>29.10.25</td>
<td>28.10.45</td>
</tr>
<tr>
<td>Bulk Density (g/ml)</td>
<td>0.650±0.01</td>
<td>0.511±0.01</td>
<td>0.610±0.01</td>
<td>0.622±0.018</td>
<td>0.650±0.015</td>
<td>0.650±0.02</td>
<td>0.630±0.01</td>
<td>0.630±0.03</td>
<td>0.630±0.015</td>
</tr>
<tr>
<td>Tapped Density (g/ml)</td>
<td>0.750±0.015</td>
<td>0.611±0.015</td>
<td>0.710±0.026</td>
<td>0.724±0.02</td>
<td>0.751±0.026</td>
<td>0.750±0.015</td>
<td>0.712±0.02</td>
<td>0.751±0.009</td>
<td>0.731±0.02</td>
</tr>
<tr>
<td>Carr’s Index</td>
<td>13.3±0.20</td>
<td>18.3±0.37</td>
<td>14.08±0.95</td>
<td>13.95±0.62</td>
<td>13.44±0.33</td>
<td>13.3±0.810</td>
<td>13.93±0.53</td>
<td>16.11±0.199</td>
<td>13.89±0.755</td>
</tr>
<tr>
<td>Hausner’s Ratio</td>
<td>1.15±0.015</td>
<td>1.19±0.04</td>
<td>1.16±0.03</td>
<td>1.162±0.03</td>
<td>1.155±0.04</td>
<td>1.153±0.08</td>
<td>1.16±0.15</td>
<td>1.19±0.11</td>
<td>1.15±0.07</td>
</tr>
</tbody>
</table>

All values mentioned as mean ± S.D: Number of trials (n) = 3
densities were required to calculate Compressibility Index and Hausner’s ratio. The Carr’s Index and Hausner’s ratio indicates the good flow ability of the powder formulation. The results of the flow properties were shown in Table 3.

**Post Compression Parameters**

Table 4. Post compression parameters of formulated MS pulsatile tablets

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness (mm) (n=3)</td>
<td>F1 3.90±0.06, F2 3.78±0.005, F3 3.89±0.06, F4 3.80±0.06, F5 3.80±0.02, F6 3.80±0.04, F7 3.80±0.03, F8 3.40±0.05, F9 3.20±0.07</td>
</tr>
<tr>
<td>Weight variation (mg)</td>
<td>F1 131.5±0.1, F2 132.2±0.01, F3 133.2±0.1, F4 131.4±0.15, F5 130.1±0.15, F6 131.8±0.15, F7 131.6±0.2, F8 131.3±0.3, F9 131.3±0.1</td>
</tr>
<tr>
<td>Hardness (kg/cm²) n=3</td>
<td>F1 4.3±0.1, F2 4.3±0.1, F3 4.5±0.1, F4 4.4±0.1, F5 4.3±0.1, F6 4.3±0.1, F7 4.2±0.15, F8 4.4±0.15, F9 4.5±0.2</td>
</tr>
<tr>
<td>Friability Test</td>
<td>F1 0.28±0.01, F2 0.30±0.01, F3 0.27±0.01, F4 0.29±0.01, F5 0.28±0.01, F6 0.28±0.01, F7 0.27±0.01, F8 0.257±0.01, F9 0.28±0.01</td>
</tr>
<tr>
<td>Rupture Test(h)</td>
<td>F1 4.54±0.01, F2 5.67±0.01, F3 4.58±0.01, F4 4.11±0.01, F5 5.08±0.01, F6 6.45±0.01, F7 4.4±0.06, F8 4.68±0.16, F9 5.08±0.12</td>
</tr>
<tr>
<td>%Drug content Uniformity</td>
<td>F1 98.64±1.02, F2 99.2±1.82, F3 99.42±0.85, F4 98.41±0.62, F5 98.53±1.08, F6 98.02±0.96, F7 97.93±1.21, F8 99.78±1.05, F9 97.23±0.85</td>
</tr>
</tbody>
</table>

All values mentioned as mean ± S.D: Number of trials (n) = 3

The weight of the tablet varied between 130.1±0.15 to 133.2±0.1 mg. The variation in weight was within the range and complying with pharmacopoeial specifications. The thickness of tablets was ranged from 3.20±0.07 to 3.90±0.06mm. The hardness for different formulations was found to be more than 4 kg/cm² and passes the hardness test. The loss on friability was found to be less than 1%, indicates the formulated tablets have good mechanical strength. The drug content in all the formulations was found to be uniform. All these values were represented in Table 4. The drug release from formulated tablets was shown in Fig.6. This dissolution was treated with kinetic modeling viz., First order, Korsmeyer Peppas, Higuchi and Hixon Crowell’s modeling. The graphs were represented in Fig 7 to 10. The best formulation was subjected to accelerated stability studies as per ICH guidelines. The formulated tablets did not show any changes in all the characters before and after stressed storage conditions.
Fig 7. First order plots for the formulated tablets

Fig 8. Korsmeyer Peppa’s plots for the formulated tablets

Fig 9. Higuchi plots for the formulated tablets
Conclusion

This study concludes by cup in core technique of Metoprolol Succinate as core layer can be prepared as novel drug delivery systems with a coating layer of Benecil K 200M, HPMCK100 M and Eudragit RSPO for achieving controlled releasing of drug.

References