FORMULATION AND EVALUATION OF FAST DISINTEGRATING METOPROLOL SUCCINATE SUBLINGUAL TABLETS

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ABSTRACT
Metoprolol succinate is a potent cardio selective beta-1 adrenoreceptor blocker, mostly used in the treatment of acute disorders such as angina pectoris and hypertension. The main objectives of fast disintegrating sublingual tablet are that delivery of drug beneath the tongue and disintegrate rapidly within few minutes in presence of saliva. First pass hepatic metabolism can be overcome by sublingual drug delivery and quick drug entry into the systemic circulation can be obtained. In the present research the comparative study between cross carmellose sodium and sodium starch glycolate was performed. The fast disintegrating sublingual tablets were prepared by different concentration of super disintegrating agents such as sodium starch glycolate (2%, 4%, 5%, and 6%) and cross carmellose sodium (2%, 4%, 5%, and 6%) by direct compression technique. The compatibility study of drug and excipients was performed by FTIR spectroscopy. The powder mixture of Metoprolol succinate and other ingredients was evaluated for various physical properties such as bulk density, tapped density, angle of repose, carr’s compressibility index and hausner’s ratio. The sublingual tablets were evaluated by different parameters such as hardness, friability, weight variation, drug content uniformity, wetting time, water absorption ratio, disintegration time and in vitro drug release. The disintegration time of optimized formulation (F7) was upto 24 sec and in vitro drug release of Metoprolol succinate was upto 3 minutes. The optimized formulation containing 5% cross carmellose sodium which gives better swelling and wicking properties offers effective drug dissolution.

Keywords: Sublingual tablet, Metoprolol succinate, Angina pectoris, Hypertension, Comparative study between cross carmellose sodium and sodium starch glycolate, Fast disintegrating tablet.

INTRODUCTION
The oral route of administration is considered as the most widely accepted and flexible route because of its convenience of self administration, compactness and easy manufacturing. Major drawback of oral dosage form is that dysphasia (difficulty in swallowing) is a common problem for all age group, especially elderly, children, and patients who are mentally retarded, uncooperative, nauseated lead to difficulties in swallowing of these dosage forms. [1]
Fast disintegrating sublingual tablet is a delivery of drug beneath the tongue and disintegrate rapidly within few minutes in presence of saliva. The sublingual dosage form offers fast release of drug from the formulation and it reaches the systemic circulation directly, which bypasses the metabolism of the Metoprolol succinate into the liver and offers a fast relieve from the anginal pain and hypertension. It also enhances the bioavailability. So, without need of swallowing, we can achieve fast release of drug. However, for acute disorders, the time to onset of action for a conventional oral tablet is generally not acceptable. So, The Sublingual drug delivery is most acceptable.\(^2\)

Angina pectoris is acute disorder characterized by chest pain or discomfort due to coronary heart disease. Hypertension (HTN) is a chronic medical condition in which the blood pressure in the arteries is elevated.\(^3,4\)

Metoprolol succinate is a cardio selective beta-1 adrenoreceptor blocker mostly used in the treatment of acute disorders such as angina pectoris and hypertension. It is a BCS (Biopharmaceutical Classification System) class-I drug. It has high solubility and high permeability. Metoprolol succinate is freely soluble in water and methanol. The half life of Metoprolol succinate is approximately 3 to 4 hours. It undergoes extensive first pass hepatic metabolism resulting in 40% oral bioavailability. Hence the prepared sublingual tablet of Metoprolol succinate lead to enhance the bioavailability and avoidance of first pass hepatic metabolism.\(^5\)

**MATERIALS AND METHODS**

Metoprolol succinate (Alembic Pharma, Vadodara), mannitol (Directly compressible material), microcrystalline cellulose (diluent and disintegrating agent), sodium starch glycolate (super disintegrating agent), cross carmellose sodium (super disintegrating agent), polyvinyl-pyrrolidone K-30 (binder), sodium saccharine (sweetener) and talc (lubricant).

**Formulation of Fast Disintegrating Sublingual Tablets:**

Sublingual tablets of Metoprolol succinate were prepared by direct compression method. Accurate amount of the active ingredients and all additives were homogenously blended using geometric dilution after passing through 40# sieve and talc was added at last for lubrication and mix thoroughly into polythene bag. Finally, the tablets were prepared by using 7 mm flat punch by rotary tablet punching machine.\(^6,7\) (Table 1)
TABLE 1: FORMULATION OF BATCH F1 TO F8 BY DIRECT COMPRESSION METHOD

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulation code (Quantity in mg/tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>12.5</td>
</tr>
<tr>
<td>Mannitol</td>
<td>64</td>
</tr>
<tr>
<td>MCC</td>
<td>18</td>
</tr>
<tr>
<td>SSG</td>
<td>2</td>
</tr>
<tr>
<td>CCS</td>
<td>-</td>
</tr>
<tr>
<td>PVP K-30</td>
<td>1.5</td>
</tr>
<tr>
<td>Sodium saccharine</td>
<td>1</td>
</tr>
<tr>
<td>Talc</td>
<td>1</td>
</tr>
<tr>
<td>Total weight of tablet (mg)</td>
<td>100</td>
</tr>
</tbody>
</table>

MCC - Microcrystalline cellulose, SSG - Sodium starch glycolate, CCS - Cross carmellose sodium, PVP- Polyvinyl-pyrrolidone

Pre-formulation study:
The pure drug Metoprolol succinate and the solid admixture of drug and various excipients used in the preparation of sublingual tablet formulations were characterized by FT-IR spectroscopy for drug-excipients compatibility.[6, 7] (Figure 6 and 7)

Micromeritic properties of Metoprolol succinate powder formulations:
The flow properties were evaluated by different parameters such as bulk density, tapped density, angle of repose, carr’s compressibility index and hausner’s ratio.[8] (Table 2)

Bulk density:
Apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume and weight of the powder was determined.[8, 9]

It is determined by following equation,

$$\rho_b = \frac{W}{V_b}$$

Where, $\rho_b$ = Bulk density, $V_b$ = Bulk volume of blend (cm$^3$), $M$ = Weight of powder (gm).
Tapped density:
The measuring cylinder containing a known mass of blend was tapped for a fixed time (100 tapping). The minimum volume occupied in the cylinder and weight of the blend was measured.[8, 9]
It is determined by following equation,
\[ \rho_t = \frac{W}{V_t} \]
Where, \( \rho_t \) = Tapped density, \( V_t \) = Final volume of blend after tapping (cm\(^3\))

Angle of repose:
Angle of repose was determined using funnel method. Funnel was set at a height of 2 cm from the surface. The blend was discharged from the funnel until the tip of pile of powder touches the lower end of funnel. Radius of the heap was measured and angle of repose was calculated.[8, 9]
It is determined by following equation,
\[ \tan \theta = \frac{h}{r} \]
Therefore, \( \theta = \tan^{-1} \left( \frac{h}{r} \right) \)
Where, \( \theta \) = Angle of repose, \( h \) = Height of pile of powder blend, \( r \) = Radius of heap

Carr’s compressibility index:
Carr’s compressibility index is determined by following equation.[8,9]
\[ C = \frac{\rho_t - \rho_b}{\rho_t} \times 100 \]
Where, \( C \) = % compressibility, \( \rho_b \) = Bulk density, \( \rho_t \) = Tapped density

Hausner’s Ratio:
This is an indirect index of ease of powder flow.[9]
It is calculated by following formula;
\[ H = \frac{\rho_t}{\rho_b} \]

Evaluation of Tablets:

Appearance:
Tablets were evaluated for shape, colour, odor, taste etc.[8]

Thickness and Diameter:
The size of tablets was evaluated by Vernier calipers.[8] (Table 3)

Hardness:
The tablet crushing strength was determined by applying a force that is required for breaking of a tablet into two halves. This was measured using Monsanto hardness tester. Three tablets were randomly selected from each formulation and the average hardness was noted.\(^7\) (Table 3)

**Friability:**
This test was performed to determine the effects of friction and shock. Pre-weighed sample of six tablets was placed in the friabilator (roche friabilator) and rotated at 25 rpm (rotation per minute) for 4 minutes. The tablets were dedusted and reweighed, and the percentage friability was calculated. Compressed tablets should not lose more than 1% of weight.\(^{6,7,9,11}\) (Table 3)

\[
\% \text{ Friability} = (W_{\text{initial}} - W_{\text{final}} / W_{\text{initial}}) \times 100
\]

Where, \(W_{\text{initial}}\) = Initial weight of tablet, \(W_{\text{final}}\) = Final weight of tablet

**Weight variation:**
Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of weight was calculated.\(^6\) (Table 3)

**Wetting Time:**
The wetting time was measured using a simple procedure. A piece of tissue paper was cut circularly (6.5 cm diameter) and placed on a petridish containing 6 ml of water at room temperature.\(^{6,7,12}\) (Table 4)

A tablet is placed on the surface of the tissue paper and the time required for the complete wetting of the tablet was noted. (Figure 1)

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![Image of wetting time](image-url)

At 0 sec  After 10 sec  After 18 sec

**Figure 1:** Wetting time of tablet
Water Absorption Ratio:
A piece of tissue paper folded twice was kept in a petridish (internal diameter 6.5cm) containing 6 ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The wetted tablet was removed and reweighted.\(^{[9]}\) (Table 4)

Water absorption ratio (R) is determined by the following equation:

\[
R = 100 \left( \frac{W_a - W_b}{W_b} \right)
\]

Where, \(W_b\) = Weight of tablet before absorption, \(W_a\) = Weight of tablet after absorption.

Drug Content Uniformity:
Here, 12.5 mg drug is present in 100 mg tablet. 10 tablets were crushed thoroughly, using mortar and pestle. The crushed tablet powder equivalent to 10.0 mg of drug was dissolved in 100 ml phosphate buffer solution pH 6.8. Then 10 ml from this solution was diluted with 100 ml phosphate buffer solutions pH 6.8. Measure the absorbance at 222 nm by using UV visible spectrophotometer. (Table 4)

Disintegration time:
1. Official method as per USP:

In vitro disintegration time was determined using a modified disintegration method (n=5) by using disintegration tester (Today tech, India) at 37±0.5°C in distilled water. The tablet was carefully kept in a basket without covering plastic disks and 2 minutes is specified as the acceptable time limit for tablet disintegration.\(^{[7,13]}\) (Table 4)

2. Modify Disintegration Test I (Petri Plate Method):

The disintegration time for fast disintegrating tablets needs to be modified as disintegration is required without water, should mimic disintegration in salivary contents. For this purpose, a petridish (10 cm diameter) was filled with 10 ml of water.\(^{[8,14,15,16]}\)

The tablet was carefully put in the centre of Petri dish and the time for the tablet to completely disintegrate into fine particles was noted. (Table 5 and Figure 2)

3. Modified Disintegration Test Method II (Basket Method):

This test was carried by placing the fast disintegrating tablets in the basket of the USP dissolution basket type apparatus. Water was dropped on it from a burette at a rate of 4 ml per minute.\(^{[8,14,15,16]}\)

The time taken by the tablet to break into particles and pass down through the mesh of the basket was noted as disintegration time. Modified disintegration type test II was
found to be performed to mimic the less amount of volume of the disintegrating medium present in the mouth. (Table 5 and Figure 3)

4. Modified Disintegration Test Method III (Measuring Cylinder Method):
In this simplest method, 6 ml of phosphate buffer of pH 6.8 was taken in a 25 ml measuring cylinder. Temperature was maintained at 37±2°C.\[8, 16, 17\]
The tablets were put into it and time required for complete disintegration was noted. (Table 5 and Figure 4)

**In-vitro dispersion time:**
The in- vitro dispersion time was measured by dropping tablet in a beaker containing 100 ml of water and stirring gently.\[9,10\] (Table 4 and Figure 5)
The time for the tablet to completely disperse into fine particles was noted.

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**Figure 2: Petri plate method**

**Figure 3: Basket method**

**Figure 4: Measuring cylinder method**

**Figure 5: In-vitro dispersion time**
In-vitro dissolution Studies:
Dissolution studies were carried out for all the formulation in USP paddle method (Apparatus 2) using Phosphate buffer pH 6.8, in the dissolution medium (300 ml) at 50 RPM and 37±0.5°C.[2, 7]
Samples were periodically withdrawn at suitable time intervals and volume was replaced with equivalent amounts of plain dissolution medium. The samples were analyzed by UV visible spectrophotometer at 222 nm. (Figure 6)

RESULTS
The pre-formulation study was performed by FTIR spectroscopy and found that there was no any interaction between Metoprolol succinate and excipients. (Figure 6 and 7)

Figure 6: Metoprolol Succinate (pure drug) FTIR spectrum

Figure 7: Mixture (Metoprolol succinate and excipients) FTIR spectrum
TABLE 2: EVALUATION OF MICROMERITIC PROPERTIES POWDER FORMULATIONS

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Formulation code</th>
<th>Bulk density</th>
<th>Tapped density</th>
<th>Angle of repose</th>
<th>Carr's compressibility index</th>
<th>Hausner ratio</th>
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<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>0.521</td>
<td>0.625</td>
<td>28.8</td>
<td>16.64</td>
<td>1.19</td>
</tr>
<tr>
<td>2</td>
<td>F2</td>
<td>0.529</td>
<td>0.626</td>
<td>28.8</td>
<td>15.49</td>
<td>1.18</td>
</tr>
<tr>
<td>3</td>
<td>F3</td>
<td>0.528</td>
<td>0.62</td>
<td>30.9</td>
<td>14.83</td>
<td>1.17</td>
</tr>
<tr>
<td>4</td>
<td>F4</td>
<td>0.523</td>
<td>0.632</td>
<td>30.1</td>
<td>17.24</td>
<td>1.20</td>
</tr>
<tr>
<td>5</td>
<td>F5</td>
<td>0.521</td>
<td>0.623</td>
<td>30.1</td>
<td>16.37</td>
<td>1.19</td>
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<tr>
<td>6</td>
<td>F6</td>
<td>0.523</td>
<td>0.62</td>
<td>30.4</td>
<td>15.64</td>
<td>1.18</td>
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<tr>
<td>7</td>
<td>F7</td>
<td>0.521</td>
<td>0.62</td>
<td>29.6</td>
<td>13.33</td>
<td>1.15</td>
</tr>
<tr>
<td>8</td>
<td>F8</td>
<td>0.521</td>
<td>0.62</td>
<td>30.1</td>
<td>15.96</td>
<td>1.19</td>
</tr>
</tbody>
</table>

TABLE 3: EVALUATION OF TABLETS

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Hardness (kg/cm²)</th>
<th>Thickness (mm)</th>
<th>Diameter (mm)</th>
<th>% Friability</th>
<th>Weight variation (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>3.5±0.25</td>
<td>1.89±0.02</td>
<td>6.74±0.03</td>
<td>0.87±0.01</td>
<td>103±0.50</td>
</tr>
<tr>
<td>F2</td>
<td>3.6±0.25</td>
<td>1.87±0.03</td>
<td>6.73±0.01</td>
<td>0.79±0.02</td>
<td>103.8±0.45</td>
</tr>
<tr>
<td>F3</td>
<td>3.5±0.20</td>
<td>1.88±0.03</td>
<td>6.74±0.03</td>
<td>0.71±0.01</td>
<td>104.2±0.38</td>
</tr>
<tr>
<td>F4</td>
<td>3.6±0.24</td>
<td>1.89±0.02</td>
<td>6.72±0.02</td>
<td>0.81±0.03</td>
<td>103.6±0.36</td>
</tr>
<tr>
<td>F5</td>
<td>3.5±0.18</td>
<td>1.87±0.01</td>
<td>6.76±0.01</td>
<td>0.77±0.01</td>
<td>103.3±0.50</td>
</tr>
<tr>
<td>F6</td>
<td>3.7±0.26</td>
<td>1.86±0.02</td>
<td>6.74±0.02</td>
<td>0.75±0.02</td>
<td>104.3±0.31</td>
</tr>
<tr>
<td>F7</td>
<td>3.6±0.23</td>
<td>1.89±0.02</td>
<td>6.75±0.01</td>
<td>0.79±0.01</td>
<td>103.4±0.45</td>
</tr>
<tr>
<td>F8</td>
<td>3.6±0.22</td>
<td>1.85±0.04</td>
<td>6.74±0.02</td>
<td>0.86±0.01</td>
<td>103.7±0.50</td>
</tr>
</tbody>
</table>
TABLE 4: DISINTEGRATION TIME, WETTING TIME, WATER ABSORPTION RATIO AND DRUG CONTENT UNIFORMITY OF FORMULATION F1 TO F8

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Wetting time (sec)</th>
<th>Water absorption ratio</th>
<th>Disintegration time (sec)</th>
<th>In-vitro dispersion time (sec)</th>
<th>% Drug content uniformity</th>
<th>Cumulative % drug release (%CCR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>41</td>
<td>48.5</td>
<td>150</td>
<td>46</td>
<td>99.28</td>
<td>105.25</td>
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<tr>
<td>F2</td>
<td>38</td>
<td>55.3</td>
<td>68</td>
<td>43</td>
<td>101.42</td>
<td>103.54</td>
</tr>
<tr>
<td>F3</td>
<td>32</td>
<td>69.6</td>
<td>60</td>
<td>39</td>
<td>102.85</td>
<td>102.68</td>
</tr>
<tr>
<td>F4</td>
<td>28</td>
<td>61.7</td>
<td>55</td>
<td>35</td>
<td>99.64</td>
<td>100.11</td>
</tr>
<tr>
<td>F5</td>
<td>23</td>
<td>72</td>
<td>101</td>
<td>28</td>
<td>102.5</td>
<td>103.54</td>
</tr>
<tr>
<td>F6</td>
<td>21</td>
<td>71.7</td>
<td>36</td>
<td>25</td>
<td>98.92</td>
<td>101.22</td>
</tr>
<tr>
<td>F7</td>
<td>18</td>
<td>79.4</td>
<td>24</td>
<td>20</td>
<td>101.78</td>
<td>101.65</td>
</tr>
<tr>
<td>F8</td>
<td>20</td>
<td>78.4</td>
<td>28</td>
<td>22</td>
<td>99.28</td>
<td>102.68</td>
</tr>
</tbody>
</table>

TABLE 5: COMPARATIVE STUDIES OF DISINTEGRATION TIME BETWEEN CROSS CARMELLOSE SODIUM AND SODIUM STARCH GLYCOLATE

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Method</th>
<th>Disintegration time (seconds)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>5 % CCS</td>
</tr>
<tr>
<td>1</td>
<td>Official method as per USP</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>Petri Plate Method</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>Basket Method</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>Measuring Cylinder Method</td>
<td>63</td>
</tr>
</tbody>
</table>
DISCUSSION

The use of superdisintegrant for the preparation of fast dissolving sublingual tablet is highly effective and easily available. These super disintegrants such as sodium starch glycolate and cross carmellose sodium when comes in to contact with aqueous environment, leads to swell and breaking of tablet. So, enhances the drug release from the formulation.

The micromeritic properties powder formulations such as angle of repose, bulk density, tapped density, carr’s compressibility index etc. were carried out. (Table 2)

The Formulation (F7) considered as optimized formulation. The hardness of tablets found was between 3.6 to 3.8 kg/cm². Percentage friability was observed between 0.71 to 0.87 %, which was within acceptable limit. Weight variation of tablets was found within acceptable limit as per united state of pharmacopeia (Table 3).

Wetting time for all formulations was found to be 18 to 41 seconds. The water absorption ratios for all formulations were found to be 48% to 80%. The in vitro disintegration time for all formulation was found to be 24 to 150 seconds. Percentage drug content of all the formulations was found to be 98.51 to 99.83 of drug which was within acceptable limit. The formulation F7 showed rapid wetting time, water absorption ratio and disintegration time because of more swelling and wicking action of CCS than SSG. (Table 4)
Hence, we can conclude that 5% cross carmellose sodium gives more swelling and wicking properties than 5% sodium starch glycolate (Table 5).

In vitro dissolution of formulation F7 showed better drug release within 3 minutes. Formulation F7 is considered as optimized formulation because of rapid disintegration time and *in vitro* dissolution profile. (Figure 8)

**CONCLUSION**

The fast disintegrating sublingual dosage form of Metoprolol succinate offers fast release of drug beneath the tongue and it reaches the systemic circulation directly with improved patient compliance particularly for those who have difficulty in swallowing.

From the above results we can concluded that 5% cross carmellose sodium gives more swelling and wicking properties than 5% sodium starch glycolate.

**ACKNOWLEDGMENT**

The authors thank Alembic Pharma, Vadodara for supplying gift samples of Metoprolol succinate to carry out this work. We are also thankful to management of RK University, Rajkot for providing infrastructure and facilities for conducting this research work.

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