FORMULATION AND EVALUATION OF FAST DISSOLVING SUBLINGUAL FILM OF METOPROLOL SUCCINATE

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ABSTRACT

Metoprolol succinate is a potent cardio selective beta-1 adrenoreceptor blocker, mostly used in the treatment of cardiovascular disorders such as angina pectoris and hypertension. The main objectives of fast disintegrating sublingual film are that delivery of drug beneath the tongue and disintegrate rapidly within few minutes in presence of saliva. First pass hepatic metabolism of Metoprolol succinate can be overcome by sublingual delivery and quick drug entry into the systemic circulation can be obtained. In present research work sublingual films were prepared by different concentration of Methanol: Water ratios 30:20, 25:25, 20:30 used. Different formulations were prepared by varying concentration of (HPMC K4M and methanol: Water) ratio by solvent casting method. The compatibility study of drug and excipients was performed by DSC study and no interaction was found. The prepared formulations were evaluated for various parameters like thickness, tensile strength, folding endurance, % elongation, weight variation, % drug content, disintegration time, and in vitro dissolution study. The prepared films were clear, transparent and smooth surface. Optimized batch F6 containing containing hydroxy propyl methyl cellulose (3.00%) and methanol: water (30:20) showed in vitro drug release within 4 minutes.

Keywords: Hypertension and angina pectoris, Metorolol succinate, Fast dissolving sublingual Film, HPMC K4M, PEG400, Methanol.

INTRODUCTION

Many pharmaceutical dosages are administered in the form of pills, granules, powders, and liquids. The pills, which include tablets and capsules, are able to retain their shapes under moderate pressure. However, some patients, particularly pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms due to fear of choking. Hence orally dissolving tablets have come into existence. Even with these differences, most of the existing oral dissolving drug delivery systems are in the form of solid tablets and designed to dissolve/disintegrate in the patient's mouth without the need to drink or chew. However, the fear of taking solid tablets and the risk of choking for certain patient populations still exist despite their short disintegration/dissolution times. Hence oral film drug delivery is a better alternative in such cases[1-5].
The delivery system consists of a very thin oral strip, which is simply placed on the patient’s tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed [6-8].

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-1 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 [27-30]

**MATERIALS AND METHODS**

**Materials:**

Metorolol succinate was obtained as gift sample from Alembic Pharma, Vadodara, India. The HPMC K4M was purchased from Astron Chemicals, Naroda, and Ahemadabad. PEG400 was purchased from Oxford Laboratory, Mumbai, India. Methanol was received
All other materials used were of analytical grade.

**Methods:**

**Calculation of Diameter of Petridish:-**

Diameter of Petridish:

Radius of the Petridish = 9 cm
Diameter = Radius/2 = 9/2 = 4.5 cm.

\[ \pi r^2 = 3.14 \times 4.5 \times 4.5 = 63.585 \text{ cm}^2 \]

Now, Dose is 12.5 mg and Cut the pieces in 2 cm x 2 cm = 4 cm

4 cm\(^2\) contain 12.5 mg Drug

So, 63.585 cm\(^2\) contain (?) Drug = 198.68 mg Drug

25 ml contain 198.68 mg Drug

Then, 50 ml contain = (?) Drug = 496 mg Drug

**Preparation of blank Films\(^{[15]}\):**

Polymers were accurately weighed and dissolved in respective solvent and then add PEG400 as a Plastsizer and casted in a glass petridish using castor oil as a lubricant. The films were allowed to dry at a normal room temperature for 24 hour.

**Formulation of Metorolol succinate fast dissolving films\(^{[15]}\):**

Weight accurate amount of polymer and socked in water for overnight. Metorolol succinate is dissolved in required quantity of Methanol. Mix the solution and add PEG 400 as a plasticizer. Heat the solution and keep standing for half an hour to get the proper viscosity. Stir the solution continuously and sonicate the solution for 15 mins to remove the air bubbles. Then keep the solution overnight and next day casting procedure carried out. Next day, lubricate the petridish with help of castor oil. Pour the solution in petridish and keep it overnight for proper drying. After complete drying of film with the help of cutter carefully take out it and wrap in aluminum foil. Store the film in the normal room temperature.
TABLE 1: FORMULATION OF METOROLOL SUCCINATE FAST DISSOLVING FILMS

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Drug (mg)</th>
<th>HPMC (gm)</th>
<th>K4MPEG (ml)</th>
<th>4000 Methanol (ml)</th>
<th>Water (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>496</td>
<td>1.8</td>
<td>1</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>F2</td>
<td>496</td>
<td>1.8</td>
<td>1</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>F3</td>
<td>496</td>
<td>1.8</td>
<td>1</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>F4</td>
<td>496</td>
<td>1.5</td>
<td>1</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>F5</td>
<td>496</td>
<td>1.5</td>
<td>1</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>F6</td>
<td>496</td>
<td>1.5</td>
<td>1</td>
<td>20</td>
<td>30</td>
</tr>
</tbody>
</table>

Figure 2: Fast Dissolving Sublingual Film of Metoprolol succinate

Drug polymer compatibility studies [8-10]:

Drug polymer compatibility studies were carried out using DSC.

UV Spectrum Analysis of Metorolol succinate [11]:

The solution was scanned in the range of 200 to 400 nm to fix the maximum wave length and UV spectrum was obtained.

Standard calibration curve of Metorolol succinate in pH 6.8 [13]:

Accurately weighed 100 mg of Metoprolol succinate was dissolved in 100 ml of phosphate buffers pH 6.8 (Stock solution). Then 10 ml of this stock solution was taken in a 100 ml volumetric flask and volume was made up to the mark with phosphate buffer pH 6.8. Then, 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 ml of above solution was transferred in a 100 ml volumetric flask and volume was made up to the mark with phosphate buffer solution pH 6.8 to make 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 µg/ml concentration.
Absorbances of above samples were determined at 222 nm wavelength using UV spectrophotometer and plotted against concentration. The concentration range over which the drugs obeyed Beer’s law was chosen.

**EVALUATION PARAMETER OF FAST DISSOLVING SUBLINGUAL FILM**

**Thickness**[^14]

The thickness of the film was measured using digital Vernier Calliper with a least count of 0.01 mm at different spots of the film. The thickness was measured at three different spots of the film and average was taken and Standard Deviation was calculated.

**Weight variation**[^12]

Four centimeter square (2 X 2 cm) of the film was cut at three different places from the casted film. The weight of each film was taken and weight variation was calculated.

**Folding endurance**[^21]

Folding endurance was determined by repeated folding of the film at the same place till the strip breaks. The number of times the film is folded without breaking was computed as the folding endurance value.

**Tensile strength**[^22]

Tensile testing was conducted using the modified method. The film was cut into 30 × 20 mm strips. Each test strip was stick on the surface of Glass slide with the help of Feviquick. Initial grip separation was 20 mm. The test was considered concluded when the film breaks. Tensile strength, was computed with help of load require to break the film and cross sectional area to evaluate tensile properties of the films.

**Tensile strength (TS)**

Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be calculated by dividing the maximum load by the original cross-sectional area of the specimen and it was expressed in force per unit area (MPa).

\[
\text{Tensile Strength} = \frac{\text{Force at break (N)}}{\text{Cross sectional area (mm}^2\text{)}}
\]

**Percentage elongation**[^22]

For the determination of percentage elongation of the film formulations, the distance between the tensile grips of the tensile strength testing film was measured before and after the fracture of the film. Then the percentage elongation of the films was computed with the help of the formula given below:-
\[
\% E = D_f - D_0 / D_0 \times 100
\]

Where:-
\[
\% E = \text{Percentage elongation}
\]

\(D_0\) = Distance between the tensile grips before the fracture of the film.
\(D_f\) = Distance between the tensile grips after the fracture of the film

**Surface pH**[^32]

The surface pH of fast dissolving film was determined in order to investigate the possibility of any side effect in vivo. As an acidic or alkaline pH may cause irritation of the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. Oral film was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film. The procedure was performed in triplicate and average with standard deviation was reported.

**Disintegration Time**[^36]

In vitro disintegration time was determined visually in a petri dish containing 25 ml of pH 7.2 artificial saliva with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates.

**% Drug Content**[^37]

Drug content determination of the film was carried out by dissolving the film of 4 cm\(^2\) in 100 ml of pH 7.2 artificial saliva using magnetic stirrer for 1 hour. The drug concentration was then evaluated spectrophotometrically at \(\lambda_{\text{max}}\) of 222 nm. The determination was carried out in triplicate for all the formulations and average with standard deviation was recorded.

**In vitro dissolution**[^38]

The dissolution study was carried out using USP Type I (Basket type) dissolution apparatus. The dissolution was carried out in 900 ml of pH 7.2 artificial saliva maintained at 37 °C at 50 rpm. 10 ml aliquots of samples were taken at various time intervals which were replaced with same volume of fresh pH 7.2 artificial saliva maintained at 37°C. Metorolol succinate in the samples was then determined spectrophotometrically at \(\lambda_{\text{max}}\) of 222 nm. The results were expressed as mean of three determinations.
RESULTS AND DISCUSSION

Determination of $\lambda_{\text{max}}$ of Metoprolol succinate in phosphate buffer pH 6.8

Figure 3: Standard Calibration Curve of Metoprolol Succinate in Phosphate Buffer pH 6.8

The Metoprolol succinate showed $\lambda_{\text{max}}$ at 222 nm in phosphate buffer pH 6.8.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Concentration (µg/ml)</th>
<th>Absorbance (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>0.089</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>0.145</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>0.200</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>0.255</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>0.313</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>0.381</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>0.424</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>0.466</td>
</tr>
<tr>
<td>9</td>
<td>18</td>
<td>0.542</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>0.600</td>
</tr>
</tbody>
</table>
The concentration range over which the drugs obeyed Beer’s law was chosen from the standard calibration curve. The range was found to be 2.0 to 20.0 µg/ml for Metoprolol Succinate. The Co-efficient of correlation value was found to be 0.998, which shows linearity between plotted values of absorbances and concentration.

**Compatibility Study:**

The compatibility study was performed by Differential Scanning Calorimetry (DSC) and found that there was no any interaction between Metoprolol succinate and excipients (Figure 2 and 3).

**Figure 4:** Linearity relationship Between Absorbance vs Concentration

**Figure 5:** DSC Study of Metoprolol succinate (pure drug)
Figure 6: DSC Study of Metoprolol succinate (pure drug) and Polymer (HPMC K4M)

Evaluation Parameter of Fast Dissolving Sublingual Film:

TABLE 3: EVALUATION PARAMETER OF THICKNESS, WEIGHT VARIATION, SURFACE PH, DISINTEGRATION TIME AND FOLDING ENDURANCE

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Thickness (mm)</th>
<th>Weight (mg)/4cm²</th>
<th>Surface PH</th>
<th>Disintegration Time in sec (starts)</th>
<th>Folding Endurance (no. of times to break)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.100±0.0057</td>
<td>49.33±0.471</td>
<td>7.03±0.152</td>
<td>25.33±0.57</td>
<td>201±3.60</td>
</tr>
<tr>
<td>F2</td>
<td>0.113±0.0057</td>
<td>51.33±0.471</td>
<td>7.10±0.100</td>
<td>23.66±0.57</td>
<td>212±2.08</td>
</tr>
<tr>
<td>F3</td>
<td>0.080±0.0000</td>
<td>62.33±0.471</td>
<td>7.06±0.057</td>
<td>19.66±0.57</td>
<td>220±5.00</td>
</tr>
<tr>
<td>F4</td>
<td>0.093±0.0057</td>
<td>64.66±0.471</td>
<td>7.06±0.057</td>
<td>22.33±0.57</td>
<td>229±7.50</td>
</tr>
<tr>
<td>F5</td>
<td>0.126±0.0057</td>
<td>66.66±0.471</td>
<td>7.16±0.057</td>
<td>19.00±1.73</td>
<td>241±9.07</td>
</tr>
<tr>
<td>F6</td>
<td>0.150±0.0000</td>
<td>60.33±0.471</td>
<td>6.90±0.100</td>
<td>17.66±0.57</td>
<td>249±6.55</td>
</tr>
</tbody>
</table>
Thickness:-
As all the formulations contain different amount of polymers, hence the thickness was gradually increases with the amount of polymers. All the film formulations were found to have thickness in the range of 0.080 mm to 0.150 mm.

Weight variation:-
Three films each of 4 cm² were cut at three different places from the casted film and weight variation was determined. Weight variation varies from 49.33 mg to 66.66 mg.

Surface pH:-
The surface pH of the films was ranging from 6.90 to 7.10. Since the surface pH of the films was found to be around the neutral pH, there will not be any kind of irritation to the mucosal lining of the oral cavity.

Folding endurance:-
Folding endurance increases with increasing with the concentration of polymer. The number of time the film fold until it broke is reported.

Disintegration Time:-
It was observed that disintegration time varies from 17 to 25 sec for all the formulations. Disintegration time of Fast Dissolving Film containing HPMC K4M as polymer was affected by the thickness of the film. Disintegration time of the films was found to increase with increase in the amount of the polymer.

### TABLE 4: EVALUATION PARAMETER OF TENSILE STRENGTH, PERCENTAGE ELONGATION, DRUG CONTENT AND IN VITRO DRUG RELEASE.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Tensile strength (M Pa)</th>
<th>Percentage elongation (mm)</th>
<th>Drug Content</th>
<th>In vitro Drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.87</td>
<td>5</td>
<td>99.56±0.23</td>
<td>99.26±0.01</td>
</tr>
<tr>
<td>F2</td>
<td>1.25</td>
<td>8</td>
<td>99.23±0.25</td>
<td>99.45±0.02</td>
</tr>
<tr>
<td>F3</td>
<td>2.26</td>
<td>10</td>
<td>101.23±0.24</td>
<td>98.23±0.06</td>
</tr>
<tr>
<td>F4</td>
<td>3.56</td>
<td>11</td>
<td>99.26±0.26</td>
<td>97.23±0.04</td>
</tr>
<tr>
<td>F5</td>
<td>3.75</td>
<td>13</td>
<td>99.48±0.28</td>
<td>100.23±0.04</td>
</tr>
<tr>
<td>F6</td>
<td>4.00</td>
<td>15</td>
<td>100.32±0.23</td>
<td>99.98±0.01</td>
</tr>
</tbody>
</table>
Tensile strength:-
The tensile strength was found to increase with increase with concentration of HPMC K4M whereas the increase in the concentration of PEG 400 leads in the decrease in the tensile strength. The tensile strength of formulation F9 was found maximum 4.0.

Percentage elongation:-
The percentage elongation of all the batches ranges from 5-20. It increased upon increasing the amount of plasticizer and polymer as shown by the formulations. Formulation F9 had highest percentage elongation.

Drug Content:-
The prepared film formulations were assayed for drug content. It was observed that all the formulations were satisfactory showing drug content as per labeled amount.

In vitro Dissolution study:-
In vitro drug release profiles of the formulations in pH 7.2 artificial saliva show differences depending on their composition as given in table. A rapid dissolution of all the film preparations was observed by the dissolution test, in which approximately 99% of Metorolol succinate within 10 min. The formulations F1 to F6 showed approximately 95 to 99% drug release within 10 minutes. It was also observed that HPMC K4M was
able to modulate the Metorolol succinate release as lower amount of HPMC K4M resulted in release of drug a faster rate.

**CONCLUSION**

The fast disintegrating sublingual dosage form of Metorolol 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 3 % HPMC K4M gives immediate release of drug as compare to other formulation batch.

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**REFERENCES**

9. Chang R, Goo X, Burnside BA, Couch R. Fast-dissolving tablets, Pharm Tech,


15. Dr Breitkreutz jorg, Heinrich-Heine-University Dusseldorf, Institute of Pharmaceutics and Bio pharmaceutics, University 1, 40225 Dusseldorf, Germany, Pharmaceutical Medicine.


24. Guidance for industry: Orally disintegrating tablets, Center for drug evaluation and research (Centre for drug evaluation and research, CDER) US FDA,
films for oral dosage from natural polysaccharides.” Materials. 2010, 3(8), 4291-4299.


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