DESIGN AND EVALUATION OF TIMOLOL MALEATE BUCCAL PATCHES USING TWEEN AS PERMEATION ENHANCER

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ABSTRACT

A mucoadhesive drug delivery system for systemic delivery of Timolol Maleate, antihypertensive (β blocker) through buccal mucosa in the form of patches was formulated. Mucoadhesive polymers such as Eudragit RL100, Eudragit RS100 and HPMC K15M were used to formulate the patches. In order to increase the permeation capacity of the drug, three grades of Tween were used – Tween 40, Tween 60 and Tween 80 as permeation enhancer. The prepared patches were evaluated for various evaluation parameters such as weight uniformity, thickness, folding endurance, swelling index, content uniformity and In vitro drug release. Based on the results obtained from the evaluation, it was concluded that patches made from Eudragit RL100 shows good drug release while the patches made from HPMC K15M shows excessive control release. Tween 40 does not act more efficiently as permeation enhancer while Tween 60 and Tween 80 do so. Formulation T3 was considered as the best among the other formulations.
INTRODUCTION:
Although the oral administration of drugs has been the preferred route of administration for the patients and clinicians, certain disadvantages such as hepatic first pass metabolism, gastric irritation, and enzymatic degradation within the gastrointestinal tract have been identified [1]. In order to overcome from these disadvantages new technologies are carried out. Over the last two decades mucoadhesion has become of interest for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (e.g. within gastrointestinal tract) or systemic delivery, by retaining a formulation in intimate contact with the absorption site (e.g. the buccal cavity) [2].
Mucoadhesion is a state in which two materials, one of which is mucous or a mucous membrane is held together for an extended period of time. Various mucoadhesive polymers have been investigated and identified are generally hydrophilic macromolecules that contain numerous hydrogen bond forming groups and will hydrate and swell when placed in contact with an aqueous solution [3].
Timolol Maleate is a β-adrenergic antagonist. Timolol maleate has been proposed as an antihypertensive, antiarrhythmic, antiangina and antiglaucoma agent. It is also used in the treatment of migraine disorders and tremor. It is having half life of 2.5-5 hrs and bioavailability around 60 %. Due to the low bioavailability and shorter half life, this drug is the best candidate to formulate as controlled release buccal patch.
MATERIALS AND METHODS
Materials
Timolol Maleate was received as a gift sample from BalPharma, Bangalore. Eudragit RL100, Eudragit RS100 and Hydroxypropylmethyl cellulose K15M were obtained from Yarrow Chemicals, Mumbai. Various grades of Tween were obtained from Ozone International, Mumbai. All the other reagents and chemicals used were of analytical grade.
Preparation of Mucoadhesive Buccal Patch
The buccal patches of Timolol maleate was prepared by solvent casting technique. Mucoadhesive polymers such as Eudragit RL100, Eudragit RS100 and HPMC K15M were used for the formulation of patches. For Eudragit RL100 and Eudragit RS100, 3.5% of polymer was dissolved in required volume of acetone with continuous stirring on magnetic stirrer. Later drug (0.75%) was dissolved in water and incorporated into above solution. For HPMC K15M, 4% of polymer was dissolved in required volume of cold water and drug is incorporated.
To improve patch performance and drug release, different grades of Tween – 40/60/80 were added as permeation enhancer. Glycerin was used as plasticizer. The dispersion was kept aside for 1 hr and poured into glass mould of 5x3 cm and allowed to dry at room temperature for 48 hrs. After drying, patch is removed and stored in dessicator.

**Table 1 Composition of buccal patches containing Timolol Maleate**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>T5</th>
<th>T6</th>
<th>T7</th>
<th>T8</th>
<th>T9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timolol Maleate (mg)</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Eudragit RL100</td>
<td></td>
<td>3.5%</td>
<td>3.5%</td>
<td>3.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Eudragit RS100</td>
<td></td>
<td></td>
<td>3.5%</td>
<td>3.5%</td>
<td>3.5%</td>
<td></td>
<td></td>
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<tr>
<td>HPMC K15M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Tween 40 (g)</td>
<td>0.0315</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tween 60 (g)</td>
<td>0.0315</td>
<td>0.0315</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tween 80 (g)</td>
<td></td>
<td></td>
<td>0.0315</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0315</td>
<td></td>
</tr>
<tr>
<td>Acetone (ml)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distilled water (ml)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Glycerin (% w/w of polymer weight)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

**EVALUATION OF PREPARED PATCHES**

**Uniformity of Weight [4-5]**
For evaluation of patch weight, three patchess of every formulation were selected randomly and individual weight of each 1x1cm patch was taken on digital balance. The average weight was calculated.

**Thickness of Patch [6-7]**
Three patches of each formulation were taken and the patch thickness was measured using Digital vernier caliper (Absolute Digimate) at six different places and the mean value was calculated.

**Folding Endurance [8-9]**
Folding endurance of the patch was determined by repeatedly folding one patch at the same place till it broke or folded manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done for three patches.
Drug Content Uniformity [10-11]
Three patches (each of 1x1 cm) of each formulation were taken in separate 100 ml volumetric flasks, 100 ml of pH 6.8 phosphate buffer was added and continuously stirred for 24 hrs. The solutions were filtered, diluted suitably and analyzed at 295 nm in a UV spectrophotometer. The average of three patches was taken as final reading.

Swelling Index [12-13]
Buccal patch was weighed (W1), placed in a 2% w/v agar gel plate and incubated at 37±1°C. At regular time interval, the patch was removed from the petri plate and excess surface water was removed carefully by blotting with a tissue paper. The swollen patch was then reweighed (W2) and the swelling index was calculated from the formula,

\[
\% \text{ Swelling Index} = \frac{(W2 - W1)}{W1} \times 100
\]

The experiment was carried out in triplicate and the average values were determined.

Table 2 Physicochemical properties of formulated patches

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Weight Uniformity (mg)</th>
<th>Thickness (mm)</th>
<th>Folding Endurance</th>
<th>Swelling Index (%)</th>
<th>Drug Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>28.05±0.082</td>
<td>0.21±0.036</td>
<td>234±2.054</td>
<td>38.42±0.049</td>
<td>42.58±0.097</td>
</tr>
<tr>
<td>T2</td>
<td>28.81±0.114</td>
<td>0.19±0.109</td>
<td>230±3.741</td>
<td>39.88±0.013</td>
<td>44.34±0.029</td>
</tr>
<tr>
<td>T3</td>
<td>28.38±0.109</td>
<td>0.22±0.059</td>
<td>237±1.247</td>
<td>37.29±0.145</td>
<td>41.56±0.063</td>
</tr>
<tr>
<td>T4</td>
<td>27.36±0.098</td>
<td>0.24±0.114</td>
<td>245±1.447</td>
<td>35.68±0.206</td>
<td>39.44±0.101</td>
</tr>
<tr>
<td>T5</td>
<td>27.11±0.092</td>
<td>0.23±0.102</td>
<td>248±2.867</td>
<td>34.52±0.112</td>
<td>38.63±0.176</td>
</tr>
<tr>
<td>T6</td>
<td>27.46±0.074</td>
<td>0.24±0.074</td>
<td>250±2.054</td>
<td>39.42±0.064</td>
<td>43.17±0.193</td>
</tr>
<tr>
<td>T7</td>
<td>30.15±0.08</td>
<td>0.17±0.118</td>
<td>246±3.299</td>
<td>45.23±0.103</td>
<td>48.76±0.105</td>
</tr>
<tr>
<td>T8</td>
<td>31.16±0.106</td>
<td>0.22±0.187</td>
<td>247±1.632</td>
<td>41.29±0.194</td>
<td>46.85±0.144</td>
</tr>
<tr>
<td>T9</td>
<td>31.92±0.108</td>
<td>0.26±0.11</td>
<td>245±0.816</td>
<td>42.71±0.137</td>
<td>47.34±0.042</td>
</tr>
</tbody>
</table>

In vitro Drug Release Studies [14-15]
The in vitro release rate of timolol maleate from buccal mucoadhesive patches was determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 500 ml of phosphate buffer pH 6.8, at 37 ± 0.5°C and 50 rpm. The backing layer of buccal patch was attached to the glass slide with instant adhesive (cyanoacrylate adhesive). The slide was allocated to the bottom of the dissolution vessel. Aliquots were withdrawn from the dissolution apparatus and the samples were replaced with fresh dissolution medium.
The samples were filtered through whatman filter paper and analyzed after appropriate dilution by UV spectrophotometer at 295 nm. The percentage cumulative drug release was plotted against time to determine the drug release profile.

![Figure 1](curve.png)

**Figure 1 Cumulative % Drug Release for prepared Timolol maleate buccal patches**

**RESULTS AND DISCUSSION**

In the present study, the buccal patches of Timolol maleate were prepared using three different polymers - Eudragit RL100, Eudragit RS100 and HPMC K15M. Various grades of Tween were used to enhance the permeation efficacy of the patch. All the formulations were evaluated for their physical characteristic and drug release. The results are shown in Table 2. Drug loaded patches were tested for uniformity of weight. The patches were found to be uniform. The average weight of the patch was found out to be in the range of 27.11 to 31.92 mg. All the patches have uniform thickness throughout. The average thickness was found out to be in the range of 0.17 to 0.26 mm. No cracks were found on the surface of the prepared patches. The average folding endurance for the prepared patches was found out to be within 230 to 250. The result of drug content uniformity indicates that the drug is uniformly dispersed. The average drug content was found out to be within 95.27 to 99.41 %.

The swelling index of the formulated patches was carried out on 2% agar plate. The percentage of swelling was observed and is notified in Table No. 2. The swelling index was observed more for the formulations prepared by HPMC K15M compared to that of Eudragit RL100 and Eudragit RS100 due to the hydrophilic matrix of HPMC K15M.
The \textit{in vitro} drug release was carried out for the prepared formulations. The drug release was in the order Eudragit RL100 > Eudragit RS100 > HPMC K15M. The cumulative \% drug release for all formulations is shown in Figure 1. The effect of various grades of tween was also studied as permeation enhancer. It was observed that maximum drug release for the various formulations after 12 hrs was within the range 66.79 to 95.11\%.

\textbf{CONCLUSION}

The present study indicates enormous potential of erodible mucoadhesive buccal films containing Timolol maleate for systemic delivery with an added advantage of circumventing the hepatic first pass metabolism. The results of the study show that therapeutic levels of Timolol maleate can be delivered buccally. The release of the drug from the patches prepared from HPMC K15M was controlled but the residence time of the drug in the body was increased by Eudragit RL100 patches. The best formulation was known to be T3. Tween 60 and Tween 80 have good permeation power but Tween 40 does not act efficiently as permeation enhancer.

\textbf{REFERENCE}


