Development Of Controlled Release Mucoadhesive Buccal Patches Containing Timolol Maleate Using Natural & Synthetic Polymers

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Abstract: The present investigation is concerned with the formulation and development of controlled release mucoadhesive buccal patch of Timolol maleate using natural and synthetic polymers. Timolol maleate is a non-selective beta-adrenergic blocker, and having short biological half-life, approximate 4.1 h, and low oral bioavailability. Therefore in order to control the release and increase the residence time these formulations are carried out. Natural polymer such as Chitosan and Synthetic polymers such as HPMC K15M and Eudragit RL100 were used to formulate the buccal patches. Various grades of Tween are used to increase the permeation capacity of the patch. All the formulations were evaluated for Weight Uniformity, Thickness, Folding Endurance, Swelling Index, Drug Content Uniformity, Tensile Strength and In vitro Drug Release. From all the prepared formulations, F6 showed good drug release characteristic. Drug release from the patches follows desire controlled release phenomenon as needed in buccoadhesive drug delivery.

Keywords: Controlled release, Chitosan, Tween, Tensile strength.

INTRODUCTION

Extensive efforts have recently been focused on targeting a drug or drug delivery system in a particular region of the body for extended period of time to get the desire benefit, not only for local targeting of drugs but also for the better control of systemic drug delivery. The concept of mucosal adhesion or mucoadhesive was introduced into controlled drug delivery area in the early 1980’s, which is become a major part of novel drug delivery system in the recent era. Some of the potential sites for attachment of any mucoadhesive system include buccal cavity, nasal cavity, eyes, vagina, rectal area, sublingual route and gastrointestinal area.¹ The oral cavity has rich blood supply that drains directly into the jugular vein and bypassing the liver. Direct access to these systemic circulation through internal jugular vein (buccal mucosa) bypasses drugs from hepatic first pass metabolism, leading to high bioavailability. These factors make the oral mucosa a very attractive and feasible site for systemic drug delivery.²

Various bioadhesive mucosal dosage forms have been developed which include adhesive tablets, gels, ointments, pastes and more recently patches. Buccal patches are preferred over adhesive tablets in terms of flexibility and patients comforts. An ideal buccal patch should be flexible, elastic and soft yet adequately strong to withstand breakage due to stress from mouth activities. Moreover, it must also exhibit good mucoadhesive strength so that it can be retained in the mouth for a desired duration. As such, the mechanical, mucoadhesive, and swelling properties of buccal patches are critical and essential to be evaluated.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. Chitosan, Eudragit RL100 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.

Drug-polymer compatibility studies
This can be confirmed by carrying out infrared light absorption scanning spectroscopy (IR) studies. Infra red spectra of pure drug and mixture of formulations were recorded by dispersion of drug and mixture of formulations in suitable solvent (KBr) using Fourier Transform Infrared Spectrophotometer (FTIR). A base line correction was made using dried potassium bromide and then the spectra of the dried mixture of drug, formulation mixture and potassium bromide were recorded on FTIR.

Preparation of Mucoadhesive Buccal Patch
The buccal patches of Timolol maleate was prepared by solvent casting technique. Mucoadhesive polymers such as Chitosan, Eudragit RL100 and HPMC K15M were used for the formulation of patches. For Chitosan, 3% of polymer was dissolved in required quantity of acetic acid and mixed continuously for 24hrs. Later drug (0.75%) was added into the mixture and stirred well. For Eudragit RL100, 3.5% of polymer was dissolved in required volume of acetone with continuous stirring on magnetic stirrer. Later drug 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.

EVALUATION OF PREPARED PATCHES

Uniformity of Weight
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
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
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
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
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.

**Tensile Strength**\(^{15,16}\)

Tensile strength of the buccal patches was determined by using universal strength testing machine. The 
sensitivity of the machine is one gram. It consists of 2 load cell grips. The lower one is fixed and upper one is 
movable as shown in the figure. The test patch of specific size 4x1cm\(^2\) was fixed between these cell grips and 
force was gradually applied, till the patch breaks. The tensile strength of the patch was taken directly from the 
dial reading.

**In vitro Drug Release Studies**\(^{17,18}\)

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.

**RESULT AND DISCUSSION**

**Compatibility studies**

The incompatibility between the drug and excipients were studied by FTIR spectroscopy. The spectral data of 
pure drug is given in Fig 1. The results indicate that there was no chemical incompatibility between drug and 
excipients used in the formulation.
Weight Uniformity
The weight variation test was conducted for each batch of all formulations F1 to F9 as per I.P and the results are shown in Table 2. The average weight of the prepared formulations was found out to be within 26.22 to 31.92.

Thickness
From the Table 2, it is found that all the patches have uniform thickness throughout the study. The formulation F9 had maximum thickness 0.46±0.119 mm and the formulation F1 shows low thickness 0.29±0.076 mm.

Folding Endurance
The recorded folding endurance of the patches was within 230 to 259 which reflect the flexibility of the patches. This test ensures that prepared patches are suitable for large scale manufacture and continuous patches without breaking.

Drug Content Uniformity
Drug content uniformity test was carried out, in order to make sure about the uniform dispersion of drug in the patch. The drug content was analysed using UV spectrophotometer at 295 nm using placebo patch solution as a blank sample. The results are reported in the Table 2. The result indicates that the drug was uniformly dispersed the procedure of preparing polymeric solutions gives reproducible results.

Tensile strength:
Tensile strength was determined using Universal strength testing machine for the blank and drug loaded patches. The data are given in the Table 3. The order of tensile strength of the patches is HPMC K15M < Eudragit RL100 < Chitosan.

Swelling index of the patches:
The percent swelling index of the drug loaded patches of size 1 x 1 cm² was determined at 30 and 60 min. The data for increase in weight due to swelling are given in the Table 3. The studies suggest that the swelling index of hydrophilic polymer is more compared to that of hydrophobic polymers. The order of swelling index of the patches is HPMC K15M>Eudragit RL100>Chitosan.

In vitro release studies:
In vitro release studies of Lornoxicam patches were carried out by using pH 6.8 phosphate buffer solutions. The release data are plotted in Fig 2. The patches prepared from Chitosan shows slow release while those prepared from Eudragit RL100 shows fast release. The effect of Tween40 is negligible as permeation enhancer.

Table 1 Composition of Timolol maleate buccal patches

<table>
<thead>
<tr>
<th>Formula-tion</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>Drug (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>Chitosan</td>
<td>3%</td>
<td>3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Eudragit RL100</td>
<td>3.5%</td>
<td>3.5%</td>
<td>3.5%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HPMC K15M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4%</td>
<td>4%</td>
<td>4%</td>
<td></td>
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</tr>
<tr>
<td>Tween 40 (g)</td>
<td>0.0315</td>
<td>0.0315</td>
<td>0.0315</td>
<td>0.0315</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Tween 60 (g)</td>
<td>0.0315</td>
<td></td>
<td>0.0315</td>
<td>0.0315</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Tween 80 (g)</td>
<td>0.0315</td>
<td></td>
<td>0.0315</td>
<td>0.0315</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Acetic Acid (%v/v)</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Glycerin (%w/v of polymer)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
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<tr>
<td>Water (ml)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
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</tr>
</tbody>
</table>
Table 2 Physicochemical properties of prepared patches

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Weight Uniformity</th>
<th>Thickness</th>
<th>Folding Endurance</th>
<th>Drug Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>26.56±0.069</td>
<td>0.29±0.076</td>
<td>257±3.991</td>
<td>96.37±1.55</td>
</tr>
<tr>
<td>F2</td>
<td>27.14±0.108</td>
<td>0.36±0.142</td>
<td>253±4.121</td>
<td>95.91±2.19</td>
</tr>
<tr>
<td>F3</td>
<td>26.22±0.173</td>
<td>0.39±0.093</td>
<td>259±1.885</td>
<td>97.72±1.44</td>
</tr>
<tr>
<td>F4</td>
<td>28.05±0.082</td>
<td>0.41±0.036</td>
<td>234±2.054</td>
<td>96.29±1.37</td>
</tr>
<tr>
<td>F5</td>
<td>28.81±0.112</td>
<td>0.43±0.109</td>
<td>230±3.741</td>
<td>99.24±0.84</td>
</tr>
<tr>
<td>F6</td>
<td>28.38±0.106</td>
<td>0.41±0.059</td>
<td>237±1.247</td>
<td>95.76±1.64</td>
</tr>
<tr>
<td>F7</td>
<td>30.15±0.08</td>
<td>0.37±0.118</td>
<td>246±3.299</td>
<td>99.41±0.76</td>
</tr>
<tr>
<td>F8</td>
<td>31.31±0.135</td>
<td>0.42±0.187</td>
<td>247±1.632</td>
<td>96.14±1.33</td>
</tr>
<tr>
<td>F9</td>
<td>31.92±0.118</td>
<td>0.46±0.119</td>
<td>245±0.816</td>
<td>98.73±1.06</td>
</tr>
</tbody>
</table>

Table 3 Tensile Strength & Swelling Index of prepared patches

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Tensile Strength</th>
<th>30 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>2.531±0.048</td>
<td>36.48±0.126</td>
<td>41.29±0.138</td>
</tr>
<tr>
<td>F2</td>
<td>2.372±0.105</td>
<td>37.93±0.092</td>
<td>39.67±0.041</td>
</tr>
<tr>
<td>F3</td>
<td>2.627±0.071</td>
<td>32.97±0.104</td>
<td>37.83±0.077</td>
</tr>
<tr>
<td>F4</td>
<td>1.942±0.046</td>
<td>38.42±0.049</td>
<td>42.58±0.097</td>
</tr>
<tr>
<td>F5</td>
<td>1.738±0.113</td>
<td>39.88±0.013</td>
<td>44.34±0.029</td>
</tr>
<tr>
<td>F6</td>
<td>1.874±0.064</td>
<td>37.29±0.145</td>
<td>41.56±0.063</td>
</tr>
<tr>
<td>F7</td>
<td>1.116±0.039</td>
<td>45.23±0.103</td>
<td>48.76±0.105</td>
</tr>
<tr>
<td>F8</td>
<td>1.297±0.081</td>
<td>41.29±0.194</td>
<td>46.85±0.144</td>
</tr>
<tr>
<td>F9</td>
<td>1.304±0.102</td>
<td>42.71±0.137</td>
<td>47.34±0.042</td>
</tr>
</tbody>
</table>

Figure 2 Percentage Cumulative Drug Release of prepared patches
CONCLUSION

The present study indicates enormous potential of erodible mucoadhesive buccal patches of 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 Chitosan 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 T6 with highest percentage of drug release among the others.

REFERENCES


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