Formulation and evaluation of buccoadhesive tablets of Atenolol

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ABSTRACT

The aim of the study was to prepare and characterize buccoadhesive tablets of atenolol using different mucoadhesive polymers such as carbopol 934P, sodium alginate and hydroxypropyl methylcellulose K100M in combination. The bilayered buccoadhesive tablets were prepared by direct compression technology. The prepared tablets were evaluated for physicochemical parameters such as hardness, thickness uniformity, weight variation, surface pH and swelling studies. Also prepared tablets were evaluated for bioadhesive strength and in vitro drug release. In vitro bioadhesive strength studies showed that formulations containing combination of carbopol 934P and hydroxypropyl methylcellulose were more bioadhesive than sodium alginate. In vitro dissolution studies revealed that all the formulations exhibited non-fickian release kinetics. The optimized formulations F4 and F10 showed 90% release in 8 hr in vitro dissolution studies.

Key words: Atenolol, carbopol 934P, sodium alginate

INTRODUCTION

Oral drug administration has been one of the most suitable and widely accepted by the patients for the delivery of most therapeutically active drugs. Various dosage forms like tablets, capsules and liquid preparations have been administered by oral route. But, due to some unsuitable physiological conditions of the gastro-intestinal tract like relatively poor absorption, presence of various digestive enzymes of the gastro-intestinal lumen and epithelium, poor absorption efflux (i.e. by P-glycoprotein, etc.) and first pass metabolism by hepatic enzymes, the administration of some drugs is affected¹. Mucoadhesive formulations have been researched for delivery to the buccal cavity, generally with the addition of permeation enhancers. Also, it may be necessary to hide the taste of drugs or excipients by the incorporation of taste masking agents².

Carbopol 934P and sodium alginate are anionic polymers, which have excellent bioadhesive strength. But their mucoadhesive properties are just satisfactory when used alone. Therefore, it is needed to combine the anionic polymers with hydroxypropyl methylcellulose so that it will increase mucoadhesion period and drug permeation across buccal mucosa³.

Atenolol, a β-blocker, is prescribed widely in diverse cardiovascular diseases, e.g. hypertension, angina pectoris, arrhythmias, and myocardial infarction. Administration of conventional tablets of atenolol has been reported to exhibit fluctuations in the plasma drug levels, resulting in manifestation of side effects or reduction in drug concentration at the receptor site. Atenolol have poor membrane permeability in the gastro-intestinal tract due to its hydrophilic nature. Also it is sparingly soluble in water, having low partition coefficient. Hence, large fraction of the drug is excreted in an unchanged form and leads to incomplete absorption⁴. Atenolol is selected as a model drug candidate for administration by buccal route. Because, it’s short half-life (6-8 hrs), low molecular weight; low dose (25-50mg) makes it a suitable candidate for administration by buccal route. Previous studies have reported
that atenolol can be successfully delivered through various controlled release systems like hydrophilic systems, osmotic pumps and transdermal drug delivery systems\(^5,6\).

In the present investigation, an attempt was made to prepare and evaluate buccoadhesive tablets of atenolol with suitable absorption enhancer, tablets of atenolol with suitable absorption enhancer, which may improve bioavailability and minimize plasma drug fluctuation in plasma drug concentration.

**MATERIAL AND METHODS**

**Materials**

Atenolol was obtained as a gift sample from Cipla Ltd., Mumbai. Carbopol 934P, Ethyl cellulose, hydroxypropyl methylcellulose K100M were obtained from Rajesh Chemicals, Mumbai. Sodium alginate low viscosity (5.5±2 cp of 1% solution at 25°C) was obtained from Loba chemicals, Mumbai. All other ingredients used in formulations were of analytical grade.

**Methods**

**Preparation of buccoadhesive tablets**

All the ingredients including drug, polymers and excipients weighed accurately according to their batch size. All the ingredients except magnesium stearate were mixed in an ascending order and blended for 20 minutes. After uniform mixing of ingredients, magnesium stearate was added and again mixed for 2 min. The prepared blend of each formulation was subjected to flow properties of granules. 100 mg of powder bed was pre-compressed, on the single station tablet-punching machine (Cadmach Ahemdabad, India) at a pressure of 0.5 ton for 30 seconds to form single layered flat-faced tablets of 8 mm diameter. Then, 50 mg of ethyl cellulose powder was added and final compression was done at a pressure of 3.5 tons for 30 seconds to get bilayer tablet. Composition of bilayer tablets is given in table 1.

**Physical properties of tablets**

It includes hardness, thickness, weight uniformity of tablets in a similar manner as stated for conventional oral tablets.

**Swelling studies**

Three tablets from each formulation were placed in empty baskets and the total weight of basket with tablet noted (\(W_1\)). The tablets containing baskets were fixed to a six-station dissolution apparatus. Baskets immersed in a 500 ml dissolution medium (phosphate buffer pH6.6), at 37°C and at 50 rpm. At regular interval of one hour, the baskets were detached from the dissolution apparatus and blotted with tissue paper to remove excess surface water. Then the weight of basket containing swollen tablet was taken and reported as (\(W_2\)). The graph of swelling index Vs time was plotted for each formulation

\[
\text{Swelling Index (SI)} = \frac{W_2 - W_1}{W_1} \times 100
\]

Where,

- \(W_1\) - dry weight of tablet.
- \(W_2\) - wet weight of swollen tablet

**Surface pH**

The surface pH of the buccal tablets was determined in order to find out the possibilities of any side effects in vivo. The tablets used for the determination of swelling index were used for determination of their surface pH using pH meter. The tablet is allowed to equilibrate for 1 minute with glass electrode. The study was carried out in triplicate.

**Ex-vivo mucoadhesive strength measurement**

A modified balance method was used for determining the ex-vivo mucoadhesive strength. Fresh sheep buccal mucosa was obtained from the local slaughterhouse and used within 2 hours after receiving. The mucosal membrane was separated by removing underlying fat and adipose tissues with the help of surgical scissor. The membrane was cut into pieces and washed with distilled water and then with phosphate buffer pH 6.8 at 37°C. Mucosa was fixed on the glass vial immediately using rubber band, which was filled with phosphate buffer. The vial with buccal mucosa was stored at 37°C for 5 minutes. Then vial with a section of mucosa was connected to the balance in inverted position. Another vial was placed on a height adjustable pan. The backing layer of mucoadhesive tablet was glued to the flat surface of vial. Then the height of pan was adjusted so that mucosal surface of vial comes in intimate contact to adhesive layer of tablet. Two minutes contact time was given to ensure intimate contact between mucosal surface and the tablet. 5 gm weight was applied as preload. Then the weight was kept rising in the pan until tablet get detached from mucosal surface. The bioadhesive force was expressed as the force of adhesion (N) and was determined from the minimal weight required to detach the tablet from mucosal tissue using following equation\(^10\).

\[
\text{Force of adhesion (N)} = \frac{W \times G}{1000}
\]

Where,

- \(W\) is weight required for detachment of two vials in grams,
- \(G\) is acceleration due to gravity
### Table 1. Composition of bilayer buccal tablet of atenolol

<table>
<thead>
<tr>
<th>Ingredients</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>
<th>F10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium alginate</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Carbopol 934P</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
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</tr>
<tr>
<td>HPMC K100M</td>
<td>6.25</td>
<td>12.5</td>
<td>18.75</td>
<td>25</td>
<td>31.25</td>
<td>6.25</td>
<td>12.5</td>
<td>18.75</td>
<td>25</td>
<td>31.25</td>
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<tr>
<td>S. D. Lactose</td>
<td>55.25</td>
<td>49</td>
<td>42.75</td>
<td>36.5</td>
<td>30.25</td>
<td>55.25</td>
<td>49</td>
<td>42.75</td>
<td>36.5</td>
<td>30.25</td>
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<tr>
<td>Magnesium stearate</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Ethyl Cellulose</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
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<tr>
<td>Total weight (mg)</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
</tbody>
</table>

### Table 2. Physical properties, surface pH and force of adhesion of atenolol buccoadhesive tablets

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Hardness (kg/cm²) Mean± S.D. n = 6</th>
<th>Thickness (mm) Mean± S.D. n = 3</th>
<th>Weight variation (mg) Mean± S.D. n = 20</th>
<th>Surface pH Mean± S.D. n = 3</th>
<th>Force of adhesion (N) Mean± S.D. n = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>3.67 ±0.5</td>
<td>2.57±0.08</td>
<td>147.36 ±1.93</td>
<td>6.24 ±0.02</td>
<td>41.53 ±3.16</td>
</tr>
<tr>
<td>F2</td>
<td>4.0 ±0.58</td>
<td>2.53±0.06</td>
<td>147.28 ±1.88</td>
<td>6.11 ±0.09</td>
<td>87.96 ±2.04</td>
</tr>
<tr>
<td>F3</td>
<td>3.33 ±0.29</td>
<td>2.52±0.03</td>
<td>145.13 ±2.59</td>
<td>6.45 ±0.05</td>
<td>118.70 ±8.55</td>
</tr>
<tr>
<td>F4</td>
<td>4 ±0.58</td>
<td>2.53±0.058</td>
<td>143.96 ±2.04</td>
<td>6.87 ±0.03</td>
<td>122.79 ±4.12</td>
</tr>
<tr>
<td>F5</td>
<td>4.33±1.02</td>
<td>2.55±0.09</td>
<td>145.36 ±2.60</td>
<td>6.23 ±0.05</td>
<td>172.98±3.97</td>
</tr>
<tr>
<td>F6</td>
<td>5.67±1.00</td>
<td>2.50±0.05</td>
<td>147.23 ±1.51</td>
<td>6.52 ±0.01</td>
<td>61.20±8.5</td>
</tr>
<tr>
<td>F7</td>
<td>5.60±0.58</td>
<td>2.55±0.1</td>
<td>146.92 ±2.52</td>
<td>6.16 ±0.08</td>
<td>159.78±9.68</td>
</tr>
<tr>
<td>F8</td>
<td>5.66±1.05</td>
<td>2.62±0.1</td>
<td>145.64 ±2.63</td>
<td>7.02 ±0.04</td>
<td>211.24±9.63</td>
</tr>
<tr>
<td>F9</td>
<td>5.67±1.04</td>
<td>2.53±0.08</td>
<td>144.64 ±2.63</td>
<td>6.93 ±0.09</td>
<td>189.69±6.64</td>
</tr>
<tr>
<td>F10</td>
<td>5.60±0.5</td>
<td>2.50±0.15</td>
<td>144.96 ±2.76</td>
<td>6.18 ±0.07</td>
<td>283.84±6.53</td>
</tr>
</tbody>
</table>

### Table 3. Drug Release mechanism for various atenolol formulations

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Zero order</th>
<th>Matrix</th>
<th>Korsemeyer Peppas</th>
<th>Best fit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>k</td>
<td>R, k</td>
<td>n, k</td>
</tr>
<tr>
<td>F1</td>
<td>0.9095</td>
<td>0.32</td>
<td>0.9979</td>
<td>5.26, 0.9949</td>
</tr>
<tr>
<td>F2</td>
<td>0.9495</td>
<td>0.3</td>
<td>0.9915</td>
<td>4.81, 0.9962</td>
</tr>
<tr>
<td>F3</td>
<td>0.9522</td>
<td>0.22</td>
<td>0.9846</td>
<td>4.07, 0.9876</td>
</tr>
<tr>
<td>F4</td>
<td>0.9845</td>
<td>0.2</td>
<td>0.9521</td>
<td>3.66, 0.9702</td>
</tr>
<tr>
<td>F5</td>
<td>0.9921</td>
<td>0.19</td>
<td>0.9293</td>
<td>3.39, 0.9819</td>
</tr>
<tr>
<td>F6</td>
<td>0.9566</td>
<td>0.22</td>
<td>0.9781</td>
<td>4.05, 0.9833</td>
</tr>
<tr>
<td>F7</td>
<td>0.9677</td>
<td>0.22</td>
<td>0.9823</td>
<td>4.03, 0.9957</td>
</tr>
<tr>
<td>F8</td>
<td>0.9939</td>
<td>0.2</td>
<td>0.9558</td>
<td>3.57, 0.9917</td>
</tr>
<tr>
<td>F9</td>
<td>0.9923</td>
<td>0.2</td>
<td>0.96</td>
<td>0.58, 0.9970</td>
</tr>
<tr>
<td>F10</td>
<td>0.9899</td>
<td>0.19</td>
<td>0.9634</td>
<td>3.46, 0.9961</td>
</tr>
</tbody>
</table>
Fig. 1. Swelling profile of formulations F1-F5

Fig. 2. Swelling profile of formulations F6-F10
Fig. 3. In vitro drug release study of atenolol formulations (F1-F5)

![Graph showing drug release over time for formulations F1 to F5.]

Fig. 4. In vitro drug release study of atenolol formulations (F6-F10)

![Graph showing drug release over time for formulations F6 to F10.]

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The buccal mucosa was changed for each measurement. This study was carried out in triplicate for each formulation.

**In vitro drug release study**

The drug release rate was determined using USP dissolution apparatus II (Veego Scientific) by using phosphate buffer pH 6.6 at 37 ± 0.5°C. The speed of rotation was maintained to 50 rpm. At predetermined time intervals 3 ml sample was withdrawn and analyzed spectrophotometrically (Shimadzu UV PharmSpec 1700) at 225 nm. To examine the release kinetics of atenolol from the prepared buccoadhesive tablets, the results were analyzed by using PCP disso software. Diffusion exponent value ‘n’ was used to study release kinetics.

**RESULT AND DISCUSSION**

**Physical properties of bucoadhesive Tablets:**

All the formulations showed acceptable uniformity of weight, hardness and thickness. Hardness of tablets was optimized on the basis of trial preparation of tablets. Hardness of tablets was maintained in the range of 4.50-6.00 kg/cm² with carbopol 934P and HPMC K100M and 3.83 - 4.33 kg/cm² with sodium alginate and HPMC K100M. Hardness was increased as the amount of concentration of HPMC K100M increased.

The release profiles from the hydrophilic matrices remain unaffected by the tablet hardness (see table 2).

**Swelling Index:**

Swelling profile of formulations F1-F5 is shown in figure 1 and swelling profile of formulation F6-F10 is shown in figure 2. Formulations containing Carbopol 934P and HPMC K100M at the ratio of 1:2.5 showed higher swelling indices than the other formulations. Adequate swelling behaviour of a buccal adhesive system is an essential property for uniform and prolonged release of drug and effective mucoadhesion. The rate and extent of swelling increased with an increasing concentration of HPMC K100M in the formulations. At fifth hours all the formulation showed maximum swelling indices due to more gel forming abilities of polymers there after swelling indices values get decreased which indicates the erosion of the polymers.

**Surface pH:**

The surface pH was determined in order to investigate the possibility of any side effects, in the oral cavity as acidic or alkaline pH is bound to cause irritation to the buccal mucosa. Surface pH of all the formulations was found to be in the range of 6-7 as shown in table 2. The surface pH of all formulations is very close to the neutral pH; hence it is assumed that these formulations cause no any irritation in the oral cavity.

**Ex- vivo mucoadhesive strength measurement**

The mucoadhesive strength for all the formulations is given in table 2. Mucoadhesive strength of all the formulations was found to be increased as the concentrations of polymers was increased. The high bioadhesive strength of carbopol 934P may be due to the formation of secondary bioadhesion bonds with mucin and interpenetration of polymeric chains in the interfacial region, while the other polymers like HPMC and sodium alginate undergo superficial bioadhesion. Bilayer tablets containing C934P and HPMC K100M at the ratio of 1:2.5 (F10) exhibited highest bioadhesive strength.

It was found that the bioadhesive polymers differ in their adhesive properties and can be arranged in descending order as follows: Carbopol 934P > Sodium alginate > HPMC K100M.

**In vitro drug release:**

Drug dissolution data of various atenolol formulations is as shown in figures 3 and 4. Drug release mechanisms for various atenolol formulations are shown in table 3. Atenolol was almost completely released from all formulations in 8 hours. The release of atenolol was decreased with increasing concentration of HPMC K100M. The possible reason for observed reduction in total drug release may be the interaction between two oppositely charged bioadhesive polymers i.e. HPMC K100M and carbopol 934P. It may be expected that interpolymer complex between carboxylic group of carbopol and hydroxyl group of HPMC K100M will be formed and complex formation may retard the dissolution rate.

Carbopol 934P is highly cross-linked polymer that swells in water and do not disintegrate upon 24 hours. Because of its structure, the drug dissolution rate from the formulation may delay in comparison with the dissolution rate of the formulation based on the linear polymers. The values of n lies between 0.5 to 1.0 in all the formulations indicating a non-Fickian release behaviour controlled by combination of diffusion and chain relaxation mechanism.

The prepared buccoadhesive tablet showed optimum mucoadhesion. The buccoadhesive bilayer tablets prepared have a novel approach, which could be considered as superior dosage form than the conventional marketed formulations.

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REFERENCES


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