PREPARATION AND PHYSICOCHEMICAL CHARACTERIZATION OF GEMFIBROZIL INLOADED MUCOADHESIVE BILAYERED TABLET
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Abstract

The purpose of this research work was to prepare the buccoadhesive bilayered tablet of Gemfibrozil for the treatment of hypercholesterolemia, by using the mucoadhesive polymers such as carbopol-934 (CP), hydroxy propyl methyl cellulose (HPMC K4M) and polyvinylpyrrolidone (PVP-K30) in different concentration. Ethyl cellulose is used in backing layer because of its water impermeable nature. Tablets were prepared by direct compression method. The first layer which adheres to mucosa was obtained by direct compression of mucoadhesive polymers and drug. The second layer containing water impermeable agent was compressed on the first layer. The tablets were evaluated by different parameters such as weight variations, content uniformity, thickness, hardness, surface pH, swelling index, exvivo mucoadhesive strength, in vitro drug release. The surface pH of all the tablets was close to neutral pH the mechanism of drug release was found to be non-Fickian diffusion (value of n between 0.5 and 1.0) for both the buccal tablets. The present study concludes that mucoadhesive buccal tablets of Gemfibrozil can be a good way to bypass the extensive hepatic first-pass metabolism and to improve the bioavailability of Gemfibrozil

Key Words: Bilayered buccal tablet, buccal delivery, Mucoadhesion

Introduction:

The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal drug delivery involves administration of desired drug through buccal mucosal membrane lining the oral cavity. For many
drugs, especially peptides and proteins, the buccal route offers many advantages over conventional routes of delivery with an improved bioavailability due to the avoidance of degradation in the gastrointestinal tract and hepatic first pass metabolism [1]. Mucoadhesion is defined as attachment of synthetic or natural macromolecules to mucin layer of mucus tissue. Mucoadhesive drug delivery systems utilize the property of bioadhesion of certain water-soluble polymers which become adhesive on hydration and hence can be used for targeting the drug to a particular region of the body for extended period of time. Mucoadhesive polymers can be used to overcome the physiological barriers in long term drug delivery, presystemic metabolism and instability in acidic environment associated with oral administration.

Gemfibrozil is a blood lipid and cholesterol-modifying medicine. It is classified as a fibric acid derivative similar to fenofibrate (Tricor). It reduces triglycerides and increases cholesterol carried in high density lipoprotein (HDL) in the blood. It works by decreasing the amount of fat produced by the liver. Lowering "bad" cholesterol and triglycerides and raising "good" cholesterol decreases the risk of heart disease and helps prevent strokes and heart attacks.

The buccal mucoadhesive dosage form of Gemfibrozil was prepared and characterized by measuring the force of detachment, swelling index to improve residence time of drug.

Materials and methods:

Gemfibrozil (G. Amphray Ltd. Mumbai), hydroxyl propylmethyl cellulose (HPMC K4M) (Colorcon Asia Ltd. Goa) and Polyvinylpyrrolidone (PVP- K30) (Sanofi-aventis Ltd Goa) were obtained as a gift sample. Carbopol 934 (CP) and Ethyl cellulose (EC) (Loba Chemie Pvt. Ltd.), magnesium stearate (Himedia laboratories Pvt ltd. Mumbai) and Mannitol (S.D.Fine chemicals,Mumbai) were obtained from commercial sources. All other reagents and chemicals used were of analytical grade

Preparation of mucoadhesive buccal tablets:

Step-1: preparation of mucoadhesive layer

Mucoadhesive buccal tablets containing Gemfibrozil were prepared by direct compression method. The ingredients of the core layer (Table 1) were weighed accurately and mixed by trituration in a glass mortar & pestle. The mix was
then compressed using 8mm die by a tablet press. In order to obtain constant tablet weight the manitol was added as 
filler excipient in the core layer. The prepared adhesive tablets were 13.32 mm in diameter and 1mm thickness.

**Step-2: formation of backing layer to the mucoadhesive layer:**

The backing layer was made up of ethyl cellulose. The solution was prepared by dissolving 6% w/v of ethyl cellulose in chloroform. The prepared solution was sprayed on to one surface of the mucoadhesive layer leaving the other side free and both sides of the tablets coated with the ethyl cellulose layer solutions. Then it was air dried at room temperature. The double layered structure design was expected to provide drug delivery in a unidirectional fashion to the mucosa. It avoids loss of drug due to wash out of saliva and the swelling profile of the buccal tablet can be changed dramatically by the amount of backing material and those changes could alter drug release profile.

The resulting bilayered tablets were 13.32 mm in diameter and 1.4 mm in thickness.

![Indigenously developed and standardized Punches and die for development of buccal tablets](image)
**Evaluation of tablets:**

Ten tablets from each batch were evaluated for uniformity of weight and medicament content. Six tablets from each batch were examined for friability using a Roche-m type friabilator (DBK, India) and hardness using a Monsanto type hardness tester (Edison, India).

**Swelling study:**

The moisture uptake studies give an indication about the relative moisture absorption capacities of polymers and an idea whether the formulations maintain their integrity after absorption of moisture. The swelling index of the tablets was evaluated by using six tablets of each formulation. The swelling rate of the bioadhesive tablets was evaluated by using 1% agar gel plate. The average weight of the tablet was calculated (w1). The tablets were placed on gel surface in a petridish placed in an incubator at 37°C. A tablet was removed at different time intervals (0.5, 1.0, 2.0, 3.0, 4.0, 5.0). Wiped with filter paper and reweighed (w2). The swelling index was calculated by the formula.

\[
\text{Swelling index} = \frac{(W2-W1)}{W1}
\]

**Surface pH study:**

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. The method adopted by Bottenberg et al was used to determine the surface pH of the tablet. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 minute.

**In- vitro dissolution studies:**

The in vitro dissolution was carried out by using Tablets Dissolution Tester (USP-II). The tablet is placed such that core faced to the dissolution medium (900 ml of 7.5 Phosphate buffer). Dissolution medium temperature was maintained at 37° ± 5°C and stirring at 50 rpm. An aliquot of the sample was periodically with drawn at suitable time intervals and the volume was replaced with fresh dissolution medium. The samples were analyzed spectrophotometrically at 276nm.
Ex-vivo mucoadhesive strength:

Bioadhesive strength of the buccal tablets was measured on modified physical balance followed by a reported method [4]. A modified physical balance was used for determining the ex vivo mucoadhesive strength of prepared buccal tablets. Fresh sheep buccal mucosa was obtained from a local slaughterhouse. The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.6 at 37°C ± 1°C. Sheep buccal mucosa was tied to the glass petri dish, which was filled with phosphate buffer so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of a thread with cyanoacrylate adhesive. The two sides of the balance were made equal by keeping a 5 g weight on the right hand pan. Next, weight of 5 g was removed from the right hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 min contact time. Then weight was added slowly to the right hand pan until the tablet detached from the mucosal surface [4, 5].

Disintegration test:

The disintegration pattern of each mucoadhesive buccal tablet was determined by immersing the tablet in a glass petri dish containing 20 to 25 ml of water at room temperature (37 ± 1°C). The morphological changes of each buccal tablet are observed [6].

Figure 2: Bioadhesion Testing Apparatus
Table 1: Composition of Formulations of Mucoadhesive Buccal Tablets.

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Drug (mg)</th>
<th>CP-934</th>
<th>HPMC K4M</th>
<th>PVPK30</th>
<th>MANNITOL</th>
<th>EC</th>
<th>Mg.Sterarate</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>600</td>
<td>-</td>
<td>30</td>
<td>-</td>
<td>84.75</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>F2</td>
<td>600</td>
<td>10</td>
<td>20</td>
<td>-</td>
<td>84.75</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>F3</td>
<td>600</td>
<td>15</td>
<td>15</td>
<td>-</td>
<td>84.75</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>F4</td>
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<td>15</td>
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<tr>
<td>F5</td>
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<td>10</td>
<td>-</td>
<td>20</td>
<td>84.75</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>F6</td>
<td>600</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>84.75</td>
<td>45</td>
<td>5</td>
</tr>
</tbody>
</table>

HPMCK4M- Hydroxyl propyl methyl cellulose, CP-934 – Carbopol-934, PVPK30 – Polyvinyl pyrrolidine, EC – Ethyl cellulose

Results

The blend of ingredients was analyzed for physical characteristics. The angle of repose of formulation blends F1 to F6 were in the range of 32°59' ± 1.464 to 33°20' ± 1.103. The bulk density, tapped density, Corr’s index were found in the range of 0.433 to 0.317 gm/cc, 0.52-0.47gm/cc, and 16.66 – 14.28 respectively. It reveals that all the formulation blends were having good flow characteristics and flow rates. All the formulations pass the test for weight variation as per the IP standard ± 7.5 % deviation. Percentage of drug content for all formulations F1 to F6 was in the range of 96.1 ± 1.31 to 98.3 ±1.00%.

Thickness of F1 to F6 formulations was found to be 0.128 to 3.35 ± 0.106 mm. Hardness of all formulations F1-F6 was found to be 4.2 ± 0.447 to 5.6 ± 0.548 kg/sq.cm.
Table 2: Physicochemical Properties of Bilayered Buccal Tablets of Gemfibrozil.

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Thickness (mm)</th>
<th>Hardness (kg/cm²)</th>
<th>% Drug Content</th>
<th>Surface pH</th>
<th>Mucoadhesive Strength (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>2.34 ± 0.128</td>
<td>4.2 ± 0.447</td>
<td>92.1 ± 1.31</td>
<td>7.0 ± 0.10</td>
<td>9.8± 0.16</td>
</tr>
<tr>
<td>F2</td>
<td>3.36 ± 0.203</td>
<td>5.4 ± 0.548</td>
<td>96.4 ± 1.52</td>
<td>7.2 ± 0.23</td>
<td>16.0 ± 0.12</td>
</tr>
<tr>
<td>F3</td>
<td>3.40 ± 0.057</td>
<td>3.8 ± 0.447</td>
<td>96.5 ± 1.31</td>
<td>7.3 ± 0.10</td>
<td>14.0 ± 0.16</td>
</tr>
<tr>
<td>F4</td>
<td>3.39 ± 0.061</td>
<td>6.6 ± 0.548</td>
<td>92.1 ± 1.46</td>
<td>7.1 ± 0.11</td>
<td>12.0 ± 0.16</td>
</tr>
<tr>
<td>F5</td>
<td>3.50 ± 0.147</td>
<td>7.4 ± 0.548</td>
<td>96.8 ± 1.45</td>
<td>6.9 ± 0.10</td>
<td>15.0 ± 0.08</td>
</tr>
<tr>
<td>F6</td>
<td>3.35 ± 0.106</td>
<td>5.6 ± 0.548</td>
<td>94.3 ± 1.00</td>
<td>7.4 ± 0.05</td>
<td>10.4 ± 0.54</td>
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</table>

Table 3: In vitro dissolution studies for release kinetics.

<table>
<thead>
<tr>
<th>Drug release Kinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula Code</td>
</tr>
<tr>
<td>K0</td>
</tr>
<tr>
<td>F1</td>
</tr>
<tr>
<td>F2</td>
</tr>
<tr>
<td>F3</td>
</tr>
<tr>
<td>F4</td>
</tr>
<tr>
<td>F5</td>
</tr>
<tr>
<td>F6</td>
</tr>
</tbody>
</table>

K0- Zero order rate constant  
K1- First order rate constant  
r – Coefficient of Correlation  
n- diffusional exponent
Fig 3: Comparative In Vitro Drug Release Profile for F1-F6 Formulations

Surface pH determination:

Surface pH of bilayered tablets was found to be in between 6.9 ± 0.10 to 7.4 ± 0.05. The investigated results indicated that the developed buccal tablets will not cause any irritation to mucosal surface.

Swelling Studies:

The bioadhesion and drug release profile are dependent upon swelling behavior of the tablets. [7]. Swelling index was calculated with respect to time. The Swelling index was for all formulations F1 to F6 (After 4 hours) were in the range 1.119 ± 0.0346 to 1.120 ± 0.0370.

Ex-Vivo Mucoadhesive Strength

Mucoadhesion may be defined as the adhesion between a polymer and mucus. The strength of mucoadhesion is affected by various factors such as molecular weight of polymers, contact time with mucus, swelling rate of the polymer, and biological membrane used in the study [9,10]. In this study, sheep buccal mucosa was used as biological membrane for mucoadhesion. The highest adhesion force and highest strength of the mucoadhesive bond was observed with the formulation as followed by F2 to F5 containing carbopol 934 p and HPMC k4m and carbopol 934 and PVP respectively. Tablets of formulation F1 to F6 containing HPMC k4m and PVP alone showed least...
adhesion force than tablet of all other formulation. The mucoadhesive strength of all the formulations F1 to F6 was found to be in the range of 9.8 ± 0.16 to 16.0 ± 0.12 gms.

**Disintegration test:**
The disintegration test for buccal tablet is required to check the integrity of formulation. When tablets immersed in water initially it hydrates and swells for longer time and then disintegrates slowly. Disintegration time for prepared buccal tablets was found to be in between 10.00 ± 0.50 to 16.00 ± 0.20 h. The obtained results indicated that disintegration time increases as amount of carbopol increases due to its high molecular weight and viscosity.

**In-Vitro Drug Release**
The In-vitro drug release of all the formulations F1 to F6 was found to be in the range of 93.02 ±0.10 to 98.61 ± 0.80. The formulation F2 showed 98.61±0.80 percentage of drug released at 12th hr with good swelling index and bioadhesion strength. The formulation F5 showed 97.61±1.10 percentage of drug released at 12th hr with good swelling index and bioadhesion strength.

Both F2 and F5 formulations obeyed zero order kinetics with non-ficikan diffusion mechanism and showed these two formulations were taken as optimized formulations for in vitro buccal permeation studies.

Both Formulation F2 and F5 showed 86.90 ± 1.10 and 83.40 ± 0.85 respectively permeation drug through the buccal mucosa over a period of time 12th hrs.

Hence it can be conclusively stated the both F2 and F5 formulations necessary buccoadhesive property and the desirable release characteristics. However the detailed In vivo studies of the above formulations will through more light on their viability for consideration in the clinical practice.

**Conclusion:**
The present work demonstrated that the possibility of making a buccoadhesive drug delivery system for Gemfibrozil Colesevelam which will be more efficacious and acceptable than the conventional drug delivery of Gemfibrozil Colesevelam and it could be a drug delivery of choice in the treatment of hypercholesterolemia.
References:


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