PREPARATION AND EVALUATION OF MUCOADHESIVE BILAYER TABLETS CONTAINING OXCARBAZEPINE

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Received on 24-02-2012                                                                                   Accepted on 10-03-2012

Abstract

The purpose of this research work was to establish mucoadhesive bi-layer buccal tablets of oxcarbazepine using bioadhesive polymer such as Hydroxy propyl methyl cellulose (HPMC), Sodium carboxymethylcellulose (SCMC), Carbopol-934 (CP) and Polyvinyl pyrrolidone (pvpk-30) as along with ethyl cellulose (EC) to act as an impermeable backing layer. Buccal tablets were evaluated by different parameters such as weight uniformity, content uniformity, thickness, hardness, surface pH, swelling index, ex vivo mucoadhesive strength, in vitro drug release, and in vitro drug permeation. The present study concludes that mucoadhesive buccal tablets of oxcarbazepine can be a good way to bypass the extensive hepatic first-pass metabolism and to improve the bioavailability of oxcarbazepine.

Key Words: Bilayered buccal tablet, Buccal delivery, Mucoadhesion, oxcarbazepine.

Introduction1-5

In the present study, the objective was to prepare mucoadhesive buccal tablets of Oxcarbazepine to prolong the residence time of the buccal tablets, which ensure satisfactory drug release in a unidirectional fashion to the mucosa, and to avoid loss of drug resulting from wash out with saliva. Hence to improve its therapeutic efficacy, patient compliance and to reduce the frequency of dosing and side effects as well as to avoid its extensive first pass metabolism. Mucoadhesive buccal drug delivery approach was considered to be better suitable for oxcarbazepine. It is widely used in the treatment of epilepsy. Although it is well absorbed in the gastrointestinal tract. The physicochemical properties of oxcarbamazepine, its suitable half-life (2 hours) and its low molecular weight 252.27 make it a suitable candidate for administration by the buccal route.
Materials and Methods

Oxcarbazepine were gift samples from Micro Labs Bangalore. Hydroxy propyl methyl cellulose (HPMC K4M), Sodium carboxymethylcellulose (SCMC), Carbopol-934 (CP) polyvinyl pyrrolidone (pvpk30), ethyl cellulose and Magnesium stearate (S.D. Fine Chemicals, Mumbai, India) were obtained from commercial sources. All other reagents and chemicals used were of analytical reagent grade.

Experimental

Preparation of Mucoadhesive Buccal Tablets

Mucoadhesive buccal tablets containing oxcarbazepine were prepared by direct compression method using two steps. 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. After compression of tablet the upper punch was removed carefully without disturbing the set up and mixed ingredients of the backing layer (Table 1) were added over the tablet and compressed again.

Modified Physical Balance

Ex Vivo Mucoadhesive Strength

A modified balance method was used for determining the ex vivo mucoadhesive strength.

Fresh sheep buccal mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter. The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with...
distilled water and then with phosphate buffer 7.4 saliva solution at 37°C. The sheep buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8, at 37 ± 1°C) so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of a rubber stopper with cyanoacrylate adhesive. The two sides of the balance were made equal before the study, by keeping a 5-g weight on the right-hand pan. A 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 minutes contact time. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min) to the right-hand pan until the tablet detached from the mucosal surface. This detachment force gave the mucoadhesive strength of the buccal tablet in grams.

**Swelling Study**

The swelling study of tablets was determined by gravimetry. The swelling rate of the bioadhesive tablets was evaluated by using 1% agar gel plate. The average weight of the tablet was calculated ($w_1$). The tablets were placed on gel surface in a petridish placed in an incubator at 37±1°C. 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 ($w_2$).

The swelling index was calculated by the formula

$$Swelling\ index = \frac{W_2-W_1}{W_2} \times 100$$

**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 Sodium lauryl sulphate). Dissolution medium temperature was maintained at 37°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 256nm.

In Vitro Buccal Permutation Studies

In vitro buccal permeation of Oxcarbazepine from matrix tablets through the goat buccal membrane was studied. The membrane was mounted over a Franz diffusion cell of i.d. 2.1cm and the selected F2 and F5 formulations containing 6.25 mg of Oxcarbazepine was placed on the membrane. The receiver compartment of the diffusion cell was filled with 12.0 mL of alcohol: propylene glycol: phosphatebuffer saline pH 7.4 mixture (40:15:45). The entire setup was placed over a magnetic stirrer and the temperature was maintained at 37 °C by placing the diffusion cell in a water bath. 1 mL samples were collected at predetermined time intervals from the receptor compartment and replaced with an equal volume of the above mixture. The amount of Oxcarbazepine in the diffusion samples was estimated by the UV method.

Stability studies

Stability studies of the formulation F1 of Oxcarbazepine buccal tablets were carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at 25°C/60% RH, 30 ºC/65% RH and 40 ºC/75% RH for 90 days. There was no significant change in the physical property and drug content during the study period.

Table No1: Composition of Formulations of Mucoadhesive Buccal Tablets.

<table>
<thead>
<tr>
<th>Core Layer mg</th>
<th>Backing Layer mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula code</td>
<td>Drug mg</td>
</tr>
<tr>
<td>F1</td>
<td>150</td>
</tr>
</tbody>
</table>
HPMCK4M- Hydroxyl propyl methyl cellulose, CP-934 – Carbopol-934, 
SCMC – Sodium carboxy methyl cellulose, Pvp k30-Polyvinylpyrrolidone 
EC – Ethyl cellulose, Mg sterate-Magnesium stearate.

Results and Discussion

In the present work efforts have been made to develop mucoadhesive buccal tablets of Oxcarbazepine using direct 
 compression technique involving mucoadhesive polymers like Carbopol, various cellulose ethers having different 
degree of solubility and swell ability, such as Hydroxy propyl methyl cellulose, polyvinyl pyrrolidone and 
Sodium carboxy methyl cellulose. Ethyl cellulose was selected as a backing material because this hydrophobic 
polymer has very low water permeability thus providing an impermeable backing layer that prevents drug loss. 
Magnesium stearate was included as anti adherent. The blend of ingredients was analyzed for physical 
 characteristics. The angle of repose of formulation blends F1 to F6 were in the range of 30°59' ± 1.45 to 33°20' ± 
1.123. The bulk density, tapped density, Corrs’ index were found in the range of 0.403 to 0.347 gm/cc, 0.50- 
0.48gm/cc, and 16.06 – 14.18 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 %.

Table No: 2 Physicochemical Properties of Bilayered Buccal Tablets of Oxcarbazepine.

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Thickness mm</th>
<th>Hardness (kg/cm²)</th>
<th>%Drug Content</th>
<th>Surface P⁹⁹</th>
<th>Muco adhesive Strength(g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>2.04 ± 0.128</td>
<td>4.2 ± 0.447</td>
<td>94.1 ± 1.31</td>
<td>7.0 ± 0.10</td>
<td>9.8± 0.16</td>
</tr>
</tbody>
</table>
Table No-3: In vitro dissolution studies for release kinetics.

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Drug release kinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zero order</td>
</tr>
<tr>
<td></td>
<td>K₀</td>
</tr>
<tr>
<td>F1</td>
<td>9.3036</td>
</tr>
<tr>
<td>F2</td>
<td>8.17987</td>
</tr>
<tr>
<td>F3</td>
<td>9.44584</td>
</tr>
<tr>
<td>F4</td>
<td>9.67705</td>
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<tr>
<td>F5</td>
<td>10.323</td>
</tr>
<tr>
<td>F6</td>
<td>8.6549</td>
</tr>
</tbody>
</table>

K₀- Zero order rate constant
K₁- First order rate constant
r – Coefficient of Correlation
n- diffusional exponent

Table No-4: In-vitro buccal permeation studies for release kinetics.

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Drug release kinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zero order</td>
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<tr>
<td></td>
<td>K₀</td>
</tr>
<tr>
<td>F1</td>
<td>9.2456</td>
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<tr>
<td>F2</td>
<td>8.7864</td>
</tr>
</tbody>
</table>
Thickness of F1 to F6 formulations was found to be 2.04±0.128 to 3.50±0.147 mm. Hardness of all formulations F1-F6 was found to be 3.8±0.447 to 5.6 ± 0.548 kg/sq.cm. The bioadhesion and drug release profile are dependent upon swelling behavior of the tablets. 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. Buccal tablets of all the formulations Surface pH values in the range of 6.9 ± 0.10 to 7.4 ± 0.05 that indicates no risk of mucosal damage or irritation. The bioadhesives property of oxcarbazepine tablets containing varying proportions of polymers was determined with an insight to develop the tablets with adequate bioadhesiveness. 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 Scmc respectively, Tablets of formulation F1o F6 containing Hpmc k4 m and Scmc 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 16.4 ± 0.12 gms. The in vitro drug release of all the formulations F1 to F6 was found to be in the range of 96.02 ± 0.10 to 99.12 ± 053. Both F2 and F5 formulations obeyed zero order kinetics with non-Fickian 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. All the formulations exhibited anomalous (non-Fickian transport) diffusion mechanism and follow zero order kinetic. Table 4 the values of n were estimated by linear regression of log ($M_t/M_\infty$) versus log $t$, and these values were between 0.5 and 1.0, indicating that the release of oxcarbazepine was found to be non-Fickian diffusion.

Conclusion

The mucoadhesive buccal tablets of oxcarbazepine may be a good way to bypass the extensive hepatic first-pass metabolism and to improve the bioavailability of oxcarbazepine through buccalmucosa.
References


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