Abstract
The purpose of this work was to evaluate the effect of formulation variables on release properties and bioadhesive strength in development of three layered buccal compact containing highly water-soluble drug propranolol hydrochloride (PRPH). Formulations were prepared based on rotatable central composite design with peripheral layer polymer ratio (carbopol 934P: HPMC 4KM) and core layer polymer ratio (HPMC 4KM: sodium alginate) as two independent formulation variables. The three layered buccal compact comprises a peripheral layer, core layer and backing layer. In order to provide the unidirectional drug release towards the mucosa and avoid backward diffusion, ethyl cellulose (EC) and magnesium stearate were included as backing layer. The dependent (response) variables were considered: bioadhesion force, and percentage PRPH release at 8 h. The decrease in PRPH release was observed with an increase in both the formulation variables and as the carbopol: HPMC ratio increases the bioadhesive strength also increases. The desirability function was used to optimize the response variables, each having a different target and the observed responses were highly agreed with experimental values. The results demonstrate the feasibility of the model in the development of three layered buccal compact containing highly water-soluble drug propranolol hydrochloride.

Key words: Bioadhesive strength, Buccal compact, Backing layer, Peripheral layer.

INTRODUCTION
Delivery of therapeutic agents through various transmucosal routes has received significant attention owing to the agents' presystemic metabolism or instability in the acidic environment associated with oral administration. The oral cavity is being increasingly used for the administration of drugs, which are mainly designed for the medicaments through the oral mucosa into the systemic circulation. Buccal mucosa consist of stratified squamous epithelium supported by a connective tissue lamina propria was investigated as a site for drug delivery several decades ago and the interest in this area for the transmucosal drug administration is still growing. Buccal mucosa makes a more appropriate choice of site if prolonged drug delivery is desired because buccal site is less permeable than the sublingual site. Buccal compacts or buccal bioadhesive drug devices designed to remain in contact with buccal mucosa and release the drug over a long period of time in a controlled fashion. Such a delivery of drug through buccal mucosa overcomes premature drug degradation with in the GI tract, as well as active drug loss due to first pass metabolism, and another is inconvenience of parenteral administration. In addition, there is excellent acceptability and the drug can be applied, localized and may be removed easily at any time during the treatment period.

The strategy for designing buccoadhesive is based principally on the utilization of polymers with suitable physicochemical properties. Combined usage of HPMC and carbopol in delivering the clotrimazole for oral canididiasis has been reported. Similar polymer combination was studied by Perez Marcos et al and concluded that the amount of water penetrated in HPMC K4M was higher. The control release mucoadhesive tablet of eugenol for gingival application has been prepared by using carbopol 934P and HPMC as polymers. Different ratio of carbopol 934P and optimize the controlled release mucoadhesive hydrophilic compressed matrices of diltiazem for buccal delivery.
However, there has been no study to date designed to evaluate the release rate and mucoadhesive property of three layered buccal compacts by using combination of polymers (carbopol 934P, sodium alginate and HPMC K4M).

The typical three layered buccal compacts was prepared containing peripheral layer, core layer and backing layer as shown in Fig. 1. The peripheral layer contains lactose, different ratio of carbopol and HPMC K4M which acts has as a rate controlling layer. The core layer consists of drug PRPH, HPMC K4M and sodium alginate at different ratio. In order to provide the unidirectional drug release towards the mucosa and avoid backward diffusion, ethyl cellulose (EC) and magnesium stearate were included in backing layer.

Propranolol hydrochloride (PRPH), a nonselective β-adrenergic blocking agent, is widely used in the treatment of hypertension, angina pectoris, and many other cardiovascular disorders. Although it is well absorbed in the gastrointestinal tract, its bioavailability is low (15%-6, 7 23%) as a result of extensive first-pass metabolism 8. Since the buccal route bypasses the hepatic first-pass effect, the dose of PRPH can be reduced. The physicochemical properties of PRPH, its suitable half-life (3-5 hours), and its low molecular weight 295.81 make it a suitable candidate for administration by the buccal route.

MATERIALS AND METHODS

Materials

Propranolol hydrochloride was received as gift sample from Alkem laboratories, Mumbai, India. Hydroxylpropylmethylcellulose (Methosil®) K4M, sodium alginate (alginic acid sodium salt) and ethyl cellulose (EC) were also obtained from Alkem laboratories, Mumbai, India. Other materials were purchased from commercial source; Magnesium stearate, and directly compressible lactose. All other chemicals used in the study were of analytical grade.

Preparation of three layered buccal compacts

The composition of various batches is shown in Table 1. All the ingredients were screened through 120 µm sieve and then thoroughly blended in glass mortar with pestle. Before direct compression blending was carried out separately for peripheral, core and backing layer. The blended powder of backing layer was compressed on 13 mm diameter flat faced punch and die set in an IR hydraulic press at a force of 50 kg cm⁻². Above this, blended powder of core layer was added and compressed at a force of 50 kg cm⁻². Finally, the blended powder of peripheral layer was added to get three layered buccal compact by compressing at a force of 240 kg cm⁻².

Table 1

<table>
<thead>
<tr>
<th>Evaluation of buccal compacts</th>
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<tbody>
<tr>
<td><strong>Weight and thickness:</strong></td>
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<tr>
<td>Weight of five compacts of every formulation were taken and weighed individually on a digital balance (Fisher Brand PS-200). The average weights were taken and the film thickness was measured using digital micrometer (Mitituo, New Delhi, India) at different places and the mean value was calculated.</td>
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<td><strong>Surface pH:</strong></td>
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<td>For determination of surface pH, three buccal compacts of each formulation were allowed to swell for 2 h on the surface of agar plate. The surface pH was measured by using a pH paper placed on the surface of swollen patch. A mean of three reading was recorded.</td>
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<td><strong>Percent swelling:</strong></td>
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<td>Buccal compact was weighed, placed in a 2% agar gel plate and incubated at 37 ± 1 °C. At regular interval of one-hour time intervals (for 3 h), the dosage form was removed from the Petri dish and excess surface water was removed carefully using the filter paper. The swollen patch was then reweighed and the swelling index was calculated. The experiments were carried out in triplicate and average values were reported.</td>
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<td><strong>Folding endurance:</strong></td>
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<td>Folding endurance was determined by repeatedly folding a compact at the same place till it broke. The number of times, the compact could be folded at the same place without breaking gave the value of folding endurance (Table 2).</td>
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<td><strong>Content Uniformity:</strong></td>
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| Drug content uniformity was determined by dissolving the compact by homogenization in 100mL of an isotonic phosphate buffer (pH 6.8) for 8h with occasional shaking. The 5 mL solution was taken and diluted with isotonic phosphate buffer pH 6.8 up to 20 mL, and the resulting solution was filtered through a 0.45 mm Whatman filter paper. The drug content was determined after proper
dilution at 290 nm using a UV spectrophotometer (Shimadzu, SPD-10 A VP, Japan). The experiments were carried out in triplicate.

**Ex Vivo Residence Time:**
The ex vivo mucoadhesion time was studied after application of buccal compact on freshly cut sheep buccal mucosa. The fresh sheep buccal mucosa was fixed in the inner side of a beaker, about 2.5 cm from the bottom, with cyanoacrylate glue. One side of each compact was wetted with 1 drop of phosphate buffer (pH 6.8) and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The beaker was filled with 200 mL of phosphate buffer (pH 6.8) and was kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate was applied to simulate the buccal cavity environment, and patch adhesion was monitored for 12 hours. The time required for the compact to detach from the sheep buccal mucosa was recorded as the mucoadhesion time.

**In Vitro Drug Release:**
The US Pharmacopoeia XXIII rotating paddle method was used to study drug release from the buccal compacts; 200 mL of phosphate buffer (pH 6.8) was used as the dissolution medium, at 37.0 ± 0.5°C, and a rotation speed of 50 rpm was used. One side of the buccal compact was attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was put in the bottom of the dissolution vessel. 5 ml Samples from each formulation were withdrawn at 1 hour interval and replaced with fresh medium. The samples were filtered through 0.45-µm Whatman filter paper and analyzed using a UV spectrophotometer at 290 nm.

**RESULTS AND DISCUSSION**

**Formulation of three layered buccal compact**
The amount of PRPH in the formulation was established according to its clinical use. Three layered buccal compact was prepared at various concentration of polymers as presented in Table 1. The backing layer contains EC and Magnesium stearate. EC was selected because of its hydrophobic nature and low water permeability, moderate flexibility, thus preventing drug loss by backward diffusion. Magnesium stearate was included as anti-adherent. PRPH, sodium alginate and HPMC K4M comprises the core layer. HPMC K4M is a water swellable polymer which controls the release of drug from the core layer by forming a matrix or gel layer. To increase the release of drug, sodium alginate was included as a water soluble polymer results in formation of porous channel. In order to study the effect of concentration of HPMC K4M, ratio of HPMC K4M: sodium alginate was increased by keeping the total polymer content at 1:1 ratio with respect to drug. Peripheral layer which adheres to the mucosa should possess good bioadhesive strength and also control the release. Hence, carbopol 934P, a potential mucoadhesive polymer along with HPMC K4M was included in peripheral layer. Directly compressible lactose was included as diluent for it’s high aqueous solubility and increase in the rate and amount of water imbibitions to peripheral layer thereby increasing the rate of swelling of polymers in peripheral layer which in turn forms a gelled matrix to control the release. As reported previously in formulating a water-soluble drug MT for sustained release, hydration of polymer is necessary in a short time, hence HPMC K4M and lactose were included.

**Thickness, weight variation and assay**
The average thickness of all prepared buccal compacts ranged from 0.89 ± 0.02 to 1.16 ± 0.03 mm. The average weight of 05 buccal compacts of each formula was range from 78-84 mg, which provided good weight uniformity. In all the formulations, the assay for drug content was found to be uniform among different batches of the buccal compacts and ranged from 64.83 to 91.63% of the theoretical value (Table 2).

**Surface pH and Swelling studies:**
Compacts surface pH ranges from 5.81 – 6.42 were found around neutral pH and hence no mucosal irritation was expected. The swelling of the compacts were observed in agar plate and shown in table 2. Swelling was more pronounced in (patches) all formulation except (comparatively less) in 6 which contain HPMC and carbopol in a ratio of (1:2) which may due to approximate quantity of ethyl cellulose as that of HPMC.

**Table 2**

**In vitro release:**
The release data of PRPH from all the patches are given in Fig. 2. A perusal to fig. 2 indicated that the drug release was higher in compact with higher concentration of HPMC (compact 1, 2, and 3). At pH 6.6, carbopol is present in the ionized state and as a result the polymeric network gets loosened comparatively, attributing for the
higher drug release\(^2\). An increase in the polymer content was associated with a corresponding decrease in the drug-release rate\(^2\).

Fig. 2
The compact No. 6 was considered to be the optimal compact on the basis of its moderate swelling, convenient ex vivo residence time, ex-vivo mucoadhesive strength, and adequate in-vitro drug release. Thus compact from this batch was thus optimized for investigation of in vitro drug permeation through sheep buccal mucosa and a stability study in natural human saliva.

Measurement of bioadhesion:
Bioadhesion studies were carried out ex-vivo using freshly obtained mucosa without any further treatment. The peak force of detachment was determined by measuring the tensile strength required for complete breakdown of bioadhesive bond between the dosage form and the surface of mucosa. The apparatus and procedure adapted was previously described\(^3\). The backing layer was glued to the Teflon® cylinder while the peripheral layer was exposed to the mucosal surface (Fig. 3). Each measurement was carried out in triplicate and the results averaged.

Residence time
The ex-vivo residence time with sheep buccal mucosa in phosphate buffer (pH 6.8) varied from 2.85 to 4.30 hours (Table 2). The three layer patch containing carbopol in higher concentration indicates good residence time as it is bioadhesive polymer.

CONCLUSION:
The present study indicates that, the peripheral layer, core layer and backing layer of buccal dosage form have their own characteristic which gives novel ideas. Different ratios of carbopol and HPMC have rate controlling effect over the time. At higher polymer concentration in peripheral layer, the PRPH release from the system can be controlled with good bioadhesion. The peripheral polymer ratio is a major factor affecting the release and bioadhesive strength of the three layered buccal patches. Ethyl cellulose and magnesium stearate plays important role to avoid backward diffusion through backing layer. So lastly we conclude that, three layered can meet the ideal requirement for buccal devices, which can be good way to bypass the extensive hepatic first pass metabolism, avoid the loss of drug into the saliva and increase bioavailability.

Fig. 1: A typical three layered buccal compact

Fig. 2: Release data of Propranolol HCl upto 8 Hour for P 1 to P 6
Table 1: Composition of three layered buccal compacts (in mg)

<table>
<thead>
<tr>
<th>Compact Code</th>
<th>Peripheral layer</th>
<th>Core layer</th>
<th>Backing layer</th>
<th>Total weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Code</td>
<td>Carbopol</td>
<td>HPMC</td>
<td>Lactose</td>
<td>PRPH</td>
</tr>
<tr>
<td>1</td>
<td>45</td>
<td>35</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>30</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>25</td>
<td>20</td>
<td>60</td>
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<tr>
<td>4</td>
<td>60</td>
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<td>20</td>
<td>60</td>
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<tr>
<td>5</td>
<td>65</td>
<td>15</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>10</td>
<td>20</td>
<td>60</td>
</tr>
</tbody>
</table>

Table 2: Primary evaluation parameter for buccal compact

<table>
<thead>
<tr>
<th>Compact Code</th>
<th>Thickness (mm)</th>
<th>eight (mg)</th>
<th>Swelling index(%) (3h)</th>
<th>Folding endurance</th>
<th>Content uniformity</th>
<th>In vitro residence time(h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.13 ± 0.02</td>
<td>84 ± 0.36</td>
<td>48.4 ± 1.21</td>
<td>&gt;200</td>
<td>77.21</td>
<td>2.85</td>
</tr>
<tr>
<td>2</td>
<td>0.89 ± 0.02</td>
<td>78 ± 0.41</td>
<td>43.0 ± 1.08</td>
<td>&gt;200</td>
<td>91.63</td>
<td>3.30</td>
</tr>
<tr>
<td>3</td>
<td>1.09 ± 0.01</td>
<td>86 ±1.09</td>
<td>45.7 ± 0.87</td>
<td>&gt;200</td>
<td>86.28</td>
<td>4.10</td>
</tr>
<tr>
<td>4</td>
<td>0.92 ± 0.04</td>
<td>87 ± 1.11</td>
<td>43.1 ± 0.36</td>
<td>&gt;200</td>
<td>82.81</td>
<td>3.75</td>
</tr>
<tr>
<td>5</td>
<td>1.16 ± 0.03</td>
<td>82 ± 0.78</td>
<td>46.8 ± 1.03</td>
<td>&gt;200</td>
<td>64.83</td>
<td>3.15</td>
</tr>
<tr>
<td>6</td>
<td>1.12 ± 0.03</td>
<td>79 ± 0.41</td>
<td>38.3 ± 0.21</td>
<td>&gt;200</td>
<td>71.26</td>
<td>4.30</td>
</tr>
</tbody>
</table>

REFERENCES


