EFFECTS OF MUCOADHESIVE POLYMERS COMBINATION ON THE PROPERTIES OF LISINOPRIL BUCCAL TABLETS PREPARED BY WET GRANULATION METHOD

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ABSTRACT
Objective: The objective of this study was to prepare and characterize buccoadhesive tablets of Lisinopril using different Mucoadhesive polymers such as HPMC K100M, CMC, Chitosan, and combination.

Methods: Six tablet formulations were prepared by wet granulation method with varying concentrations of polymers using combination of two polymers in each formulation. The prepared tablets were evaluated for physiochemical parameters such as hardness, thickness, content uniformity, weight variation, surface pH, and swelling studies. The prepared tablets were also evaluated for bioadhesive strength and in vitro drug release.

Results: In vitro bioadhesive strength and in vitro release studies showed that formulation (F6) containing HPMC K100M and CMC in the ratio of (4:1) showed good mucoadhesive strength and maximum drug release in 6 hrs. The in vitro release kinetics studies reveal that all formulations fit well with zero order kinetics followed by Korsmeyer-Peppas.

Conclusion: From the results it can be concluded that the formula (F6) will be promising drug delivery in buccal cavity for the treatment of anti hypertension with high possibility of increase in bioavailability due to avoidance of first pass effect.

Keywords: Lisinopril, Buccoadhesive tablets, Wet granulation, Combined polymers.

INTRODUCTION
Mucoadhesive drug delivery system has a high potential of being useful means of delivering drugs to the body throughout targeting the stratified squamous epithelium which is supported by a connective tissue lamina propria in buccal mucosal membrane [1]. Drug penetrating into the membrane passes through net of capillaries & arteries in lamina propria and reaches the systemic circulation through internal jugular vein [2].

This drug delivery system utilizes property of bioadhesion of certain water soluble polymers which become adhesive on hydration and hence can be used for targeting buccal mucosa (lining of the cheek) to the systemic circulation [3].

The mucoadhesive drug delivery system appears to offer a number of advantages, like enhancing drug bioavailability due to avoidance of first-pass metabolism , ease of therapy termination in case of toxicity by removing the dosage form from the buccal cavity, less frequency of administration and therefore better patient compliance , significant cost reduction may be achieved and dose-related local or systemic side effects may be reduced due to targeting of disease sites or tissues and reduction in fluctuation in steady-state levels[4,5]. Hence, adhesive mucosal dosage forms were prepared for oral delivery, in the form of adhesive tablets, adhesive gels, and adhesive patches [6].

From technical point of view, an ideal buccal dosage form must have the following three properties (a) a bioadhesive to retain the system in the oral cavity and maximize the intimacy of contact with mucosa (b) a vehicle the release the drug at an appropriate rate under the conditions prevailing in the mouth and (c) strategies for overcoming the low permeability of the oral mucosa [7].

The strong adhesive contact to the mucosa is established by using mucoadhesive polymers as excipients. In formulation of buccal mucoadhesive drug delivery system, various polymer structural and functional groupings can have an effect on degree of polymer/mucus interaction and control the release rate of drug [8].

Lisinopril is a synthetic peptide derivative, is an oral long acting angiotensin converting enzyme inhibitor (ACE) [9]. It is widely used in treatment of hypertension; it has the biological half-life of 12.6 hrs. Its bioavailability is 25% and it is mainly excreted in urine [10].

The aim of the present study was to develop a bioadhesive sustained-release tablets for buccal drug delivery of lisinopril using different polymers (carboxy methyl cellulose, chitosan and hydroxypropylmethy cellulose) in order to increase bioavailability, reduce dosing frequency and improve patient compliance.

MATERIALS AND METHODS
Materials
Lisinopril, Hydroxypropyl methylcellulose (HPMC K100M), Carboxy methylcellulose (CMC) and Chitosan were purchased from Sigma Chemical Co., USA. All other chemicals and reagents used were of analytical reagent grade.

Methods
Preparation of Mucoadhesive Buccal Tablets
Mucoadhesive buccal tablets of Lisinopril were prepared by wet granulation method using different polymers as shown in Table (1). All the ingredients were screened through sieve no. 60 and then blended (except magnesium stearate) for 15 min. A blend of all ingredients was granulated with 95% alcohol. The wet masses were passed through sieve no. 12 and the resulting granules were dried at 40°C. Finally magnesium stearate was added and mixed for 5min. The blend was compressed into 130 mg tablets using a single flat punch (KORSCH Erwela, Frankfurt Germany).

Evaluation of Flowability of prepared granules
Fifty gm of the prepared granules will poured through glass funnel which had a distance of 10 cm from the flat surface. The height of the heap (h) formed as well as the radius of the heap (r) was measured. The value of angle of repose was calculated by using the formula: \( \tan \theta = h / r \) [11].

Evaluation of Prepared Mucoadhesive Tablets
Thickness, Weight variation test, Hardness
The thickness, weight variation, hardness of buccal tablets was determined using digital micrometer, electronic balance and monsanto hardness tester respectively. Twenty individual tablets from each batch were used and the average results were calculated according to USP Specification [12, 13].
Friability

The friability of 10 tablets will determine using Roche friabilator (Electrolab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets will place in the friabilator and will subject to 100 revolutions. Tablets will dedust using a soft muslin cloth and reweigh [14].

Drug content uniformity

Ten tablets from each formulation were taken, crushed and mixed. From the mixture, 10 mg of Lisinopril equivalent was extracted thoroughly with 100 ml of methanol. The amount of drug present in extract was determined using Shimadzu UV spectrophotometer at 246 nm.

In vitro swelling studies

Buccal tablets were weighed individually (designated as W) and in agar gel plates 2% in a petri dish incubated at 37±1°C for up to 5 hr. At regular intervals of time, the swollen tablets were removed from petri dish, the excess water is removed with the help of filter paper weighed again (Wt). The swelling index (SI) can be calculated using the following formula [15].

\[
SI = \left(\frac{W_t - W}{W}\right) \times 100
\]

Surface pH

The surface pH of the buccal tablets was determined in order to investigate the possibility of any in vivo side effects. An acidic or alkaline pH may cause irritation to the buccal mucosa. The method developed by Battenberg et al was used [16]. A combined glass electrode was used for this purpose. The tablets were allowed to swell by keeping it in contact with distilled water (5ml) (pH 6.5 ± 0.05) for 2 hrs 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 min.

In vitro Mucoadhesive Study

Mucoadhesive strength of the tablets was measured on a modified two arm physical balance. Sheep buccal mucosa was used as biological membrane for the studies. The mucosa was obtained from the local slaughter house and stored in buffer at 4°C from the time of collection and used within 3 hrs of procurement. The membrane was washed with distilled water and then with phosphate buffer pH 6.8 at 37°C. Force needed to detach tablet from mucus membrane is called the mucoadhesive force and is represented in Newton [17].

\[
\text{Force of adhesion} (N) = \text{Mucoadhesive strength (g)} \times 100 \times 9.81
\]

In vitro drug release study

The tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed on the other side of the tablet. The tablet was further fixed to a 2x2 cm glass slide with a solution of cyanoacrylate adhesive. In vitro drug release studies were carried out in 900 ml of phosphate buffer solution pH 6.6 for 6 h using a USP dissolution paddle apparatus (II) (Copley scientific, UK.) at 50rpm and 37 ± 0.5°C. At predetermined time intervals samples were withdrawn and replaced with fresh medium. The samples were filtered, dried suitably and then analyzed spectrophotometrically at 246nm. All dissolution studies were performed in triplicate. The mechanism of drug release from the buccal tablets was determined by finding the best fit of the release data to Zero order, First order, Higuchi and Korsmeyer-Peppas plots [18].

**RESULTS AND DISCUSSION**

The main objective of this study was to develop buccoadhesive tablets to release the drug at mucosal site for extended period of time using two buccoadhesive polymers each time. HPMC K100M, Chitosan and CMC were selected as buccoadhesive polymers for retaining the drug for extended period. All the formulations passed test for Angle of repose, weight variation, content uniformity and show acceptable results with respect to drug content (97 to 99) and friability (0.12 to 0.58%) as shown in Table (2). The high hardness value of range (12.5-14) indicates that the method of preparation of tablets has the main effect on mechanical strength of prepared tablets. The surface pH values of 5 to 6 indicate no risk of mucosal damage or irritation.

On the modified physical balance and measure the force (N) required detaching the tablet. The bioadhesive property of the prepared tablets of the formulations (F1, F2, and F3) with combined polymers, HPMC K100M and Chitosan showed the bioadhesive strengths of 2.64, 3.12, and 3.43 N respectively. The formulations (F4, F5, and F6) with HPMC K100M and CMC showed the bioadhesive strengths of 3.62, 3.77, and 4.16 N respectively. The formulations prepared tablets required detaching the tablet.

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisinopril</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>HPMC K100M</td>
<td>32.5</td>
<td>39</td>
<td>52</td>
<td>32.5</td>
<td>39</td>
<td>52</td>
</tr>
<tr>
<td>Chitosan</td>
<td>32.5</td>
<td>26</td>
<td>13</td>
<td>32.5</td>
<td>26</td>
<td>13</td>
</tr>
<tr>
<td>CMC</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Mannitol</td>
<td>26</td>
<td>26</td>
<td>26</td>
<td>26</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Lactose</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Mg. Stearate</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
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<tr>
<td>Tak</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Total weight</td>
<td>130</td>
<td>130</td>
<td>130</td>
<td>130</td>
<td>130</td>
<td>130</td>
</tr>
</tbody>
</table>
Table 2: Physicochemical parameters of Lisinopril buccal tablets

<table>
<thead>
<tr>
<th>Formula No.</th>
<th>Hardness (Kg/cm²)</th>
<th>Thickness (mm)</th>
<th>Weight average (mg)</th>
<th>Assay (%)</th>
<th>Surface pH</th>
<th>Mucoadhesive force (N)</th>
<th>Swelling index at 5hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>14.0±0.23</td>
<td>3.2±0.05</td>
<td>132.5±1.4</td>
<td>98±1.9</td>
<td>5.0±0.02</td>
<td>2.64±0.01</td>
<td>1.8±0.007</td>
</tr>
<tr>
<td>F2</td>
<td>13.5±0.51</td>
<td>3.1±0.03</td>
<td>130.0±2.7</td>
<td>97±1.2</td>
<td>5.0±0.01</td>
<td>3.12±0.02</td>
<td>2.4±0.012</td>
</tr>
<tr>
<td>F3</td>
<td>13.5±0.48</td>
<td>3.2±0.02</td>
<td>131.0±1.9</td>
<td>98±1.7</td>
<td>5.2±0.03</td>
<td>3.43±0.04</td>
<td>2.68±0.037</td>
</tr>
<tr>
<td>F4</td>
<td>14.0±0.22</td>
<td>3.1±0.03</td>
<td>131.0±2.2</td>
<td>99±1.4</td>
<td>5.5±0.05</td>
<td>3.62±0.01</td>
<td>1.80±0.021</td>
</tr>
<tr>
<td>F5</td>
<td>14.0±0.39</td>
<td>3.1±0.04</td>
<td>130.5±2.6</td>
<td>98±1.3</td>
<td>5.9±0.06</td>
<td>3.77±0.03</td>
<td>2.55±0.062</td>
</tr>
<tr>
<td>F6</td>
<td>12.5±0.34</td>
<td>3.2±0.06</td>
<td>130.5±1.4</td>
<td>98±1.8</td>
<td>6.0±0.04</td>
<td>4.16±0.01</td>
<td>3.32±0.033</td>
</tr>
</tbody>
</table>

Fig. 1: *In vitro* Lisinopril release profiles from buccal tablets (F1-F6)

*In-vitro* drug release data of F1 to F6 were fitted to zero order, first order, Higuchi and Korsmeyer-Peppas equations to ascertain the pattern of drug release (Table 3). The R² values were found to be higher in zero-order followed by Korsmeyer-Peppas which indicates all the formulations followed zero-order release pattern.

Table 3: Release kinetics of different formulations of Lisinopril buccal tablets

<table>
<thead>
<tr>
<th>Formula No.</th>
<th>Zero Order (R²)</th>
<th>First Order (R²)</th>
<th>Higuchi (R²)</th>
<th>Korsmeyer-Peppas (R²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.946</td>
<td>0.833</td>
<td>0.873</td>
<td>0.941</td>
</tr>
<tr>
<td>F2</td>
<td>0.991</td>
<td>0.971</td>
<td>0.940</td>
<td>0.988</td>
</tr>
<tr>
<td>F3</td>
<td>0.965</td>
<td>0.950</td>
<td>0.945</td>
<td>0.962</td>
</tr>
<tr>
<td>F4</td>
<td>0.985</td>
<td>0.970</td>
<td>0.895</td>
<td>0.974</td>
</tr>
<tr>
<td>F5</td>
<td>0.987</td>
<td>0.881</td>
<td>0.939</td>
<td>0.982</td>
</tr>
<tr>
<td>F6</td>
<td>0.987</td>
<td>0.963</td>
<td>0.894</td>
<td>0.982</td>
</tr>
</tbody>
</table>

CONCLUSION

It can be concluded that formulation F6 using combination of two mucoadhesive polymers in ratio of 4:1 (HPMC K100M: CMC) could be used to release the Lisinopril in buccal cavity for extended period of time without the risk of mucosal irritation and as promising alternative routes of administration to avoid first pass effect.

REFERENCES