FORMULATION AND EVALUATION OF A BUCCOADHESIVE CAPTOPRIL TABLETS

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Buccoadhesive tablets of captopril were prepared by direct compression of the drug with different polymers; Carbopol 934 (CP 934), Eudragit RS 100 (EU RS 100), Chitosan (Ch), Hydroxypropyl methylcellulose (HPMC) and Polyvinylpyrrolidone K30 (PVP K30) either singly or in blends of different ratios. The tablets were evaluated for their weight variation, drug content uniformity, friability, hardness, swelling index, surface pH, in-vitro

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bioadhesive strength and release characteristics. The bioavailability and the pharmacokinetics parameters of captopril from two selected formulations (CP 934:HPMC 6:4 and Ch:HPMC 6:4) were evaluated.

The in-vitro bioadhesive strength and release characteristics were found to be a function of the type of polymer and ratio of polymer blends. Swelling and bioadhesive characteristics were determined for both plain and medicated tablets. The high concentration of carbopol and chitosan containing formulations showed the greatest adhesive strength. The mean pharmacokinetic parameters of captopril after buccoadhesive tablet administration were: C\text{max} 506.9 \text{ng/ml}, T\text{max} 4 \text{hr}, AUC\text{0-8} 2359.5 \text{ng.hr/ml} for CP 934: HPMC (6:4), while C\text{max} 429.02 \text{ng/ml}, T\text{max} 2.67 \text{hr}, AUC\text{0-8} 1637.43 \text{ng.hr/ml} for Chitosan: HPMC (6:4). In comparison, in case of oral administration of control tablet the C\text{max} 591.28 \text{ng/ml}, T\text{max} 1.5 \text{hr}, AUC\text{0-8} 1869.29 \text{ng.hr/ml}.

INTRODUCTION

Captopril, (1-[(2S)-3-mercaptop-2-methyl propionyl]-L-proline), an orally active inhibitor of angiotensin-converting enzyme (ACE)\textsuperscript{11,2}, has been widely used for the treatment of hypertension and congestive heart failure. The drug is considered as a drug of choice in antihypertensive therapy due to its effectiveness and low toxicity\textsuperscript{3-6}.

Captopril is freely water soluble and has a relatively short elimination half life (1.7 hr) in plasma after an oral dose\textsuperscript{7}. Food may decrease oral absorption of captopril by up to 25–40\%\textsuperscript{8}. Captopril is usually prescribed to patients who are chronically ill and require long-term treatment for its therapeutic benefit. Development of a once daily captopril oral formulation would be a significant advantage for patient compliance which is accompanied by minimization of the drug side effects as a result of reduction of the drug blood concentration fluctuations especially in long-term therapy\textsuperscript{9-11}.

Mucoadhesive drug delivery system is a new system of drug delivery and has recently gained great concern in pharmaceutics\textsuperscript{12}. The most important goals in mucoadhesion consist of drug targeting, controlled and sustained releasing, increasing of residence time, decreasing of adverse effects and minimizing of the first-pass effect and long-term drug delivery\textsuperscript{13,14}. The buccal mucosa has been investigated for local and systemic delivery of therapeutic peptides and other drugs that subjected to first-pass metabolism or are unstable within the rest of the gastrointestinal tract\textsuperscript{15}.

Mucosal-adhesive polymers are hydrophilic macromolecules contain-
ing numerous hydrogen bond-forming groups. Bioadhesive polymers not only cause the adhesion effects, but also control the release rate of drug. Also, different blends of two or more adhesive polymers may be used as mucoadhesive systems.

Water soluble drugs are considered difficult to deliver in the form of sustained or controlled release preparation due to their susceptibility to "dose dumping phenomenon". Attempts have been made to regulate their release process by using of mucoadhesive polymers in order to achieve a once-a-day dose treatment.

The short half-life and severe first pass metabolism of captopril makes it suitable for administration via a buccal delivery system that provides controlled drug delivery, by passing first-pass effect. Successful buccal delivery requires at least three of the following: (a) a bioadhesive to retain the drug in the oral cavity and maximize the intimacy of contact with the mucosa; (b) a vehicle that releases the drugs at an appropriate rate under the conditions prevailing in the mouth; and (c) strategies for overcoming the low permeability of the oral mucosa.

The objective of the present study was to formulate captopril buccoadhesive tablets. The prepared tablets were evaluated for their physical properties and in-vitro release characteristics. The in-vitro bioadhesive strength, swelling behavior and surface pH of the tablets were also considered. In addition, the bioavailability and the pharmacokinetic parameters of captopril from two selected formulations on the basis of good physical properties regarding bioadhesive strength and acceptable sustained-release profiles were studied.

**EXPERIMENTAL**

**Material**

Captopril (CP), was obtained from Chang Zhou Pharmaceutical Company (Chang Zhou, China). Hydroxpropylmethyl cellulose 4000 cp (HPMC) was provided by Colorcon Company (Shanghai, China). Polyvinylpyrrolidone K₃₀ (PVP K₃₀) was obtained from BASF (Ludwigshafen, Germany). Chitosan (Ch), high molecular weight was supplied from Sigma-Aldrich chemie GmbH Chemical Co. Germany. Carbopol 934 (CP 934) was obtained from BF Goodrich, Hounslow, U. K. Eudragit RS 100 (Eu RS 100) and spray-dried lactose (Zeparoxe), were kindly provided by Röhm Pharma (Darmstadt, Germany). Magnesium stearate was supplied from European Egyptian Pharmaceutical Industries, Egypt. D(-) mannitol, potassium dihydrogen orthophosphate, EDTA, acetic acid and sodium dibasic phosphate were kindly supplied by Adwic, El Nasr Pharmaceutical Chemicals, Egypt. P-bromophenacyl bromide (p-BPB) and Diazepam were supplied from Sigma Chemical Company, St Louis, USA. Acetonitrile for HPLC was supplied from Sigma-Aldrich Chemie GmbH Chemical Co., Germany.
distilled water has been used in HPLC assay. All other chemicals were of an analytical grade and were used without further purification.

**Apparatus**


**Methods**

**Preparation of buccoadhesive tablets**

Captopril bioadhesive tablets (160 mg) were prepared by mixing the drug (50 mg) with 100 mg of each of the selected polymers or their mixtures as mentioned in Table 1. Each tablet contains 1% magnesium stearate, 1% mannitol and spray dried lactose and then compressed directly on a 9-mm flat-faced punches and die using the single punch tablet press. Control tablets (160 mg) containing 50 mg drug, 1% magnesium stearate, 1% mannitol and spray dried lactose were prepared in a similar manner as mentioned above.

**Evaluation of tablets**

**Physical characteristics**

The prepared tablets were evaluated for their uniformity of weight, thickness, hardness, friability and drug content uniformity (USP XXIII).

**In-vitro drug release**

**In-vitro** release studies of captopril were performed in 500 ml of phosphate buffer solution (pH 6.6) at 37±0.5°C using the USP XXVII dissolution apparatus 2 (paddle). The rotational speed of the paddles was set at 50 rpm throughout the dissolution studies. Each tablet was inserted in a metal die having a central hole which was sealed at the lower end with paraffin wax, so that, the drug could be released from one surface of tablet. Samples of 1 ml were withdrawn at different time intervals (0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5 and 6 hrs), diluted with 0.1 N sodium hydroxide and then analyzed spectrophotometrically at 230 nm. The same volume of buffer solution of pH 6.6 was added to the dissolution medium after each sampling. Blank experiments were carried out using non-medicated tablets and served as control. The obtained data are the mean of the release of three tablets.
Table 1: Compositions of prepared buccoadhesive captapril tablet formulae.

<table>
<thead>
<tr>
<th>Formulae</th>
<th>Formulae Code</th>
<th>Drug</th>
<th>CP 934</th>
<th>Chitosan</th>
<th>EU RS 100</th>
<th>PVP K30</th>
<th>HPMC</th>
<th>Mg stearate 1%</th>
<th>Spray dried Lactose</th>
<th>Mannito 1%</th>
<th>Total weight</th>
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<td>50</td>
<td>20</td>
<td>80</td>
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<td>6.8</td>
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<tr>
<td>CP 934:HPMC (4:6)</td>
<td>CH 2</td>
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<tr>
<td>CP 934:HPMC (6:4)</td>
<td>CH 3</td>
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<tr>
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<td>PVP K30:HPMC (4:6)</td>
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Swelling studies of buccoadhesive tablets

Three tablets of each formulation were separately placed in a series of baskets made of stainless steel mesh. Each set (the tablet and the basket) was accurately weighed before being vertically placed in a beaker containing 40 ml phosphate buffer of pH 6.6 at 37°C. At time intervals (0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, and 6 hrs), excess fluids were removed; the set containing the swollen tablet was weighed. The weight of the swollen tablet was calculated. The swelling index (S.I.) was determined from the following relation:

\[ S.I. = \frac{(W_t - W_o)}{W_o} \]

Where,
- \( W_t \) The weight of swollen tablet at each time interval \( t \)
- \( W_o \) The initial weight of each tablet.

Surface pH of the tablets

The surface pH of tablets was determined to evaluate the possible irritative effects of the formulation on the buccal mucosa. The tablets were left to swell for 2 hrs in 2 ml of distilled water; after this time the surface pH was measured by placing the electrode in contact with the surface of tablets.

In-vitro bioadhesion test

The tensile strength required to detach the bioadhesive tablet from the mucosal surface, obtained from rabbit intestine, was applied as a measure for the bioadhesive performance. The apparatus is locally assembled and is composed mainly of a modified two-arm balance (Fig. 1). A piece of 0.636 cm² surface area of rabbit intestinal mucosa was fixed to the stainless steel piece with cyanoacrylate adhesive and then placed in a beaker. Saline solution was added into the beaker up to the upper surface of intestinal mucosa to maintain intestinal mucosal viability during the experiments.

Fig. 1: Modified apparatus for in-vitro bioadhesion test.
The tablet was attached to the upper clamp of the apparatus and then the beaker was raised slowly until contact between rabbit intestinal mucosa and tablet was established. A preload of 50 gm was placed on the clamp for 5 min. (preload time) to establish adhesion bonding between tablet and rabbit intestinal mucosa. The preload and preload time were kept constant for all the formulations. After completion of the preload time, preload was removed from the clamp, and water was then added into the beaker from the burette at a constant rate. The addition of water was stopped when tablet was detached from either rabbit intestinal mucosa. The weight of water required to detach tablet from intestinal mucosa was measured and expressed as weight (gm). This experiment was repeated, with fresh mucosa, three times and the mean was considered.

The bioadhesion force was calculated per unit area of the tablet as follows:

\[ F = \frac{W \cdot g}{A} \]

where,
- \( F \): is the bioadhesion force (dyne.cm\(^2\))
- \( W \): is the minimum weight required to break the bioadhesive bond (gm)
- \( g \): is the acceleration due to gravity (cm.sec\(^{-2}\)) = 981 cm.sec\(^{-2}\)
- \( A \): is the surface area of the tablet (cm\(^2\)) = \((\pi r^2) = \frac{22}{7} \times (0.45)^2 = 0.636 \text{ cm}^2\)

**Determination of the in-vitro residence time**

The in-vitro residence time was determined using a locally modified USP disintegration apparatus (Fig. 2). The disintegration medium was composed of 800 ml phosphate buffer solution (pH 6.6) maintained at 37±0.5°C. A segment of rabbit intestinal mucosa, 5 cm long, was glued to the surface of a glass slab, vertically attached to the apparatus. The buccoadhesive tablet was hydrated from one surface using 15 μl buffer and then the hydrated surface was brought into contact with mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that it was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the tablet from the mucosal surface was recorded. This experiment was repeated, with fresh mucosa, three times and the mean was considered.

**Fig. 2:** Schematic diagram of the apparatus used for the in-vitro determination of residence time.

where,
- (S) glass slab
- (D) disintegration apparatus
- (B) glass beaker
- (M) mucosal membrane
- (T) mucoadhesive tablet
- (P) phosphate buffer pH 6.6
Bioavailability study

For this study, two formulations were selected in comparison with the control. The two selected formulae are CH₃, KH₃ (Table 1) on the basis of their acceptable physical characteristics, good bioadhesive force and sustained release profiles.

In this study, three groups (6 each) of albino rabbits weighing 2.0-2.5 kg were selected. The rabbits were fasted for 24 hr before drug administration and anaesthetized with secobarbital (25 mg/kg). A buccal adhesive tablet containing 25 mg captopril was attached on the cheek pouch of each rabbit. For control tablet, the tablet was taken orally by a stomach tube. At different time intervals (0.5, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hrs after drug administration), blood samples were taken from the ear vein. Venous blood samples (2 ml) were withdrawn to the tubes containing 0.05 ml of EDTA (0.1 M) and 0.05 ml of ascorbic acid (0.1 M). The blood samples were centrifuged for 10 min at 3000 rpm and 0.5 ml of plasma was added immediately (time <15 min) to the screw-cap glass tube containing 0.03 ml of p-BPB (1 mg/ml) in acetonitrile and 0.05 ml of sodium hydroxide (0.1 M). The sample was shaken for 15 min and allowed to stand to 30 min, to essentially complete the process of derivatization. Resulting captopril-adduct was stabilized by adding 0.075 ml of HCl (1 M). The obtained mixture was stored in the frozen state for subsequent assays.

Analysis of the plasma samples

The plasma concentration of captopril was determined according to the HPLC method reported by Jankowski et al., with a slight modification. To 1 ml of plasma, the internal standard, diazepam (1 µg/ml) and 0.15 ml of acetate buffer, pH 4.0 (0.2 M) were added. Extraction was made by 4.0 ml of benzene. After centrifugation (10 min at 4000 rpm), the organic phase was evaporated to dryness under a stream of nitrogen and reconstituted in 0.5 ml of mobile phase, then filtered through millipore filter (0.45 µm). An aliquot of 20 µl was injected into the column. Separation was performed on reversed phase column C18 (5 µm particle size and 4.6 x 250 mm dimensions). The mobile phase used was a mixture of acetonitrile and 1% acetic acid (60:40% v/v) and was pumped at a flow rate 0.8 ml/min. The column temperature was maintained at ambient temperature. The U.V. detector was adjusted at 260 nm. Triplicate 20 µL injections of the filtrate were made for each standard sample to see the reproducibility of the detector at each concentration. A standard curve was plotted by analysis of drug-free plasma samples spiked with different amounts of captopril ranging from 25 to 2000 ng/ml. The peak height ratio of captopril to diazepam (as internal standard) was constructed against the concentration of captopril in plasma to obtain the standard calibration curve.
Pharmacokinetic parameters

The maximum plasma concentration ($C_{\text{max}}$) and the time required to reach maximum plasma concentration ($T_{\text{max}}$) after tablet administration were directly determined from the plasma concentration-time curves. Also, the area under the plasma concentration-time curve from 0 to 8 hr (AUC$_{0-8}$ hr) was calculated. Data are expressed as mean ± S.D. Statistical analysis was carried out using one way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparisons test. Statistical calculations were carried out using Instat - 2 computer program (Graphpad software Inc., V2. 04 San Diego, CA, USA).

RESULTS AND DISCUSSION

Tables 2 & 3 summarize the physical, mechanical and bioadhesive characteristics of the prepared tablets. The results revealed that, physical and mechanical properties of the prepared tablets were within the acceptable pharmacopoeal limits.

All the prepared tablets containing CP 934 and HPMC swelled but not eroded within 6 hrs. In case of tablets containing Ch: HPMC and Eu RS 100: HPMC swelled except their tablets in ratio of (6:4 and 8:2) were eroded. Also all tablets containing PVP K$_{30}$ in different ratios were eroded.

Table 2: Physical characteristics of buccoadhesive captopril tablets formulated with a single polymer.

<table>
<thead>
<tr>
<th>Physical characteristics</th>
<th>HPMC</th>
<th>Carbopol 934</th>
<th>Chitosan</th>
<th>Eudragit RS 100</th>
<th>PVP K$_{30}$</th>
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</thead>
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<tr>
<td>1- Tablet weight (mg)</td>
<td>160 ± 2.2</td>
<td>159 ± 1.99</td>
<td>161 ± 2.35</td>
<td>158 ± 1.8</td>
<td>159 ± 2.05</td>
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<td>mean ± SD</td>
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<tr>
<td>2- Tablet thickness (mm)</td>
<td>2.1 ± 0.09</td>
<td>2.2 ± 0.05</td>
<td>2.1 ± 0.04</td>
<td>1.9 ± 0.05</td>
<td>2 ± 0.08</td>
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<tr>
<td>mean ± SD</td>
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<td>3- Drug content (%)</td>
<td>99.5 ± 1.9</td>
<td>98.7 ± 2.2</td>
<td>97.6 ± 2.0</td>
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<td>mean ± SD</td>
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<td>4- Friability %</td>
<td>0.23 ± 0.06</td>
<td>0.35 ± 0.009</td>
<td>0.56 ± 0.023</td>
<td>1 ± 0.08</td>
<td>0.72 ± 0.06</td>
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<td>mean ± SD</td>
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<tr>
<td>5- Hardness (kg)</td>
<td>12 ± 2</td>
<td>9 ± 1.5</td>
<td>9 ± 1.9</td>
<td>2.5 ± 1.1</td>
<td>5 ± 1.6</td>
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<tr>
<td>mean ± SD</td>
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<tr>
<td>6- Swelling index (S.I.)</td>
<td>0.618 ± 0.005</td>
<td>0.984 ± 0.006</td>
<td>0.482 ± 0.008</td>
<td>——</td>
<td>0.005 ± 0.004</td>
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<td>(after 6 hr) mean ± SD</td>
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<tr>
<td>7- Surface pH</td>
<td>6.7 ± 0.15</td>
<td>3.5 ± 0.09</td>
<td>7 ± 0.3</td>
<td>5.5 ± 0.9</td>
<td>6 ± 0.52</td>
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<tr>
<td>mean ± SD</td>
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<td>8- Bioadhesion force x 10$^3$ (dyne.cm$^{-2}$)</td>
<td>30.83 ± 3.56</td>
<td>154.14 ± 3.51</td>
<td>47.78 ± 2.37</td>
<td>0.154 ± 0.07</td>
<td>15.41 ± 2.866</td>
</tr>
<tr>
<td>mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9- In-vitro residence Time (hr)</td>
<td>5.5 ± 1.3</td>
<td>&gt; 6 ± 1.25</td>
<td>6 ± 1.33</td>
<td>——</td>
<td>&lt; 30 min ± 3.2</td>
</tr>
</tbody>
</table>
### Table 3: Physical characteristics of buccoadhesive captopril tablets formulated with polymer blends.

<table>
<thead>
<tr>
<th>Physical characteristics</th>
<th>Formulae</th>
<th>CH 1</th>
<th>CH 2</th>
<th>CH 3</th>
<th>CH 4</th>
<th>KH 1</th>
<th>KH 2</th>
<th>KH 3</th>
<th>KH 4</th>
<th>PH 1</th>
<th>PH 2</th>
<th>PH 3</th>
<th>PH 4</th>
<th>EH 1</th>
<th>EH 2</th>
<th>EH 3</th>
<th>EH 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Tablet weight (mg)</td>
<td>mean ± SD</td>
<td>158±2.2</td>
<td>158±2.2</td>
<td>159±2.2</td>
<td>161±3.3</td>
<td>159±2.2</td>
<td>159±2.2</td>
<td>159±2.2</td>
<td>157±3.3</td>
<td>157±2.2</td>
<td>156±2.2</td>
<td>157±2.2</td>
<td>157±2.2</td>
<td>157±2.2</td>
<td>158±2.2</td>
<td>157±2.2</td>
<td></td>
</tr>
<tr>
<td>2- Tablet thickness (mm)</td>
<td>mean ± SD</td>
<td>2.1±0.01</td>
<td>2.18±0.08</td>
<td>2.02±0.05</td>
<td>2.00±0.05</td>
<td>2.10±0.02</td>
<td>2.15±0.05</td>
<td>2.07±0.03</td>
<td>2.10±0.04</td>
<td>2.05±0.07</td>
<td>2.18±0.08</td>
<td>2.18±0.10</td>
<td>2.08±0.05</td>
<td>2.10±0.06</td>
<td>1.98±0.04</td>
<td>2.18±0.08</td>
<td></td>
</tr>
<tr>
<td>3- Drug content (%)</td>
<td>mean ± SD</td>
<td>99±1.8</td>
<td>98.84±1.75</td>
<td>101.9±1.75</td>
<td>97.90±0.75</td>
<td>99.10±0.52</td>
<td>98.90±0.52</td>
<td>99.20±0.75</td>
<td>99.10±0.52</td>
<td>100.2±0.32</td>
<td>99.30±0.32</td>
<td>98.80±0.43</td>
<td>96.80±0.38</td>
<td>100.6±0.32</td>
<td>97.80±0.39</td>
<td>96.34±0.30</td>
<td>93.40±0.08</td>
</tr>
<tr>
<td>4- Friability %</td>
<td>mean ± SD</td>
<td>0.6±0.02</td>
<td>0.17±0.02</td>
<td>0.14±0.02</td>
<td>0.13±0.002</td>
<td>0.17±0.005</td>
<td>0.57±0.001</td>
<td>0.57±0.003</td>
<td>0.66±0.006</td>
<td>0.49±0.004</td>
<td>0.35±0.001</td>
<td>0.28±0.003</td>
<td>0.43±0.0008</td>
<td>0.87±0.0005</td>
<td>0.75±0.0007</td>
<td>0.91±0.0012</td>
<td>1.00±0.008</td>
</tr>
<tr>
<td>5- Hardness (Kg)</td>
<td>mean ± SD</td>
<td>3.5±1.5</td>
<td>8±1.17</td>
<td>7.5±1.17</td>
<td>7.5±1.17</td>
<td>6.5±1.21</td>
<td>6.75±1.12</td>
<td>6.0±1.12</td>
<td>6.5±1.12</td>
<td>6.5±1.12</td>
<td>6.5±1.12</td>
<td>5.3±1.12</td>
<td>5.3±1.12</td>
<td>5.0±1.12</td>
<td>5.0±1.12</td>
<td>4.5±1.12</td>
<td>4.0±1.12</td>
</tr>
<tr>
<td>6- Swelling index (S.I.)</td>
<td>after 6 hr</td>
<td>---</td>
<td>0.66±0.06</td>
<td>0.71±0.06</td>
<td>0.75±0.012</td>
<td>0.89±0.005</td>
<td>0.65±0.006</td>
<td>0.71±0.001</td>
<td>0.73±0.003</td>
<td>0.48±0.001</td>
<td>0.53±0.001</td>
<td>0.57±0.001</td>
<td>0.57±0.001</td>
<td>0.57±0.001</td>
<td>0.57±0.001</td>
<td>0.6±0.001</td>
<td>0.53±0.001</td>
</tr>
<tr>
<td>7- Surface pH</td>
<td>mean ± SD</td>
<td>---</td>
<td>6.3±0.12</td>
<td>5.7±0.23</td>
<td>5.6±0.17</td>
<td>5.2±0.24</td>
<td>5.9±0.24</td>
<td>6.2±0.32</td>
<td>6.6±0.41</td>
<td>6.6±0.13</td>
<td>6.12±0.35</td>
<td>6.6±0.32</td>
<td>6.2±0.22</td>
<td>5.5±0.12</td>
<td>5.8±0.32</td>
<td>5.6±0.41</td>
<td>5.2±0.32</td>
</tr>
<tr>
<td>8- Biadhesion force x 10¹⁰ (dyne cm⁻²)</td>
<td>mean ± SD</td>
<td>---</td>
<td>30.828±42.1</td>
<td>53.949±2.7</td>
<td>86.319±3.01</td>
<td>107.89±3.9</td>
<td>29.306±2.5</td>
<td>37.018±2.9</td>
<td>43.188±3.3</td>
<td>49.36±4.1</td>
<td>27.76±3.6</td>
<td>21.59±3.2</td>
<td>16.59±3.2</td>
<td>12.33±3.2</td>
<td>24.66±3.2</td>
<td>18.49±3.2</td>
<td>12.33±3.2</td>
</tr>
<tr>
<td>9- In-vitro residence time (hr)</td>
<td>mean ± SD</td>
<td>---</td>
<td>6±1.5</td>
<td>&gt;6±1.5</td>
<td>&gt;6±1.5</td>
<td>&gt;6±1.5</td>
<td>&gt;6±1.5</td>
<td>6±1.5</td>
<td>6±1.5</td>
<td>6±1.5</td>
<td>4±1.5</td>
<td>3±1.5</td>
<td>4±1.5</td>
<td>2±1.5</td>
<td>30±3.5</td>
<td>3±1.5</td>
<td>5±1.2</td>
</tr>
</tbody>
</table>

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The surface pH of the tablets varied according to the polymer nature and their ratios; tablet containing HPMC, Ch and PVP K\textsubscript{30} alone showed surface pH from 5 to 7, so, no irritation is expected from these polymers when applied to the buccal mucosa. On the other hand, CP 934 being acidic has a surface pH of 3.5. The acidity surface may induce high mucosal irritation. In case of combinations of CP 934 with HPMC, the values of pH were increased with reduced percentage of CP 934 in the formulation, so no mucosal irritation could be observed.

Figure 3 shows the swelling profiles of plain mucoadhesive tablets containing polymers. Tablets containing CP 934 alone showed a maximum swelling behavior at all time intervals. While, tablets containing HPMC showed comparatively limited water uptake; swelling index varied from 0.172 after 15 min to 0.618 after 6 hrs. Mortazavi and Smart\textsuperscript{30} suggested that, the limited hydration of HPMC was responsible for its prolonged duration of adhesion despite its relatively weak mucoadhesive strength. Chitosan tablets showed low swelling behavior at all time intervals. This could be explained by its poor water solubility at buccal pH. Hydrphobicity and weak gel forming capacity at neutral and alkaline pH were reported to be responsible for the weak swelling characteristics of chitosan\textsuperscript{31}. Polyvinylpyrrolidone K\textsubscript{30} tablets has minimum swelling behavior, swelling index= 0.05 after 15 min and swelling index= 0.217 after 1 hr, after which the polymer started to erode slowly in the medium. Eudragit RS 100 tablets show no swelling behavior. Figure 4 shows the different swelling behavior after 6 hrs for different tablet formulations containing different polymer combinations.
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Fig. (   ): Histogramic representation of swelling index of captopril tablets containing different polymers in phosphate buffer (pH 6.6)

0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
CP 934: HPMC
Ch:HPMC
Eu RS 100: HPMC
PVP K 30: HPMC

Fig. 4: Swelling index of captopril tablets containing different polymers in phosphate buffer (pH 6.6) after 6 hr.

The values of the bioadhesion force (Table 2), for tablets containing the polymer alone, show the superiority of the anionic polymer (F for tablet containing CP 934 alone = 154.14 x 10³ dyne.cm⁻²), over the cationic one (F for tablet containing Ch alone = 47.78 x 10³ dyne.cm⁻²), and then non-ionic polymer (F for tablet containing HPMC alone = 30.83 x 10³ dyne.cm⁻²). PVP K 30 has low bioadhesion force (F = 15.414 x 10³ dyne.cm⁻²) compared with other polymers. Negligible bioadhesion force was observed for Eu RS 100 containing tablets (F = 0.154 x 10³ dyne.cm⁻²).

The physicochemical interactions at the adhesive substrate interface were studied by Jacques and Buri. The authors have suggested that, mucoadhesion of cellulose derivatives resulted mainly from the pressure developed by their swollen gels against the mucin, whereas that, of CP 934, is a polyacrylic acid, was driven by attractive interactions at the polymer-mucin interface. The comparatively weak bioadhesion force of non-ionic polymer may be attributed to the presence of only hydroxyl groups and absence of a proton-donating carboxyl group. So, it could form a weak hydrogen bond with mucus layer.

The bioadhesion force of the cationic polymer (Ch) was less than that of anionic one CP 934. Chitosan is a promising bioadhesive material at neutral or alkalin pH, which was found to be advantageous for adsorption on the mucosal surface. They have suggested that, at this pH, chitosan has numerous amine and hydroxyl groups as well as a number of amino groups that may increase the interaction with negative charged mucin so, cause a strengthening of the mucoadhesive interface.

Polyvinylpyrrolidone K 30 has a high water solubility that critically limits its application as an effective mucoadhesive polymer, because after hydration, the formed gel starts to disintegrate due to dissolution.

From the results of bioadhesion force of different formulations containing different polymers, it is found that, the addition of HPMC to CP 934 or Ch, reduce the bioadhesion force. On the other hand, the addition of HPMC to PVP K 30 or Eu RS 100 can enhance the adhesive properties of them.

In general, the swelling behavior of the mucoadhesive polymer was
extensively related to its bioadhesive performance. According to Jacques and Buri\textsuperscript{32}, materials have highest initial rate of hydration reach the highest mucoadhesive strength.

Values of the \textit{in-vitro} residence time are shown in Tables 2 & 3. From the tablet containing individual polymer evaluation, it can be concluded that, CP 934 was characterized by very strong mucoadhesive force and so prolonged residence time between the tablet and mucosal membrane (> 6 hrs), followed by Ch (6 hrs) and then HPMC (5.5 hrs). On the other hand, the residence time of PVP K\textsubscript{30} (< 30 min), while, Eu RS 100 has negligible residence time. The addition of HPMC to different polymers can improve the residence time of different polymers. In case of Ch and CP 934, the addition of HPMC decreases the residence time and facilitate erosion and promote tablet disintegration. But the addition of HPMC to PVP K\textsubscript{30} and Eu RS 100 increases the residence time of these polymers.

The release profiles of the drug from different buccoadhesive tablets are shown in Figures 5-8. The percent release of the drug from different formulations varied with the polymer types and the ratios of polymer in each formulation. On the other hand, complete release of the drug after 30 min. in case of control tablet.

The release of the drug from buccoadhesive tablets containing CP 934 and HPMC, varied according to the ratio of these polymers. The increase in percent of CP 934 was found to increase the drug release. This may be due to the ionization of CP 934 at pH 6.6, a pH environment higher than its ionization constant (pKa = 6). Ionization of CP 934 leads to development of negative charges along the backbone of the polymer. Repulsion of like charges (polymer and mucin) leading to slightly higher uptake of water that might have contributed to higher drug release from the polymer matrix system\textsuperscript{36}. The release of the drug from these formulations can be arranged as follows according to the ratio of two polymers: CH 4>CH 3 >CH 2>CH 1. These results are in agreement with results obtained by Çelebi and Kişlar\textsuperscript{37}, who have reported that, increase in the ratio of CP 934 causes an increase in the amount of propranolol hydrochloride release.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig5.png}
\caption{\textit{In-vitro} release profiles of captopril from buccoadhesive tablets containing Carpobol 934: HPMC.}
\end{figure}
The release of the drug from buccoadhesive tablets containing Ch and HPMC, varied according to the ratio of these polymers. The release of the drug from these formulations can be arranged as follows: KH$_4$ > KH$_3$ > KH$_2$ > KH$_1$.

The release of the drug from buccoadhesive tablets containing Eu RS 100 and HPMC, can be arranged as follows: EH$_4$ > EH$_3$ > EH$_2$ > EH$_1$.

Also, the release of the drug from buccoadhesive tablets containing PVP K$_{30}$ and HPMC, can be arranged as follows: PH$_4$ > PH$_3$ > PH$_2$ > PH$_1$. The initial drug release from these formulations was 10.6, 15, 25 and 35% for formula PH$_1$, PH 2, PH 3 and PH 4, respectively, after 15 min. Complete release was observed after 300 min for formulation PH 1 and PH 2, 240 min for formula PH 3 and
180 min. for formula PH 4. This variation in the release can be attributed to ratio of PVP K30. As PVP K30 water soluble polymer and so rapid erosion of the resultant gel layer upon increasing the polymer concentration and so increase the drug release.

From the previous results, increase the percent of HPMC to those formulations lead to a decrease in the release of the drug and so give sustained release pattern of the drug.

Data of the in-vitro release of captopril were fitted to different equations and kinetic models to explain the release kinetics of the drug from formulated buccoadhesive tablets. The kinetic models used were, zero-order equation\(^{38}\), first order, Higuchi model\(^{39,40}\). The best fit with the highest correlation coefficient “r\(^2\)” was shown with Higuchi model \((r^2:0.9708-0.9944)\) for formulae containing (Ch & HPMC) and \((r^2:0.9568-0.9930)\) for formula containing (PVP K30 & HPMC) in different ratio. While, in case of formula containing (CP 934 & HPMC) and (Eu RS 100 & HPMC) the best fit with the highest correlation coefficient “r\(^2\)” was shown with first-order equation \((r^2:0.9699-0.9925\) and 0.9839-0.9942, respectively). To explore the kinetics behavior further, the release data were analyzed using Korsmeyer and Peppas equation\(^{40}\):

\[
\frac{M_t}{M_\infty} = K t^n
\]

where,

- \(M_t\): amount of drug released at time \(t\);
- \(M_\infty\): fraction of drug released at time \(t\);
- \(K\): Kinetic constant incorporating the structural & geometric characteristics of the drug/polymer system and
- \(n\): The release exponent, is a parameter which depends on the release mechanism and is thus used to characterize it.

For non-Fickian release (an anomalous), the value of \(n\) falls between 0.5 and 1 \((0.5 < n < 1)\), \(n\) equals 0.5 corresponds to a Fickian diffusion release (case I diffusion), \(n=1\) corresponds to a zero-order release (case II transport) and for \(n>1\) corresponds to super case II transport\(^{26}\). The kinetic parameters, \(n\) and \(K\), were calculated by plotting log \(M_t/M_\infty\) versus log \(t\) where log \(K\) is the intercept and \(n\) is the slope of the straight line. \(K\) is a characteristic constant of the tablet and \(n\) is an indicative of release order. Hence, as the \(K\) value increases, the release of drug occurs faster\(^{41}\). It is obvious that the values of \(n\) for all these formulae fall between 0.5 and 1 (except KH 2, KH 3, KH 4, and EH 4 where \(n\) value nearly 0.5 so, indicating Fickian transport) indicating non-Fickian release behavior controlled by a combination of diffusion and chain relaxation mechanism\(^{37}\). This is in agreement with Desai and Kumar\(^{26}\), who have reported that the swellable matrices such as CP 934 exhibit anomalous non-Fickian release kinetic. Also, these results are in agreement with the results obtained
by Yaziksiz-iscan et al.\textsuperscript{42} which indicated that, the release behavior of the system containing captopril and the two polymers, CP 934 and HPMC, at different ratios found to be non-Fickian.

**Bioavailability study**

The mean plasma concentration as a function of time of tested formulations is illustrated in Figure 9 and the pharmacokinetic parameters are listed in Table 4. It could be observed that, there is a difference between the mean plasma concentrations as a function of time for captopril after oral administration of control formula and the other buccoadhesive formulations at all time intervals. The pharmacokinetic parameters of captopril represented by the value of $C_{\text{max}}$ (ng/ml), $T_{\text{max}}$ (hr) and AUC$_{0-8}$ hr (ng.hr.ml$^{-1}$).

![Plasma concentration-time profiles of captopril after oral administration of control and buccoadhesive tablets in rabbits.](image)

From these results it was evident that, the absorption of captopril from control tablets was rapid and reached its peak plasma concentration in $1.5\pm0.316$ hr whereas, following buccoadhesive administration of the developed tested formulations, CH 3 and KH 3, the mean $T_{\text{max}}$ was $4\pm0.632$ hrs and $2.67\pm0.516$ hrs, respectively. These result indicates the sustained release effect of both tested formulae compared to the control tablets.

The mean plasma concentration ($C_{\text{max}}$) is $506.9 \pm 11.365$ (ng/ml) for CH 3 and $429.02\pm39.554$ (ng/ml) for KH 3 compared to $591.28 \pm 37.489$ (ng/ml) for the control tablets. While the mean AUC$_{0-8}$ is found to be $2359.5 \pm 113.94$ (ng.hr.ml$^{-1}$) for CH 3 and $1637.43 \pm 81.35$ (ng.hr.ml$^{-1}$) for KH 3 compared to $1869.29 \pm 64.1$ (ng.hr.ml$^{-1}$) for the control tablet. These results indicated the more suitability of both CH 3 and KH 3 as sustained-release systems than the control tablets. However, the more suitability of CH 3 as a sustained-release system than KH 3 was also observed. These findings assure the goal of sustained release concept which has been estimated in reducing high peak plasma concentration ($C_{\text{max}}$), prolong the time required to reach maximum plasma concentration ($T_{\text{max}}$), increasing the total amount of captopril present in the blood for longer time as indicated by the high values of AUC$_{0-8}$ values and finally increasing the bioavailability of the drug. These results are in agreement with the results obtained by Yaziksiz-
iscan et al.\textsuperscript{32}, who have indicated that, the formulation of captopril as buccoadhesive tablet containing Carbopol 934 and Hydroxypropyl methylcellulose only at different ratios produced sustained-release systems.

The results listed in Table 5, represents the statistical analysis for the pharmacokinetic parameters of captopril from the three tested formulations. From these results it could be observed that, the pharmacokinetic parameters of captopril in buccoadhesive tablets containing CP 934: HPMC in ratio of 6:4 are significantly different from the pharmacokinetic parameters of captopril in buccoadhesive tablets containing Chitosan: HPMC in ratio of 6:4. The pharmacokinetic parameters of both formulae are significantly different from those of captopril in case of the control tablet using one way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparisons test.

**Table 4:** The mean pharmacokinetic parameters of captopril from the control tablets and buccoadhesive tablets.

<table>
<thead>
<tr>
<th>The mean pharmacokinetic parameters</th>
<th>Formulae</th>
<th>CT</th>
<th>CH 3</th>
<th>KH 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(_{\text{max}}) (ng/ml)</td>
<td></td>
<td>591.28±37.49</td>
<td>506.9±11.37</td>
<td>429.02±39.55</td>
</tr>
<tr>
<td>T(_{\text{max}}) (hrs)</td>
<td></td>
<td>1.50±0.3160</td>
<td>4.00±0.6320</td>
<td>2.67±0.516</td>
</tr>
<tr>
<td>AUC(_{0-8}) (ng.hr.ml(^{-1}))</td>
<td></td>
<td>1869.29±64.1</td>
<td>2359.5±113.94</td>
<td>1637.43±81.35</td>
</tr>
</tbody>
</table>

**Table 5:** Statistical analysis of the pharmacokinetic parameters of captopril from control and buccoadhesive tablets.

<table>
<thead>
<tr>
<th>Formulae</th>
<th>The mean pharmacokinetic parameters</th>
<th>C(_{\text{max}}) (ng/ml)</th>
<th>T(_{\text{max}}) (hrs)</th>
<th>AUC(_{0-8}) (ng.hr.ml(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH 3 vs KH 3</td>
<td>** at P &lt; 0.01</td>
<td>** at P &lt; 0.01</td>
<td>* at P &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>CH 3 vs CT</td>
<td>** at P &lt; 0.01</td>
<td>* at P &lt; 0.05</td>
<td>* at P &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>KH 3 vs CT</td>
<td>* at P &lt; 0.05</td>
<td>** at P &lt; 0.01</td>
<td>* at P &lt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

where

* Significantly different ** Highly significant difference
Conclusion

A bucco-adhesive system for the release of captopril was developed using different polymers; CP 934, Ch, Eu RS 100, PVP K30 and HPMC in various ratios. The non-Fickian release behavior obtained, suggests that, the release of the drug is controlled by a diffusion mechanism. The adhesion characteristics were significantly affected by the various ratios of bioadhesive polymers in each tablet. Tablets containing CP 934/HPMC and Ch/HPMC showed good bioadhesive characteristics in contact with rabbit intestinal mucosa, good swelling characteristics and good residence time in the buccal cavity. In-vivo study of captopril from two selected formulations (CP 934/HPMC and Ch/HPMC) produced extended drug release when compared with control tablet taken orally. The formula containing CP 934/HPMC gives more sustained effect than the other one Ch/HPMC. Thus, our results suggest that the captopril buccoadhesive tablet would be useful to deliver the drug in a sustained release manner.

REFERENCES

14- C. Eouani, P. H. Piccerelle, P. P. Rinderre, E. Bourret and C.