DEVELOPMENT AND EVALUATION OF KETOROLAC TROMETHAMINE MUCOADHESIVE BUCCAL TABLETS

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INTRODUCTION
Mucosal drug delivery systems offer many advantages over conventional systems such as ease of administration, be promptly terminated in case of toxicity by removing the dosage form from buccal cavity and it is also possible to administer drugs to patients who cannot be dosed orally via this route[1-2].

Mucoadhesive buccal drug delivery systems offer many advantages over conventional systems such as ease of administration, be promptly terminated in case of toxicity by removing the dosage form from buccal cavity and it is also possible to administer drugs to patients who cannot be dosed orally via this route[1-2].

Recently much attention has been focused on the design and evaluation of buccal drug delivery systems keeping in view their potential for future market. Therefore a buccal drug delivery system needs to be developed and optimized. An ideal buccal adhesive system must have the following properties: should adhere to the site of attachment for few hours, should release the drug in controlled manner and should provide the drug release in a unidirectional way in the mucosa[3]. The unique environment of the oral cavity offers its potential as a site for drug delivery. Through this route it is possible to realize mucosal (local effect) and transmucosal (systemic effect) drug administration. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation. Therapeutic agents administered through buccal mucosa enters directly to the systemic circulations and thereby circumvent the first pass hepatic metabolism, gastric irritation and other problems associated with conventional oral route[4-5].

Ketorolac Tromethamine (KT) was generously provided by Amirya Pharm. Ind. Co. (Alexandria, Egypt). Carboxylate 934 (CP) (B. F. Goodrich Chemical Company, Ohio, USA), Hydroxypropyl methylcellulose (HPMC K4M); Biochemica, Switzerland, Sodium Carboxymethylcellulose (SCMC) (C. B. H. Lab Chemicals, Nottingham, U. K.), Polyvinyl pyrrolidone K30 (PVP k30); Sigma, USA. All other chemicals and solvents used were of pharmaceutical grade.

Drug excipients compatibility study

To investigate any possible interactions between the drug and the used bioadhesive polymers, infrared spectroscopy (IR) was adopted. The IR spectrum of a) pure ketorolac, b) physical mixture containing drug, CP 934 and HPMC K4M c) physical mixture containing drug, CP 934 and SCMC were taken, interpreted and compared with each other. The IR spectra were carried out using Shimadzu IR-470 spectrophotometer (Tokyo, Japan). The samples were prepared as KBr disks compressed under a pressure of 6 tones/cm2. The scanning range was 400-4000 cm⁻¹.

Preparation of Mucoadhesive Buccal Tablets
Mucoadhesive buccal tablets each containing 10 mg ketorolac were prepared by direct compression method. Composition of various formulations employing carboxylate 934, SCMC and HPMC are shown in table (1) was mixed homogeneously in a glass mortar for 15 minutes. The mixture (100 mg) is compressed using 7 mm flat faced punch on 16 stages rotary tablet press machine.
**Table 1: Composition of Ketorolac Tromethamine buccal tablets**

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Drug (mg)</th>
<th>Cp 934 (mg)</th>
<th>HPMC (mg)</th>
<th>SCMC (mg)</th>
<th>PVP K30 (mg)</th>
<th>D -mannitol (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>10</td>
<td>35</td>
<td>35</td>
<td>-</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>F2</td>
<td>10</td>
<td>23</td>
<td>46</td>
<td>-</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>F3</td>
<td>10</td>
<td>18</td>
<td>54</td>
<td>-</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>F4</td>
<td>10</td>
<td>14</td>
<td>56</td>
<td>-</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>F5</td>
<td>10</td>
<td>35</td>
<td>-</td>
<td>35</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>F6</td>
<td>10</td>
<td>23</td>
<td>-</td>
<td>46</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>F7</td>
<td>10</td>
<td>18</td>
<td>-</td>
<td>54</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>F8</td>
<td>10</td>
<td>14</td>
<td>-</td>
<td>56</td>
<td>6</td>
<td>14</td>
</tr>
</tbody>
</table>

**Surface pH**

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 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[9].

**Swelling index**

Buccal tablets were weighed individually (W0) and placed separately in 2% agar gel plates and incubated at 37°C ±1°C. At regular 1-hour time intervals until 6 hours, the tablet was removed from the Petri dish and excess surface water was removed carefully with filter paper. The swollen tablet was then reweighed (W1) and the swelling index (S.I) was calculated using the formula[10] given in Equation 1.

\[
\text{Swelling index} = \frac{100 (W_1 - W_0)}{W_0} \ldots \ldots (1)
\]

**Drug content**

Five tablets were taken and powdered; powder equivalent to one tablet was taken and dissolved in 100 ml of pH 6.8±0.5 phosphate buffer on a rotary shaker overnight. The solution was centrifuged and the supernatant was collected[11]. The absorbance was measured by using UV-visible spectrophotometer at 322 nm. Each measurement was carried out in triplicate and the average drug content in the buccal tablet was calculated.

**In vitro drug release**

The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus. The dissolution medium consisted of 200 ml of phosphate buffer pH 6.8 ±0.5. The release was performed at 37°C ± 0.5°C with a rotation speed of 50 rpm. The tablet was supposed to release drug from one side only hence a one side of tablet was fixed to glass disk with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. Samples (3 mL) were withdrawn at predetermined time intervals and replaced with fresh medium[12]. The samples were filtered through filter paper and analyzed by UV spectrophotometer at 322 nm.

Release data were fitted to various mathematical models Korsmeyer-Peppa’s [13], zero order, first order and Higuchi release models [14] in order to determine the release mechanism.

**Ex-vivo mucoadhesion time**

The ex-vivo mucoadhesion time was performed (n = 3) after application of the buccal tablet on freshly cut sheep buccal mucosa. A segment of fresh sheep buccal mucosa (2 cm) was glued to the surface of glass slide, and a mucoadhesive buccal tablet was wetted with 1 drop of phosphate buffer pH 6.8±0.5 and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 100 mL of the 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 tablet adhesion was monitored for 8 hours. The time for the tablet to detach from the sheep buccal mucosa was recorded as the mucoadhesion time[15].

**Ex-vivo drug permeation**

The ex-vivo buccal permeation studies was carried out for optimized ketorolac buccal tablet. The permeation study of ketorolac through the excised layer of goat buccal mucosa was performed using Franz diffusion cell at 37°C ± 0.5°C. Fresh goat buccal mucosa was mounted between the donor and receptor compartments. The buccal tablet was placed with the core facing the mucosa, and the compartments were clamped together. The donor compartment was filled with 1 ml of phosphate buffer pH 6.8. The receptor compartment (45 ml capacity) was filled with phosphate buffer pH 6.8 ± 0.5 and the hydrodynamics in the compartment was maintained by stirring with a magnetic bead at uniform slow speed[16]. The amount of drug permeated through the buccal mucosa was determined by withdrawing samples (1 ml) at predetermined time intervals and analyzed for drug content by UV spectrophotometer at 322 nm.

**RESULTS AND DISCUSSION**

FTIR studies revealed that, no interaction between the drug and the used polymers occurred as there was no shift in the IR peaks of the drug (Figure 1).

The physico-chemical characteristics of Ketorolac mucoadhesive buccal tablets are shown in Table 2. All the tablet formulations showed almost uniform weight, thickness and favorable hardness. The weight of the tablets was varied between 107.7 mg and 96.6 mg with SD values 0.4 - 0.8. The thicknesses of the various tablet formulations were observed to be in the range of 2.6 mm to 3.64 mm with SD values of 0.06-0.28.
The swelling profile of different buccal tablets is shown in figures 2 and 3. The results of swelling study revealed that the swelling index of all tablets was increased by time because the polymers gradually absorb water due to hydrophilicity of the polymers. The swelling state of the polymer (in the formulation) was reported to be crucial for its bioadhesive behavior. Appropriate swelling behavior of mucoadhesive buccal system is an essential property for uniform and prolonged drug release and effective mucoadhesion. The adhesion will increase with the degree of hydration until a point where over-hydration leads to an abrupt drop in adhesive strength due to disentanglement at the polymer/tissue interface[17].

The swelling index was directly proportional to the concentration of the second polymer (HPMC or SCMC) and inversely proportional to CP934. The higher swelling rate and extent of buccal tablets containing SCMC can be explained due to the faster rate of water uptake by SCMC than by HPMC.

The swelling index after 6 hrs was in the range of 7.75% ± 2.06 to 100.1% ± 8.5 for buccal tablets containing CP 934 and SCMC at the ratios of 1:2 and 1:3, respectively. The highest swelling index was observed for buccal tablets containing CP934 with SCMC (F5–F8) in the range from 32.59% to 52.3%. Buccal tablets containing Cp934 while for buccal tablets containing CP934 with SCMC (F5–F8) was in the range from 16.94% to 21.4. The obtained values of n (diffusional exponent), and r² values were between 0.5 and 1.0, indicating that the release of ketorolac was found to be a non-Fickian diffusion. The only exception was formulation F2, as the ‘n’ value of formulation F2 is closer to 0.5, the drug release mechanism from this formulation is non-Fickian diffusion.

Table 2: Physicochemical properties of Ketorolac Tromethamine mucoadhesive buccal tablets

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Weight (mg)</th>
<th>Thickness (mm)</th>
<th>Hardness (kg/cm²)</th>
<th>Surface pH</th>
<th>Drug Content (%)</th>
<th>Ex-vivo mucoadhesion time (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>106.5±0.5</td>
<td>2.6±0.08</td>
<td>3.9±0.11</td>
<td>6.4±0.05</td>
<td>95.3±0.21</td>
<td>&gt;8</td>
</tr>
<tr>
<td>F2</td>
<td>96.6±0.52</td>
<td>3.6±0.12</td>
<td>3.9±0.17</td>
<td>6.8±0.1</td>
<td>97.2±0.28</td>
<td>&gt;8</td>
</tr>
<tr>
<td>F3</td>
<td>99.6±0.4</td>
<td>2.63±0.22</td>
<td>3.8±0.1</td>
<td>6.9±0.05</td>
<td>96.7±0.46</td>
<td>&gt;8</td>
</tr>
<tr>
<td>F4</td>
<td>104.8±0.8</td>
<td>2.99±0.1</td>
<td>3.7±0.25</td>
<td>7.02±0.15</td>
<td>95.5±0.51</td>
<td>5.3±0.5</td>
</tr>
<tr>
<td>F5</td>
<td>101.3±0.57</td>
<td>3.62±0.11</td>
<td>3.8±0.15</td>
<td>6.6±0.05</td>
<td>98.6±0.35</td>
<td>&gt;8</td>
</tr>
<tr>
<td>F6</td>
<td>99.2±0.33</td>
<td>3.26±0.13</td>
<td>4.1±0.15</td>
<td>6.9±0.05</td>
<td>98.7±0.2</td>
<td>5.5±1.05</td>
</tr>
<tr>
<td>F7</td>
<td>107.7±0.45</td>
<td>3.36±0.06</td>
<td>4.8±0.21</td>
<td>7±0.1</td>
<td>99.1±0.32</td>
<td>6.5±0.5</td>
</tr>
<tr>
<td>F8</td>
<td>100.6±0.5</td>
<td>2.6±0.28</td>
<td>4.6±0.21</td>
<td>7.1±0.1</td>
<td>101.4±0.25</td>
<td>5±0.7</td>
</tr>
</tbody>
</table>

The swelling index after 6 hrs was in the range from 16.94% to 42.18% for buccal tablets containing CP 934 with HPMC (F1–F4), while for buccal tablets containing CP934 with SCMC (F5–F8) was in the range from 32.59% to 52.3%. Buccal tablets containing Cp934 and SCMC at the ratios of 1:2 and 1:3 exhibited the highest swelling (48.5% and 52.3%, respectively).

In vitro drug release studies revealed that the release of ketorolac from different formulations varies with characteristics and composition of matrix forming polymers as shown in figure 4 and 5. The drug release rate appeared to increase with decreasing carbopol 934 and increasing concentration of SCMC and HPMC. The gradual swelling of buccal tablets containing CP 934 and SCMC inevitably facilitated the release of ketorolac due to easier diffusion in the swelled region of the polymer network. The prolonged release of drug from buccal tablets containing higher percentages of CP 934 may be explained by its properties of in situ gelling and slow dissolution.

Therefore increase of carbopol content delays the drug release from tablets. The in vitro drug release of formulations F1 to F4 (containing CP 934 and HPMC at different ratios) was found to be in the range of 44.6% ± 1.5 to 63.93% ± 1.07. On the other hand, formulations F5 to F8 (containing CP 934 and SCMC at different ratios) was found to be in the range of 77.55% ± 2.06 to 100.1% ± 1.85. This finding was also supported by the results of swelling studies where the highest swelling index was also exhibited by the formulation containing SCMC and CP 934 (Fig. 3). It is anticipated that the high amount of water uptake by SCMC may lead to considerable swelling of the polymer matrix, allowing the drug to diffuse out at a faster rate.

Among the formulation studied F7 and F8 (containing CP 934 and SCMC at ratios 1:3 and 1:4, respectively) showed the highest amount of drug release within 6 hours (100% and 98%, respectively).

Kinetics of drug release and mechanism

The obtained values of n (diffusional exponent), and r² (correlation coefficient) are depicted in table 3. The values of n are estimated by linear regression of log (Mt/M∞) versus log (t), and these values were between 0.5 and 1.0, indicating that the release of ketorolac was found to be non-Fickian diffusion. The only exception was formulation F2, as the ‘n’ value of formulation F2 is closer to 0.5, the drug release mechanism from this formulation is Fickian diffusion.

The order of drug release from all the formulations was studied, and it followed zero-order kinetics.
The obtained data are presented in Table 4. Buccal tablets did not exhibit change in color or shape. Physical properties of the buccal tablets such as diameter increased slightly owing to swelling of the buccal tablets in human saliva. But the buccal tablets did not collapse in the human saliva until the end of the study. No change in drug content was observed over the period of 6 hours in human saliva, the drug content was in the range of 97% to 99.2%.

**Table 4: Stability study of the selected F7 ketorolac buccal tablet formulation in normal human saliva**

<table>
<thead>
<tr>
<th>Sampling Time (hours)</th>
<th>Color changes*</th>
<th>Change in shape Diameter(mm)**</th>
<th>Collapsing</th>
<th>Drug Recovered (%)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No</td>
<td>9</td>
<td>No</td>
<td>99.2</td>
</tr>
<tr>
<td>1</td>
<td>No</td>
<td>10</td>
<td>No</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>11</td>
<td>No</td>
<td>98.5</td>
</tr>
<tr>
<td>6</td>
<td>No</td>
<td>11</td>
<td>No</td>
<td>97.6</td>
</tr>
</tbody>
</table>

*Visual observation **Mean of three readings

**CONCLUSION**

It was concluded that development of mucoadhesive buccal tablets of ketorolac was one of the alternative routes of administration to avoid gastrointestinal irritation as it is the most pronounced adverse effects associated with its use. In addition, these formulations reduce the need of frequent administration and enhance patient compliance. F7 formulation containing Carbopol 934 and SCMC (at the ratio 1:3, respectively) showed good swelling, a convenient residence time as well as promising drug release pattern. In addition to the good correlation obtained between in vitro drug release and ex-vivo drug permeation study with the correlation coefficient of 0.974.

**CONFLICT OF INTERESTS**

Declared None

**REFERENCES**


