FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL TABLETS BY USING NATURAL POLYMER

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INTRODUCTION: Buccal route of drug delivery is a good alternative amongst the various routes of drug delivery. The oral route is perhaps the most preferred for the patients. Buccal routes of drug delivery offer distinct advantages over oral administration for systemic drug delivery. These advantages include a bypass of first-pass effect and avoidance of pre-systemic elimination within the GI tract. These factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery.

Carvedilol is a nonselective β-adrenergic blocking agent with α1-blocking activity; it has vasodilating activity at alpha-1-receptors; at higher doses calcium channel blocking activity may contribute. Carvedilol is used in the management of hypertension and angina pectoris, and as an adjunct to standard therapy in symptomatic heart failure. The absolute bioavailability is about 25%, and the elimination half-life is about 6 h.

This is because of undergoing of the drug to first-pass metabolism in liver and gut wall. The buccal mucosa is an attractive route for systemic delivery of many drugs since it is relatively permeable with a rich blood supply. The mucoadhesive buccal drug delivery system offers several advantages as compared to traditional methods of systemic drug administration. Casein, the major milk protein, comprises about 80% total protein content of milk.
Casein forms an integral part of the daily diet in many parts of the world. It is in soluble in water, and organic solvents. Casein possesses a number of interesting properties that make it a good candidate for conventional and novel drug delivery systems. It has a mucoadhesive property. Industrially it is used in sizing of textile and as an adhesive, in preparation of Casein plastic and Casein paints.

MATERIALS AND METHODS: Carvedilol pure drug was obtained as a gift sample from M/s Dr. MACS Bio-Pharma Private limited, Kukatpally, Hyderabad, Andhra Pradesh India. Hydroxypropylmethyl cellulose K4M (HPMC-K4M) and Casein was obtained from S.D. Fine Chemicals Limit, Mumbai, India, Polyvinylpyrrolidone K30 (PVP-K30) was obtained from Himedia Laboratories, Mumbai, India, Polyvinylpyrrolidone K30 (PVP-K30) was obtained from Himedia Laboratories, Mumbai, India, Isopropyl alcohol and Dicalcium Phosphate was obtained from Finar chemicals limited, Ahmedabad, India. Magnesium stearate was obtained from Himedia Laboratories, Mumbai, India. All other chemicals used were of analytical grade.

Formulation of Mucoadhesive Tablets: Wet granulation method was employed to prepare buccal tablets of Carvedilol using, HPMC-K4M, Casein, PVP-K30.

Factorial Design: A 3² full factorial design was constructed, where the amounts of Casein (X₁) and HPMC K4M (X₂) selected as the independent factors. Hardness (Y₁), cumulative % drug release at 6 h (Q₆, Y₂) and 12 h (Q₁₂, Y₃) were selected as dependent variables. The levels of the two factors were selected on the basis of studies carried out before implementing the experimental design. Table 1 summarizes the experimental runs, their factor combinations and the translation of the coded levels to the experimental units used in the study.

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<tr>
<th>Factor</th>
<th>Name</th>
<th>Units</th>
<th>Low (-)</th>
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<th>High (+)</th>
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<td>mg</td>
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<td>40</td>
</tr>
<tr>
<td>X₂</td>
<td>HPMC K4M</td>
<td>mg</td>
<td>60.00</td>
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</table>

Preparation: Mucoadhesive Buccal tablet each containing 6.25mg of Carvedilol were prepared by wet granulation method (using isopropyl alcohol). All the ingredients except lubricants were mixed in the order of ascending weights and blended for 10 min in an inflated polyethylene pouch. Carvedilol was added in this mixture and mixed for 2 min. Granulation was done with binder solution of PVP-K30 which was previously dissolved in isopropyl alcohol, and the damp mass passed through sieve no 10.

The granules were dried in air and passed through sieve no. 16, magnesium stearate & talc were added and mixed and compressed using a 10-station rotary compression machine (Karnavati Engineering Hd, Gujarat, India) into 150 mg tablet, using 6.5 mm punch. Composition of the different bioadhesive buccal tablet formulations of Carvedilol is as shown in Table 2.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Carvedilol (mg)</th>
<th>Casein (mg)</th>
<th>HPMC K4M (mg)</th>
<th>PVP-K30 (mg)</th>
<th>Dicalcium Phosphate (mg)</th>
<th>Magnesium Stearate (mg)</th>
<th>Talc (mg)</th>
<th>Isopropyl Alcohol</th>
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<tr>
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<td>3</td>
<td>q.s</td>
</tr>
<tr>
<td>F2</td>
<td>6.25</td>
<td>25</td>
<td>35</td>
<td>15</td>
<td>65.75</td>
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<td>25.10</td>
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<td>15</td>
<td>43.36</td>
<td>3</td>
<td>3</td>
<td>q.s</td>
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</tbody>
</table>
All the weights are taken in mg, except isopropyl alcohol is taken in q.s; the total weight of tablet is 150 mg.

**Evaluation of Mucoadhesive Buccal Tablets Compatability Studies:**

**Fourier Transform Infrared (FTIR) Spectroscopy:** The drug-polymer compatibility was confirmed by carrying out FTIR and DSC studies. Drug, polymer, and physical mixture of drug-polymer were subjected to FTIR analysis using FTIR 8400 Shimadzu, Japan. Samples were prepared in KBr disks and scanned between 450-4000cm⁻¹ with a resolution of 4 cm⁻¹. FTIR studies were carried out for Carvedilol pure drug, physical mixture of optimized formulation and optimized formulation.

**Differential Scanning Calorimetry (DSC):** DSC analysis using DSC-60 Shimadzu, Japan. Differential scanning calorimetry was performed for pure drug, physical mixture of optimized formulation, and optimized formulation. Accurately weighed samples were placed on aluminum plate sealed with aluminum seals and heated at a constant temp. of 5 °C/min over a temp. range of 0 - 400 °C in an inert (nitrogen) atmosphere.

**Thickness:** The thickness of buccal tablets was determined using vernier calipers. Ten tablets from each batch were evaluated and the results averaged.

**Weight Variation Test:** Twenty tablets from each formulation were weighed using an electronic digital balance and the average weight was calculated.

**Hardness:** Hardness was determined by compressing the tablets diametrically on six tablets from each batch using Monsanto hardness tester and average values were calculated.

**Friability:** Friability is the measure of tablet strength. Roche type friabilator (Tropical Equipment Pvt. Ltd. Mumbai, India) was used for testing the friability the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with revolution. After 4 min, the tablets were weighed and the percentage loss was determined⁵,⁶.

**Drug Content Uniformity:** Ten tablets were weighed and grounded in a glass mortar with a pestle to obtain fine powder. Powder equivalent to the mass of one tablet from each batch was taken in separate 100 ml volumetric flask containing 100 ml of 6.8 phosphate buffer, 20% of methanol and kept for 15 mins constant stirring. The solution was filtered, diluted and analyzed at 244 nm using UV spectrophotometer (UV Spectrophotometer 1800, Shimadzu, Japan).

**Surface pH:** The microenvironment pH (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 Battenberg 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 5 ml of distilled water (pH 7.0 ± 0.05) for 2 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablets and allowing it to equilibrate for 1 min⁹.

**Mucoadhesion Studies:** The apparatus used for testing bioadhesion was assembled in the laboratory. Mucoadhesion strength of the tablet was measured on a modified physical balance employing the method described by using sheep buccal mucosa as model mucosal membrane. A double beam physical balance was taken, the left pan was removed. To left arm of balance a thick thread of suitable length was hanged. To the bottom side of thread a glass vial of 30 ml capacity with uniform surface was tied. A clean 500 ml glass beaker was placed below hanging glass vial within which was placed another glass beaker of 100 ml capacity in inverted position. The temperature control system involves placing the thermometer in 500 ml beaker and intermittently adding hot simulated saliva (pH 6.8) into 500 ml beaker containing simulated saliva (pH 6.8) maintained at 37.0 ± 0.5 °C. The balance was so adjusted that right-hand-side was exactly 5 g heavier than the left¹⁰-¹².

**Swelling Studies:** The tablets were individually weighed (W₁) and placed separately in Petri dishes
with 5 ml of simulated saliva of pH 6.8. At the time
interval of 0.5, 1, 2, 4, 6, 8, 10 and 12 hrs, tablet
was removed from the petri dish and excess water
was removed carefully using the filter paper. The
swollen tablet was then reweighed ($W_2$) and the
percentage hydration was calculated using the
following formula $^{13,14}$.

\[
\% \text{ Swelling Index (S.I)} = \left(\frac{W_2 - W_1}{W_1}\right) \times 100
\]

$W_1 =$ initial weight; $W_2 =$ final weight

**In-vitro Drug Release Study from Carvedilol Loaded Tablets:** *In-vitro* study was carried out in
USP II apparatus (Electro lab TDT 08L USP),
employed paddle stirrer at 50 rpm and 900 ml of
phosphate buffer pH 6.8 as dissolution medium
maintained at 37 ± 0.5 °C. The tablets were
designed to release drug from one side only,
therefore, one side of tablet was fixed to a glass
disk with cyanoacrylate adhesive $^{15,16}$.

The disk was placed at the bottom of the
dissolution vessel. Aliquots of 5 ml were
withdrawn at predetermined time intervals and
replaced with fresh medium. The samples were
filtered through Whatman filter paper and analyzed
it at 240 nm using UV-Visible spectroscopy (UV-
1800 Shimadzu Corporation, Japan).

**Statistical and Kinetic Analysis:** The data
obtained from all the formulations were
fitted into various mathematical models including zero order, first order, Higuchi, Hixon Crowell,
and Korsmeyer - Peppas release models. The
Korsmeyer - Peppas model is widely used, when
the release mechanism is not well known or more
than one type of release could be involved. For
non-fickian release, the value of $n$ falls between 0.5
and 1.0; while in case of fickian diffusion, $n \leq 0.5$;
for zero-order release (case II transport), $n = 1$; and
for super case II transport, $n > 1$ $^{17,18}$.

**RESULTS AND DISCUSSION:**

**Compatibility Studies:**

**Fourier Transform Infrared (FTIR) Spectroscopy:** FTIR studies were carried out for
the pure drug – Carvedilol, formulation F3 and
their spectra are as shown in **Fig. 1** and **Fig. 2**
respectively. The characteristic peaks of the pure
drug – Carvedilol were assigned from standard
literature. These included O-H stretching, =C-H
stretching, N-H stretching.

The spectra for carvedilol exhibits a broad peak at
344.68 cm$^{-1}$ due to alcohols and phenols (O-H)
stretching vibration, 3061.13 cm$^{-1}$ due to alkenes
(=C-H) stretching vibration and 2956.97 cm$^{-1}$ due
to alkanes (C-H) stretching vibration **Fig. 1**.

The FTIR results from formulation F3 exhibited
broad peaks at 3527.29 cm$^{-1}$ due to alcohols and
phenols (O-H) stretching vibration, 3066.92 cm$^{-1}$ due to alkenes
(=C-H) stretching vibration, 2837.31 cm$^{-1}$ due
to alkanes (C-H) stretching vibration **Fig. 1**.

The intensity and position of these characteristic
peaks permit easy interpretation of any possible
interaction between the drug and the excipients in
the formulation. The results clearly showed that
there was no interaction between the drug and the
excipients in the prepared formulation F3. Carvedilol was intact, and there was no sign of any
degradation due to preparative processes adopted
during the loading of the drug into buccal tablets.
Differential Scanning Calorimetry (DSC): Thermal characterization and analysis of DSC curves of the pure drug, physical mixture of formulation F3 were carried out. The studies provided thermal behavior of the pure drug, its physical mixture with Casein, HPMC K4M, PVP K-30, Dicalcium phosphate. Carvedilol showed an endothermic peak at 117 ºC and an exothermic peak at 118.9 ºC. A physical mixture of Formulation F3 showed an endothermic peak at 19 ºC and exothermic peaks at 186 ºC. The above results indicated that the characteristic peaks of Carvedilol appeared in the physical mixture of Formulation F3 indicating that there was no possible interaction between the drug and the excipients in the mucoadhesive buccal formulation. The drug in all probability was present in its stable form without any possible degradation.

Factorial Design: Experimental trials were performed for all 13 possible combinations by $3^2$ randomized full factorial design. The quadratic model was fitted to the data for two responses simultaneously using Design-Expert software 7.0.0 and adequacy and good fit of the models was tested using analysis of variance (ANOVA). Data were analyzed using Design expert 7.0.0 software. The formulation layout for the factorial design batches F1–F13 is shown in Table 3.

<table>
<thead>
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<th>TABLE 3: OBSERVED RESPONSES FOR $3^2$ FULL FACTORIAL DESIGN WITH RESPONSE SURFACE METHODOLOGY</th>
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<td>Formulation Code</td>
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<tr>
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</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>13</td>
</tr>
</tbody>
</table>

Thickness: The thickness of the tablets was found to be almost uniform in all formulations F1 to F13. The thickness was found to be in the range of 2.1 to 3.3 mm. None of the formulations (F1 to F13) showed a deviation. Hence, it is concluded that all the formulations compiled the thickness test and the results are shown in Table 4.

Weight Variation Test: The weight variation test was conducted for each batch of all formulations F1 to F13 as per I.P, and the results are shown in Table 4. The weight variation test for all the formulations complies with the IP limit (± 10%).
TABLE 4: EVALUATION CHARACTERISTICS OF MUCOADHESIVE BUCCAL TABLETS

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Weight variation* (mg)</th>
<th>Thickness* (mm)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability %</th>
<th>Drug content estimation %</th>
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<tbody>
<tr>
<td>F1</td>
<td>150.13±0.05</td>
<td>2.62±0.01</td>
<td>5.53±0.17</td>
<td>0.85±0.08</td>
<td>98.72±0.02</td>
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<td>F2</td>
<td>150.25±0.04</td>
<td>2.93±0.01</td>
<td>5.45±0.16</td>
<td>0.78±0.07</td>
<td>96.96±0.01</td>
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<tr>
<td>F3</td>
<td>150.88±0.26</td>
<td>2.55±0.03</td>
<td>5.42±0.11</td>
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<td>97.44±0.05</td>
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<td>F4</td>
<td>148.25±0.35</td>
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<td>95.68±0.04</td>
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<td>F5</td>
<td>150.28±0.25</td>
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<td>97.61±0.02</td>
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<td>F6</td>
<td>151.87±0.34</td>
<td>3.35±0.07</td>
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<td>0.66±0.09</td>
<td>96.80±0.03</td>
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<tr>
<td>F7</td>
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<td>93.91±0.03</td>
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<td>F8</td>
<td>151.65±0.26</td>
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<td>F9</td>
<td>150.22±0.16</td>
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<td>149.22±0.17</td>
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<td>F11</td>
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<td>5.41±0.18</td>
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<td>97.28±0.05</td>
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<td>5.70±0.18</td>
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<td>0.88±0.03</td>
<td>94.13±0.01</td>
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<td>S1</td>
<td>149.87±0.25</td>
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<td>5.23±0.15</td>
<td>0.92±0.06</td>
<td>98.56±0.07</td>
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<tr>
<td>S2</td>
<td>150.55±0.22</td>
<td>3.21±0.08</td>
<td>5.43±0.18</td>
<td>0.69±0.02</td>
<td>97.12±0.02</td>
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</table>

*Mean ± SD; n = 3

**Hardness**: Adequate tablet hardness is a necessary requisite for consumer acceptance and handling. The hardness of tablets of all formulations (F1 to F13) ranged between 3.0 to 7.0 kg/cm² and the results are shown in Table 4. As the Casein and HPMC K4M ratio increased, the hardness of the tablet increased. The lowest hardness value of 4.5 kg/cm² was obtained for Formulation F1 and highest of 5.7 kg/cm² for Formulation F3. For hardness two-dimensional contour plot and three-dimensional surface response plots are shown in Fig. 5 and Fig. 6. Hardness v increased with increase in concentration of Casein (X₁) and HPMC K4M. The low-level factor of X₁ and a high level of X₂ predicted. The regression coefficient for Y₁ (hardness) is as follows.

\[ Y_1 = +5.33+0.017X_1+0.20X_2-0.040X_1X_2 \]

Two-dimensional contour plot and three-dimensional surface response plots are shown for hardness. Hardness values increased with increase in concentration of Casein (X₁). Median level factor (0) of X₁ and X₂ predicted an optimal hardness value which would impart adequate mechanical properties and desired rate of drug release.

**Friability**: The friability test for all the formulations was done as per the standard procedure in I.P. The results of the friability test are tabulated in Table 4. The results indicated that the friability was less than 1% for all formulations ensuring that the tablets were mechanically strong.

**Drug Content**: The drug content of each batch of all the formulations (F1 to F13) was evaluated as per the standard protocol maintained in I.P and the results are as shown in Table 4. The results indicate that the percentage of drug content was found to be 6.06 to 6.18 hence it was concluded...
that all the formulations were within the acceptable limits as per Indian Pharmacopeia, i.e. ± 5 %.

**Surface pH:** Surface pH of all the formulations F1 to F13 was found to be 7.01 ± 0.25 to 7.23 ± 0.33 Table 5. Hence, it can be expected that there would be no local irritation to the mucosal surface, and all the formulation can be used safely.

**Bioadhesive Strength:** The *In-vitro* bioadhesion study was performed using a modified physical balance and measure the force (N) required to detach the tablet was noted. The bioadhesion characteristics were affected by the concentration of bioadhesive polymers used. Increase in concentration of polymer increased the bioadhesive strength of the formulation shown as Table 5. The strength of bioadhesion was between 23.12 ± 0.17 to 33.52 ± 0.03 N.

### Table 5: Evaluation Parameters of Mucosal Buccal Tablets

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Surface pH (±SD)</th>
<th>Mucoadhesive strength (N)</th>
<th>Cumulative % drug release 6 h</th>
<th>Cumulative % drug release 12 h</th>
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<tr>
<td>F1</td>
<td>7.10 ± 0.33</td>
<td>29.66 ± 0.07</td>
<td>35.59</td>
<td>78.03</td>
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<td>F2</td>
<td>7.20 ± 0.21</td>
<td>25.49 ± 0.02</td>
<td>36.82</td>
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<td>F3</td>
<td>7.20 ± 0.11</td>
<td>33.52 ± 0.03</td>
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<td>F4</td>
<td>7.11 ± 0.22</td>
<td>32.19 ± 0.27</td>
<td>35.74</td>
<td>77.79</td>
</tr>
<tr>
<td>F5</td>
<td>7.09 ± 0.32</td>
<td>27.89 ± 0.28</td>
<td>26.63</td>
<td>44.76</td>
</tr>
<tr>
<td>F6</td>
<td>7.01 ± 0.25</td>
<td>23.97 ± 0.22</td>
<td>21.63</td>
<td>62.14</td>
</tr>
<tr>
<td>F7</td>
<td>7.11 ± 0.66</td>
<td>26.03 ± 0.27</td>
<td>21.63</td>
<td>62.14</td>
</tr>
<tr>
<td>F8</td>
<td>7.13 ± 0.33</td>
<td>31.21 ± 0.05</td>
<td>37.14</td>
<td>94.17</td>
</tr>
<tr>
<td>F9</td>
<td>7.11 ± 0.32</td>
<td>30.52 ± 0.05</td>
<td>51.90</td>
<td>78.01</td>
</tr>
<tr>
<td>F10</td>
<td>7.10 ± 0.22</td>
<td>27.17 ± 0.29</td>
<td>31.78</td>
<td>70.83</td>
</tr>
<tr>
<td>F11</td>
<td>7.11 ± 0.15</td>
<td>23.12 ± 0.17</td>
<td>37.08</td>
<td>77.25</td>
</tr>
<tr>
<td>F12</td>
<td>7.23 ± 0.33</td>
<td>31.52 ± 0.21</td>
<td>46.65</td>
<td>82.08</td>
</tr>
<tr>
<td>F13</td>
<td>7.21 ± 0.11</td>
<td>25.30 ± 0.17</td>
<td>23.15</td>
<td>46.09</td>
</tr>
<tr>
<td>S1</td>
<td>7.13 ± 0.17</td>
<td>29.39 ± 0.29</td>
<td>50.46</td>
<td>92.15</td>
</tr>
<tr>
<td>S2</td>
<td>7.21 ± 0.30</td>
<td>27.38 ± 0.15</td>
<td>53.38</td>
<td>95.11</td>
</tr>
</tbody>
</table>

*Mean ± SD; n = 3

**Swelling Studies:** The swelling studies were conducted for all formulations, i.e. F1 to F13 and the results are as shown in Table 6. All the formulations were hydrated generally by keeping the tablets in contact with water for 1 h to 12 h. The highest hydration (swelling), i.e. 80 was observed with the formulation F3. This may be due to the quick hydration of polymers (Casein and HPMC K4M). The swelling rate of tablets increased in case of formulation F3 containing Casein and HPMC K4M in the ratio of 40:60.

### Table 6: Swelling Index of Mucosal Buccal Tablets

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>0.5 hrs</th>
<th>1 hrs</th>
<th>2 hrs</th>
<th>4 hrs</th>
<th>6 hrs</th>
<th>8 hrs</th>
<th>10 hrs</th>
<th>12 hrs</th>
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</thead>
<tbody>
<tr>
<td>F1</td>
<td>22</td>
<td>27</td>
<td>32</td>
<td>35</td>
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<td>40</td>
<td>43</td>
<td>45</td>
</tr>
<tr>
<td>F2</td>
<td>17</td>
<td>23</td>
<td>35</td>
<td>37</td>
<td>42</td>
<td>44</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>F3</td>
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<td>48</td>
<td>54</td>
<td>62</td>
<td>74</td>
<td>80</td>
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<tr>
<td>F4</td>
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<td>49</td>
<td>51</td>
</tr>
<tr>
<td>F5</td>
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<td>34</td>
<td>37</td>
<td>41</td>
<td>48</td>
<td>52</td>
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<td>31</td>
<td>33</td>
<td>37</td>
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<tr>
<td>F7</td>
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<td>27</td>
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<td>32</td>
<td>35</td>
<td>39</td>
<td>43</td>
<td>47</td>
</tr>
<tr>
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<td>55</td>
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<td>49</td>
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<td>55</td>
<td>61</td>
<td>64</td>
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<tr>
<td>F10</td>
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<td>43</td>
<td>47</td>
<td>49</td>
<td>51</td>
<td>53</td>
</tr>
<tr>
<td>F11</td>
<td>33</td>
<td>41</td>
<td>47</td>
<td>49</td>
<td>51</td>
<td>52</td>
<td>57</td>
<td>60</td>
</tr>
<tr>
<td>F12</td>
<td>38</td>
<td>41</td>
<td>47</td>
<td>49</td>
<td>51</td>
<td>52</td>
<td>57</td>
<td>61</td>
</tr>
<tr>
<td>F13</td>
<td>29</td>
<td>33</td>
<td>35</td>
<td>39</td>
<td>41</td>
<td>45</td>
<td>57</td>
<td>61</td>
</tr>
<tr>
<td>S1</td>
<td>25</td>
<td>33</td>
<td>39</td>
<td>43</td>
<td>46</td>
<td>53</td>
<td>54</td>
<td>66</td>
</tr>
<tr>
<td>S2</td>
<td>27</td>
<td>28</td>
<td>33</td>
<td>38</td>
<td>48</td>
<td>55</td>
<td>64</td>
<td>79</td>
</tr>
</tbody>
</table>
**In-vitro Drug Release Studies:** In-vitro drug release experiments were performed at 37 ± 0.5 °C in the USP II dissolution apparatus. The results showed that all formulations released the drug within 12 h. It was found that the rate of drug release was different for formulations with different proportions of Casein \((X_1)\) and HPMC K4M \((X_2)\) which were used as independent variables in low (-1), median (0) and high (+1). At low levels of Casein (formulations F10, F12 & F13), Q6 was ranging from 23.25 to 46.57% and Q12 was between 46.09 to 82.08 at the end of 6 and 12 h respectively Table 5 and Fig. 11. At median levels of Casein (formulations F1, F2, F4, F7, F8, F9 & F11), Q6 was ranging from 21.66 to 51.95 % and Q12 was between 42.14 to 94.17% at the end of 6 and 12 h respectively Table 5 and Fig. 11. At high levels of Casein (formulations F3, F5 & F6), Q6 was ranging from 21.67 to 53.39 % and Q12 was between 44.76 to 95.16% at the end of 6 and 12 h respectively Table 5 and Fig. 11.

In all the formulations the effect of HPMC K4M \((X_2)\) had a profound effect on drug release. As its concentration increased the rate of drug release increased. The in-vitro release data of F1 to F13 formulations fitted into zero-order, first-order, Higuchi, Hixon Crowell and Korsmeyer - Peppas release models and evaluated Co-efficient of regression values \((r^2)\) suggested the best fit kinetic model indicating zero-order release for all the formulations with an exception of formulations F5 & F6 which followed first-order Table 9.

The release exponent (n) value of the optimized formulation F3 was 0.5143 confirming the release mechanism to follow anomalous transport i.e., drug release is being governed by both diffusion and erosion mechanism. The regression coefficient for \(Y_2\) and \(Y_3\) are as follows.

\[
Y_2 = 36.53 - 6.667E^{-0.03 X_1} + 11.61 X_2 - 27.73 X_1^2 + 7.57 X_2^2 \quad \ldots \quad 2
\]

\[
Y_3 = 76.56 - 3.03 X_1 + 21.59 X_2 + 6.38 X_1 X_2 - 16.10 X_1^2 + 4.26 X_2^2 \quad \ldots \quad 3
\]

All the 13 formulations were optimized, and the results were entered and analyzed using Design-Expert software trial version 7.0.0 (Stat-Ease Inc., Minneapolis, USA) in 3 level factorial design using quadratic model. Two formulations were developed with a predicted set of values Table 8 whose quadratic model was found to be significant Q6 \((F=18.83, p<0.06)\) and Q12 \((12.03, p<0.25)\). Two-dimensional contour plot and three-dimensional response surface plots for Q6 \((Y_2)\) and Q12 \((Y_3)\) in Fig. 8, 9, 10 & 11 respectively. The actual values of formulations S1 and S2 were close to the predicted Q6 & Q12 values Table 8.

![FIG. 7: SWELLING INDEX OF BUCCAL TABLETS](image)

![FIG. 8: TWO-DIMENSIONAL CONTOUR PLOT FOR Q6](image)

![FIG. 9: THREE DIMENSIONAL RESPONSE SURFACE PLOT FOR Q6](image)
Drug Release Kinetics: The data of drug release from different formulations of buccal tablets were processed to understand the linear relationship. The data were processed for regression analysis using MS EXCEL Statistical functions. The parameters and equations are given in Table 9. The release kinetics of carvedilol found to follow zero-order and mechanism is Korsmeyer Peppas.

**Table 9: Kinetics Values Obtained from Different Plots of Formulations F1-F13**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Zero-order</th>
<th>First-order</th>
<th>Higuchi</th>
<th>Hixon-Crowell</th>
<th>Korsmeyer-Peppas</th>
<th>n value</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.9409</td>
<td>0.8467</td>
<td>0.9224</td>
<td>0.2078</td>
<td>0.9993</td>
<td>0.3055</td>
</tr>
<tr>
<td>F2</td>
<td>0.9790</td>
<td>0.8979</td>
<td>0.8834</td>
<td>0.2859</td>
<td>0.8209</td>
<td>0.7174</td>
</tr>
<tr>
<td>F3</td>
<td>0.9734</td>
<td>0.9004</td>
<td>0.9774</td>
<td>0.3847</td>
<td>0.9853</td>
<td>0.5143</td>
</tr>
<tr>
<td>F4</td>
<td>0.9717</td>
<td>0.8703</td>
<td>0.9118</td>
<td>0.2568</td>
<td>0.9588</td>
<td>0.6072</td>
</tr>
<tr>
<td>F5</td>
<td>0.8554</td>
<td>0.9296</td>
<td>0.9316</td>
<td>0.0107</td>
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<td>0.2491</td>
</tr>
<tr>
<td>F6</td>
<td>0.9181</td>
<td>0.9623</td>
<td>0.9561</td>
<td>0.0096</td>
<td>0.9700</td>
<td>0.2936</td>
</tr>
<tr>
<td>F7</td>
<td>0.9822</td>
<td>0.9803</td>
<td>0.9228</td>
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<td>F8</td>
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<tr>
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<td>0.9860</td>
<td>0.9472</td>
<td>0.8939</td>
<td>0.3148</td>
<td>0.8992</td>
<td>0.8300</td>
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<tr>
<td>F10</td>
<td>0.9585</td>
<td>0.9169</td>
<td>0.9192</td>
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<td>0.9863</td>
</tr>
<tr>
<td>F11</td>
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<td>0.8987</td>
<td>0.9282</td>
<td>0.2450</td>
<td>0.9849</td>
<td>0.5330</td>
</tr>
<tr>
<td>F12</td>
<td>0.9720</td>
<td>0.9535</td>
<td>0.8921</td>
<td>0.3447</td>
<td>0.7174</td>
<td>0.7297</td>
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<tr>
<td>F13</td>
<td>0.8970</td>
<td>0.897</td>
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<td>0.0483</td>
<td>0.9717</td>
<td>0.2598</td>
</tr>
<tr>
<td>S1</td>
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<td>0.9397</td>
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<tr>
<td>S2</td>
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<td>0.7938</td>
<td>0.9464</td>
<td>0.3127</td>
<td>0.7912</td>
<td>0.3889</td>
</tr>
</tbody>
</table>
CONCLUSION: In the present study, an attempt to formulate mucoadhesive buccal tablets of Carvedilol for treatment of hypertension using novel polymer (Casein) obtained from milk protein and HPMC K4M was made by an optimization technique. Using 3² full factorial design, the effect of interaction of independent variables Casein (X₁) and HPMC K4M (X₂) on dependent hardness (Y₁) and cumulative % drug release at 6 h (Q₆, Y₂) and 12 h (Q₁₂, Y₃) were studied and optimized.

The optimal formulation had the approximated percentage drug release which met the required rate of drug release for a period of 12 h through the buccal mucosa thus preventing first-pass hepatic metabolism. Casein showed the good mucoadhesive property. The optimized formulation followed zero-order release kinetics with non-Fickian drug release mechanism. From the results it can be concluded that mucoadhesive buccal tablets can be successfully formulated using Casein.

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REFERENCES:


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