Formulation Development of Olmesartan Medoxomil Mucoadhesive Buccal Film

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Abstract

Aim: Olmesartan medoxomil is an angiotensin II antagonist used in the management of hypertension. Mucoadhesive buccal films offer an attractive route of administration for systemic drug delivery through jugular vein leading to high bioavailability and greater therapeutic efficacy. Materials and Methods: Different formulations were carried out using natural polymer such as almond gum along with synthetic polymers. Formulations of F₁ to F₈ buccal films were prepared by solvent casting method by employing hydroxypropyl methylcellulose (HPMC) E50LV and almond gum alone, and in combination of HPMC E50LV and Eudragit RL100 and combination of HPMC E50LV and almond gum in different proportions. Results and Discussion: Buccal films were evaluated for their physicochemical characterization such as thickness, weight uniformity, folding endurance, drug content and surface pH, swelling index, percentage moisture loss, and uptake. Conclusion: Among all the formulations, F₁ was found to be satisfactory and surface pH of all films was found to be neutral. The in vitro release in optimized formulation F₇ was found to be 47.69% in 7 h, and drug release was found to be diffusion following first order as per kinetics (R² = 0.9937). Stability studies were carried out with selected formulations of F₇ and F₈.

Key words: Almond gum, Eudragit RL100, folding endurance, glycerin, hydroxypropyl methylcellulose E50LV, solvent casting technique, Tween 80

INTRODUCTION

Over the last two decades, throughout the world, there is an increasing demand from Pharmaceutical Companies for the development of buccal drug delivery techniques, with an estimated US market share of US$ 1208 million in 2020. It minimizes toxicity and improves efficacy, palatable, and patient compliance due to small size, dose, and thickness of buccal film over other dosage form. Other advantages include excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action. Buccal films provide satisfactory attachment with buccal layers, and hence it is most convenient and suitable dosage form as compared to others.

Many researchers have explored natural polysaccharides such as gums and mucilages abundantly found in many higher plants have been extensively used for the development of dosage forms. Mucilages are naturally occurring, high-molecular weight (approximately 200,000), and polyuronides consisting of sugar and uronic acid units. Gums swell in water to form sticky, colloidal dispersions, and pectins gelatinize in water while mucilages form slippery, aqueous colloidal dispersions. Hence, the natural almond gums in low concentration were used for the preparation of buccal film, and hence such dosage forms are easy to handle.

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cost-effective, fast absorbable, non-irritating, elegant, and mostly preferred by consumer.[13,14]

Olmesartan medoxomil (OMX) is described chemically as the (5-methyl-2-oxo-1,3-dioxol-4-yl) methyl ester of 4-(1-hydroxy-1-methylethyl) -2-propyl-1-[[20-(1H-tetrazol-5-yl)[1,10- biphenyl]-4-yl]methyl]-1H-imidazole-5-carboxylic acid. It is a pro-drug and hydrolyzed to olmesartan during absorption from the gastrointestinal tract. It is an angiotensin antagonist (angiotensin receptor blockers).[8-11] It is a white crystalline powder and has limited solubility.

Although OMX has 100% oral absorption, due to high first-pass metabolism, it has a low and variable bioavailability. The drug is given in dose 20-80 mg twice a day, and hence there is less patient compliance. The physicochemical properties of OMX are slight water solubility and low molecular weight (558.585 g/mol). To overcome high first-pass metabolism, buccal patches were designed with an objective to increase its bioavailability which is a new route to develop a revolution in drug industry.[15,16]

Sustained release formulation was developed with polymers (Eudragit RL100), hydroxypropyl methyl cellulose (HPMC) E50LV, natural gum (almond gum) in various proportions which released the drug over an extended period of more than 12 h, giving an advantage of once a day dosing. Tween 80 was used as permeation enhancer and glycerin as plasticizer. Eudragit RL100 and HPMC are release-retardant mucoadhesive polymers with high swellability and hydrophilicity. Anionic polyelectrolytes like HPMC have been extensively used for designing mucoadhesive delivery systems due to their ability to exhibit strong hydrogen bonding with the mucin present in the mucosal layer.[17,18] Eudragit RL100 is a hydrophobic polymer with high mechanical strength. Hence, they will provide delayed release of drug from buccal patches for long time. Glycerin is used as an additive that increases the plasticity or fluidity of the formulation. Tween 80 modifies the solvent nature of stratum corneum, thus improving drug partitioning into skin and also increasing diffusivity of the drug into skin.[19,20]

MATERIALS AND METHODS

OMX was obtained as a gift sample from AstraZeneca, Bangalore, India. HPMC E50LV and Eudragit were obtained from Yarrow Chem, Products, Mumbai, whereas almond gum was procured from Arumuga Siddha Centre, Chennai.

Collection, purification, and identification of gum

The natural almond gum was collected from the local market available in Chennai. The almond gum was taken and well dried and powered in a motor and passed through sieve No. 100. Almond gum was soluble in distilled water and heated for some time and cooled. Then, the concentrated solution was precipitated in ethanol in ice-cold condition. The precipitate was separated and dried at 60°C. The dried gum was powdered and stored in tightly closed container. The characterization of gum is carried out by means of various tests for the identification of almond gum.[8]

Preformulation studies

The polymer and drug compatibility were checked by Fourier transform infrared (FTIR) analysis (Jasco FTIR 100) using potassium bromide discs to ensure there was no incompatibility. $\lambda_{\text{max}}$ determination of OMX was done by ultraviolet (UV) spectroscopy using phosphate buffer pH 6.8 and a calibration curve of OMX was plotted by taking 2-18 µg/ml which was measured at 257 nm using phosphate buffer solution pH 6.8 as blank.

Preparation of OMX buccal film

The films containing OMX were prepared by solvent casting technique as shown in Table 1 using film-forming polymer

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>$F_1$</th>
<th>$F_2$</th>
<th>$F_3$</th>
<th>$F_4$</th>
<th>$F_5$</th>
<th>$F_6$</th>
<th>$F_7$</th>
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<tr>
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<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
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<tr>
<td>HPMC E50LV (mg)</td>
<td>400</td>
<td>300</td>
<td>250</td>
<td>200</td>
<td>-</td>
<td>300</td>
<td>250</td>
<td>200</td>
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<tr>
<td>Eudragit RL 100 (mg)</td>
<td>-</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Almond gum (mg)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>400</td>
<td>100</td>
<td>150</td>
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<td>Glycerine (ml)</td>
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<td>8-10</td>
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<td>Acetone (ml)</td>
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<tr>
<td>Tween (ml)</td>
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<td>0.1</td>
<td>0.1</td>
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<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
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<tr>
<td>Water (ml)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>3</td>
<td>3</td>
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</tr>
</tbody>
</table>

HPMC: Hydroxypropyl methylcellulose, OMX: Olmesartan medoxomil

Table 1: Formulation of OMX
HPMC E50LV alone and in combination with Eudragit, almond gum using solvents such as ethanol (drug, HPMC, Eudragit, almond gum), acetone (Eudragit), and water. Tween 80 was used as solubilizing agent, and glycerin was used as plasticizer. Drug-polymer solution was prepared by stirring on magnetic stirrer and then films were casted in Petri plate (3 inch). The solvent was allowed to evaporate slowly by inverting funnel containing cotton in its stem. The films were allowed to dry at room temperature for 24-72 h, and then were packed in aluminum foil and stored in desiccator.

**Evaluation properties of OMX buccal films**

**Appearance**

The film was observed visually for their physical appearance and transparency. The film was examined for their surface texture such as smooth, rough, or very smooth.

**Thickness**

The thickness of each patch is measured using digital vernier caliper at five different positions of the patch, and the average is calculated.

**Average weight**

Five different randomly selected patches from each batch are weighed and the weight variation is calculated.

**Drug content uniformity**

For drug content uniformity, a 3 cm patch (without backing membrane) is separately dissolved in 100 ml of ethanol and simulated saliva solution (pH 6.2) mixture (20:80) for 12 h under occasional shaking. The resultant solution is filtered and the drug content is estimated spectrophotometrically. The averages of three determinations are taken.

**Surface pH**

The prepared buccal patches are left to swell for 2 h on the surface of an agar plate, prepared by dissolving 2% (w/v) agar in warm phosphate buffer of pH 6.8 under stirring and then pouring the solution into a Petri dish till gelling at room temperature. The surface pH is determined by placing pH paper on the surface of the swollen patch. The mean of three readings is recorded.

**Folding endurance**

The folding endurance of each patch is determined by repeatedly folding the patch at the same place till it is broken or folded up to 300 times, which is considered satisfactory to reveal good film properties.

**Swelling index (SI)**

Buccal patches are weighed individually (Wᵢ) and placed separately in Petri dishes containing phosphate buffer pH 6.8. The patches are removed from the Petri dishes and excess surface water is removed using filter paper. The patches are reweighed (Wᵢ) and SI is calculated as follows:

\[
SI = \frac{(W₂-Wᵢ)}{W₁}
\]

**Moisture absorption and moisture loss**

The buccal patches are weighed accurately and kept in desiccator containing anhydrous calcium chloride. After 3 days, the patches are taken out and weighed. The moisture content (%) is determined by calculating moisture loss (%) using the formula as follows:

\[
\text{Moisture content (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100
\]

**In vitro dissolution study**

The drug release studies were performed with USP dissolution test apparatus (Paddle method). The USP dissolution apparatus was thermostated at the temperature of 37 ± 1°C and stirred at rate of 50 rpm. Each film was fixed on a glass slide with the help of cyanoacrylate adhesive so that the drug could be release only from upper face. Then, the slide has immersed in the vessel containing 500 ml of pH 6.8 phosphate buffer solution. The aliquots of 5 ml were withdrawn at the time interval of every hour and replaced with equal volume of dissolution medium for 6 h. The sink condition was maintained throughout the study. The samples were analyzed at 257 nm in UV-VIS Spectrometer and cumulative amount of drug release at various time intervals was calculated.

**Release kinetics**

For determination of drug release kinetics from the buccal tablet, the *in vitro* release data were analyzed by zero order, first order, Higuchi and Korsmeyer and Peppas equations.

**Stability studies**

Best formulation was stored in screw capped small glass bottles at room temperature and in stability chamber at 40 ± 1°C and 75% RH. Samples were analyzed for physical
appearance, residual drug content, and in vitro release after a period of 15, 30, and 45 days. Initial drug content was taken as 100% for each formulation.

RESULTS AND DISCUSSION

Pure OMX compound was examined for the solubility. It is insoluble in water and freely soluble in ethanol and alcohol. The OMX is highly soluble in methanol and ethanol and insoluble in water. Solubility studies were also performed in different buffer solutions to select the dissolution media which could maintain the sink conditions during in vitro release studies. The drug is slightly soluble in all buffers but has shown maximum solubility in pH 6.8 (0.0425 mg/ml) and was selected as a dissolution medium for in vitro dissolution study.

Preformulation studies on drug

OMX $\lambda_{\text{max}}$ was determined to be 257 nm. The calibration curve with concentration 2-18 µg/ml obeyed Beer’s law is shown in Figure 1.

The patches from the all formulation were all uniform, translucent appearance, and flexible with smooth surface. The diameter was 3.5 cm and the area was of 49 cm. The prepared batches of F$_7$ and F$_8$ are taken as best formulations after drying as shown in Figure 3. All the patches have uniform thickness throughout from formulations F$_1$ to F$_8$. The thickness of the various films varies from 0.17 ± 0.002 to 0.28 ± 0.041 mm with low standard deviation values. The thinnest being of F$_1$ and thickest of F$_8$ formulations are shown in Table 2.

The weight of 2 cm × 2 cm patch was in the range of 80-174 mg. It was observed that formulation F$_1$ and F$_2$ showed low average weight whereas formulation F$_6$-F$_8$ containing almond gum and HPMC showed high average weight as shown in Table 2.

The drug content in all formulations varies between 94.82 ± 0.02 and 99.83 ± 0.05. As the drug was uniformly dispersed in the matrix of the polymer, a significantly good amount of drug was loaded in the formulation. The order of drug content was found to be F$_7$ > F$_8$ > F$_6$ > F$_5$ > F$_2$ > F$_1$ > F$_4$ as shown in Table 2. The acidic or alkali pH caused irritation to buccal mucosa and may affect the drug release and degree of hydration of polymers. Therefore, the surface infrared spectrum shows all prominent peaks of OMX. IR spectrum of pure OMX is shown in Figure 2; an absorption band was observed, peaks 2995.87/cm (C-H, str, Sp2), 2923.56/cm (C-H, str, Sp3), 1708/cm, 1832/cm (C-O, str) and 3300-3100/cm (N-H, str). These peaks can be considered as characteristic peaks of OMX and were not affected and prominently observed in IR spectra of OMX along with pure drug and mixture of drug and polymer, so there was no any chemical incompatibility between drug and polymers. Functional groups and their IR range of OMX, HPMC, Eudragit RL100, and almond gum spectra are shown in Figure 2.

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pH of buccal film was determined to optimize both drug release and mucoadhesion. The surface pH of all formulation is within ±0.5 units of the neutral pH, and hence no mucosal irritations were expected and ultimately achieve patient compliance as shown in Table 3.

The folding endurance was found to be in the range of 277 ± 0.0042-326 ± 0.062 and did not show any crack even after folding for more than 300 times. The values were found to be optimum to review good film properties. The comparative folding endurance in different formulation wherein the order of F₁ > F₃ > F₅ > F₆ > F₄ > F₃ > F₂ is shown in Table 3.

The swelling of films were observed at pH 6.8 phosphate buffer solution. The comparative percentage swelling behavior for various formulations is shown in Table 3. The percentage swelling of HPMC films was reduced by the addition of Eudarjit RL100 and increased by the addition of almond gum. The almond gum containing formulations F₅ showed higher percentage swelling due to freely soluble in water. The water soluble hydrophilic additive dissolves rapidly resulting in high porosity. The percentage moisture absorption and moisture loss was found to be minimal, hence ensures the stability of films in different environmental conditions. However, it was found that percentage moisture absorption and moisture loss is increased with increase in addition of hydrophilic polymers such as HPMC and almond gum (F₆-F₈). The percentage moisture loss and absorption in hydrophilic polymers were found to be high in F₅ when compared to F₁ as shown in Table 3.

In vitro dissolution studies

The data obtained as shown in Table 4 for in vitro drug release study performed up to 7 h provide a clear indication that prepared patches show necessary controlled release profile desired for buccal adhesive drug delivery. The in vitro release studies of various formulations were performed in 500 ml pH 6.8 phosphate buffer solution at 257 nm as shown in Figure 4.

Among them, formulation F₇ shows highest drug release at the end of 7 h. It was observed that in vitro drug release

| Table 2: Physico chemical characteristics for formulation F₁-F₈ |  |
|---|---|---|---|
| Formulation | Thickness (mm)±SD, n=3 | Average weight (mg)±SD, n=3 | Drug content (%)±SD, n=3 |
| F₁ | 0.17±0.002 | 80±0.05 | 97.49±0.03 |
| F₂ | 0.19±0.004 | 80±0.003 | 98.10±0.001 |
| F₃ | 0.22±0.002 | 120±0.003 | 94.82±0.02 |
| F₄ | 0.24±0.006 | 142±0.86 | 96.62±0.11 |
| F₅ | 0.28±0.041 | 159±0.081 | 98.64±0.09 |
| F₆ | 0.24±0.009 | 162±0.024 | 98.26±0.02 |
| F₇ | 0.23±0.026 | 168±0.002 | 99.83±0.05 |
| F₈ | 0.26±0.040 | 174±0.004 | 99.24±0.06 |

SD: Standard deviation

| Table 3: Physiochemical properties of buccal film |  |
|---|---|---|---|
| Formulation | Surface pH±SD, n=3 | Folding endurance±SD, n=3 | % SI±SD, n=3 | % Moisture absorbance±SD, n=3 | % Moisture loss±SD, n=3 |
| F₁ | 6.39±0.025 | 326±0.062 | 56±2.642 | 10±0.14 | 1.52±0.026 |
| F₂ | 6.35±0.096 | 277±0.0042 | 42±3.005 | 9.8±0.002 | 1.42±0.624 |
| F₃ | 6.70±0.075 | 282±0.324 | 56±1.527 | 11.2±0.015 | 1.36±0.157 |
| F₄ | 6.23±0.120 | 289±0.420 | 58±0.845 | 9.62±0.026 | 1.30±0.124 |
| F₅ | 6.48±0.051 | 302±0.360 | 92±0.721 | 12.11±0.12 | 2.36±0.006 |
| F₆ | 6.36±0.105 | 294±0.020 | 64±0.423 | 10.25±0.011 | 1.62±0.72 |
| F₇ | 6.38±0.120 | 286±2.42 | 78±0.627 | 10.45±0.62 | 1.98±0.012 |
| F₈ | 6.35±0.052 | 310±2.645 | 82±0.246 | 11.25±0.012 | 2.21±0.07 |

SD: Standard deviation
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Table 4: In vitro dissolution studies of buccal films

<table>
<thead>
<tr>
<th>Time in hrs</th>
<th>F₁</th>
<th>F₂</th>
<th>F₃</th>
<th>F₄</th>
<th>F₅</th>
<th>F₆</th>
<th>F₇</th>
<th>F₈</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14.20±0.014</td>
<td>15.13±0.013</td>
<td>18.32±0.015</td>
<td>18.33±0.010</td>
<td>20.24±0.011</td>
<td>18.52±0.010</td>
<td>11.62±0.065</td>
<td>11.52±0.061</td>
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<tr>
<td>2</td>
<td>23.82±0.019</td>
<td>26.72±0.019</td>
<td>32.45±0.050</td>
<td>18.62±0.015</td>
<td>36.20±0.013</td>
<td>32.67±0.015</td>
<td>18.52±0.075</td>
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<td>37.21±0.021</td>
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<td>28.36±0.011</td>
<td>31.66±0.080</td>
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<td>4</td>
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<td>42.23±0.020</td>
<td>65.61±0.044</td>
<td>42.23±0.017</td>
<td>57.18±0.020</td>
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<td>30.59±0.012</td>
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<td>7</td>
<td>83.27±0.011</td>
<td>82.56±0.032</td>
<td>80.45±0.014</td>
<td>72.51±0.011</td>
<td>89.73±0.051</td>
<td>78.13±0.011</td>
<td>47.69±0.019</td>
<td>64.13±0.015</td>
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</tbody>
</table>

for formulation F₂-F₄ after 7 h was found to be in the order F₂>F₃>F₄ and was found that F₅ containing almond gum showed highest SI with release of drug when compared to F₆ containing HPMC alone. The formulation F₇ containing 2.5:1.5 of HPMC E50LV and almond gum showed highest SI which could retard the release of drug up to 18 h showing 47.69 ± 0.019 at the end of 7 h. The formulation F₆ and F₈ containing 3:1, 2:2 of HPMC E50LV and almond gum showed SI 64 ± 0.42 and 82 ± 0.246 with drug release of 78.13% and 64.13%. The rank order of drug release after 7 h was found to be 89.73% > 33.27% > 82.56% > 80.45% > 78.13% > 72.15% > 64.13% > 47.69% for formulation F₅, F₁, F₂, F₃, F₆, F₄, F₈, F₇, respectively, as shown in Figures 5 and 6.

It was observed that during dissolution films containing equal amount of HPMC and almond gum swelled forming a gel layer on the exposed film surfaces. The loosely bound polymers molecules in these films were readily eroded, allowing the easy release of drug as compared to F₇. It was concluded that the formulation F₇ containing 2.5:1.5 of HPMC and almond gum showed good swelling a convenient residence time as well as promising drug release on the basis of release pattern and SI F₇ formulation chosen as the best formulation. F₇ proved to be a better candidate to other formulation of slow release for longer duration.

Release kinetics

Different model dependent approaches (zero order, first order, Higuchi, Korse Meyer-Peppas model was performed for best formulation F₇). The results of these models follow Korse Meyer-Peppas model as “best fit model” follows diffusion mechanism. This is due to previously proved fact depending on R² value obtained from model fitting. From the results, F₇ showed more retarding effect and thus found that T 50% value increases as concentration of almond gum increases. Korse Meyer-Peppas release exponent (n) values of all OMX l buccal film are >1 indicating drug diffusion is rapid due to swelling in the polymer as shown in Table 5 and Figure 7a-e.

Stability studies

According to ICH guidelines, stability study at room temperature for 7 days at RH 75 ± 5% of best formulation (F₇ and F₈) was carried out. It showed negligible change over time for parameters such as average weight, SI, folding endurance, percentage moisture loss, percentage moisture absorption, and in vitro drug release. There was no
significant difference in the drug content between initial and formulations stored at room temperature for 7 days at RH 75 ± 5% in a desiccator as shown in Table 6.

### Table 6: Stability studies of best formulations (F₇ and F₈)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>F₇</th>
<th>F₈</th>
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<tr>
<td>Average weight (mg)</td>
<td>168±0.002</td>
<td>174±0.004</td>
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<tr>
<td>SI (%)</td>
<td>78±0.624</td>
<td>82±0.246</td>
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<tr>
<td>Percentage moisture loss</td>
<td>1.98±0.012</td>
<td>2.21±0.07</td>
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<tr>
<td>Percentage moisture absorption</td>
<td>10.45±0.62</td>
<td>11.25±0.012</td>
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<tr>
<td>In vitro release (%)</td>
<td>47.69±0.019</td>
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<tr>
<td>Folding endurance</td>
<td>286±2.42</td>
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</table>

SI: Swelling index

The results of all the physical characterization of all formulation F₁-F₄ were found to be satisfactory. The results of the study show that therapeutic levels of OMX can be delivered through buccal. The present study concludes that these erodible mucoadhesive buccal films containing olmesartan can be very promising for effective doses to systemic circulation. These may also provide an added advantage of circumventing the hepatic first pass metabolism. The films exhibited controlled release over more than 7 h. It was concluded that the films containing 14 mg of OMX in HPMC E50LV and almond gum (formulation F₇) showed good swelling and promising controlled drug release. Thus, F₇ buccal film can be used for effective therapeutic uses. Buccal films have gained relevance in pharmaceutical industry as a novel, patient-friendly convenient products. The study may be extended for assessing the in vivo release and in vitro–in vivo correlation. The future scope could be tested in human volunteers to evaluate bioavailability parameters.

### CONCLUSION

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