FORMULATION, IN VITRO AND EX VIVO CHARACTERIZATION OF MUCOADHESIVE BUCCAL TABLETS FOR ANTIHYPERTENSIVE DRUG

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INTRODUCTION

Oral drug administration is the most preferred and common route for drug delivery. Although, sometimes it entails with certain major disadvantages such as first-pass metabolism, gastrointestinal enzymatic degradation, and poor bioavailability. These difficulties have provided the impulsion for exploring alternative routes for the delivery of drugs, which includes pulmonary, ocular, nasal, rectal, vaginal, and buccal [1]. Transmucosal routes of drug delivery (i.e. the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer attractive possible routes for administration of drugs and may avoid the significant drawbacks of peroral and parenteral administration for systemic effect [2]. The oral cavity, however, is a highly accepted route for both local and systemic drug delivery [3]. Indeed, buccal delivery is increasingly being considered to be the preferred route for many drug classes [4]. The buccal delivery is in which drug administration through the mucosal membranes lining of the cheeks to systemic circulation [5]. Buccal mucosa is a potential site for the delivery of drugs to the systemic circulation, a drug administered through the buccal mucosa enters directly the systemic circulation, thereby minimizing the first-pass hepatic metabolism and adverse gastrointestinal effect [6]. The oral mucosa, mainly the buccal site rather attractive for drug delivery [7], because the mucosa is relatively permeable with a rich blood supply, it is easily accessible, relatively immobile mucosa, suitable for administration of retentive dosage forms, termination of therapy at any time, comparatively less susceptibility to enzymatic activity, and useful for pediatric and geriatric patients. Hence, various mucoadhesive dosage forms were prepared for oral delivery, in the form of adhesive tablets [8-13], adhesive gels, buccal ointments [14,15], Bioadhesive Wafers [16], Bioadhesive lozenges [17], Bioadhesive Microparticles [18], and adhesive patches [19,20].

Olmesartan belongs to a class of drugs called angiotensin II receptor blockers (ARBs). It is approved and used for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents [21]. The molecular weight of drug is 446.511 g/mol. Olmesartan has excellent lipophilicity, so the drug can get easily absorbed and permeable through buccal mucosa. The half-life is approximately 6–7 h. Orally administered olmesartan was rapidly absorbed from the gastrointestinal tract but undergoes extensive first-pass metabolism, resulting in low oral bioavailability is about 26%. Olmesartan dose-dependently reduces the blood pressure through arterial vasodilation and reduced sodium retention, as do other ARBs [22]. Based on the above criteria, it was considered an essential alternative to develop buccal drug delivery system for delivery of olmesartan, which can improve its bioavailability by avoiding hepatic metabolism using suitable mucadhesive polymers. Hence, the aim of this study was to prepare mucoadhesive buccal tablets of olmesartan to ensure satisfactory drug release within oral cavity with the use of the optimum polymer.

MATERIALS AND METHODS

Materials

Olmesartan (Drug) was a gift sample from Cipla, Ltd., Mumbai, India. Hydroxypropyl methylcellulose K4M (HPMC K4M) and sodium carboxymethyl cellulose (SCMC) were gift samples from Horizon Pharma, Gujarat, India. Carbopol 934P was a gift sample from Dr. Reddys Laboratories, Hyderabad, India. Microcrystalline cellulose 102 was purchased from Apotex Pharmachem (Bengaluru, India). Mannitol was purchased from S.D. Fine Chem. Ltd., Mumbai, India. Talc and magnesium stearate were purchased from HMedia Laboratories Pvt. Ltd., Mumbai, India.

ABSTRACT

Objective: Olmesartan belongs to a class of angiotensin II receptor blockers. It is used in the treatment of hypertension. However, it undergoes extensive hepatic first-pass metabolism, resulting in low oral bioavailability is about 26%. The aim of this study was to prepare and evaluate the mucoadhesive buccal tablets of olmesartan with a goal to increase the bioavailability and improve the patient compliance.

Methods: Mucoadhesive buccal tablets were prepared by a direct compression technique using mucoadhesive polymers such as hydroxypropyl methylcelulose (HPMC K4M), sodium carboxymethylcellulose (SCMC), and Carbopol 934P. The tablets were evaluated for weight variation, thickness, hardness, friability, surface pH, swelling index, drug content uniformity, in vitro drug release, ex vivo mucoadhesive strength, ex vivo mucoadhesive time, and ex vivo permeation studies. The release kinetics was calculated to determine the drug release mechanism.

Results: The physicochemical properties of all the formulations were shown to be within the limits. The optimized buccal tablets F2, F7, and F11 showed satisfactory drug release rates with the diffusion controlled mechanism. Optimized buccal tablets developed for olmesartan possess reasonable mucoadhesive strength, mucoadhesive time, and surface pH was in an acceptable salivary pH 6.7±0.26–6.89±0.34. The ex vivo permeation studies for optimized tablets were shown satisfactory drug permeation and could meet the target flux 0.991 mg.h⁻¹.cm⁻².

Conclusion: The obtained results could be used as a platform to develop the buccal delivery of this drug, which bypasses the first-pass metabolism and results in the improvement of bioavailability. Hence, the present study concludes that the olmesartan could be delivered through the buccal route.

Keywords: Mucoadhesive buccal tablets, Olmesartan, Direct compression method, ex vivo permeation studies.

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**Methods**

**Preformulation studies**

Determination of absorption maxima values ($\lambda_{max}$) using ultraviolet (UV)-visible spectrophotometer

Standard stock solution of olmesartan (100 μg/ml) was prepared in pH 6.8 phosphate buffer. For the selection of analytical wavelength, a solution of olmesartan of concentration 30 μg/ml was prepared by appropriate dilution of the standard stock solution with phosphate buffer pH 6.8 and scanned in the spectrum range from 200 to 400 nm. From the overlain spectrum of the drug, wavelength 256 nm was selected for analysis. The wavelength with maximum absorption was chosen for further analysis (Fig. 1).

Preparation of standard graph of olmesartan in pH 6.8 phosphate buffer and pH 7.4 phosphate buffer by UV-visible spectrophotometer

The stock solution was freshly prepared by dissolving 100 mg of olmesartan in pH 6.8 phosphate buffers in a 100 ml volumetric flask and then making up the solution up to the mark using pH 6.8 pH phosphate buffers for obtaining the solution of strength 1000 µg/ml (stock 1). From this primary stock, 10 ml of this solution is diluted to 100 ml with distilled water to obtain a solution of strength 100 µg/ml (stock II). From this secondary stock 0.2, 0.4, 0.8, 1.0, 2.0, 3.0, 4.0, 5.0, and 6.0 ml were taken separately and made up to 10 ml with pH 6.8 phosphate buffer, to produce 2, 4, 8, 10, 20, 30, 40, 50, and 60 µg/ml, respectively. The absorbance was measured at 256 nm using a UV-visible spectrophotometer (Elico Pvt., Ltd., Hyderabad). Similarly, standard graph of olmesartan in pH 7.4 phosphate buffer was plotted (Fig. 2 and 3, Table 1).

**Drug excipients compatibility studies**

**Fourier transform infrared (FTIR) spectroscopy**

The FTIR spectra for the samples were obtained using potassium bromide (KBr) disk method by FTIR spectrophotometer. Pure drug olmesartan, physical mixture of olmesartan and HPMC K4M, physical mixture of olmesartan and SCMC and physical mixture of olmesartan and Carbopol 934P were prepared and subjected to FTIR study. About 2–3 mg of sample was mixed with dried KBr of equal weight and compressed to form a KBr disk. The samples were scanned from 400 to 4000 cm$^{-1}$ spectral region with a resolution of 4 cm$^{-1}$.

**Ex vivo drug permeation studies through goat buccal mucosa**

**Tissue isolation**

The objective of this study was to investigate the permeability of buccal mucosa to olmesartan. Goat buccal tissue was taken from a local slaughter-house. It was collected within 10 min after the slaughter of the goat and tissue was stored in Krebs buffer solution. It was transported immediately to the laboratory and was used within 2 h of isolation of buccal tissue [23,24]. The buccal epithelium was carefully separated from the underlying connective tissue with surgical technique, and then the remaining buccal mucosa was carefully trimmed with the help of surgical scissors to a uniform thickness (Fig. 4). Sufficient care was taken to prevent any damage to the buccal epithelium. Finally, the membrane was allowed to equilibrate for approximately 1 h in receptor buffer to regain the lost elasticity [25].

**Table 1: Absorbance of olmesartan against different concentrations at $\lambda_{max}$ (256 nm) in phosphate buffer pH 6.8 and phosphate buffer pH 7.4**

| Concentration (µg/ml) | Absorbances 6.8 pH Phosphate buffer | Absorbances 7.4 pH Phosphate buffer |
|----------------------|-------------------------------------|-------------------------------------|
| 2                    | 0.053                               | 0.029                               |
| 4                    | 0.082                               | 0.045                               |
| 8                    | 0.143                               | 0.119                               |
| 10                   | 0.191                               | 0.148                               |
| 20                   | 0.323                               | 0.271                               |
| 30                   | 0.471                               | 0.411                               |
| 40                   | 0.611                               | 0.552                               |
| 50                   | 0.745                               | 0.684                               |
| 60                   | 0.893                               | 0.816                               |

**Fig. 1: Ultraviolet absorption spectrum of olmesartan in phosphate buffer pH 6.8**

**Fig. 2: Standard graph of olmesartan in pH 6.8 phosphate buffer**

**Fig. 3: Standard graph of olmesartan in pH 7.4 phosphate buffer**
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Table 2: Composition of olmesartan buccal tablets containing hydroxylpropyl methylcellulose and sodium carboxymethyl cellulose

| Ingredients        | Formulations (weight in mg) |
|--------------------|-----------------------------|
|                    | F1  | F2  | F3  | F4  | F5  | F6  | F7  | F8  | F9  | F10 |
| Drug polymer       | 1:0.5 | 1:1 | 1:2 | 1:2:5 | 1:3 | 1:0:5 | 1:1 | 1:1:5 | 1:2 | 1:2:5 |
| Olmesartan         | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  |
| HPMC K4M           | 20  | 40  | 80  | 100 | 160 | -    | -   | -   | -   | -   |
| SCMC               | -   | -   | -   | -   | 20  | 40   | 80  | 100 | 100 |
| MCC102             | 170 | 150 | 110 | 90  | 30  | 170  | 150 | 130 | 110 | 90  |
| Mannitol           | 15  | 15  | 15  | 15  | 15  | 15   | 15  | 15  | 15  | 15  |
| Magnesium stearate | 160 | 250 | 150 | 130 | 170 | 150  | 130 | 110 | 110 | 110 |
| Talc               | 2   | 2   | 2   | 2   | 2   | 2    | 2   | 2   | 2   | 2   |
| Total tablet weight (in mg) | 250 | 250 | 250 | 250 | 250 | 250  | 250 | 250 | 250 | 250 |

HPMC K4M: Hydroxypropyl methylcellulose, SCMC: Sodium carboxymethylcellulose

Table 3: Composition of olmesartan buccal tablets containing Carbopol 934P

| Ingredients        | Formulations (weight in mg) |
|--------------------|-----------------------------|
|                    | F11 | F12 | F13 | F14 | F15 |
| Drug polymer       | 1:0.5 | 1:1 | 1:1.5 | 1:2 | 1:2.5 |
| Olmesartan         | 40  | 40  | 40  | 40  | 40  |
| Carbopol 934P      | 20  | 40  | 60  | 80  | 100 |
| MCC102             | 170 | 150 | 130 | 110 | 90  |
| Mannitol           | 15  | 15  | 15  | 15  | 15  |
| Magnesium stearate | 3   | 3   | 3   | 3   | 3   |
| Talc               | 2   | 2   | 2   | 2   | 2   |
| Total tablet weight (in mg) | 250 | 250 | 250 | 250 | 250 |

Procedural

Ex vivo permeation study of olmesartan was performed through the goat buccal mucosa using modified Franz diffusion cell. The isolated buccal epithelium was carefully mounted between the two compartments of a modified Franz diffusion cell, and the membrane was allowed to equilibrate for approximately 1 h. After the buccal membrane was equilibrated for 1 h with pH 7.4 phosphate buffer solution between both the chambers, the receiver compartment was filled with 25 ml fresh phosphate buffer solution (pH 7.4), and the donor compartment was charged with 4 ml (1 mg/ml) of drug solution. The entire setup was placed over magnetic stirrer at 50 rpm, and the temperature was maintained at about 37°C. The 2 ml of samples were collected at predetermined time intervals 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, and 6.0 h from receptor compartment and replaced with an equal volume of fresh buffer solution and stored under refrigerated conditions till the analysis was carried out. All the experiments were performed in triplicates. Finally, the amount of drug permeated through the buccal mucosa was determined by measuring the absorbance at 256 nm using a UV-visible spectrophotometer (Elico Pvt., Ltd., Hyderabad). The studies were repeated in triplicate (n=3), and the mean was calculated.

Preparation of mucoadhesive buccal tablets

Buccal tablets were prepared by a direct compression method [9,26]. The required quantities of the drug, polymer, and excipients were accurately weighed, and all the ingredients were screened through sieve no.40, to get uniform particle size. The drug and the all ingredients except lubricants were taken into a polythene bag with the help of stainless steel spatula, and the ingredients were mixed in the order of ascending weights and blended for about 10 min. After uniform mixing of ingredients, lubricant and glidant were added and again mixed for 2 min (Tables 2 and 3). The prepared blend of each formulation was compressed using 6 mm punch on a tablet punching machine.

Evaluation of the prepared buccal tablets

Weight variation test

Twenty tablets from each batch were individually weighed on a digital balance. The average weight and standard deviation were calculated. The percent deviation was calculated using the following formula.

\[
\text{% Deviation} = \frac{\text{Individual Weight} - \text{Average weight}}{\text{Average weight}} \times 100
\]

Thickness test

The thickness of buccal tablets was measured for 10 individual tablets from each batch by using Vernier calipers. The average thickness and standard deviation were reported.

Hardness test

Tablet hardness was measured for 6 tablets from each batch using a Pfizer hardness tester. The mean±standard deviation values were calculated for all the formulations.

Friability test

Roche friabilator was used to determine the friability by the following procedure. Pre-weighed tablets (10 tablets) were placed in the friabilator. The tablets were rotated at 25 rpm for 4 min (100 rotations). At the end of the test, the tablets were re-weighed; loss in the weight of tablet was measured in percentage using following formula. The studies were repeated in triplicate (n=3), and the mean was calculated.

\[
\text{% Friability} = \frac{\text{Individual Weight} - \text{Average weight}}{\text{Average weight}} \times 100
\]

Where \( W_i \) = Initial weight of 10 tablets

\( W_f \) = Weight of the 10 tablets after testing

Assay of tablets

Ten tablets were weighed and grounded in a mortar with pestle to get fine powder; powder equivalent to the mass of one tablet was dissolved in 100 ml of pH 6.8 of phosphate buffer. The solution was filtered through 0.45 μm filter paper and diluted approximately with pH 6.8 phosphate buffer and the drug content was estimated using UV-visible spectrophotometer at 256 nm.

In vitro drug release studies

The drug release from the bioadhesive buccal tablets was studied using the USP type II dissolution test apparatus. The dissolution medium
correlation between cumulative percentage permeation of olmesartan from the buccal membrane was performed for percentage permeation at 37°C. Samples of 2 ml were collected at predetermined time points up to 6 h from receptor compartment and replaced with an equal volume of buffer. The amount of drug permeated from optimized formulation through the buccal mucosa was then determined by measuring the absorbance at 256 nm using a UV-visible spectrophotometer. The experiments were performed in triplicate (n=3), the cumulative percentage drug permeated was calculated.

### Stability of buccal tablets

Stability studies of buccal tablets were performed for optimized formulations (F2, F7, and F11) in normal human saliva [31]. The saliva was collected from humans aged 22–26 and filtered through Whatman (0.2 µm) filter paper. Buccal tablets were placed in separate Petri dishes containing 5 ml of human saliva and placed in a temperature-controlled oven for 6 h at 37±0.2°C. At regular time intervals (0, 2, 4, and 6 h), the buccal tablets were examined for change in color, integrity, and change in pH [14]. The experiments were repeated in triplicate (n=3) in a similar manner.

### In vitro ex vivo correlation between cumulative percentage drug release in vitro and percentage drug permeated ex vivo of optimized olmesartan buccal tablets

A possible in vitro ex vivo correlation was performed for percentage drug release in vitro and percentage drug permeated ex vivo for optimized formulations [32].

### RESULTS AND DISCUSSION

**Determination of absorption maximum values**

An UV-visible spectrophotometric method was used for estimation of absorption maxima of olmesartan. The λ<sub>max</sub> of olmesartan (30 μg/ml) in 6.8 pH phosphate buffer was scanned in UV-visible spectrophotometer in the wavelength range of 200–400 nm and found to have a maximum absorbance at 256 nm.

**Preparation of standard graph of olmesartan in pH 6.8 phosphate buffer and pH 7.4 phosphate buffer by UV-visible spectrophotometer**

Different concentrations of olmesartan were prepared in phosphate buffer pH 6.8 and phosphate buffer pH 7.4 (2–60 µg/ml), and absorbance values at λ<sub>max</sub> (256 nm) were noted. The calibration curves showed good linearity with a correlation coefficient of R<sup>2</sup> 0.999.

**Drug-excipient compatibility studies**

**FTIR spectroscopy studies**

The potential chemical interaction between drug and polymer may change the therapeutic efficacy of the drug. FTIR spectroscopic studies were carried out to investigate the possibility of any chemical interaction between drug and polymers used in the preparation of tablets. The different samples were analyzed over the range 400–4000 cm<sup>-1</sup>. The FTIR spectrum of olmesartan showed principal bands at 2923.56–2995.87 cm<sup>-1</sup> for C-H, 1708–1832 cm<sup>-1</sup> for amide, 1642 cm<sup>-1</sup> for C=O, and 3100 cm<sup>-1</sup> for N-H. These peaks can be considered as characteristic peaks of olmesartan. These FTIR bands of the drug remain intact and also no new peak was found in both the spectra of the drug and its mixture. This indicates the absence of interaction between olmesartan and excipients used in the preparation of tablets.

**In vivo drug permeation studies through goat buccal mucosa**

Goat buccal mucosa had been the most frequently chosen model tissue for ex vivo permeation studies because of its similarity to human tissue in terms of thickness and is easily available in large quantities from the slaughterhouse.
The cumulative percentage amount of olmesartan permeated through the buccal membrane in first 2 h was 49.43% and 84.23% in 6 h clearly indicates that the penetration of the drug through the goat buccal epithelium was initially rapid and followed by slow penetration rate. The cumulative percentage amount of olmesartan that had penetrated through the buccal epithelium was shown in Fig. 9. The flux was calculated to be 0.148±0.168 mg h⁻¹ cm⁻² (Target flux 0.154 mg h⁻¹ cm⁻²).

**Evaluation of physical parameters buccal tablets of olmesartan**

All the prepared formulations were tested for physical parameters such
as weight variation, hardness, thickness, and friability and found to be within the pharmacopeia limits. The results of the tests were tabulated in Table 4.

The results of the physical tests of the formulations were within the limits and complied with the standards. The weights of the tablets ranged from 244 mg to 259 mg; the thickness was found to be in the range 2.11 mm–2.19 mm. The hardness of the tablets was in the range of 4.1–4.7 kg/cm² and friability was in the range 0.14–0.24%, indicating that the tablets are hard enough to withstand breakage. The drug content on an average was found to be 98.874%. All these parameters were within acceptable limits. This study indicated that all the prepared formulations were good.

**In vitro drug release of buccal tablets**

*In vitro* drug release studies were conducted in pH 6.8 phosphate buffer and revealed that the release of olmesartan from different formulations varies with characteristics and composition of the matrix forming polymers as shown in graphs. An increase in the polymer concentration causes an increase in the viscosity of the gel as well as the formation of a gel layer with a longer diffusional path length. This causes a decrease in the effective diffusion coefficient of the drug and that could substantially reduce the penetration of the dissolution medium into the tablet matrix and therefore a reduction in the drug release rate.

The formulations F1–F5 formulated using HPMC K4M, In case of formulation F1, the rate of drug release was much faster and found to be 99.78% in 5 h, and formulation F2 released faster rate than the other formulations in 6 h. Because with an increase in the polymer concentration from F2 to F5, the percentage drug release was decreased from 98.72% to 90.84% in 6 h. Only the formulation F2 had shown more than 97% drug release in 6 h. The formulations F6–F10 formulated using SMMC. In case of formulations F6 had shown 99.85% of drug release in 5 h, respectively. Increasing the concentration of the polymer in the formulation showed the sustained effect on olmesartan release. The percentage of drug release from formulations F7 to F10 was decreased from 99.83% to 80.38% in 6 h. For the Carbopol 934P based formulations, the percentage drug release from formulations F11 to F15 was decreased from 81.63% to 51.04% in 6 h due to increase in the polymer concentration. Only F11 formulation showed better release about 81.63% in a desired period of time and drug release pattern was shown in figures 10–12.

Buccal tablets containing lower concentrations of these polymers tend to release the drug in a shorter period of time. Increasing the concentration of the polymer in the formulation showed the sustained effect on olmesartan release, thus confirming the dominant role of the rapidly hydrating polymer in controlling the release of olmesartan from buccal tablets as seen from dissolution profile. The difference in the drug release profiles of various formulations was due to the release of olmesartan from buccal tablets. The method described by Korsmeyer and peppers was used to describe the mechanism of drug release [33].

**Table 4: Physicochemical parameters of mucoadhesive buccal tablets of olmesartan**

| Formulation code | Weight variation (mg) | Thickness (mm) | Hardness (kg/cm²) | Friability (%) | Assay (%) |
|------------------|-----------------------|----------------|------------------|---------------|-----------|
| F1               | 25.4±1.26             | 2.14±0.02      | 4.1±0.5          | 0.14          | 99.57     |
| F2               | 24.5±1.43             | 2.13±0.03      | 4.4±0.3          | 0.16          | 98.77     |
| F3               | 25.4±3.78             | 2.14±0.02      | 4.3±0.4          | 0.14          | 98.69     |
| F4               | 25.3±2.1              | 2.12±0.04      | 4.5±0.2          | 0.23          | 99.32     |
| F5               | 25.2±2.25             | 2.15±0.05      | 4.7±0.3          | 0.18          | 99.53     |
| F6               | 24.7±1.75             | 2.13±0.03      | 4.2±0.2          | 0.16          | 99.71     |
| F7               | 25.0±1.83             | 2.19±0.04      | 4.4±0.5          | 0.20          | 98.47     |
| F8               | 25.3±2.24             | 2.13±0.03      | 4.3±0.5          | 0.13          | 98.81     |
| F9               | 25.2±3.56             | 2.11±0.03      | 4.5±0.3          | 0.24          | 99.58     |
| F10              | 25.9±2.28             | 2.2±0.02       | 4.2±0.4          | 0.15          | 97.44     |
| F11              | 25.3±1.91             | 2.19±0.04      | 4.1±0.5          | 0.14          | 98.96     |
| F12              | 25.4±3.64             | 2.18±0.04      | 4.5±0.3          | 0.21          | 98.89     |
| F13              | 25.8±2.12             | 2.12±0.01      | 4.7±0.5          | 0.17          | 97.88     |
| F14              | 24.4±3.32             | 2.17±1.03      | 4.3±0.6          | 0.15          | 98.66     |
| F15              | 25.3±2.12             | 2.16±0.02      | 4.5±0.2          | 0.19          | 99.33     |

Each value represents the mean±SD (n=3). SD: Standard deviation
Table 5: Kinetic parameters for the *in vitro* release of olmesartan from different formulations

| Formulation | Zero-order $R^2$ | First-order | Higuchi | Korsmeyer–Peppas $n$ |
|-------------|------------------|-------------|---------|---------------------|
| F1          | 0.923            | 0.918       | 0.982   | 0.912               |
| F2          | 0.979            | 0.879       | 0.969   | 0.899               |
| F3          | 0.914            | 0.913       | 0.973   | 0.924               |
| F4          | 0.956            | 0.921       | 0.971   | 0.943               |
| F5          | 0.959            | 0.893       | 0.943   | 0.935               |
| F6          | 0.949            | 0.842       | 0.981   | 0.915               |
| F7          | 0.957            | 0.789       | 0.955   | 0.898               |
| F8          | 0.943            | 0.898       | 0.982   | 0.952               |
| F9          | 0.962            | 0.913       | 0.974   | 0.943               |
| F10         | 0.964            | 0.923       | 0.988   | 0.928               |
| F11         | 0.931            | 0.984       | 0.967   | 0.982               |
| F12         | 0.940            | 0.972       | 0.972   | 0.942               |
| F13         | 0.971            | 0.926       | 0.964   | 0.938               |
| F14         | 0.956            | 0.959       | 0.994   | 0.962               |
| F15         | 0.986            | 0.974       | 0.971   | 0.968               |

In *vitro* release kinetic parameters of olmesartan from mucoadhesive buccal tablets

In *vitro* drug release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas equations to ascertain the pattern of drug release. The presence of different concentrations of polymer. Formulation F2, F7, and F11 was considered as optimized formulations among all these formulations because they released the drug within the desired period of time 6 h.
From Table 5, it could be inferred that the order of release for F2 and F7 was zero-order and F11 was first-order. The mechanism was further confirmed by Korsmeyer–Peppas equation. For formulations F2 and F7, the n values were 0.421 and 0.441, indicating Fickian diffusion; whereas, for formulation F11, the n value was 0.655, indicating non-Fickian diffusion. It was concluded that the drug release from the tablet matrix followed the diffusion controlled mechanism in all the formulations.

Swelling studies of buccal tablets
The swelling index values of all the tablets increased with increasing amounts of polymer concentration. Swelling index was calculated with respect to time. The swelling indices of the tablets increased with increasing amounts of HPMC K4M, SCMC, and Carbopol 934P. Appropriate swelling property of a buccal device is essential for uniform and prolonged release of drug and proper mucoadhesion. An increase in the polymer concentration causes an increase in the viscosity of the gel as well as the formation of a gel layer with a longer diffusional path length. This causes a decrease in the effective diffusion coefficient of the drug and that could substantially reduce the penetration of the dissolution medium into the tablet matrix and therefore a reduction in the drug release rate. The maximum swelling index was observed with the formulations F5, F10, and F15. Swelling index profiles of all the formulations at different time points up to 4 h were represented in Figs. 13-15.

Ex vivo mucoadhesion strength, ex vivo mucoadhesive time and surface pH values of optimized formulations
The surface pH of the buccal tablets was determined 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. Surface pH of the optimized formulations was found to be 6.76±0.28–6.89±0.34. The pH was found to be near to the neutral, from the results it was found that, the formulations do not cause any irritation to the buccal mucosa. The ex vivo mucoadhesion strength and time of the tablets was determined for optimized formulations using goat buccal mucosa. Surface pH values, mucoadhesive strength and mucoadhesive time values for the optimized formulations were shown in Table 6.

Ex vivo permeation of olmesartan through goat buccal membrane from optimized buccal tablets
Based on the in vitro drug release of all formulations, the F2, F7, and F11 formulations were selected for ex vivo drug permeation studies.
Mucoadhesive strength (gram force)

| Formulation Code | Mucoadhesive strength | Mucoadhesive time (h) | Surface pH |
|------------------|-----------------------|-----------------------|------------|
| F2               | 13.2±0.12             | 6.73±0.13             | 6.76±0.37  |
| F7               | 26.45±0.08            | 6.32±0.21             | 6.82±0.28  |
| F11              | 32.19±0.05            | 6.43±0.3              | 6.89±0.34  |

**Table 6: Ex vivo mucoadhesive strength, ex vivo mucoadhesive time, and surface pH values of optimized formulations**

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The mucoadhesive buccal tablets of olmesartan were prepared by direct compression method using mucoadhesive polymers HPMC K4M, SCMC, and Carbopol 934P. FTIR studies concluded that there was no interaction between drug and excipients. The physicochemical properties of all the formulations were shown to be within the limits. Among all the formulations, the formulations F2, F7, and F11 were selected as optimized formulations because they showed satisfactory drug release rates with the Higuchi diffusion controlled release pattern. The optimized buccal tablets possess reasonable mucoadhesive strength, mucoadhesive time, and satisfactory surface pH. Ex vivo permeation studies for optimized tablets were conducted and shown satisfactory drug permeation. This could demonstrate that the optimized formulations could meet the target flux and optimized formulations also showed satisfactory stability in natural human saliva. Ex vivo permeation studies for optimized tablets were conducted and shown satisfactory drug permeation. Good in vitro ex vivo correlation for an optimized buccal tablet of olmesartan demonstrates the validity of the release tests conducted. It was concluded that the development of buccal delivery of olmesartan tablets was one of the potential alternative routes of administration to avoid hepatic first-pass effect and to improve the bioavailability of olmesartan through buccal mucosa and enhance the release of drug for extended period of time, by which these formulations reduce the need for frequent administration and enhance the patient compliance. Hence, this study concludes that the olmesartan could be delivered through the buccal route. Further, work is recommended to support its efficacy claims by pharmacokinetic and pharmacodynamic studies in a human being.

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**CONFLICTS OF INTEREST**

There are no conflicts of interest.

**AUTHOR’S CONTRIBUTION**

All authors contributed to the design and implementation of the research, to the analysis of the results and to the writing of the final manuscript. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

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