Journal of Applied Pharmaceutical Research
Volume 13 Issue 4, Year of Publication 2025, Page 266 – 278
DOI: https://doi.org/10.69857/joapr.v13i4.1298

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Research Article

JOURNAL OF APPLIED PHARMACEUTICAL RESEARCH | JOAPR
www.japtronline.com ***ISSN: 2348 – 0335***

CHITOSAN-BASED MUCOADHESIVE PATCHES FOR BUCCAL DELIVERY OF OLMESARTAN IN HYPERTENSION TREATMENT

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Article Information
Received: 2nd May 2025
Revised: 6th July 2025
Accepted: 26th July 2025
Published: 31st August 2025

Keywords
Hypertension, Buccal patches, Olmesartan-Chitosan, hypertension, mucoadhesive

ABSTRACT

Background: Delivering poorly soluble drugs like Olmesartan (OMS) effectively remains a key challenge due to low oral bioavailability and extensive first-pass metabolism. To address this, buccal patches incorporating chitosan were developed as an alternative route to enhance systemic absorption. **Methodology:** A series of buccal patch formulations (F1–F17) was prepared using combinations of chitosan, polyvinyl alcohol (PVA), HPMC K4M, and Eudragit RL via solvent casting. These patches were evaluated for uniformity in weight, thickness, pH, mechanical strength, folding endurance, and mucoadhesion. Structural and morphological assessments were carried out using X-ray diffraction and SEM. *Ex vivo* and *in vivo* studies explored drug release, permeation, pharmacokinetics, and mucosal safety. An HPLC method was employed for accurate quantification, and stability was assessed under both accelerated and ambient conditions. **Results and Discussion:** The optimised patch (F2) demonstrated consistent physical properties, high flexibility, and strong mucoadhesion. XRD patterns confirmed the amorphous dispersion of OMS in the polymer matrix, aiding solubility. Drug release was sustained over 12 hours, and permeation studies showed controlled transport across the buccal membrane. In vivo results revealed a substantial improvement in drug bioavailability via buccal delivery (83.2%) compared to oral administration (30.2%). Histological analysis indicated no signs of tissue irritation. Patches maintained integrity and potency throughout six months of storage. **Conclusion:** The findings support the buccal patch as a viable, non-invasive platform for enhancing OMS delivery, offering improved therapeutic efficiency and patient compliance.

INTRODUCTION

Hypertension, commonly referred to as high blood pressure, is a widespread chronic condition that affects over a billion individuals globally and stands as a primary contributor to early mortality and long-term disability [1,2]. Despite available treatments, issues such as poor adherence, inconsistent absorption, and low bioavailability limit their effectiveness [3,4]. This study addresses the lack of optimized buccal delivery systems for Olmesartan by developing chitosan-based mucoadhesive patches to enhance its bioavailability and therapeutic efficacy in hypertension treatment. This drives the

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need for improved drug delivery methods that improve efficacy, reduce dosing frequency, and lower side effects [5]. Olmesartan (OMS), an angiotensin II receptor blocker for hypertension, has low water solubility and undergoes significant first-pass metabolism, resulting in limited and variable oral bioavailability (~26%) [5–7]. These pharmacokinetic limitations necessitate higher doses and long-term treatment to sustain adequate drug levels, prompting the need for alternative delivery routes that bypass hepatic metabolism [8–10]. Delivering drugs via the buccal route offers a promising alternative to conventional oral administration.[11] The buccal mucosa enables direct drug absorption into systemic circulation, bypassing the GI tract and liver, allowing rapid uptake and improved compliance, especially in elderly and pediatric patients. Effective buccal delivery requires strong mucoadhesion, mechanical strength, flexibility, and controlled release [12–14].

Chitosan, a cationic biopolymer, is widely used in mucoadhesive systems for its biocompatibility, biodegradability, and ability to enhance mucosal drug transport [15][16]. Eudragit RL, a water-insoluble yet permeable polymer, aids in controlled release and structural stability. Hydrophilic polymers like PVA support patch formation, while glycerine acts as a plasticiser to improve flexibility [17,18].

This study aimed to develop chitosan-based OMS buccal patches using solvent casting. A Box–Behnken Design was employed to optimise 17 formulations by varying Eudragit RL, chitosan, and PVA levels, assessing their effects on swelling, adhesion, and drug release to identify the optimal patch [19,20]. In vitro release studies and *ex vivo* permeation experiments using Franz diffusion cells and excised sheep buccal mucosa were performed to analyse the drug's release profile and its permeability through the mucosa [21,22]. The release data were fitted to kinetic models such as zero-order, Higuchi, and Korsmeyer–Peppas to determine the mechanism of drug diffusion. Long-term stability testing was conducted under standard ICH guidelines to examine the patches' shelf life [23,24]. In vivo pharmacokinetic studies in Wistar rats compared systemic exposure of OMS via buccal and oral routes. Histological analysis confirmed that the buccal patches were safe and non-toxic [25]. The objective of this study was to develop and optimize mucoadhesive buccal patches of Olmesartan using chitosan-based polymer blends, aiming to enhance drug bioavailability and provide sustained antihypertensive effects.

MATERIALS AND METHODS

Materials

Olmesartan was obtained from Yarrow Chem. Products (Mumbai, India). PVA and glycerine were sourced from Loba Chemie Pvt. Ltd. HPLC-grade acetonitrile, ammonium acetate, methanol, and ammonium dihydrogen orthophosphate were purchased from Research-Lab Fine Chem (Mumbai). Oleic acid was procured from Burgoyne Urbidges & Co. All other reagents were of analytical grade.

Methods

Formulation of OMS-CH buccal patches

Buccal patches were prepared using the solvent casting technique. OMS (APIs) were triturated with 2–3 drops of Tween 80. Chitosan was dissolved in 1% v/v acetic acid solution under continuous magnetic stirring at room temperature until a clear, homogenous solution was obtained. The solution was filtered to remove any undissolved particles before further use in formulation studies, and the other polymers (HPMC K4M and Eudragit RL) were dissolved in ethanol and stirred at 500 rpm for 4 hours. Separately, polyvinyl alcohol was dissolved in ethanol at 900 rpm for 4 hours. Glycerine was added as a plasticiser, and the mixture was stirred for 10–15 minutes, then sonicated for 1 hour to remove air bubbles. The resulting solution was cast into 7.5 cm Petri plates and dried in a hot air oven at 40 °C for 12 hours. Patches were then cut into 2 cm discs (3.14 cm^2), each containing 10 mg of OMS [16,26].

Optimisation of patches by Box-Behnken design

A Box–Behnken design (BBD) was employed to optimise buccal patch formulations by evaluating the effects of three independent variables: Eudragit RL, chitosan (CH), & polyvinyl alcohol (PVA) concentrations, each at three levels (coded as -1, 0, +1). Actual levels ranged from 0.5% to 1%. The dependent responses were swelling index (Y1), drug release (%) (Y2), and mucoadhesive strength (Y3). BBD, chosen for its efficiency with three or more factors and multiple responses, was conducted using Design Expert (v13), yielding 17 experimental runs & supporting a quadratic model with polynomial equations & 3D response surface plots [19,20]. The quadratic model equation is:

$$Y = b_0 + b_1A + b_2B + b_3C + b_{12}AB + b_{13}AC + b_{23}BC + b_{11}A^2 + b_{22}B^2 + b_{33}C^2$$

Where Y is the predicted response, b_0 is the intercept, b_1 to b_{33} are regression coefficients, and A, B, and C are independent variables.

CHARACTERIZATIONS OF FORMULATION

X-ray diffraction

The X-ray crystal patterns of OMS were achieved utilising a bulk X-ray diffractometer (Diffrac. EVA. V2.1), and CuKα was employed as the radiation source. Around 45 kV (40 mA) current was utilised for scanning, which was conducted at 2° to 90° (2θ), and the scanning rate was 2° per minute at ambient temperature [27].

Weight and thickness of patches

Three patches were randomly selected from each formulation, each with a diameter of 2 cm, and weighed separately using an analytical balance. The average weight was estimated along with the standard deviation. The thickness of the patches was evaluated utilising a vernier calliper (Mitutoyo, Japan) with a minor count of 0.01 mm [28].

Surface pH measurement

Surface pH was assessed to ensure buccal compatibility. Three patches were placed in Petri dishes with 0.5 mL deionised water for 1 hour to allow swelling. A pH meter electrode was then placed on each swelled patch to record the surface pH, confirming non-irritant properties [29].

Drug Content Uniformity

Drug content uniformity was assessed using a validated RP-HPLC method. Circular patches (20 mm) from three areas were dissolved in pH 6.8 PBS, and 2 mL of the solution was diluted to 10 mL. Absorbance was measured at 230 nm using a UV/Vis spectrophotometer, and drug content (%) was calculated using a standard curve. This was repeated for three patches per formulation [19,20].

Folding endurance

The folding strength of the developed patches was demonstrated manually by constantly folding the patch until it broke/ruptured. The number of foldings needed to break the patch was noted as the folding endurance. The investigations were conducted in triplicate, and average values were reported [30].

Tensile strength

Tensile strength was measured using a Universal Testing Machine (LS5, Lloyd Instruments, UK) with a 500 N load cell under standard lab conditions. A randomly selected 400 mm² film sample was tested following ASTM D-882. The upper clamp pulled the film at 50 mm/min while the lower clamp remained fixed, and the force at break was recorded. Data were processed using Nexygen Plus3 software. Tests were performed in triplicate, and average values were reported [31,32]. The following formula was used to get the tensile strength at break value:

$$\textbf{\textit{Tensile strength}} = \frac{\textbf{\textit{Force to break}}\ (\boldsymbol{N})}{\textbf{\textit{Initial cross}} - \textbf{\textit{section area}}(\boldsymbol{mm^2})}$$

Scanning electron microscopy (SEM)

The optimised patch internal morphology was examined by utilising SEM (JEOL JMS-7400, Japan). On the SEM sample stub, TSpherical samples (5 mm^2) were mounted. Samples underwent gold sputter coating, and a 15 kV emission current was employed for imaging. At room temperature, the gold-coated samples were analysed utilising a scanning electron microscope, and appropriate magnification photomicrographs were captured [33].

Swelling studies

The swelling index of patches was assessed by immersing the patches in PBS pH 6.8 at 37 ± 0.5 ºC. For every batch, three patches were cut and weighed; W1 is the average beginning weight. After being immersed in PBS, the patches were removed at intervals of 5, 10, 15, 20, 25, 30, and 720 minutes, or until their weight increased as much as possible. Any remaining water on the surface was carefully absorbed with filter paper, and swollen patches were weighed again [33,34]. The following formula was used to get the swelling index and average weight W2.

$$\%\ \textbf{\textit{Swelling Index}} = \frac{\boldsymbol{W2 - W1}}{\boldsymbol{W1}} \times \boldsymbol{100}$$

Ex vivo mucoadhesive time/ strength

Mucoadhesive strength was measured using a modified two-arm balance at room temperature. Fresh sheep buccal mucosa (≈2 mm thick) was collected from a local slaughterhouse within 2 h of slaughter, cleaned with PBS (pH 6.8–7.4) to remove debris and connective tissue, fixed to a beaker base with cyanoacrylate glue, and stored in PBS at 4 °C for use within 24 h. A patch was attached to one pan, balanced with a 5 g counterweight, and allowed to contact the mucosa for 5 minutes. Water was added dropwise (100 drops/min) to the opposite pan until detachment occurred. The required weight was recorded as mucoadhesive strength. Tests were done in triplicate, and mean values were reported [21,35].

HPLC Method for estimation of OMS release/ permeation/ pharmacokinetic studies

HPLC was performed using a Shimadzu SCL-10AVP system with a UV detector, injector (20 µL), and Zodiac C8 column (150 × 4.6 mm, 5 µm). A gradient mobile phase of 15 mM ammonium acetate (A) and acetonitrile–methanol (90:10, B) was used, increasing B from 25% to 80% over 15 min at 1.0 mL/min. Detection was at 230 nm, with the column at 28 °C. Olmesartan stock (1 mg/mL) was prepared in acetonitrile–methanol–water (4:4:2), sonicated, filtered, and used to create calibration standards (3.12–1000 ppm) for linearity, LOD, and LOQ. All reagents were HPLC grade; standard lab equipment was used as per protocol [36].

***Ex vivo* drug release study**

Drug release from the optimised formulations was evaluated using a Franz diffusion cell over 12 hours at 37 ± 0.5 °C. Fresh sheep buccal mucosa (≈2 mm thick) was collected from a local slaughterhouse within 2 h of slaughter, cleaned with PBS (pH 6.8–7.4) to remove debris and connective tissue, fixed to a beaker base with cyanoacrylate glue, and stored in PBS at 4 °C for use within 24 h. The donor chamber received evenly placed patches, and the receiver PBS was stirred continuously.

At set intervals, 0.1 mL samples were withdrawn and replaced with fresh PBS. Drug content was analysed using a validated RP-HPLC method. Release data were fitted to various kinetic models, including Korsmeyer-Peppas, Higuchi, First-order, Hixson-Crowell, and Zero-order, to determine the release mechanism [37]. The model that best suited the data was chosen after the models were evaluated for each formulation [32].

***Ex* vivo permeation of OMS and OMS-CH**

Ex vivo buccal permeation was evaluated using a vertical Franz diffusion cell with sheep buccal mucosa (0.2 cm thick, 3.14 cm²), equilibrated in PBS (pH 6.8) at 37 ± 1 °C. After 15 minutes, the patch was applied, and permeation was assessed under constant stirring (50 rpm).

At set intervals, 0.1 mL samples were withdrawn, replaced with fresh PBS, diluted with acetonitrile, centrifuged (5000 rpm, 10 min), and analysed via validated HPLC. Permeation coefficient (P) and steady-state flux (Jss) were calculated using:

$$P = \frac{slope}{S} \times VD \qquad Jss = P \times VD$$

Where S is the membrane area, VD is the donor volume, and CD is the drug concentration [32,38].

***In Vivo* Pharmacokinetic Investigation (OMS)**

The study was approved by the CPCSEA (Protocol No. 1697/PO/Re/S/13/CPCSEA/2020/06) and conducted under the guidelines of the Institutional Animal Ethics Committee, HSBPVT's College of Pharmacy, Kashti. Female Wistar rats (160–200 g, 21 days old) were acclimated to standard lab conditions (25 ± 2 °C, 55 ± 5% RH). Animals were divided into four groups (n = 6 each) for evaluating OMS buccal patch formulations, with retro-orbital sampling performed during the experimental period. Animals were anaesthetised with diethyl ether, and buccal patches were applied using light fingertip pressure. OMS was administered via micropipette. Blood samples (20 µL) were collected at 0, 0.25, 0.5, 1, 2, 4, 8, 12, and 24 hours via the retro-orbital plexus. After the final collection, animals were sacrificed. Samples were centrifuged, and serum was analysed for drug levels [39,40].

***In vivo* buccal Histopathological Screening**

In vivo buccal tissue toxicity was evaluated using female Wistar rats housed under standard laboratory conditions (25 ± 2 °C, 50–60% humidity, 12 h light/dark cycle) with free access to food and water. Animals were acclimatized for 7 days before experiments. Patches were applied to the buccal mucosa for 24 hours, and after 12 hours of exposure, the animals were sacrificed for histopathological analysis. The study aimed to detect any mucosal changes caused by the treatment. Treated mucosa served as the test group, CH-treated mucosa as the positive control, and untreated mucosa as the negative control. Tissue samples were fixed in 10% formalin, embedded in paraffin & stained with hematoxylin & eosin. A pathologist examined the sections microscopically for structural alterations [41].

Stability studies

For six months, the optimised patch formulations were kept in a stability chamber (BioTechniques, India) at various temperatures and relative humidity levels according to ICH requirements (Q1aR2). Lastly, during 6-month intervals, samples were inspected for significant physicochemical properties such as microscopic appearance, swelling index, mucoadhesive strength, surface pH, and drug content.

RESULTS AND DISCUSSION

Formulation and optimisation of OMS buccal patches by Box-Behnken design

The formulations were developed by varying three key factors: Chitosan (CH%) as a mucoadhesive polymer (Factor 1), Eudragit RL (mg) as a controlled-release polymer (Factor 2), and Polyvinyl Alcohol (PVA%) as a film-forming agent (Factor 3). The composition had moderate viscosity in the range of 45-50 pascals before casting. Each formulation was tailored to assess how these components influence the overall performance of the drug delivery system. Chitosan concentrations ranged from 0.1% to 0.2%, Eudragit RL from 10 to 50 mg, and PVA from 1% to 5%.

The design aimed to evaluate the interplay between these polymers in affecting the swelling behaviour, mucoadhesion, and drug release profile. The statistical validation of the Box–Behnken Design models was performed using ANOVA. For the swelling Index, the model showed a high F-value of 9.52, with a significant $p < 0.001$ and a strong correlation ($R^2 = 0.9745$). The drug Release model was also significant, with an F-value of 7.32, $p = 0.0012$, and $R^2 = 0.9060$.

Similarly, the Mucoadhesive Strength model demonstrated good predictability, with an F-value of 6.67, $p = 0.0102$ & $R^2 = 0.9156$. These results confirm that the quadratic models developed are statistically valid and reliable for optimization. (Tables 1& 2)

CHARACTERIZATION OF BUCCAL PATCHES

X-ray diffraction

Figure 1 shows the XRD patterns of pure OMS and the OMS-CH patch (F2). Pure OMS displays sharp peaks between 20°–35° (2θ), indicating crystallinity. In contrast, the OMS-CH film shows a broad, diffused pattern, suggesting an amorphous structure. This shift implies successful dispersion of OMS within the chitosan matrix, potentially enhancing its dissolution and bioavailability in buccal delivery.

Weight and thickness of patches

Weight uniformity across formulations F1–F17 ranged from 5.15 to 5.18 mg with minimal variation, indicating precise casting and uniform component distribution. This consistency ensures dose accuracy, manufacturing reproducibility, and supports clinical and regulatory reliability.

Surface pH

All OMS-CH patches showed surface pH values between 6.8 and 7.7, aligning with the oral cavity's natural range. This ensures mucosal compatibility, minimises irritation, and supports safe, prolonged buccal application.

Table 1: Variables and observed responses in Box-Behnken design for OMS-CH buccal Patches.

Formulation	Factor 1 CH%	Factor 2 Eudragit RLmg	Factor 3 PVA%	Swelling index %	Mucoadhesive strength N/cm^2	Drug release %
F1	0.15	50	5	308.25 ± 5	0.284 ± 0.00088	83.2 ±0.20
F2	0.15	30	3	298 ± 4	0.274 ± 0.00088	90.2 ±0.35
F3	0.2	10	3	316.04 ± 4	0.343 ± 0.000098	79.8 ±0.20
F4	0.15	30	3	285.45 ± 3	0.284 ± 0.00088	89.3 ±0.35
F5	0.15	30	3	281.45 ± 5	0.274 ± 0.00088	88.4 ±0.30
F6	0.15	30	3	284.45 ± 4	0.294 ± 0.00059	87.5 ±0.35
F7	0.2	30	1	288.23 ± 4	0.314 ± 0.00088	85.6 ±0.20
F8	0.1	50	3	234.06 ± 3	0.245 ± 0.00088	91.6 ±0.25
F9	0.1	30	5	232.06 ± 4	0.255 ± 0.00078	94.5 ±0.40
F10	0.15	10	5	295.03 ± 5	0.284 ± 0.00098	91.1 ±0.30
F11	0.15	10	1	287.38 ± 3	0.265 ± 0.00088	91.8 ±0.20
F12	0.2	50	3	314.2 ± 3	0.343 ± 0.00078	78.4 ±0.35
F13	0.1	30	1	255.19 ± 5	0.265 ± 0.00088	90.2 ±0.20
F14	0.1	10	3	253.01 ± 3	0.186 ± 0.00078	96.2 ±0.20
F15	0.2	30	5	396.02 ± 5	0.334 ± 0.00049	82.6 ±0.40
F16	0.15	30	3	289.09 ± 3	0.274 ± 0.00059	90.1 ±0.35
F17	0.15	50	1	310.02 ± 3	0.294 ± 0.00069	86.7 ±0.20

Table 2: Components used in the formulation of OMS-CH buccal patches

Ingredient	Olmesartan (mg)	Tween 80(ml)	Chitosan(mg)	Eudragit RL(mg)	HPMC K4M(mg)	PVA(mg)	Glycerine(ml)	Ethanol(ml)
F1	20	0.8	0.15	50	1.25	5	0.3	20
F2	20	0.8	0.15	30	1.25	3	0.3	20
F3	20	0.8	0.2	10	1.25	3	0.3	20
F4	20	0.8	0.15	30	1.25	3	0.3	20
F5	20	0.8	0.15	30	1.25	3	0.3	20
F6	20	0.8	0.15	30	1.25	3	0.3	20
F7	20	0.8	0.2	30	1.25	1	0.3	20
F8	20	0.8	0.1	50	1.25	3	0.3	20
F9	20	0.8	0.1	30	1.25	5	0.3	20
F10	20	0.8	0.15	10	1.25	5	0.3	20
F11	20	0.8	0.15	10	1.25	1	0.3	20
F12	20	0.8	0.2	50	1.25	3	0.3	20
F13	20	0.8	0.1	30	1.25	1	0.3	20
F14	20	0.8	0.1	10	1.25	3	0.3	20
F15	20	0.8	0.2	30	1.25	5	0.3	20
F16	20	0.8	0.15	30	1.25	3	0.3	20
F17	20	0.8	0.15	50	1.25	1	0.3	20

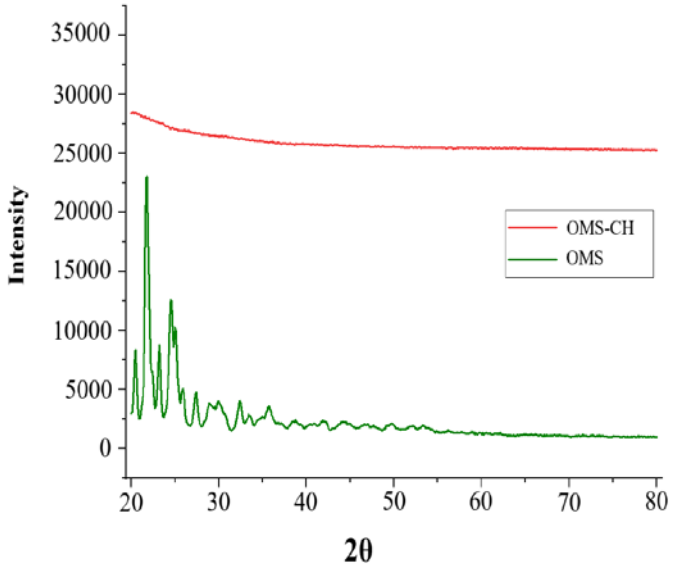

Figure 1: XRD pattern of OMS and Buccal patches of OMS-CH

Drug Content Uniformity

All patches showed uniform drug content around 20 mg with minimal variation, indicating effective drug incorporation. This consistency is crucial for reliable dosing and therapeutic efficacy in buccal delivery.

Folding Endurance

OMS-CH patches showed high folding endurance (353–434), indicating strong flexibility and mechanical stability. This ensures durability during handling and intraoral use, reflecting the strength and elasticity of the polymers used.

Tensile strength

Tensile strength of OMS-CH patches ranged from 9.06 to 18.08 N/mm², with formulations like F9, F10, F15, and F17 showing higher strength. This indicates good mechanical durability, reflecting optimal polymer selection and a balance between flexibility and integrity (Table 3).

Scanning Electron Microscopy

Figure 2 (Images A–C) shows SEM scans of OMS-CH buccal patches at varying magnifications. Image A (X6,000) reveals a porous, fibrous surface, suggesting strong polymer interaction for improved mucoadhesion. Image B (X3,000) displays a uniformly rough texture, indicating even dispersion of OMS and chitosan. Image C (X1,000) shows a smooth, stable surface with minimal irregularities. These features support effective adhesion and controlled drug release in buccal delivery.

Effect of formulation variables on swelling index

The swelling index ranged from 232.06% (F9) to 396.02% (F15) with higher values observed in formulations containing greater amounts of chitosan & PVA, such as F15 & F3 (0.2% CH), due to chitosan's hydrophilic & gel-forming properties that enhance mucosal contact & influence drug release. As shown in Figure 3, 3D response surface plots highlight that swelling increases significantly with higher chitosan (Plots A & B) while PVA also contributes moderately (Plots B & C). In contrast, Eudragit RL slightly reduces swelling, indicating its limited role in water uptake.

Table 3: Physicochemical parameters of OMS-CH buccal patches.

	Weight uniformity mg, SD, %CV	Thickness mm, SD, (% CV)	Surface pH(SD, (% CV)	DC uniformity mg, SD, %CV	FE	TS (N)	*Ex-vivo* mucoadhesion time(min)	%Transmittance At 600nm ±SD	Patch integrity	Flexibility tests
F1	5.16 ± 0.02 (0.39)	0.17 ±0.00 (0.00)	6.8 ± 0.01 (0.15)	20 ± 0.01 (0.05)	378 ± 3	11.12 ±0.06	285 ± 3	95 ±1	Intact	Flexible
F2	5.17 ± 0.06 (1.16)	0.18 ±0.00 (0.00)	6.9 ± 0.04 (0.58)	20 ± 0.02 (0.10)	358 ± 4	11.13 ±0.07	276 ± 3	94 ±1	Intact	Flexible
F3	5.18 ± 0.02 (0.39)	0.15 ±0.01 (6.67)	6.9 ± 0.01 (0.14)	20 ± 0.01 (0.05)	358 ± 3	13.06 ±0.08	284 ± 5	96 ±1	Intact	Flexible
F4	5.15 ± 0.03 (0.58)	0.18 ±0.00 (0.00)	7.2 ± 0.02 (0.28)	20 ± 0.04 (0.20)	355 ± 4	11.03 ±0.09	296 ± 5	94 ±1	Intact	Flexible
F5	5.18 ± 0.01 (0.19)	0.17 ±0.01 (5.88)	7.4 ± 0.05 (0.68)	20 ± 0.05 (0.25)	412 ± 5	13.06 ±0.10	276 ± 3	95 ±1	Intact	Flexible
F6	5.16 ± 0.02 (0.39)	0.16 ±0.01 (6.25)	7.2 ± 0.07 (0.97)	20 ± 0.04 (0.20)	410 ± 3	10.07 ±0.11	283 ± 5	95 ±1	Intact	Flexible
F7	5.16 ± 0.09 (1.74)	0.16 ±0.01 (6.25)	7.6 ± 0.08 (1.05)	20 ± 0.02 (0.10)	400 ± 4	15.08 ±0.12	295 ± 4	93 ±2	Intact	Very Flexible
F8	5.15 ± 0.01 (0.19)	0.17 ± 0.01 (5.88)	6.8 ± 0.09 (1.32)	20 ± 0.02 (.10)	358 ± 4	15.04 ±0.13	282 ± 3	96 ±1	Intact	Very Flexible
F9	5.17 ± 0.02 (0.39)	0.17 ± 0.00 (0.00)	7.3 ± 0.06 (0.82)	20 ± 0.06 (0.30)	412 ± 3	18.06 ±0.14	287 ± 3	92 ±2	Intact	Very Flexible
F10	5.16 ± 0.01 (0.19)	0.18 ± 0.01 (5.56)	6.9 ± 0.02 (0.29)	20 ± 0.02 (0.10)	434 ± 3	18.08 ±0.15	282 ± 3	92 ±2	Intact	Very Flexible
F11	5.18 ± 0.03 (0.58)	0.16 ± 0.00 (0.00)	7.3 ± 0.01 (0.14)	20 ± 0.03 (0.15)	426 ± 3	14.04 ±0.16	296 ± 4	93 ±1	Intact	Very Flexible
F12	5.18 ± 0.06 (1.16)	0.17 ± 0.01 (5.88)	7.4 ± 0.05 (0.68)	20 ± 0.02 (0.10)	427 ± 4	16.02 ±0.17	276 ± 3	92 ±2	Intact	Very Flexible
F13	5.18 ± 0.08 (1.54)	0.16 ± 0.01 (6.25)	6.9 ± 0.02 (0.29)	20 ± 0.02 (0.10)	359 ± 5	14.06 ±0.18	285 ± 3	94 ±1	Intact	Very Flexible
F14	5.16 ± 0.06 (1.16)	0.18 ± 0.01 (5.56)	7.7 ± 0.03 (0.39)	20 ± 0.01 (.05)	353 ± 3	15.03 ±0.19	289 ± 3	91 ±2	Intact	Very Flexible
F15	5.15 ± 0.06 (1.17)	0.15 ± 0.00 (0.00)	7.6 ± 0.04 (0.53)	20 ± 0.04 (0.20)	403 ± 5	18.02 ±0.18	279 ± 4	93 ±2	Intact	Flexible
F16	5.18 ± 0.08 (1.54)	0.17 ± 0.01 (5.88)	6.8 ± 0.01 (0.15)	20 ± 0.04 (0.20)	408 ± 3	09.06 ±0.18	275 ± 5	95 ±1	Intact	Very Flexible
F17	5.17 ± 0.08 (1.55)	0.18 ± 0.00 (0.00)	7.4 ± 0.02 (0.27)	20 ± 0.02 (0.10)	401 ± 5	18.03 ±0.19	289 ± 4	91 ±2	Intact	Very Flexible
All values are mean ± SD, n = 3.										

Ex Vivo Mucoadhesion Time (min)/Strength

Mucoadhesion time ranged from 275 to 296 minutes, reflecting strong adhesion for sustained drug release. Mucoadhesive strength varied from 19 g/cm² (F14) to 35 g/cm² (F3, F12), with higher chitosan content (0.2%) enhancing adhesion via electrostatic interaction with mucin. Eudragit and PVA contributed to structural support. Figure 4's 3D plots show that increasing chitosan with either Eudragit RL or PVA significantly improved adhesion, while the Eudragit RL–PVA combination had minimal effect, confirming chitosan's dominant role.

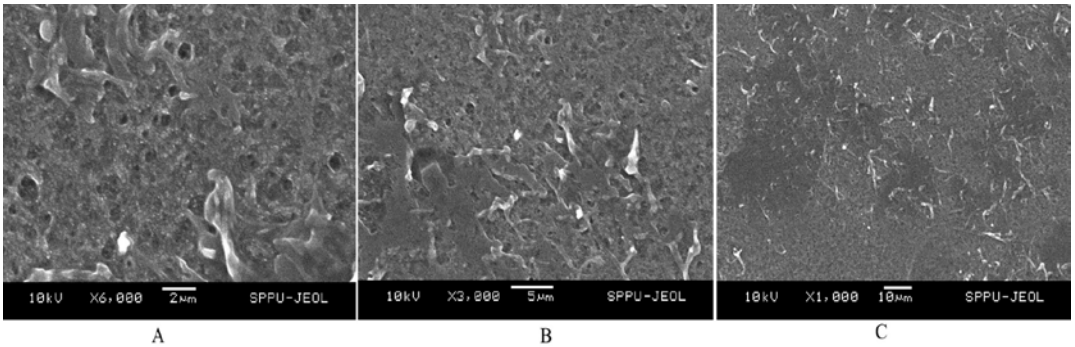

Figure 2: SEM of Buccal patches of OMS-CH

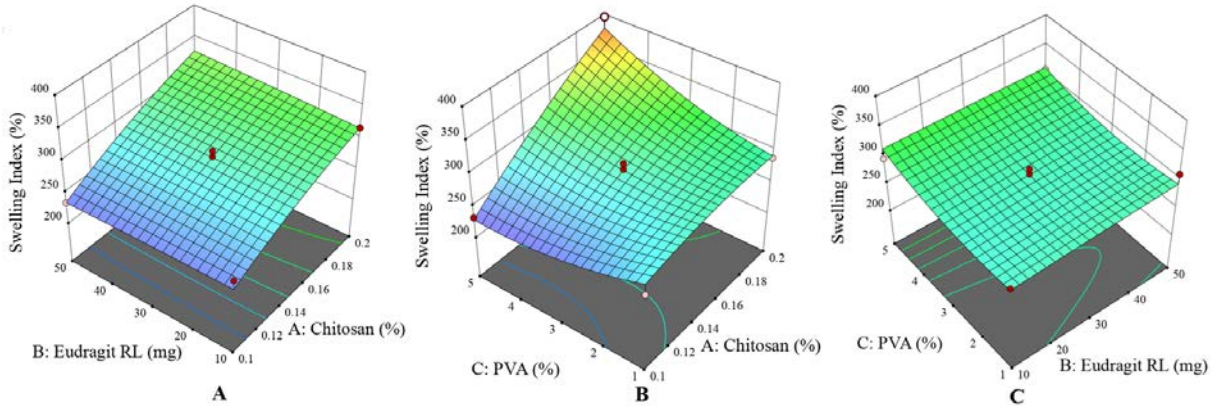

Figure 3: 3D response surface plots of swelling Index, A (Chitosan and Eudragit RL), B (Chitosan and PVA), C (PVA and Eudragit RL)

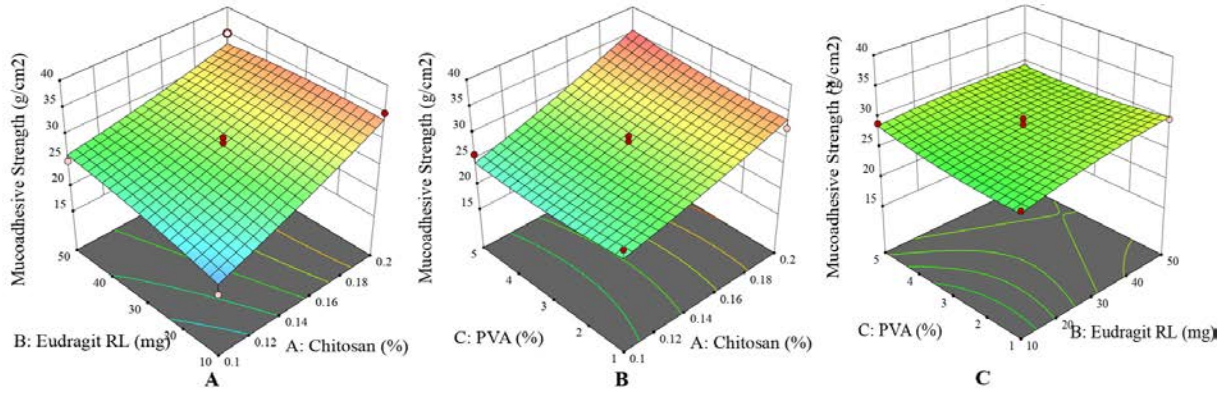

Figure 4: 3D response surface plots mucoadhesive strength of A (Chitosan and Eudragit RL), B (Chitosan and PVA), C (PVA and Eudragit RL)

HPLC method for OMS release/ permeation/ pharmacokinetic studies

The developed HPLC method for Olmesartan was precise, reliable, and suitable for routine analysis. It showed high theoretical plates (31,993), a capacity factor of 3.799, and good separation (factor 2.256). The peak was symmetrical (tailing factor 1.075) with stable retention (8.706 min). The HPLC method for Olmesartan was validated as per ICH guidelines. Specificity was confirmed with no interference at the analyte retention time (8.706 min).

Linearity was established over 3.13–100 µg/mL with a regression equation of y = 59875x – 69838 and r^2 = 0.9996. Accuracy was verified through recovery studies (80%, 100%, 120%) with mean recoveries within 98–102%. Precision showed %RSD of 1.45 (repeatability), 0.31–1.34 (intraday), and 0.30–0.71 (interday), all <2%. Sensitivity was confirmed with LOD = 2.90 µg/mL and LOQ = 3.05 µg/mL. These results demonstrate that the method is specific, linear, accurate, precise, and sensitive for Olmesartan estimation.

***Ex vivo* drug release study**

Drug release ranged from 78.4% (F12) to 96.2% (F14), influenced by polymer composition. Higher chitosan and Eudragit slowed release via a controlled matrix, while lower CH and higher PVA (e.g., F14, F9) promoted faster release through matrix erosion. Figure 5 shows F2's profile, with an initial burst and sustained release (~90–100% in 12 h), indicating its suitability for prolonged buccal delivery.

The Higuchi model fit shows a high correlation with an R^2 value of 0.9248, Zero order model fit shows a high correlation with an R^2 value of 0.7213, first order model fit shows a high correlation with an R^2 value of 0.8554 and hixson model fit shows a high correlation with an R^2 value of 0.8138 indicating a strong agreement between the experimental data and the Higuchi release kinetics. Comparative R^2 values have now been included in the revised manuscript. The Higuchi model showed the highest correlation (R^2 = 0.9248) compared to Zero-order (R^2 = 0.7213), First-order (R^2 = 0.8554), and Hixson–Crowell (R^2 = 0.8138), confirming that the release follows Higuchi kinetics.

Ex vivo permeation of OMS and OMS-CH

The transdermal permeation of OMS from OMS-Solution and OMS-CH Patch was evaluated over 24 hours. As shown in Figure 6 and Table 4, OMS-Solution exhibited faster permeation, with a higher apparent permeability (1.5×10^{-4} cm/h) and steady-state flux (1.5×10^{-3} µg/cm²/h) compared to the patch (9.3×10^{-5} cm/h and 9.3×10^{-4} µg/cm²/h, respectively). However, both delivered a similar cumulative amount of OMS after 24 hours (9852.3 ± 510 µg for the solution vs. 9835.1 ± 42 µg for the patch). These findings indicate that the solution offers rapid delivery, while the patch ensures more controlled, consistent release. Appropriate statistical comparisons were conducted to validate the significance of pharmacokinetic parameters (Cmax, AUC, t½) between treatment groups. One-way ANOVA was employed to assess overall differences among groups.

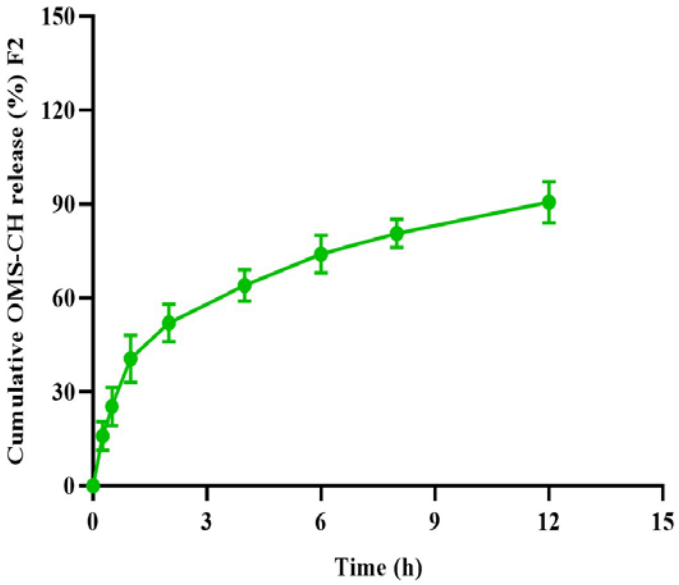

Figure 5:Cumulative drug release of F2 formulation for 12 h

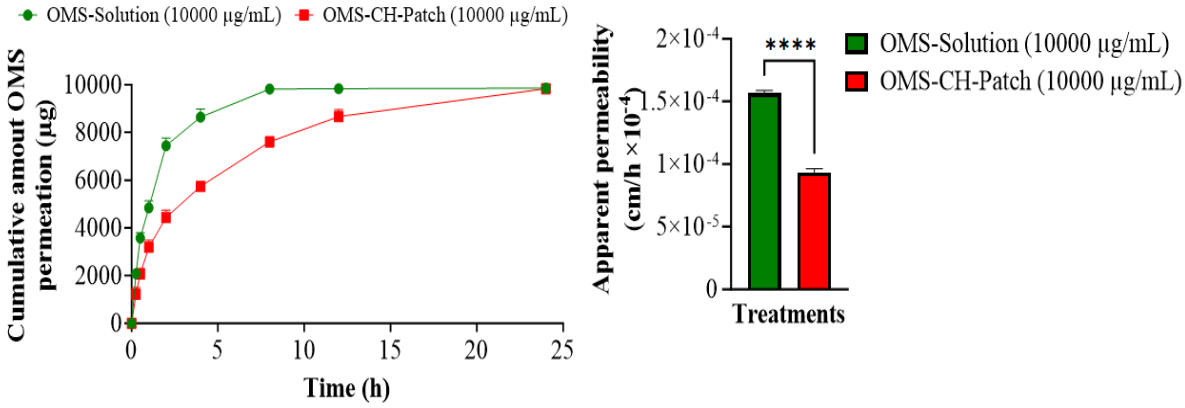

Figure 6: *Ex vivo* permeation of OMS and OMS-CH

Table 4: *Ex vivo* permeation of OMS and OMS-CH

Formulation	P_{app} (cm/h × 10^{-x})	Flux J_{ss}(µg /cm^2h	Cumulative OMS permeated at 24 h(µg)
OMS-Solution (10000 ug/mL)	1.5 ×10^{-4}	1.5 ×10^{-3}	9852.3 ± 510
OMS-CH-Patch (10000 ug/mL)	9.3 ×10^{-5}	9.3 ×10^{-4}	9835.1 ± 142

OMS-Solution: Olmesartan solution; OMS-CH-Patch: Olmesartan Chitosan buccal patch; P_{app}: Apparent permeability; J_{ss}: Steady state flux.

In vivo Pharmacokinetic parameters(Figure 7, Table 5)

A comparative pharmacokinetic study showed that IV OMS had the highest Cmax (165.9 µg/mL), shortest half-life (2.5 h) & 100% bioavailability. Oral delivery had lower Cmax (75.0 µg/mL), delayed Tmax (4 h), longer half-life (5.2 h) & poor bioavailability (30.2%). The buccal patch offered high Cmax (146.7 µg/mL), extended half-life (6.8 h) & significantly improved bioavailability (83.2%), indicating it as a non-invasive & more effective alternative to oral dosing. Four groups of 6 animals each were studied. The normal control received no treatment. The positive control was administered intravenously as OMS (2mg/kg). Two test groups received OMS at 4 mg/kg—one as an oral suspension, the other via a buccal patch (OMS-CH). Relative bioavailability of the buccal patch compared to IV (dose-normalized) = 163.6%.

In vivo Buccal Histopathological Screening

Figure 8 shows H&E-stained histological images of buccal mucosa. Section A (control) displays normal epithelial and connective tissue without signs of damage. Section B (treated with OMS-CH (F2) for 24 hours) shows similar structural integrity with no pathological changes, indicating the

formulation is safe and well-tolerated for buccal use. The section shows typical upper epithelial skin layers (indicated by the black arrow) along with deeper submucosal tissue containing muscle fibers (highlighted with the red arrow). There are no signs of inflammation or any abnormal changes in cellular structure observed in this sample. (Figure 8). Quantitative histological assessment revealed that the mean epithelial thickness in treated mucosa (99.8 ± 7.9 µm) was comparable to that of the control group (102.4 ± 8.6 µm), with no significant difference ($p > 0.05$). Similarly, inflammatory cell counts were low in both groups (4.2 ± 1.1 vs. 4.5 ± 1.3 cells/HPF; $p > 0.05$). Irritation scoring showed a value of 0 in all samples, confirming the absence of mucosal toxicity.

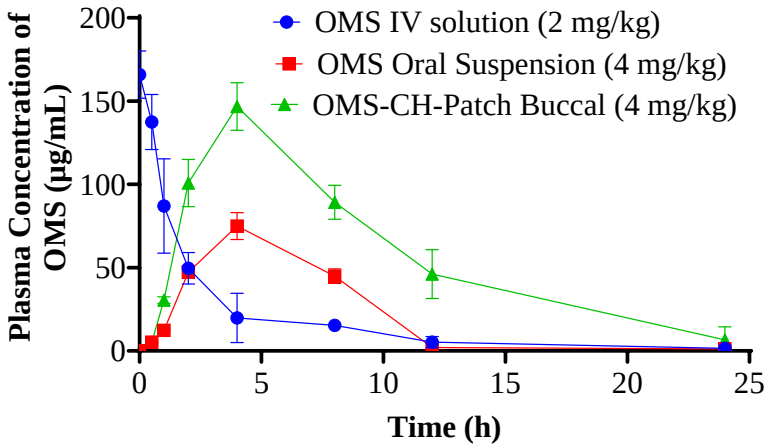

Figure 7: Pharmacokinetic parameter of OMS IV solution, OMS Oral Suspension and OMS-CH Patch.

Table 5: Pharmacokinetic parameter of OMS IV solution, OMS Oral Suspension and OMS-CH Patch.

Route of adm.	Dose mg/kg	C_{max} (µg/mL)	T_{max}(h)	$t_{1/2}$(h)	$AUC_{0-\infty}$(h.µg/mL)	AB(%)
OMS solution (IV)	2	165.9 ±11.6	0	2.5 ±0.9	422.8 ± 14.7	100
OMS suspension (Oral)	4	75.0 ±6.6	4	5.2 ±0.1	510.4 ± 22.9	30.2 ±1.4
OMS-CH-Patch BuccalF2	4	146.7 ±11.7	4	6.8 ±0.2	1383.4 ± 195.1	83.2 ±12.3

AB= absolute bioavailability

Stability studies

Table 6 summarises the six-month accelerated stability study of the OMS-CH patch (F2) stored at 40 °C ± 2 °C/75% ± 5% RH and room temp. The films retained their physical appearance, thickness (0.191 ± 0.02 to 0.198 ± 0.05 mm), FE (>200 folds), and surface pH (~6.8), showing no significant changes. Drug content remained stable (98 ± 0.15% to 98 ± 0.30%). Minor variations in swelling index and mucoadhesive strength were within acceptable limits. These results confirm the physical and chemical stability of the formulation under both conditions.

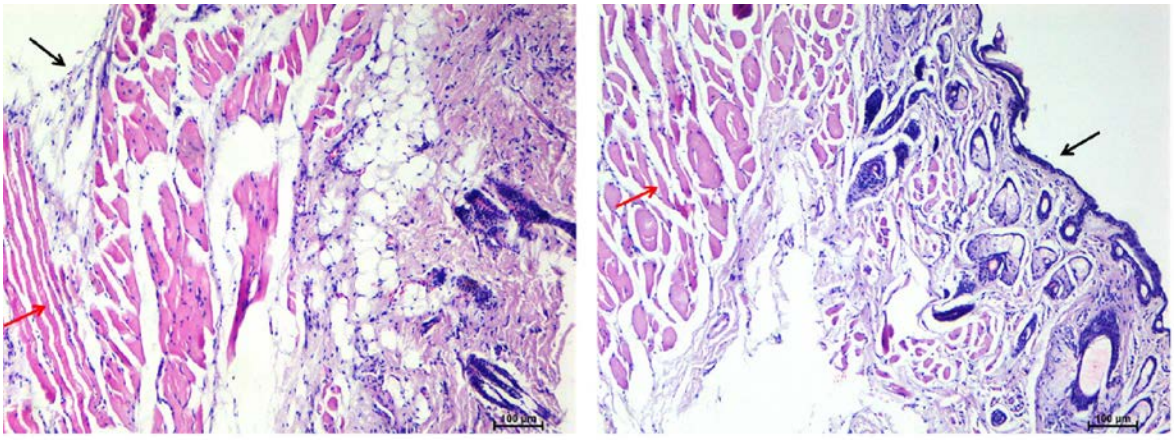

Figure 8: Histopathological sections of buccal mucosa (A) control (untreated) mucosa, (B) section treated with OMS-CH patch for 24 h

Table 6: Accelerated stability study of OMS-CH for six months

Parameter	40°C+ 2 / 75+ 5% RH				Room temperature			
	Initial	Month			Initial	Month		
		2	4	6		2	4	6
Physical appearance	**No change**	**No change**	**No change**	**No change**	**No change**	**No change**	**No change**	**No change**
Thickness (mm)	0.191± 0.02	0.192± 0.04	0.198± 0.01	0.191± 0.05	0.198± 0.04	0.197± 0.08	0.195± 0.04	0.191± 0.05
Folding Endurance(times)	>310	>310	>310	>310	>310	>310	>310	>310
Surface pH	**6.8 ± 0.15**	**6.8 ± 0.02**	**6.8 ± 0.06**	**6.8 ± 0.07**	**6.8 ± 0.05**	**6.8 ± 0.02**	**6.8 ± 0.13**	**6.8 ± 0.03**
Swelling Index (%)	340 ±2	325 ±2	295 ±3	301 ±2	342 ±3	328 ±2	332 ±1	337 ±3
Mucoadhesive strength g	28 ±0.02	29 ±0.03	31 ±0.02	29 ±0.03	29 ±0.01	30 ±0.02	27 ±0.02	28 ±0.02
Drug content (%)	98± 0.15	99 ± 0.16	98± 0.12	98± 0.17	98± 0.15	99± 0.15	98± 0.30	98± 0.26

CONCLUSION

The study successfully developed and optimized buccal patches of Olmesartan (OMS) using chitosan (CH) as a primary polymer, aiming to enhance its bioavailability and ensure sustained drug release. Employing a Box–Behnken design, the research systematically evaluated the effects of CH, polyvinyl alcohol (PVA), and Eudragit RL on key formulation parameters such as swelling index, mucoadhesive strength, and drug release.

Among the 17 formulations tested, formulation F2 was identified as optimal, demonstrating excellent physicochemical and mechanical properties, including suitable thickness, folding endurance, and mucoadhesion, along with a neutral surface pH compatible with buccal tissues. The F2 patch provided sustained drug release over 12 hours and followed the Higuchi model, indicating a diffusion-controlled release mechanism. Ex vivo studies using porcine buccal mucosa showed significantly enhanced drug permeation compared to plain OMS suspension.

In vivo pharmacokinetic studies in Wistar rats revealed a marked improvement in bioavailability (83.2%) from the buccal patch versus the oral suspension (30.2%), mainly by avoiding first-pass metabolism. Stability studies confirmed the patch's shelf-life potential, and histopathological analysis validated its safety for buccal administration. Overall, the OMS–CH buccal patch offers a promising, non-invasive alternative to conventional oral dosage forms for effective and sustained management of hypertension.

ACKNOWLEDGEMENTS

The author gratefully acknowledges Savitribai Phule Pune University, Pune, India, for providing XRD and SEM instrumental support essential to this work.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Ram Nikhate developed the research idea, carried out the practical work, and handled the data collection and analysis. Dr. Sanjay Patil provided overall guidance and supervision during the research, helped shape the direction of the study, and reviewed the manuscript to ensure clarity and accuracy.

REFERENCES

[1] Zhou B, Perel P, Mensah GA, Ezzati M. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. *Nat. Rev. Cardiol.*, **18**, 785–802 (2021) https://doi.org/10.1038/s41569-021-00559-8

[2] Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat. Rev. Nephrol.*, **16**, 223–37 (2020) https://doi.org/10.1038/s41581-019-0244-2

[3] Qelliny MR, Mustafa WW, Al Fatease A, Alamri AH, Alany R, Abdelkader H. Biofunctional Excipients: Their Emerging Role in Overcoming the Inherent Poor Biopharmaceutical Characteristics of Drugs. *Pharmaceutics*, **17**, 598 (2025) https://doi.org/10.3390/pharmaceutics17050598

[4] Le NN, Frater I, Lip S, Padmanabhan S. Hypertension precision medicine: the promise and pitfalls of pharmacogenomics. *Pharmacogenomics*, 1–24 (2025) https://doi.org/10.1080/14622416.2025.2504865

[5] Rind L, Mahmood T, Siddiqui MH, Ahsan F, Shamim A, Anwar A, Yadav RK. From Hypertension to Beyond: Unraveling the Diverse Mechanisms of Olmesartan in Disease Modulation. *Drug Res. (Stuttg).*, **74**, 93–101 (2024) https://doi.org/10.1055/a-2244-3136

[6] Agata J, Ura N, Yoshida H, Shinshi Y, Sasaki H, Hyakkoku M, Taniguchi S, Shimamoto K. Olmesartan is an angiotensin II receptor blocker with an inhibitory effect on angiotensin-converting enzyme. *Hypertens. Res.*, **29**, 865–74 (2006) https://doi.org/10.1291/hypres.29.865

[7] Chaure VA, Shirkhedkar AA. An Investigative Review for PharmaceuticalAnalysis of Angiotensin receptor blockers: Olmesartan Medoxomil, *Annales Pharmaceutiques Françaises*, **83**, 33-44 (2024) https://doi.org/10.1016/j.pharma.2024.10.001

[8] Lee BS, Kang MJ, Choi WS, Choi YB, Kim HS, Lee SK, Lee J, Choi YW. Solubilized formulation of olmesartan medoxomil for enhancing oral bioavailability. *Arch. Pharm. Res.*, **32**, 1629–35 (2009) https://doi.org/10.1007/s12272-009-2117-x

[9] Tamargo J, Ruilope LM. Investigational calcium channel blockers for the treatment of hypertension. *Expert Opin. Investig. Drugs*, **25**, 1295–309 (2016) https://doi.org/10.1080/13543784.2016.1241764

[10] Godfraind T. Discovery and development of calcium channel blockers. *Front. Pharmacol.*, **8**, 286 (2017) https://doi.org/10.3389/fphar.2017.00286

[11] Mathias NR, Hussain MA. Non-invasive systemic drug delivery: developability considerations for alternate routes of administration. *J. Pharm. Sci.*, **99**, 1–20 (2010) https://doi.org/10.1002/jps.21793

[12] Junginger HE, Hoogstraate JA, Verhoef JC. Recent advances in buccal drug delivery and absorption—in vitro and in vivo studies. *J. Control. release*, **62**, 149–59 (1999) https://doi.org/10.1016/S0168-3659(99)00032-2

[13] Rossi S, Sandri G, Caramella CM. Buccal drug delivery: a challenge already won? *Drug Discov. Today Technol.*, **2**, 59–65 (2005) https://doi.org/10.1016/j.ddtec.2005.05.018

[14] Patel VF, Liu F, Brown MB. Modeling the oral cavity: in vitro and in vivo evaluations of buccal drug delivery systems. *J. Control. release*, **161**, 746–56 (2012) https://doi.org/10.1016/j.jconrel.2012.05.026

[15] Mura P, Maestrelli F, Cirri M, Mennini N. Multiple roles of chitosan in mucosal drug delivery: an updated review. *Mar. Drugs*, **20**, 335 (2022) https://doi.org/10.3390/md20050335

[16] Patel VM, Prajapati BG, Patel MM. Design and characterization of chitosan-containing mucoadhesive buccal patches of propranolol hydrochloride. *Acta Pharm.*, **57**, 61–72 (2007) https://doi.org/10.2478/v10007-007-0005-9

[17] Jadhav S, Mishra S. The spray-dried mucoadhesive microparticles of rizatriptan with chitosan and carbopol in migraine. *Egypt. Pharm. J.*, **21**, 293–301 (2022) https://dx.doi.org/10.4103/epj.epj_37_22

[18] Jadhav SM, Mishra SK. Spray Dried Mucoadhesive Microparticles of Donepezil with Chitosan and Carbopol in Alzheimer's Disease. *Int. J. Pharm. Investig.*, **12**, (2022) https://doi.org/10.5530/ijpi.2022.2.36

[19] Navamanisubramanian R, Nerella R, Duraipandian C, Seetharaman S. Quality by design approach for optimization of repaglinide buccal tablets using Box-Behnken Design. *Futur. J. Pharm. Sci.*, **4**, 265–72 (2018) https://doi.org/10.1016/j.fjps.2018.10.002

[20] Hashemi M, Ramezani V, Seyedabadi M, Ranjbar AM, Jafari H, Honarvar M, Fanaei H. Formulation and optimization of oral mucoadhesive patches of myrtus communis by box behnken design. *Adv. Pharm. Bull.*, **7**, 441 (2017) https://doi.org/10.15171/apb.2017.053

[21] Baus RA, Haug MF, Leichner C, Jelkmann M, Bernkop-Schnürch A. In vitro–in vivo correlation of mucoadhesion studies on buccal mucosa. *Mol. Pharm.*, **16**, 2719–27 (2019) https://doi.org/10.1021/acs.molpharmaceut.9b00254

[22] Kumar M, Sharma A, Mahmood S, Thakur A, Mirza MA, Bhatia A. Franz diffusion cell and its implication in skin permeation studies. *J. Dispers. Sci. Technol.*, **45**, 943–56 (2024) https://doi.org/10.1080/01932691.2023.2188923

[23] Paarakh MP, Jose PA, Setty CM, Peterchristoper G V. Release kinetics–concepts and applications. *Int. J. Pharm. Res. Technol.*, **8**, 12–20 (2018) https://doi.org/10.31838/ijprt/08.01.02

[24] Askarizadeh M, Esfandiari N, Honarvar B, Sajadian SA, Azdarpour A. Kinetic modeling to explain the release of medicine from drug delivery systems. *ChemBioEng Rev.*, **10**, 1006–49 (2023) https://doi.org/10.1002/cben.202300027

[25] Devadhe AS, Dighe SB, Yadav SS, Bhawar SB, Ghogare RD. Antioxidant and hepatoprotective activity of Nigella sativa alcoholic extract in a CCl4-induced rat. *J. Appl. Pharm. Res.*, **13**, 115–26 (2025) https://doi.org/10.69857/joapr.v13i2.985.

[26] Pawar O, Godge R, Shinde G, Barde K, Vikhe A. Design, Development, and Optimization of Mucoadhesive Buccal Films of Ganaxolone for Enhanced Bioavailability. *J. Appl. Pharm. Res.*, **13**, 95–107 (2025) https://doi.org/10.69857/joapr.v13i2.943.

[27] Jaipakdee N, Pongjanyakul T, Limpongsa E. Preparation and characterization of poly (vinyl alcohol)-poly (vinyl pyrrolidone) mucoadhesive buccal patches for delivery of lidocaine HCL. *Int. J. Appl. Pharm*, **10**, 115–23 (2018) http://dx.doi.org/10.22159/ijap.2018v10i1.23208

[28] Aggarwal D, Gupta RD, Sharma V. Qbd Enabled Optimization Study of the Variable Concentration of Phospholipid and Stabilizer in the Development of Liposomal Pastilles of Solid Dispersion Polymeric Composite of Antihypertensive Drug. *J. Appl. Pharm. Res.*, **13**, 259–71 (2025) https://doi.org/10.69857/joapr.v13i3.995.

[29] Pranay R, Tatikayala RK, Damera S, Pathakala N, Jadi RK. Insights of Nose To Brain Delivery in Treating Parkinson'S Disease: a Systematic Review. *J. Appl. Pharm. Res.*, **12**, 57–72 (2024) https://doi.org/10.69857/joapr.v12i6.625.

[30] Coluzza I, van Oostrum PDJ, Capone B, Reimhult E, Dellago C. Design and folding of colloidal patchy polymers. *Soft Matter*, **9**, 938–44 (2013) https://doi.org/10.1039/C2SM26967H

[31] Cilurzo F, Gennari CGM, Minghetti P. Adhesive properties: a critical issue in transdermal patch development. *Expert Opin. Drug Deliv.*, **9**, 33–45 (2012) https://doi.org/10.1517/17425247.2012.637107

[32] Nair AB, Kumria R, Harsha S, Attimarad M, Al-Dhubiab BE, Alhaider IA. In vitro techniques to evaluate buccal films. *J. Control. Release*, **166**, 10–21 (2013) https://doi.org/10.1016/j.jconrel.2012.11.019

[33] Rohani Shirvan A, Hemmatinejad N, Bahrami SH, Bashari A. Fabrication of multifunctional mucoadhesive buccal patch for drug delivery applications. *J. Biomed. Mater. Res. Part A*, **109**, 2640–56 (2021) https://doi.org/10.1002/jbm.a.37257

[34] Shelke P V, Rachh PR, Mankar S, Amin S, Jain D. Optimization and evaluation of nebivolol hydrochloride loaded transferosomes using Box-Behnken experimental design. *J. Appl. Pharm. Res.*, **12**, 124–38 (2024) https://doi.org/10.69857/joapr.v12i4.590.

[35] Hassan MA, Barakat NS, El-Badry M, Shehata SM. Formulation and in vitro/in vivo evaluation of naproxen mucoadhesive buccal patches for local effect. *J. Drug Deliv. Sci. Technol.*, **21**, 423 (2011) https://doi.org/10.1016/S1773-2247(11)50068-1

[36] Sagirli O, Önal A, Toker SE, Şensoy D. Simultaneous HPLC analysis of olmesartan and hydrochlorothiazide in combined tablets and in vitro dissolution studies. *Chromatographia*, **66**, 213–8 (2007) https://doi.org/10.1365/s10337-007-0304-9

[37] Al-Ali M, Al-Ali LI. Modeling Kinetics and Transport Mechanism Study of Poorly Soluble Drug Formulation in High Acidic Medium. *Tikrit J. Eng. Sci.*, **31**, 76–91 (2024) https://doi.org/10.25130/tjes.31.4.8

[38] Rajab NA, Sulaiman HT. Olmesartan Medoxomil Nanomicelle Using Soluplus for Dissolution Enhancement: Preparation, In-vitro and Ex-vivo Evaluation. *Iraqi J. Pharm. Sci.*, **34**, 47–59 (2025) https://doi.org/10.31351/vol34iss2pp47-59

[39] Landry L, Dong X. Investigation of hydrolysis of olmesartan medoxomil in different pH buffers by simultaneously measuring olmesartan medoxomil and olmesartan. *PLoS One*, **20**, e0321142 (2025) https://doi.org/10.1371/journal.pone.0321142

[40] Shivaraj D, Bellaiah PG, Srinivasa S. Development and characterization of Olmesartan Medoximil Self-Microemulsifying Fast Disintegrating Tablet. *J. Drug Deliv. Ther.*, **15**, (2025) https://orcid.org/0009-0006-6790-1235

[41] Gannu R, Vamshi Vishnu Y, Kishan V, Madhusudan Rao Y. Development of nitrendipine transdermal patches: in vitro and ex vivo characterization. *Curr. Drug Deliv.*, **4**, 69–76 (2007) https://doi.org/10.2174/156720107779314767