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Research Article

MUCOADHESIVE SODIUM ALGINATE PATCHES FOR ENHANCED BUCCAL DELIVERY OF OLMESARTAN IN HYPERTENSION MANAGEMENT

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ABSTRACT

Objective: To develop and optimize olmesartan (OMS) buccal patches using sodium alginate (SA) for enhanced bioavailability and sustained release.

Methods: A Box–Behnken design evaluated the effects of SA, hydroxypropyl methylcellulose (HPMC) K4M, and polyvinyl alcohol (PVA) on patch performance across 17 formulations. Patches were assessed for swelling, mucoadhesion, drug release, physical properties, pH, and drug content. X-ray diffraction and scanning electron microscopy analyzed the drug state and surface morphology. *In vitro*, *ex vivo*, and pharmacokinetic studies were conducted.

Results: The optimal formulation (SA, HPMC K4M, PVA in a ratio of 2:1.5:1) showed strong mucoadhesion, uniform drug dispersion, and sustained release. Higher HPMC K4M enhanced adhesion and release control. The optimized patch achieved 78.2% bioavailability, compared to 27.8% for oral suspension.

Conclusion: Box–Behnken optimization yielded an effective buccal patch for OMS, offering improved bioavailability and sustained drug delivery.

Keywords: Hypertension, Box–Behnken design, Buccal patches, Bioavailability, Olmesartan-Sodium alginate

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INTRODUCTION

Hypertension is a widespread chronic condition and a major risk factor for cardiovascular diseases, often leading to serious complications such as stroke, renal dysfunction, and heart failure if not adequately managed [1,2]. Effective long-term control of blood pressure is crucial to minimizing these risks. Olmesartan (OMS), a fourth-generation calcium channel blocker of the dihydropyridine class, shows considerable therapeutic potential due to its ability to block both L-type and N-type calcium channels [3]. This dual mechanism enhances vasodilation while simultaneously suppressing sympathetic nerve activity, resulting in superior blood pressure regulation and renal protection compared to earlier agents in the same class [2].

However, the clinical application of OMS is hampered by certain biopharmaceutical limitations. It exhibits poor aqueous solubility, is highly lipophilic, and undergoes extensive first-pass metabolism, which collectively lead to low and inconsistent oral bioavailability, typically around 13%. These challenges underscore the need for alternative delivery strategies that can bypass hepatic metabolism and improve systemic drug availability [4,5].

Among various novel delivery approaches, mucoadhesive buccal systems have gained traction due to their ability to deliver drugs directly into the systemic circulation via the buccal mucosa, avoiding first-pass hepatic clearance [6]. These systems offer controlled and sustained drug release, ease of administration, and better patient compliance. In particular, buccal patches are advantageous because they can adhere to the mucosa for extended periods, deliver drugs unidirectionally, and be easily removed if necessary [7,8].

The current investigation is centered on formulating OMS-loaded mucoadhesive buccal patches using a combination of biocompatible and bioadhesive polymers. The patch matrix includes hydroxypropyl methylcellulose (HPMC) and Carbopol 934P, both known for their strong mucoadhesive properties and film-forming abilities. Polyvinyl alcohol K30 (PVA K30) is incorporated to improve drug dispersion and solubility [9].

Another critical polymer in the formulation is sodium alginate (SA), a naturally derived, biodegradable polysaccharide with excellent mucoadhesive properties. It aids in forming a hydrogel structure that promotes prolonged retention on the buccal surface and modulates drug release kinetics. Moreover, SA enhances the mechanical integrity and flexibility of the patches, contributing to their overall stability and patient acceptability [10,11]. Glycerine is used as a plasticizing agent to improve the pliability of the patches and as a permeation enhancer to facilitate better drug absorption through the mucosal tissues [12].

To optimize the formulation, a Box-Behnken Design (BBD) based on response surface methodology was employed. This statistical tool allows for the evaluation of interactive effects among multiple formulation variables with a minimal number of experimental runs, leading to a more efficient and targeted development process [13,14].

The developed buccal patches were subjected to comprehensive physicochemical evaluations, including assessments of thickness, uniformity in weight, drug content, pH, folding endurance, and swelling capacity [15]. Functional performance tests covered mucoadhesive strength, *in vitro* release studies, *ex vivo* permeation studies using buccal mucosa, and *in vivo* pharmacokinetic profiling in suitable animal models [16,17].

The overarching aim of this work is to develop an OMS buccal patch that ensures enhanced bioavailability, sustained release, and improved patient compliance, thereby offering a promising alternative to conventional oral therapy for hypertension management.

MATERIALS AND METHODS

Materials

OMS was purchased from Yarrow Chem. Products (Mumbai, India). PVA and glycerine were purchased from Loba Chemie Pvt. Ltd. (Mumbai). Acetonitrile, ammonium acetate, methanol, and ammonium dihydrogen orthophosphate of high-performance liquid chromatography (HPLC) grade were purchased from Research-Lab Fine Chem (Mumbai). Oleic acid was obtained from Burgoyne Urbidges and Co. (Mumbai). All other chemicals and solvents were of analytical grade.

Methods

Formulation of buccal patches

Formulation of OMS buccal patches

The formulations (buccal patches) were developed through the solvent casting technique. OMS are triturated through 2–3 drops of Tween 80 in a mortar and pestle. The SA and HPMC K4M are dissolved into ethanol at 500 rpm with a constant magnetic stirrer for 4 h. PVA is a hydrophilic polymer dissolved in ethanol at 900 rpm for 4 h to obtain a solution. Further, add glycerine to the above blend, which acts as a plasticizer, and mix in a beaker with uniform stirring for 10–15 min. The solution was sonicated for 1 h to eliminate the air bubbles. The resulting clear solution was put into a Petri plate with a diameter of 7.5 cm. Then, this plate was placed into a hot air oven for 12 h at 40°C. Finally, the developed patches were cut into 2 cm diameters with an area of 3.14 cm^2, including OMS 20 mg in individual patches [18,19].

Optimization of buccal patches formulation by BBD

A Box–Behnken statistical design (BBD) was utilized to optimize buccal patch formulations. The statistical data illustrate the impact of formulation factors such as SA and PVA concentration on the physicochemical characteristics of patches. This investigation selected three independent variables, such as the amount of matrix-forming polymer Eudragit RL, the amount of mucoadhesive polymer SA, and the amount of film former PVA, for formulation development. These three factors were assessed, each at three levels. The concentrations of SA, HPMC K4M, and PVA were varied in the ratios 0.5–1: 0.625–1.875: 0.5–1, respectively. The coding was −1, 0, and +1 for each factor's lower, middle, and higher levels. The dependent variables/responses included swelling index (Y_1), % drug release (Y_2), and mucoadhesive strength (Y_3). The BBD proposed a significant model for demonstrating polynomial equations and response surface 3D plots with Stat-Ease software (Version 13, Design Expert). The BBD was most desired because it provides at least three factors with more than three responses compared to other designs. The statistical design was provided with 17 experimental runs and suggested the quadratic model [14]. The model validation using analysis of variance to affirm statistical adequacy. The software-developed equation of the quadratic model is presented in the equation below.

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

Where Y expressed the calculated response associated with each factor level combination, an intercept was represented by b_0; the regression coefficients of observed practical values of *Y* were represented by b_1 to b_{33}, and independent variables are represented with *A*, *B*, and *C*.

Characterizations of formulation

X-ray diffraction (XRD)

The X-ray crystal patterns of OMS were accomplished utilizing a bulk X-ray diffractometer (Diffrac. EVA. V2.1), and CuKα was employed as the radiation source. Around 45 kV (40 mA) current was utilized for scanning, which was conducted at 2–90° (2θ), and the scanning rate was 2°/min at ambient temperature [20].

Weight and thickness of patches

Three patches were picked randomly from every formulation with a diameter of 2 cm and were weighed separately through an analytical balance. The average weight was estimated along with the standard deviation. The thickness of the patches was evaluated utilizing a vernier calliper (Mitutoyo, Japan) with a minor count of 0.01 mm [7].

Surface pH measurement

The surface pH of a patch was demonstrated to confirm whether the film irritated the buccal mucosa. The surface pH examination was conducted by randomly assigning three patches and estimating pH utilizing a pH meter (Equip-Tronic's, EQ-610, India). Wherein the patch was poured under a Petri dish containing 0.5 mL of deionized water for 1 h. After complete swelling, the pH electrode was incorporated in close contact with the swelled patch surface, and pH was recorded for every patch [21].

Drug content uniformity (mg)

The drug content uniformity of developed patches was demonstrated utilizing the validated reverse phase-HPLC (RP-HPLC) method. The patches were cut at exactly 20 mm in diameter from three different areas of the cast patches. Each patch was poured under a 100 mL volumetric flask and dissolved in pH 6.8 phosphate-buffered saline (PBS) (8 g NaCl, 0.2 g KCl, 1.44 g Na_2HPO_4, 0.24 g KH_2PO_4 in 1 L water, adjust pH to 6.8). From this solution, a 2 mL sample was taken and diluted for 10 mL (equivalent to 5 g/mL concentration). The absorbance of this solution was measured at 230 nm through an ultraviolet (UV)/visible spectrophotometer. The % drug content was demonstrated employing the standard graph, and the same process was repeated for three patches of every formulation [22].

Folding endurance

The folding strength of the developed patches was demonstrated manually by constantly folding the patch until it broke/ruptured. The number of folds needed to break the patch was noted as the folding endurance. The investigations were conducted in triplicate, and average values were noted [23].

Tensile strength

The tensile strength of the developed formulation was demonstrated utilizing the Universal Tensile Strength Testing Machine (LS5, Lloyd Instruments Limited, UK) connected with a 500 N load cell. The test was performed in typical laboratory conditions. The 400 mm^2 film was selected randomly, and the test was conducted using the American Society for Testing and Materials D-882. The upper clamp tore the patch apart at a rate of 50 mm/min, whereas the bottom clamp was kept in place. At the moment the patch broke, the force applied to it was noted. Nexygen Plus3 software was utilized to obtain data calculations. Three duplicates of the experiment were run, and the average results were given [24]. The following formula was used to get the tensile strength at break value:

$$\textit{Tensile strength}=\textit{Force to break (N)}/\textit{Initial cross-sectional area (mm}^2\textit{)}$$

Scanning electron microscopy (SEM)

The optimized patch internal morphology was examined by utilizing 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 analyzed utilizing a scanning electron microscope, and appropriate magnification photomicrographs were captured [25].

Swelling studies

The swelling index of patches was assessed by immersing the patches in PBS pH 6.8 at 37±0.5°C. 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, and 30 min, 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 [26]. The following formula was used to get the swelling index and average weight W2.

$$\%\ \textit{Swelling Index}=W2-W1/W1\times100$$

Ex vivo mucoadhesive time/strength

The two-arm balancing method was employed to estimate the mucoadhesive potency of the developed patches at room temperature, with a few minor adjustments. Within 2 h of the sheep slaughter, fresh buccal mucosa was collected from a nearby slaughterhouse and employed in the research. After separating the mucosal membrane from loose tissues and underlying fat, a 2 mm thickness was achieved. At 37°C, the membrane was cleaned utilizing distilled water and PBS pH 6.8. After being divided into pieces, the buccal mucosa was cleaned with PBS pH 6.8. Next, utilizing cyanoacrylate glue, a buccal mucosa section was adhered to the bottom of a smaller beaker. A 5 g weight was placed on the pan on the right side of the balance to balance two pans. After using two-way adhesive tape to attach the buccal patch to the lower edge of the left pan, the right pan of the balance's 5 g weight was removed to make contact with the mucosa that was put on a tiny beaker. After holding the balance in this position for 5 min, water was gradually poured into the right-side pan at a rate of 100 drops/min or until the patch separated from the mucosal surface. The force needed to detach the patch from the mucosa is equal to the extra weight on the pan or the total weight of <5 g. Mucoadhesive strength was demonstrated by weighing the patch in grams until it detached from the mucosal surface. Three duplicates of the tests were run, and average results were given [27,28].

HPLC method development for estimation of OMS drug release/ permeation/pharmacokinetic studies

A Shimadzu SCL-10AVP HPLC system, equipped with a binary pump (LC-10ATVP), UV detector (SPD-10AVP), and a manual injector fitted with a 20 µL Rheodyne loop, was used throughout the study. Data were processed using liquid chromatography - Solution software. Separation was carried out on a Zodiac C8 column (150×4.6 mm ID, 5 µm) obtained from Ultrachrom Innovatives Pvt. Ltd. The mobile phase consisted of 15 mm ammonium acetate (solvent A) and a mixture of acetonitrile and methanol (90:10, v/v) as solvent B, with a gradient program running from 25% to 80% B over 15 min. The flow rate was set at 1.0 mL/min, detection wavelength at 230 nm, column temperature at 28°C, and injection volume at 20 µL. A stock solution of OMS (1 mg/mL), prepared in a solvent mix of acetonitrile, methanol, and water (4:4:2, v/v), was used to generate calibration standards ranging from 3.12 to 1000 ppm. Each solution was ultrasonicated, filtered through a 0.20 µm nylon membrane, and analyzed under the described conditions. The calibration curve was plotted using peak area versus concentration to evaluate linearity, limit of detection (LOD), limit of quantitation (LOQ), and regression parameters. All solvents and reagents used were HPLC grade, sourced from Merck and other certified suppliers. Instruments such as the digital balance (Mettler-Toledo), sonicator (Labman®), and pH meter (Mettler-Toledo) were used as per standard protocols [29].

Ex vivo drug release study

Using a vertical Franz diffusion cell, the release investigation from optimized formulations was accomplished for 12 h at 37±0.5°C. For 15 min, the isolated sheep buccal mucosa was equilibrated in PBS at a pH of 6.8. The pH 6.8 PBS was continually stirred by a magnetic stirrer whereas the patches were evenly dispersed around the donor chamber. At predetermined intervals, aliquots (0.1 mL) were collected from the receiver compartment and utilized to replace each cell's volume with the same volume of fresh PBS pH 6.8. The amount of drug release was calculated using the validated RP-HPLC technique. Further, the results were correlated with different release kinetic models. It was necessary to assess drug release using the formulation for several kinetic models, including the Korsmeyer–Peppas, Higuchi, First-order, Hixon–Crowel cube root, and Zero-order models. The model that best suited the data were chosen after the models were evaluated for each formulation [8].

Ex vivo permeation of OMS and OMS-SA

A vertical Franz diffusion cell was used to achieve *ex vivo* buccal penetration of patch formulations across the sheep buccal mucosa. After obtaining freshly isolated sheep buccal mucosa from the closest slaughterhouse, it was promptly preserved in fresh PBS pH 6.8. The buccal membrane had a thickness of 0.2 cm and a conventional diffusion cell surface area of 3.14 cm^2. The mucosa (3.14 cm^2) was immersed in PBS for 15 min after 7.5 mL of the cell's volume (pH 6.8) was filled with PBS. A diffusion cell with continuously circulating water was used to regulate the temperature of a receiver compartment at 37±1°C. A magnetic stirrer operating at 50 rpm was used to constantly agitate the PBS until the patch compositions were evenly dispersed across the donor chamber. The permeation parameters of the drug were investigated utilizing**.**

$$P=(slope/s)*VD$$

$$Jss=P*CD$$

S is the effective surface area of buccal mucosa (3.14 cm^2), VD is the donor compartment's volume (mg/mL), CD is the drug concentration in the donor compartment, and P is the permeation coefficient; Jss is steady-state flux.

At the scheduled intervals, aliquots (0.1 mL) were taken from the receiver compartment. To maintain the cell volume, the same amount of new PBS was replenished at the same temperature in a receiver compartment. After diluting the samples with acetonitrile, they were centrifuged for 10 min at 5000 rpm. After separating the supernatant, a validated HPLC technique was used to quantify the drug's penetration (µg/cm^2) within 12 h [8].

In vivo pharmacokinetic investigation OMS

The committee for the purpose of control and supervision of experiments on animals (CPCSEA), Government of India (Protocol No. 1697/PO/ Re/S/13/CPCSEA/2020/06), governed by the Institutional Animal Ethics Committee of HSBPVI's College of Pharmacy, Kashti, Ahmednagar, approved, and their guidelines were adhered to throughout the study. The experimental animals were first acclimated to typical laboratory environments, which included a temperature of 25±2°C and a relative humidity (RH) of 55±5%. In this investigation, female Wistar rats (average weight: 160–200 g, age: 21 days) were preferred. For the buccal patches' formulation of OMS, all animals were split into four groups, with six animals (n=24) in each group. The allotment of retro-orbital study for the different groups of the optimized formulations during the experimental period.

Diethyl ether was used as an anesthetic for the experimental groups. The buccal patches are placed with gentle force using a fingertip for a few seconds to ensure the correct application of the patch. The oral medicine (OMS) is delivered via a micropipette. For this investigation, several predefined time points (0, 0.25, 0.5, 1, 2, 4, 8, 12, and 24 h) were used. Five to seven droplets (20 µL) of blood were sampled using the retro-orbital plexus technique. The animals were ultimately sacrificed. The serum was separated by centrifuging the blood samples. The medication release from the serum was then examined [30].

In vivo buccal histopathological screening

The *in vivo* buccal tissue toxicity was assessed using female Wistar rats. Then, the patches were administered to female Wistar rats for 24 h. Following a 12-h exposure to patch formulations on rat mucosa, the animals were sacrificed, and a toxicity investigation was conducted. This study's main goal was to identify the pathological alterations in the mucosa that occurred during therapy. The formulation was applied to treat and control the mucosa to conduct the tests. A positive control was the mucosa portion treated with patches SA for 24 h, whereas the untreated mucosa section served as a negative control. After being subjected to a 10% formalin solution, all mucosa slices were paraffin-fixed and stained using hematoxylin and eosin staining techniques. Following staining, a pathologist inspected the mucosa sections under a microscope to show the structural alteration [31].

Stability studies

For 6 months, the optimized patch formulations were kept in a stability chamber (Bio Techniques, India) at various temperatures and RH levels according to International Council for Harmonisation requirements (Q1aR2). Finally, during 6-month intervals, samples were inspected for significant physicochemical properties such as microscopic appearance, swelling index, mucoadhesive strength, surface pH, and drug content [32].

RESULTS AND DISCUSSION

Formulation and optimization of OMS buccal patches by BBD

A total of 17 formulations (F1–F17) were developed by varying the concentrations of these three polymers systematically. The concentrations of SA, HPMC K4M, and PVA were varied in the ratio 0.5–1: 0.625–1.875: 0.5–1, respectively, allowing for the assessment of individual and interactive effects of these factors on key performance parameters such as swelling index, mucoadhesive strength, and drug release. Optimal concentrations of SA and HPMC ensure adequate hydrogen bonding and proper adhesion. Below this range, insufficient bonding leads to poor stickiness, whereas excess levels may cause over-swelling, irritation, and inflammation. The design aimed to identify optimal polymer ratios that would yield patches with desirable swelling behavior, sufficient adhesion to the buccal mucosa, and a sustained release profile of the drug. This factorial design approach provides a robust framework for understanding the influence of formulation variables and optimizing the overall performance of buccal drug delivery systems. p-value for models was <0.0500, indicating model terms as significant. The R^2 value of the model was found to be 0.8807 (Tables 1 and 2).

Characterization of buccal patches

XRD

The XRD analysis, shown in Fig. 1, compares the structural characteristics of the raw OMS material and the OMS-SA buccal patch. The OMS sample exhibits multiple sharp peaks between 20° and 40° (2θ), which reflect its crystalline nature. These peaks are indicative of a regular, ordered molecular arrangement. In contrast, the OMS-SA buccal patch shows a broad, hump-like pattern with no distinct peaks, suggesting a transition to an amorphous state. This change is likely due to the formulation process, which may involve the incorporation of polymers and solvents that disrupt the original crystal structure. The resulting amorphous form is often advantageous in drug delivery applications, as it can improve the solubility and absorption of APIs.

Weight and thickness of patches

The weights of the prepared buccal patches remained consistent across all formulations, generally falling within a narrow range between 5.11 mg and 5.19 mg. The small variation observed (e.g., F14 at 5.11 mg and F13 at 5.19 mg) suggests precise formulation techniques and ensures reliable dosing. This level of consistency is essential for therapeutic uniformity in drug delivery systems.

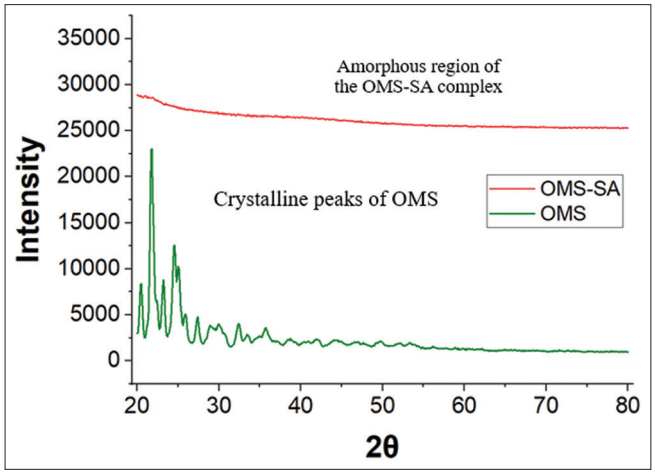

Fig. 1: X-ray diffraction pattern of olmesartan (OMS), buccal patches of OMS – sodium alginate

Surface pH

The pH of the patch surfaces was close to neutral for all batches, ranging from 6.8 to 7.3. These values are within the safe range for the oral mucosa, indicating that the patches are unlikely to cause irritation or discomfort when applied. A near-neutral pH also helps preserve the integrity of the drug and improves patient compliance.

Drug content uniformity (mg)

All formulations contained 20 mg of drug, with very little variation across samples. This consistent drug content highlights the accuracy of the formulation method and confirms that each patch delivers an equal amount of the active pharmaceutical ingredient, which is critical for dose reliability.

Folding endurance

The flexibility and mechanical resilience of the patches were assessed through folding endurance. Results ranged from just over 330 folds to more than 430, indicating good physical stability. Higher values, as seen in F11 and F10, suggest those patches are more resistant to damage from handling, an important characteristic for storage and administration.

Tensile strength

There was a noticeable range in tensile strength across the formulations, with values from about 11 to 18 N/mm^2. Stronger patches, such as F17 and F15, are better suited for buccal application as they withstand mechanical stress without breaking. Formulations with lower strength may still be usable but could be more prone to tearing.

SEM

The SEM images of OMS-SA buccal patches (Fig. 2), captured at different magnifications (×6000, ×3000, and ×1000), display a moderately rough and irregular surface. At higher magnification (×6000), the images show small pores and cracks, which could play a role in facilitating drug release by creating diffusion pathways. The fibrous appearance observed at ×3000 magnification indicates a network-like structure, suggesting partial distribution of the drug and polymers throughout the matrix. At a lower magnification (×1000), the surface appears more compact and less porous, reflecting the patch's overall mechanical stability. The presence of both porous and dense regions points to a biphasic structure that can aid in sustained release while ensuring good adhesion to the buccal mucosa. These surface characteristics align with the intended design of the patch for sustained and effective drug delivery.

Effect of formulation variables on swelling index

The swelling index across the formulations varied significantly, ranging from 210% to 398%. This variation clearly reflects the influence of the polymer composition, particularly the concentration of SA and HPMC K4M, on the hydration capacity of the matrix. The highest swelling index (398%) was recorded in the formulation containing 1% SA, 1.875% HPMC K4M, and 0.75% PVA, suggesting that higher levels of HPMC K4M enhance water absorption due to its gel-forming ability. Conversely, formulations with lower HPMC K4M concentrations showed comparatively reduced swelling, indicating the importance of hydrophilic polymers in modulating water uptake and swelling behavior. The role of polymer concentration, particularly the hydrophilicity of HPMC K4M, in formulation F4 leads to higher swelling.

Fig. 3 shows 3D response surface plots that depict how different combinations of polymers influence the swelling index (%) of the buccal patches. In plot A, the interaction between SA and HPMC K4M indicates that as the concentration of both polymers increases, the

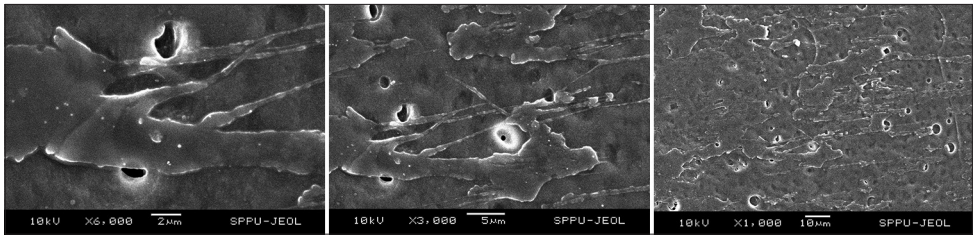

Fig. 2: Scanning electron microscopy of buccal patches of olmesartan-sodium alginate

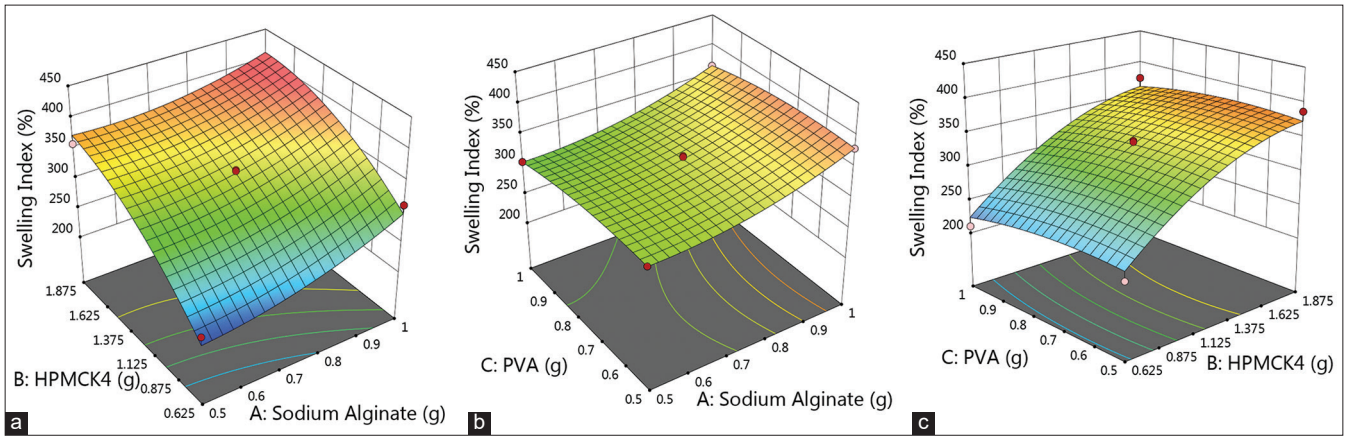

Fig. 3: 3D response surface plots of swelling index (a) (sodium alginate and hydroxypropyl methylcellulose [HPMC] K4M), (b) (sodium alginate and polyvinyl alcohol [PVA]), (c) (PVA and HPMC K4M)

swelling index rises significantly. This suggests that the hydrophilic nature of both materials enhances water absorption and gel formation. Plot B examines SA with PVA, revealing that higher levels of these two also improve swelling, although SA contributes more strongly to the effect. In plot C, the combination of PVA and HPMC K4M is illustrated. Here, HPMC K4M plays a dominant role in increasing swelling, whereas PVA shows a relatively mild influence. These findings highlight the importance of polymer ratios in optimizing the swelling behavior, which is essential for achieving effective mucoadhesion and sustained drug release in buccal formulations.

Ex vivo mucoadhesion time (min)/strength

Mucoadhesive strength varied significantly among the formulations, ranging from 16 g (F3) to 42 g (F4). Higher mucoadhesive strength was generally observed in formulations with increased concentrations of HPMC K4M, a well-known mucoadhesive polymer. Formulation F4, which exhibited the maximum mucoadhesive force (42 g), also had the highest amount of HPMC K4M (1.875%), highlighting the strong influence of this polymer on mucosal adhesion. Similarly, formulations such as F14 (40 g) and F5 (36 g) demonstrated enhanced mucoadhesiveness due to their higher polymer load. Conversely, formulations with lower HPMC K4M content, such as F3 (16 g) and F2 (19 g), recorded significantly reduced mucoadhesive strength. These findings reinforce the importance of polymer selection and concentration in achieving optimal adhesion to the buccal mucosa, which is essential for prolonged residence time and sustained drug delivery.

Fig. 4 presents 3D response surface plots illustrating the combined effects of polymeric components on the mucoadhesive strength of buccal patches. Plot P shows the interaction between SA and HPMC K4M, where an increase in both components leads to enhanced mucoadhesive strength, likely due to their synergistic swelling and gel-forming properties. In plot Q, the interaction between SA and PVA reveals that higher concentrations of SA significantly improve adhesion, whereas PVA has a moderate effect. Plot R illustrates the combined influence of HPMC K4M and PVA, with both polymers contributing positively, though HPMC K4M exerts a more prominent impact, possibly due to its viscosity and hydration capacity. These trends collectively indicate that optimizing polymer ratios plays a crucial role in achieving desirable mucoadhesive performance (Table 3).

HPLC method development for estimation of OMS drug release/ permeation/pharmacokinetic studies

The developed chromatographic method for OMS met all system suitability criteria, confirming its reliability and precision. Theoretical plates (31,993) indicated high column efficiency, and the capacity factor (3.799) reflected adequate retention. Although resolution was not specified, the separation factor (2.256) suggested good selectivity. A tailing factor of 1.075 confirmed peak symmetry, and the retention time of 8.706 min showed consistent elution. Detection at 230 nm ensured sensitivity, while %RSD values for repeatability (1.45%), intra-day (0.31–1.34%), and inter-day (0.30–0.71%) precision were all within limits, indicating method reproducibility. Linearity was established over 3.13–100 μg/mL (r^2=0.9996), with strong sensitivity shown by an LOD of 3.62 μg/mL and LOQ of 12.08 μg/mL. These results confirm the method's suitability for accurate and routine analysis of OMS.

***Ex vivo* drug release study**

Drug release from the buccal patches ranged between 84% (F4) and 97% (F3 and F10). A general trend observed was that formulations with higher polymer content, especially HPMC K4M, tended to retard drug release due to the formation of a thicker and more viscous gel barrier upon hydration. For instance, F4, with the highest HPMC K4M concentration (1.875%), exhibited the slowest release rate (84%), followed closely by F13 (85%) and F5 (86%), both of which also contained higher polymer levels. In contrast, F3 and F10, which had lower concentrations of both SA and HPMC K4M, achieved maximum drug release (97%), likely due to thinner matrices and less resistance to drug diffusion. These observations confirm that polymer composition and concentration play a pivotal role in modulating the release kinetics, enabling the formulation of patches with tailored drug release profiles suited for sustained delivery via the buccal route.

The *in vitro* drug release profile of the OMS-SA formulation (F8) is presented in Fig. 5. The cumulative release (%) of the drug was evaluated

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

Formulation	Factor 1: SA	Factor 2: HPMC K4 M	Factor 3: PVA	Swelling index %	Mucoadhesive strength g/mm²	Drug release %
F1	0.75	1.25	0.75	335±2	28±0.15	95
F2	0.5	0.625	0.75	230±1	19±0.35	96
F3	0.75	0.625	1	210±3	16±0.45	97
F4	1	1.875	0.75	398	42±0.25	84
F5	1	1.25	0.5	380±2	36±0.15	86
F6	0.5	1.875	0.75	358±3	34±0.30	90
F7	0.5	1.25	1	305±3	32±0.10	95
F8	0.75	1.25	0.75	340±2	32±0.15	94
F9	0.75	1.875	0.5	387±2	33±0.25	93
F10	0.75	0.625	0.5	228±3	29±0.15	97
F11	0.75	1.25	0.75	336±3	30±0.15	95
F12	0.5	1.25	0.5	320±2	25±0.20	92
F13	1	0.625	0.75	312±1	32±0.15	85
F14	1	1.25	1	365±3	40±0.15	91
F15	0.75	1.25	0.75	342±2	29±0.40	93
F16	0.75	1.875	1	375	34±0.15	92
F17	0.75	1.25	0.75	329±3	32±0.30	94

All values are mean±standard deviation, n=3. HPMC: Hydroxypropyl methylcellulose, OMS: Olmesartan, SA: Sodium alginate, PVA: Polyvinyl alcohol

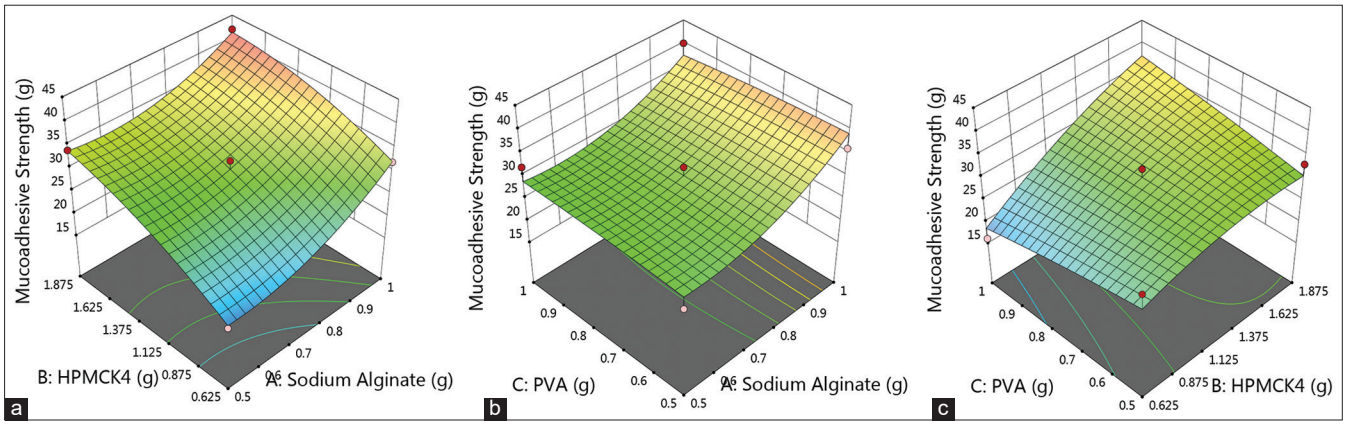

Fig. 4: 3D response surface plots mucoadhesive strength of (a) (sodium alginate and hydroxypropyl methylcellulose [HPMC] K4), (b) (sodium alginate and polyvinyl alcohol [PVA]), (c) (PVA and HPMC K4)

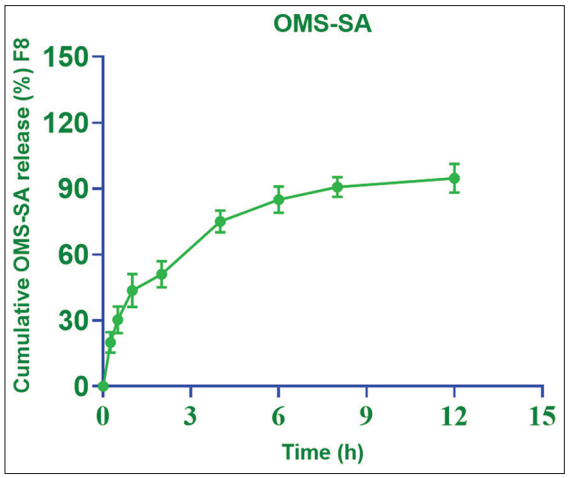

Fig. 5: Cumulative drug release from olmesartan-sodium alginate buccal patch formulations for 12 h. All values are mean±standard deviation, n=3

over a period of 12 h, showing an initial burst release within the first 3 h, followed by a sustained and gradual release phase. Approximately 60% of the drug was released within the first 3 h, indicating rapid initial availability, which is beneficial for achieving therapeutic levels quickly. Beyond this point, the release continued at a slower rate, reaching around 95–100% by 12 h, suggesting a sustained and prolonged release behavior. This biphasic release pattern demonstrates the effectiveness of the OMS-SA formulation in providing both immediate and sustained drug delivery, which is desirable for maintaining consistent drug levels over an extended period.

Ex vivo permeation of OMS and OMS-SA

The *ex vivo* permeation data comparing OMS-solution and OMS-SA-Patch (both at 10,000 µg/mL) are presented in Fig. 6 and summarized in Table 4. The OMS-solution exhibited a higher initial cumulative permeation and permeability, with a Papp value of 1.7×10^{-4} cm/h and a steady-state flux (Jss) of 1.7×10^{-3} µg/cm²/h, resulting in a cumulative drug permeation of 9894.1±430 µg at 24 h. In contrast, the OMS-SA-Patch showed a lower Papp of 1.0×10^{-4} cm/h and Jss of 1.0×10^{-3} µg/cm²/h, with a comparable cumulative permeation of 9876.8±228 µg after 24 h. Despite the slower initial release, the patch maintained a steady and controlled permeation profile. These results confirm that while the solution delivers the drug more rapidly, the patch formulation ensures sustained release, making it a promising approach for prolonged buccal delivery with reduced dosing frequency.

In vivo pharmacokinetic parameters

Pharmacokinetic evaluation of OMS administered via IV solution, oral suspension, and OMS-SA buccal patch at a dose of 0.333 mg/kg revealed distinct absorption profiles (Fig. 4 and Table 6). The IV solution exhibited the highest C_{max} of 170±13 µg/mL with immediate systemic availability (T_{max}=0 h) and a short half-life of 2.2±0.8 h. The oral suspension showed a delayed T_{max} of 4 h, a lower C_{max} of 48.4±5.4 µg/mL, an extended half-life of 6.0±0.1 h, and low absolute

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

Ingredient	OMS (mg)	Tween 80 (mL)	Sodium alginate (mg)	HPMC K4M (mg)	PVA (mg)	Glycerine (mL)	Ethanol (mL)
F1	20	0.8	0.75	1.25	0.75	0.3	20
F2	20	0.8	0.5	0.625	0.75	0.3	20
F3	20	0.8	0.75	0.625	1	0.3	20
F4	20	0.8	1	1.875	0.75	0.3	20
F5	20	0.8	1	1.25	0.5	0.3	20
F6	20	0.8	0.5	1.875	0.75	0.3	20
F7	20	0.8	0.5	1.25	1	0.3	20
F8	20	0.8	0.75	1.25	0.75	0.3	20
F9	20	0.8	0.75	1.875	0.5	0.3	20
F10	20	0.8	0.75	0.625	0.5	0.3	20
F11	20	0.8	0.75	1.25	0.75	0.3	20
F12	20	0.8	0.5	1.25	0.5	0.3	20
F13	20	0.8	1	0.625	0.75	0.3	20
F14	20	0.8	1	1.25	1	0.3	20
F15	20	0.8	0.75	1.25	0.75	0.3	20
F16	20	0.8	0.75	1.875	1	0.3	20
F17	20	0.8	0.75	1.25	0.75	0.3	20

HPMC: Hydroxypropyl methylcellulose, OMS: Olmesartan, SA: Sodium alginate, PVA: Polyvinyl alcohol

Table 3: Physicochemical evaluation parameters of OMS-SA buccal patches

F	Weight uniformity (mg)	Thickness (mm)	Surface pH	Drug content uniformity (mg)	Folding endurance (Folds)	Tensile strength (N/mm^2)	*Ex vivo* mucoadhesion time (min)
F1	5.15±0.03	0.15±0.05	6.9±0.01	19.8±0.03	365±4	9.12±0.06	276±3
F2	5.18±0.08	0.17±0.04	6.8±0.04	20.2±0.04	355±6	11.15±0.07	278±2
F3	5.16±0.05	0.18±0.07	6.9±0.05	19.7±0.03	353±3	13.04±0.08	285±7
F4	5.15±0.06	0.15±0.09	7.1±0.03	20.3±0.04	354±9	10.03±0.09	296±8
F5	5.18±0.07	0.16±00.9	7.2±0.06	20.0±0.04	401±9	12.06±0.10	286±1
F6	5.16±0.08	0.18±0.10	7.4±0.08	19.9±0.02	408±4	11.07±0.11	286±2
F7	5.17±0.09	0.16±0.01	7.5±0.08	20.1±0.04	395±5	14.08±0.12	293±5
F8	5.15±0.01	0.16±0.03	6.8±0.08	19.6±0.03	356±8	16.04±0.13	290±3
F9	5.16±0.02	0.18±0.05	7.2±0.09	20.4±0.04	402±8	17.06±0.14	286±6
F10	5.18±0.02	0.17±0.08	6.8±0.02	20.0±0.04	431±6	18.08±0.15	285±5
F11	5.17±0.03	0.16±0.05	7.4±0.03	20.1±0.03	422±4	12.04±0.16	297±7
F12	5.17±0.06	0.17±0.06	7.3±0.05	19.8±0.02	402±6	13.02±0.17	286±9
F13	5.18±0.08	0.16±0.01	6.8±0.01	20.2±0.02	356±8	15.06±0.18	285±6
F14	5.15±0.07	0.15±0.04	7.6±0.03	19.7±0.03	350±8	16.03±0.19	279±9
F15	5.16±0.06	0.18±0.04	7.4±0.06	20.0±0.04	403±5	17.02±0.18	289±5
F16	5.17±0.08	0.16±0.01	6.9±0.01	19.9.±0.03	358±8	18.06±0.18	285±4
F17	5.18±0.07	0.15±0.04	7.5±0.03	20.3±0.02	355±8	16.03±0.19	289±9

All values are mean±standard deviation, n=3. OMS: Olmesartan, SA: Sodium alginate

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

Formulation	P_{app} (cm/h×10^{-x})	Flux J_{ss} (μg/cm^2/h	Cumulative OMS permeated at 24 h (μg)
OMS-Solution (10000 ug/mL)	1.7×10^{-4}	1.7×10^{-3}	9894.1±430
OMS-SA-Patch (10000 ug/mL)	1.0×10^{-4}	1.0×10^{-3}	9876.8±228

All values are mean±standard deviation, n=3. OMS-Solution: Olmesartan solution, OMS-SA-Patch: Olmesartan sodium alginate buccal patch, Papp: Apparent permeability, Jss: Steady state flux

Table 5: Group: 1: OMS-SA buccal patch

Serial No.	Group	OMS dose (mg/kg)	No. of Animals
1.	Normal Control	-	6
2.	Positive Control (OMS IV)	2	6
3.	Test Group (OMS Oral Suspension)	4	6
4.	Test Group Buccal Patch (OMS-SA)	4	6

Total animal−24+24=48 rats. OMS: Olmesartan, SA: Sodium alginate

bioavailability (27.8±6.7%), indicating limited absorption. In contrast, the OMS-SA buccal patch achieved a significantly higher C_{max} (109.1±6.5 μg/mL) than the oral route, with a similar T_{max} of 4 h and a prolonged half-life of 7.5±0.2 h. Notably, the buccal patch exhibited the highest AUC (961.0±76.8 h·μg/mL) among all routes, and an absolute bioavailability of 78.2±5.9%, indicating enhanced systemic exposure and sustained drug release. These findings support the buccal patch as an effective alternative to conventional delivery routes, offering improved bioavailability and extended therapeutic action (Fig. 7 and Table 5).

***In vivo* buccal histopathological screening**

Histopathological examination of buccal mucosa tissues is presented in Fig. 8. Section A, representing the control (untreated) group, shows disrupted epithelial architecture with signs of inflammation, cellular infiltration, and intercellular edema, indicating tissue damage. In contrast, section B, which represents the mucosa treated with OMS-SA for 24 h, demonstrates a more organized tissue structure with intact epithelium, reduced inflammatory infiltration, and preserved connective tissue integrity. These findings suggest that OMS-SA treatment aids in maintaining mucosal structure and promotes tissue

Table 6: Pharmacokinetic parameters of OMS IV solution, OMS Oral Suspension, and OMS-SA-patch buccal

Route of administration	Dose (mg/kg)	C_{max} (µg/mL)	T_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (h. µg/mL)	Absolute bioavailability (%)
OMS solution (IV)	2	170±13	0	2.2±0.8	314.1±14.2	100
OMS suspension (Oral)	4	48.4±5.4	4	6.0±0.1	348.7±84.1	27.8±6.7
OMS-SA-Patch (Buccal)	4	109.1±6.5	4	7.5±0.2	961.0±76.8	78.2±5.9

All values are mean±standard deviation, n=3. Normal control=0.0%, Positive control=OMS-IV 0.333 mg/kg, Test group=OMS-Oral 0.333 mg/kg, and Test group Buccal patch (OMS-SA) 0.333 mg/kg. OMS: Olmesartan, SA: Sodium alginate

Table 7: Accelerated stability study of OMS-SA for 6 months

Parameter	40°C+2/75+5% RH				Room temperature			
	Initial	2 month	4 month	6 month	Initial	2 month	4 month	6 month
Physical appearance	No change	No change	No change	No change	No change	No change	No change	No change
Thickness (mm)	0.17±0.02	0.17±0.05	0.17±0.03	0.17±0.05	0.17±0.06	0.17±0.07	0.17±0.0.2	0.18±0.05
Folding endurance (times)	>300	>300	>300	>300	>300	>300	>300	>300
Surface pH	6.8±0.03	6.8±0.02	6.8±0.05	6.8±0.17	6.8±0.05	6.8±0.12	6.8±0.35	6.8±0.19
Swelling index (%)	305	307	305	305	305	307	307	307
Mucoadhesive strength g	32	30	31	32	32	30	32	31
Drug content (%)	98±0.07	98±0.18	98±0.05	98±0.07	98±0.12	98±0.6	98±0.50	98±0.35

All values are mean±standard deviation, n=3. OMS: Olmesartan, SA: Sodium alginate, RH: Relative humidity

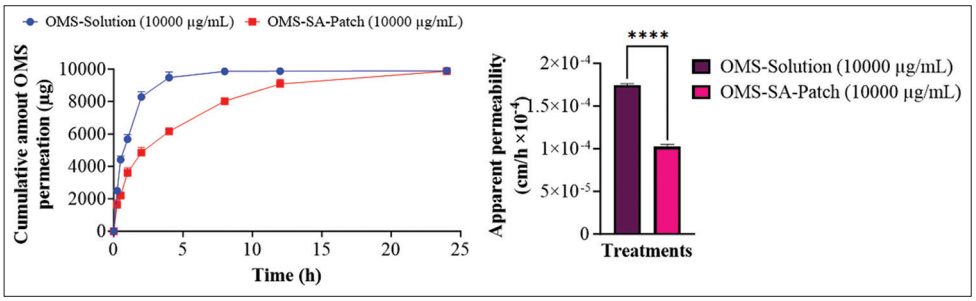

Fig. 6: *Ex vivo* permeation of olmesartan (OMS) and OMS-sodium alginate. All values are mean±standard deviation, n=3

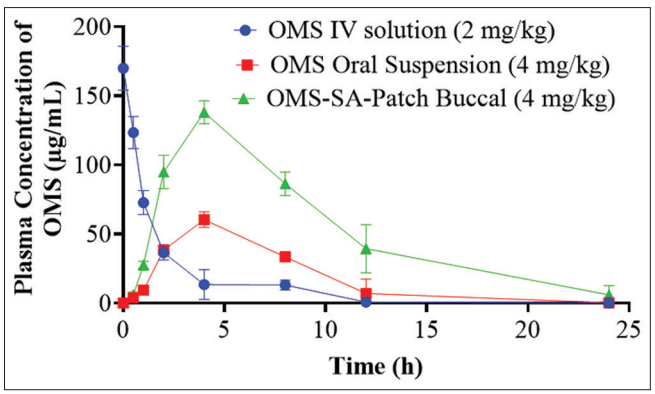

Fig. 7: Pharmacokinetic parameter of olmesartan (OMS) IV solution, OMS oral suspension, and OMS – sodium alginate – patch buccal. All values are mean±standard deviation, n=3

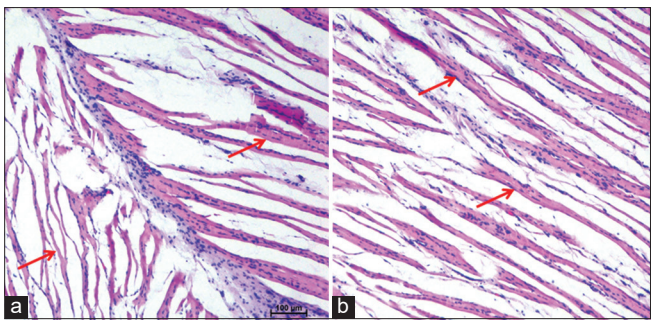

Fig. 8: Histopathological sections of buccal mucosa (a) control (untreated) mucosa, (b) section treated with olmesartan-sodium alginate 24 h

recovery compared to the untreated condition. The section shows typical 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 (Fig. 8).

Stability studies

A 6-month stability study was conducted under accelerated (40±2°C/75±5% RH) and room temperature conditions, with evaluations at 0, 2, 4, and 6 months. The formulation showed no changes in appearance, and thickness remained consistent with minor acceptable variations. Folding endurance exceeded 300 folds, confirming mechanical stability. Surface pH stayed around 6.8, indicating suitability for mucosal use. Swelling index and mucoadhesive strength (30–32 g) showed minimal variation, reflecting maintained hydration and adhesion. Drug content remained stable at ~98%, confirming chemical integrity. Overall, the formulation demonstrated strong physicochemical and mechanical stability under both conditions (Table 7).

CONCLUSION

The study successfully formulated a mucoadhesive buccal patch system for OMS medoxomil that offers sustained drug release and superior systemic availability compared to conventional oral forms. Optimization using statistical modeling provided insight into how polymer ratios influence drug delivery characteristics. Notably, SA and HPMCK4M significantly contributed to enhancing both adhesion and

release control. Pharmacokinetic results from *in vivo* trials confirmed the improved absorption profile of the patch, and histological analysis validated its safety for buccal application. Overall, the formulated patch demonstrates promising potential as a more efficient and patient-compliant option for managing hypertension through controlled drug release.

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AUTHOR CONTRIBUTIONS

Ram Nikhate conducted the experimental work and manuscript drafting; Dr. Sanjay Patil supervised the study and reviewed the final manuscript.

CONFLICTS OF INTEREST

The author reports no financial or any other conflicts of interest in this paper.

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ETHICAL APPROVALS

The Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). (Protocol No. 1697/PO/Re/S/13/CPCSEA/2020/06).

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