

Amlodipine besylate and valsartan combined mucoadhesive buccal patch formulations: *In-vitro* release and *ex-vivo* permeation studies

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Abstract: Background: Oral fixed-dose combinations of Amlodipine Besylate and Valsartan are widely prescribed for hypertension but are associated with first-pass metabolism and variable bioavailability. Buccal drug delivery provides a favorable substitute to improve systemic availability and provide sustained release. **Objectives:** This study aimed to develop and assess mucoadhesive buccal patches containing Amlodipine Besylate and Valsartan to enhance bioavailability and achieve controlled drug release over 24 hours. **Methods:** Buccal patches were developed via the solvent-casting method using Hydroxypropyl Methylcellulose, Polyvinylpyrrolidone, Methylcellulose, Sodium Alginate and Metolose as backing membrane polymers. All the prepared films were evaluated for physicochemical parameters by means of X-ray Diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), Scanning electron microscopy (SEM) and *in vitro* and *ex vivo* drug release. *In-vitro* drug release was studied with USP Apparatus II (paddle method) in 500 ml 6.8 pH phosphate buffer at $37 \pm 0.5^\circ\text{C}$ and 50 rpm for 24 hours. *Ex vivo* permeation studies were performed using a Franz diffusion cell fitted with rabbit buccal mucosa under similar conditions. **Results:** The formulations generally exhibited acceptable physicochemical characteristics within the evaluated parameters. The developed films appeared transparent with a uniform distribution of components. FTIR analysis did not indicate any detectable incompatibility or significant interaction between the drugs and excipients under the study conditions. Among all formulations, F1 contained the highest drug release and permeation. After 24 hours, cumulative release reached 84.45% for amlodipine and 88.03% for valsartan. *Ex-vivo* permeation was 76.31% and 78.42% for amlodipine and valsartan, respectively. Furthermore, buccal films' histopathological and stability studies were found to be harmless and functioned as an efficient dosage system. **Conclusion:** The developed mucoadhesive buccal patches successfully delivered both drugs in a sustained manner. Formulation F1 showed superior release and permeation profiles, suggesting its potential as substitute to conventional oral dosage forms for improved hypertension management.

Keywords: Amlodipine; Franz diffusion cell; Mucoadhesive buccal patch; Rabbit buccal mucosa; Release kinetics; USP dissolution apparatus II; Valsartan

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INTRODUCTION

The oral route is thought to be preferable for patient administration because of better absorption and metabolism. However, numerous medications cannot be delivered effectively due to their high pre-systemic clearance and the lack of a relationship between membrane permeability and absorption (Pathak and Kumar, 2017). Mucosal layers (nasal, rectal, vaginal, ocular and oral) offer unique benefits for systemic medication delivery compared to the oral route. Advantages include the potential for hepatic bypass and increased bioavailability by avoiding pre-systemic gastrointestinal tract clearance (Akhtar *et al.*, 2012). Mucoadhesive medication delivery systems use bioadhesive polymers to localize medication to body's specific areas for a prolonged duration. This prolonged retention at the target site is especially beneficial

for enhancing both local and systemic drug bioavailability. Recent interest in mucoadhesion in pharmaceuticals features from its potential to prevent medication degradation via gastrointestinal contents and liver first-pass deactivation. Mucoadhesive drug distribution methods include various systems designed for targeted administration, such as buccal, sublingual, rectal, vaginal, ocular and nasal drug delivery systems (Krishnarajan *et al.*, 2016).

Buccal drug delivery offers an alternative to systemic drug distribution, as the buccal tissue layer has a robust blood supply that permits drug particles to move directly through the blood circulation. To exploit the availability of biological medications and minimize dose-dependent adverse effects, extensive research has recently been conducted on the targeted delivery of drugs to specific body parts. Buccal drug administration refers to the administration of medication via the buccal mucosa within

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the mouth. Because of its rich blood supply and relative permeability, the buccal mucosa serves as an effective location for drug administration (Cavallari *et al.*, 2013). Buccal mucosa is generally porous, has a robust blood supply and is a great place for drug absorption. Buccal distribution of medications offers an attractive alternative to more traditional routes of systemic drug administration (Saha and Das, 2017).

In contrast to oral delivery, which is frequently affected by liver first-pass and gastrointestinal drug degradation. Buccal administration allows drug molecules to enter the systemic circulation directly. The buccal cavity's easy accessibility for self-administration makes buccal patches safe and patient friendly drug delivery option. They may be withdrawn from the application site at any time, allowing the treatment to be stopped anytime desired. In addition, buccal patches offer greater versatility than alternative medication delivery methods (Khairnar *et al.*, 2009). Mucoadhesive polymers have generated considerable interest in recent decades for buccal drug administration because of their ability to restrict the dosage form to specific sites; they also improve drug availability in the bloodstream. In buccal medication administration, mucoadhesive polymers are used in adhesive tablets, patches and, gels. The most flexible and comfortable being patches (Saha and Das, 2017).

Amlodipine besylate (AMB) is a class IV antiarrhythmic dihydropyridine calcium channel blocker that prevents calcium ions entry into vascular smooth muscle and cardiac muscle cells. It lowers peripheral vascular resistance by relaxing vascular smooth muscle and decreases blood pressure, acting as a peripheral artery vasodilator. The medicine is absorbed orally at around 90%, but it undergoes substantial hepatic first-pass metabolism, resulting in about 20% bioavailability. This medication has a short half-life that is 2-4 hours and removed swiftly. Daily administration is necessary to maintain effective plasma levels. AMB's substantial first-pass metabolism and short half-life make it the best option for buccal delivery, which provides sustained drug distribution without pre-systemic metabolism (Marabathuni *et al.*, 2017).

A non-peptide triazole-derived angiotensin II antagonist with antihypertensive properties, valsartan (VAL) is an oral medication. According to the Biopharmaceutical Classification System (BCS), this drug is in class II. It has a high permeability and a low water solubility (3.08 µg/mL). It has a low oral bioavailability (<25%) and a high log P value (5.8). Additionally, the AUC is reduced by 40% due to its variable oral bioavailability in the presence of meals, substantial P-gp efflux and considerable hepatic first-pass metabolism. It has been proposed that the best candidates for sustained-release formulations are active compounds with biological half-lives between 2 and 8 hours (Abu-Huwaij *et al.*, 2019).

The present study aims to develop and evaluate combined controlled-release mucoadhesive buccal patches of amlodipine and valsartan for the management of hypertension. Various polymers, including Hydroxypropyl Methylcellulose, Polyvinylpyrrolidone, Methylcellulose, Sodium Alginate and Metolose, were employed as backing membrane materials. Polyethylene glycol was used as a plasticizer, while Eudragit RL100 served as the matrix-forming polymer to ensure uniform drug distribution within the patches. The prepared buccal patches were evaluated through physicochemical characterization, FTIR, SEM, XRD, in vitro drug release and ex vivo permeation studies using validated analytical methods.

MATERIAL AND METHODS

Chemicals

Amlodipine Besylate (AMB) USP was received as free sample from Aurore Life Science Pvt Ltd. Valsartan (VAL) was supplied as gift sample from Zhejiang Tianyu Pharmaceutical Co., Ltd China. HPMC (Hydroxypropyl methylcellulose), PVP (Polyvinylpyrrolidone), MC (Methyl cellulose), SA (Sodium alginate) and MET (Metolose), Eudragit RL 100, DMSO (dimethyl sulfoxide), Methanol, Ethanol, Polyethylene Glycol. All chemicals and polymers were provided by pharmaceuticals laboratory of Faculty of Pharmacy and Health Sciences of University of Balochistan.

Backing membrane's preparation

The patch backing membrane was prepared using various polymers, including HPMC (Hydroxypropyl Methylcellulose), PVP (Polyvinylpyrrolidone), MC (Methylcellulose), SA (Sodium Alginate) and MET (Metolose). A conical flask containing a 4% w/v aqueous polymer solution was continuously stirred using a hot plate stirrer at 80 °C. When solutions were turned cold, it was sonicated for about 2 minutes using a sonicator. To create films, 15mL of the solution was transferred to 61 cm² glass Petri plates and allowed to dry at room temperature for 24 hours (Yousuf *et al.*, 2013).

Matrix solution casting and preparation

The preparation variables used for each 100mL of matrix dispersion are listed in Table 1. In a 250 mL conical flask containing 100 mL of ethanol, about 5 g of Eudragit was stirred for 30 minutes by means of a magnetic stirrer at 500 rpm. Subsequently, polyethylene glycol (plasticizer) and dimethyl sulfoxide (permeation enhancer) were added and mixed further 30 min. Next, 1800 mg amlodipine (AMB) and 28800 milligrams valsartan (VAL) were combined into the solution and stirred for another 30 minutes to get a uniform dispersion. The mixture was then sonicated for about 5 minutes to eliminate trapped air bubbles. An aliquot of 10mL from the resulting matrix dispersion was transferred into Petri plates pre-lined with different polymer-based backing membranes.

Table 1: Formulation variables of buccal patches.

Formulation code	Eudragit gms	PEG gms	DMSO ml	HPMC gms	SA gms	MC gms	MET gms	PVP Gms	Ethanol ml
F1	5	0.5g	0.5	4	-	-	-	-	100
F2	5	0.5g	0.5	-	4	-	-	-	100
F3	5	0.5g	0.5	-	-	4	-	-	100
F4	5	0.5g	0.5	-	-	-	4	-	100
F5	5	0.5g	0.5	-	-	-	-	4	100

These plates were covered with upturned funnels to prevent rapid solvent vaporization and were kept dry at ambient temperature for 24 hours. After drying, patches containing a combination of antihypertensive drugs were removed, covered with aluminum foil and stored at 25 °C. A specifically made stainless steel cutter with 1.5 cm² diameter was used, to cut the dry films into circular patches. Eighteen identical patches of this size were produced in each Petri plate (Yousuf *et al.*, 2013).

Mucoadhesive buccal patches evaluation

Weight variation

Ten randomly selected patches are weighed individually and their approximate average weight is calculated. The average weight and the individual's weight shouldn't differ considerably (Reddy *et al.*, 2013).

Thickness

All prepared patch thicknesses were measured using a digital Vernier caliper and the average thickness was then calculated (Rasool and Khan, 2010).

Folding endurance

The films' folding durability is evaluated by assessing their folding capability under frequent, harsh folding conditions. It is determined by frequently folding different films at the same point until it breaks down. Folding endurance is represented as the total number of times the film can be folded at the same point without tearing (Manubolu *et al.*, 2014).

Surface pH

It was assessed to define their potential for mucosal irritation. Small beakers containing 5 ml distilled water at pH 6.8 were used; the films were permitted to swell in them. Surface pH was measured at 2, 4 and 6-hour intervals by gently applying pH paper to the swollen films' surface (Nafee *et al.*, 2003; Chen and Hwang, 1992).

Content uniformity

To assess content uniformity, a 2 × 2 cm² section of patch was dissolved in 100 ml phosphate buffer (pH 6.8) for 60 minutes by magnetic agitator. Then solution was filtered and appropriately diluted with phosphate buffer. Uniformity of content was assessed using a UV-Visible spectrophotometer at 237 nm and 250 nm, with

measurements performed in triplicate (Sadeq and Rajab, 2017).

Swelling index (SI)

The SI was determined by applying a 2 × 2 cm² patch to a pre-weighed microscope slide (W₀). The slide, along with the patch, was then placed in a Petri dish containing 50 ml of buffer solution. At regular time intervals over a period of one hour, the slide was carefully removed, surface moisture was gently blotted and the slide was reweighed (W_t). This procedure was repeated 3 times and the average reading was used for analysis.

SI calculation formula:

$$SI(\%) = \frac{W_t - W_0}{W_0} \times 100$$

W₀ = Primary weight of patch before immersion in buffer solution

W_t = Weight of the patch after immersion at the specified time interval (Viswanadhan *et al.*, 2012).

Mucoadhesive strength

A texture analyzer (Stable Micro Systems) was used to assess how well the patches adhered to mucus. For mucoadhesiveness tests, freshly cut cow buccal mucosa was cut into 2 mm-thick slices. A buffered saline solution with a pH of 6.8 was used to wet the mucosa that was connected to the top probe of the analyzer. This was done to make it look like the oral mucosa. After that, the material was firmly attached to the instrument probe. The probe moved vertically from the mucosal face at 0.5 mm/s to separate the specimen and mucosal interfaces, after being lowered at 0.5 mm/s and applying 0.5 N for 120 s to make contact with the mucosa. We figured out F_{max}, which is the most forceful way to separate. Three replicates of each. Three duplicates of each experiment were done (Perveen *et al.*, 2026).

Fourier transform infrared spectroscopy

To assess possible interactions among the excipients and active substances used, FTIR analysis was performed. The Bruker Alpha II (Compact series, Fremont, CA, USA) equipment was utilized in the 500–4000 cm⁻¹ wavelength range (Rashid *et al.*, 2022).

Scanning electron microscopy

It was conducted to observe surface characteristics, shape and internal structure of the patches, as well as to estimate particle size. For SEM imaging, on a metal stub the patches

were fixed by means of double-sided adhesive tape. The patches were dried in a vacuum chamber and a 10 nm-thick layer of gold was sputter-coated to ensure conductivity. The coated patches were subsequently detected underneath high-resolution SEM (JSM-840, JEOL Instruments, Tokyo, Japan) (Panahandeh *et al.*, 2024).

X-ray powder diffraction

It is a rapid analytical procedure commonly used to identify crystalline modifications that may occur during patch formulation. In this study, XRD analysis was carried out on the prepared patches containing amlodipine and valsartan, as well as on the blank formulation. The diffractograms were recorded over a 2θ range of 5° to 50° to assess blank and drug-loaded patches amorphous and crystalline nature. This analysis helped to determine any changes in crystallinity resulting from the creation procedure (Vamshi Vishnu *et al.*, 2007).

Analytical method development and validation

UV-Visible spectrophotometer conditions for the analysis and quantification of (AMB) and (VAL) were assessed using a Shimadzu UV-1601 (Japan) at 237nm and 250nm, respectively, to determine drug release via concentration. The average of three determinations was reported.

Preparation of working solutions

About 10 mg AMB and VAL in 100 mL 6.8 pH phosphate buffer as stock solution was made for linearity investigations. Concentrated solutions of 10, 15, 20, 25, 30 and 35 $\mu\text{g/mL}$ in phosphate buffer were prepared from the stock solution. For each concentration, three identical samples were prepared. For AMP and VAL, the calibration curve's equation and correlation coefficient were determined. Different concentrations of the solution (10, 15, 20, 25, 30 and 35 $\mu\text{g/mL}$) were prepared and a calibration curve was generated.

Method validation

The UV-Visible spectrophotometer technique was validated for accuracy, stability, linearity, repeatability, specificity and reproducibility in aqueous solution in accord with the International Council for Harmonization Guidelines. For precision and reproducibility studies, three samples at 15, 20 and 25 $\mu\text{g/mL}$ were prepared. Using replicates, the 15 $\mu\text{g/mL}$ concentration solution of AMB and VAL in phosphate buffer was assessed for repeatability and stability. At 0, 24 and 48 h the solutions were examined.

In-vitro release study

To determine *in-vitro* release from patches, the USP dissolution equipment (PT-DT7 Pharma Test, Germany) was rotated at 50 rpm and retained at $37 \pm 0.5^\circ\text{C}$ temperature. Using clips and stainless steel mesh, the 1.5 cm² patch having 10 mg AMB and 160 mg VAL was held in place against the watch glass. Both antihypertensive active ingredients (AMB and VAL) are less water soluble. Afterward, the disk was positioned at the bottom of the

dissolution vessel containing 500mL of dissolution medium (pH 6.8 phosphate buffer). To preserve sink conditions, a 5 mL sample was removed at programmed time intervals (0.5, 1, 2, 3, 4, 5, 6, 12 and 24 hours) and exchanged with fresh buffer of equivalent volume. Taken out samples were filtered, appropriately diluted with phosphate buffer. A UV-Visible spectrophotometer at 237nm and 250nm was used to determine drug release by measuring concentration. The average of three determinations was reported (Khan *et al.*, 2024; Samanthula *et al.*, 2021).

Ex-vivo permeation studies

Buccal mucosa of rabbit preparation

Rabbit cheek pouch was obtained from the abattoir within 2h of rabbit death and immediately transported in phosphate buffer to the laboratory. In distilled water, the tissue was soaked, then in isotonic buffer (pH 6.8) for about 2 min at $37 \pm 1^\circ\text{C}$. After 2 min, the buccal mucosa was detached from the tissue's full thickness. Using a scalpel, fatty layers were trimmed away and from the underlying tissue, the buccal mucosa was isolated. Lastly, mucosa was washed away using isotonic phosphate buffer (Adhikari *et al.*, 2010).

Ex-vivo permeation studies

These studies were conducted via Franz diffusion cell and prepared rabbit buccal mucosa. The receptor compartment was filled with 20mL of phosphate buffer (pH 7.4) as the medium and a tiny magnetic bead. A $2 \times 2 \text{ cm}^2$ measurement mucoadhesive buccal patch was kept above buccal mucosal membrane of rabbit and fixed amongst both compartment. Entire assembly was positioned on magnetic stirrer with maintained temperature that is $37 \pm 0.5^\circ\text{C}$ at 50 rpm. About 0.5 mL of sample was taken from the receptor compartment at regular time intervals of 15 min, 30 min, 45 min, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h and 24 h and replaced with an equal volume of fresh medium. An appropriate dilution was prepared and *ex-vivo* permeation studies were evaluated spectroscopically at 237 nm and 250 nm using UV-visible spectroscopy (Shimadzu UV-1601, Japan). The quantity of drug permeated was then determined (Haju and Yadav, 2021).

Kinetic modeling of in-vitro diffusion data

The extent of Amlodipine and Valsartan released during the *in-vitro* diffusion studies was quantified and linear regression analysis was applied to evaluate drug release kinetics for all preparations. Numerous kinetic models were utilized to define membrane release behavior, comprising zero-order, first-order, Korsmeyer-Peppas, Hixon Crowell and Higuchi models. For each preparation, the correlation coefficient (R^2) was determined for the best-fitting kinetic model, which defines the drug release mechanism. The highest R^2 significance model was considered most appropriate for characterizing the release profile. The following kinetic equations were applied for analysis (Gul *et al.*, 2017; Gul *et al.*, 2019).

1. Zero-order model

$$A = K_0t + A_0 \quad \text{Eq. (1)}$$

2. First-order model

$$\log A = Kt/2.303 + \log A_0 \quad \text{Eq. (2)}$$

3. Higuchi-diffusion model

$$Q = K_h t^{1/2} \quad \text{Eq. (3)}$$

4. Korsmeyer-Peppas model

$$Ct/C_\infty = Kt^n \quad \text{Eq. (4)}$$

5. Hixson-Crowell diffusion release model

$$Q_t/Q = Kt^n \quad \text{Eq. (5)}$$

Histopathological buccal mucosa's evaluation

Buccal mucosa's histopathological assessment was conducted to describe whether the film during the *ex-vivo* drug penetration testing affected any cellular damage. For the analysis, buccal mucosa that had previously been used for *ex vivo* analysis was collected and linked to mucosa treated in phosphate buffer (pH 6.8). To fix the tissue on a glass slide 10% buffered formalin was used. Hematoxylin and eosin were used to stain paraffin sections cut onto glass slides. A pathologist who was unaware of the study examined these sections under a light microscope to detect tissue damage during *ex vivo* drug penetration (Ammanage et al., 2020).

Stability studies

To detect the stability of the developed films, were placed in a stability chamber. For three months, films were kept at 40 °C and 75% ±5% relative humidity (RH) and 30 °C and 65% ±5% RH. Films were evaluated for color, folding endurance, drug concentration and *in vitro* drug release after 3 months (Ammanage et al., 2020).

Statistical analysis

The *In-vitro* results were statistically analyzed using DD Solver (Microsoft Excel 2007). ANOVA computations were performed using SPSS (version 18.0, IBM, USA). The kinetic model was used to analyze all formulation data (Gul et al., 2017; Gul et al., 2019).

RESULTS**Visual evaluation**

The core aim of the recent research efforts was to formulate and evaluate novel buccal patches of antihypertensive drugs comprising a mucoadhesive polymeric layer, such as sodium alginate, HPMC, PVP, MC and MET. Films of HPMC, PVP and MET were transparent, constant and peel easily from petri plates. However, SA and MC patches were not completely transparent due to air bubbles present throughout air drying and were not peeled easily. Additionally, HPMC and, MET films showed extreme flexibility. The main purpose of the plasticizer is to overcome the films' brittleness and provide elasticity.

The physical and visual evaluation of patches (Table 2). Specifies that the weight variation varied among 0.056±0.087g (F4) and 0.097±0.033 g (F1). The thickness varied among 0.43±0.01 mm to 0.85±0.05 mm, F1 is the thinnest where as F4 is the thickest being formulation. Swelling Index ranges from 75.963±0.44 (F4) to 97.432±0.90 (F5). Folding endurance was manually calculated. F1 (166±0.34) revealed maximum folding endurance and F3 (134.9±0.79) revealed lowest. The flexibility of these formulated buccal patches was ensured through range of folding endurance study. Surface pH 6.39±0.29 F2 to 6.6±0.15 F1. Amlodipine drug content (%) in entire preparations varied amongst the range 97.56±0.11% (F4) and 99.32±0.09% (F1). Valsartan drug content % age in entire preparations varied amongst the range 96.98±0.20% (F3) and 99.80±0.08% (F2). This specifies that the drug spread homogeneously all through the polymeric film.

Mucoadhesive strength

We measured the force needed to pull the buccal patches away from the buccal mucosa to see how well they stuck to the mucosa *in-vitro*. The results that were gathered are shown in table 3. The mucoadhesive strength of the F1 to F5 formulations was 49±2.13 ×10⁻³ N, 50±2.43×10⁻³ N, 51±2.33×10⁻³ N, 54±3.13×10⁻³ N and 56±2.43×10⁻³ N.

Scanning electron microscopy

Fig. 1 shows cross-sectional SEM microphotographs of buccal patches containing amlodipine and valsartan. These microphotographs show how efficiently mucoadhesive materials, such as HPMC, MC, PVP, SA and MET, were laminated onto the drug's polymer backing layer. This proves that drug-containing mucoadhesive layer and backing membrane's adhesive layer are perfectly bound.

FTIR analysis

The FTIR spectrum of the pure drug revealed characteristic peaks at 1203.58 cm⁻¹, 1182.36 cm⁻¹, 3417.86 cm⁻¹, 2962.66 cm⁻¹ and 1739.79 cm⁻¹, 1604.77 cm⁻¹. The spectra of the polymer formulations (HPMC, MC, MET PVP and SA with co-loaded drugs) showed similar characteristic peaks with slight shifts and slight disappearance of major peaks, indicating minor chemical interaction between the drug and the polymers and confirming compatibility, as shown in fig. 2.

X-ray powder diffraction

Crystalline-amorphous characteristics of preliminary compounds and the films was observed by mean of XRD. Usually, amorphous compounds have broad peaks comparatively to crystalline compounds have sharp peaks. For different preliminary materials and produced films, the crystalline: amorphous ratios can also be determined by XRD. Fig. 3. Demonstrate pure XRD diffractograms.

Table 2: Thickness, weight variation, swelling index and folding endurance and % drug content of amlodipine and valsartan of F1-F5.

Formulation code	Weight variation (g) $\pm$ SD	Thickness (mm) $\pm$ SD	Swelling index $\pm$ SD	Folding durability $\pm$ SD	Surface pH $\pm$ SD	% Drug content of amlodipine	%Drug content of valsartan
F1	0.097 $\pm$ 0.033	0.43 $\pm$ 0.01	94.390 $\pm$ 0.04	166.0 $\pm$ 0.34	6.6 $\pm$ 0.15	99.32% $\pm$ 0.09	97.98% $\pm$ 0.12
F2	0.087 $\pm$ 0.074	0.54 $\pm$ 0.02	86.348 $\pm$ 0.33	154.6 $\pm$ 0.83	6.39 $\pm$ 0.29	98.22% $\pm$ 0.10	99.80% $\pm$ 0.08
F3	0.077 $\pm$ 0.054	0.45 $\pm$ 0.07	94.188 $\pm$ 0.41	134.9 $\pm$ 0.79	6.42 $\pm$ 0.30	98.13% $\pm$ 0.08	96.98% $\pm$ 0.20
F4	0.056 $\pm$ 0.087	0.85 $\pm$ 0.05	75.963 $\pm$ 0.44	145.5 $\pm$ 0.71	6.48 $\pm$ 0.30	97.56% $\pm$ 0.11	99.00% $\pm$ 0.11
F5	0.090 $\pm$ 0.022	0.64 $\pm$ 0.03	97.432 $\pm$ 0.90	135.2 $\pm$ 0.65	6.47 $\pm$ 0.36	97.88% $\pm$ 0.12	98.12% $\pm$ 0.18

Table 3: Mucoadhesive strength of the formulations F1 to F5

Formulation code	Mucoadhesive strength, Fmax(10-3 N)
F1	49 $\pm$ 2.13
F2	50 $\pm$ 2.43
F3	51 $\pm$ 2.33
F4	54 $\pm$ 3.13
F5	56 $\pm$ 2.43

XRD diffractograms for pure amlodipine and valsartan, HPMC (Hydroxy propyl methylcellulose), MC (Methylcellulose), MET (Metolose), PVP (Polyvinyl pyrrolidone) and SA (Sodium alginate) with Co-loaded drugs). Fig. 2 presents the diffractogram of the blank plasticized films, which exhibit broad peaks characteristic of amorphous materials—similar to what was observed in the pure polymers. The diffractograms of pure AMB, Valsartan and the drug-loaded film are also shown. Notably, the drug-loaded film displays an amorphous pattern, suggesting that the drug may be molecularly distributed within the film matrix. While these findings are promising, it is well established that amorphous forms are generally thermodynamically unstable and tend to recrystallize over time.

Analytical method's development and validation

AMB and VAL within the definite concentration range of 10–35 μ g/mL showed linearity calibration curve. The calibration curve equation was $y = 274.78x$ and $R^2 = 0.9999$ and $y = 255.18x$ and $R^2 = 0.9998$ (Fig. 4A&B). AMB and VAL at three given concentrations (15, 20 and 25 μ g/mL) revealed adequate recovery of AMB and VAL. The mean recovery of AMB was 101.58%, 100.78% and 99.86%, while that of VAL was 101.13%, 100.31% and 99.56%, respectively (Table 4). In accordance with ICH guidelines, the technique was thus deemed precise. According to Table 5, the precision study outcomes were suitable and appropriate for the ICH guideline. After 48 hours, in the stability study, there was no discernible drop in the amount of the active ingredient, as shown in table 6.

In-vitro release study

This study conducted by means of dissolution apparatus type 2. Fig. 5 A, Fig. 5 B. Revealed *in-vitro* drug release design of finished AMB and VAL patches for buccal use. During 24 hours' period these buccal patches gradually drug released which show controlled and constant released help in regulate drug diffusion and maintains therapeutic level constant over extended period of time. Drug release in different rates depending on nature and composition of polymer form buccal patches. More hydrophilic in nature the polymers show high drug release from buccal patches. Among all formulations of AMB and VAL, formulation no. F1. Statistically, it was observed that the membranes have good released. F1 shows highest *In-vitro* drug release ($84.45 \pm 1.10\%$) and ($88.03 \pm 0.01\%$), while formulation no. F5 show lowest *In-vitro* drug release ($75.31 \pm 0.51\%$) and ($73.2 \pm 1.08\%$) during 24 hours' period respectively.

The results of curve fitting to numerous kinetic models comprising zero-order, first-order, Korsmeyer–Peppas, Hixon Crowell and Higuchi revealed underlying medication release mechanisms from the formulated buccal patches of AMB and VAL. The curve results fitting into various kinetics models revealed the release mechanisms from the formulated AMB and VAL buccal patches, as summarized in table 7. While rate of AMB and VAL release and their particular correlation coefficients were linked, it was originating to follow first-order release kinetics for AMB ($R^2=0.9859$ and 0.9944) and VAL ($R^2=0.9948$ and 0.9774)

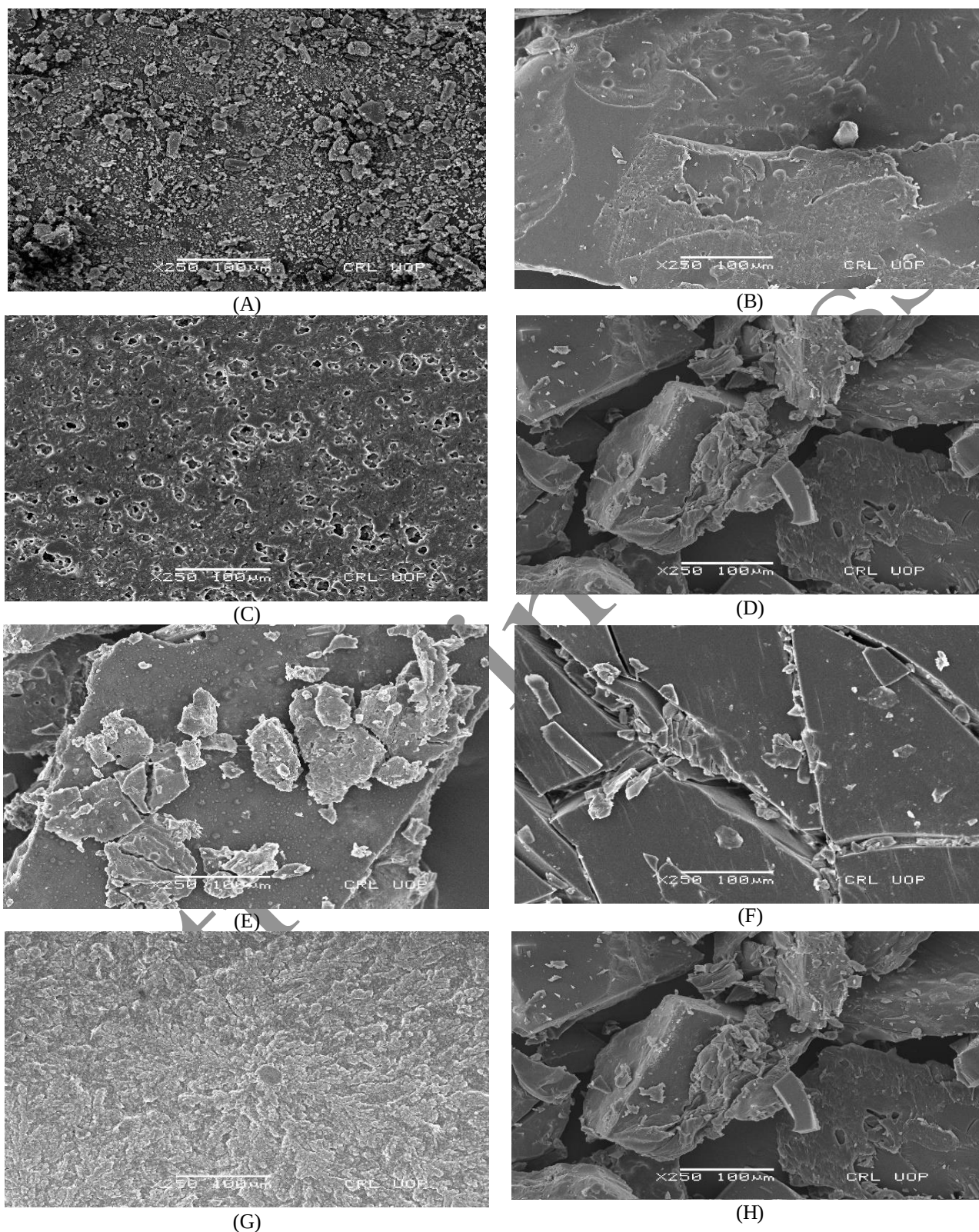


Fig. 1: Scanning electron microscope images of various combine Amlodopine and Valsartan containing buccal patches (a) Pure Drug (AMB); (b) HPMC-B (Hydroxypropylmethylcellulose Blank); (c) HPMC-I (Hydroxypropylmethylcellulose) (VAL); (d) MCE-I (Methylcellulose); (e) MT-I (Metolose); (f) PVP-I (Polyvinyl propylene); (g) SA-BI (Sodium alginate Blank); (h) SA-I (Sodium alginate with (AMB+VAL)).

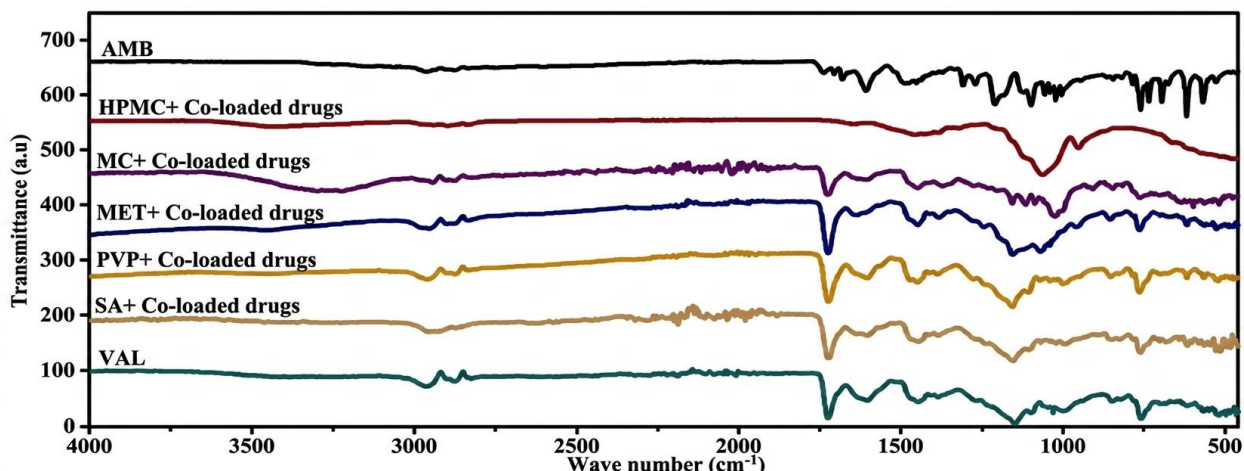


Fig. 2: FTIR spectra of AMB (black) VAL (green), HPMC (red), MC (Purple), MET (dark blue), PVP (light blue), S SA (brown).

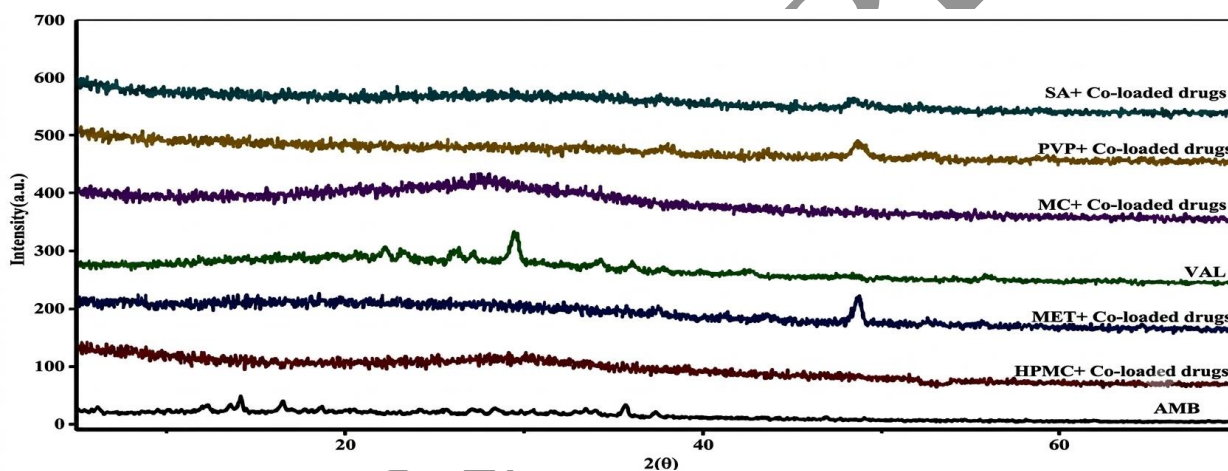


Fig. 3: XRD diffractograms for AMB (black) VAL (green), HPMC (red), MC (purple), MET (dark blue), PVP (brown) SA (light blue)

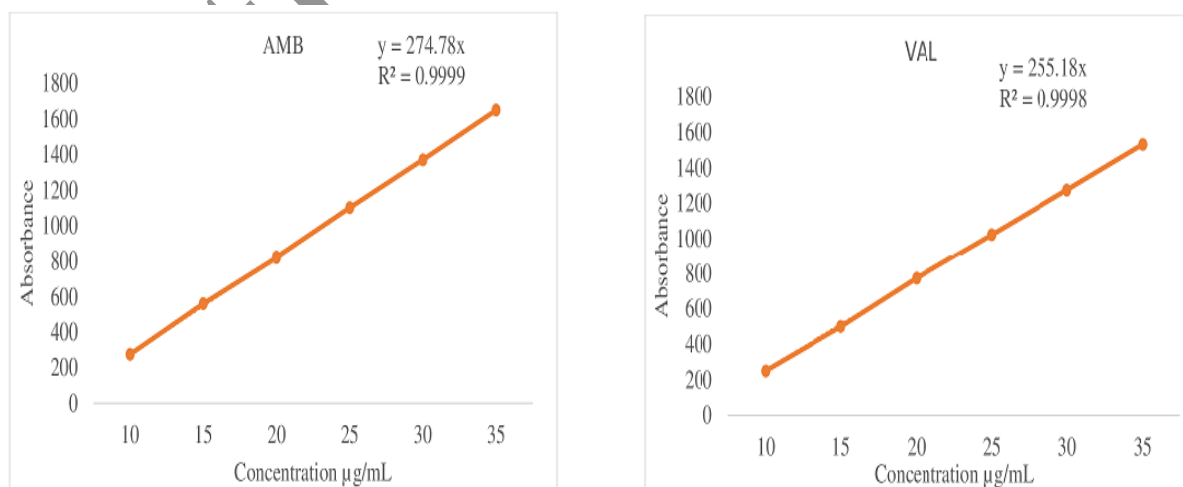


Fig. 4: Calibration curve (A) Amlodipine; (B) Valsartan in phosphate buffer solution

Table 4: Accuracy study results (AMB and VAL in Phosphate Buffer), (n = 3)

Concentration	Sample	Area (AU)	Amount recovered (µg/mL)	Recovery%
15 µg/mL	1	552.13	13.21	101.22
	2	551.23	13.10	101.01
	3	553.22	13.11	101.38
	Average	521.193	13.14	101.58
	SD	0.999	0.06	0.22
	RSD %	0.180	0.463	0.22
20 µg/mL	1	725.11	18.22	100.21
	2	721.23	18.11	100.71
	3	724.10	18.31	100.31
	Average	723.48	18.21	100.78
	SD	2.01	0.10	0.06
	RSD %	0.27	0.55	0.06
25 µg /mL	1	924.87	21.91	99.61
	2	921.21	22.22	99.77
	3	923.22	22.72	99.21
	Average	923.10	22.28	99.86
	SD	1.83	0.40	0.09
	RSD %	0.19	1.83	0.09
15 µg/mL	1	550.12	13.11	101.11
	2	551.00	13.01	101.00
	3	550.91	13.13	101.30
	Average	550.67	13.08	101.13
	SD	0.484	0.06	0.15
	RSD %	0.088	0.49	0.15
20 µg/mL	1	721.10	18.11	100.11
	2	720.11	18.10	100.61
	3	721.10	18.21	100.21
	Average	720.77	18.14	100.31
	SD	0.57	0.06	0.26
	RSD %	0.079	0.35	0.26
25 µg /mL	1	924.10	21.11	99.67
	2	923.91	20.90	99.79
	3	923.11	21.23	99.23
	Average	923.70	21.04	99.56
	SD	0.52	0.12	0.29
	RSD %	0.05	0.65	0.29

AU: arbitrary units; RSD: relative standard deviation.

Table 5: Precision Study Results (15 µg/mL AMB and VAL in Phosphate Buffer), n = 6

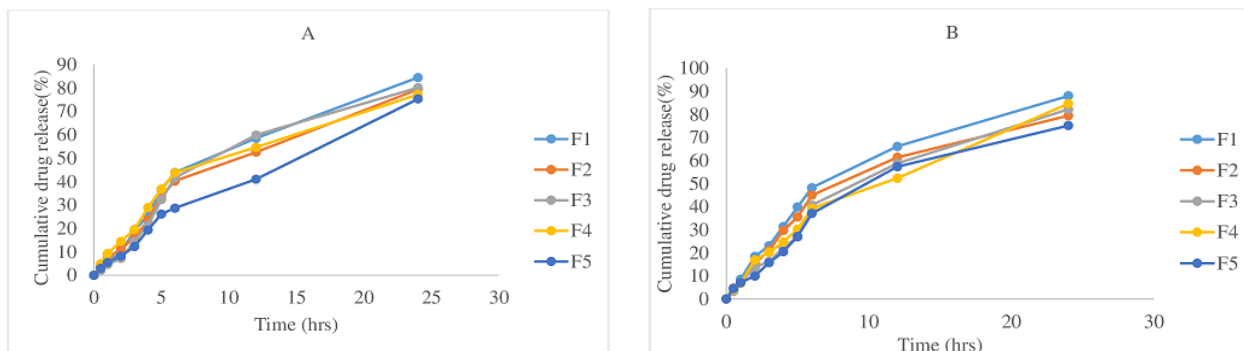
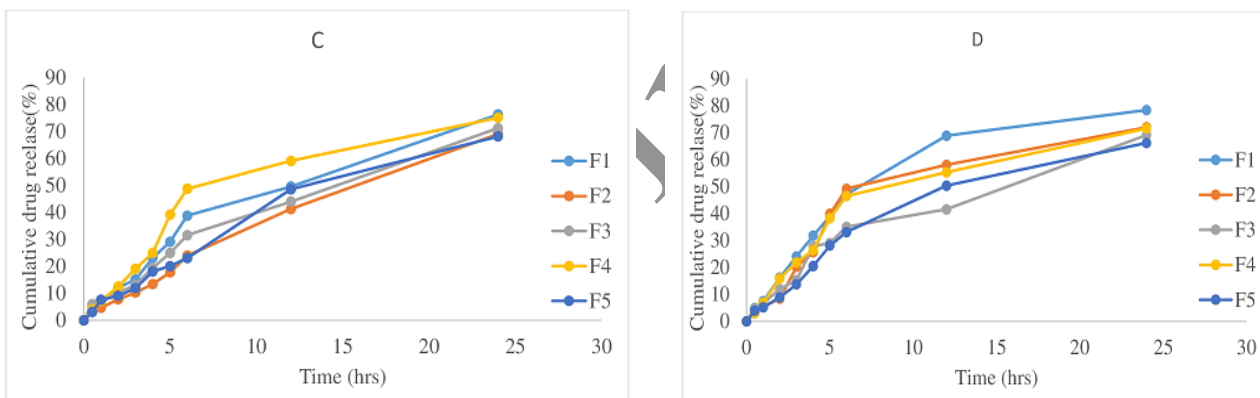
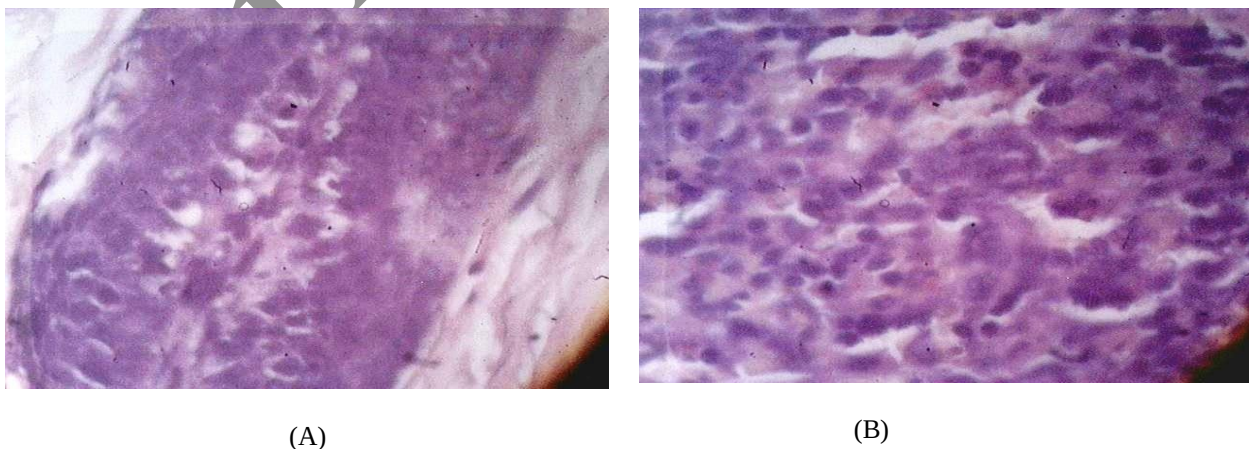
Sample	Area (AU)	Mean area (AU)	RSD %
1	550.12	5501.083	0.116
2	551.20		
3	551.11		
4	550.12		
5	551.10		
6	550.88		
1	550.12	550.53	0.474
2	551.00		
3	550.90		
4	550.11		
5	551.00		
6	550.08		

AU: arbitrary units; RSD: relative standard deviation.

Table 6: Stability study results (15 µg/mL AMB and VAL in Phosphate Buffer)

Time	Area (AU)	Concentration (ug/mL)
0.0h	551.21	15.21
24.0h	552.13	14.77
48.0h	549.99	14.9

AU: arbitrary units


Fig. 5A: In-vitro release of Amlodipine (A) and Valsartan (B) from buccal patch via dissolution apparatus.

Fig. 6: In-vitro release of Amlodipine (A) and Valsartan (B) from buccal patch via franz diffusion cell

Fig. 7: Histopathological images of (A) normal mucosa (B) Mucosa exposed to formulation

Ex-vivo permeation studies

Drug-permeation study outcomes from a mucoadhesive buccal patch with a backing layer showed one-way release of AMP and VAL, indicating that the drugs were successfully released from the patch and passed through the rabbit buccal mucosa. This indicates that the drugs may also permeate the human buccal membrane. The outcome indicated that drug penetration was slow and stable across the preparations; F1 exhibited the highest release, reaching $76.31 \pm 1.28\%$, while F5 showed the lowest release at $68.21 \pm 1.08\%$ over the same period. In comparison, the VAL formulation demonstrated a slightly higher maximum release of $78.42 \pm 1.30\%$, with the lowest recorded permeate release of $66.21 \pm 1.10\%$ through the buccal membrane from the improved preparation in 24 h. The P-Value was less than (0.05) which is the considerable limit. The cumulative % age distribution of AMB and VAL that had entered via the buccal epithelium from the buccal patch is shown in Fig. 6 (A) and Fig. 6 (B).

Histopathological study

Fig. 7 presents the achieved histological pictures of the buccal mucosa. Examinations of collective segments revealed the buccal mucosal membrane's typical structure. In contrast to tissue immersed in phosphate buffer at pH 6.8, the buccal mucosal tissue exposed to the formulation for 8 hours was found to be unharmed and showed no adverse effects. Consequently, it appears that the buccal film of AMB+ VAL is safe to provide the formulation through the buccal mucosa.

Stability studies

The formulations were stored for three months at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ relative humidity. After eight hours, their folding endurance, drug content and percent drug release were measured. After three months of storage, the characteristics of F1 to F5 had barely changed, as Table 8 demonstrates.

DISCUSSION

The present study aimed to develop and evaluate mucoadhesive buccal patches containing a combination of Amlodipine besylate and Valsartan to overcome the limitations of conventional oral administration, particularly extensive first-pass metabolism and variable bioavailability. Buccal drug delivery systems have attracted considerable attention in recent years due to their ability to deliver drugs directly into systemic circulation through the highly vascularized buccal mucosa, thereby bypassing hepatic first-pass metabolism and improving therapeutic efficacy (Patel *et al.*, 2021). In addition, mucoadhesive polymers play an essential role in prolonging the residence time of dosage forms at the site of absorption, thereby enhancing drug bioavailability and prolonging therapeutic action (Boddupalli *et al.*, 2020). In this study, mucoadhesive buccal patches were successfully prepared using the solvent-casting method

with different hydrophilic polymers, including HPMC, PVP, MC, sodium alginate and Metolose. The prepared films exhibited satisfactory physicochemical characteristics, including uniform thickness, acceptable weight variation and adequate folding endurance. These results are consistent with previous reports demonstrating that the solvent-casting technique is an effective method for producing uniform, flexible buccal films with homogeneous drug distribution (Kumar *et al.*, 2022). The use of polyethylene glycol as a plasticizer enhanced film flexibility and reduced brittleness, which is in agreement with earlier findings that plasticizers improve the mechanical strength and elasticity of polymeric films (Desai *et al.*, 2020).

The surface pH of the prepared buccal patches ranged between 6.3 and 6.6, which is close to the physiological pH of buccal mucosa. Maintaining an appropriate surface pH is important to prevent irritation or discomfort at the application site. Similar pH ranges have been reported in recent buccal drug-delivery studies, confirming the suitability of these formulations for mucosal administration (Singh and Sharma, 2021). Moreover, the drug content uniformity, ranging from 97% to 99%, confirmed that both Amlodipine and Valsartan were uniformly dispersed within the polymer matrix, indicating efficient mixing during the formulation process. The Mucoadhesive strength ranged from $49 \pm 2.13 \times 10^{-3} \text{ N}$ to $56 \pm 2.43 \times 10^{-3} \text{ N}$, also reported as almost the same by Perveen *et al.* (2026).

FTIR spectra of pure amlodipine and valsartan exhibited characteristic absorption bands consistent with recent literature reports. Amlodipine typically shows prominent peaks corresponding to N–H stretching ($\sim 3300\text{--}3400 \text{ cm}^{-1}$), aromatic C–H stretching ($\sim 2950 \text{ cm}^{-1}$) and C=O stretching ($\sim 1670\text{--}1690 \text{ cm}^{-1}$), while valsartan exhibits characteristic bands at O–H stretching ($\sim 3400 \text{ cm}^{-1}$), C=O stretching ($\sim 1730 \text{ cm}^{-1}$) and C=N stretching ($\sim 1600\text{--}1610 \text{ cm}^{-1}$) (Bhyan *et al.*, 2011; Patil *et al.*, 2015). In the present study, these characteristic peaks were retained in the optimized buccal patch formulations containing HPMC, PVP, MC, MET and SA, with only minor shifts and intensity variations, indicating hydrogen bonding and physical interactions without chemical incompatibility. No new peaks or disappearance of major functional groups were observed, confirming the stability of both drugs within the polymeric matrix. Compatibility between drugs and excipients was confirmed through FTIR analysis (Reddy *et al.*, 2023).

The XRD diffractograms of pure amlodipine and valsartan exhibited distinct sharp diffraction peaks, confirming their crystalline nature. Characteristic diffraction peaks of amlodipine have been reported at 2θ values around 8.5° , 11.8° , 16.8° , 19.0° and 23.5° , whereas valsartan exhibits prominent peaks at approximately 10.5° , 13.8° , 20.3° and 22.4° (Prieto *et al.*, 2021; Chavhan *et al.*, 2013).

Table 7: Results of *in-vitro* drug release kinetics.

Kinetic model		Drug released in USP dissolution apparatus after 24Hrs of Amlodipine				
		F1	F2	F3	F4	F5
Zero-order	R2	0.8449	0.8534	0.8644	0.7460	0.9499
First-order	R2	0.9859	0.9844	0.9784	0.9698	0.9856
Higuchi	R2	0.9231	0.9318	0.8907	0.9573	0.8915
Korse Meyers- Peppas	R2	0.9663	0.9748	0.9516	0.9705	0.9894
Hixon crowell	R2	0.9754	0.9689	0.9709	0.9338	0.9863
Kinetic model		Drug released in USP dissolution apparatus after 24Hrs of Valsartan				
		F1	F2	F3	F4	F5
Zero-order	R2	0.7685	0.7561	0.8823	0.8786	0.8651
First-order	R2	0.9948	0.9851	0.9901	0.9887	0.9880
Higuchi	R2	0.9556	0.9515	0.9189	0.9447	0.9174
Korse Meyers- Peppas	R2	0.9732	0.9676	0.9762	0.9912	0.9695
Hixon crowell	R2	0.9798	0.9562	0.9846	0.9802	0.9741
Kinetic model		Drug released in Franz Cell apparatus after 24Hrs of Amlodipine				
		F1	F2	F3	F4	F5
Zero-order	R2	0.8653	0.9785	0.9067	0.7078	0.9347
First-Order	R2	0.9944	0.9923	0.9880	0.9523	0.9909
Higuchi	R2	0.9320	0.8613	0.9276	0.9205	0.8932
Korse Myeres- Peppas	R2	0.9786	0.9952	0.9901	0.9328	0.9836
Hixon Crowell	R2	0.9682	0.9973	0.9768	0.9146	0.9863
Kinetic model		Drug released in Franz Cell apparatus after 24Hrs of Valsartan				
		F1	F2	F3	F4	F5
Zero-Order	R2	0.6772	0.6812	0.8012	0.6631	0.8399
First-Order	R2	0.9774	0.9300	0.9472	0.9379	0.9758
Higuchi	R2	0.9401	0.8967	0.9481	0.9393	0.9255
Korse Meyers-Peppas	R2	0.9468	0.9079	0.9720	0.9442	0.9671
Hixon	R2	0.9444	0.8872	0.9163	0.8857	0.9500

Note: Best Fitting Model in all First order

Table 8: Stability profiling of films (Films Stability Describing at different storage conditions)

40°C and 75% RH after 1st month			
Color	Drug content	<i>In-vitro</i> drug release	Folding endurance
No change	99.12 % ± 0.19	86.03±0.01	147.5 ± 0.71
40°C and 75% RH after 3rd month			
No change	98.32 % ± 0.01	85.03±0.21	143.5 ± 0.41
30°C and 65% RH at the end of 1st month			
No change	99.22 % ± 0.29	88.33±0.11	147.7 ± 0.31
30°C and 65% RH after 3rd month			
No change	98.72 % ± 0.19	87.03±0.01	144.5 ± 0.41

Furthermore, X-ray diffraction analysis indicated that the drug-loaded films exhibited an amorphous pattern, unlike the crystalline structures of the pure drugs, suggesting that the drugs were molecularly dispersed within the polymer matrix. This amorphous dispersion may enhance drug dissolution and diffusion from the film (Ali *et al.*, 2022).

Scanning electron microscopy images demonstrated smooth and uniform surfaces with proper lamination between the drug-containing layer and the backing membrane. The absence of visible drug crystals indicates homogeneous distribution of the drugs within the

polymeric matrix, which is essential for consistent and controlled drug release.

In-vitro drug release studies demonstrated sustained release of both drugs from the buccal patches over a 24-hour period. The drug release profile varied depending on the polymer used in the formulation. Among all formulations, F1 containing HPMC exhibited the highest drug release, reaching 84.45% for Amlodipine and 88.03% for Valsartan after 24 hours. The higher release observed with HPMC may be attributed to its hydrophilic nature, which promotes swelling and formation of a gel layer that facilitates drug diffusion. Similar findings have been

reported in recent buccal patch formulations where hydrophilic polymers improved drug release behavior (Ahmed *et al.*, 2024). Drug release kinetics analysis revealed that the release pattern followed predominantly first-order kinetics, indicating that the release rate depended on the drug concentration remaining in the matrix.

Ex vivo permeation studies using rabbit buccal mucosa confirmed that both drugs permeated effectively through the mucosal membrane. The optimized formulation (F1) showed the highest permeation values, with 76.31% for Amlodipine and 78.42% for Valsartan over 24 hours. The enhanced permeation may be attributed to the presence of dimethyl sulfoxide (DMSO), which acts as a permeation enhancer by altering the lipid structure of the mucosal membrane and facilitating drug diffusion (Khan *et al.*, 2023). Similar improvements in permeation have been reported in mucoadhesive buccal drug delivery systems incorporating permeation enhancers (Rahman *et al.*, 2021).

Histopathological evaluation indicated that the buccal mucosa exposed to the formulation maintained normal tissue architecture, with no evidence of cellular damage or irritation. These findings confirm the safety and biocompatibility of the developed formulation. In addition, stability studies performed under accelerated conditions showed minimal changes in drug content, folding endurance and drug release profile over three months, demonstrating good stability of the prepared buccal films.

Overall, the findings of this study suggest that mucoadhesive buccal patches containing Amlodipine and Valsartan provide sustained drug release and effective permeation through buccal mucosa. Such a drug delivery system may enhance systemic availability, reduce dosing frequency and improve patient compliance by bypassing hepatic first-pass metabolism. Therefore, the developed buccal patches represent a promising alternative to conventional oral dosage forms for improved management of hypertension.

CONCLUSION

Buccal patches containing Amlodipine and Valsartan were successfully formulated using PEG as a plasticizing agent. DMSO as a permeation enhancer, by means of polymers like sodium alginate, HPMC, PVP, MC and MET in the same quantities, showed suitable physio-mechanical and mucoadhesive features. It was found to significantly enhance the penetration of both drugs across the membrane, especially with the HPMC polymer, which showed high release. Furthermore, the formulated buccal patches demonstrated a high *in-vitro* drug release rate. It can be determined that buccal patches of Amlodipine and Valsartan may deliver controlled and constant buccal delivery for extended periods in hypertension

management, which can be a good way to bypass the broad hepatic first-pass metabolism.

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Authors' contributions

Nosheen Anwar: Conceptualization, methodology, investigation, writing original draft; Rahman Gul: Project administration, supervision, writing review and editing; Syed Umer Jan: Investigation, data curation, writing; Ghulam Razaque Shahwani: Data analysis, Asif Mahmood: manuscript writing and revision., Tehmina Rabbani, Ahmed Abdullah, Seemab Naz and Falsafa Jamal edited and refined the manuscript, focusing on critical intellectual contributions and made significant contributions to date interpretation and manuscript preparation.

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Data availability statement

All data generated and analyzed during this research study are included in this article

Ethical approval

The study was approved by the ethical committee of Faculty of Pharmacy and Health Sciences, University of Balochistan (UOB), Quetta, Pakistan (Reference No. FoP & HS/ICE/214/20). This study was performed in adherence with the ARRIVE guidelines. See supplementary file for the ARRIVE checklist.

Conflict of interest

The Authors state that they have no conflict of interest.

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