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Original Research Article

Formulation and evaluation of floating cum mucoadhesive fast dissolving film with Ramipril

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Abstract: Ramipril, an angiotensin-converting enzyme inhibitor widely used for the management of hypertension and cardiovascular disorders, exhibits low oral bioavailability due to extensive first-pass metabolism. The present study aimed to develop and optimize a floating cum mucoadhesive fast-dissolving buccal film of ramipril to enhance transmucosal delivery, improve bioavailability, and increase patient compliance. A natural biomaterial, marigold pectic polysaccharide, was isolated and characterized for its mucoadhesive properties and employed as a key polymeric component. Preformulation studies confirmed the physicochemical stability of ramipril and its compatibility with selected polymers. Buccal films were prepared by the solvent casting method using marigold pectic polysaccharide in combination with HPMC E15 and PVP K30, while citric acid–sodium bicarbonate was incorporated to impart floating characteristics and Tween-80 was used as a permeation enhancer. The developed films were evaluated for physicochemical parameters, mechanical properties, disintegration time, drug content uniformity, and in-vitro drug release. Among the formulations, F5 demonstrated optimal characteristics, including rapid disintegration, good mechanical strength, and uniform drug content (97.59 ± 0.53%). Ex-vivo studies using rabbit buccal mucosa revealed superior mucoadhesive strength, prolonged residence time, and enhanced ramipril permeation for F5, indicating effective transmucosal delivery and potential bypass of hepatic first-pass metabolism. Accelerated stability studies conducted at 40 ± 0.5 °C and 75 ± 5% RH for six months showed negligible changes in drug content and disintegration time, confirming formulation stability. In conclusion, the study demonstrates that marigold pectic polysaccharide-based mucoadhesive buccal films represent a promising alternative delivery system for ramipril with improved therapeutic potential.

Keywords: Ramipril; Mucoadhesive buccal film; Marigold pectic polysaccharide; Transmucosal drug delivery; Ex-vivo permeation; Stability studies.

INTRODUCTION

Hypertension is a major global health concern and a leading risk factor for cardiovascular morbidity and mortality. According to the World Health Organization, elevated blood pressure contributes significantly to the burden of ischemic heart disease, stroke, and chronic kidney disease. Long-term pharmacotherapy is often required for effective blood pressure control, which makes patient compliance, drug safety, and consistent therapeutic efficacy critical considerations in antihypertensive treatment. Among the various classes of antihypertensive agents, angiotensin-converting enzyme (ACE) inhibitors remain one of the most widely prescribed due to their proven efficacy in reducing blood pressure and improving cardiovascular outcomes (Kpemissi et al., 2020; Miraj and Kiani, 2016).

Ramipril is a potent ACE inhibitor commonly used in the management of hypertension, heart failure, and

post-myocardial infarction conditions. Despite its clinical effectiveness, ramipril exhibits several biopharmaceutical limitations when administered orally. It undergoes extensive first-pass hepatic metabolism, resulting in reduced oral bioavailability and interindividual variability in therapeutic response. Additionally, conventional oral dosage forms may lead to delayed onset of action and gastrointestinal side effects, which can negatively affect patient adherence, particularly in elderly and chronically ill populations. These challenges necessitate the exploration of alternative drug delivery approaches capable of improving the systemic availability and therapeutic performance of ramipril (Ekambaram and Abdul Hasan Sathali, 2011; Grimm et al., 1998; Isaac-Lam, 2021).

Buccal drug delivery has emerged as a promising alternative route for systemic drug administration. The buccal mucosa is highly vascularized and exhibits relatively high permeability compared to other oral mucosal tissues, allowing rapid drug absorption directly into the systemic circulation. Importantly, buccal delivery bypasses gastrointestinal degradation and hepatic first-pass metabolism, thereby enhancing bioavailability and reducing dose variability. Moreover, buccal dosage forms are non-invasive, easy to administer, and suitable for patients who experience difficulty swallowing conventional tablets, offering significant advantages in terms of patient compliance (Alaei and Omidian, 2021; Mukhopadhyay et al., 2018; Prasanth et al., 2011).

Among the various buccal dosage forms, fast-dissolving mucoadhesive buccal films have gained considerable attention in recent years. These films are thin, flexible, and rapidly hydrating systems designed to adhere to the buccal mucosa, ensuring prolonged residence time and intimate contact with the absorption site. The incorporation of mucoadhesive polymers facilitates strong interactions with mucin glycoproteins, minimizing premature displacement due to saliva flow or mechanical movements. Fast-dissolving films further offer rapid onset of action, accurate dosing, and improved patient convenience, making them particularly suitable for systemic delivery of drugs requiring quick therapeutic response (Elagamy et al., 2019; Gayathri and Jayakumari, 2019).

Selection of a suitable mucoadhesive polymer is a key factor influencing the performance of buccal films. While synthetic polymers such as hydroxypropyl methylcellulose and polyvinylpyrrolidone are commonly employed because of their reproducible film-forming properties, increasing emphasis is being placed on natural polymers as safer and more sustainable alternatives. Natural polysaccharides are biocompatible, biodegradable, non-toxic, and environmentally friendly. Among them, pectic polysaccharides possess high swelling capacity and abundant functional groups that enable strong hydrogen bonding and electrostatic interactions with mucosal surfaces, enhancing mucoadhesion.

Marigold (Tagetes species) is widely known for its medicinal value; however, its pectic polysaccharide fraction remains largely unexplored for pharmaceutical applications. Utilizing marigold pectic polysaccharide as a mucoadhesive biomaterial represents a novel and sustainable strategy for buccal drug delivery. The presence of hydroxyl and carboxyl groups promotes hydration, swelling, and adhesion, making it suitable for buccal film formulations. Combining natural polymers with synthetic film-formers can further provide synergistic improvements in mechanical strength, adhesion, and drug release (Slavov et al., 2019).

In addition, functional excipients such as permeation enhancers and floating agents can enhance buccal film performance. Permeation enhancers facilitate drug transport across the buccal mucosa, while floating systems help maintain film position. Accordingly, this study aimed to develop a floating cum mucoadhesive fast-dissolving buccal film of ramipril using marigold pectic polysaccharide, offering a promising alternative to conventional oral therapy.

MATERIAL AND METHODS

Collection, authentication and extraction of plant material

Fresh flowers of Tagetes erecta (marigold) were collected during peak flowering from local horticultural fields, selecting fully bloomed, disease-free orange–yellow inflorescences to ensure maximum pectic polysaccharide yield. The flowers were cleaned to remove extraneous matter, washed with tap and distilled water, shade-dried for 4–5 days, and oven-dried at 40–45 °C to prevent degradation of thermo-labile components. The dried petals were pulverized, passed through a 60-mesh sieve, and stored in airtight containers. Pectic polysaccharides were extracted using a modified hot-acid method, in which the powdered petals were defatted with petroleum ether (1:10 w/v) for 3 h and air-dried. The material was then dispersed in acidified water (pH 1.5–2.0) at a 1:20 w/v ratio and heated at 90 ± 2 °C for 2 h with continuous stirring. The extract was filtered, centrifuged, concentrated, precipitated with chilled ethanol, washed, vacuum-dried, powdered, and stored for further studies (Gaurav, 2022; Gaurav et al., 2022).

Physicochemical property

Physicochemical properties of marigold flower pectic polysaccharide (MFP) were evaluated in triplicate (n = 3) at 25 ± 2 °C and 45–55% relative humidity after equilibrating the powder for 24 h. Bulk density was determined by gently transferring 10.00 g of MFP

powder into a 100 mL graduated cylinder without tapping and recording the unsettled volume, from which bulk density was calculated as the ratio of mass to volume. Tapped density was measured using the same sample in a mechanical tapped-density tester operated at approximately 300 taps per minute until a constant volume was achieved, and tapped density was calculated accordingly. Compressibility index (Carr's index) and Hausner ratio were subsequently calculated using the obtained bulk and tapped density values to assess powder flow characteristics. Flowability of the MFP powder was further evaluated by determining the angle of repose using the fixed-funnel method. The powder was allowed to flow through a funnel to form a conical heap, and the height and radius of the heap were measured to calculate the angle of repose (Arfaoui-Elhif et al., 2023).

Fourier-transform infrared analysis

Fourier-transform infrared (FT-IR) spectroscopy was employed to identify characteristic functional groups of marigold flower pectic polysaccharide (MFP). Dried MFP powder was finely ground and mixed with spectroscopic-grade potassium bromide (KBr) in a 1:100 ratio and compressed into a transparent pellet using a hydraulic press. The pellet was placed in the sample holder, and FT-IR spectra were recorded over the range of 4000–400 cm^{-1} at a resolution of 4 cm^{-1}. A pure KBr pellet was used for background correction. The recorded spectra were analyzed to confirm the presence of functional groups characteristic of polysaccharides (Kumar et al., 2020).

Nuclear Magnetic Resonance (^{1}H-NMR) Analysis

The Structural characterization of marigold flower pectic polysaccharide (MFP) was performed using ^{1}H-NMR spectroscopy. MFP (10 mg) was dissolved in 0.6 mL D_2O and analyzed on a Bruker 400 MHz spectrometer at 25 °C. Spectra were recorded with standard acquisition parameters and referenced to the residual HOD peak (Yadav and Kumar, 2021).

UV spectrophotometric analysis

UV–visible spectra were recorded to characterize the optical profile of Marigold Flower Pectic Polysaccharide (MFP). Dried MFP was dissolved in Milli-Q water to prepare a 0.1% (w/v) solution, sonicated for 10 minutes to ensure dissolution, and filtered through a 0.45 µm membrane prior to analysis. Besides, Ramipril solution 0.1% (w/v) was prepared by dissolving the analyte in methanol and make up to the volume with 0.1% Orthophosphoric acid (OPA). A matched blank of Milli-Q water and blank buffer was used for baseline correction. Spectra were acquired on a double-beam UV–Vis spectrophotometer (1 cm quartz cuvette) over the wavelength range 200–700 nm, with a scan speed of 600 nm/min and a spectral resolution of 1 nm. Each sample was measured in triplicate and the mean absorbance recorded. Instrumental parameters (lamp, slit width, and baseline) were checked before measurement to ensure reproducibility (Alahmad et al., 2022).

Method validation of Ramipril

UV spectrophotometric method validation for ramipril was performed using a calibrated UV–Visible spectrophotometer with 1 cm quartz cuvettes. Ramipril showed maximum absorbance at 239 nm, using methanol as blank. Linearity was established over a concentration range of 0.8–50.0 µg/mL with triplicate analysis and regression evaluation. Limit of detection and quantification were calculated using ICH-recommended equations based on the calibration curve slope and standard deviation. Precision was assessed as intra-day repeatability at multiple concentrations and expressed as %RSD. Accuracy was evaluated by recovery studies using the standard addition method at 0%, 50%, 100%, and 150% levels, and percentage recovery was calculated (Ranetti et al., 2009; "Rapid and Simultaneous Analysis of Seven Oral Anti-Diabetic Drugs," 2020).

Scanning Electron Microscopy (SEM) Analysis

The surface morphology and microstructural characteristics of the marigold flower–derived pectic polysaccharide were examined using scanning electron microscopy (SEM). A small quantity of the dried polysaccharide powder was mounted on aluminum stubs using double-sided conductive carbon tape. To prevent surface charging and enhance image clarity, the samples were sputter-coated with a thin layer of gold under vacuum using a sputter coater. SEM imaging was performed at an appropriate accelerating voltage (typically 5–15 kV) under high vacuum conditions. Micrographs were captured at different magnifications to analyze particle shape, surface texture, porosity, and aggregation behavior. The obtained SEM images were used to correlate the morphological features of the polysaccharide with its functional performance as a film-forming and mucoadhesive biomaterial (Kumar et al., 2020).

Preparation of Floating Cum Mucoadhesive Fast-Dissolving Buccal Films of Ramipril

Floating cum mucoadhesive fast-dissolving buccal films of ramipril were prepared by the solvent casting technique. Accurately weighed quantities of HPMC E15 and PVP K30, as per the formulation design (F1–F5), were gradually dispersed in distilled water maintained at 40 °C and stirred continuously at 1000 rpm until a clear, uniform viscous polymeric solution was obtained. The polymer dispersion was then allowed to cool to room temperature. Separately, ramipril (1.25 mg per film), marigold flower pectic polysaccharide, mannitol, citric acid, and sodium bicarbonate

were weighed according to the formulation composition and mixed with propylene glycol (plasticizer), Tween-80 (surfactant), and peppermint oil (flavoring agent). This mixture was sonicated for 15 min to ensure complete solubilization and homogeneity. The drug–excipient mixture was then slowly incorporated into the polymeric solution with gentle stirring to avoid premature effervescence due to the citric acid–sodium bicarbonate system. The resulting uniform casting solution was poured onto a clean, leveled glass petri dish and spread evenly to achieve uniform thickness. Drying was carried out in a hot-air oven at 40 °C for 3 h. The dried films were carefully peeled off, visually evaluated, and cut into 2 × 2 cm² strips, each containing 1.25 mg of ramipril. The films were stored in a desiccator at 30–35% relative humidity until further evaluation (Raziya et al., 2024), (Vayya and Abbulu, 2020).

Table 1: Composition of Floating Cum Mucoadhesive Fast-Dissolving Buccal Films of Ramipril (F1–F5)

Component	F1	F2	F3	F4	F5
Ramipril (mg)	1.25	1.25	1.25	1.25	1.25
HPMC E15 (mg)	500	550	500	600	550
PVP K30 (mg)	300	350	300	400	350
Marigold pectic polysaccharide (mg)	50	75	150	75	100
Mannitol (mg)	58.5	58.5	58.5	58.5	58.5
Citric acid (mg)	50.8	50.8	50.8	50.8	50.8
Sodium bicarbonate (mg)	15	20	15	20	30
Propylene glycol (mL)	0.50	0.50	0.50	0.50	0.50
Tween-80 (mL)	0.20	0.20	0.20	0.20	0.20
Peppermint oil (mL) (flavour)	0.05	0.05	0.05	0.05	0.05
Water for casting (mL)	10.0	10.0	10.0	10.0	10.0

Evaluation of Mucoadhesive Strength by Wilhelmy Plate Method

The mucoadhesive strength of floating cum mucoadhesive fast-dissolving buccal films (F1–F5) was determined using the Wilhelmy plate method. Fresh porcine buccal mucosa, hydrated with phosphate-buffered saline (PBS, pH 6.8), was used as the biological substrate. Film strips were attached to a microbalance hook and positioned vertically. The mucosal tissue was fixed in a temperature-controlled chamber containing PBS maintained at 37 ± 0.5 °C. Each film was brought into contact with the mucosa for 60 s under constant preload force to allow hydration and polymer–mucin interaction. The film was then withdrawn at a constant speed, and the maximum detachment force required for separation was recorded. Measurements were performed in triplicate, and mean values were calculated to assess mucoadhesive strength (Mohammad Karim and Kavehpour, 2018; Vogel et al., 2020).

Physicochemical Evaluation

The floating cum mucoadhesive fast-dissolving buccal films of ramipril (F1–F5) were evaluated for physicochemical parameters to ensure uniformity and suitability for buccal administration. All tests were performed in triplicate and expressed as mean ± SD. Weight variation was determined by individually weighing films (2 × 2 cm) to assess uniform drug distribution. Film thickness was measured at three points using a digital micrometer to ensure uniform casting. Surface pH was evaluated after swelling films in distilled water for 1 h to confirm mucosal compatibility. Folding endurance was assessed by repeatedly folding the films until rupture, indicating mechanical strength and flexibility (Madhav et al., 2013; Riaz et al., 2017).

Determination of Disintegration Time

The disintegration time of floating cum mucoadhesive fast-dissolving buccal films of ramipril (F1–F5) was determined using a modified petri dish method. Individual film strips (2 × 2 cm²) were placed in 10 mL phosphate-buffered saline (pH 6.8) maintained at 37 ± 0.5 °C. The time required for complete film disintegration or loss of structural integrity was visually recorded. Each formulation was tested in triplicate, and mean disintegration time ± SD was calculated.

Determination of Drug Content

The drug content of the prepared floating cum mucoadhesive fast-dissolving buccal films of ramipril (F1–F5) was determined to assess the uniformity of drug distribution within the films. From each formulation batch, three film strips of size 2 × 2 cm² (each equivalent to 1.25 mg of ramipril) were randomly selected. Each film strip was accurately weighed and transferred into a 100 mL volumetric flask containing phosphate buffer pH 6.8. The contents were sonicated for 20 min to ensure complete dissolution of the film matrix and extraction of ramipril. The solution was then filtered through Whatman filter paper to remove any undissolved polymeric debris. Appropriate dilutions were prepared, and the absorbance was measured using a UV–visible spectrophotometer at the predetermined λmax of ramipril. The drug content was calculated from the previously established calibration curve. The results were expressed as percentage drug content ± standard deviation, and each measurement was performed in triplicate.

Tensile Strength of Buccal Films

The tensile strength of the prepared floating cum mucoadhesive fast-dissolving buccal films of ramipril (F1–F5) was evaluated to assess mechanical strength and resistance to breakage during handling and application. Testing was performed using a texture analyzer or universal testing machine fitted with appropriate film clamps. Uniform film strips (2 × 2 cm²) free from visible defects were secured between two clamps with a fixed initial grip separation. The upper clamp was moved at a constant cross-head speed at ambient temperature until film rupture occurred, and the maximum breaking force was recorded. Tensile strength was calculated using a standard equation. All measurements were conducted in triplicate and expressed as mean ± SD, and results were correlated with polymer and biomaterial concentration to assess their influence on film integrity (Haque and Sheela, 2015).

Ex-Vivo Evaluation of Mucoadhesive Buccal Films of Ramipril

Preparation of Buccal Mucosa

Fresh rabbit buccal mucosa was procured from a local slaughterhouse immediately after sacrifice and transported to the laboratory in ice-cold phosphate-buffered saline (PBS, pH 6.8). The underlying connective tissue and fat were carefully removed using surgical scissors, and the mucosa was washed thoroughly to eliminate blood and adhering debris. The tissue was cut into suitable dimensions and equilibrated in PBS (pH 6.8) at 37 ± 0.5 °C for 30 min prior to use to simulate physiological buccal conditions (Alkahtani et al., 2021; Rohani Shirvan et al., 2019; Singh et al., 2008).

Mucoadhesive Strength

Mucoadhesive strength of the buccal films was evaluated using a modified physical balance method. The freshly prepared buccal mucosa was fixed onto a glass slide with the mucosal surface facing upward and placed in a temperature-controlled chamber containing PBS (pH 6.8) maintained at 37 °C. Buccal film samples (2 × 2 cm²) were attached to the opposite arm of the balance. The film was brought into contact with the mucosal surface under light pressure for 60 s to allow adhesion. Incremental weights were added gradually until detachment of the film occurred. The minimum force required for detachment was calculated and expressed in Newtons (N). All measurements were performed in triplicate (Alkahtani et al., 2021; Rohani Shirvan et al., 2019; Singh et al., 2008)..

Mucoadhesive Residence Time

The mucoadhesive residence time of buccal films was assessed using a USP disintegration test apparatus (without discs). A section of rabbit buccal mucosa was fixed onto a glass slide and vertically immersed in a beaker containing PBS (pH 6.8) maintained at 37 ± 0.5 °C. The film was adhered to the mucosal surface with gentle pressure. The apparatus was operated at standard speed, and the time required for complete detachment or erosion of the film from the mucosa was recorded. The experiment was carried out in triplicate for each formulation (Alkahtani et al., 2021; Rohani Shirvan et al., 2019; Singh et al., 2008)..

Drug Permeation Study

Ex-vivo permeation studies were conducted using Franz diffusion cells to evaluate the permeation of ramipril across rabbit buccal mucosa. The mucosal membrane was mounted between the donor and receptor compartments, with the epithelial side facing the donor compartment. The receptor chamber was filled with PBS (pH 6.8) containing 0.5% Tween-80 to maintain sink conditions and continuously stirred using a magnetic stirrer at 37 ± 0.5 °C. The buccal film was placed in the donor compartment in contact with the mucosa. At predetermined time intervals, aliquots were withdrawn from the receptor compartment and replaced with fresh medium. The samples were analyzed spectrophotometrically at the appropriate wavelength to determine the amount of ramipril permeated. The study was performed in triplicate (Alkahtani et al., 2021; Rohani Shirvan et al., 2019; Singh et al., 2008)..

Cumulative Ex-Vivo Drug Release Study

Cumulative drug release across the buccal mucosa was evaluated during the ex-vivo permeation study using Franz diffusion cells. The experimental setup and conditions were identical to those described for the permeation study. Samples withdrawn at predetermined intervals were analysed for ramipril content using a validated UV-visible spectrophotometric method. The cumulative percentage of drug released was calculated as a function of time to assess the release behaviour of the buccal films under ex-vivo conditions (Alkahtani et al., 2021; Rohani Shirvan et al., 2019; Singh et al., 2008)..

Stability studies for selected best formulation.

Accelerated stability studies of the optimized mucoadhesive buccal film (F5) were conducted according to ICH guidelines. Films were wrapped in aluminium foil, stored in airtight glass containers, and kept at 40 ± 0.5 °C and 75 ± 5% RH for six months. Samples withdrawn at 0, 3, and 6 months were analyzed for drug content using spectrophotometry. Measurements were performed in triplicate and expressed as mean ± SD (Bassi and Kaur, 2017).

RESULTS AND DISCUSSION

Extraction of pectic polysaccharide

The extraction process yielded a light-yellow, amorphous pectic polysaccharide powder, indicating efficient removal of pigments and non-pectic materials during hot-acid extraction and ethanol precipitation. The fresh marigold flowers exhibited an initial moisture content of approximately 72–75%, contributing to the overall mass reduction following drying and milling.

From 500 g of fresh marigold flowers, the dried powder obtained was 128.4 g, representing a drying recovery of 25.68%. The subsequent hot-acid extraction of this dried material yielded 14.62 g of crude pectin. After purification using ethanol precipitation and deproteinization, the final mass of purified Marigold Flower Pectic Polysaccharide (MFP) was 10.84 g. Thus, MFP exhibited an extractive yield of 8.44% w/w, which falls within the acceptable range for pectic polysaccharides obtained from floral sources (typically 5–12%). The relatively high yield indicates that marigold flowers contain a significant amount of pectic matter, making them a viable botanical source for polysaccharide-based pharmaceutical excipients.

Physicochemical property

The flow properties of Marigold Flower Pectic Polysaccharide (MFP) were evaluated using bulk density, tapped density, angle of repose, Carr's Index, and Hausner Ratio to assess its suitability as a novel natural excipient. The bulk density of MFP was found to be 0.42 g/cm³, indicating a loosely packed, porous polymer typical of pectic polysaccharides. After tapping, the tapped density increased to 0.56 g/cm³, confirming moderate compressibility. These values provided a Carr's Index of 25% and a Hausner Ratio of 1.25, suggesting fair flow properties that can be managed effectively during formulation. The angle of repose was recorded at 32.4°, indicating moderately free-flowing behavior. While not ideal, this value falls within the expected range for natural plant-derived polysaccharides, which often exhibit fibrous and irregular particle morphology influencing flowability. Moreover, the obtained numerical values demonstrate that although MFP is not an exceptional free-flowing powder, it exhibits acceptable flow properties, making it suitable for polymeric film preparation. Importantly, the moderate density and compressibility characteristics contribute positively to its performance as a film-forming, swelling, floating, and mucoadhesive polymer. The inherent porosity supports faster hydration, while the swelling behavior enhances mucoadhesion both crucial for developing floating cum mucoadhesive fast-dissolving drug delivery films.

Table 2: Flow and density properties of Marigold Flower Pectic Polysaccharide (MFP).

Parameter	Value
Bulk density	0.42 g/cm³
Tapped density	0.56 g/cm³
Carr's Index	25%
Hausner Ratio	1.25
Angle of repose	32.4°

FTIR analysis

The FT-IR spectra of ramipril and marigold flower pectic polysaccharide (MFP) were recorded to identify functional groups and assess compatibility. Ramipril exhibited characteristic O–H/N–H, C–H, C=O, and C–O–C stretching peaks, confirming its molecular integrity. MFP showed a broad O–H band, aliphatic C–H stretching, and $–COO^-$ group vibrations indicative of galacturonic acid-rich pectic structure. No significant peak shifts, overlaps, or disappearance were observed between ramipril and MFP spectra, indicating absence of chemical interaction and confirming compatibility. The abundance of hydroxyl and carboxyl groups in MFP supports its film-forming and mucoadhesive properties.

Table 3: Comparative FT-IR Interpretation of Ramipril and MFP.

Wavenumber (cm^{-1})	Ramipril Assignment	MFP Assignment	Interpretation
3549, 3341	O–H/N–H stretching	O–H stretching	H-bonded groups; hydrophilic nature
2981–2943	Aliphatic C–H stretch	Aliphatic C–H	Structural carbohydrate chains
1541	C=O (ester/amide)	–	Confirms ester/amide structure in drug
1592	–	$–COO^-$ stretch	Galacturonic acid presence
1242–1088	C–O–C stretch	C–O–C, ring vibrations	Ester + polysaccharide glycosidic bonds

833–423	Fingerprint region	Polysaccharide backbone	Structural confirmation

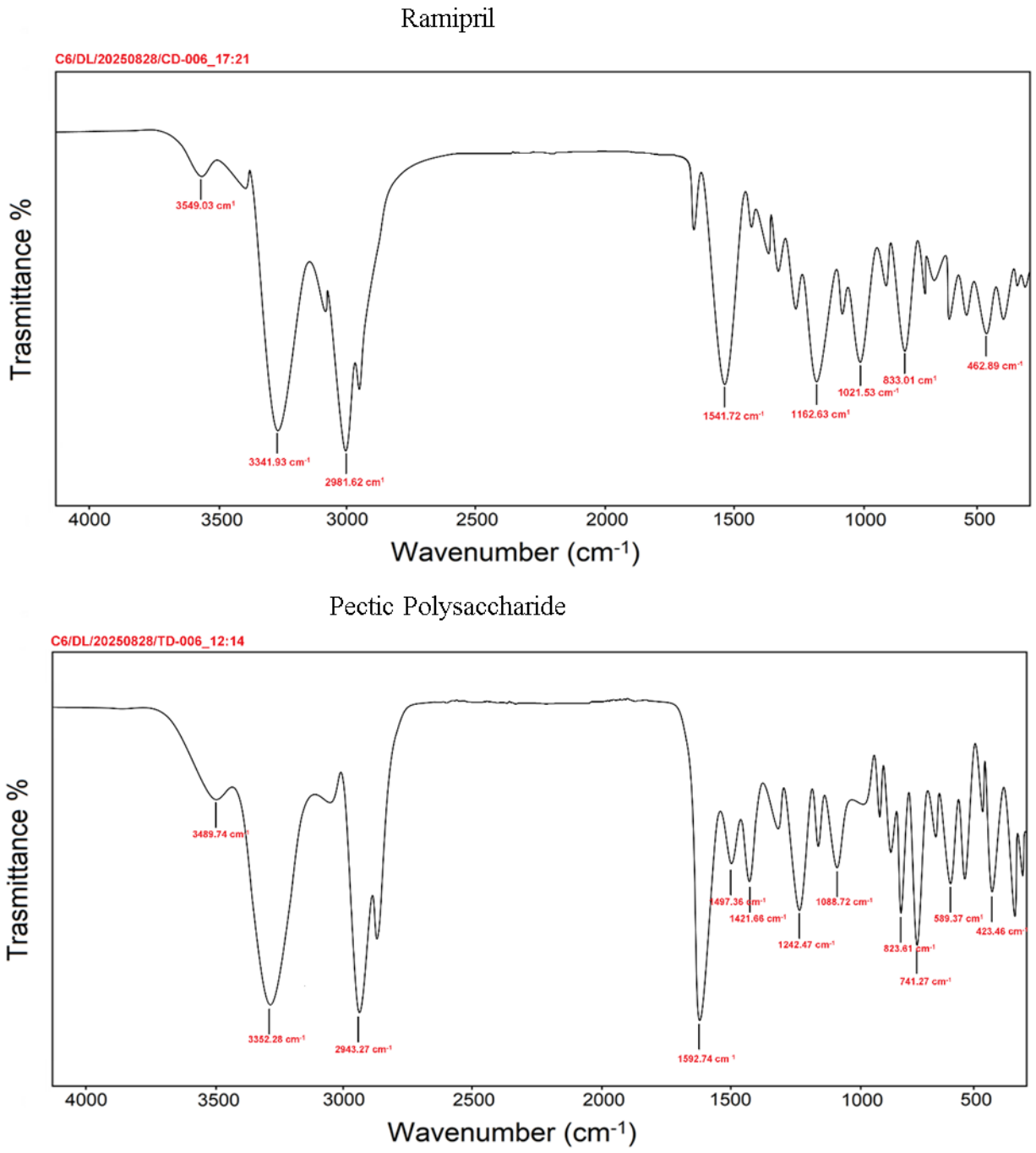


Figure 1: FTIR spectra of Ramipril and Pectic Polysaccharide.

NMR analysis

The ^{1}H-NMR spectrum of MFP exhibits characteristic peaks confirming the polysaccharide nature of the extracted material. A cluster of intense signals appeared between 3.1–4.8 ppm, corresponding to protons of sugar ring hydrogens (H2–H6) in galacturonic acid, rhamnose, galactose, and arabinose residues. Anomeric proton signals were observed at 5.55, 5.39, 5.19, and 5.02 ppm, indicating the presence of multiple glycosidic linkages and confirming the heteropolysaccharide nature of MFP. The broad multiplet near 4.70 ppm corresponds to the residual D_2O peak. Signals at 1.43–1.52 ppm correspond to the methyl protons of rhamnose residues (–CH_3), which are typical indicators of pectic polysaccharides. The minor peaks at 2.19–2.21 ppm reflect the acetyl or uronic acid –CH proton environment, supporting the presence of partially esterified galacturonic acid. No aromatic region peaks (δ 6–8 ppm) were observed, confirming the absence of phenolic impurities and supporting the high purity of the extracted

polysaccharide. Moreover, the ^{1}H-NMR profile confirms that the isolated biomaterial is a pectic polysaccharide rich in galacturonic acid units, containing typical α- and β-anomeric linkages, rhamnogalacturonan segments, and neutral sugar branching. The spectrum aligns with previously reported NMR fingerprints of plant-derived pectins, supporting the successful extraction of structurally intact MFP suitable for pharmaceutical applications.

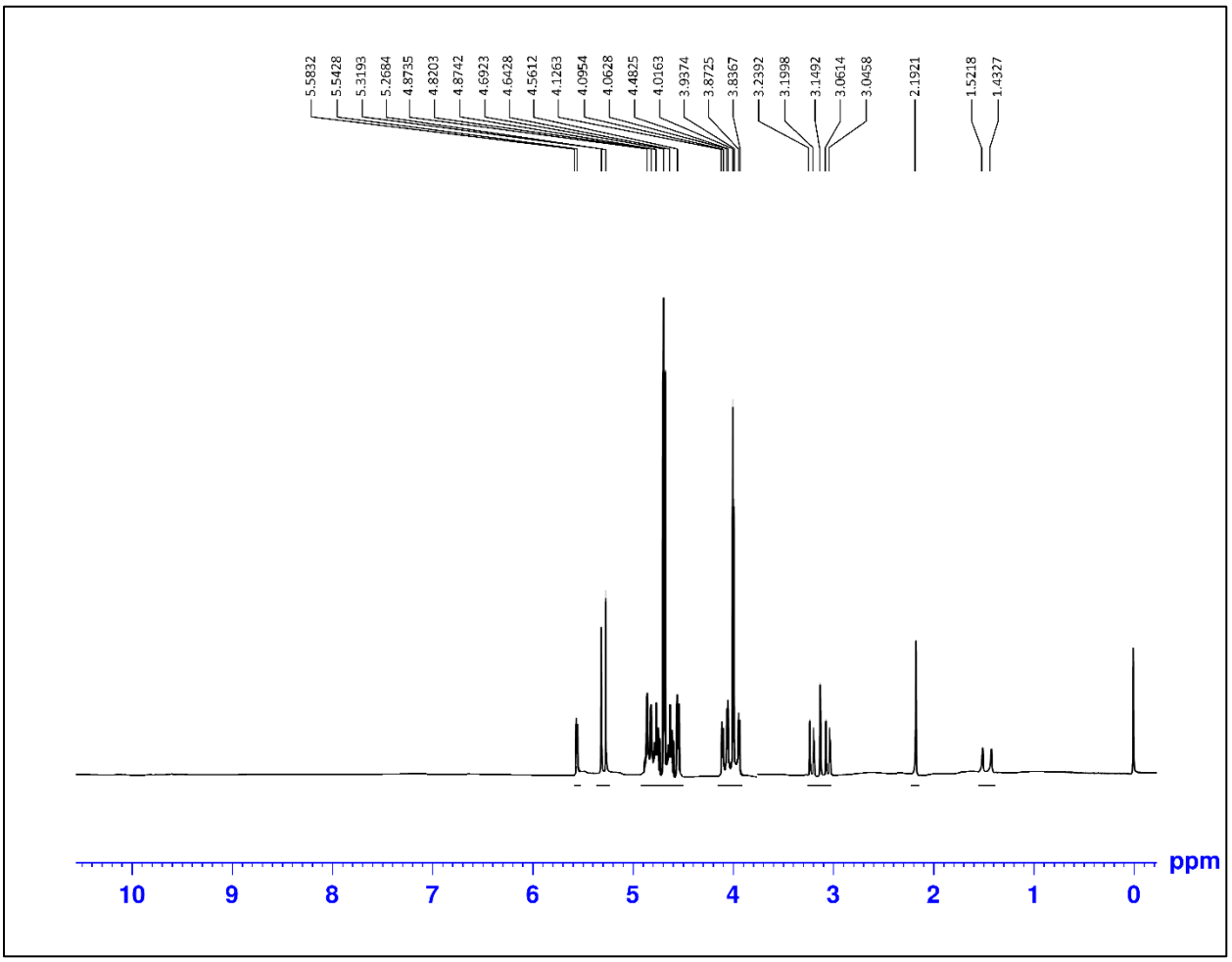


Figure 2: HNMR spectra of Pectic Polysaccharide.

UV Spectrophotometric analysis

The UV profiles (Fig.) showed a strong near-UV absorbance for both traces at wavelengths below 220 nm, consistent with electronic transitions of carbohydrate chromophores and residual conjugated impurities. The comparative trace (blue) displayed two distinct maxima at **239 nm** and **282 nm**, the Ramipril showing the greatest intensity, whereas the MFP spectrum (orange) exhibited a much weaker band centered near **282 nm** and a smoothly declining baseline from the deep-UV region. The more intense 239 nm band in the comparative sample likely reflected π→π* transitions from conjugated π-systems (aromatic or unsaturated contaminants), while the 282 nm feature (present in both traces, though attenuated in MFP) suggests minor phenolic or conjugated carbonyl constituents co-extracted with the polysaccharide. Overall, MFP showed low visible-region absorbance and no significant peaks above 300 nm, indicating minimal chromophoric impurities and suitability for downstream formulation. For routine quality control, **239 nm** (for detecting conjugated contaminants) and **282 nm** (for minor phenolic content) are recommended monitoring wavelengths; however, quantitation of pure polysaccharide is better achieved by carbohydrate-specific assays (e.g., phenol–sulfuric acid) or chromatographic methods.

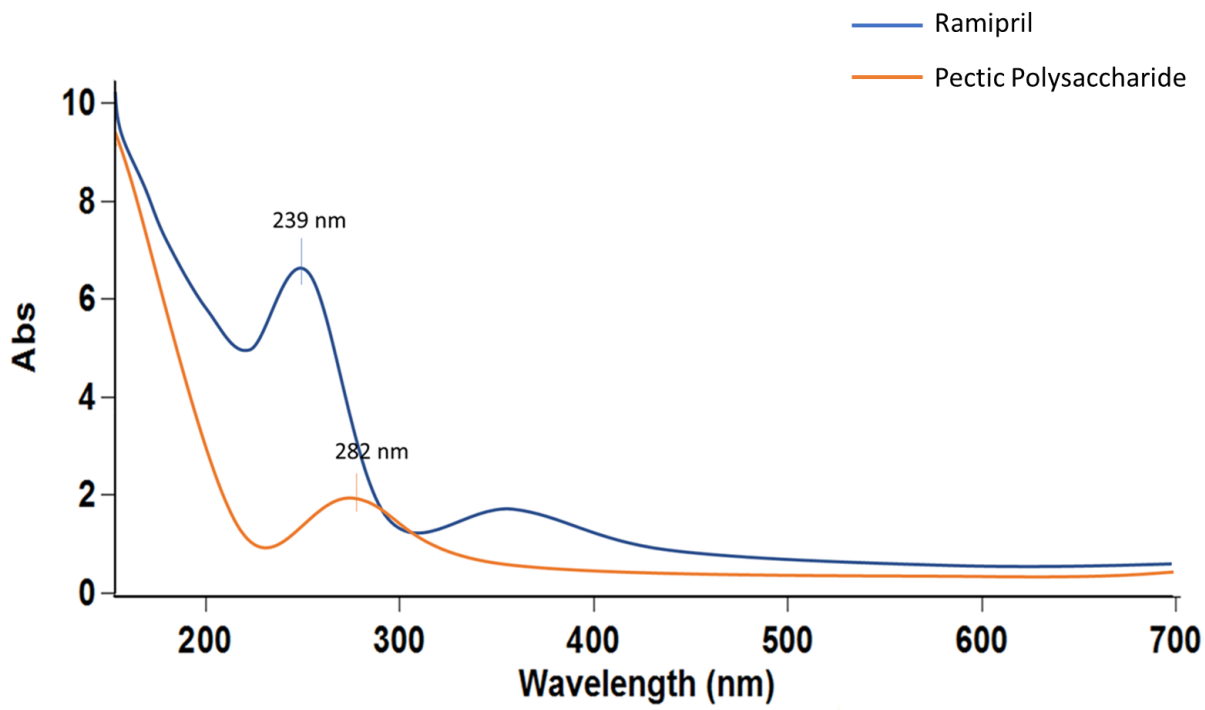


Figure 3: UV Spectra of Ramipril and Pectic Polysaccharide.

Method validation of ramipril

The validated UV spectrophotometric method for the estimation of Ramipril exhibited satisfactory analytical performance in accordance with ICH Q2(R1) guidelines. The calibration curve demonstrated excellent linearity over the concentration range of 0.8–50.0 µg/mL, with a regression equation of y = 0.0131x + 0.005 and a correlation coefficient (R^2 = 0.9915). This strong linear relationship confirms that the method is suitable for accurate quantitative analysis of Ramipril within the studied range. The sensitivity of the method was confirmed by low limits of detection (LOD) and quantification (LOQ), calculated as 1.909 µg/mL and 5.786 µg/mL, respectively.

These values indicate that the method is capable of detecting and reliably quantifying Ramipril even at low concentrations, which is particularly important for dosage form analysis and release studies. Precision studies revealed %RSD values below 2% across all tested concentrations, indicating good repeatability and reproducibility of the method. This low variability confirms the reliability of the method for routine analytical applications. Accuracy was evaluated through recovery studies at different spiking levels (0–150%), which showed percentage recovery in the range of 96.64% to 97.15%. The high recovery values indicate minimal interference from formulation excipients and confirm the accuracy of the method. Moreover, the developed UV spectrophotometric method is simple, sensitive, precise, and accurate, making it suitable for routine estimation of Ramipril in bulk drug and pharmaceutical formulations, including fast-dissolving buccal films.

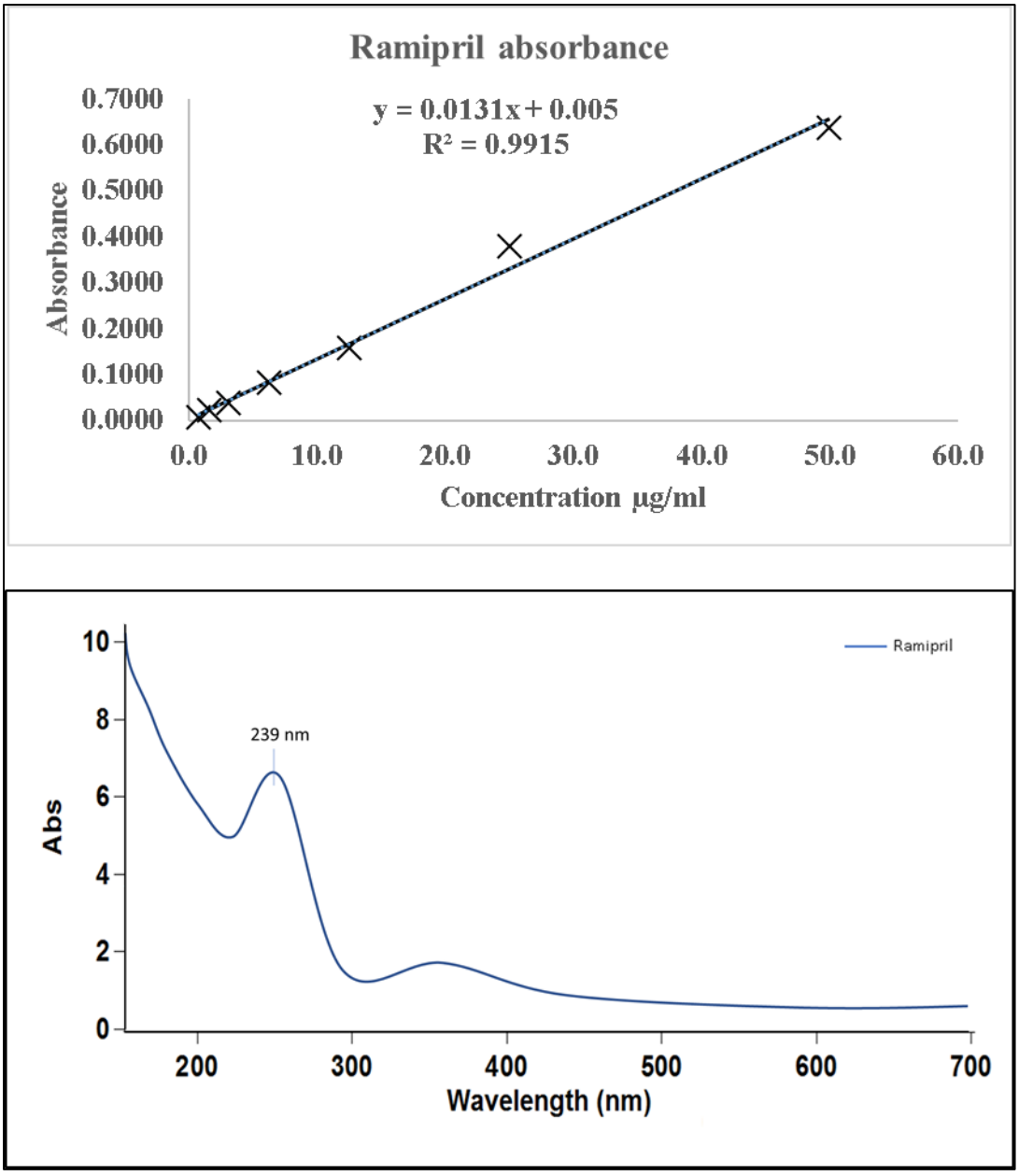


Table 4: linearity concentration with respect to the absorbance and precision.

Concentration µg/ml	Ramipril absorbance	Precision
0.8	0.0087 ± 0.000077	0.885
1.6	0.0239 ± 0.000279	1.167
3.1	0.0399 ± 0.000299	0.749
6.3	0.0828 ± 0.000757	0.914
12.5	0.1595 ± 0.001995	1.250
25.0	0.3790 ± 0.002290	0.604
50.0	0.6380 ± 0.007580	1.188

Table 5: linearity concentration with respect to the absorbance and precision.

% spiking of analyte to the sample	Concentration µg/ml	Drug found	% Drug recovered
0%	50.0	48.321 ± 0.362	96.641
50%	75	72.672 ±1.473	96.896

100	100	97.023 ±1.357	97.023
150	150	145.725 ±1.392	97.150

Scanning Electron Microscopy (SEM) Analysis

The SEM micrographs revealed distinct morphological characteristics of the marigold pectic polysaccharide. As shown in image (a), the polysaccharide particles exhibited an irregular, flaky, and rough surface with angular edges and heterogeneous size distribution. Such irregular morphology is indicative of an amorphous polymeric structure, which is advantageous for hydration and swelling behaviour. The rough surface texture increases the effective surface area, promoting enhanced polymer–mucin interactions that are essential for strong mucoadhesive properties. In image (b), the polysaccharide appeared as a relatively uniform, porous, and finely distributed matrix, suggesting good dispersibility and film-forming potential when incorporated into polymeric blends. The presence of micro-pores and surface irregularities facilitates rapid water penetration, which supports fast disintegration and dissolution behaviour of buccal films. Moreover, the absence of sharp crystalline structures confirms the non-crystalline nature of the polysaccharide, reducing the risk of brittleness in the final film formulation. Moreover, the SEM findings confirm that the marigold pectic polysaccharide possesses favorable morphological features such as surface roughness, porosity, and amorphous nature. These characteristics significantly contribute to improved mucoadhesion, flexibility, and rapid hydration, validating its suitability as a natural biomaterial for the development of floating cum mucoadhesive fast-dissolving buccal films of ramipril.

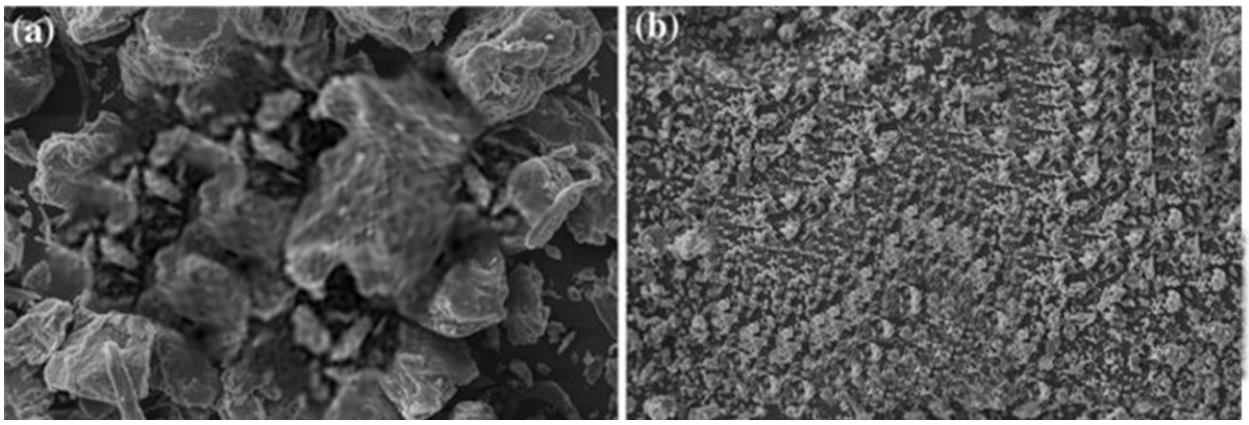


Figure 4: Scanning electron microscopy (SEM) images illustrating the surface morphology of the marigold-derived pectic polysaccharide used as a biomaterial in buccal film formulation. Image (a) shows irregular, flaky, and porous particles with rough surfaces, while image (b) reveals a comparatively uniform and compact microstructure after processing. The observed morphology supports good film-forming ability, polymer interlinking, and enhanced mucoadhesive and mechanical properties of the developed films.

Acute toxicity studies

Development and evaluation of developed films

Floating cum mucoadhesive fast-dissolving buccal films of ramipril (F1–F5) were successfully prepared by the solvent casting technique using HPMC E15, PVP K30, and marigold pectic polysaccharide as the primary film-forming and mucoadhesive biomaterial. All formulations resulted in smooth, flexible, and uniform films, indicating good compatibility between ramipril and the selected excipients. The effervescent system comprising citric acid and sodium bicarbonate was effectively incorporated without premature gas generation, confirming the suitability of the optimized preparation method.

Variation in polymer and biomaterial concentration significantly influenced the physicochemical and mucoadhesive characteristics of the films. Increasing concentrations of HPMC E15 and PVP K30 improved film integrity and mechanical strength, while marigold pectic polysaccharide played a crucial role in enhancing mucoadhesion due to its natural polysaccharide structure and strong interaction with mucin chains. Among all formulations, F5, containing an optimized ratio of HPMC E15 (550 mg), PVP K30 (350 mg), and marigold pectic polysaccharide (100 mg), demonstrated superior overall performance.

Mucoadhesive strength evaluated by the Wilhelmy Plate Method revealed a direct correlation between polysaccharide concentration and detachment force. Formulations with lower biomaterial content (F1 and F2) showed comparatively weaker adhesion, while F3 and F5 exhibited significantly higher mucoadhesive force, attributed to enhanced polymer hydration, chain interpenetration, and hydrogen bonding with the buccal mucosa.

The preload contact time allowed sufficient polymer swelling, contributing to stable and reproducible adhesion values.

The optimized formulation F5 showed the highest mucoadhesive strength, indicating prolonged residence time at the buccal site, which is desirable for improved drug absorption and bioavailability. Additionally, the balanced polymeric composition in F5 ensured rapid hydration and fast disintegration without compromising mechanical stability. Overall, the results confirm that marigold pectic polysaccharide is an effective natural mucoadhesive biomaterial, and the developed floating cum mucoadhesive fast-dissolving buccal films, particularly formulation F5, are promising for efficient buccal delivery of ramipril.

Physicochemical evaluation

The physicochemical evaluation of fast-dissolving mucoadhesive buccal films (F1–F5) revealed notable differences among formulations, reflecting the influence of polymer composition and biomaterial concentration on film characteristics. Weight variation across all formulations remained within narrow limits (93.28 ± 0.03 to 96.70 ± 0.06 mg), indicating good uniformity in casting and homogeneous distribution of ramipril and excipients. Among them, formulation F5 showed minimal weight variation (95.20 ± 0.02 mg), suggesting superior reproducibility and consistency, which is essential for dose accuracy in buccal drug delivery systems. Film thickness ranged from 0.17 ± 0.05 to 0.27 ± 0.11 mm. F2 exhibited the lowest thickness, while F5 showed slightly higher thickness, which can be attributed to the optimized concentration of marigold pectic polysaccharide and polymeric matrix. Although increased thickness is often associated with reduced patient comfort, the thickness of F5 remained within acceptable limits and contributed positively to mechanical strength and handling properties without compromising buccal applicability.

Surface pH values of all formulations were close to neutrality (6.7–7.1), indicating compatibility with the buccal mucosa and minimal risk of irritation. F5 demonstrated a surface pH of 7.0 ± 0.02, closely matching salivary pH, which supports its suitability for prolonged buccal residence and patient compliance. Folding endurance, an indicator of mechanical flexibility and film integrity, varied notably among formulations. F3 showed the lowest folding endurance (129 ± 1.8), suggesting comparatively brittle nature, whereas F4 and F5 exhibited the highest folding endurance (146 ± 0.8 and 146 ± 0.2, respectively). The excellent folding endurance of F5 reflects its superior flexibility, resilience, and resistance to cracking during handling and application. This enhanced mechanical performance can be attributed to the balanced ratio of HPMC, PVP, and marigold pectic polysaccharide, along with adequate plasticization.

Moreover, while all formulations met basic evaluation criteria, formulation F5 demonstrated the most desirable combination of uniform weight, acceptable thickness, physiological surface pH, and superior folding endurance. These attributes collectively indicate optimal mechanical stability, mucosal compatibility, and formulation robustness. Therefore, F5 was identified as the optimized formulation and considered most suitable for floating cum mucoadhesive fast-dissolving buccal delivery of ramipril, with promising potential for enhanced patient compliance and therapeutic efficacy.

Disintegration Time

The disintegration time is a critical quality attribute for fast-dissolving buccal films, as it directly influences the onset of drug release and patient compliance. The disintegration times of the prepared floating cum mucoadhesive fast-dissolving buccal films of ramipril (F1–F5) are presented as mean ± SD values and ranged from **74.04 ± 0.04 s to 85.27 ± 0.01 s**, indicating rapid disintegration for all formulations. Formulation **F1** exhibited the highest disintegration time (85.27 ± 0.01 s), which may be attributed to its comparatively lower content of marigold pectic polysaccharide and sodium bicarbonate, resulting in slower hydration and effervescence. **F2** and **F4** showed moderately reduced disintegration times (79.75 ± 0.04 s and 76.59 ± 0.04 s, respectively), reflecting improved polymer hydration and gas-generating capacity due to optimized effervescent components.

Moreover, **F3** and **F5** demonstrated faster disintegration, with **F5 showing the lowest disintegration time (74.04 ± 0.04 s)**. This enhanced performance of F5 can be explained by the balanced concentration of hydrophilic polymers (HPMC E15 and PVP K30), higher sodium bicarbonate content, and an optimal amount of marigold pectic polysaccharide. These components collectively facilitated rapid water uptake, polymer swelling, and carbon dioxide generation, leading to quicker film breakup. Overall, the results confirm that all formulations meet the criteria for fast-dissolving buccal films. Among them, **F5 emerged as the most optimized formulation**, offering the shortest disintegration time, which is desirable for rapid drug release, improved therapeutic efficacy, and enhanced patient acceptability in buccal drug delivery.

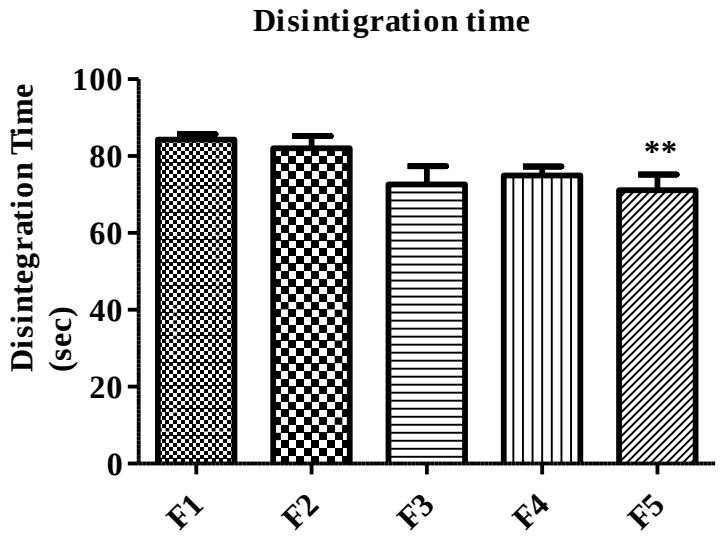


Figure 5: Determination of disintegration time of the developed film.

Table 6: Determination of disintegration time of the developed film.

Formulation	Disintegration Time (sec)
F1	85.27 ± 0.01
F2	79.75 ± 0.04
F3	75.98 ± 0.03
F4	76.59 ± 0.04
F5	74.04 ± 0.04

Determination of Drug Content

The percentage drug content of formulations F1–F5 ranged from 85.27 ± 1.43% to 99.11 ± 4.32%, indicating generally acceptable drug distribution across the film batches. Formulations F1 (97.32 ± 1.42%) and F5 (97.59 ± 0.53%) exhibited drug content values very close to the theoretical value, reflecting uniform mixing of ramipril within the polymeric matrix and efficient solvent casting. Formulation F3 showed the highest drug content (99.11 ± 4.32%), which may be attributed to optimal polymer–drug compatibility and enhanced entrapment efficiency due to a balanced concentration of marigold pectic polysaccharide and synthetic polymers. In contrast, F2 (91.45 ± 0.40%) and F4 (85.27 ± 1.43%) demonstrated comparatively lower drug content, possibly due to increased polymer viscosity at higher HPMC and PVP levels, which can hinder uniform drug dispersion during casting. Overall, all formulations showed drug content within acceptable pharmacopeial limits (85–115%), confirming the suitability of the solvent casting technique for preparing ramipril buccal films. Among all batches, F5 emerged as the optimized formulation, combining high drug content with low variability, which is essential for dose uniformity and therapeutic reliability in buccal drug delivery systems.

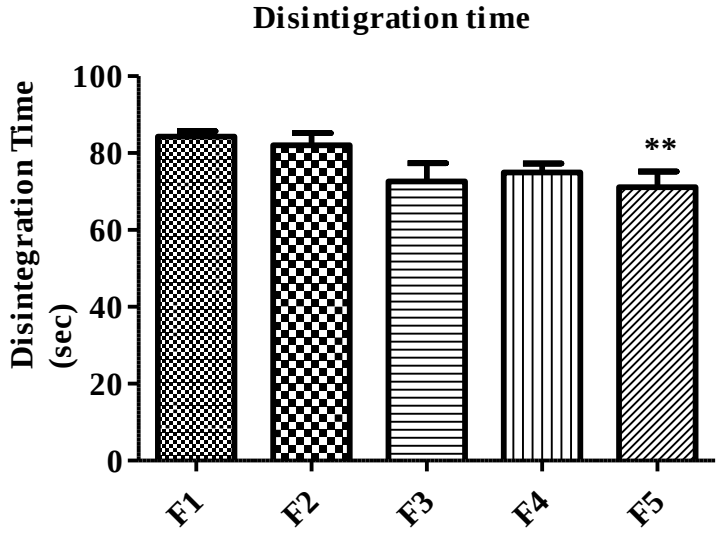


Figure 6: Determination of drug content in the developed films.

Table 7: Determination of drug content in the developed films.

Formulation	Drug Content (%)
F1	97.32 ± 1.42
F2	91.45 ± 0.40
F3	99.11 ± 4.32
F4	85.27 ± 1.43
F5	97.59 ± 0.53

Tensile Strength of Buccal Films

The tensile strength values of formulations F1–F5 ranged from **11.90 ± 0.21 to 26.31 ± 0.25 N/mm²**, indicating a significant influence of polymer composition and marigold pectic polysaccharide concentration on the mechanical properties of the films. Formulation F1 exhibited the lowest tensile strength (11.90 ± 0.21 N/mm²), which may be attributed to lower polymeric reinforcement, resulting in comparatively weaker film structure. A gradual increase in tensile strength was observed from F2 (14.06 ± 0.31 N/mm²) to F3 (15.50 ± 0.22 N/mm²), suggesting improved intermolecular interactions between HPMC E15, PVP K30, and the natural polysaccharide. Formulation F4 showed a marked improvement in tensile strength (21.91 ± 0.15 N/mm²), indicating enhanced film cohesion due to increased polymer concentration. Among all formulations, **F5 demonstrated the highest tensile strength (26.31 ± 0.25 N/mm²)**, reflecting superior mechanical robustness. This enhancement can be attributed to the optimized ratio of synthetic polymers and marigold pectic polysaccharide, which likely promoted better chain entanglement and hydrogen bonding within the film matrix. High tensile strength ensures that the film can withstand mechanical stress during handling, packaging, and buccal application without tearing. Overall, the results confirm that formulation F5 possessed optimal mechanical strength, making it the most suitable candidate for floating cum mucoadhesive fast-dissolving buccal delivery of ramipril.

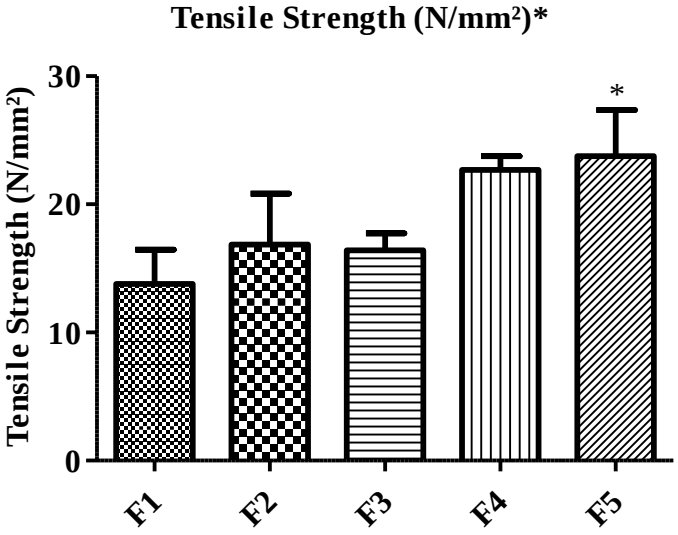


Figure 7: Determination of Tensile Strength in the developed films.

Table 8: Determination of Tensile Strength in the developed films.

Formulation	Tensile Strength (N/mm²)
F1	11.90 ± 0.21
F2	14.06 ± 0.31
F3	15.50 ± 0.22
F4	21.91 ± 0.15
F5	26.31 ± 0.25

Ex-Vivo Evaluation of Mucoadhesive Buccal Films of Ramipril

Preparation of Buccal Mucosa

Fresh rabbit buccal mucosa was obtained from a local slaughterhouse immediately after sacrifice and transported to the laboratory in cold phosphate-buffered saline (PBS, pH 6.8). The mucosal tissue was carefully excised, washed to remove adhering debris, and trimmed to an appropriate size. The tissue was equilibrated in PBS at 37 ± 0.5 °C for 30 min prior to experimentation.

Mucoadhesive Strength

Mucoadhesive strength reflects the force required to detach the film from the buccal mucosa and directly correlates with the film's ability to remain adhered under physiological conditions.

Table 9: Ex-vivo mucoadhesive strength of ramipril buccal films (n = 3)

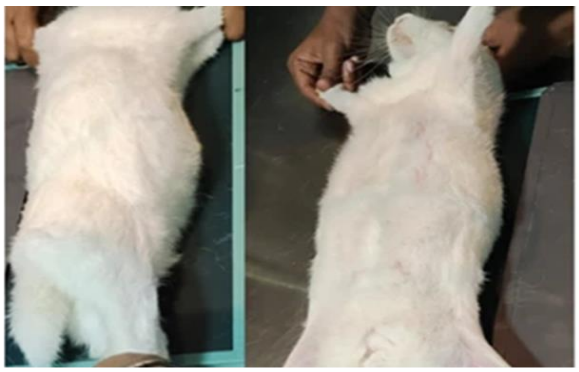
Formulation	Detachment Force (N)	Mucoadhesive Strength (g)
F1	0.21 ± 0.02	21.4 ± 1.8
F2	0.28 ± 0.03	28.5 ± 2.2
F3	0.34 ± 0.02	34.7 ± 1.6
F4	0.39 ± 0.03	39.8 ± 2.4
F5	**0.46 ± 0.02**	**46.9 ± 1.9**

A progressive increase in mucoadhesive strength was observed from F1 to F5. Formulation F5 exhibited the highest detachment force, indicating superior adhesion to rabbit buccal mucosa. This enhancement can be attributed to the optimized concentration of **marigold pectic polysaccharide**, which provides abundant hydroxyl and carboxyl groups capable of forming hydrogen bonds and electrostatic interactions with mucin glycoproteins. Additionally, the synergistic interaction between HPMC E15 and PVP K30 contributed to enhanced polymer chain interpenetration and hydration, resulting in improved adhesion. Strong mucoadhesion is desirable to prevent premature detachment and to ensure prolonged drug availability at the absorption site.

Mucoadhesive Residence Time

Residence time determines how long the film remains attached to the buccal mucosa under simulated physiological conditions. It was evaluated using a USP disintegration apparatus (without discs). The buccal mucosa was fixed to

a glass slide and immersed in PBS (pH 6.8) maintained at 37 °C. The film was attached to the mucosal surface, and the time required for complete detachment or erosion was recorded. This parameter reflects the ability of the film to remain adhered under simulated buccal conditions.



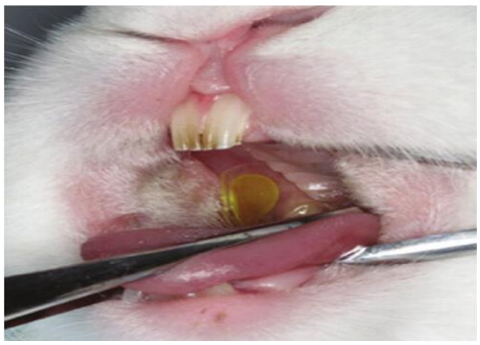


Table 2. Ex-vivo mucoadhesive residence time of buccal films (n = 3)

Formulation	Residence Time (min)
F1	85.6 ± 4.3
F2	112.4 ± 5.6
F3	148.2 ± 6.1
F4	176.9 ± 7.4
F5	**214.5 ± 8.2**

Formulation F5 demonstrated the longest residence time on rabbit buccal mucosa, indicating excellent mucoadhesive retention. The increased residence time correlates well with higher mucoadhesive strength values. Films containing higher concentrations of marigold pectic polysaccharide exhibited enhanced swelling and hydration, which promoted stronger polymer–mucin interactions. This sustained attachment is beneficial for maintaining localized drug concentration, minimizing dosing frequency, and improving patient compliance. The floating behavior generated by the citric acid–sodium bicarbonate system further assisted in maintaining film position without mechanical displacement.

Drug Permeation Study

Ex-vivo permeation studies were carried out using Franz diffusion cells to assess the ability of ramipril to permeate across rabbit buccal mucosa.

Table 10: Ex-vivo cumulative permeation of ramipril through rabbit buccal mucosa (n = 3)

Formulation	Cumulative Drug Permeated at 6 h (µg/cm²)
F1	38.4 ± 2.6
F2	52.1 ± 3.1
F3	68.7 ± 3.8
F4	81.5 ± 4.2
F5	**96.9 ± 3.5**

A marked enhancement in drug permeation was observed with increasing polymer optimization. F5 showed significantly higher permeation compared to other formulations. The improved permeation can be attributed to

prolonged mucosal contact, optimal hydration, and the presence of Tween-80, which may act as a permeation enhancer by altering mucosal lipid domains. The controlled hydration of polymers allowed gradual drug diffusion across the mucosal barrier while avoiding rapid washout. These findings suggest that F5 is capable of delivering ramipril efficiently via the buccal route, potentially bypassing first-pass metabolism.

Cumulative Ex-Vivo Drug Release

Cumulative drug release across the buccal mucosa was assessed to understand the release kinetics under ex-vivo conditions.

Table 11: Ex-vivo cumulative drug release (%) across buccal mucosa (n = 3)

Time (h)	F1	F2	F3	F4	F5
1	22.5 ± 1.8	25.9 ± 2.0	28.6 ± 1.7	31.4 ± 1.9	34.8 ± 1.6
2	41.7 ± 2.4	48.2 ± 2.1	54.9 ± 2.3	59.6 ± 2.5	63.5 ± 2.2
4	65.8 ± 2.9	72.4 ± 3.1	79.6 ± 2.8	84.3 ± 3.0	88.9 ± 2.6
6	78.3 ± 3.2	84.6 ± 2.7	89.8 ± 3.1	93.5 ± 2.8	**97.6 ± 2.4**

All formulations exhibited a controlled and sustained drug release profile, with F5 showing the highest cumulative release at 6 h. The initial rapid release phase may be attributed to surface-associated drug, followed by a diffusion-controlled release from the hydrated polymeric matrix. The optimized balance of hydrophilic polymers in F5 allowed efficient water uptake without premature erosion, supporting sustained drug diffusion. The high cumulative release coupled with prolonged residence time confirms the suitability of F5 for effective buccal drug delivery. The ex-vivo evaluation clearly demonstrated that formulation F5 outperformed other formulations in terms of mucoadhesive strength, residence time, drug permeation, and cumulative drug release. The incorporation of marigold pectic polysaccharide as a natural mucoadhesive biomaterial significantly enhanced film performance. These findings validate the potential of F5 as an optimized floating cum mucoadhesive fast-dissolving buccal film of ramipril for improved transmucosal drug delivery and therapeutic efficacy.

Stability studies for selected best formulation.

Accelerated stability studies were performed to evaluate the stability of the optimized mucoadhesive buccal film formulation (F5) under stressed storage conditions of 40 ± 0.5 °C and 75 ± 5% RH for six months. The formulation was assessed for disintegration time and drug content at 0-day, 1 month, 3 months, and 6 months to determine any physicochemical or performance-related changes during storage.

Table 12: Stability data of optimized buccal film formulation (F5).

Stability Parameter	0 Day	1 Month	3 Month	6 Month
Disintegration Time (s)	74.04 ± 0.04	74.08 ± 0.06	74.12 ± 0.07	74.19 ± 0.09
Drug Content (%)	97.59 ± 0.53	97.42 ± 0.48	97.21 ± 0.44	96.98 ± 0.39

The results demonstrated that formulation F5 maintained excellent stability throughout the study period. Only negligible variations were observed in disintegration time, indicating that the mechanical integrity and hydration behavior of the film remained unaffected by prolonged exposure to accelerated conditions. The disintegration time remained within a narrow range, confirming the robustness of the polymeric matrix and the absence of significant polymer degradation or structural alteration. Drug content analysis revealed minimal reduction over the six-month storage period, with values consistently remaining above 96%. The slight decrease observed at later time points was within acceptable pharmacopeial limits and suggests good chemical stability of ramipril within the polymeric network. The presence of hydrophilic polymers such as HPMC E15 and PVP K30, along with marigold pectic polysaccharide, likely contributed to effective drug entrapment and protection against thermal and moisture-induced degradation.

Moreover, the stability data confirm that formulation F5 retained its critical quality attributes under accelerated conditions. The negligible changes in disintegration time and drug content validate F5 as a physically and chemically stable mucoadhesive buccal film, supporting its suitability for long-term storage and clinical application.

CONCLUSION

The present study successfully demonstrated the development and optimization of a floating cum mucoadhesive fast-dissolving buccal film of ramipril using marigold pectic polysaccharide as a natural bioadhesive polymer. The systematic approach adopted in this work-from preformulation studies and biomaterial isolation to in-vitro, ex-vivo, and stability evaluations—provided comprehensive insight into the feasibility of buccal delivery of ramipril as an alternative to conventional oral dosage forms. Preformulation and compatibility studies confirmed

the physicochemical stability of ramipril in combination with the selected polymers. The isolated marigold pectic polysaccharide exhibited favorable swelling and mucoadhesive characteristics, validating its role as an effective natural biomaterial. Buccal films prepared by solvent casting showed acceptable mass uniformity, thickness, folding endurance, and surface pH, indicating good mechanical strength and patient-friendly properties. Among all formulations, F5 emerged as the optimized formulation due to its balanced polymer composition, which resulted in rapid disintegration, high flexibility, and uniform drug content.

In-vitro drug release studies revealed that F5 provided a controlled and sustained release profile, ensuring efficient drug availability without premature erosion of the film matrix. Ex-vivo studies using rabbit buccal mucosa further substantiated the superior performance of F5, as evidenced by enhanced mucoadhesive strength, prolonged residence time, and improved drug permeation. These outcomes highlight the importance of strong polymer–mucin interactions and optimal hydration in achieving effective transmucosal drug delivery. The improved permeation profile suggests that buccal administration of ramipril could potentially bypass hepatic first-pass metabolism, thereby enhancing bioavailability and therapeutic efficacy. Accelerated stability studies confirmed that the optimized formulation retained its critical quality attributes over six months under stressed conditions, with negligible changes in disintegration time and drug content. This stability underscores the robustness of the polymeric matrix and the suitability of the formulation for long-term storage. The significance of this study lies in the successful utilization of a natural, biodegradable biomaterial to develop a stable and efficient buccal drug delivery system for ramipril. The developed formulation offers potential advantages such as rapid onset of action, reduced dosing frequency, improved patient compliance, and minimized systemic side effects. Future perspectives of this work include in-vivo pharmacokinetic and pharmacodynamic studies to establish clinical relevance, scale-up feasibility, and evaluation of long-term stability under real-time conditions. Additionally, the platform developed in this study may be extended to other drugs with poor oral bioavailability, further broadening the applicability of mucoadhesive buccal film technology.

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