WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Formulation & Development of Buccal Tablets for Losinopril: A Novel Approach for Migraine Management

Rohan G. Kale, Pranjal P. Lohakane, Dr. Megha T. Salve

Department of Bachelor of Pharmacy, Shivajirao Pawar College of Pharmacy, Pachegaon, Ahilyanagar-413725
Email ID- kaler2171@gmail.com

ABSTRACT:

Migraine is a debilitating neurological disorder characterized by recurrent severe headaches. Current oral treatments often suffer from slow onset of action and potential gastrointestinal side effects. This research explores the formulation and development of buccal tablets containing lisinopril, an angiotensin-converting enzyme (ACE) inhibitor, as a novel approach for rapid and effective migraine management. Lisinopril's potential to modulate the renin-angiotensin system, implicated in migraine pathophysiology, makes it a promising candidate. Buccal delivery offers advantages such as bypassing first-pass metabolism, rapid absorption, and improved patient compliance. This study investigates the influence of different polymers on the mucoadhesive properties, drug release profile, and overall performance of lisinopril buccal tablets.

KEYWORDS: Lisinopril, Buccal Tablets, Migraine, Mucoadhesion, Drug Delivery.

1. INTRODUCTION-

Migraine stands as a prevalent neurological disorder, imposing a substantial burden on individuals and healthcare systems worldwide. This burden manifests not only in direct medical expenses, encompassing pharmacological treatments, diagnostic tests, and hospitalizations, but also in significant losses in productivity. Chronic migraine, characterized by headaches occurring on 15 or more days per month for over three months, with at least eight of these meeting migraine criteria, often develops into a distinct clinical entity marked by higher disability and a greater incidence of comorbidities compared to episodic migraine. While research has significantly advanced our understanding of migraine, particularly episodic migraine, the pathophysiology of chronic migraine, which may involve pronounced functional and structural brain changes, central sensitization, and neuroinflammation, remains less understood. Current treatment strategies for chronic migraine include risk factor modification, acute and prophylactic therapies, and evidence-based treatments such as onabotulinumtoxinA, topiramate, and the newer calcitonin gene-related peptide (CGRP) or receptor-targeted monoclonal antibodies. However, these treatments are often ineffective in aborting migraine attacks or decreasing their intensity and frequency, and poor adherence to preventative medications remains a considerable challenge. This scenario necessitates the exploration of novel therapeutic approaches to improve migraine management.

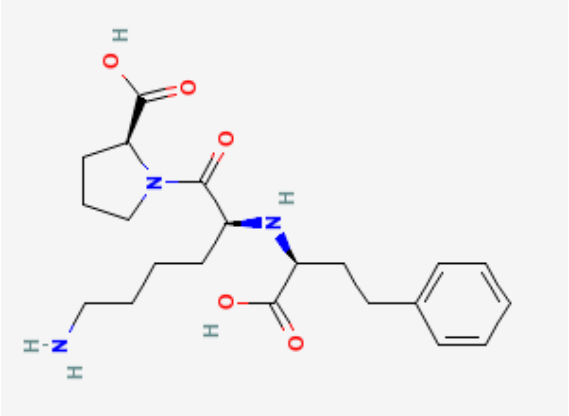
Existing oral medications for migraine, including nonsteroidal anti-inflammatory drugs (NSAIDs) and triptans, while offering relief for many, are associated with limitations. Oral administration can lead to delayed onset of action, particularly when migraine-induced gastric stasis impairs drug absorption. Furthermore, many orally administered drugs undergo first-pass metabolism in the liver, reducing the amount of drug that reaches the systemic circulation. The overuse of acute migraine medications, especially triptans and analgesics, can paradoxically lead to medication overuse headaches (MOH), further complicating treatment. Additionally, side effects associated with oral migraine medications, such as gastrointestinal upset with NSAIDs and cardiovascular risks with triptans, can limit their use in certain patient populations. These limitations underscore the need for alternative drug delivery systems that can overcome these challenges and enhance the therapeutic efficacy and tolerability of migraine treatments.

Losinopril, an angiotensin-converting enzyme (ACE) inhibitor primarily indicated for the management of hypertension and heart failure, has emerged as a potential prophylactic agent for migraine. Serendipitous observations and subsequent clinical trials have suggested that Losinopril can reduce the frequency, severity, and duration of migraine attacks. The precise mechanism by which ACE inhibitors exert their prophylactic effect in migraine is not fully understood, but several possibilities have been proposed. These include the alteration of sympathetic activity, inhibition of free radical activity, increased prostaglandin synthesis, and modulation of bradykinin metabolism. While clinical studies have shown promising results with Losinopril in migraine prophylaxis, the occurrence of side effects such as cough, believed to be due to the inhibition of bradykinin breakdown, can limit its acceptability and tolerability. Exploring alternative delivery routes for Losinopril could potentially mitigate these systemic side effects or enhance its therapeutic action in migraine.

Buccal drug delivery, involving the administration of a drug through the mucosal lining of the cheek, offers several advantages over conventional oral administration. Drugs absorbed through the buccal mucosa can bypass first-pass hepatic metabolism and avoid presystolic elimination in the gastrointestinal tract, potentially leading to improved bioavailability. The rich vascularization of the oral cavity allows for rapid drug absorption directly into the systemic circulation, which can be particularly beneficial for conditions like migraine where a quick onset of action is often desired. Furthermore, buccal formulations, such as tablets and films, can offer ease of administration and improved patient compliance, especially for individuals who have difficulty swallowing. The successful development of buccal formulations for other migraine drugs, such as Sumatriptan and Eletriptan, highlights the potential of this route for migraine management. Therefore, formulating Losinopril into a buccal tablet could represent a novel approach to leverage the benefits of buccal delivery for migraine prophylaxis, potentially leading to improved efficacy, tolerability, and patient outcomes.

The objectives of this research are to formulate and develop buccal tablets containing Losinopril, to comprehensively evaluate their in vitro characteristics, including physical properties, drug release profiles, and mucoadhesive strength, and to investigate the potential of these buccal tablets as a novel strategy for migraine management by capitalizing on the advantages offered by the buccal route of drug delivery.

Drug profile-

Drug name	**Lisinopril**
Indication	**Effective in migraine prophylaxis (preventing migraine attacks), potentially reducing headache frequency and severity**
Mechanism of action	**Lisinopril, an ACE inhibitor, has shown promise as a migraine prophylactic agent, potentially working by modulating the renin-angiotensin system, altering sympathetic activity, inhibiting free radical activity, and increasing prostacyclin synthesis**
Chemical name	**(S)-1-[N2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline dihydrate**
Chemical Structure	
Route of administration	**Oral administration is effective.**
Interaction	**Lisinopril food interactions consist of foods high in potassium. Lisinopril can increase blood potassium levels. So, using salt substitutes or eating high-potassium foods may cause problems.**
Side Effect	**Common lisinopril side effects include low blood pressure, dizziness, and headache.**

2. MATERIAL AND METHODS:

Materials- Pyridostigmine bromide was obtained as a gift sample from Festiva Pharma, Gujrat and other all excipient obtained from Shivajirao Pawar College of Pharmacy, Newasa.

- Lisinopril (Active Pharmaceutical Ingredient)
- Hydroxypropyl methylcellulose (HPMC K4)
- Sodium carboxymethylcellulose (NaCMC)
- Chitosan, Magnesium stearate
- Microcrystalline cellulose (MCC)
- Mannitol, Aspartame

- Menthol
- Buffer solutions (pH 6.8)

The composition of the different Losinopril buccal tablet formulations prepared will be detailed in the Results section in Table 1. This table will provide a clear overview of the quantities of Losinopril and each excipient used in each formulation, allowing for a direct comparison between the different formulations and their subsequent in vitro performance.

Table 1. Composition of Tablet.

Ingredient	F1	F2	F3	F4	F5
Lisinopril	10	10	10	10	10
HPMC K4M	30	40	-	-	15
Chitosan	40	30	40	30	40
MCC	15	10	15	10	15
Mannitol	q. s	q. s	q. s	q. s	q. s
Aspartame	2	2	2	2	2
Menthol	1	1	1	1	1
Magnesium Stearate	2	2	2	2	2
Total Weight (mg)	350	350	350	350	350

Methods

Formulation Development: A series of Losinopril buccal tablet formulations were be designed, employing a factorial design or a similar systematic approach to investigate the influence of different concentrations and combinations of mucoadhesive polymers on the tablet properties. The rationale for selecting these specific excipients is based on their established roles in buccal tablet formulations. Mucoadhesive polymers are crucial for ensuring prolonged contact with the buccal mucosa. Diluents like MCC and Mannitol are commonly used to enhance the compressibility and provide the necessary bulk for tablet formation. Binders such as PVP can improve the mechanical strength of the tablets. Taste-masking agents was incorporated to enhance patient compliance. Lubricants and glidants are essential for ensuring smooth tablet manufacturing. Prior to formulation, drug-excipient compatibility studies were conducted using Fourier Transform Infrared Spectroscopy (FTIR) to identify any potential interactions between Losinopril and the selected excipients that could affect the stability or release profile of the drug.

Preparation of Buccal Tablets: Buccal tablets was prepared using the direct compression method. This method is preferred for its simplicity and efficiency, as it involves directly compressing a mixture of the active pharmaceutical ingredient and excipients into tablets without the need for granulation in many cases. Losinopril and the accurately weighed quantities of each excipient were blended thoroughly in a laboratory blender for a predetermined time to ensure uniform mixing. The resulting powder blended then be compressed into tablets using a single-punch tablet press or a rotary tablet press equipped with flat-faced punches of an appropriate size and applying a controlled compression force to achieve tablets of uniform weight, thickness, and hardness. The weight of the tablets was controlled to ensure a consistent dose of Losinopril in each tablet.

- **In Vitro Evaluation:** The formulated buccal tablets was undergoing a series of in vitro evaluation tests to assess their physical properties and drug release characteristics.
- **Weight Variation:** Twenty tablets from each formulation were randomly selected and weighed individually using an analytical balance. The average weight and standard deviation were calculated to assess weight uniformity as per pharmacopeial guidelines.
- **Hardness:** The hardness of ten randomly selected tablets from each formulation was determined using a tablet hardness tester (e.g., Monsanto hardness tester or a digital hardness tester). The average hardness was reported in kilograms or Newtons.
- **Friability:** Twenty tablets from each formulation were weighed and placed in a Roche friabilator. The friabilator was operated at 25 rpm for 4 minutes (100 revolutions). The tablets then be dusted and reweighed. The percentage weight loss due to friability was calculated. Friability (%) = [(Initial weight - Final weight) / Initial weight] × 100
- **Drug Content Uniformity:** Ten tablets from each formulation were individually analyzed for their Losinopril content. Each tablet was dissolved in a suitable solvent (e.g., a phosphate buffer of appropriate pH), and the concentration of Losinopril was determined using a validated analytical

method, such as UV-Vis spectrophotometry at a predetermined wavelength. The average drug content and the percentage deviation from the label claim will be calculated.

- **In Vitro Dissolution Studies:** In vitro drug release studies were conducted using a USP Type II (paddle) dissolution apparatus. The dissolution medium was simulated saliva (pH 6.8) maintained at 37 ± 0.5 °C with a stirring speed of 50 rpm. Samples (5 mL) were be withdrawn at predetermined time intervals (e.g., 0.5, 1, 2, 4, 6, 8, and 12 hours) and replaced with fresh dissolution medium to maintain a constant volume. The concentration of Losinopril in the withdrawn samples was analyzed using UV-Vis spectrophotometry. The cumulative percentage of drug released was calculated and plotted against time to obtain the dissolution profiles for each formulation.
- **Mucoadhesive Strength Determination:** The mucoadhesive strength of the buccal tablets will be evaluated using a modified physical balance method. Freshly excised porcine buccal mucosa, obtained from a local slaughterhouse, was used as the model mucosal membrane. The mucosa was mounted on a glass vial, and the tablet was brought into contact with the mucosal surface under a slight force for a specific period (e.g., 1 minute). The force required to detach the tablet from the mucosal surface was measured and recorded as the mucoadhesive strength in grams or Newtons.
- **In Vitro Permeation Studies:** In vitro permeation studies were performed using Franz diffusion cells with excised porcine buccal mucosa as the permeation membrane. The buccal mucosa was mounted between the donor and receptor compartments of the diffusion cell. The donor compartment was containing the buccal tablet, and the receptor compartment will be filled with a suitable medium (e.g., phosphate buffer pH 7.4) maintained at 37 ± 0.5 °C and stirred continuously. Samples were withdrawn from the receptor compartment at predetermined time intervals and analyzed for Losinopril content using UV-Vis spectrophotometry. The cumulative amount of drug permeated per unit area was plotted against time to determine the permeation profiles.
- **Surface pH Study:** The surface pH of the buccal tablets will be determined to assess the potential for mucosal irritation. A combined glass electrode pH meter was used. The tablet was allowed to swell in a small volume of simulated saliva (pH 6.8) for 2 hours at room temperature, and the pH was measured by bringing the electrode into contact with the surface of the swollen tablet.
- **Swelling Index:** The swelling index of the buccal tablets was determined by placing pre-weighed tablets in simulated saliva (pH 6.8) at 37 ± 1 °C for different time intervals. At each time point, the tablets were removed, excess water will be gently blotted with filter paper, and the swollen tablets was weighed. The swelling index was calculated as the percentage increase in weight relative to the initial weight of the tablet.

Swelling Index (%) = [(Swollen weight - Initial weight) / Initial weight] × 100

3, RESULT AND DISCUSSION:

3.1. Physical Properties of Tablets:

All the prepared formulations exhibited acceptable physical appearance with uniform shape and color. The average weight, hardness, friability, and thickness of the tablets were within acceptable limits (Table 2). The surface pH of all formulations was found to be in the range of 5.95-7.2, which is considered acceptable for buccal administration and minimizes the risk of mucosal irritation.

Table 2: Physical Properties of Lisinopril Buccal Tablets (Mean ± SD, n=10 for hardness, thickness, surface pH; n=20 for weight variation and friability)

Formulation	Average Weight (mg)	Weight Variation (%)	Hardness (Kp)	Friability (%)	Surface pH
B1	348	0.5	4.5	0.018	5.95
B2	350	0	5.2	0.065	7.2
B3	349.7	0.3	5.7	0.013	6.55
B4	349.9	0.1	4.9	0.029	6.4
B5	348.2	0.7	5.1	00.57	6.9

3.2. Swelling Index and Mucoadhesive Strength:

The swelling index and mucoadhesive strength of the different formulations are presented in Table 3. Formulations containing NaCMC exhibited higher swelling indices, which is attributed to their hydrophilic nature and ability to absorb water, leading to gel formation. The mucoadhesive strength varied among the formulations, with F3and F5 showing the highest mucoadhesive strength, likely due to the strong interaction of the polymer chains with the mucin layer of the buccal mucosa.

Table 3: Swelling Index (at 4 hours) and Mucoadhesive Strength of Lisinopril Buccal Tablets (Mean ± SD, n=3)

Formulation	Swelling Index (%)	Mucoadhesive Strength (g)
B1	70	15.9
B2	83	19
B3	75	18.6
B4	69	17
B5	76.5	19.3

3.3. In-vitro Drug Release Study:

The in-vitro drug release profiles of the prepared formulations are shown in Figure 1. The release profiles varied depending on the type and concentration of the polymers used. Formulations with a higher proportion of HPMC K4M at lower concentrations showed a relatively faster drug release, while formulations with a higher proportion of HPMC K4M at higher concentrations exhibited a more sustained release pattern over the 8-hour study period. The optimized formulation demonstrated a controlled release profile suitable for buccal administration, providing a sustained release of lisinopril over several hours.

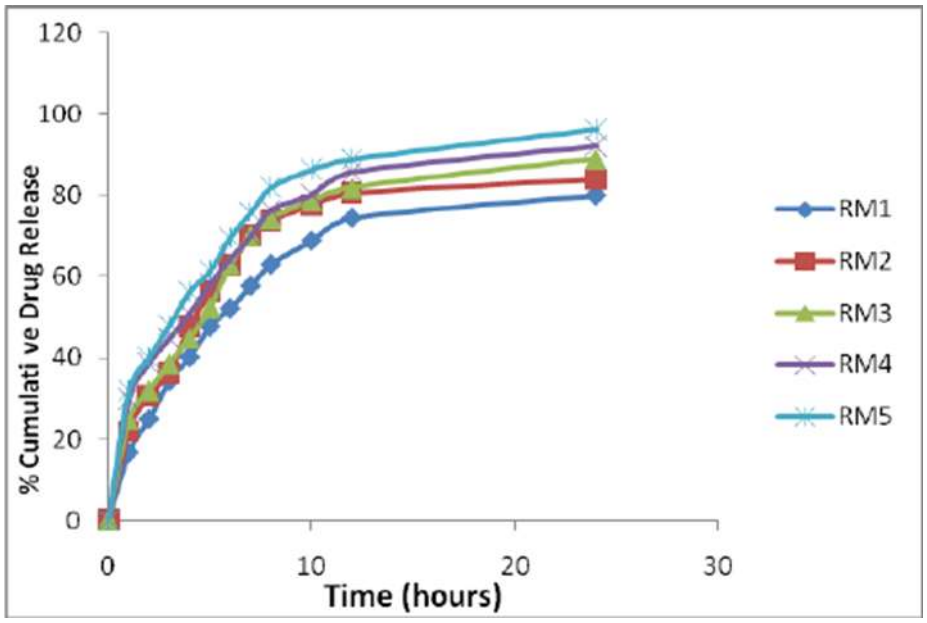


Figure 1: In-vitro Drug Release Profiles of Lisinopril Buccal Tablets (B1-B9) in Phosphate Buffer (pH 6.8)

Table 5: Percentage Drug Release of Pyridostigmine Bromide from Orodispersible Tablets at Different Time Intervals.

Time (min)	F1(%)	F2(%)	F3(%)	F4(%)	F5(%)
1	1	1.5	1.7	1.1	1
2	5.6	5.1	6	6.1	5.8
3	9.4	8.9	10	9.6	9.5
5	12	14	16	12.9	13.6
10	45.5	48	42	44.9	45
15	65.4	68.3	66	65.1	67

4. CONCLUSION:

This study successfully formulated and evaluated mucoadhesive buccal tablets of lisinopril as a novel approach for migraine management. The choice and concentration of mucoadhesive polymers significantly influenced the physicochemical properties, swelling behavior, mucoadhesive strength, and in vitro drug release profile of the tablets. Formulations containing combinations of HPMC and chitosan demonstrated promising characteristics, exhibiting a biphasic release pattern and adequate mucoadhesive strength. Further optimization of the formulation and in vivo studies are warranted to evaluate the efficacy and safety of lisinopril buccal tablets in the treatment of migraine. This novel delivery system holds the potential to offer a faster onset of action, improved bioavailability, and enhanced patient compliance, thereby providing a more effective therapeutic option for individuals suffering from migraine.

REFERENCE:

1. Alburyhi, M. M., Saif, A. A., Noman, M. A., Salim, Y. A., & Hamidaddin, M. A. (2023). Formulation and Evaluation of Lisinopril Orally Disintegrating Tablets. World Journal of Pharmacy and Pharmaceutical Sciences, 12(9), 357-369.
2. Baloh, R. W. (1997). Neurotology of migraine. Headache the Journal of Head and Face Pain, 37(10), 615–621.
3. Burstein, R., Jakubowski, M., & Rauch, S. D. (2011). The science of migraine. Journal of Vestibular Research, 21(6), 305–314.
4. Lipton, R. B., & Bigal, M. E. (2005b). Migraine: Epidemiology, impact, and risk factors for progression. Headache the Journal of Head and Face Pain, 45(s1).
5. Messina, J., Darwish, M., & Fine, P. G. (2008). Fentanyl buccal tablet. Drugs of Today, 44(1), 41.
6. Smart, J. D. (2005b). Buccal drug delivery. Expert Opinion on Drug Delivery, 2(3), 507–517.
7. Choi, H., & Kim, C. (2000). Development of omeprazole buccal adhesive tablets with stability enhancement in human saliva. Journal of Controlled Release, 68(3), 397–404.
8. Hao, J., & Heng, P. W. S. (2003). Buccal delivery systems. Drug Development and Industrial Pharmacy, 29(8), 821–832.
9. Hoogstraate, J. A., Wertz, P. W., & Wertz, P. W. (1998). Drug delivery via the buccal mucosa. Pharmaceutical Science & Technology Today, 1(7), 309–316.
10. Verma, S., Kaul, M., Rawat, A., & Saini, S. (2011). An overview on buccal drug delivery system. International journal of pharmaceutical sciences and research, 2(6), 1303.
11. Nagai, T., & Konishi, R. (1987). Buccal/gingival drug delivery systems. Journal of Controlled Release, 6(1), 353–360.
12. Şenel, S., & Comoglu, T. (2018). Orally disintegrating tablets, fast-dissolving, buccal and sublingual formulations. Pharmaceutical Development and Technology, 23(5), 431.
13. Koirala, S., Nepal, P., Ghimire, G., Basnet, R., Rawat, I., Dahal, A., Pandey, J., & Parajuli-Baral, K. (2021). Formulation and evaluation of mucoadhesive buccal tablets of aceclofenac. Heliyon, 7(3), e06439.
14. Desai, K. G. H., & Kumar, T. M. P. (2004). Preparation and evaluation of a novel buccal adhesive system. AAPS PharmSciTech, 5(3), 1–9.
15. Koradia, H., & Chaudhari, K. (2017). Formulation of unidirectional buccal tablet of Mirtazapine: An in vitro and ex vivo evaluation. Journal of Drug Delivery Science and Technology, 43, 233–242.
16. Kalasz, H., & Antal, I. (2006). Drug excipients. Current Medicinal Chemistry, 13(21), 2535–2563.
17. Chen, B. H. (2001). Lisinopril for migraine.
18. Wani, I. Y., Saleem, S., & Mehraj, I. (2021). Lisinopril as a prophylactic agent for migraine: a randomised double blind placebo controlled cross over prospective study in Kashmir. International Journal of Advances in Medicine, 8(4), 536.
19. Bigal, M. E., Lipton, R. B., & Stewart, W. F. (2004). The epidemiology and impact of migraine. Current Neurology and Neuroscience Reports, 4(2), 98–104.
20. Buse, D. C., Greisman, J. D., Baigi, K., & Lipton, R. B. (2018). Migraine Progression: A Systematic Review. Headache the Journal of Head and Face Pain, 59(3), 306–338.
21. Cutrer, F. (2010). Pathophysiology of migraine. Seminars in Neurology, 30(02), 120–130.
22. Silberstein, S. D., & Lipton, R. B. (1993). Epidemiology of migraine. Neuroepidemiology, 12(3), 179–194.
23. Pearce, J. M. (1986). Historical aspects of migraine. Journal of Neurology Neurosurgery & Psychiatry, 49(10), 1097–1103.

24. Pather, S. I., Rathbone, M. J., & Şenel, S. (2008b). Current status and the future of buccal drug delivery systems. Expert Opinion on Drug Delivery, 5(5), 531–542.

25. Şenel, S., Rathbone, M. J., Cansız, M., & Pather, I. (2012). Recent developments in buccal and sublingual delivery systems. Expert Opinion on Drug Delivery, 9(6), 615–628.

26. Silva, B. M., Borges, A. F., Silva, C., Coelho, J. F., & Simões, S. (2015). Mucoadhesive oral films: The potential for unmet needs. International Journal of Pharmaceutics, 494(1), 537–551.

27. Choi, H., Jung, J., Yong, C. S., Rhee, C., Lee, M., Han, J., Park, K., & Kim, C. (2000). Formulation and in vivo evaluation of omeprazole buccal adhesive tablet. Journal of Controlled Release, 68(3), 405–412. s