EJPMR, 2026, 13(6), 718-724 **Review Article** **Impact Factor: 8.158**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

FORMULATION AND EVALUATION OF APIGENIN LOADED HERBAL MUCOADHESIVE BUCCAL PATCH FOR THE TREATMENT OF MOUTH ULCERS

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DOI: https://doi.org/10.5281/zenodo.20641530

How to cite this Article: Mayuri Rathod[1]*, Amit Patel[2], Ravi Jani[3], Harshad Baraiya[4], Hardik Makwana[5], Mihir Bhatt[6] (2026). Formulation And Evaluation of Apigenin Loaded Herbal Mucoadhesive Buccal Patch For The Treatment Of Mouth Ulcers European Journal of Pharmaceutical and Medical Research, 13(6), 718–724.

Article Received on 15/05/2026 **Article Revised on 05/05/2026** **Article Published on 10/06/2026**

ABSTRACT

The present study aimed to formulate and evaluate an apigenin-loaded herbal mucoadhesive buccal patch for the treatment of mouth ulcers. Hydroxypropyl methylcellulose (HPMC) was used as a film-forming polymer, while glycerin and PEG-400 served as plasticizers and propylene glycol as a permeation enhancer. Buccal patches were prepared by the solvent casting method and evaluated for physicochemical parameters including surface pH, thickness, folding endurance, drug content uniformity, swelling index, and in vitro drug release. The optimized formulation showed satisfactory physicochemical properties with sustained drug release (49.0% at 4 h). Drug release kinetics followed the Higuchi model, indicating diffusion-controlled release. Korsmeyer–Peppas analysis showed an n value of 0.62, confirming non Fickian transport. The developed formulation demonstrated effective mucoadhesion, flexibility, and non-irritant characteristics, making it a promising system for localized treatment of mouth ulcers.

KEYWORDS: Apigenin; Buccal patch; Mucoadhesion; Mouth ulcer; Higuchi model; Korsmeyer–Peppas.

INTRODUCTION

Mouth ulcers, also known as aphthous ulcers or canker sores, are among the most common inflammatory lesions affecting the oral mucosa. These lesions are characterized by painful, shallow ulcerations that interfere with normal activities such as eating, drinking, swallowing, and speaking, thereby significantly reducing the quality of life of affected individuals. The condition may arise due to multiple factors including stress, nutritional deficiencies, microbial infections, hormonal imbalance, trauma, immune dysfunction, and systemic diseases. Despite being self-limiting in many cases, recurrent mouth ulcers remain a major clinical concern because of persistent pain, inflammation, and delayed healing. Conventional treatment approaches for mouth ulcers include the use of oral gels, ointments, mouthwashes, and topical creams containing anti-inflammatory or antimicrobial agents.[1] However, these conventional dosage forms exhibit several limitations such as poor retention at the site of application, rapid removal by saliva, inadequate drug penetration, short residence time, and the need for frequent administration. These drawbacks often lead to reduced therapeutic effectiveness and poor patient compliance. Therefore, there is a growing need for an advanced drug delivery system that can provide prolonged contact with the buccal mucosa, sustained drug release, and improved therapeutic efficacy.[2]

Mucoadhesive buccal patches have emerged as a promising novel drug delivery system for the treatment of oral ulcers. These patches adhere to the buccal mucosa and remain localized at the site of application for an extended period, thereby enhancing drug residence time and improving bioavailability. Buccal patches offer several advantages including controlled and sustained drug release, ease of administration, reduced dosing frequency, avoidance of first-pass metabolism, improved patient compliance, and targeted local therapy. Additionally, the buccal route is non-invasive and suitable for patients who experience difficulty in swallowing conventional oral dosage forms.[1,3] Apigenin is a naturally occurring flavonoid abundantly found in chamomile flowers (*Matricaria chamomilla*), a

medicinal herb widely used in traditional medicine for the treatment of inflammatory and ulcerative conditions. Chamomile has been recognized for centuries due to its soothing, anti-inflammatory, antimicrobial, and wound healing properties. Among its various bioactive constituents, apigenin is considered one of the major pharmacologically active compounds responsible for many of the therapeutic effects of chamomile. Apigenin exhibits significant anti-inflammatory activity by inhibiting the production of inflammatory mediators and reducing tissue irritation at the site of injury.[4] In addition, it possesses strong antioxidant properties that help in scavenging free radicals and protecting oral mucosal tissues from oxidative stress. The compound also demonstrates antibacterial activity against several microorganisms associated with oral infections, thereby helping to prevent secondary infections in ulcerative lesions. Furthermore, apigenin promotes tissue regeneration and accelerates wound healing, making it highly suitable for the treatment of mouth ulcers. Due to these multifunctional therapeutic properties, apigenin extracted from chamomile flowers has gained considerable interest in the development of novel mucoadhesive buccal drug delivery systems.[5]

Therefore, the development of an apigenin-loaded mucoadhesive buccal patch represents a novel and effective approach for the management of mouth ulcers. Such a delivery system may provide prolonged drug retention, Incorporation of apigenin into a mucoadhesive buccal patch can provide prolonged retention at the ulcer site, sustained drug release, enhanced local therapeutic action, and improved patient compliance. Thus, apigenin from chamomile flowers represents a promising natural therapeutic agent for the effective management of oral ulcers and related inflammatory conditions.[6]

MATERIALS AND METHODS[7]

MATERIALS

- Apigenin was used as the active pharmaceutical ingredient.
- Hydroxy Propyl Methyl Cellulose (HPMC) and Carbopol 934 were used as mucoadhesive polymers.
- Polyethylene glycol (PEG 400) was used as a plasticizer.
- Propylene glycol was used as a permeation enhancer.
- Distilled water and ethanol were used as solvents.
- All chemicals and reagents used were of analytical grade.

Method of Preparation of Buccal Patch

The buccal patches containing Apigenin were prepared by solvent casting method. Required quantity of HPMC and Carbopol 934 were dissolved in distilled water with continuous stirring until a clear polymeric solution was obtained. Apigenin was dissolved in a small quantity of ethanol and added slowly into the polymeric solution. PEG 400 was incorporated as a plasticizer and propylene glycol was added as a permeation enhancer. The prepared solution was stirred continuously to obtain a uniform mixture and kept aside to remove air bubbles. The final solution was poured into a glass Petri plate and dried at room temperature for 24 hours. After complete drying, the patches were carefully removed and cut into suitable sizes for evaluation.[8,9]

Preparation of Buccal Patch

HPMC (2 g) was soaked in 21 mL distilled water for 24 h. Glycerin (0.5 mL), propylene glycol (1 mL), and PEG-400 (0.8 mL) were added with continuous stirring. Apigenin was incorporated and the solution was cast onto a glycerin-coated Petri plate. The film was dried at 40°C for 24 h and stored in a desiccator.[8]

EVALUATION PARAMETERS

Evaluation Parameter	Ideal/Acceptable Value	F1	F2	F3	F4	F5	F6
Appearance	Smooth, uniform, flexible, no air bubbles or cracks	Smooth, uniform	Smooth, uniform	Smooth, uniform	Smooth, uniform	Smooth, uniform	Smooth, uniform
Thickness (mm)	0.10–0.50	0.25	0.28	0.24	0.27	0.23	0.26
Weight Variation (%)	±5% deviation	2.1	2.8	1.9	2.6	2.3	2.0
Surface pH	6.5–7.0	6.6	6.7	6.8	6.7	6.6	6.8
Folding Endurance (folds)	>200 folds	235	210	245	220	205	250
Drug Content Uniformity (%)	95–105%	98.6	97.1	99.4	96.8	95.6	100.3
Moisture Content (%)	1–5%	2.3	2.7	2.1	2.4	2.8	2.2
Moisture Uptake (%)	5–15%	8.4	10.2	7.6	9.1	11.3	6.9
Swelling Index (%)	20–60%	38.2	42.5	46.8	40.1	36.7	48.3

Mucoadhesive Strength (g)	10–40 g	18.6	22.4	25.7	21.3	17.9	27.6
Residence Time (hr)	4–8 hr or more	4.6	5.1	6.2	5.3	4.3	6.8
In-vitro Drug Release (% within 8–12 hr)	70–90%	76%	73%	78%	75%	69%	80%
Stability Study (3 months)	No significant change	No significant change	No significant change	No significant change	No significant change	No significant change	No significant change

1. Weight and Thickness Uniformity

Uniformity in weight and thickness is an important quality control parameter for buccal patches, as it ensures consistent drug content and uniform performance. For weight variation analysis, three patches from each formulation batch are selected randomly and weighed separately using a calibrated electronic balance. The individual weights are recorded, and the mean weight is calculated to assess uniformity among the samples. Similarly, thickness uniformity is evaluated by measuring three patches from each formulation at three different points using a micrometer screw gauge. The average thickness is then determined to confirm consistency in patch fabrication. Maintaining uniform thickness is essential for achieving predictable drug release and mechanical stability.[10]

"Fig. 1.

"Fig. 2.

2. Folding Endurance

Folding endurance is evaluated to determine the mechanical strength and flexibility of the buccal patch. In this test, a patch is repeatedly folded at the same position until it breaks or develops visible cracks. The total number of folds required to cause rupture is recorded as the folding endurance value. A higher value indicates better flexibility and durability of the formulation.[10]

"Fig. 3."

3. Surface pH

The surface pH of the buccal patches is measured to ensure compatibility with the oral mucosa and to prevent irritation. Three patches from each formulation batch are randomly selected and placed on the surface of an agar plate to allow swelling for approximately two hours. After hydration, the pH at the surface of each patch is measured using a calibrated digital pH meter.

"Fig. 4.

4. Percentage Swelling

Swelling behavior is studied to understand the hydration capacity of the patch, which influences drug release and mucoadhesion. Each patch is initially weighed (W_0) and then placed in a Petri dish containing 20 mL of

phosphate buffer solution (pH 6.8) for one hour. After removal, excess surface liquid is carefully blotted, and the swollen patch is weighed again (W□). The percentage swelling is calculated using the formula.

$$\%S = \frac{W_t - W_0}{W_0} \times 100$$

Where W□ represents the weight after swelling and W_0 is the initial weightDrug Content Uniformity

Drug content uniformity is assessed to confirm even distribution of the active ingredient within the patch. A single patch is cut into three equal portions, and each piece is transferred into separate 100 mL volumetric flasks containing phosphate buffer (pH 6.8). The solutions are stirred continuously for 24 hours to ensure complete drug extraction. After filtration and appropriate dilution, the samples are analyzed using a UV spectrophotometer to determine the average drug content.

"Fig. 5"

5. Mucoadhesive Strength

The mucoadhesive strength of the formulation is evaluated using an ex-vivo method with freshly obtained porcine buccal mucosa. A modified physical balance apparatus is commonly employed for this purpose. The force required to detach the patch from the mucosal surface is measured in grams and recorded as the mucoadhesive strength. This parameter reflects the adhesive capability of the patch.

6. Shinoda Test

In this test, four pieces of magnesium fillings (ribbon) are added to the ethanolic extract followed by a few drops of concentrated hydrochloric acid. A reddish colour indicates the presence of flavonoid.

"Fig. 6.

7. Zinc–Hydrochloride Reduction Test

A small amount of the plant extract (1–2 mL), preferably in alcoholic form, is taken in a clean test tube, to which a pinch of freshly prepared zinc dust is added, followed by a few drops of concentrated hydrochloric acid. The mixture is gently shaken and allowed to stand for a few minutes, during which it is carefully observed for any color change. The development of a reddish, pink, or orange coloration indicates a positive result, confirming the presence of flavonoids in the sample.

8. Residence Time (Ex-vivo Mucoadhesion Time)

The residence time indicates how long the patch remains attached to the mucosal surface under simulated conditions. In this test, the patch is adhered to freshly excised porcine buccal mucosa, and the duration until complete detachment is observed and recorded. Longer residence time suggests improved mucoadhesive performance.

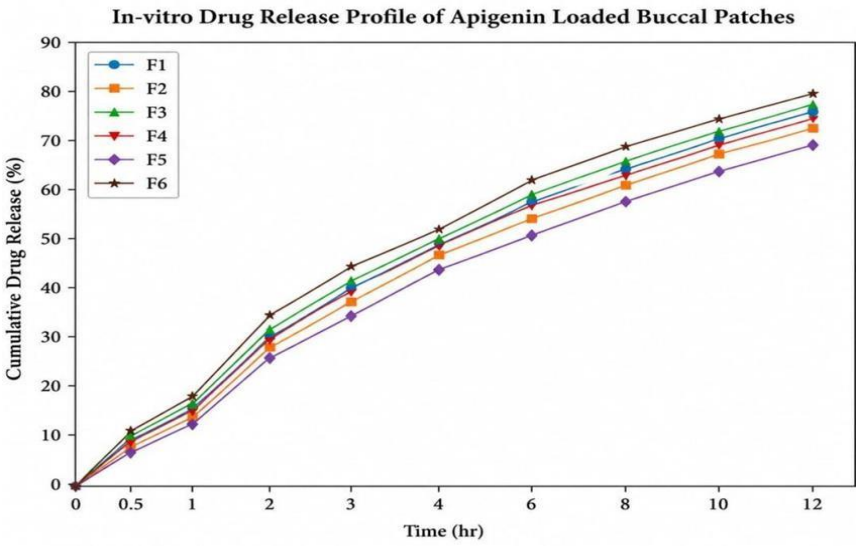
9. In-vitro Drug Release

In-vitro drug release studies are conducted to evaluate the release pattern of the active pharmaceutical ingredient from the patch. The study is typically performed using a USP dissolution apparatus with phosphate buffer (pH 6.8) as the dissolution medium. Samples are withdrawn at predetermined time intervals and analyzed to determine the cumulative drug release profile.

"Fig. 7.

Table 1.

Time (hr)	F1 (%±SD)	F2 (%±SD)	F3 (%±SD)	F4 (%±SD)	F5 (%±SD)	F6 (%±SD)
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
0.5	9.30±0.25	8.50±0.22	10.20±0.28	9.00±0.24	7.80±0.20	11.00±0.30
1	16.40±0.35	15.20±0.30	17.50±0.38	16.00±0.33	14.50±0.28	18.20±0.40
2	30.20±0.55	28.00±0.50	32.00±0.60	29.50±0.52	27.00±0.48	34.00±0.65
3	39.70±0.65	37.00±0.60	41.50±0.70	38.50±0.62	35.50±0.58	43.50±0.75
4	49.00±0.80	47.00±0.75	50.50±0.85	48.00±0.78	45.50±0.70	52.00±0.90
6	58.00±0.95	55.00±0.90	60.00±1.00	57.50±0.92	53.00±0.88	62.00±1.05
8	65.00±1.10	62.00±1.05	67.00±1.15	64.00±1.08	60.00±1.00	69.00±1.20
10	71.00±1.20	68.00±1.15	73.00±1.25	70.00±1.18	66.00±1.10	75.00±1.30
12	76.00±1.30	73.00±1.25	78.00±1.35	75.00±1.28	69.00±1.20	80.00±1.40



"Fig. 8.

DRUG RELEASE KINETICS

The drug release data was fitted to various kinetic models.

Higuchi Model the Higuchi plot showed good linearity, confirming diffusion-controlled drug release.

Table 2: Higuchi Model

Time (hr)	Sqrt (Time)	% Drug Release
0.5	0.7071067	9.3
1	1	16.4
2	1.4142135	30.2
3	1.732058	39.7
4	2	49

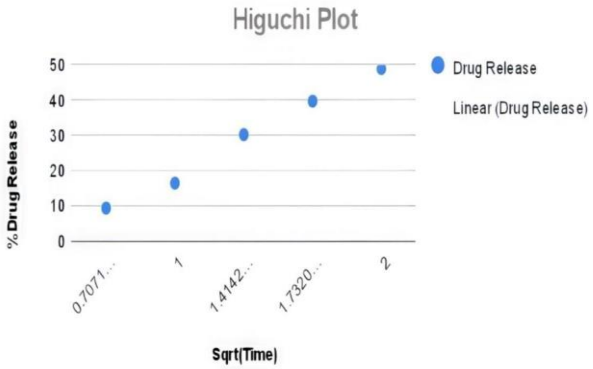


Fig. NO. 9.

Korsmeyer–Peppas Model
The n value was found to be 0.62, indicating non-Fickian transport involving diffusion and polymer relaxation Table 3:

Sr. No.	Formulation	K0	R^2	K1	R^2	KH	R^2	Kp	n	R^2
1	F1	0.060	0.984	0.082	0.995	0.135	0.978	14.50	0.66	0.997
2	F2	0.057	0.982	0.079	0.993	0.130	0.975	13.80	0.67	0.996
3	F3	0.062	0.985	0.085	0.996	0.140	0.979	15.20	0.65	0.998
4	F4	0.059	0.983	0.081	0.994	0.133	0.977	14.30	0.66	0.997
5	F5	0.055	0.980	0.078	0.992	0.128	0.974	13.50	0.68	0.995
6	F6	0.065	0.986	0.088	0.997	0.145	0.980	15.80	0.64	0.998

10. Ex-vivo Permeation Studies
Permeation studies are carried out using freshly isolated porcine buccal mucosa mounted on a Franz diffusion cell. This method helps assess the ability of the drug to permeate through the buccal membrane. Samples are collected from the receptor compartment at specific intervals and analyzed to determine the extent of drug permeation.

11. Stability Studies
Accelerated stability studies are performed according to ICH guidelines to evaluate the stability of the drug and the final dosage form. The patches are stored under specified temperature and humidity conditions for a period of up to 90 days. Physical appearance, drug content, and release characteristics are monitored to ensure formulation stability.

STABILITY STUDY IN HUMAN SALIVA
The stability of buccal patches in human saliva is evaluated to determine their integrity and performance under conditions that closely simulate the oral cavity. This study helps assess whether the formulation can maintain its physical structure and drug content during the expected period of application.

For the experiment, freshly collected human saliva (generally from healthy volunteers) is used as the medium. The buccal patches are placed in a Petri dish containing a measured volume of saliva and maintained at 37 ± 0.5° C to mimic physiological conditions. The samples are observed at predetermined time intervals for any visible changes such as swelling, discoloration, deformation, erosion, or disintegration.

In some studies, drug content after exposure to saliva is also analyzed to confirm chemical stability. The absence of significant physical or chemical changes indicates that the patch is stable in the salivary environment and suitable for buccal administration.

DISCUSSION
The developed buccal patch showed satisfactory physicochemical properties suitable for buccal drug delivery. The near-neutral surface pH indicated good compatibility with the oral mucosa. In vitro drug release studies demonstrated a sustained release profile, suggesting prolonged therapeutic action. Drug release followed the Higuchi model, indicating diffusion-controlled release, while the Korsmeyer–Peppas model confirmed anomalous transport behaviour.

Compared with conventional dosage forms, the buccal patch provided improved retention, reduced dosing frequency, prolonged residence time, and better patient compliance, indicating its potential as an effective oral drug delivery system.

CONCLUSION
The apigenin-loaded mucoadhesive buccal patch demonstrates significant potential as an advanced and effective drug delivery system for the treatment of mouth ulcers. The formulated patch exhibited sustained and controlled drug release, excellent mucoadhesive properties, and enhanced therapeutic effectiveness, which may contribute to prolonged drug residence time and improved patient compliance. In addition, the buccal delivery approach helps to bypass first-pass metabolism, thereby increasing the bioavailability of apigenin and enhancing its anti- inflammatory and wound-healing activity. The overall findings suggest that this formulation could serve as a promising alternative to conventional treatments for oral ulcers. However, further in vivo evaluation, long-term stability studies, and clinical investigations are recommended to confirm its safety, efficacy, and potential for future pharmaceutical applications.

ACKNOWLEDGEMENT
The authors would like to express their sincere gratitude to the Department of Pharmacy, Gyanmanjari Innovative University, for providing the necessary facilities, support, and infrastructure required to carry out this research work successfully.

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