(J I D P T S)
ISSN(O):2581-6934

DESIGN, DEVELOPMENT & INVITRO EVALUATION OF BRIVERACETAM BUCCAL FILM FOR IMPROVED BIOAVAILABILITY

B. VENKATA PHANI DEEPTHI[1]*, G. SRUJANA[2], A. SARITHA[3]
[1]*Associate Professor, [2] Student, [3] Professor and HOD
[1,2,3] Department of Pharmaceutics, SSJ College of Pharmacy, Vattinagulapally, Gandipet, Rangareddy District
Corresponding Author: B. Venkata Phani Deepthi, Associate Professor,
Department of Pharmaceutics, Sri Sai Jyothi College of Pharmacy, Gandipet Main Road, Vattinagulapally, Hyderabad, Telangana 500075.

Abstract: The present study was aimed at the design, development, and in-vitro evaluation of Brivaracetam buccal films to improve drug bioavailability by bypassing hepatic first-pass metabolism and providing controlled drug release through the buccal mucosa. Buccal films were prepared by the solvent casting method using Hydroxypropyl Methylcellulose (HPMC) and Carbopol 934 as film-forming and mucoadhesive polymers, respectively. Eight formulations (F1–F8) were developed by varying the polymer concentration while maintaining a constant drug dose of 25 mg. The thickness of the films ranged from 0.71 to 0.89 mm, while drug content varied from 79.86% to 95.86%. Moisture studies and swelling behavior indicated acceptable stability and hydration characteristics suitable for buccal application. In-vitro drug release studies were carried out using phosphate buffer (pH 6.8), and all formulations demonstrated sustained drug release over 300 minutes. Among the formulations, F7 exhibited the highest cumulative drug release (98.88%) along with excellent folding endurance (195) and drug content (95.86%), indicating optimum formulation performance. Drug release kinetic analysis revealed that the optimized formulation best fitted the Korsmeyer–Peppas model ($R^2 = 0.973$), followed by the Higuchi model ($R^2 = 0.965$), suggesting diffusion-controlled drug release from the hydrated polymeric matrix. The optimized formulation was subjected to accelerated stability studies at 40 ± 2°C and 75 ± 5% RH for 90 days according to ICH guidelines.

Keywords: Brivaracetam, Buccal film, Solvent casting, Mucoadhesion, HPMC, Carbopol 934, In-vitro drug release, Bioavailability, Epilepsy

INTRODUCTION

The oral route remains the most preferred method for drug administration because of its convenience, patient acceptance, cost-effectiveness, and ease of manufacturing.1 Buccal drug delivery has emerged as a promising alternative to conventional oral dosage forms due to its ability to deliver drugs directly through the buccal mucosa into the systemic circulation.2 The buccal mucosa is highly vascularized, relatively permeable, and easily accessible, allowing drugs to bypass hepatic first-pass metabolism and gastrointestinal degradation.3 Buccal films are thin, flexible polymeric dosage forms prepared using hydrophilic film-forming polymers, plasticizers, saliva-stimulating agents, and other suitable excipients. Upon application to the buccal mucosa, the film hydrates rapidly, adheres to the mucosal surface, and releases the incorporated drug in a controlled or immediate manner depending on the formulation design.3 Epilepsy is one of the most common chronic neurological disorders, affecting millions of people worldwide. It is characterized by recurrent, unprovoked seizures resulting from abnormal electrical activity in the brain. Brivaracetam is a third-generation antiepileptic drug chemically designated as (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide.4 It exhibits a high affinity for synaptic vesicle protein 2A (SV2A), approximately 15–30 times greater than levetiracetam, resulting in potent anticonvulsant activity. Buccal administration can facilitate

All rights reserved by www.jidps.com

rapid drug absorption through the richly vascularized buccal mucosa while bypassing hepatic first-pass metabolism and gastrointestinal degradation.5 The solvent casting method is the most widely adopted because it produces smooth, transparent, flexible films with excellent content uniformity and reproducibility. The prepared films are generally evaluated for physicochemical properties, moisture absorption, moisture loss, folding endurance, drug content, in vitro residence time, and in vitro drug release.6 7 The optimized formulation was further characterized using various physicochemical and in vitro evaluation techniques to establish its suitability as an effective alternative to conventional oral dosage forms for the management of epilepsy.8

MATERIALS

Brivaracetam was procured from Hetero Labs, Hyderabad. HPMC and Carbopol 934 were obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY

Formulation design

Table-1: Formulation Design of Brivaracetam Buccal films

F. Code	Drug (mg)	HPMC (mg)	Carbopol 934 (mg)	Propylene glycol (ml)	Methanol (ml)	Aspartame (mg)
F1	25	100	-	2	5	2
F2	25	200	-	2	5	2
F3	25	300		2	5	2
F4	25	400		2	5	2
F5	25	-	100	2	5	2
F6	25	-	200	2	5	2
F7	25	-	300	2	5	2
F8	25	-	400	2	5	2

Solvent casting technique

Brivaracetam buccal films were prepared by the solvent casting method using Hydroxypropyl Methylcellulose (HPMC) or Carbopol 934 as film-forming and mucoadhesive polymers, respectively. The composition of each formulation (F1–F8) is presented in the formulation table. Initially, the required quantity of HPMC (for formulations F1–F4) or Carbopol 934 (for formulations F5–F8) was accurately weighed and dispersed separately in the required volume of methanol (5 mL). The polymeric solution was stirred continuously using a magnetic stirrer for approximately 30–45 minutes until a clear and homogeneous solution was obtained. The solution was then allowed to stand for 30 minutes to ensure complete hydration of the polymer and to remove entrapped air bubbles. Brivaracetam (25 mg) was accurately weighed and dissolved in a small quantity of methanol. The drug solution was then slowly incorporated into the polymeric solution with continuous stirring to obtain a uniform drug-polymer mixture. Subsequently, propylene glycol (2 mL) was added as a plasticizer to impart flexibility to the films, followed by the addition of Aspartame (2 mg) as a sweetening agent to improve palatability. The resulting solution was stirred continuously for 15–20 minutes until all the ingredients were uniformly dispersed. The final casting solution was kept undisturbed for 15–30 minutes to eliminate any entrapped air bubbles. The homogeneous solution was then poured onto a clean, leveled glass Petri dish or glass mould of known surface area and spread uniformly to obtain films of uniform thickness. The cast films were dried in a hot air oven at 40 ± 2°C for 24 hours or allowed to dry at room temperature in a dust-free environment until complete evaporation of the solvent. After drying, the films were carefully peeled from the casting surface and visually inspected for smoothness, transparency, and the absence of air bubbles or imperfections. The dried films were cut into 2 × 2 cm^2 pieces, each containing the required dose of 25 mg of Brivaracetam, and stored individually in aluminum foil or butter paper inside airtight containers until further evaluation.9

Evaluation of mucoadhesive buccal patch formulation 10,11,12

Physical appearance:

The prepared buccal films were visually inspected for their physical appearance. The films were examined under normal daylight for color, transparency, smoothness, flexibility, surface texture, uniformity, and the presence of any air bubbles, cracks, wrinkles, or visible imperfections. The observations were recorded for each formulation to assess the overall quality and acceptability of the films.

Folding endurance:

The folding endurance of the buccal films was determined manually to evaluate their mechanical strength and flexibility. A film of known dimensions (2 × 2 cm^2) was repeatedly folded at the same position until it broke or developed visible cracks. The number of folds required to break the film was recorded as the folding endurance. The test was performed in triplicate for each formulation, and the average value was calculated.

Thickness of the film:

The thickness of each buccal film was measured using a calibrated digital Vernier caliper or digital micrometer screw gauge with an accuracy of 0.01 mm. The thickness was measured at five different locations (center and four corners) of each film to ensure uniformity. The average thickness and standard deviation were calculated and reported.

Weight uniformity:

Individual buccal films of identical dimensions (2 × 2 cm^2) were cut from different regions of the cast film and weighed separately using a calibrated analytical balance. The weight of each film was recorded in milligrams. Five films from each formulation were weighed, and the average weight and standard deviation were calculated to evaluate the uniformity of film weight.

Drug content:

A buccal film equivalent to 25 mg of Brivaracetam was accurately weighed and transferred into a 100 mL volumetric flask containing approximately 50 mL of phosphate buffer pH 6.8 (or a suitable solvent such as methanol if required). The solution was stirred continuously until the film completely dissolved, and the volume was made up to 100 mL with the same solvent. The resulting solution was filtered through Whatman No. 1 filter paper, and suitable dilutions were prepared. The absorbance was measured using a UV–Visible spectrophotometer at the predetermined λmax of Brivaracetam (approximately 210–214 nm, depending on the validated method) against a suitable blank. The drug content was calculated using the previously prepared calibration curve. The analysis was carried out in triplicate, and the average percentage drug content was determined.

Measurement of swelling index :

The swelling behavior of the buccal films was determined using phosphate buffer pH 6.8. A pre-weighed buccal film (W_1) was placed on the surface of a 2% agar gel plate prepared with phosphate buffer pH 6.8 or immersed in a small volume of phosphate buffer maintained at 37 ± 0.5°C. At predetermined time intervals (15, 30, 45, 60, 90, and 120 minutes), the film was carefully removed, gently blotted with filter paper to remove excess surface moisture, and reweighed (W_2). The swelling index was calculated using the following equation:

$S.I = (wt-w0) / w0$

where

S.I is the Swelling Index,

wt is the weight of film at time 't' and

w0 is the weight of the film at time 0.

Moisture absorption studies:

The moisture absorption capacity of the prepared Brivaracetam buccal films was determined to evaluate their hygroscopic nature and stability under humid conditions. Individual buccal films of uniform dimensions (2 × 2 cm^2) were accurately weighed using an analytical balance, and the initial weight (W_1) was recorded. A saturated solution of aluminum chloride was prepared in a desiccator to maintain a relative humidity of approximately 79% RH at room temperature. The pre-weighed films were placed on a wire mesh or perforated platform inside the desiccator without coming into contact with the saturated salt solution. The desiccator was tightly closed and maintained at 25 ± 2°C for 72 hours. After the specified storage period, the films were carefully removed, gently wiped to remove any surface moisture (if present), and immediately reweighed to obtain the final weight (W_2). The percentage moisture absorption was calculated using the following equation:

$$\text{Perentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture loss studies:

The moisture loss study was carried out to determine the amount of moisture lost from the prepared Brivaracetam buccal films under dry storage conditions and to evaluate their stability and resistance to drying. Individual buccal films of uniform dimensions (2 × 2 cm^2) were accurately weighed using an analytical balance, and the initial weight (W_1) was recorded. The pre-weighed films were placed individually in a desiccator containing anhydrous calcium chloride (or fused calcium chloride) as a desiccant to maintain a dry environment (approximately 0% relative humidity). The desiccator was tightly closed and kept at room temperature (25 ± 2°C) for 72 hours. After the storage period, the films were removed from the desiccator and immediately reweighed using the analytical balance to obtain the final weight (W_2). The percentage moisture loss was calculated using the following equation:

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

In-vitro Drug release studies:

The in-vitro drug release study of Brivaracetam buccal films was carried out using the USP Dissolution Apparatus Type II (Paddle method) to evaluate the drug release profile. The dissolution medium consisted of 900 mL of phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C, which simulates the pH of the buccal cavity. The paddle rotation speed was adjusted to 50 rpm throughout the study. A buccal film of known dimensions containing 25 mg of Brivaracetam was fixed onto a clean glass slide using a small amount of cyanoacrylate adhesive, with the drug-loaded surface exposed to the dissolution medium. The glass slide was carefully placed at the bottom of the dissolution vessel to prevent the film from floating during the study. At predetermined time intervals (5, 10, 15, 20, 30, 45, 60, 90, and 120 minutes), 5 mL of the dissolution medium was withdrawn and immediately replaced with an equal volume of fresh phosphate buffer maintained at the same temperature to maintain sink conditions. The withdrawn samples were filtered through Whatman No. 1 filter paper, suitably diluted when necessary, and analyzed using a UV–Visible spectrophotometer at the predetermined λmax of Brivaracetam (approximately 210–214 nm, depending on the validated analytical method) against phosphate buffer pH 6.8 as the blank. The cumulative percentage drug release was calculated from the calibration curve of Brivaracetam. Each formulation was evaluated in triplicate, and the average cumulative percentage drug release with standard deviation was determined.

Drug release kinetics:

In order to predict and correlate the release behavior of Brivaracetam from different films, it is necessary to fit into a suitable mathematical model. The in vitro Brivaracetam release data from buccal films were evaluated kinetically using various mathematical models like zero-order, first-order, Higuchi, and Korsmeyer–Peppas model equations.

Zero-Order Kinetics

$F = Kot$, where F represents the fraction of drug released in time t, and Ko is the zero-order release constant.

First-Order Kinetics

$\ln(1 - F) = -K1t$, where F represents the fraction of drug released in time t, and K1 is the first-order release constant.

Higuchi Model

$F = KHt1/2$, where F represents the fraction of drug released in time t, and KH is the Higuchi dissolution constant.

Korsmeyer–Peppas Model

$F = Kptn$, where F represents the fraction of drug released in time t, Kp is the Korsmeyer–Peppas release rate constant, and n is the diffusion exponent. The results of curve fitting into these above-mentioned mathematical models indicates the drug release behavior from these formulated buccal films of Brivaracetam. When the release rate of Brivaracetam and their respective correlation coefficients were compared, it was found to follow first-order release kinetics (R2 = 0.9866 to 0.9984).

Stability studies:

The stability studies of the optimized Brivaracetam buccal film formulation were carried out in accordance with the International Council for Harmonization (ICH) Guideline Q1A(R2) to evaluate the physical and chemical stability of the formulation during storage. The optimized buccal films were individually wrapped in aluminum foil and packed in airtight polyethylene pouches to protect them from environmental factors. The packaged films were stored in a stability chamber maintained at 40 ± 2°C and 75 ± 5% relative humidity (RH) (accelerated stability conditions) for a period of 3 months.

RESULTS AND DISCUSSION

Evaluation of Buccal formulation

Table-1: Physicochemical evaluation of Brivaracetam buccal films

Formulation code	Weight (mg)	Thickness (mm)	Folding endurance	Drug content (%)	% Moisture loss	% Moisture absorption	% Swelling index
F1	162	0.79	192	82.13	7.9	8.5	49
F2	158	0.82	187	84.59	8.2	8.9	53
F3	156	0.86	193	89.76	7.8	8.6	61
F4	172	0.84	86	79.86	8.3	9.1	55
F5	176	0.89	180	92.25	8.8	9.5	53
F6	170	0.78	193	93.67	8.2	9.2	45
F7	169	0.73	195	95.86	8.9	9.9	42
F8	173	0.71	191	94.89	8.5	9.3	50

Discussion

Weight Uniformity

The weight of the prepared Brivaracetam buccal films ranged from 156 mg (F3) to 176 mg (F5). The slight variation in weight among the formulations can be attributed to differences in polymer concentration and minor variations during solvent casting and drying. Nevertheless, all formulations exhibited acceptable weight uniformity, indicating uniform distribution of the casting solution and reproducibility of the preparation method. Films containing higher concentrations of Carbopol

(F5–F8) showed slightly higher weights due to the greater polymer content and higher moisture retention.

Thickness of the Films

The thickness of the buccal films varied between 0.71 mm (F8) and 0.89 mm (F5). The increase in polymer concentration generally resulted in thicker films because of the formation of a denser polymeric matrix. Films prepared with Carbopol showed slightly greater thickness than those prepared with HPMC at comparable concentrations owing to the higher viscosity and swelling characteristics of Carbopol. Uniform thickness among the formulations indicates proper casting and even distribution of the polymeric solution.

Folding Endurance

Folding endurance values ranged from 86 (F4) to 195 (F7). Most formulations exhibited excellent flexibility with folding endurance values greater than 180, indicating sufficient mechanical strength to withstand handling during packaging and administration. Formulation F7 showed the highest folding endurance (195), suggesting an optimum polymer concentration that produced flexible and durable films. In contrast, F4 exhibited the lowest value (86), which may be due to excessive HPMC concentration causing increased brittleness after drying.

Drug Content

The percentage drug content ranged from 79.86% (F4) to 95.86% (F7). Formulations F6, F7, and F8 demonstrated drug content greater than 93%, indicating efficient incorporation and uniform distribution of Brivaracetam within the polymer matrix. The lower drug content observed in F1 and particularly F4 may be due to non-uniform drug dispersion or drug loss during solvent evaporation. Among all formulations, F7 exhibited the highest drug content, suggesting superior formulation homogeneity.

Moisture Loss Studies

The percentage moisture loss of the buccal films ranged from 7.8% (F3) to 8.9% (F7). All formulations showed relatively low moisture loss, indicating adequate moisture retention and good physical stability under dry storage conditions. The differences observed among the formulations may be related to the hygroscopic nature of the polymers used. Films containing Carbopol exhibited slightly higher moisture loss because of their greater water-binding capacity.

Moisture Absorption Studies

The moisture absorption values ranged between 8.5% (F1) and 9.9% (F7). The films absorbed only a limited amount of moisture under humid conditions, indicating acceptable stability. Carbopol-containing formulations showed comparatively higher moisture absorption than HPMC formulations because Carbopol possesses numerous hydrophilic carboxylic acid groups capable of absorbing atmospheric moisture. Despite this increase, the moisture absorption values remained within acceptable limits, and the films maintained their structural integrity.

Swelling Index

The swelling index varied from 42% (F7) to 61% (F3). Formulation F3 exhibited the highest swelling index, indicating excellent hydration and potential for prolonged mucoadhesion due to the higher concentration of HPMC. Conversely, F7 showed the lowest swelling index, which may be attributed to the denser polymeric matrix formed by Carbopol, limiting excessive water uptake. Moderate swelling is desirable because it enhances intimate contact with the buccal mucosa without causing rapid erosion of the film.

In-vitro Dissolution Study

Table-2: In vitro drug release profiles of Brivaracetam buccal films (F1-F8)

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
15	15.93	16.39	17.45	18.12	17.49	18.69	19.86	18.45
30	30.25	28.56	25.37	32.59	29.86	31.59	32.56	30.25
45	45.89	41.17	40.19	46.83	41.13	47.82	49.83	43.18
60	56.32	50.28	52.37	53.19	50.25	57.89	59.15	55.78
120	62.37	60.18	63.25	65.78	61.48	63.58	65.80	61.49
180	74.82	72.23	75.59	76.39	74.16	74.81	78.84	75.68
240	81.15	82.25	83.15	81.15	80.25	83.26	85.95	83.69
300	92.26	93.69	95.55	96.35	94.85	97.48	98.88	96.83

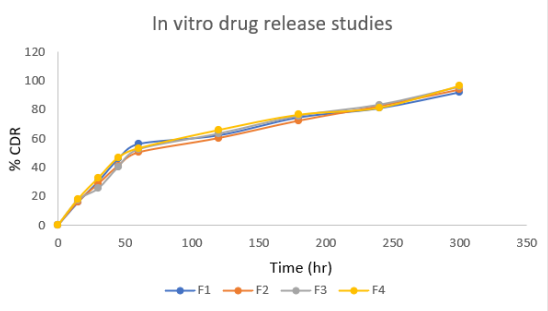


Fig-1: In vitro drug release studies of F1-F4 formulations

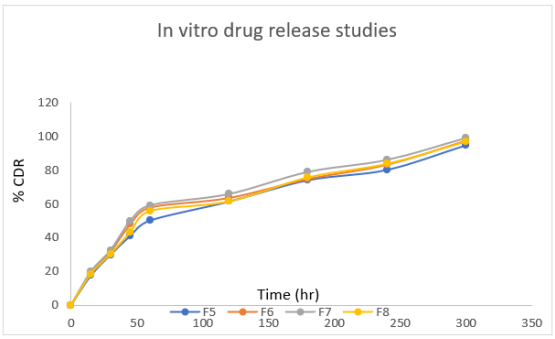


Fig-2: In vitro drug release studies of F5-F8 formulations

Overall, formulation F7 demonstrated the most desirable release profile with rapid initial release followed by sustained drug release, making it the optimized formulation for buccal drug delivery.

Kinetic modelling of drug release

All the 8 formulations of prepared buccal films of Brivaracetam were subjected to in vitro release studies these studies were carried out using diffusion apparatus.

Zero order kinetics

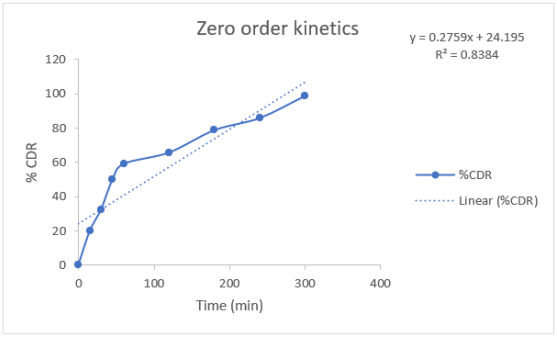


Fig-3: Zero order kinetics of optimized formulation

First order kinetics

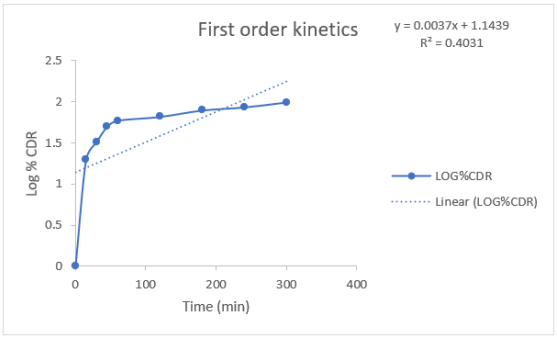


Fig-4: First order kinetics of optimized formulation

Higuchi model

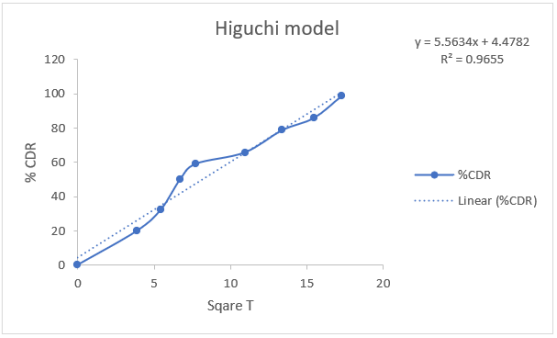


Fig-5: Higuchi model of optimized formulation

Korsmeyer peppas

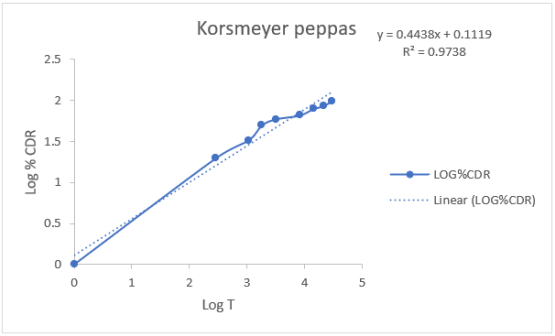


Fig-6: Korsmeyer peppas of optimized formulation

The kinetic values obtained for formulation F7 were shown. The values of in vitro release were attempted to fit into various mathematical models. Regression values are higher with First order release kinetics. Therefore, all the Brivaracetam buccal films follow Korsmeyer peppas release mechanism.

Table-3: Stability studies of optimized formulations at 40 ± 2 0C and 75 ± 5% RH for 3 months

Time in days	Drug content (%)	Folding endurance	Physical appearance	% Cumulative drug release
0	94.89	191	No change in color	98.88
90	93.56	189	Slight yellowish color	97.12

Discussion

No significant physical changes were observed except for a slight yellowish discoloration, which may be attributed to prolonged exposure to elevated temperature and humidity. Importantly, the cumulative drug release remained high, decreasing only from 98.88% to 97.12%, indicating that the release characteristics of the formulation were essentially unaffected by storage.

CONCLUSION

The present investigation successfully formulated and evaluated Brivaracetam buccal films using HPMC and Carbopol 934 by the solvent casting technique. All prepared formulations possessed satisfactory physicochemical characteristics, including acceptable weight uniformity, thickness, folding endurance, moisture content, swelling behavior, and drug content. Among the developed formulations, F7 was identified as the optimized formulation based on its superior physicochemical properties and highest cumulative drug release (98.88%). The optimized formulation also exhibited excellent mechanical strength, uniform drug distribution, and desirable swelling characteristics, making it suitable for prolonged residence in the buccal cavity. The release kinetic studies confirmed that Brivaracetam release followed the Korsmeyer–Peppas diffusion mechanism, indicating controlled drug release through the hydrated polymer matrix. Furthermore, accelerated stability studies demonstrated that the optimized formulation remained stable under ICH-recommended storage conditions without significant changes in drug content, mechanical properties, or dissolution profile. Therefore, the developed Brivaracetam buccal film represents a promising alternative to conventional oral dosage forms by providing sustained drug release, bypassing hepatic first-pass metabolism, improving bioavailability, and enhancing patient compliance.

REFERENCES

[1]. Aulton ME, Taylor KMG. Aulton's Pharmaceutics: The Design and Manufacture of Medicines. 6th ed. Elsevier; 2022.

[2]. Rathbone MJ, Senel S, Pather SI. Oral Mucosal Drug Delivery and Therapy. Springer; 2015.

[3]. Boateng JS, Ayensu I, Mitchell JC, Stevens HNE. Mucoadhesive drug delivery systems for buccal administration. Drug Development and Industrial Pharmacy. 2013;39(3):327–338.

[4]. Löscher W, Potschka H, Sisodiya SM, Vezzani A. Drug resistance in epilepsy: Clinical impact, potential mechanisms, and new therapeutic approaches. Nature Reviews Neurology. 2020;16(12):661–676.

[5]. Klein P, Schiemann J, Sperling MR, et al. A randomized, double-blind, placebo-controlled, multicenter trial of brivaracetam in patients with uncontrolled focal epilepsy. Neurology. 2015 ; 84(10) : 1007 – 1017.

[6]. Perioli L, Ambrogi V, Rubini D, et al. Novel mucoadhesive buccal formulation containing metronidazole for the treatment of periodontal disease. Journal of Controlled Release. 2004; 95(3) : 521–533.

[7]. Shipp L, Liu F, Kerai-Varsani L, Okwuosa TC. Buccal films: A review of therapeutic opportunities, formulations and relevant evaluation approaches. J Control Release. 2022;352:1071-1092.

[8]. Haju S, Yadav S, Baig R, Sawant G. Buccal film: A novel approach for oral mucosal drug delivery system. Asian J Pharm Clin Res. 2021;14(1):15-22.

[9]. Okwuosa TC, Kerai-Varsani L, Liu F, Shipp L. Buccal film drug delivery: Linking formulation design with pharmacokinetic control and clinical translation. J Pharm Sci. 2026.

[10]. Steinig I, von Podewils F, Möddel G. Brivaracetam in the treatment of epilepsy: A review of clinical trial data. Neuropsychiatr Dis Treat. 2019;15:2587-2600.

[11]. Boateng JS, Ayensu I, Mitchell JC, Stevens HNE. Mucoadhesive drug delivery systems for buccal administration. Drug Dev Ind Pharm. 2013;39(3):327-338.

[12]. Semalty A, Semalty M, Nautiyal U. Formulation and evaluation of mucoadhesive buccal films of enalapril maleate. Indian J Pharm Sci. 2010;72(5):571-575.