

Formulation and Optimization of Rizatriptan Benzoate Buccal Tablets for the Management of Acute Migraine

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Received: 24th July, 2026; Revised: 17th Aug, 2026; Accepted: 27th Sep, 2026; Available Online: 14th Oct, 2026

ABSTRACT

The present study aimed to formulate and optimize an efficient mucoadhesive buccal tablet of Rizatriptan benzoate using a 3² design to avoid first-pass hepatic metabolism and also to deliver the drug rapidly at an optimized rate over a prolonged period through the transmucosal route. Validation of the drug through organoleptic evaluation, solubility studies, melting point studies, method development by UV spectrophotometry, drug identification, drug purity, and polymer compatibility studies using FTIR and DSC with specified polymers confirmed drug identification, drug purity, and polymer compatibility, respectively. Nine buccoadhesive tablets were prepared by direct compression and subsequently optimized statistically by using 3² factorial designs to formulate nine batches of buccal tablets by fixing the concentrations of HPMC K15M and chitosan as variables, where the dependent variables were the cumulative drug release at 6 h (CDR) and the mucoadhesive strength. Flow and all pharmacopoeial values of compression were evaluated. The flow of all nine formulations was observed to be in an acceptable range, and all the pharmacopoeial values of compression were maintained satisfactorily. F5 (HPMC K15M 75 mg + chitosan 75 mg) formulation was regarded as the best formulation giving drug content of 99.36 ± 0.24 , surface pH of 6.83 ± 0.03 , swelling index of $69.30 \pm 0.89\%$ at 8 h, highest mucoadhesive strength of 8.56 ± 0.35 gm, adhesive force of 0.84 ± 0.034 N among nine batches, maximum cumulative in vitro drug release of $76.69 \pm 0.98\%$ and permeation of $83.74 \pm 1.02\%$ at 6 h. Release kinetic analysis of F5 showed the best fit to the zero order model ($r^2 = 0.9961$) with $k_p (= 0.847)$ indicating the non-Fickian (anomalous swelling/relaxation coupled with drug diffusion controlled) release mechanism. The comparison of the dissolution profile of F5 with marketed Rizatriptan benzoate tablet showed an acceptable and comparable release profile, with a model-independent difference ($f_1 = 13.92$) and similarity factors ($f_2 = 51.54$). F5 formulation was found to be physically and chemically stable up to 3 months of accelerated storage (40 ± 2 °C/75% RH). It is therefore concluded that the mucoadhesive buccal tablet offers a promising delivery system for Rizatriptan benzoate, which might act as a statistically optimized, alternative, and feasible dosage form in the acute management of migraine.

Keywords: Rizatriptan benzoate; Buccoadhesive tablet; Factorial design; Migraine; Transmucosal delivery

How to cite this article: Dhamsheela N Gondane, Sachidanand Angadi, Anuneet Kaur, Harsha I Raut, Pravinkumar M. Shahare, Rahul Deo Yadav, Sneha Anand, Ramesh Abhimanyu Gadekar. *Formulation and Optimization of Rizatriptan Benzoate Buccal Tablets for the Management of Acute Migraine. Int J Drug Deliv Technol.* 2026;16(88s):221-234. DOI: 10.25258/ijddt.16.88s.23.

Source of support: Nil.

Conflict of interest: None

1. Introduction

Migraine is a chronic debilitating neurologic disease with episodic attacks of moderate to severe headache and autonomic and sensory symptoms. Rizatriptan benzoate is a selective 5-hydroxytryptamine (5-HTB/5-HTD) receptor agonist in the triptan class of antimigraine medication. It is indicated in the treatment of acute migraine with and without aura. 5-HTB/5-HTD receptors on cranial blood vessels and presynaptic trigeminal nerve terminals are stimulated by it to cause vasoconstriction of the affected cranial blood vessels and to suppress the release of vasoactive neuropeptides[1].

The bioavailability of oral Rizatriptan benzoate is 70%, with mean peak plasma concentrations noted at 1 – 2 h following dosing and plasma concentrations rapidly declining thereafter. Rizatriptan benzoate undergoes extensive first-pass hepatic metabolism (approximately 80%) via monoamine oxidase A, with the metabolized components primarily excreted renally and through metabolism. Rizatriptan benzoate was found to have advantages within the realm of acute migraine therapy due to its rapid onset of action. Based on the physical and chemical properties of the drug as well as its pharmacology, Rizatriptan benzoate is also a promising molecule upon which alternative drug-delivery systems such as transdermal, buccal, nasal, and other targeted drug-delivery systems could be developed to increase convenience and to reduce the discomfort associated with conventional oral dosage forms[2].

The availability of subcutaneous and intranasal Rizatriptan benzoate formulations offers a more rapid onset of action but is limited by the acceptability of these modes of administration (impaired venous access, less acceptable route of delivery), discomfort from needle injections, and the development of a nasty taste and nasal irritation. The buccal mucosa offers an interesting, non-invasive alternative route for the systemic delivery of drugs such as Rizatriptan benzoate, which are poorly suited for traditional oral administration. Buccal absorption allows the drug to bypass hepatic first-pass metabolism and intestinal breakdown in the gut by draining directly into the systemic circulation via the internal jugular vein. In addition, the buccal cavity provides a relatively permeable, highly vascularized, and easily accessible epithelial surface, with the practical benefits of ease of administration and removal if therapy needs to be terminated, and some patient preference relative to

parenteral and nasal routes. The main obstacle of drug delivery through this route stems from the continuous flow of saliva washing the dosage form away from absorption sites before sufficient absorption of the drug can be achieved. Mucoadhesive systems provide a means of prolonging the residence time at the mucous surface and thus increase the contact time for drug absorption and presentation to the systemic circulation, thereby providing a more controlled and prolonged input. Mucoadhesive buccal tablets contain one or more hydrophilic mucoadhesive polymers that hydrate and swell on contact with saliva and form physical, non-covalent bonds (principally hydrogen bonding and polymer chain interpenetration) with mucin, the principal component of the buccal epithelium[3]. Hydroxypropyl methylcellulose (HPMC) is a well-known hydrophilic, water-swelling, gel-forming, and mucoadhesive cellulose derivative polymer, and chitosan (a cationic polymer that can be obtained from naturally occurring chitin) has been shown to possess mucoadhesive properties as well as permeation-enhancing activity due to its ability to reversibly open epithelial tight junctions. The anionic or non-ionic nature of cellulose derivatives and cationic polymer properties of chitosan suggest a selected combination of the two cellulosic and cationic polymers might exert synergistic effects on mucoadhesive strength and duration as well as controlled drug release from the buccal matrix. Given that the performance of a mucoadhesive buccal tablet—principally the type and concentration of mucoadhesive polymer(s) employed—is governed by a host of formulation variables, the systematic optimization of the dosage form using a statistically driven methodology is much more advantageous than a traditional trial-and-error approach[4, 5]. DoE-based factorial designs facilitate the efficient, concurrent study of the individual and combined influence of formulation variables on a mucoadhesive buccal tablet's performance traits, e.g., drug release and mucoadhesion.

Given this background, the current work was carried out with the following specific aims: (i) to characterize Rizatriptan benzoate through preformulation studies comprising of organoleptic evaluation, solubility, melting point, development of UV spectrophotometric method, and compatibility studies using FTIR and DSC with the candidate mucoadhesive polymers (HPMC K15M, guar gum, and chitosan), (ii) to develop Rizatriptan benzoate mucoadhesive buccal

tablets by direct compression using a two-factor (10 levels each), three level factorial design with HPMC K15M and chitosan as independent factors affecting the dependent variables, i.e. drug release at 6 h and mucoadhesive strength, (iii) to characterize the pre- and post-compression physical parameters of the prepared tablets, their drug content, surface pH, swelling index (SI), *in vitro* drug release, mucoadhesive strength, and *ex vivo* permeation in the ramified mucosa[6], (iv) to determine the kinetics and mechanism of drug release of the optimized mucoadhesive tablets, (v) to compare the dissolution profiles of the optimized formulation with the marketed Rizatriptan benzoate tablet by calculating the model independent similarity and difference factors, and (vi) to evaluate the short-term stability of the optimized formulation. Ultimately, this combined approach of formulation development and in-depth evaluation of the optimized mucoadhesive buccal tablets was aimed at creating a solid platform to address the limitations of conventional oral Rizatriptan benzoate in the intervention of acute migraine.

2. Materials and Methods

2.1 Materials

Rizatriptan benzoate was obtained as a gift sample (Cipla Limited, Bengaluru). Hydroxypropyl methylcellulose (HPMC) K15 M, guar gum, and chitosan were purchased from SD Fine Chemicals. All the chemicals and reagents used were of analytical grade.

2.2 Preformulation Studies

2.2.1 Organoleptic evaluation

The sample of Rizatriptan benzoate received was checked for its appearance, colour, and smell, and compared with the standard pharmacopoeial description to determine the identity of the drug.

2.2.2 Solubility

Known concentration solutions of Rizatriptan benzoate in water, methanol, and phosphate-buffered saline (PBS) pH 6.8 were made and measured spectrophotometrically, and the corresponding solubilities were determined by back calculation; solubility was qualitatively categorised according to class descriptors found in the pharmacopoeia. This information was used to help choose a suitable solvent for future work and to help find a dissolution medium[7].

2.2.3 Melting Point

The melting point of Rizatriptan benzoate was determined in triplicate using the capillary method, and the mean value was compared with the literature value, as well as the pharmacopoeial range (I.P.) of the drug, to check its purity[8].

2.2.4 Selection of wavelength (λ -max)

The λ -max of Rizatriptan benzoate in PBS of pH 6.8 was determined by spectrophotometric scanning. A

standard calibration curve was plotted over the range of 2-12 $\mu\text{g/mL}$ at the λ -max and was used to establish the calibration equation and coefficient of determination (r) from linear regression data for all subsequent quantitative estimations of the drug[9].

2.2.5 Drug-excipient compatibility studies

Compatibility of Rizatriptan benzoate with the three selected mucoadhesive polymers, HPMC K15M, guar gum, and chitosan was studied by FTIR using the potassium bromide (KBr) pellet technique for the pure drug and its physical mixtures with polymers. The FTIR spectra of the drug were compared with the spectra of physical mixtures of drug and polymers for any shifting, broadening, or disappearance of any bands representing interaction. The compatibility was further substantiated by differential scanning calorimetry (DSC) of the pure drug and its physical mixtures with polymers. The DSC thermograms of the drug were compared for any shifting, broadening, or disappearance of the melting endotherm of the drug.

2.3 Formulation of Mucoadhesive Buccal Tablets

Mucoadhesive buccal tablets of Rizatriptan benzoate were formulated by the direct compression method. The drug, mucoadhesive polymer or polymers (HPMC K15M and chitosan in the concentration as per experimental design), and other excipients in the form of diluent, disintegrant, glidant, and lubricant were accurately weighed and mixed thoroughly by the geometric dilution method to disperse the drug uniformly and then passed through a suitable sieve to get a fine powder. The powder blend was evaluated for precompression properties (Section 2.5) and compressed into tablets of the desired weight and size with the help of a rotary/ single punch tablet compression machine fitted with punches of suitable size[10-12].

2.4 Experimental Design for Formulation Optimization

A 3^2 factorial design was used for the optimization of the buccoadhesive tablet. HPMC K15M concentration (Factor A; 50, 75, and 100 mg) and chitosan concentration (Factor B; 50, 75, and 100 mg) were considered as independent formulation variables based on their commonly known mucoadhesive and drug release modulating activities and their well-documented compatibility with the drug. Response 1, CDR (cumulative percentage drug released at 6 h), and Response 2, mucoadhesive strength, were considered as dependent response variables. Nine formulations (F1-F9) were formulated as per the design matrix (Table 1) and prepared as shown in Section 2.3. The effect of two independent factors, both independently and in interaction, on the two responses was observed by analyzing the trend of these responses across the design matrix, and the formulation that gave the most optimum combination of sustained drug release and

robust mucoadhesion was finalized as the optimized (standard) formulation and was subjected to further evaluations[13, 14].

Table 1. Various formulations of buccoadhesive tablets

Formulation	Rizatriptan benzoate	HPMC K15 M	Chitosan (mg)	Mannitol	Lactose	starch	Methyl paraben	Propyl paraben	Magnesium stearate	aspartame
F1	10	50	50	150	200	30	2	1	5	2
F2	10	50	75	125	200	30	2	1	5	2
F3	10	50	100	100	200	30	2	1	5	2
F4	10	75	50	125	200	30	2	1	5	2
F5	10	75	75	100	200	30	2	1	5	2
F6	10	75	100	75	200	30	2	1	5	2
F7	10	100	50	100	200	30	2	1	5	2
F8	10	100	75	75	200	30	2	1	5	2
F9	10	100	100	50	200	30	2	1	5	2

2.5 Pre-Compression Evaluation of Powder Blends

Powders of the blends F1-F9, before compression, were weighed in a graduated cylinder, and the bulk density was determined by the graduated cylinder method, and the tapped density was measured according to the standard tapping procedure. F9, F1-F8: The angle of repose for each blend was determined using the fixed-funnel method[15].

2.6 Post-Compression Evaluation of Tablets

The tablets were then compressed and evaluated for thickness (digital vernier callipers), weight variation (as per pharmacopoeias specified using analytical balance), diameter (digital vernier callipers), friability (assessed using therech type friabilator and expressed in percentage loss in weight after the stipulated no of turns of the tablet), hardness (tablet hardness tester in kg/cm), drug content (by disintegrating the tablet powder in PBS of pH6.8 and assay of the drug spectrophotometrically at the maximum previously discovered) and surface pH (by swelling the tablet in contact with a small quantity of PBS of pH6.8 and directly taking the pH with a calibrated pH metre at the surface of the tablet[16, 17].

2.7 Swelling Index

Study of SI of all formulations (F1-F9). It was studied by the weight-gain method. Each tablet of individual weight was kept in PBS at pH 6.8. Tablets were taken out at predetermined time intervals, blotted dry, and reweighed. Percentage of SI was calculated as the percentage increase in weight with reference to the initial weight of the tablets[18, 19].

2.8 In vitro Drug Release Study

The *in vitro* drug release studies of F1- F9 formulations were performed in an appropriate dissolution test apparatus with PBS of pH 6.8 as the medium, and the medium was maintained with agitation at 37±0.5°C. Samples of the dissolution medium were withdrawn at defined time intervals for 6 h, replaced with an equal volume of fresh dissolution medium, and then the amount of drug was evaluated at 225 nm[20, 21].

2.9 Mucoadhesive Strength

The buccal tablet mucoadhesive strength was measured using a modified physical balance/mucoadhesion test apparatus in which tissue of the buccal mucosa was adhered to one side of a platform and the tablet attached to the mucosal tissue with a specified contact time and weight. The weight necessary to separate the tissue and the tablet was recorded and defined as the mucoadhesive strength (g), and the force of adhesion was calculated as the weight (N)[22].

2.10 Ex vivo Drug Permeation Study

The *ex vivo* permeation study of Rizatriptan benzoate from F1-F9 was investigated across buccal mucosal tissue excised and mounted in a Franz diffusion cell, with PBS pH 6.8) serving as the receiver medium. The diffusion cell was stirred continuously at 37°C, and samples were withdrawn at specific time intervals from the receiver compartment for 6 h. The withdrawn samples were replaced with fresh buffer solution[23].

2.11 Selection of the Optimized Formulation

Overall, considering the total physical tablet profile, drug content, SI, *in vitro* release, mucoadhesive strength, and *ex vivo* permeation of the 9 formulations, formulation F5 (HPMC K15M 75 mg, chitosan 75 mg) was found to be the optimized/standard formulation and was hence subjected to further studies such as release kinetics, comparative dissolution studies, and stability studies.

2.12 Drug Release Kinetics

The *in vitro* release data of the optimized formulation (F5) were subjected to mathematical modeling to determine the order and mechanism of drug release by fitting the data to zero-order, first-order, Higuchi, and Korsmeyer-Peppas equations. Based on the coefficient of correlation (r), the most appropriate model was selected. The value of the release exponent (n) was determined for all the formulations. Based on the value of n, the mechanism of drug release was defined as Fickian diffusion, non-Fickian (anomalous) transport, or Case-II transport.

2.13.4 Comparative Dissolution Testing: Similarity and Difference Factors

The *in vitro* dissolution profile of the optimized formulation (F5) was then statistically compared with that of the marketed Rizatriptan benzoate tablet. For comparison of the two dissolution profiles, model-independent difference and similarity factors (f), derived from the pairs of drug-release values of the two products at matched time points, were used. The acceptance criteria for similarity of dissolution profiles were f_1 of 15 and f_2 of 50.

2.14 Accelerated Stability Studies

For accelerated stability studies, a trial sample of the optimized formulation (F5) was packed in an amber-coloured screw-capped bottle and stored at 40 ± 2 °C and 75 ± 5% relative humidity for a period of three months.

Samples were withdrawn at specified time intervals of 0, 30, 60, and 90 days and examined for friability, hardness, drug content, surface pH, SI, and % cumulative drug release.

2.15 Statistical Analysis

All experiments were carried out in triplicate and, unless indicated otherwise, results are presented as mean standard deviation (SD).

3. Results

3.1 Preformulation Studies

The procured Rizatriptan benzoate was obtained as a pure white, odourless, amorphous solid, consistent with its standard description and confirming drug identity. Solubility analysis showed that the drug was freely soluble in both water and methanol and highly soluble in PBS of pH 6.8 (Table 2), an aqueous solubility profile favourable for the development of a hydrophilic, swellable buccal matrix and confirming the suitability of PBS of pH 6.8 as the dissolution/release medium for subsequent evaluation. The average melting point of Rizatriptan benzoate, determined over three trials, was found to be 179.3 °C, in close agreement with the reported literature value (178–181 °C) and within the specified pharmacopoeial range, confirming the purity and identity of the drug sample.

Table 2. Solubility profile of Rizatriptan benzoate

Solvent	Solubility (mg/mL)	Solubility category
Water	0.22	Freely soluble
Methanol	0.17	Freely soluble
Phosphate buffer pH 6.8	0.35	Highly soluble

UV spectral scanning of Rizatriptan benzoate in PBS at pH 6.8 identified a λ_{max} of 225 nm. The calibration curve constructed at this wavelength over 2–12 $\mu\text{g/mL}$ (Figure 1) was linear, with a coefficient of determination exceeding 0.99, confirming compliance with the Beer–Lambert law across the studied range and validating the method for reliable quantitative estimation of the drug throughout the study.

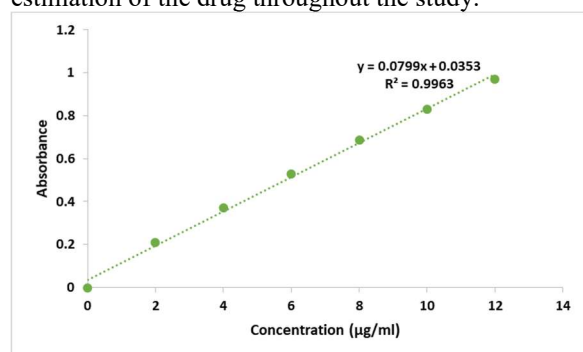


Fig.1. Standard calibration curve of Rizatriptan benzoate in phosphate buffer pH 6.8

The thermal compatibility of the drug-polymer physical mixtures was further supported by the DSC examination of the physical mixtures of the drug with the three candidate polymers, in which the characteristic melting endotherm of Rizatriptan benzoate remained essentially unaltered, supporting thermal compatibility. In view of these studies of compatibility and the promising results of the swelling, release, and mucoadhesion behavior in the screening experiments, HPMC K15M and chitosan were the two polymers selected for the subsequent full factorial optimization experiment involving the buccal tablet (Figure 2).

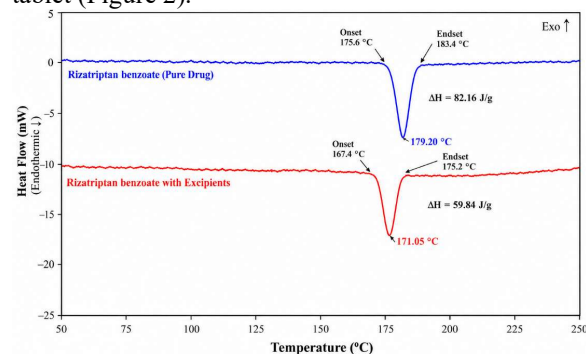


Fig.2. FTIR spectrum of Rizatriptan pure drug and its combination with the excipients

FTIR spectra of pure Rizatriptan benzoate and the physical mixtures with HPMC K15M, guar gum, and chitosan revealed that the main peaks associated with drug IR absorption are retained in all physical mixtures without any major shift, broadening, or disappearance, suggesting that no major physicochemical interaction between Rizatriptan benzoate and the three proposed mucoadhesive polymers occurs (Figure 3).

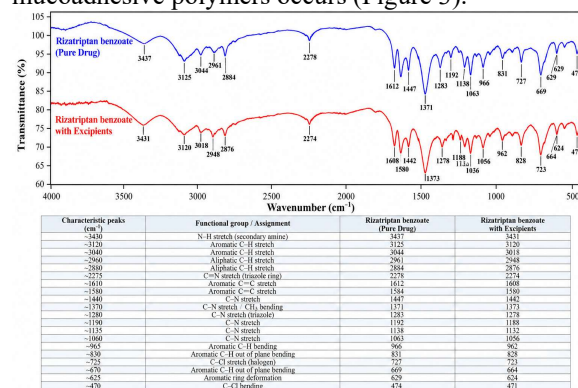


Fig.3. FTIR spectral details of drug and drug with the excipients

3.2 Pre-Compression Evaluation of Powder Blends

All the bulk densities were similar, ranging from 0.54±0.01 g/cm to 0.57±0.01 g/cm, while tap densities were all comparable, ranging from 0.62±0.01 g/cm to

0.66±0.01 g/cm. All nine demonstrated acceptable to good flow and compressibility, as indicated by the angle of repose (25.82±0.25 to 28.36±0.36), Carr's index (11.11±0.24% to 16.92±0.38%), and Hausner's ratio (1.13±0.01 to 1.20±0.01). The formulation F5 has the lowest (best) values of the above: angle of repose 25.82±0.25; Carr's index 11.11±0.24%; Hausner's ratio 1.13±0.01; and shows the best powder to be compressed in a uniform and reproducible manner.

3.3 Post-Compression Tableting Properties

The post-compression physical parameters of F1-F9 were summarised in Table 3. The physical parameters of the prepared tablets, i.e., thickness, were in the range of 3.06±0.03 to 3.24±0.03 mm, and weight variation was in the range of 199.4±1.31 to 201.2±1.15 mg, suggesting the tablets' dimensions were consistent. The tablets' diameter was in the range of 8.01±0.02 to 8.03±0.03 mm, indicating that the tablets' size was in good uniformity. Friability of the prepared tablets was in the range of 0.38±0.04 to 0.54±0.03 %, which was within the limit of the pharmacopoeia (<1 %), and the hardness was in the range of 4.6±0.21 to 5.5±0.27 kg/cm², giving the mechanical strength of the tablet to survive mechanical shocks during handling, packing, and transport. The results of the post-compression parameters of the optimized formulation F5, with 3.15±0.03 mm thickness, 201.2±1.15 mg weight, 8.01±0.02 mm diameter, 0.40±0.02 % friability, and 5.3±0.25 kg/cm² hardness found in the physical and mechanical properties.

Table 3. Post-compression parameters of buccoadhesive tablets (F1–F9)

Formulation	Thickness (mm)	Weight variation (mg)	Diameter (mm)	Friability (%)	Hardness (kg/cm ²)
F1	3.12 ± 0.03	199.6 ± 1.24	8.02 ± 0.02	0.48 ± 0.03	4.6 ± 0.21
F2	3.18 ± 0.04	200.8 ± 1.18	8.01 ± 0.02	0.43 ± 0.02	4.8 ± 0.24
F3	3.24 ± 0.03	199.4 ± 1.31	8.03 ± 0.03	0.39 ± 0.02	5.0 ± 0.26

F4	3.08 ± 0.02	200.6 ± 1.27	8.02 ± 0.02	0.46 ± 0.03	5.1 ± 0.23
F5	3.15 ± 0.03	201.2 ± 1.15	8.01 ± 0.02	0.40 ± 0.02	5.3 ± 0.25
F6	3.21 ± 0.04	199.8 ± 1.22	8.03 ± 0.03	0.35 ± 0.02	5.5 ± 0.27
F7	3.06 ± 0.03	200.4 ± 1.34	8.02 ± 0.02	0.52 ± 0.03	4.8 ± 0.22
F8	3.12 ± 0.03	201.0 ± 1.20	8.01 ± 0.02	0.45 ± 0.03	5.0 ± 0.24
F9	3.19 ± 0.04	200.2 ± 1.16	8.02 ± 0.02	0.38 ± 0.02	5.2 ± 0.25
Values in mean ±SD; n=3					

Drug content and surface pH data of F1-F9 are presented in Table 4. The drug content was within the range of 98.76±0.28% to 99.73±0.21%, thereby reflecting the satisfactory uniformity of distribution of the drug within the compressed tablets, whilst the surface pH of the compressed tablets was within the range of 6.76±0.05 to 6.88±0.05, which was similar to the physiological pH of the buccal cavity, and this proved that the tendency of the drug to cause mucosal irritation at the site of drug administration was minimal. The drug content and surface pH of formulation F5 were observed to be 99.36±0.24% and 6.83±0.03, which satisfied the acceptability criteria of the compress tablets.

Table 4. Drug content and surface pH of buccoadhesive tablets (F1–F9)

Formulation	Drug content (%)	Surface pH
F1	98.76 ± 0.28	6.82 ± 0.04
F2	99.24 ± 0.31	6.85 ± 0.03
F3	99.58 ± 0.22	6.88 ± 0.05
F4	98.92 ± 0.27	6.79 ± 0.04
F5	99.36 ± 0.24	6.83 ± 0.03
F6	99.68 ± 0.19	6.87 ± 0.04

F7	98.84 ± 0.33	6.76 ± 0.05
F8	99.42 ± 0.26	6.80 ± 0.03
F9	99.73 ± 0.21	6.84 ± 0.04

3.4 Swelling Index

The SI of formulations F1-F9 during 8 hours has also been studied and found to show a gradual time-dependent increase in percentage weight variation for all batches, which represents hydration of the polymeric matrix when it comes into contact with the release media. The percentage SI at 8 h was observed to range from 65.40±0.83% (F6) to 138.40±1.23% (F3), showing greater SI for formulations F1-F3 (lower chitosan concentration with a fixed concentration of HPMC K15M), comparatively lesser SI for formulations F4-F6, and intermediate-to-high SI for formulations F7-F9. SI at 8 h was found to be highest for F3 and lower for F6, indicating that a sufficient amount of chitosan and HPMC K15M polymers in the formulation could produce the required SI. Formulation F5 showed the SI of 69.30±0.89% at 8 h, as predicted; this shows a mild to moderate SI of the matrix-a behaviour that is considered optimal for buccoadhesive tablets, as excessive SI may result in the tablet falling apart with a loss of contact with the buccal mucosa, while moderate-to-mild swelling promotes intimate contact with the mucprhn opposite to other conventional tablets.

3.6 *In vitro* Drug Release Study

The *in vitro* release profiles of all the formulations F1-F9 (up to 6 h) are given in Table 5. The gradual release of Rizatriptan benzoate was observed, which showed a sustained release profile from the formulation. There was a slow release of drug F1, which ranged from 8.00 0.31% up to 0.5 hour to 69.50±0.85 to 90.51±1.02% up to 6 h, respectively. The formulation F5 showed a cumulative release of 9.65±0.41% up to 0.5 h and 76.69±0.98% up to 6 h, respectively. The results of the samples showed low standard deviations, which suggest that the concentration of the drug released at each time point was reproducible. This proves that sustained release was confirmed by hydration of the sustained buccodeposit-forming polymer HPMC K15M by swelling, followed by diffusion of the drug through the hydrated matrix. The prepared buccoadhesive formulation F5 showed a slow sustained release pattern. This formulation was hence considered as a standard formulation for the subsequent comparative evaluation (Figure 4).

Table 5. *In vitro* cumulative percentage drug release from buccoadhesive tablet formulations (F1-F9)

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	12.79	10.56	8.00	8.09	9.65	8.50	10.92	9.50	8.50
1	17.22	15.89	12.50	14.16	15.58	13.00	16.70	15.00	14.00
1.5	28.15	25.64	18.50	22.44	23.30	21.00	26.40	23.00	22.00
2	39.98	37.71	27.00	31.34	32.10	30.00	36.90	32.00	30.00
3	51.29	48.70	37.00	43.72	42.90	41.00	49.40	43.00	40.00
4	61.79	58.82	47.00	55.60	53.40	52.00	60.20	53.00	49.00
5	75.49	70.38	59.00	68.74	65.70	62.00	72.30	64.00	59.00
6	90.51	82.95	72.00	82.88	76.69	70.00	81.30	75.00	69.00

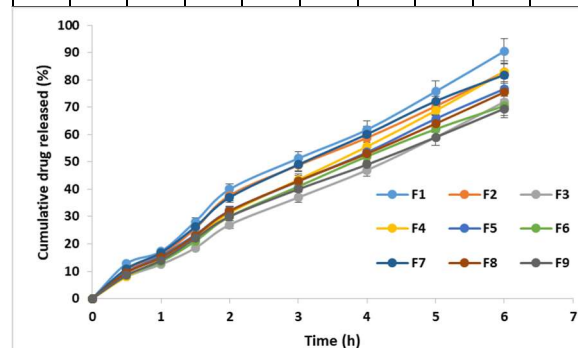


Fig.4. *In vitro* cumulative drug release from buccoadhesive tablet formulations (F1–F9)**3.7 Mucoadhesive Strength**

The mucoadhesive strength and corresponding force of adhesion of formulations F1-F9 are summarized in Table 6. Mucoadhesive strength was in the range of 6.85 ± 0.24 g (F1) to 8.56 ± 0.35 g (F5) and force of adhesion 0.672 ± 0.024 N to 0.840 ± 0.034 N, indicating all formulations had acceptable mucoadhesive property as a result of the formation of hydrogen-bonding and electrostatic interactions between the mucoadhesive polymer and buccal mucosa. The F5 formulation showed the highest mucoadhesive strength (8.56 ± 0.35 g) and force of adhesion (0.840 ± 0.034 N), as compared to the other formulations, demonstrating mucoadhesion to the maximum extent (and therefore the maximum time spent on adhesion). F8 and F6 formulations showed the next highest values, while the F1 formulation showed the lowest value (showing the difference between the F1 formulation and the F4 formulation). Accordingly, the F5 formulation was selected as the optimized formulation based on the mucoadhesive strength value.

Table 6. Mucoadhesive strength and force of adhesion of buccoadhesive tablets (F1–F9)

Formulation	Mucoadhesive strength (g)	Force of adhesion (N)
F1	6.85 ± 0.24	0.672 ± 0.024
F2	7.62 ± 0.31	0.748 ± 0.030
F3	8.18 ± 0.28	0.803 ± 0.027
F4	7.42 ± 0.26	0.728 ± 0.026
F5	8.56 ± 0.35	0.840 ± 0.034
F6	8.21 ± 0.29	0.806 ± 0.028
F7	7.68 ± 0.27	0.754 ± 0.026
F8	8.32 ± 0.32	0.816 ± 0.031
F9	7.94 ± 0.25	0.779 ± 0.025

3.8 *Ex vivo* Drug Permeation Study

The pattern of *ex vivo* permeation of F1-F9 formulations through excised buccal mucosa over 6 hours is presented in Table 7 and Figure 5. The release data revealed that the permeation of the drug increased gradually with time in all the tested formulations. The cumulative permeation was observed to be within the range of $70.01 \pm 0.91\%$ (F1) to $83.74 \pm 1.02\%$ (F5) after 6 h. Formulation F5 was found to have the highest permeation after 6 h among all the formulation batches ($83.74 \pm 1.02\%$), followed by F9 ($82.18 \pm 1.00\%$), F6 ($80.62 \pm 0.99\%$), and F8 ($80.12 \pm 0.98\%$). Formulations F1 and F4 were found to have the lowest permeation

among all the formulation batches. The high permeation shown by F5 formulations is probably due to the optimum ratio of HPMC K15M and chitosan that enables such formulations to sustain contact with the mucosa for a longer period, while the permeation-enhancing effect of chitosan on the epithelial tight junctions could have facilitated drug transport across the mucous membrane. The low standard deviations indicate that the permeation data were reproducible. The findings from this *ex vivo* study seem to confirm the ability of the developed mucoadhesive buccal tablets F1-F9, especially F5, to facilitate sustained transmucosal delivery of Rizatriptan benzoate.

Table 7. *Ex vivo* cumulative percentage drug permeation across buccal mucosa (F1–F9)

Ti m e (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	8.76	9.65	10.85	9.29	12.14	11.30	10.21	11.18	11.66
1	14.28	15.81	17.66	15.12	19.60	18.33	16.33	18.66	18.77
1.5	21.34	23.60	25.95	22.47	28.62	26.88	24.88	26.88	27.99
2	30.21	33.13	35.81	31.67	39.05	36.44	34.22	36.66	38.88
3	39.84	43.66	46.92	41.80	50.88	48.00	45.77	47.99	49.44
4	49.33	53.33	57.88	52.17	62.71	59.11	56.77	58.88	61.22
5	60.55	65.13	69.44	63.66	74.66	71.22	67.44	70.33	72.88

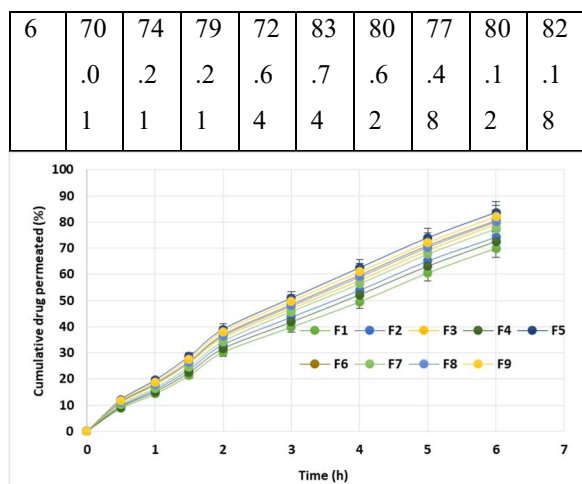


Fig.5. Ex vivo cumulative drug permeation across buccal mucosa (F1-F9)

3.9 Drug Release Kinetics

The kinetic model fitting of drug release from rizatriptan benzoate formulations (F1-F9) is shown in Table 8.

Table 8: Kinetic Model Fitting of Drug Release from Rizatriptan benzoate Formulations (F1-F9)

Formulation	Zero-order R ²	Firster R ²	Higuchi R ²	Korsmeyer-Peppas R ²	n value	Release mechanism
F1	0.9940	0.9897	0.9899	0.9962	0.8525	Case-II borderline
F2	0.9912	0.9907	0.9928	0.9960	0.8384	Non-Fickian
F3	0.9911	0.9984	0.9935	0.9966	0.8137	Non-Fickian
F4	0.9933	0.9989	0.9912	0.9963	0.8452	Non-Fickian

F5	0.9882	0.9982	0.9953	0.9964	0.7928	Non-Fickian
F6	0.9895	0.9985	0.9943	0.9962	0.8082	Non-Fickian
F7	0.9914	0.9987	0.9928	0.9960	0.8034	Non-Fickian
F8	0.9904	0.9985	0.9940	0.9965	0.8086	Non-Fickian
F9	0.9885	0.9983	0.9950	0.9961	0.8011	Non-Fickian

The release data of the Rizatriptan benzoate formulations were fitted to various mathematical models to understand the mechanisms dominating the drug release. Zero-order data showed very high R² values (0.9882-0.9940), suggesting that the drug-release pattern of the selected formulations is more or less the same with respect to time. Formulation F1 obtained the highest value of the zero-order R² value (0.9940), and F4 is the second formulation that follows (0.9933).

The first-order model had R² values ranging from 0.9822 to 0.9907. The high values of the correlation coefficients suggested that the data fitted the first-order model but were in fact lower than the correlation coefficients obtained by using the Korsmeyer-Peppas model, which suggested that concentration-dependent release did not describe the release.

Higuchi model (Diffusion) showed good correlation, with values of R² from 0.9899 to 0.9953. The highest Higuchi R² was for F5 (0.9953), then F9 (0.9950) and F6 (0.9943), indicating that diffusion from the formulation matrix played a major role in the release of Rizatriptan benzoate.

Using the regression analysis, the highest R² was obtained for the Korsmeyer-Peppas model, with R² values of 0.9960- 0.9966 for all formulations. The models that showed the highest correlation were F3 (R²=0.9966), F8 (0.9965), and F5 (0.9964). The calculated n ranged from 0.7928-0.8525, which implied the formulation had mainly anomalous/non-Fickian release behaviour, i.e., drug diffusion was considered to be coupled with polymer relaxation,

swelling, or reorganization of the matrix instead of being solely controlled by simple Fickian diffusion. In conclusion, the exceptionally high R^2 values for the Korsmeyer-Peppas model were indicative that this model provides the best explanation for the release profile of all the Rizatriptan benzoate formulations. The drug release appears to be controlled by a combination of diffusion and polymer relaxation, indicating, for the most part, a swelling-controlled release process as evidenced by the presence of HPMC K15M and chitosan. The high n values implied a controlled release mechanism through extensive polymer-mediated transport.

3.10 Stability Studies

The selected formulation F5 was subjected to a stability study on accelerated conditions at $40 \pm 2^\circ \text{C}$ and $75 \pm 5\%$ RH for 3 months. There was no change in visual appearance throughout the study. Friability remained unchanged at 0.280.02 in days 0-90, and hardness was slightly reduced from 4.80.10 to 4.70.13 kg/cm; thus, the strength of the formulation was not affected by storage. The drug content was only slightly reduced from 97.20 ± 0.42 to $96.58 \pm 0.41\%$; thus, the formulations were chemically stable, and no degradation of the drug was observed. The surface pH of the dosage form was also found to be unchanged (6.76 ± 0.04 to 6.72 ± 0.03). The SI was only slightly decreased from $67.50 \pm 0.86\%$ to $66.30 \pm 0.78\%$, and cumulative drug release at 6 hours was also only slightly decreased from $96.84 \pm 0.58\%$ to $95.76 \pm 0.55\%$, demonstrating stability of all parameters for the tablet formulation (Table 9).

Table 9. Stability data for optimized formulation F5 stored at $40 \pm 2^\circ \text{C}$ and $75 \pm 5\%$ RH

D	Friability	Hardness	Drug content	Surface pH	Swelling index	Cumulative release at 6 h
ay	(%)	(kg/cm ²)	(%)		(%)	(%)
0	0.28 ± 0.02	4.8 ± 0.10	97.2 ± 0.42	6.76 ± 0.04	67.50 ± 0.86	96.84 ± 0.58

30	0.27 ± 0.01	4.8 ± 0.12	97.0 ± 0.38	6.75 ± 0.03	67.10 ± 0.74	96.51 ± 0.51
60	0.28 ± 0.02	4.7 ± 0.11	96.8 ± 0.45	6.73 ± 0.04	66.70 ± 0.81	96.18 ± 0.62
90	0.29 ± 0.02	4.7 ± 0.13	96.5 ± 0.41	6.72 ± 0.03	66.30 ± 0.78	95.76 ± 0.55
Values in mean $\pm$ SD						

3.11 Comparative Dissolution Study: Similarity and Difference Factors

The release profile of F5 was generally similar to that of the marketed Rizatriptan benzoate at earlier time points, but with a higher level of cumulative release at later time points (e.g., $90.51 \pm 0.98\%$ versus $67.73 \pm 1.02\%$ at 6 h), reflective of the different sustained-release characteristics of the buccoadhesive system versus the immediate-release marketed control. The calculated difference factor ($f_1 = 13.92$) was within the required limit of 15 for two comparable dissolution profiles, and the similarity factor ($f_2 = 51.54$) exceeded the prescribed limit; the dissolution profile of the optimized F5 buccoadhesive tablet was deemed to be comparable to that of the marketed Rizatriptan benzoate reference product, but with a more extended release profile, supporting its use as an alternative to this transmucosal buccoadhesive delivery system (Tables 10 and 11).

Table 10. Comparative *in vitro* drug release profile of marketed Rizatriptan benzoate tablet and optimized buccoadhesive tablet (F5)

Time (h)	Marketed tablet (% release)	Optimized F5 (% release)
0.5	10.00 ± 0.32	12.79 ± 0.42
1	18.00 ± 0.41	17.22 ± 0.51
1.5	27.00 ± 0.53	28.15 ± 0.63
2	38.00 ± 0.62	39.98 ± 0.74

3	50.00 ± 0.75	51.29 ± 0.86
4	58.00 ± 0.81	61.79 ± 0.92
5	64.00 ± 0.94	75.74 ± 1.05
6	67.73 ± 1.02	90.51 ± 0.98
Difference factor (f_1)	—	13.92
Similarity factor (f_2)	—	51.54

Table 11. Acceptance evaluation of the comparative dissolution profile

Parameter	Result for F5	Acceptance criterion	Inference
Difference factor (f_1)	13.92	≤ 15	Pass — acceptable difference
Similarity factor (f_2)	51.54	≥ 50	Pass — profiles considered similar
Overall inference	$f_1 = 13.92$ $2; f_2 = 51.54$	$f_1 \leq 15$ and $f_2 \geq 50$	F5 shows similarity/equivalence with the marketed reference tablet

4. Discussion

The findings generated in this research work all contribute to giving a consistent, mechanistically oriented framework to predict buccoadhesive tablet behaviour over the considered factorial design space. Preformulation data validated the nature/purity of Rizatriptan benzoate and its excellent aqueous solubility. In the presence of substantial drug-polymer interaction from FTIR and DSC, these data also provided a firm rationale for selecting a hydrophilic, swellable buccoadhesive matrix from HPMC K15M and chitosan. The systematic trends defined by formulation F1-F9 exemplify the individual and combined roles of these two polymers in determining tablet properties. A higher level of HPMC K15M matrix hydration and gel-layer formation at a higher level of tablet hydration, yielding a diffusion barrier that can delay drug release, is complemented by a higher level of chitosan, producing a higher level of

mucoadhesive interaction with mucin via electrostatic interaction, and higher epithelial membrane permeability, due to the effect of chitosan at tight junctions[24]. The general trend of increased total percent drug released and mucoadhesive strength at a higher concentration of either polymer is consistent with these mechanisms, with F9 exhibiting the highest mucoadhesive strength and highest total percent drug released. Yet, F5 was selected over F9 as the optimal formulation, because these ideal characteristics are not necessarily advantageous for a patient-administered buccal tablet. Excessively high mucoadhesion (which could inhibit the safe and comfortable removal of the tablet), or rapid and extensive release may be undesirable for sustained plasma drug concentration, especially during the course of a developing migraine attack[25]. Amongst all 9 formulations, F5 also gave the highest permeation and mucoadhesion values individually, indicating a ratio of HPMC K15M: chitosan that more effectively balanced the properties of swelling/gel-layer formation and interaction with mucin than either of the two polymers at a higher level. The zero-order-dominant, non-Fickian release for F5 (K_p/K_n 0.847) is mechanistically consistent with the SI data obtained for the same formulation (section 3.4): the measured intermediate, controlled SI would be expected to produce the matrix SI required to sustain uniform, near-linear release without the premature, Fickian release expected from exceedingly slow or excessive swelling. The comparative dissolution data versus the marketed tablet further supports this assessment, with the higher f_1 , lower f_2 contributions derived from later points reflecting the controlled, sustained release matrix design in contrast to the fast, reduced Fickian release of the immediate-release commercial product (though the pattern of model-independent similarity criteria is met). From a clinical translational standpoint, then, the combination of a good mucoadhesive profile (favourable residence at the buccal mucosa), sustained and at the same time significant drug release and permeation over the 6 h period of the study, and an acceptable short-term physical and chemical stability of the F5 buccoadhesive tablet all suggest that it has the potential to deliver a more consistent and first-pass-metabolism-avoiding systemic absorption of Rizatriptan benzoate than a traditional oral tablet. This would be achieved without the practical inconveniences of subcutaneous or intranasal delivery[26].

Certain limitations of the present work must also be acknowledged. The pharmacokinetic benefits of the buccal route, predicted by the extent of first-pass avoidance and the resulting bioavailability and time-to-peak plasma concentration, could only be established *in vivo*. The stability assessment was limited to three months; this could be extended in real-time studies to define the shelf-life. Additionally, the formulation variables of a third polymer (guar gum, studied only in preliminary compatibility assessments) and tablet compression force remain avenues for subsequent optimization[27-46].

5. Conclusion

The current investigation successfully developed, optimized, and characterized mucoadhesive buccal tablets of Rizatriptan benzoate as a viable alternative to the conventional oral Rizatriptan benzoate therapy for the acute management of migraine. The preformulation screening studies established the identity and purity of the drug and validated its optimized solubility as well as its compatibility with candidate mucoadhesive polymers, i.e., HPMC K15M, guar gum, and chitosan. A 3^2 design efficiently optimized the concentrations of HPMC K15M and chitosan, leading to 75 mg HPMC K15M +75 mg chitosan (F5) as a formulation with optimum overall physical quality of the resultant tablets, SI and sustained drug release (76.69% at 6 h), maximum mucoadhesive strength (8.56 g), and *ex vivo* permeation (83.74% at 6 h) of the nine formulations evaluated. Release kinetic analysis revealed a predominantly zero-order, non-Fickian mechanism of drug release from F5, governed by diffusion and polymer relaxation. Comparative dissolution studies with a marketed Rizatriptan benzoate tablet revealed that F5 conformed to an acceptable and comparable ($f_1=13.92$), albeit more sustained ($f_2=51.54$), drug-release profile. Moreover, three-month accelerated stability studies revealed no significant physical or chemical changes in F5. Collectively, these results validate a statistically, mechanistically, and pharmacokinetically optimized formulation of Rizatriptan benzoate buccal tablets as a promising, viable alternative to the limitations of conventional Rizatriptan benzoate oral therapy.

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