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DESIGN, OPTIMIZATION OF BIO FLEXIBLE FILMS OF SUMATRIPTAN SUCCINATE AND NAPROXEN SODIUM VIA ORO TRANS SOFT PALATAL DELIVERY

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ABSTRACT

Background: Bio-flexible films are polymeric drug delivery systems designed to enhance systemic drug absorption through the oral mucosa. This study aimed to develop and optimize bio-flexible, mucoadhesive films containing Sumatriptan Succinate and Naproxen Sodium for oro-trans soft-palatal delivery. The drug combination provides rapid and sustained therapeutic effects for migraine management. **Methodology:** Bio-flexible films were prepared by solvent casting using hydroxypropyl methylcellulose (HPMC E15), HPMC K100, and glycerine. A Box–Behnken Design was employed to optimize the formulation by evaluating three independent variables and five dependent responses. Films were characterized for thickness, surface pH, folding endurance, disintegration time, swelling index, drug content, ex vivo permeation, and in vitro drug release. Drug release kinetics were analyzed using mathematical models. **Results and Discussion:** All formulations exhibited satisfactory physicochemical and mechanical properties. The optimized formulation showed a disintegration time of 153 s, with cumulative drug release of 96.33% for Sumatriptan Succinate and 94.00% for Naproxen Sodium within 40 min. The optimized film demonstrated adequate mechanical strength, uniform drug content, acceptable swelling behavior, and enhanced ex vivo permeation. Drug release followed the Higuchi and Korsmeyer–Peppas models. **Conclusion:** The optimized bio-flexible mucoadhesive film demonstrated rapid drug release and efficient ex vivo permeation, indicating its potential as a patient-friendly platform for oro-trans soft palatal delivery of Sumatriptan Succinate and Naproxen Sodium. Further in vivo studies are required to confirm its clinical potential.

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INTRODUCTION

Migraine is a common and debilitating neurovascular disorder characterized by severe, recurrent headaches episode frequently accompanied by phonophobia, photophobia, and nausea. It represents a major global health burden and is a leading cause of disability worldwide, particularly among individuals in their most productive years. Although the precise etiology of migraines remains complex and not fully elucidated, current evidence suggests a multifactorial interplay of neurochemical, environmental, and genetic factors. During a migraine attack, intracranial blood vessels undergo alterations in dilation and constriction, leading to activation of trigeminal sensory pathways and subsequent release of vasoactive neuropeptides that mediate pain and inflammation. Migraine affects more than one million people globally and is recognized as a highly disabling neurological condition. Therapeutic strategies vary across the regions but generally encompass acute, preventive, and non-pharmacological options. Advances in understanding migraine pathophysiology have facilitated the development of novel mechanism-based therapies, thereby broadening the spectrum of effective interventions [1]. Headache remains one of the most frequent causes of emergency department (ED) visits, ranking fourth or fifth globally and accounting for approximately 3% of annual ED presentations. Epidemiological analysis further indicates that individuals aged 18 to 44 years experience the highest prevalence of migraines [2]. Overall, Migraine is characterized by recurrent, typically unilateral head pain associated with phonophobia, photophobia, nausea, neurogenic inflammation, activation of the trigeminovascular system, and the release of vasoactive neuropeptides.

The primary objective of pharmacological management in migraine is to reduce the frequency of attacks and relieve acute symptoms. Among the various treatment options, Naproxen Sodium, a non-steroidal anti-inflammatory drug (NSAID), and Sumatriptan Succinate, a selective 5-hydroxytryptamine (5-$HT_1B/_1D$) receptor agonist, have demonstrated clinical efficacy in both as monotherapies and in combination [3,4,5]. Naproxen Sodium exerts its therapeutic effect by inhibiting cyclooxygenase (COX) enzymes, thereby suppressing prostaglandin synthesis and attenuating inflammation. In contrast, Sumatriptan Succinate is widely used for acute migraine episodes owing to its ability to induce cranial vasoconstriction and to inhibit the release of pro-inflammatory neuropeptides through selective activation of 5-HT1B/1D receptors. The concurrent administration of these agents has shown synergistic benefits, improving the magnitude and duration of symptomatic relief compared with either drug alone [6]. Conventional oral dosage forms, however, present inherent limitations, including delayed onset of action, reduced bioavailability due to hepatic first-pass metabolism, and patient inconvenience during migraine episodes, particularly in the presence of nausea and vomiting. Oro-transmucosal delivery systems offer a non-invasive, patient-centric alternative, characterized by rapid onset, enhanced bioavailability, and greater ease of administration. Among these platforms, mucoadhesive bioflexible films have received particular attention for their ability to adhere to the soft palate, allowing for localized, sustained, and more predictable drug absorption [7,8]. This study aims to develop a mucoadhesive, bioflexible film incorporating Sumatriptan Succinate and Naproxen Sodium for oro-trans soft palatal delivery. The formulation is intended to bypass hepatic first-pass metabolism, facilitate rapid systemic absorption, and enhance patient compliance. The investigation framework includes formulation development, optimization, and comprehensive physicochemical and pharmaceutical evaluation of the developed films [9]. Anatomically, the soft palate is a pliable muscular structure located posteriorly in the oral cavity, delineating the oral and nasal segments of the pharynx. Owing to its rich vascularization, the soft palatal mucosa offers an advantageous route for systemic drug delivery, thereby avoiding pre-systemic gastrointestinal elimination and improving drug bioavailability [10]. Drug absorption across this mucosa occurs predominantly via passive diffusion through the lipid bilayer. Moreover, the concave architecture of the soft palate facilitates patient-friendly administration, allowing direct placement of bioflexible films using the thumb. Consequently, oro-trans soft palatal delivery has been increasingly adopted as a promising platform for optimizing systemic drug delivery [11].

Despite the availability of conventional oral tablets, orally disintegrating tablets, buccal films, and transdermal systems for migraine management, these options have significant limitations, including delayed onset of action, first-pass metabolism, variable absorption, dose dumping, and reduced patient compliance during migraine-associated nausea and vomiting. Several studies have examined single-drug oromucosal delivery systems. Still, very little information is available on the simultaneous delivery of Sumatriptan Succinate and Naproxen Sodium using an oro-trans soft-palatal bio-flexible film platform. This study fills the gap by developing a dual-drug bio-flexible film with special emphasis on oro-trans

soft palatal delivery. The highly vascularized soft palate permits rapid systemic absorption, bypassing gastrointestinal degradation and hepatic first-pass metabolism. Furthermore, the combination of triptan and NSAID in a single flexible dosage form provides synergistic advantages, rapid onset of action, prolonged retention, and improved patient compliance compared with conventional oral and single-drug delivery systems. The objective of this study was to optimize a dual-drug bio-flexible film using Box–Behnken Design by evaluating the effects of HPMC E15, HPMC K100, and glycerine conc. on folding endurance, swelling index, disintegration time, drug release, and drug content.

MATERIALS AND METHODS

Materials

Sumatriptan Succinate was obtained as a gift sample from Intas Lab. Pvt. Ltd., Dehradun, India. Naproxen Sodium was obtained as a gift sample from Mankind Pharma Ltd., Paonta Sahib, Himachal Pradesh, India. HPMC E15, HPMC K100, PVPK30, Sucralose, and Glycerine were purchased from Central Drug House. All the chemicals and reagents were of analytical grade.

Analytical method adoption by UV spectrophotometer-

To prepare the calibration curve for Sumatriptan Succinate and Naproxen Sodium, phosphate buffer (pH 6.8) was used. Accurately weigh 10 mg of the drug and dissolve it in 10 mL of phosphate buffer to obtain a stock concentration of 1 mg/mL (1000 µg/mL)**.** Mix thoroughly to ensure complete dissolution. From this stock, prepare the desired dilutions of 2 µg/mL, 6µg/mL 8 µg/mL, 10 µg/mL, and 12 µg/mL in a 10 mL volumetric flask. The absorbance of the stock solution was measured using a UV spectrophotometer (1900-1, SHIMADZU). The UV spectrophotometer's determined λmax was also used to note the absorbance of the dilutions [12,13,14]. Using absorbance values, a typical graph was created plotting absorbance (Y-axis) against concentration (X-axis).

Optimization of Bioflexible film

A Box-Behnken design (BBD) was undertaken to evaluate the influence of key film-forming excipients on the mechanical, physicochemical, and performance attributes of oral film development. The present investigation was performed to prepare and optimize a bioflexible film containing Sumatriptan Succinate and Naproxen Sodium for oro-trans soft-palatal delivery using a Box–Behnken experimental design. The Box-Behnken Design was employed to systematically evaluate factor interactions, generate predictive models, and identify the optimum formulation with minimal experimental runs. Three independent variables were selected based on their functional roles in film formation and drug-release characteristics: concentration of HPMC E15, Concentration of HPMC K100, and quantity of plasticizer, glycerine. The selected ranges were determined through preliminary trials to ensure adequate film-forming capacity, mechanical strength, and uniformity. The effects of these independent variables were assessed with respect to five critical formulation quality attributes identified as dependent variables. These included folding endurance, swelling index, disintegration time, cumulative drug release, and drug content. Folding endurance served as an indicator of mechanical robustness, while swelling index and disintegration time reflected hydration and breakdown kinetics essential for rapid-release films. Drug release and drug content analysis ensured consistency in active pharmaceutical ingredient loading and performance [15]. The design of experiments (DoE) approach enabled the systematic evaluation of factor-response relationships, facilitating the optimization of the polymer ratio and plasticizer concentration to achieve a film exhibiting superior mechanical integrity, rapid disintegration, optimal swelling behavior, and enhanced drug-release performance. The resulting model provided statistical insights into each variable's contribution and guided the selection of an optimized formulation for further characterization. The statistical analysis of the response variable was performed using Analysis of Variance (ANOVA), and a quadratic model was found to be most suitable based on the results. Table 1 presents the selected independent and dependent variables [16]. All experimental responses were measured in triplicate and expressed as mean ± standard deviation. Statistical analysis of the Box–Behnken Design responses was performed using Design-Expert® software. Analysis of variance (ANOVA) was used to evaluate model significance and the influence of formulation variables on the measured responses.

Selection of Independent Variables & Experimental Ranges

A preliminary risk assessment and screening study was conducted to identify the formulation variables most likely to affect the critical quality attributes of the bioflexible films. The most significant effects on film-forming ability, mechanical properties, swelling behavior, disintegration properties, and drug-release performance were observed for the studied factors: HPMC E15, HPMC K100, and glycerine. Hence, these variables were chosen as independent factors for Box–Behnken

optimization. HPMC E15 was chosen as the main film-forming polymer due to its excellent film-forming properties, rapid hydration behavior, homogeneous drug distribution, and potential to promote rapid drug release. HPMC K100 was added as a high-viscosity, hydrophilic polymer to improve mucoadhesion, structural integrity, hydration capacity, and residence time at the site of administration. Glycerine was chosen as the plasticizer for its compatibility with both polymers and its ability to enhance flexibility, folding endurance, and resistance to film cracking during handling and storage. The concentration range of HPMC E15 (300-500 mg) was fixed based on preliminary trials. The preliminary trials revealed that at concentrations below 300 mg, the films were fragile and had poor mechanical strength. On the other hand, at concentrations above 500 mg, the films were too thick, and the disintegration time was prolonged. HPMC K100 was tested in the range of 100-300 mg, as lower concentrations resulted in insufficient mucoadhesion, and higher concentrations resulted in excessive swelling and delayed drug release. Glycerine was studied in the range of 1–2 mL, since concentrations lower than 1 mL produced brittle films and concentrations higher than 2 mL produced overly soft films with poor handling properties. Variables other than film thickness, such as drug loading, total polymer weight, solvent system, casting area, drying temperature, and drying time, were deliberately kept constant throughout the experiment. The drug loading was kept constant to maintain consistency in the therapeutic dose regardless of experimental run. The solvent system and the drying parameters were kept constant to minimize the effect of process variation. Total polymer weight was kept constant to minimize variations due to film integrity. Film thickness was deliberately excluded as an independent variable because it depends on polymer concentration and plasticizer content. Consequently, HPMC E15, HPMC K100, and glycerine were identified as the most critical formulation variables and selected for optimization using Box–Behnken Design.

Preparation of bioflexible films (Solvent Casting Method)

The solvent casting method was utilized as previously outlined, with minor adjustments [17]. Mucoadhesive polymers, HPMC E15 and HPMC K100, were accurately weighed according to the amounts specified in Table 2 for each formulation, and both were dissolved in 10 mL of distilled water. PVP K-30 was gradually added while continuously stirring with a magnetic stirrer. The beaker containing the polymer solution was left to stand for a few minutes to allow the polymers to swell. An additional 10 mL of distilled water was then added to the polymer solution, and the mixture was stirred. Subsequently, a specific quantity of glycerine, as indicated in Table 2A and 2B, was added to the previously prepared polymer solution [18]. At the same time, Sumatriptan Succinate was introduced into the polymer solution. Naproxen Sodium was dissolved in 5 mL of ethanol in a separate beaker, then combined with the polymer solution and thoroughly mixed using a sonicator. The total solvent used consisted of 20 mL distilled water and 5 mL ethanol, with a water/ethanol ratio of 80:20 (v/v). Stirring was performed using a magnetic stirrer at 500 rpm for 30 minutes. After the addition of the drug, the solution was sonicated for 10 minutes. Each formulation was cast into a glass Petri dish of fixed internal diameter (9 cm). Drying was carried out in a hot air oven maintained at 40 ± 2°C for 4 hours under controlled conditions. Once dried, the films were inspected for imperfections after removal from the Petri dish and then cut into 2 × 2 cm^2 pieces.

Table 1: List of Independent and Dependent variables selected for experimental design

S. No.	Independent Variables	Units	Low	High
1	HPMC E15	mg	300	500
2	HPMC K100	mg	100	300
3	Glycerine	ml	1	2
S. No.	**Dependent variables**			**Units**
1	Folding Endurance			No.
2	Swelling Index			%
3	Disintegration time			Sec
4	Drug release of Sumatriptan Succinate and Naproxen Sodium			%
5	Drug Content of Sumatriptan Succinate and Naproxen Sodium			%

EVALUATION OF BIOFLEXIBLE FILMS

Thickness

The thickness of the bioflexible films (F1-F17) was measured using a digital Vernier Caliper. The thickness of each film was measured at six different locations, and the average thickness was calculated.

Weight Uniformity

The film was cut into a 2x2 cm2 area, and the weight of each film (F1-F17) was recorded, and weight uniformity was calculated.

Percent Elongation

It was determined by the increase in the film's length immediately before it broke. The formula used for calculating % Elongation is as shown below:

$$\% \textit{Elongation} = \frac{\textit{Final length} - \textit{Initial length}}{\textit{Initial length}} \times 100$$

Surface pH

The oral film was slightly moistened with water. Then the pH of the film was measured by bringing the electrode in contact with the surface of the oral film [19,20].

Percent Moisture Absorption

The films (F1-F17) were weighed accurately and placed in desiccators containing 100 ml of a saturated aluminum chloride solution. After 3 days, the patches were taken out and weighed.

$$\textit{Percentage moisture absorption} = \frac{\textit{Final Weight} - \textit{Initial weight}}{\textit{Initial weight}} \times 100$$

Swelling Index of films

For the determination of swelling index, the pre-weighed films (2×2 cm^2) from each formulation (F1-F17) were placed in Petri dishes (containing 20 ml of phosphate buffer of pH 6.8). The strips were removed, and the excess water on their surfaces was carefully blotted with filter paper. The swollen patches were weighed accurately.

$$\% \textit{Swelling Index} = \frac{\textit{Final Weight} - \textit{Initial weight}}{\textit{Initial weight}} \times 100$$

Moisture content

The bioflexible films (F1-F17) were accurately weighed and stored in desiccators containing anhydrous calcium chloride. After 3 days, the patches were taken out and weighed. The moisture content (%) was determined by calculating moisture loss (%) using the formula:

$$MC = \frac{\textit{Initial weight} - \textit{final weight}}{\textit{final weight}} \times 100$$

Folding endurance

The folding endurance is expressed as the number of folds required to break the specimen or to develop visible cracks. This indicates the film's brittleness. The folding endurance of all bioflexible films (F1-F17) was determined manually by repeatedly folding each film at the same location until it broke [22].

Drug content

100 mL of phosphate buffer at pH 6.8 was used to dissolve a 2 × 2 cm2 strip of each formulation in a beaker. The solution was homogeneous after a specific period of constant shaking. Filter paper with a pore size of 0.45µm was used to filter the mixture. Once the arrangement was filtered, 1 milliliter was removed and diluted with 10 milliliters of water. By measuring the arrangement's absorbance at 228 nm and 230 nm, the drug content was ascertained [23].

Disintegration time

In vitro disintegration times of all the bioflexible films (F1-F17) were measured using a disintegration test apparatus in phosphate buffer (pH 6.8) at 37 ± 0.5°C. The film of 2×2 cm² was placed individually in each tube of the disintegration basket, without the use of discs, to prevent mechanical damage to the thin bioflexible film. The basket was allowed to move vertically at the specified frequency. The disintegration time was recorded as the time taken for the film to completely disintegrate and pass through the mesh, with no palpable residue remaining on the screen. The test was performed in triplicate; the mean disintegration time ± standard deviation was calculated, and the disintegration time was defined as the time at which the film begins to break.

Drug release

All formulations (F1-F17) were subjected to drug dissolution tests using a Franz diffusion cell. As a model membrane, an egg membrane was employed after its extraction. It was mounted between the donor and the recipient compartments. A 20 mL addition of phosphate buffer was made to the receiver compartment. It was stirred with a magnetic bead. The receiver and donor compartments were clipped together. The film was applied to the egg membrane via the donor chamber. Temperature control was maintained by placing the Franz diffusion cell on a magnetic stirrer. Samples were taken at the appropriate intervals. Using a UV-visible spectrophotometer, the absorbance was measured to calculate the cumulative percentage of drug release. [24,25].

Kinetic Release Study

The drug-release kinetics of the bioflexible films were analyzed by fitting the dissolution data to several kinetic equations: zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell. The coefficient of regression was calculated. Graphs of the kinetic model were plotted using the relevant data. [26,27].

FTIR study

The FTIR study was conducted on Sumatriptan Succinate, Naproxen Sodium, and the optimized bioflexible film formulation using the KBr pellet method. This study was primarily used to assess the structural integrity and interactions between drugs and polymers.

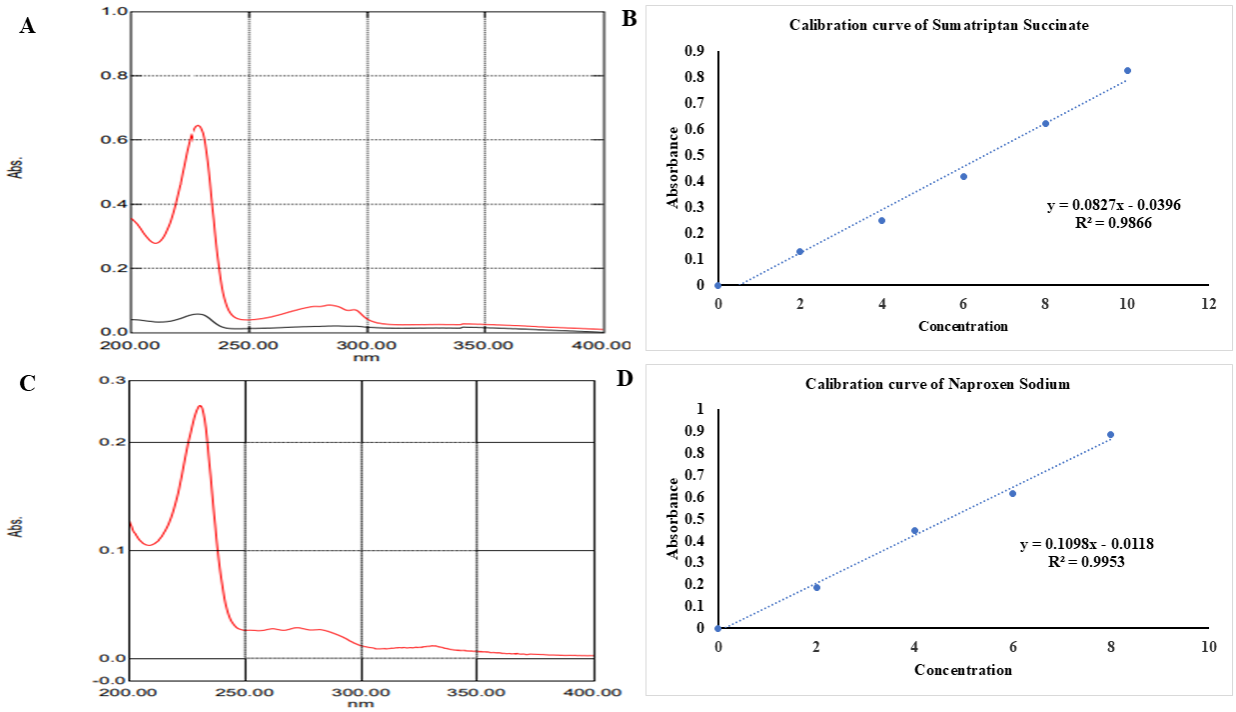

Figure 1: Determination of λ_{max} and Calibration Curve of Sumatriptan Succinate & Naproxen Sodium (A-D)

RESULT

Determination of absorbance maxima of Sumatriptan Succinate and Naproxen Sodium

The peak absorbance for Sumatriptan Succinate and Naproxen Sodium was observed at λ_{max} 228 nm and 230 nm, respectively, as shown in Figure 1. Further dilutions of the stock solutions were made, ranging from 2-10µg/ml, and absorbance measurements were taken at both λ_{max} values. The absorption peaks for Sumatriptan Succinate and Naproxen Sodium were found close to 228 nm and 230 nm, respectively; thus, the "first derivative UV spectrophotometric technique was used for resolving overlapping spectra using zero-crossing wavelengths." Zero-crossing wavelengths of 236 nm and 241 nm were successfully applied to resolve overlapping spectra for the two drugs. The method was validated in accordance with ICH guidelines, demonstrating good linearity, precision, accuracy, and specificity.[28]. UV spectrophotometry for the determination of Sumatriptan Succinate and Naproxen Sodium has been established in accordance with the International Conference on Harmonization (ICH) guidelines for linearity, accuracy, precision, specificity, LOD, LOQ, and robustness, as shown in Table 2 [29,30]. The validation results demonstrated that the first-derivative UV spectrophotometric method was linear, accurate, precise, specific, sensitive, and robust for the quantitative estimation of Sumatriptan Succinate and Naproxen Sodium.

Table 2: Summary of Validation Parameters

Parameter	Sumatriptan Succinate	Naproxen Sodium
λmax (nm)	236	241
Regression Equation	y = 0.0827x − 0.0076	y = 0.0995x − 0.0133
Correlation Coefficient (R^2)	0.9966	0.9993
Accuracy (% Recovery)	99.35–99.99	99.35–99.97
Repeatability (%RSD)	0.46	0.46
Intermediate Precision (%RSD)	0.59	0.59
Specificity (% Interference)	0.71	1.32
LOD (µg/mL)	1.25	1.04
LOQ (µg/mL)	3.79	3.15
Robustness (%RSD)	1.04	1.04

Table 3A: Bio-flexible film of Sumatriptan Succinate and Naproxen Sodium with their independent and dependent variables.

Formula-tions (F)	Sumatriptan Succinate (mg)	Naproxen Sodium (mg)	PVP K-30 (mg)	HPMC E15 (mg)	HPMC K100 (mg)	Glycerin (ml)	FE* (±SD)	DT* (sec) (±SD)
F1	60	250	100	300	100	1.5	314.67±3.1	87.33±6.1
F2	60	250	100	500	100	1.5	321.33±3.1	99.67±4.9
F3	60	250	100	300	300	1	337.33±5.0	125.33±2.3
F4	60	250	100	500	200	1	324.67±5.0	142.00±4.0
F5	60	250	100	400	100	1	314.00±2.0	134.00±5.3
F6	60	250	100	400	300	1	338.00±2.0	163.00±5.0
F7	60	250	100	400	200	1.5	325.33±1.2	143.00±5.2
F8	60	250	100	300	300	1.5	344.00±4.0	184.67±4.6
F9	60	250	100	300	200	2	318.00±2.0	164.67±3.1
F10	60	250	100	400	200	1.5	320.67±4.2	144.67±4.2
F11	60	250	100	500	300	1.5	340.67±4.2	192.00±3.5
F12	60	250	100	400	200	1.5	324.67±3.1	141.33±5.8
F13	60	250	100	400	100	2	316.67±1.2	153.33±1.2
F14	60	250	100	400	300	2	342.67±3.1	185.33±3.1
F15	60	250	100	400	200	1.5	320.67±3.1	149.33±2.3
F16	60	250	100	400	200	1.5	322.00±2.0	141.33±4.2
F17	60	250	100	500	200	2	322.67±3.1	164.67±3.1

All values are expressed as mean ± standard deviation (SD) of three independent determinations (n = 3).

Table 3B: Bio-flexible film of Sumatriptan Succinate and Naproxen Sodium with their independent and dependent variables.

Formula tions (F)	DT* (sec) (±SD)	CDR of (Sumatriptan Succinate) (±SD)	CDR of Naproxen Sodium (±SD)	Adhesion time* (min) (±SD)	SI (%)	DC* (Sumatriptan Succinate) (±SD)	DC* (Naproxen Sodium) (±SD)
F1	87.33±6.1	90.33±4.0	86.67±5.5	41.67±1.5	120	89.67±2.5	89.33±2.5
F2	99.67±4.9	89.67±2.5	80.33±2.5	42.00±1.7	140	78.67±1.5	81.00±3.6
F3	125.33±2.3	72.67±1.5	68.00±1.0	40.67±1.2	160	82.33±1.5	78.33±2.1
F4	142.00±4.0	90.67±1.2	72.33±3.1	44.00±1.0	160	84.33±3.5	81.67±1.5
F5	134.00±5.3	74.00±2.6	70.67±2.5	40.67±2.1	130	92.00±2.6	89.67±1.5
F6	163.00±5.0	82.67±2.5	71.67±1.5	44.67±2.5	180	87.33±2.1	82.67±1.5
F7	143.00±5.2	81.67±2.1	72.67±3.1	42.67±2.5	150	88.00±2.6	80.67±2.1
F8	184.67±4.6	70.67±1.5	61.00±2.6	44.33±3.8	170	83.67±1.5	82.33±2.1
F9	164.67±3.1	94.00±4.0	89.00±3.0	43.00±1.7	130	97.00±1.0	93.67±3.5
F10	144.67±4.2	87.33±1.5	77.33±2.5	45.67±3.2	150	85.67±2.1	79.67±1.5
F11	192.00±3.5	77.33±2.1	68.00±1.7	44.67±2.1	190	82.67±1.5	77.00±2.6
F12	141.33±5.8	73.33±3.2	67.00±3.0	43.67±1.5	150	85.00±2.6	79.33±2.1
F13	153.33±1.2	96.33±0.6	94.00±1.0	46.33±1.5	160	95.67±1.5	95.67±0.6
F14	185.33±3.1	76.67±2.3	71.67±1.5	40.00±1.0	160	82.33±2.1	79.33±2.1
F15	149.33±2.3	87.67±1.5	71.67±2.1	43.67±2.1	150	85.33±4.7	84.67±1.5
F16	141.33±4.2	87.67±2.5	70.33±2.1	45.00±2.6	160	86.67±2.1	83.67±1.2
F17	164.67±3.1	88.33±3.1	86.33±1.2	43.67±1.5	140	81.67±1.5	79.00±1.7

All values are expressed as mean ± standard deviation (SD) of three independent determinations (n = 3).

Evaluation: Bio-flexible films of Sumatriptan Succinate and Naproxen Sodium were evaluated. The formulation table explains how the solvent casting method was used to successfully create the Bio-flexible films of Sumatriptan Succinate and Naproxen Sodium. Every film was assessed for weight uniformity, thickness, disintegration time, surface pH, % elongation, Moisture content, Moisture absorption, folding endurance, Swelling index, percentage of drug content, and percentage of drug release. The outcomes for all Bio-flexible films are listed in Tables 3A, 3B, and 4.

Table 4: Evaluation parameters of Bio-flexible films of Sumatriptan Succinate and Naproxen Sodium

Formulations	Appearance	Avg.wt. (gm ± SD)	Weight Uniformity	Surface pH (±SD)	% elongation (%±SD)	Moisture content (% ± SD)	Moisture absorption(%± SD)	Thickness (µm ± SD)
F1	Smooth film	0.746±.02	-3.1%, +2.8%	6.16±0.1	14.3±1.70	5.13±0.17	6.2±0.08	197±2.16
F2	Smooth, cracked from corners	0.50±0.04	-2.6%, +2.9%	5.63±0.1	20.3±0.94	4.76±0.12	6.83±0.12	207.6±2.05
F3	Smooth, cracked from corners	0.45±0.01	-2.9%, +2.5%	6.87±0.2	18.67±0.94	4.93±0.12	6.37±0.12	205.67±1.7
F4	Smooth film	0.48±0.01	-3.4%, +3.5%	7±0.16	22±0.82	5.26±0.09	5.8±0.21	208.33±1.2
F5	Non-uniform surface	0.45±0.02	-3.6%, +2.9%	6.63±0.1	19.67±1.25	5.2±0.14	6.13±0.12	209.33±1.2
F6	Non-uniform surface	0.54±0.02	-2.3%, +2.2%	6.23±.05	22±1.63	5.13±0.12	5.53±0.17	202.33±1.2
F7	Non-uniform surface	0.53±0.01	-4.2%, +3.8%	6.53±0.1	23±0.82	5.37±0.12	5.77±0.12	208±0.82
F8	Non-uniform surface	0.55±0.01	-3.7%, +2.6%	5.77±0.1	17.67±1.25	4.67±0.09	5.57±0.20	213±2.16
F9	Smooth, non-gritty & uniform film	0.44±0.01	-2.2%, +2.7%	6.17±0.1	18.33±0.94	5.43±0.12	5.77±0.05	208.67±1.7
F10	Cracked from corners	0.46±0.01	-2.7%, +2.7%	6.77±0.1	23±0.82	5.33±0.09	5.83±0.20	208.33±1.2
F11	Smooth film	0.53±0.01	-2.8%, +2.5%	6.3±0.08	22.67±1.25	4.7±0.08	5.7±0.14	202.33±1.2
F12	Smooth, cracked from corners	0.49±0.02	-3.3%, +3.7%	7±0.08	18.67±1.25	5.63±0.12	6.3±0.08	194.67±1.7
F13	Smooth, non-gritty & uniform film	0.47±0.01	-2.8%, +2.1%	6.2±0.08	18.33±0.47	5.13±0.05	5.83±0.09	206.67±0.4
F14	Smooth, uniform film	0.47±0.01	-2.6%, +2.1%	5.97±.09	23.67±1.25	5.23±0.12	6.27±0.12	208.33±1.7
F15	Cracked from corners	0.48±0.02	-3.2%, +4.0%	5.8±0.08	20.67±1.25	5.37±0.12	6.23±0.12	205.67±1.2
F16	Smooth but corner cracked	0.48±0.01	-3.5%, +3.8%	6.53±0.1	21.67±1.25	4.77±0.09	5.73±0.09	207.33±1.2
F17	Smooth but cracked	0.48±0.01	-3.4%, +3.6%	6.67±0.1	18.33±0.94	5.3±0.08	5.7±0.16	206.33±2.0

All values are expressed as mean ± standard deviation (SD) of three independent determinations (n = 3)

OPTIMIZATION OF BIO-FLEXIBLE FILMS USING BBD

Bio-flexible films of Sumatriptan Succinate and Naproxen Sodium were successfully prepared by the solvent casting technique using film-forming Mucoadhesive polymers. BBD was used to optimize Bio-flexible films and assess the effects of independent variables on the dependent variables more accurately and precisely. There were 17 runs conducted; the results of the experimental runs were demonstrated in Figure 2.

Effect on Folding Endurance

The 3D response surface plot in Figure 2(A) represents the effect of HPMC E15 and HPMC K100 concentrations on the folding endurance of the Bio-flexible film. The graph shows that folding endurance increases gradually with higher concentrations of both polymers. At lower polymer levels, the folding endurance remains low (260–280), whereas at higher polymer concentrations, the films exhibit good flexibility and improved mechanical strength, with folding endurance exceeding 310. This indicates that increasing the proportion of both HPMC grades increases the film's flexibility.

Swelling Index

Figure 2(F) presents a surface plot illustrating the effect of A and B on the swelling index. The swelling index increases with increasing concentrations of A and B. The plot indicates that higher polymer concentration leads to greater matrix swelling, which in turn controls drug release.

Effect on disintegration time

The 3D surface plot in Figure 2(B) illustrates the combined influence of HPMC E15 (Factor A) and HPMC K100 (Factor B)

on the disintegration time of the formulated film. A progressive increase in disintegration time was observed as the concentration of both polymers increased. At lower levels of HPMC E15 and HPMC K100, the films exhibited minimum disintegration time (80–100 seconds), whereas higher concentrations of both polymers significantly prolonged the disintegration time up to 160–180 seconds. The linear increase in the surface plot suggests a synergistic effect between the two polymers in retarding disintegration.

Effect on drug release: Sumatriptan Succinate and Naproxen Sodium

Figures 2(C) and (D) illustrate the influence of HPMC E15 and HPMC K100 on the release of Sumatriptan Succinate and Naproxen Sodium. The observed trends were interpreted using the fitted regression models generated by the Box–Behnken Design. The response surface plots indicate that polymer concentration influenced drug release within the investigated design space.

Adhesion time

Figure 2(E) presents a surface plot illustrating the effect of HPMC E15 and HPMC K100 on the adhesion time of the formulation. The plot shows a clear upward trend, where increasing the concentration of both polymers significantly increases the adhesion time, with the highest values observed at the upper concentration limits.

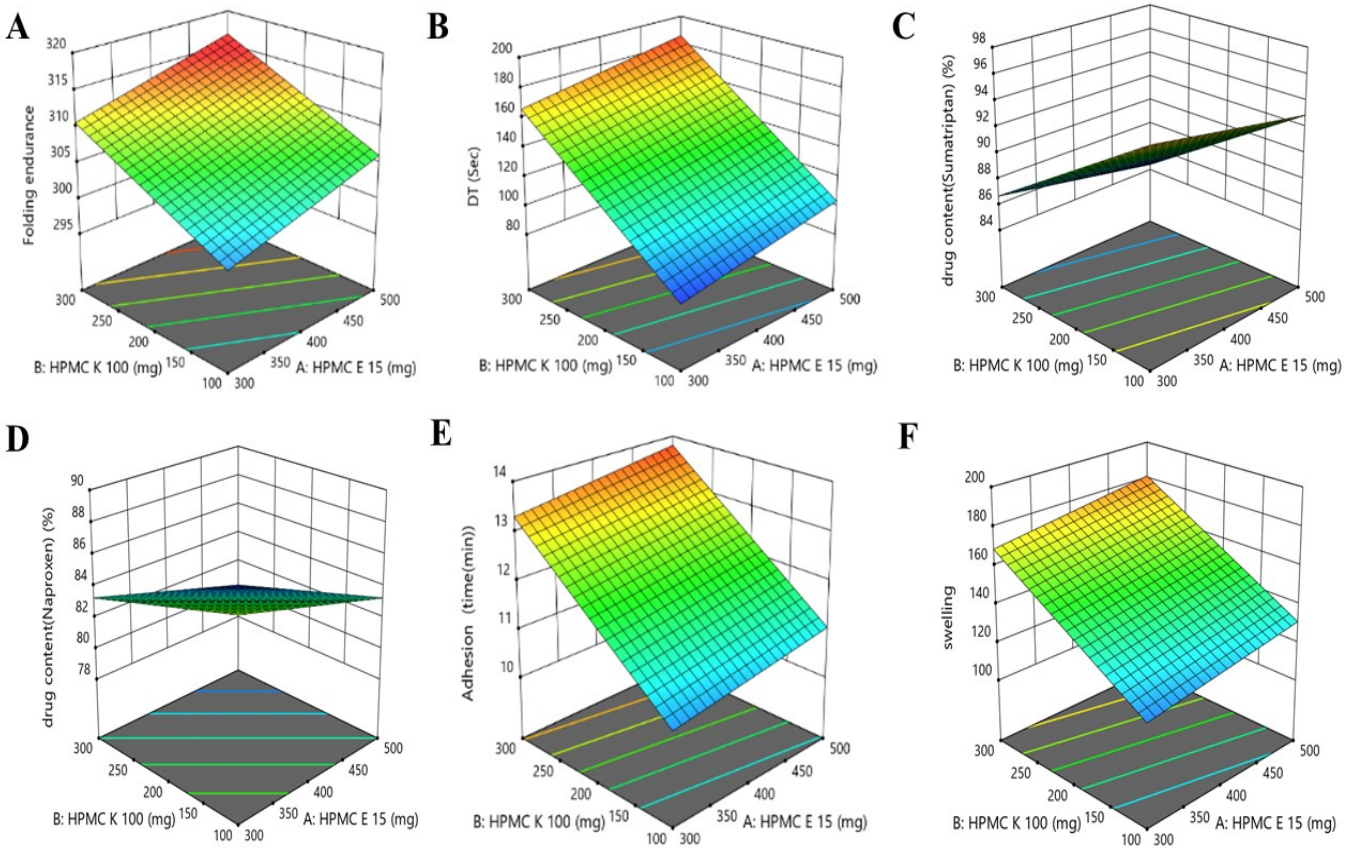

Figure 2: Representation of 3D-response surface plot showing the effect of independent variables on (A) Folding Endurance, (B) disintegration time, (C) drug release (Sumatriptan Succinate), (D) drug release (Naproxen Sodium), (E) adhesion time, (F) swelling Index

Final Equations

Folding Endurance = +295.96324+0.005000 HPMC E 15+0.066250 HPMC K 100-1.75000 Glycerine

DT = -14.04412+0.100000 HPMC E 15+0.412500 HPMC K 100+17.50000 Glycerine

In vitro Diffusion(Sumatriptan) = +69.52941+0.040000 HPMC E 15-0.037500 HPMC K 100+3.00000 Glycerine

In vitro Diffusion (Naproxen) = +67.10294+0.018750 HPMC E 15-0.058750 HPMC K 100+7.00000 Glycerine

Swelling Index = +108.75000+0.062500 HPMC E 15+0.250000 HPMC K 100-22.50000 Glycerine

Model Adequacy and Statistical Validation of Box–Behnken Design

The adequacy of the developed Box–Behnken Design models was evaluated using ANOVA, lack-of-fit analysis, adjusted R^2, predicted R^2, and adequate precision values generated by Design-Expert® software. For folding endurance, a linear model was selected with an adjusted R^2 of 0.8741 and predicted R^2 of 0.8266. The model was significant ($p < 0.0001$) and exhibited a non-significant lack of fit ($p = 0.7117$), indicating good agreement between experimental and predicted values. For disintegration time, a linear model was selected with an adjusted R^2 of 0.9521 and predicted R^2 of 0.9260. The model was statistically significant ($p < 0.0001$). Although the lack-of-fit was significant ($p = 0.0032$), the response exhibited excellent predictive capability and was retained for optimization as shown in Table 5. The response surface model for Sumatriptan Succinate release was best described by a quadratic model with an adjusted R^2 of 0.9441 and predicted R^2 of 0.8366. The model was highly significant ($p < 0.0001$) and demonstrated a non-significant lack of fit ($p = 0.5841$), confirming model adequacy. For the release of Naproxen Sodium, a linear model was selected, with an adjusted R^2 of 0.8425 and a predicted R^2 of 0.7620. The model was statistically significant ($p < 0.0001$) and showed non-significant lack of fit ($p = 0.3894$). In all selected models, adequate precision values exceeded 4, indicating a sufficient signal-to-noise ratio and confirming their suitability for navigating the design space.

Overall, the developed Box–Behnken models demonstrated satisfactory predictive capability and statistical adequacy for optimization of the bioflexible films. The adjusted R^2 values ranged from 0.8425 to 0.9521, while the predicted R^2 values ranged from 0.7620 to 0.9260, indicating good agreement between the experimental observations and model predictions. Furthermore, the lack-of-fit was not significant for most responses, confirming the suitability of the selected regression models for describing the experimental data and predicting formulation performance within the investigated design space.

Table 5: Model Adequacy Statistics of Box–Behnken Design Models

Response	Selected Model	Adjusted R^2	Predicted R^2	Lack-of-Fit (p-value)	Adeq Precision
Folding Endurance	Linear	0.8741	0.8266	0.7117	20.62
Disintegration Time	Linear	0.9521	0.9260	0.0032	30.89
Cumulative Drug release of Sumatriptan Succinate	Quadratic	0.9441	0.8366	0.5841	15.77
Cumulative Drug release of Naproxen Sodium	Linear	0.8425	0.7620	0.3894	18.21

For Naproxen Sodium release, a linear model was selected with an adjusted R^2 of 0.8425 and a predicted R^2 of 0.7620. The model was statistically significant ($p < 0.0001$) and exhibited a non-significant lack-of-fit ($p = 0.3894$), confirming that the model adequately described the experimental data. The adequate precision value of 18.21 further indicated an acceptable signal-to-noise ratio and demonstrated the model's suitability for navigating the design space. The response surface model for Sumatriptan Succinate release was best described by a quadratic model with an adjusted R^2 of 0.9441 and predicted R^2 of 0.8366. The model was highly significant ($p < 0.0001$) and showed a non-significant lack of fit ($p = 0.5841$), confirming model adequacy (see Table 6). The adequacy of the developed response surface models was further verified using diagnostic plots generated by Design-Expert®. The normal probability plots of externally studentized residuals showed an approximately linear distribution, indicating that the assumption of normality was satisfied. Likewise, the Predicted versus Actual plots exhibited close agreement between experimental and predicted values with minimal deviation from the reference line, confirming the excellent predictive capability and robustness of the developed statistical models. Figure 3 shows Diagnostic plots demonstrating the adequacy of the response surface models. (A) Normal probability plot of externally studentized residuals for Folding Endurance, (B) Predicted versus Actual plot for Folding Endurance, (C) Normal probability plot of externally studentized residuals for Disintegration Time, and (D) Predicted versus Actual plot for Disintegration Time. The close alignment of data points with the reference line and the random distribution of residuals confirmed satisfactory model adequacy and predictive performance.

Table 6: Predicted vs Observed Table

Response	Predicted	Observed	% Error
FE	317.5	316.67 ±1.2	0.26
DT (sec)	152.4	153.33 ±1.2	0.61
SI (%)	159.2	160	0.50
DR(Sumatriptan)(%)	95.90	96.33 ±0.6	0.45
DR (Naproxen) (%)	93.70	94.00 ±1.0	0.32

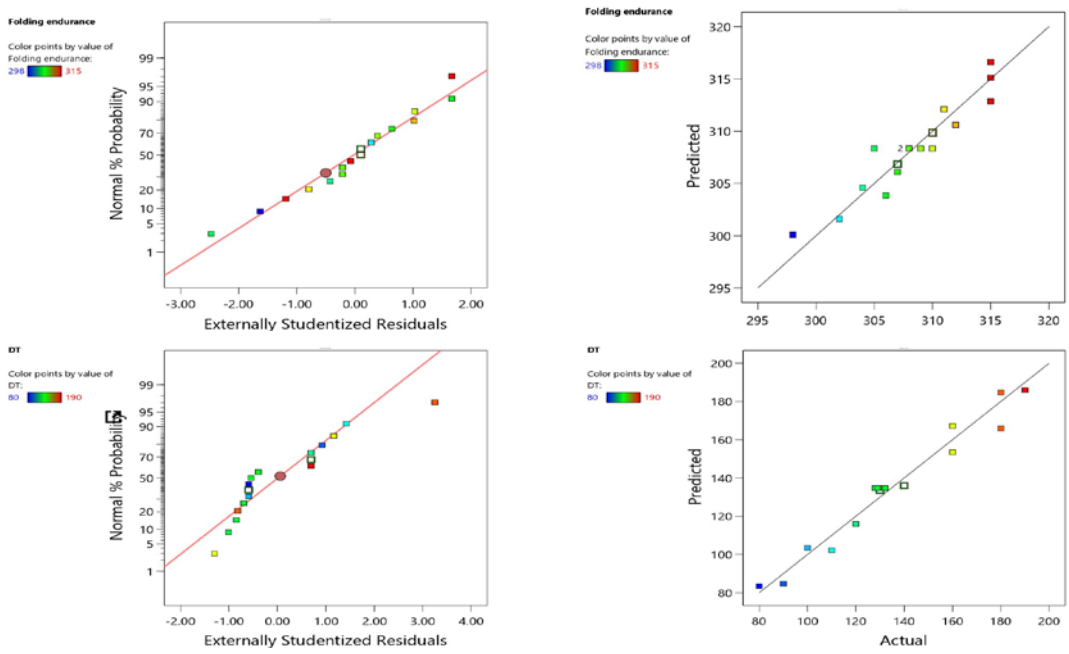

Figure 3: Diagnostic plots demonstrating the adequacy of the response surface models

Optimization and Selection of Formulation F13

Numerical optimization was performed using the desirability function approach in Design-Expert® software. The optimization criteria were established to maximize folding endurance, drug release, and drug content while minimizing disintegration time. Among the 17 experimental runs, formulation F13 satisfied all predefined optimization constraints and was therefore selected as the optimized formulation for further evaluation, as shown in Table 5. Therefore, F13 was selected as the optimized formulation for further evaluation.

An overlay plot generated by the optimization model identified the design space region that satisfies all response criteria simultaneously. The composition corresponding to formulation F13 (HPMC E15: 400 mg, HPMC K100: 100 mg, and Glycerine: 2 mL) was within the optimum region and provided the most desirable balance among mechanical strength, drug release, and drug content while maintaining an acceptable disintegration time.

Although formulations F9 and F17 also demonstrated acceptable performance for certain individual responses, formulation F13 exhibited the most balanced overall performance across all critical quality attributes. F13 showed superior drug release for both Sumatriptan Succinate (96.33%) and Naproxen Sodium (94.00%), high drug content (95.67% for both drugs), acceptable disintegration time (153.33 sec), and adequate folding endurance (316.67). Therefore, F13 was selected as the optimized formulation for further characterization and validation studies as shown in Figure 5. Numerical optimization was performed using the desirability function approach in Design-Expert® software to simultaneously optimize folding endurance, disintegration time, swelling index, cumulative drug release, adhesion time, and drug content.

The optimized formulation (F13) exhibited an overall desirability value of 0.98, indicating excellent simultaneous fulfillment of all predefined optimization criteria. The high desirability value confirmed that F13 represented the optimum compromise among all selected responses. Furthermore, the experimentally observed responses showed close agreement with the predicted values, confirming the adequacy, robustness, and predictive capability of the developed Box–Behnken Design model.

Optimized formulation (Formulation F13)

The optimized formulation table is shown in Table 7.

Table 7: Formulation table of optimized (F13) formulation

Ingredients for optimized formulation F13	Quantity
Sumatriptan Succinate(mg)	60
Naproxen Sodium (mg)	250
PVP K- 30 (mg)	100
HPMC E15 (mg)	400
HPMC K100 (mg)	100
Glycerin (ml)	2

Figure 4: Bio-flexible Film (F13)

Evaluation of F13 formulation

A smooth, non-gritty, and uniform film was obtained, as shown in Figure 4, and the evaluation results are presented in Table 8. To validate the optimization model, the optimized formulation (F13) predicted by the Design-Expert® software was prepared experimentally and evaluated under identical conditions. The experimentally observed responses were in close agreement with the predicted values, demonstrating the adequacy and reliability of the developed response surface models. The low prediction errors obtained for all critical quality attributes confirmed the robustness and predictive capability of the optimization process.

Table 8: Evaluation parameters of F13 formulation

Test Parameter	Formulation F13(±SD)
Folding endurance	316.67±1.2
Disintegration Time (sec)	153.33±1.2
%CDR of Sumatriptan Succinate	96.33±0.6
% CDR of Naproxen Sodium	94.00±1.0
Adhesion time (min)	46.33±1.5
Swelling Index	163.33±5.8
DC (Sumatriptan Succinate)	95.67±1.5
DC (Naproxen Sodium)	95.67±0.6

Values are expressed as mean ± standard deviation (n = 3).

Table 9: Comparison of Predicted and Experimental Responses of Optimized Formulation F13

Response	Predicted Value	Experimental Value	% Error
FE	303.85	316.67 ± 1.2	4.22
DT (sec)	144.71	153.33 ± 1.2	5.96
DR (%) – Naproxen Sodium	83.03	94.00 ± 1.0	13.21
DR (%) Sumatriptan Succinate	86.50	96.33 ± 0.6	11.37

Experimental values are expressed as mean ± standard deviation (n = 3).

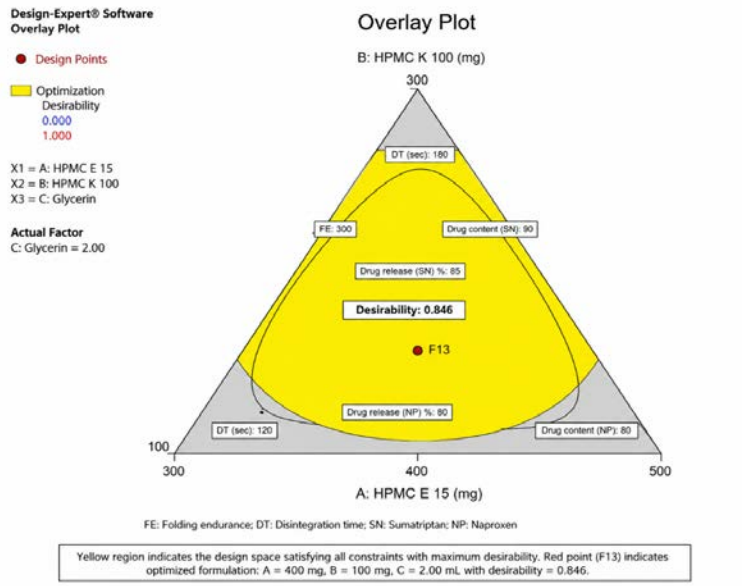

Figure 5: Schematic overlay plot showing the design space generated using Box–Behnken Design. The shaded desirability region represents the factor combinations that satisfy the predefined optimization criteria: maximum folding endurance, high drug release, high drug content, and acceptable disintegration time. Formulation F13 (HPMC E15 = 400 mg, HPMC K100 = 100 mg, Glycerine = 2 mL) was located within the optimum region and selected for further characterization.

Validation of Optimization Model

To validate the optimization model generated by Box–Behnken Design, the optimized formulation (F13) suggested by the software was prepared and experimentally evaluated. The predicted responses obtained from the mathematical models were compared with the experimentally observed values. The

percentage prediction error across all responses was within acceptable limits, indicating satisfactory agreement between predicted and observed results. As shown in Table 9. These findings confirm the reliability and predictive capability of the developed optimization model. Formulation F13 was selected because it provided the most desirable balance among all critical quality attributes, including high drug release, high drug content, acceptable disintegration time, and adequate mechanical strength. Furthermore, the optimized factor combination (HPMC E15 400 mg, HPMC K100 100 mg, and Glycerine 2 mL) met the predefined optimization criteria. It was therefore considered the optimal formulation for further characterization, as shown in Figure 5. Numerical optimization was performed using the desirability function approach. The overlay plot identified the factor space where all response constraints were simultaneously satisfied. The optimized formulation F13, containing 400 mg HPMC E15, 100 mg HPMC K100, and 2 mL glycerine, was located within the acceptable design space and was therefore selected for further characterization. Numerical optimization identified formulation F13 as the optimum formulation based on simultaneous satisfaction of the predefined criteria for folding endurance, disintegration time, drug release, and drug content. The optimized formulation was located within the feasible design space and was selected for further characterization. The close agreement between predicted and experimental responses further confirmed the adequacy and predictive capability of the developed Box–Behnken Design model. Kinetic release study of optimized (F13) formulation of Sumatriptan Succinate and Naproxen Sodium. By applying different kinetic models, such as zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell, to the in vitro release data, the mechanism of drug release from the Bioadhesive films of Sumatriptan Succinate and Naproxen Sodium was examined, and the results are shown in Table 10. The kinetic analysis indicated that both the Higuchi and Korsmeyer–Peppas models adequately described the release behavior of the optimized formulation, as evidenced by the higher correlation coefficients obtained for the Korsmeyer–Peppas model (R^2 = 0.9797 for Sumatriptan Succinate and 0.9875 for Naproxen Sodium). The estimated release exponent (n) obtained from the Korsmeyer–Peppas power-law fitting was approximately 0.4894 for Sumatriptan Succinate and 0.5060 for Naproxen Sodium. Since both values fall within the range associated with anomalous (non-Fickian) transport, the drug release mechanism is governed by a combination of Fickian diffusion through the hydrated polymer matrix and polymer relaxation/swelling. These findings confirm that the optimized bioflexible film exhibits a mixed release mechanism, as shown in Figures 6A and 6B, rather than a purely Higuchi-controlled diffusion process, thereby supporting transmucosal drug delivery.

Table 10: Kinetic release study of optimized (F13) formulation - Sumatriptan Succinate and Naproxen Sodium.

Kinetic Model	R_obs-pre for sumatriptan succinate	R_obs-pre for naproxen sodium	R sqr for sumatriptan succinate	R sqr For naproxen sodium	MSC for sumatriptan succinate	MSC For naproxen sodium
Zero order	0.9806	0.9907	0.7283	0.8514	1.0529	1.6562
First order	0.9773	0.9775	0.9459	0.9448	2.6660	2.6462
Higuchi	0.9899	0.9918	0.9649	0.9462	3.0990	2.6721
Korsmeyer Peppas	0.9898	0.9937	0.9797	0.9875	3.3995	3.8837
Hixson-Crowell	0.9868	0.9871	0.9712	0.9735	3.2964	3.3807

Robs-pre = correlation between observed and predicted values; R^2 = coefficient of determination; MSC = model selection criterion.

Drug	Release exponent (n)	Release constant (k)	Mechanism
Sumatriptan Succinate	0.4894	0.1448	Anomalous (non-Fickian) transport
Naproxen Sodium	0.5060	0.1234	Anomalous (non-Fickian) transport

Although egg membrane was employed as a preliminary permeation barrier for comparative formulation evaluation, it cannot fully replicate the physiological, histological, and permeability characteristics of human soft-palatal mucosa. Consequently, the ex vivo permeation results provide supportive evidence regarding membrane transport behavior.

Interpretation of n (thin films / polymeric matrices)

n value	Release mechanism
<0.45	Fickian diffusion
0.45–0.89	Non-Fickian (anomalous) transport
0.89	Case II transport
>0.89	Super Case II transport

Ex-Vivo Permeation Studies

Ex vivo permeation studies were conducted to evaluate the drug's ability to diffuse across the soft palatal mucosa and assess the performance of the optimized formulation. The study was conducted using a Franz diffusion cell to evaluate drug permeation across the soft-palatal mucosal membrane [31]. Fresh soft-palatal mucosa was obtained from a slaughterhouse in accordance with ethical guidelines. The collected tissue was transported in chilled phosphate buffer of pH 6.8. The adhering connective tissue and fatty materials were removed, and the isolated membrane was washed thoroughly with phosphate buffer to remove debris and equilibrated in Phosphate buffer of pH 6.8. The prepared soft-palatal membrane was carefully mounted between the donor and receptor compartments with the epithelial side facing the donor compartment. The bioflexible film was placed directly on the mucosal surface in the donor compartment [32,33].

At predetermined time intervals, aliquots of sample were withdrawn from the receptor compartment and replaced with an equal volume of fresh prewarmed buffer to maintain sink conditions. The collected samples were analyzed using UV–visible spectrophotometry at the selected λmax to determine drug permeation. The cumulative amount of drug permeated per unit area was calculated and plotted as a function of time. The ex vivo cumulative drug release data are summarized in Figure 7. The optimized formulation F13 exhibited a cumulative drug release of approximately 93% (for Sumatriptan Succinate) and 95% (for Naproxen Sodium), reflecting efficient permeation through the mucosal membrane

FTIR study

Fourier Transform Infrared (FTIR) spectroscopy of the mixture containing Sumatriptan Succinate, Naproxen Sodium, HPMC E15, HPMC K100, and PVP K30 shows characteristic absorption peaks corresponding to the functional groups of each component. Broad peaks are observed at 3300–3500 cm^{-1}, indicating O–H stretching vibrations, likely attributable to polymeric excipients such as HPMC and PVP. A sharp peak near 1650 cm^{-1} corresponds to C=O stretching, which is characteristic of both Naproxen Sodium and PVP.

The presence of aromatic and amine groups, likely from Sumatriptan Succinate and Naproxen Sodium, is confirmed by peaks in the 1600–1500 cm^{-1} range. Additionally, a peak around 2123 cm^{-1} suggests a nitrile (C≡N) group associated with Sumatriptan Succinate. Multiple peaks in the fingerprint region (1200–900 cm^{-1}) further support the presence of complex polymeric structures such as HPMC and PVP. Overall, the FTIR data confirm the presence of all five components in the mixture, with no significant shifts in major peaks, suggesting that no strong chemical interactions occurred among them in the physical mixture.

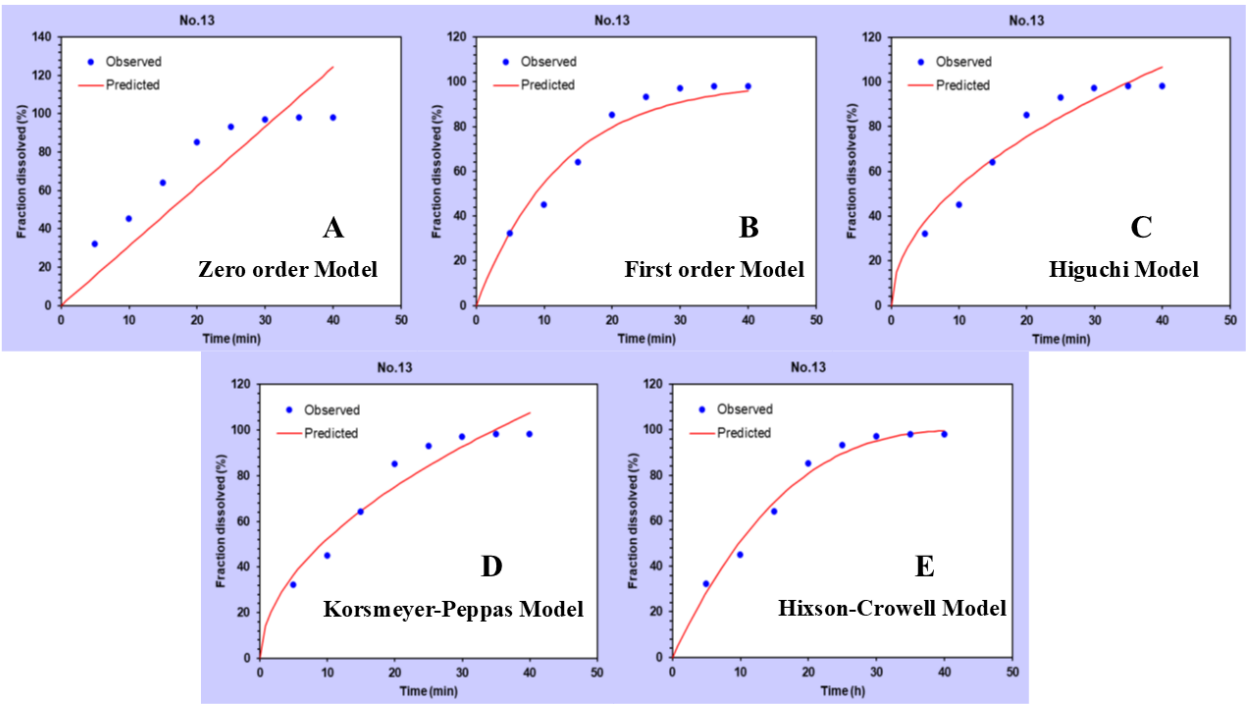

Figure 6 A: Kinetic release study of optimized (F13) formulation - Sumatriptan Succinate

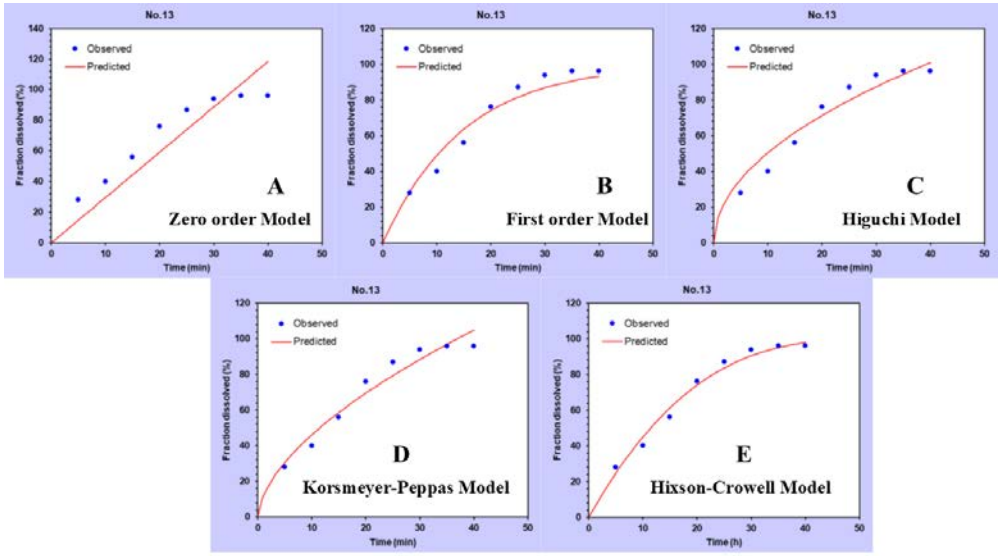

Figure 6 B: Kinetic release study of optimized (F13) formulation - Naproxen Sodium

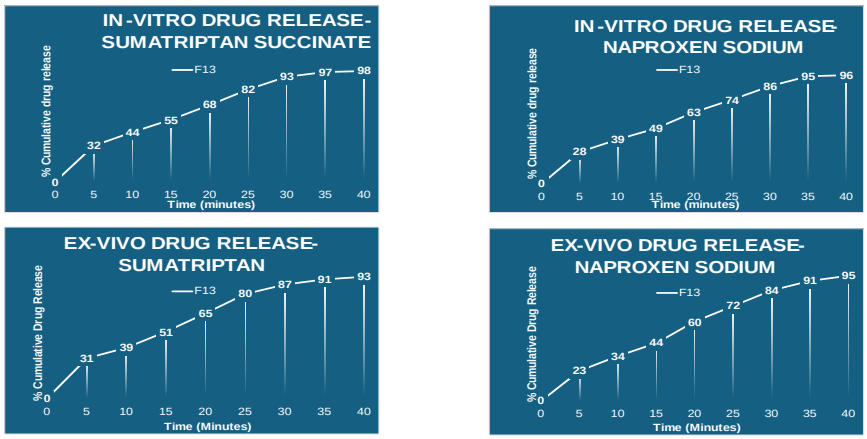

Figure 7: In- Vitro and Ex-Vivo Drug release of Sumatriptan and Naproxen sodium from optimized formulation (F13)

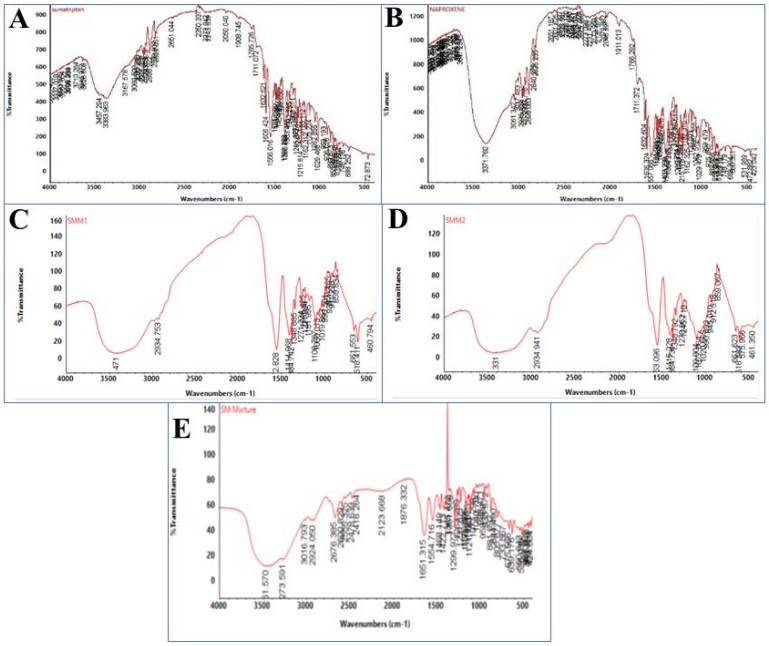

Figure 8: FTIR Analysis of (a) Sumatriptan Succinate, (b) Naproxen Sodium, (c) HPMC E15, (d) HPMC K100, and (E) Optimized formulation

Table 11: Characteristic FTIR Peaks of Pure Drugs and Optimized Formulation

Functional Group	Reported Peak of Drug (cm^{-1})	Peak in Optimized Film (cm^{-1})	Observation
O–H Stretching	3300–3500	3290–3480	Retained
C=O Stretching	~1650	~1648	Retained
Aromatic C=C Stretching	1600–1500	1598–1498	Retained
C–O Stretching	1100–1300	1095–1290	Retained
S=O Stretching (Sumatriptan)	~1340	~1335–1345	Retained

The FTIR spectra of the optimized formulation showed retention of the characteristic peaks of Sumatriptan Succinate and Naproxen Sodium, with no significant new peaks or major peak shifts. These observations suggest the absence of major chemical incompatibilities between the drugs and formulation excipients. Therefore, the FTIR analysis supports compatibility of the formulation components rather than confirming specific molecular interactions, as shown in Table 11 and Figure 8.

DISCUSSION

In this study, various bio-flexible films of Sumatriptan Succinate and Naproxen Sodium were successfully developed by the solvent-casting method. Optimized formulations were prepared using a Box–Behnken design with the excipients HPMC E15, HPMC K100, PVP K-30, and glycerine to achieve desirable physicochemical properties. The prepared bioflexible films showed a highly uniform drug content, a good disintegration time of 150 seconds, optimized folding endurance, and a well-balanced swelling index, which is necessary for good mucoadhesion. The *in vitro* release profile was nearly 96.33% and 94% of the drug loaded bioflexible film within 40 minutes, and ex vivo release permeation was nearly 93% and 95% of the drug loaded, indicating both quick onset and efficient delivery. The release kinetics showed the Higuchi model, implying that drug release was governed by gradual changes in the film's surface area as it eroded, a favorable mechanism for controlled and predictable drug release.

Response surface analysis indicated that HPMC E15 and HPMC K100 exerted measurable effects on folding endurance, disintegration time, swelling behavior, and permeation characteristics of the bioflexible films. The observed trends suggest that increasing polymer concentration contributed to improved mechanical strength and prolonged disintegration time. However, the magnitude and direction of these effects were dependent on the factor levels evaluated within the experimental design space. Therefore, the conclusions are based on the fitted Box–Behnken Design models and response surface analysis rather than on direct cause-and-effect assumptions.

The performance of the optimized bioflexible film was compared with previously reported buccal and oromucosal film formulations described in the literature. Reported bioflexible films exhibit disintegration times between 153 seconds and drug release above 80%. The optimized formulation F13 demonstrated a disintegration time of 153.33 seconds and ex vivo permeation of 93% for Sumatriptan Succinate and 95% for Naproxen Sodium, indicating performance comparable to that of previously reported oromucosal delivery systems. Differences between studies may be attributed to variations in polymer composition, plasticizer concentration, membrane models, and experimental conditions. Therefore, the present findings should be interpreted in the context of the specific formulation design and evaluation methods employed.

The optimized bioflexible film (F13) exhibited a disintegration time of 153.33 ± 1.2 s and a folding endurance of 316.67 ± 1.2, demonstrating an appropriate balance between rapid disintegration and mechanical integrity. Rizatriptan mucoadhesive buccal films reported by Salehi and Boddohi [34] exhibited considerably longer disintegration times (11–18 min), reflecting stronger mucoadhesion but slower film erosion. The present formulation achieved a shorter disintegration time while maintaining higher mechanical integrity, which can be attributed to the synergistic combination of HPMC E15 and HPMC K100 along with glycerin as a plasticizer. Fast-dissolving sumatriptan films developed by Soni and Yadav [35] and Bonthagarala et al.[36] were primarily designed for rapid oral dissolution, exhibiting disintegration times of less than one minute but comparatively lower folding endurance, generally below 200 folds. Although these formulations dissolved rapidly, their lower mechanical strength may limit handling and increase the risk of tearing during administration. These characteristics make the developed bioflexible film particularly suitable for oro-trans soft palatal drug delivery, where sufficient flexibility, ease of handling, and timely drug release are all required simultaneously. The higher mechanical strength of the present formulation may be attributed to the synergistic film-forming

properties of HPMC E15 and HPMC K100, while maintaining high cumulative drug release (96.33% for Sumatriptan Succinate and 94.00% for Naproxen Sodium within 40 min). Overall, these findings indicate that the optimized formulation exhibits competitive physicomechanical characteristics suitable for oro-trans soft-palatal drug delivery.

Conventional oral dosage forms of Sumatriptan succinate and Naproxen sodium, including tablets, commonly exhibit delayed onset of action and inconsistent absorption due to hepatic first-pass metabolism [37]. Patients with migraine suffer from nausea and vomiting, which results in less effectiveness of orally administered drugs [38]. Transdermal and intranasal routes also exhibited variable absorption, irritation, and manufacturing limitations [39]. In contrast to these dosage forms, the soft palatal mucosa provides a highly vascularized absorption site with direct systemic entry, which ensures faster drug delivery. This may facilitate systemic absorption owing to its rich vascularization.

In the present study, dual-drug bioflexible films were developed that provide controlled yet rapid release, delivering both drugs within 40 minutes and demonstrating substantial permeation of triptan and NSAID during the experimental study period. The film exhibits greater mechanical strength and bioflexibility, reducing the risk of mucosal irritation and leading to longer retention at the target site, with enhanced patient compliance due to its no-water administration and dual-mechanism design, which may support effective drug delivery; however, therapeutic performance requires confirmation through in vivo studies. Thus, the developed formulation demonstrated performance characteristics comparable to previously reported buccal and oromucosal film systems. Conventional and previously reported single-drug oromucosal films in terms of onset of action, stability, and patient acceptability [40]. The results indicate that the developed bio-flexible film for oro-trans-soft palatal delivery is a promising delivery system for Sumatriptan Succinate and Naproxen Sodium.

CONCLUSION

The study successfully evaluated bioflexible films for the co-delivery of Sumatriptan Succinate and Naproxen Sodium using the solvent-casting method with a Box–Behnken statistical design. Compared with monotherapy, the combination of naproxen sodium and sumatriptan succinate offers significant advantages. The combination of a triptan with an analgesic in a multi-mechanism therapy produces superior results compared to monotherapy with the standard antimigraine drugs. The optimized films exhibited excellent mechanical strength and flexibility, as indicated by a high folding endurance of 316 and a disintegration time of 150 seconds, thereby facilitating rapid drug release. *In vitro* diffusion studies demonstrated efficient drug release, with 96,33% for Sumatriptan Succinate and 94% for Naproxen Sodium, due to the optimal concentrations of HPMC E15 and HPMC K100 in F13. Ex-vivo permeation studies exhibited a cumulative drug release of approximately 93% (for Sumatriptan Succinate) and 95% (for Naproxen Sodium), reflecting efficient permeation through the mucosal membrane.

The kinetic analysis revealed that the drug release profile was best described by the Higuchi and Korsmeyer–Peppas models, indicating that drug release occurred through a combination of diffusion-controlled and polymer relaxation mechanisms. Compared with previously reported single-drug formulations, the dual-drug system presented here offers superior release efficiency and a faster onset of action due to synergistic action. The combination of good release and optimized swelling index supports buccal application, particularly by the oro-trans-soft palatal route. The 46-minute adhesion time is sufficient to ensure prolonged contact with the skin, thereby enhancing drug absorption. A swelling index of 160% indicates the film's capacity to swell and diffuse. These results suggest that the F13 formulation possesses desirable physicochemical properties and good drug-release characteristics.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Srishti Morris contributed to conceptualization of the study, preparation of the original draft, and data collection. Nidhi Gairola was involved in conceptualization, review, and editing of the manuscript, as well as formal analysis. Ashutosh Badola contributed to conceptualization, supervision of the research work, and review and editing of the manuscript. Mahendra Prajapati provided resources and participated in review and editing of the manuscript. All authors read and approved the final version of the manuscript.

DECLARATION OF USE OF AI TOOLS

The authors used ChatGPT for language editing and improving readability. All content, analysis, and conclusions were reviewed and verified by the authors. The authors take full responsibility for the originality, accuracy, and integrity of the work

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