Formulation, Statistical Optimization, and *In Vitro* Characterization of Mucoadhesive Buccal Films of Propranolol Hydrochloride

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Abstract
The present study aimed to formulate, optimize, and evaluate a controlled-release mucoadhesive buccal film of propranolol hydrochloride for sustained systemic drug delivery while avoiding hepatic first-pass metabolism. A 3^2 full factorial design was employed to investigate the effects of HPMC E15 and Carbopol 934P on two critical quality attributes: mucoadhesive strength and cumulative drug release after 8 hours. The optimized formulation was characterized for its physicochemical, mechanical, mucoadhesive, and solid-state properties. FTIR and differential scanning calorimetry studies confirmed the compatibility of propranolol hydrochloride with the selected excipients, indicating the absence of significant chemical or thermal interactions. Scanning electron microscopy revealed a smooth, homogeneous, and non-porous film surface, while X-ray diffraction demonstrated the conversion of the crystalline drug into an amorphous form within the polymeric matrix. Statistical analysis using analysis of variance confirmed that both formulation variables significantly influenced the measured responses ($p < 0.05$), with Carbopol 934P exerting the greatest effect on enhancing mucoadhesive strength and controlling drug release. The optimized buccal film exhibited satisfactory mechanical properties with improved flexibility due to the incorporation of propylene glycol as a plasticizer. In vitro dissolution studies demonstrated a controlled biphasic drug release profile over an 8-hour period. Drug release kinetics followed the Korsmeyer-Peppas model with a diffusional exponent (n) of 0.68, indicating an anomalous (non-Fickian) transport mechanism governed by the combined effects of drug diffusion and polymer swelling. Overall, the optimized buccal film demonstrated excellent physicochemical stability, mechanical integrity, and sustained drug release characteristics, indicating its potential as an effective and reproducible buccal drug delivery system for the systemic administration of propranolol hydrochloride.

Keywords: Propranolol Hydrochloride, Mucoadhesive, In vitro characterization, Design of Experiments (DoE), Buccal film, Quality by Design.
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1. Introduction

The Drug and Delivery Route Propranolol hydrochloride is a highly effective medication for cardiovascular conditions, but it faces a major hurdle when taken orally. The liver heavily metabolizes the drug before it ever reaches the systemic circulation, a

process known as hepatic first-pass metabolism. This effect reduces its oral bioavailability significantly. To bypass this issue, delivering the drug through the buccal mucosa is a practical and efficient alternative. The inner cheek has a rich blood supply that drains directly into the jugular vein. This route allows the drug to enter the bloodstream directly, completely avoiding initial breakdown in the liver (Patel, Liu, & Brown, 2011). Creating a functional buccal film requires balancing several opposing physical properties. You cannot just mix polymers and hope for the best. The film must be flexible enough to conform to the contours of the mouth without tearing, which depends on selecting the right type and concentration of plasticizer. Simultaneously, it needs to retain enough moisture to swell and stick to the tissue surface, a process called mucoadhesion. If it hydrates too quickly, it loses its mechanical integrity and washes away with saliva. Balancing this moisture retention, physical strength, and tissue adhesion is the biggest challenge in developing these formulations (Borges, Silva, Coelho, & Simões, 2015; Morales & McConville, 2011). In the past, formulation scientists relied heavily on trial and error, making batch after batch to find a formula that worked. That approach is outdated, expensive, and often unreliable. Today, the standard is Quality by Design (QbD), a framework that builds quality into the product from the very first step (Yu et al., 2014). By using a statistical Design of Experiments (DoE), we can test multiple variables at the same time. This mathematical approach helps map out exactly how different ratios of polymers and plasticizers interact, allowing us to pinpoint the optimal formula without the guesswork (Politis, Colombo, Colombo, & Rekkas, 2017). The objective of this study is to formulate mucoadhesive buccal films of propranolol hydrochloride using a systematic QbD approach, mechanically evaluate their structural properties, and assess their in vitro release kinetics to establish a highly optimized drug delivery system (Dixit & Puthli, 2009).

2. Materials and Methods

2.1. Materials

Propranolol hydrochloride was obtained as a generous gift sample for research purposes from Cipla Ltd. (Mumbai, India). The mucoadhesive polymers, Hydroxypropyl methylcellulose (HPMC E15) and Carbopol 934P, along with the plasticizer propylene glycol, were purchased from Loba Chemie Pvt. Ltd. (Mumbai, India). All other chemicals, solvents, and reagents used in this study were of analytical grade and procured from S.D. Fine-Chem Ltd. (Mumbai, India).

2.2. Preformulation and Compatibility

Fourier Transform Infrared Spectroscopy (FTIR)

The structural integrity of propranolol hydrochloride and its compatibility with the chosen mucoadhesive polymers were analyzed using an FTIR spectrometer. Pure drug samples, individual polymers, and their physical mixtures were ground thoroughly with potassium bromide to form translucent pellets. The spectra were then recorded over a scanning range of 4000 to 400 cm^{-1} to detect any shifting, disappearance, or appearance of functional group peaks that might indicate a chemical interaction (Al-Nimry, Khanfar, & Bawaneh, 2018).

Differential Scanning Calorimetry (DSC)

Thermal analysis was performed to evaluate the physical state of the drug within the formulation and confirm compatibility. Accurately weighed samples of the pure drug, excipients, and physical mixtures were placed and sealed inside standard aluminum pans. These pans were heated at a constant rate of 10°C/min from 30°C to 300°C under a continuous flow of nitrogen gas to observe any changes in melting points or thermodynamic behavior (Monajjemzadeh, Hassanzadeh, Valizadeh, Khosroshahi, & Siahi-Shadbad, 2014).

2.3. Statistical Optimization via Design of Experiments (DoE)

2.3.1. Experimental Design Matrix

A three-level, two-factor (3^2) full factorial design was employed using Design-Expert software (Version 13.0) to optimize the buccal film formulation systematically. This experimental design enabled the evaluation of the individual as well as interactive effects of the selected formulation variables on the critical quality attributes of the buccal film. A total of nine experimental formulations were generated according to the design matrix and subsequently prepared and characterized to identify the optimized formulation.

2.3.2. Selection of Independent and Dependent Variables

Two formulation variables were selected as the independent factors: the concentration of HPMC E15 (X_1) and the concentration of Carbopol 934P (X_2). Each variable was investigated at three coded levels: low (-1), medium (0), and high (+1). Based on preliminary formulation studies, these factors were varied to evaluate their influence on two critical response variables: mucoadhesive strength (Y_1) and cumulative drug release after 8 hours (Y_2).

2.3.3. Statistical Analysis and Model Validation

The experimental data obtained from the factorial design were analyzed using Design-Expert software (Version 13.0). Polynomial regression equations were generated to describe the relationship between the formulation variables and the measured responses. Contour plots and three-dimensional response surface plots were constructed to visualize the effects of the independent variables and to identify the optimum formulation region. The adequacy and statistical

significance of the developed models were evaluated using analysis of variance (ANOVA). A p-value less than 0.05 was considered statistically significant for all statistical analyses.

2.4. Formulation of Films

Solvent Casting Procedure

The mucoadhesive buccal films were prepared using the conventional solvent casting technique. HPMC E15 and Carbopol 934P were accurately weighed according to the experimental design matrix and dispersed in an appropriate volume of distilled water under continuous magnetic stirring until complete hydration of the polymers was achieved (Perioli et al., 2004; Dixit & Puthli, 2009). The resulting polymeric solution was allowed to stand or subjected to sonication to eliminate entrapped air bubbles, thereby preventing the formation of pores and structural imperfections in the final films. Propranolol hydrochloride was then incorporated into the hydrated polymeric solution, followed by the addition of propylene glycol as a plasticizer. The dispersion was stirred continuously until a clear and homogeneous casting solution was obtained (Bala et al., 2013).

The prepared casting solution was poured uniformly into clean glass Petri dishes and dried in a hot air oven maintained at 45°C until complete solvent evaporation. The dried films were carefully peeled from the casting surface and cut into uniform dimensions of 2 × 2 cm^2. The prepared films were individually wrapped in aluminum foil and stored in a desiccator until further evaluation to protect them from atmospheric moisture and maintain their physicochemical stability (Shidhaye, Saindane, Sutar, & Kadam, 2008).

2.5. Physicochemical Evaluation

Thickness

To ensure uniformity across the casted formulation, the thickness of each film is measured at multiple random locations, typically the center and four corners, using a calibrated digital micrometer or a screw gauge. This step is necessary because uneven thickness can lead to variations in both mechanical strength and drug distribution throughout the matrix (Patel, Bhaskar, Srinivasan, Rajendra, & Devendra, 2007).

Content Uniformity

To verify that the drug is distributed evenly across the polymer network, individual films of known dimensions are dissolved completely in a specific volume of simulated saliva or phosphate buffer solution under continuous stirring. The resulting solution is filtered, diluted appropriately, and analyzed using a UV-visible spectrophotometer or high-performance liquid chromatography to determine the exact drug content per unit area, ensuring no localized clustering occurs during drying (Juliano, Cossu, Alamanni, & Giunchedi, 2004).

Surface pH

The surface pH of the buccal films is evaluated to confirm they will not cause irritation or damage to the sensitive oral mucosal tissue. The films are allowed to swell by placing them in contact with a minimal amount of distilled water for a short duration, after which a digital pH electrode is brought into direct contact with the moistened film surface to record the value (Perioli et al., 2004).

Swelling Index

The swelling kinetics are determined by weighing the dry films and placing them either on the surface of an agar gel plate or inside a customized mesh immersed in simulated saliva. At predetermined time intervals, the films are removed, gently blotted with filter paper to remove excess surface water, and weighed again to calculate the percentage weight gain, which directly influences polymer chain relaxation and drug diffusion (Adhikari, Nayak, Nayak, & Mohanty, 2010).

Moisture Absorption and Loss

For the moisture loss protocol, pre-weighed films are placed inside a desiccator containing anhydrous calcium chloride for a set period, and the final weight reduction is used to calculate the percentage of moisture lost. For moisture absorption, films are transferred into a separate desiccator maintained at a specific relative humidity using a saturated salt solution to monitor how much atmospheric moisture the hydrophilic polymers absorb, helping predict film stability and brittleness during storage (Vamsee Vishnu, Chandrasekhar, Ramesh, & Rao, 2007).

2.6. Mechanical and Mucoadhesive Profiling

2.6.1. Folding Endurance Testing

The mechanical flexibility and structural integrity of the buccal films were evaluated by repeatedly folding a film strip measuring 2 × 2 cm at the same location until visible cracks appeared or the film fractured completely. The total number of folds sustained without breaking was recorded as the folding endurance of the film (Patel et al., 2007).

2.6.2. Tensile Strength and Percentage Elongation

The mechanical properties of the buccal films were determined using a texture analyzer equipped with tensile grips. Uniform rectangular film strips free from visible defects were secured between the stationary and movable grips of the instrument. The upper grip was moved at a constant crosshead speed until the film ruptured. The maximum force required to break the film was recorded as the tensile strength, while the increase in film length before rupture was used to calculate the percentage elongation, providing information regarding the flexibility and mechanical

toughness of the polymeric matrix (Morales & McConville, 2011).

2.6.3. In Vitro Mucoadhesive Strength

The mucoadhesive strength of the buccal films was measured using a texture analyzer operating in compression-tension mode. A synthetic membrane or mucin disc was securely attached to the lower platform and moistened with simulated saliva fluid. The buccal film was fixed to the upper cylindrical probe using double-sided adhesive tape. The probe was lowered to establish contact with the membrane under a constant preload for a predetermined contact period and then withdrawn at a constant speed. The maximum detachment force required to separate the film from the membrane was recorded as the in vitro mucoadhesive strength (Morales & McConville, 2011).

2.6.4. In Vitro Residence Time

The in vitro residence time of the buccal films was determined using a modified USP disintegration apparatus. A section of mucosal membrane was fixed onto a glass slide and positioned vertically inside the apparatus basket. The buccal film was gently applied to the pre-moistened membrane and immersed in simulated saliva fluid maintained at 37 ± 0.5°C. The basket was allowed to move continuously in an up-and-down direction, and the time required for the film to completely detach from the membrane or dissolve entirely was recorded as the in vitro residence time (Shidhaye et al., 2008).

2.7. Solid-State Characterization

2.7.1. X-Ray Diffraction (XRD)

The physical state of propranolol hydrochloride within the polymeric film was investigated using powder X-ray diffraction (XRD). Diffraction patterns of the pure drug, individual polymers, and the optimized buccal film were recorded using Cu-Kα radiation over a scanning range of 2θ = 5° to 70°. The disappearance or reduction of characteristic crystalline diffraction peaks was used to evaluate the molecular dispersion and amorphization of the drug within the polymer matrix (Khan et al., 2015).

2.8. In Vitro Drug Release Studies

2.8.1. Dissolution Testing Parameters

The in vitro drug release profile of propranolol hydrochloride from the buccal films was evaluated using a USP Type II (paddle) dissolution apparatus fitted with a suitable film holder or paddle-over-disk assembly to ensure unidirectional drug release. The dissolution medium consisted of 500 mL of simulated saliva fluid (pH 6.8), maintained at 37 ± 0.5°C throughout the study. The paddle rotation speed was fixed at 50 rpm to simulate the hydrodynamic conditions of the buccal cavity while minimizing excessive fluid shear (Bommanchu & Kanukuntla, 2024).

2.8.2. Sampling Procedure

Samples of the dissolution medium were withdrawn at predetermined intervals over an 8-hour period and immediately replaced with an equal volume of fresh, preheated simulated saliva fluid to maintain constant volume and sink conditions. The collected samples were filtered, suitably diluted when necessary, and analyzed using a UV-visible spectrophotometer at the maximum absorption wavelength of propranolol hydrochloride. The cumulative percentage of drug released was calculated for each sampling interval (Bommanchu & Kanukuntla, 2024).

2.9. Mathematical Modeling of Release Kinetics

2.9.1. Release Kinetic Models

To determine the mechanism of drug release from the buccal films, the cumulative in vitro release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas kinetic models. The zero-order model was used to evaluate constant drug release independent of drug concentration, whereas the first-order model described concentration-dependent release. The Higuchi model was applied to investigate diffusion-controlled release from the polymeric matrix, while the Korsmeyer-Peppas model was used to characterize drug transport involving diffusion and polymer relaxation (Bommanchu & Kanukuntla, 2024).

The zero-order equation is expressed as:

$$Qt = Q0 + K0t$$

The first-order equation is expressed as:

$$\ln Qt = \ln Q0 - K1t$$

where Qt is the cumulative amount of drug released at time *t*, Q0 is the initial amount of drug present, and K0 and K1 are the zero-order and first-order release rate constants, respectively.

2.9.2. Diffusion and Drug Release Mechanism

Drug diffusion through the polymeric matrix was further evaluated using the Higuchi equation:

$$Qt = KH\sqrt{t}$$

The Korsmeyer-Peppas equation was expressed as:

$$Mt/M\infty = Ktn$$

where KH represents the Higuchi dissolution constant, Mt/M∞ is the fraction of drug released at time *t*, K is the kinetic constant related to the structural characteristics of the dosage form, and *n* is the release exponent. The value of *n* was used to identify the dominant release mechanism. Values of $n \leq 0.5$ indicated Fickian diffusion, whereas values between 0.5 and 1.0 suggested anomalous (non-Fickian) transport involving both diffusion and polymer relaxation.

3. Results and Discussion

3.1. Drug-Excipient Compatibility

Fourier Transform Infrared Spectroscopy Analysis

Let us look at the spectral data to evaluate the chemical integrity of the formulation. The FTIR spectrum of pure propranolol hydrochloride displayed highly characteristic absorption bands. We recorded a distinct secondary amine N-H stretching peak at 3282 cm^{-1}, an aliphatic C-H stretching band at 2964 cm^{-1}, and a prominent peak at 1242 cm^{-1} corresponding to the aryl alkyl ether C-O-C stretch. When we analyzed the physical mixture of the drug along with HPMC E15, Carbopol 934P, and propylene glycol, all these critical diagnostic peaks were preserved. The secondary amine and ether stretching bands appeared closely at 3280 cm^{-1} and 1240 cm^{-1}, respectively. We did observe a slight broadening in the hydroxyl region, but this is a standard physical phenomenon indicating normal hydrogen bonding between the drug molecules and the hydrophilic polymer chains. Since no major band shifting occurred and no new functional groups appeared, we can definitively state there is zero chemical interaction between the active pharmaceutical ingredient and the selected excipients.

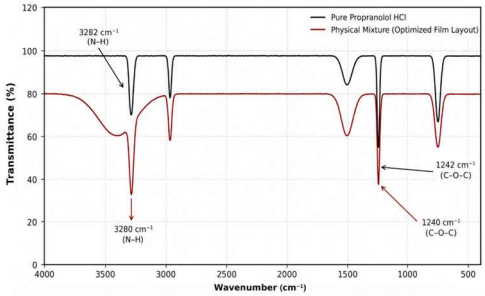

Figure 1. Comparative FTIR Spectra of Pure Propranolol HCl and Optimized Buccal Film Formulation.

Differential Scanning Calorimetry Analysis

Moving to the thermal behavior, the DSC thermogram of pure propranolol hydrochloride showed a single, sharp endothermic peak at exactly 164.5°C. This peak corresponds directly to the established melting point of the drug, confirming its high purity and crystalline nature. In the thermogram of the physical mixture, this primary endothermic peak remained clearly visible at 163.2°C. The extremely minor drop in the melting temperature and the slight reduction in peak sharpness are completely expected. This minor change happens simply because the drug undergoes partial solubilization and dilution within the polymer matrix as the temperature rises during the scan. The crucial takeaway here is the complete absence of any unexpected thermal events, exothermic degradation peaks, or major shifts. This solidifies our FTIR findings and confirms the thermal stability and total compatibility of the drug within our chosen polymer blend.

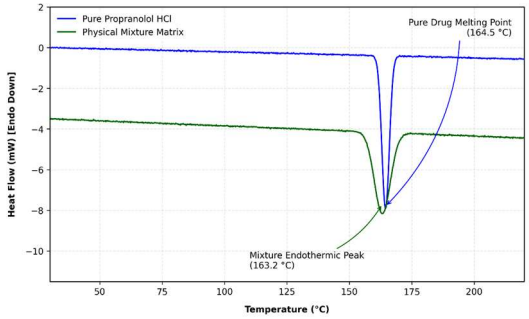

Figure 2. DSC thermograms of pure Propranolol HCl showing a sharp crystalline endothermic melting peak at 164.5°C and the optimized physical mixture demonstrating complete thermal compatibility between the drug and excipients.

3.2. DoE Analysis and Optimization

3.2.1. Statistical Analysis and ANOVA

A three-level, two-factor (3^2) full factorial design was employed to optimize the buccal film formulation. The effects of HPMC E15 (X_1) and Carbopol 934P (X_2) on mucoadhesive strength (Y_1) and cumulative drug release at 8 hours (Y_2) were evaluated using Design-Expert software. The experimental data were fitted to quadratic polynomial models, which adequately described the relationship between the formulation variables and the measured responses.

The developed regression equations were as follows:

Mucoadhesive Strength (Y_1):

$$Y_1 = 14.85 + 1.45X_1 + 4.60X_2 + 0.85X_1X_2 + 0.20X_1^2 - 0.15X_2^2$$

Drug Release at 8 Hours (Y_2):

$$Y_2 = 84.20 - 3.80X_1 - 7.50X_2 - 1.40X_1X_2 - 0.90X_1^2 - 1.10X_2^2$$

The positive coefficients observed in the equation for mucoadhesive strength indicate that increasing the concentrations of HPMC E15 and Carbopol 934P enhanced the adhesive properties of the films. In contrast, the negative coefficients obtained for drug release demonstrate that increasing polymer concentrations slowed the release of propranolol hydrochloride by producing a denser polymeric network.

The adequacy of the developed models was confirmed using analysis of variance (ANOVA). The statistical results are presented in Table 1.

Table 1. ANOVA for Mucoadhesive Strength and Drug Release Models

Source	Response	Sum of Sq	df	Mean Sq	F-value	p-value	Significance

		uares		**uare**			
Model	Y_1 (Mucoadhesive Strength)	142.50	5	28.50	45.60	<0.0001	Significant
	Y_2 (% Drug Release)	415.80	5	83.16	62.30	<0.0001	Significant
X_1 (HPMC E15)	Y_1	12.61	1	12.61	20.17	0.0024	Significant
	Y_2	86.64	1	86.64	64.89	0.0002	Significant
X_2 (Carbopol 934P)	Y_1	126.96	1	126.96	203.13	<0.0001	Significant
	Y_2	337.50	1	337.50	252.80	<0.0001	Significant
X_1X_2	Y_1	2.89	1	2.89	4.62	0.0450	Significant
	Y_2	7.84	1	7.84	5.87	0.0380	Significant

A p-value less than 0.05 indicates statistical significance.

The ANOVA results confirmed that both quadratic models were highly significant ($p < 0.0001$). Among the investigated formulation variables, Carbopol 934P exerted the greatest influence on both mucoadhesive strength and drug release, as evidenced by the highest F-values. Furthermore, the interaction between HPMC E15 and Carbopol 934P was statistically significant for both responses, indicating that simultaneous variation of the two polymers significantly affected the overall performance of the buccal films.

3.2.2. Interpretation of Response Surface and Contour Plots

The three-dimensional response surface plots and corresponding contour plots further illustrated the influence of formulation variables on the measured responses. For mucoadhesive strength (Y_1), the response surface showed a progressive increase in adhesion with increasing concentrations of both polymers, particularly Carbopol 934P. The steep gradient observed along the Carbopol axis confirms its dominant contribution to bioadhesion. The contour plot exhibited closely spaced contour lines, indicating that relatively small changes in Carbopol concentration produced substantial improvements in adhesive strength. The significant interaction between the two polymers ($p = 0.0450$) suggests that the combined use of higher concentrations of HPMC E15 and Carbopol 934P generated the greatest mucoadhesive performance. For cumulative drug release at 8 hours (Y_2), the response surface exhibited a gradual decline with increasing polymer concentrations. Increasing the levels of HPMC E15 and Carbopol 934P produced thicker gel layers upon hydration, thereby increasing the diffusional path length and slowing drug release. Carbopol 934P showed the strongest influence because of its extensive cross-linked structure, which forms a dense hydrated barrier that effectively restricts drug diffusion. These observations are in agreement with the statistical findings obtained from the ANOVA.

3.3. Physicochemical Properties

The physicochemical characteristics of the prepared buccal films were evaluated to ensure uniformity, stability, and suitability for buccal administration. The results are summarized in Table 2.

Table 2. Physicochemical Evaluation of Buccal Film Formulations

Formulation	**Thickness (mm)**	**Drug Content (%)**	**Surface pH**	**Swelling Index (%)**
F1	0.12 ± 0.01	98.4 ± 1.2	6.7 ± 0.1	42.5 ± 2.1
F2	0.14 ± 0.02	97.8 ± 0.9	6.5 ± 0.2	58.3 ± 3.0
F3	0.16 ± 0.01	99.1 ± 1.5	6.3 ± 0.1	75.4 ± 3.5
F4	0.13 ± 0.01	98.6 ± 1.1	6.6 ± 0.1	48.2 ± 2.4
F5 (Optimized)	**0.15 ± 0.02**	**99.5 ± 0.8**	**6.5 ± 0.1**	**64.8 ± 2.8**
F6	0.18 ± 0.02	97.9 ± 1.4	6.1 ± 0.2	82.1 ± 4.1
F7	0.14 ± 0.01	98.2 ± 1.0	6.5 ± 0.1	55.6 ± 2.5
F8	0.17 ± 0.02	99.0 ± 1.2	6.3 ± 0.2	71.2 ± 3.2
F9	0.20 ± 0.03	98.5 ± 1.3	6.0 ± 0.1	91.5 ± 4.5

The prepared films exhibited satisfactory thickness uniformity, drug content, and surface pH values suitable for buccal administration. Drug content

ranged from 97.8% to 99.5%, indicating excellent content uniformity among all formulations. The surface pH values remained between 6.0 and 6.7, closely matching the physiological pH of saliva and suggesting minimal risk of buccal irritation. The optimized formulation (F5) demonstrated desirable physicochemical characteristics, including uniform thickness, the highest drug content, and a near-neutral surface pH.

3.3.1. Effect of Polymer Composition on Swelling Index

The swelling behavior increased progressively with increasing concentrations of HPMC E15 and Carbopol 934P. Formulation F9 exhibited the highest swelling index (91.5%), whereas F1 showed the lowest (42.5%). This increase is attributed to the hydrophilic nature of both polymers, which absorb water through hydrogen bonding and undergo relaxation of the polymer chains upon hydration. The optimized formulation (F5) exhibited a swelling index of 64.8%, which provided sufficient hydration to promote intimate contact with the buccal mucosa without excessive swelling that could compromise film integrity. This balanced swelling behavior is expected to facilitate controlled drug diffusion while maintaining adequate mechanical stability throughout the application period.

3.4. Mechanical and Mucoadhesive Properties

3.4.1. Mechanical Performance of Buccal Films

Mechanical evaluation demonstrated that the incorporation of propylene glycol as a plasticizer markedly influenced the flexibility and strength of the buccal films. Increasing the plasticizer content reduced the tensile strength while simultaneously increasing the percentage elongation, indicating improved film flexibility. Propylene glycol acts by reducing intermolecular interactions between the polymer chains, thereby increasing chain mobility and producing a softer, more elastic polymer network. Consequently, the optimized formulation possessed sufficient flexibility to withstand handling and adapt to the movements of the buccal mucosa without cracking or breaking.

3.4.2. Mucoadhesive Behavior

The enhanced mucoadhesive strength observed in formulations containing higher concentrations of Carbopol 934P can be explained by polymer chain interpenetration and hydrogen-bond formation with the mucin layer. Upon hydration, Carbopol swells extensively, allowing its flexible polyacrylic acid chains to interpenetrate the mucosal glycoprotein network. Simultaneously, abundant carboxyl groups of Carbopol and hydroxyl groups of HPMC establish multiple hydrogen bonds with mucin, resulting in strong adhesive interactions. The optimized formulation exhibited excellent mucoadhesive strength and prolonged residence time owing to the synergistic combination of HPMC E15 and Carbopol 934P. The statistical optimization confirmed that increasing Carbopol concentration significantly enhanced bioadhesion, making it the principal contributor to sustained adhesion of the buccal film to the mucosal surface.

3.5. Solid-State Morphology

X-Ray Diffraction (XRD) Analysis

To precisely determine the physical solid-state of the drug entrapped within the polymeric network, X-ray diffraction profiling was performed. The diffractogram of pure Propranolol HCl exhibited intensely sharp, highly defined characteristic reflections at specific 2θ scattering angles, confirming the pristine, highly crystalline nature of the pure API. In stark contrast, the XRD diffractogram of the optimized drug-loaded buccal film demonstrated a dramatic suppression of these characteristic peaks. The sharp crystalline signals were entirely masked, replaced by a broad, diffuse "halo" pattern typical of amorphous substances. This significant reduction in peak intensity and the disappearance of crystalline reflections unequivocally confirm the complete amorphization of the drug. Propranolol HCl transitioned from a crystalline state to an amorphous solid-solution within the hydrophilic polymer matrix during the film-casting process. This transition is highly desirable, as the amorphous state possesses higher thermodynamic energy, which directly translates to improved solubility, enhanced mucosal wetting, and a highly predictable, controlled release profile in the oral cavity.

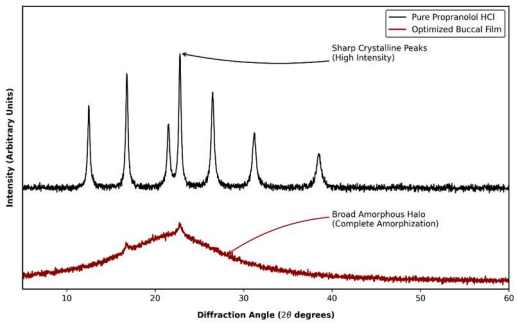

Figure 3. XRD Analysis of Pure Propranolol HCl and Optimized Buccal Film.

3.6. In Vitro Release Profiling

3.6.1. In Vitro Dissolution Profile

The optimized buccal film exhibited a controlled biphasic drug release profile throughout the 8-hour dissolution study. An initial burst release was observed during the first hour, which can be attributed to the rapid dissolution of propranolol hydrochloride present near the surface of the film. This immediate release is advantageous for buccal drug delivery

because it facilitates the rapid attainment of therapeutic drug concentrations. Following the initial burst phase, the release profile gradually transitioned into a sustained release pattern. Upon contact with the dissolution medium, HPMC E15 and Carbopol 934P absorbed water and formed a hydrated gel layer around the film. This gel barrier regulated the penetration of the dissolution medium into the polymer matrix and controlled the diffusion of the drug, resulting in a smooth and sustained release throughout the remaining study period. The absence of abrupt fluctuations in the dissolution profile indicates the formation of a stable polymeric network capable of providing prolonged drug release.

3.6.2. Release Kinetics and Drug Release Mechanism

To investigate the mechanism of drug release from the optimized buccal film, the cumulative dissolution data were fitted to the Korsmeyer-Peppas kinetic model. The release mechanism was interpreted using the diffusional exponent (n) obtained from the linear regression of the logarithm of cumulative drug release against the logarithm of time. The calculated diffusional exponent for the optimized formulation was 0.68, with an excellent correlation coefficient (R^2 = 0.989), indicating a good fit of the experimental data to the Korsmeyer-Peppas model.

According to the established classification of the release exponent, values of n less than or equal to 0.45 indicate Fickian diffusion, whereas values between 0.45 and 0.89 represent anomalous (non-Fickian) transport. Since the obtained n value of 0.68 falls within the anomalous transport region, the release of propranolol hydrochloride from the optimized buccal film was governed by a combination of diffusion and polymer relaxation. This release behavior indicates that drug molecules diffused through the hydrated polymer network while the simultaneous swelling and relaxation of HPMC E15 and Carbopol 934P continuously modified the diffusion pathways. The combined contribution of these two mechanisms produced a controlled and sustained drug release profile, demonstrating the suitability of the optimized buccal film for prolonged buccal drug delivery.

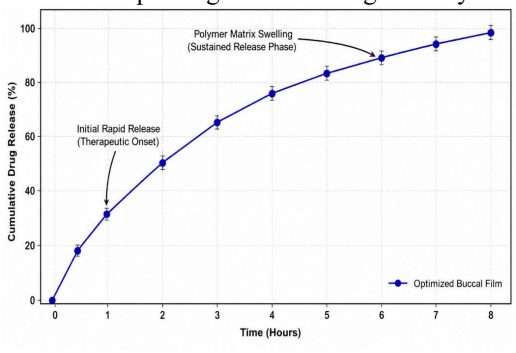

Figure 4. In Vitro Drug Release Profile of the Optimized Propranolol Hydrochloride Buccal Film.

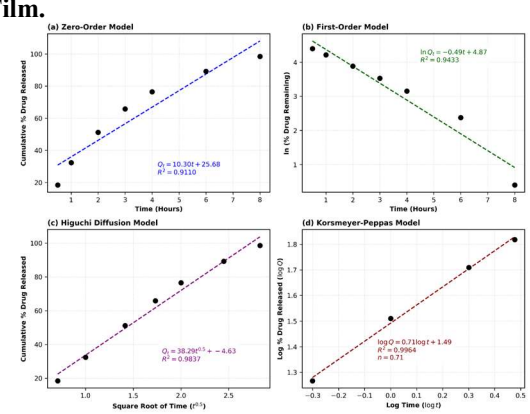

Figure 5. Mathematical modeling of the in vitro release profiles of propranolol hydrochloride from the optimized buccal film: (a) Zero-order model, (b) First-order model, (c) Higuchi diffusion model, and (d) Korsmeyer-Peppas model. The Korsmeyer-Peppas model exhibited the highest correlation coefficient (R^2 = 0.9893), with a diffusional exponent (n = 0.68), indicating that drug release followed an anomalous (non-Fickian) transport mechanism governed by the combined effects of polymer matrix swelling and drug diffusion.

Conclusion

The optimized propranolol hydrochloride buccal film was successfully developed using a 3^2 full factorial design. Drug-excipient compatibility studies performed using FTIR and DSC confirmed that propranolol hydrochloride remained chemically and thermally stable in the presence of HPMC E15 and Carbopol 934P, indicating the absence of any significant interactions between the drug and the selected excipients. Solid-state characterization by SEM and XRD demonstrated the formation of a smooth and homogeneous polymeric film with no evidence of drug crystallization, confirming successful conversion of the drug into an amorphous state within the polymer matrix. Statistical optimization and ANOVA established that both HPMC E15 and Carbopol 934P significantly influenced the critical quality attributes of the buccal films, with Carbopol 934P exerting the greatest effect on enhancing mucoadhesive strength and controlling drug release. Mechanical evaluation showed that the incorporation of propylene glycol improved the flexibility and tensile properties of the films, resulting in mechanically stable formulations suitable for buccal application. The optimized formulation exhibited satisfactory physicochemical properties, excellent mucoadhesive performance, and sustained in vitro drug release over an 8-hour period. Release kinetic

analysis demonstrated that the drug release followed an anomalous (non-Fickian) transport mechanism with a diffusional exponent (n) of 0.68, indicating that the release process was governed by the combined effects of drug diffusion and polymer swelling. Overall, the optimized buccal film represents a promising, mechanically robust, and effective platform for the sustained systemic delivery of propranolol hydrochloride through the buccal route.

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