ORIGINAL ARTICLE

Experimental Design-Based Formulation Optimization of Fast Dissolving Oral Film of Caffeine

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Abstract

Background: Caffeine, generally used in the treatment of fatigue, drowsiness, and lack of mental alertness, requires a rapid onset of action on the central nervous system as a stimulant through its fast and effective drug delivery. It has a naturally bitter taste, which can severely impact patient compliance, so it needs to be masked, and palatability needs to be improved. **Objective:** The caffeine fast-dissolving oral film, formulated using the solvent casting technique, delivers a quick onset of action and an immediate therapeutic effect. **Materials and Methods:** The fast-dissolving oral film was optimized using a Box–Behnken design with three factors at three levels, where Polyox N80, Polyox N1105, and HPMC E5 served as independent variables, and the swelling index, adhesion time, mucoadhesive strength, along with cumulative percentage drug release, were considered response variables. **Results:** The optimized fast-dissolving oral film showed uniform thickness and drug content. It had a swelling index of 125.21%, adhesion time of 1.16 min, and mucoadhesive strength of 0.049N. The film showed an immediate release of 95.86% over 30 min. **Conclusion:** The caffeine fast-dissolving oral film, produced via the solvent casting technique, ensures a rapid onset and immediate action. The research aims to focus on formulating caffeine oral film possessing desired critical quality attributes, i.e., good physical properties, thickness, and film weight, tensile strength, and drug content uniformity. In addition, the proposed oral film formulation is expected to have a fast drug release profile, better *ex vivo* mucoadhesion time, and higher *ex vivo* drug permeation compared to the conventional formulation.

Key words: Caffeine, oral drug delivery system, fast dissolving oral film, design of experiment, Box–Behnken optimization

INTRODUCTION

Caffeine is a naturally occurring alkaloid that appears as a white powder. Caffeine is obtained from the seeds, nuts, or leaves of several plants such as coffee, tea, cola, cocoa beans, and guarana. It is frequently found in soft drinks, energy beverages, and non-prescription medications such as painkillers, dietary aids, migraine remedies, appetite suppressants, and stimulants.[1] It functions as a stimulant by enhancing energy levels and alertness, primarily through its ability to block adenosine receptors, specifically the A1 and A2A subtypes.[2]

Caffeine helps increase alertness and keep mild arousal levels, even in small amounts such as those from a single cup of coffee. It also blocks the phosphodiesterase enzyme and supports wakefulness by targeting the central nervous system.[3,4]

Oral administration is the most commonly used route, accounting for approximately 50–60% of all pharmaceutical formulations due to its ease of use, avoidance of pain, flexibility in accommodating different drug types, and, most importantly, better patient compliance.[5] Research has shown that 26% of 1576 patients reported difficulty in swallowing tablets, mainly due to factors such as tablet size, surface texture, and taste.[6] Oral fast-dissolving films or strips are dosage forms composed of water-soluble polymers

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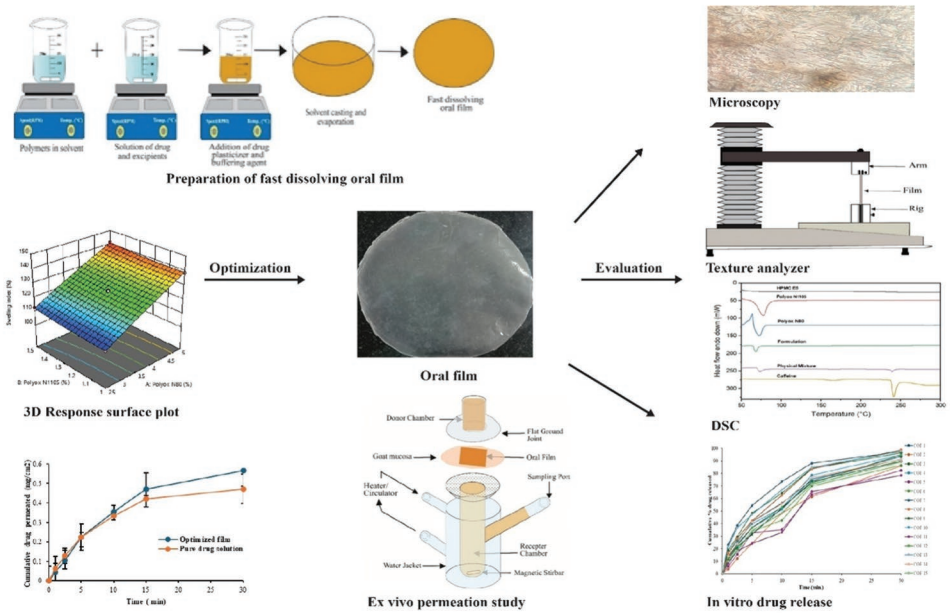
Received: 18-08-2025
Revised: 23-09-2025
Accepted: 29-09-2025

GRAPHICAL ABSTRACT



that quickly hydrate in saliva, adhere to the oral mucosa, and disintegrate within seconds, enabling drug release for absorption through the oral mucosal tissue when placed on the tongue or inside the mouth.[7,8]

Solid oral dosage forms do not need sterile environments, making their production more cost-effective.[9] A wide range of therapeutic dosages is provided in forms such as pills, granules, powders, and liquids. Typically, pills are designed to be swallowed whole or chewed to ensure the accurate delivery of a specific dose of medication to the patient.[10]

However, certain patients, especially pediatric and geriatric populations, experience difficulty in swallowing or chewing solid dosage forms. Many individuals in these groups are hesitant to take such forms due to the potential risk of choking.[11] The oral fast-dissolving drug delivery system represents a novel and patient-friendly approach aimed at improving compliance and ease of use. This system is specifically developed to rapidly disintegrate in the oral cavity, allowing the drug to be administered effortlessly without the need for water or chewing.[12] Around 50% of the population is believed to suffer from dysphagia, which contributes to poor medication adherence and suboptimal treatment outcomes.[13]

The present study outlines the formulation development and optimization of a fast-dissolving oral film of caffeine using a design of experiments approach. The film was formulated using different fast-dissolving polymers, i.e., Polyox N80, Polyox N1105, and HPMC E5. To optimize the formulation, a Box–Behnken design was implemented, with selected formulation components considered independent variables and the critical quality attributes of the oral film as response parameters. The finalized fast-dissolving oral film was thoroughly characterized in terms of physicochemical properties and subjected to *in vitro* and *ex vivo* testing to evaluate its functional performance.

MATERIALS AND METHODS

Materials

Caffeine was obtained as a complimentary sample from M/s. Encube Ethicals Pvt. Ltd., Mumbai, India. HPMC E5, Polyox N80, Polyox N1105, Citric acid, and Acesulfame-K were procured as a free sample from M/s. Alkem Laboratories Pvt. Ltd., Mumbai, India. All other chemicals and solvents used in this work were of laboratory grade.

Preparation and casting of fast-dissolving films

The fast-dissolving oral film was formulated using the solvent casting technique, a widely adopted method for developing thin films intended for oral drug delivery as shown in figure 1.[14,15] A specific quantity of HPMC E5 was dissolved in a 10 mL mixture of ethanol and water in a 1:1 ratio. This solution was gradually introduced into a hydroalcoholic mixture (10 mL) containing Polyox N80 and Polyox N1105, under continuous stirring to ensure homogeneity. To this blend, 0.1% w/w of Polyethylene glycol was added as a plasticizer. The pH of the mixture was adjusted using sodium hydroxide, and 25 mg of caffeine was then incorporated into the polymeric solution. The resulting mixture was poured into a glass petri dish and spread uniformly to form a thin film, which was allowed to

dry at room temperature for over 24 h. The dried films were collected and stored in aluminium foil until further evaluation.

Optimization of fast-dissolving caffeine oral films

The optimization strategy aimed to reduce the number of experimental trials while maintaining result accuracy. The fast-dissolving caffeine oral films were prepared via the solvent casting method, and a Box–Behnken design involving three variables at three levels was applied as part of the response surface methodology.[16,17] The experimental design included three independent variables: the amount of Polyox N80 (A), Polyox N1105 (B), and HPMC E5 (C). The responses analyzed were swelling index (R1), adhesion time (R2), mucoadhesive strength (R3), and percentages of cumulative drug release at 1 min (R4), 5 min (R5), 10 min (R6), 15 min (R7), and 30 min (R8). A constant drug dose of 25 mg and a fixed plasticizer concentration of 0.1% w/w were maintained across all batches. The experimental setup and variable levels are provided in Table 1. Design-Expert® software (version 12, Stat-Ease Inc., Minneapolis, MN) was used for data analysis, and 3D response surface plots were generated to interpret the influence of formulation variables on each response.[18,19] Using the Box–Behnken design, 15 experimental runs were carried out. Statistical significance of the response variables was determined through analysis of variance, showing $P < 0.05$. The model's predictive accuracy and fitness were evaluated using correlation (R^2) and adjusted R^2 values. The statistical equations obtained for various response variables are shown in Table 2. The optimized formulation was then developed, and experimental findings were compared with estimated data to validate the optimization process.

Characterization of fast-dissolving caffeine oral film

Assessment of surface pH

An acidic or alkaline pH in the film can irritate the oral mucosa; therefore, the goal was to maintain the surface pH close to neutral. To measure this, the surface pH of the films was evaluated using a pH meter (Cyberscan 510) by immersing an oral film in a beaker containing 10 mL of water.[20,21]

Table 1: Selected independent and response variables

Independent variables	Unit	Low level	High level
A: Polyox N80	%	2.5	5.0
B: Polyox N1105	%	1.0	1.5
C: HPMC E5	%	1.5	2.5
Response variables			**Criteria**
R1: Swelling index			Maximize
R2: Adhesion time			Maximize
R3: Mucoadhesive strength			Maximize
R4: Cumulative drug release (%) at 1 min			Maximize
R5: Cumulative drug release (%) at 5 min			Maximize
R6: Cumulative drug release (%) at 10 min			Maximize
R7: Cumulative drug release (%) at 15 min			Maximize
R8: Cumulative drug release (%) at 30 min			Maximize

Film weight and thickness

The weight and thickness of the film are critical parameters for maintaining the uniform distribution of the drug and excipients. Since the drug is highly potent, any inconsistency in thickness or weight could lead to variations in the administered dose. To assess this, three uniform sections of the film measuring 2 cm × 2 cm were selected, weighed, and the average weight was recorded. The thickness of the film was evaluated using a digital micrometer (Digimatic micrometer, Mitutoyo, Tokyo, Japan). To ensure uniformity, the film's thickness was assessed at five separate areas, and the average of these readings was recorded.[22]

Folding durability

The folding endurance test was conducted to examine the film's mechanical strength under repetitive stress conditions typical of handling. The test involved continuously folding the film at one location until a visible crack or break was observed. The test was performed 3 times, and the mean result was recorded.[22]

Tensile strength and extensibility

Tensile strength represents the maximum stress a material can endure before it fractures, whereas extensibility indicates its ability to stretch or elongate without breaking. These parameters were assessed to evaluate the mechanical stress the film might experience due to jaw movement within the oral cavity. The tensile strength and extensibility of the fast-dissolving caffeine oral film were measured using a texture analyzer (Stable Microsystems Ltd., Surrey, UK) equipped with probe tensile grips (A/TG). During testing, the film was secured between mounting cards, and the speed was maintained at 0.5 mm/s. The outcomes were recorded accordingly as shown in figure 2.[23]

Swelling index

A fast-dissolving polymer needs to undergo hydration to swell and develop a suitable macromolecular network, which increases the mobility of polymer chains and reveals bioadhesive sites.[24] These sites allow for hydrogen bonding or electrostatic interactions with the mucosal surface, thereby promoting mechanical interlocking. The fast-dissolving oral film (2 cm × 2 cm) was weighed, immersed in phosphate buffer pH 6.8 for a set timeframe, blotted with filter paper, and then weighed again.[25] The formula below was applied to determine the percent swelling index.

$$\% SI = W2-W1/W1$$

Where W1 = initial weight of the dry film, W2 = weight of the hydrated film.

Adhesion time

The adhesion time of a fast-dissolving oral film is evaluated by measuring how long the film remains attached before detaching from a surface. To enhance bioavailability and prolong the retention of the delivery system, it is essential for oral films to maintain strong adhesive contact with the mucosal membrane. A prolonged adhesion time is usually favored because it enhances consistent and sustained drug delivery. In the case of the fast-dissolving caffeine oral film, adhesion time was manually assessed by applying the film to a moist surface mimicking the oral mucosa and recording the duration until detachment occurred.[25,26]

Mucoadhesive strength

To determine the mucoadhesive strength, a texture analyzer (Stable Microsystems Ltd., Surrey, UK) was utilized, employing goat oral mucosa as the adhesion surface. The mucosal membrane was mounted on the stationary platform, while a 2 cm × 2 cm film sample was secured on the movable probe. The probe was lowered gradually until it contacted the mucosa and held in that position for 1 min to establish adhesion. It was then retracted at a controlled speed of 0.5 mm/s, and the force required to detach the film was recorded to quantify mucoadhesive strength.[26]

Drug content uniformity

The drug content plays a crucial role in confirming the uniform distribution and availability of the drug within the film. A 2 cm × 2 cm section of the prepared film was excised and immersed in 100 mL of phosphate buffer (pH 6.8) in a beaker. The film was allowed to dissolve, the resulting solution was filtered and analyzed using a ultraviolet (UV) spectrophotometer (Shimadzu, 1700) at 273.5 nm.[27]

In vitro drug release

The *in vitro* drug release study of the formulated fast-dissolving caffeine oral film was conducted using a paddle-over-disc (65 mm) type dissolution apparatus (Electro Lab Dissolution Apparatus) to quantify the amount of caffeine released into the medium. The oral film was placed beneath the disc in the dissolution vessel, which contained 900 mL of phosphate buffer pH 6.8[28] maintained at (37 ± 0.5°C) and 50 rpm. The test involved withdrawing 5 mL samples at specified intervals over 30 min. After filtration through a 0.45 µm membrane filter, an equal volume of phosphate buffer pH 6.8 (pre-warmed 37 ± 0.5°C) was added to maintain sink conditions. The absorbance of aliquots was measured using a UV spectrophotometer (Shimadzu, 1700) at 273.5 nm, and the cumulative % drug release was calculated.[29]

Ex vivo adhesion time

To determine *ex vivo* adhesion time, the fast-dissolving caffeine oral film was tested for its ability to adhere to freshly excised goat oral mucosal tissue. The mucosal tissue was mounted onto a glass slide using an adhesive. One side of the film was moistened with phosphate buffer (pH 6.8) and gently pressed onto the mucosa with a fingertip. Following preparation, the glass slide was placed into a beaker containing 100 mL of phosphate buffer at pH 6.8. After 2 min, the contents were gently swirled to replicate buccal cavity movements. The time taken for the film to separate from the mucosal surface served as a measure of mucoadhesion time.[30]

Ex vivo drug permeation

For this study, goat oral mucosa was utilized as the biological barrier. The mucosa, freshly collected from a sacrificed goat at a nearby slaughterhouse, was thoroughly rinsed using isotonic phosphate buffer (pH 6.8). It was then carefully mounted between the donor and receptor compartments of a diffusion apparatus, ensuring an exposed area of 2.54 cm^2. The fast-dissolving oral film was adhered directly to the mucosal surface.[30] The receptor chamber was filled with phosphate buffer (pH 6.8) and maintained at a stable temperature of 37 ± 0.5°C. A magnetic stirrer operating at a low speed of 50 ± 5 rpm was used to ensure continuous agitation. At fixed time intervals over 30 min, 5 mL aliquots were withdrawn, filtered through a 0.45 µm membrane filter, and analyzed using a UV spectrophotometer (Shimadzu, 1700) at 273.5 nm. After each sampling, the withdrawn volume was replaced with pre-warmed dissolution medium (37 ± 0.5°C). The experiment was conducted in triplicate (n = 3), and the average value was calculated to determine *ex vivo* drug permeation.

RESULTS AND DISCUSSION

Optimization of fast-dissolving oral film

The formulation of fast-dissolving caffeine oral films was optimized using a Box–Behnken response surface design, involving three independent variables: Polyox N80(A), Polyox N1105(B), and HPMC E5(C). The concentration ranges selected for optimization were 2.5–5.0% for Polyox N80, 1.0–2.5% for Polyox N1105, and 1.5–2.5% for HPMC E5. The corresponding response variables included swelling capacity (R1), adhesion duration (R2), mucoadhesive force (R3), and cumulative drug release at various time points, 1 min (R4), 5 min (R5), 10 min (R6), 15 min (R7), and 30 min (R8). The effect of the formulation variables on these responses is presented in Table 3.

As illustrated in Figure 4, an increase in the concentration of HPMC E5 and Polyox N80 led to a corresponding rise in the swelling index, whereas Polyox N1105 exhibited no significant influence. This can be attributed to the hydrophilic nature of HPMC E5 and Polyox N80, which enables them to absorb water from the surrounding medium, resulting in the expansion of the film's size and volume, ultimately contributing to a slower drug release. As illustrated in

Figure 5, an increase in the concentrations of HPMC E5 and Polyox N80 also led to an extended adhesion time. HPMC E5 forms a gel in an aqueous environment that adheres to the mucosal membrane due to the increased surface charge of the film.

It was found that the mucoadhesive strength improved with increasing concentrations of HPMC E5 and Polyox N80, as shown in Figure 6. HPMC E5 contributes to enhanced mechanical strength and flexibility of the film, whereas Polyox N80 facilitates stronger interaction with the oral mucosa due to its higher surface charge. In addition, since both Polyox N80 and Polyox N1105 are pH-sensitive polymers, a slight reduction in caffeine release was observed with increasing concentrations of these polymers.

It was observed that the concentration of Polyox N80, Polyox N1105, and HPMC E5 affected the % drug release profile (R4-R8) at 1 min, 5 min, 10 min, 15 min, and 30 min, respectively. Figures 7-11 show that higher polymer concentrations led to a decrease in the rate of drug release.

Therefore, the optimization process helped in selecting the right amounts of polymers to achieve the desired features of the fast-dissolving caffeine oral film. as shown in figure 12

Table 2: Derived polynomial equations for each response

Factors		Polynomial expression
R1	=	125.29+14.58A+1.34B+2.44C−0.2575AB−1.50AC+0.7300BC−0.5867A^2+0.7358B^2+2.083C^2
R2	=	1.45+0.2525A+0.0163B+0.0337C+0.0700AB−0.0200AC−0.0125BC−0.0321A^2-0.0546B^2+0.0154C^2
R3	=	0.0451+0.0258A+0.0017+0.0032C+0.0007AB+0.0005AC+0.0004BC-0.0009A^2−0.0014B^2+0.0019C^2
R4	=	12.89−6.90A1.09B2.48C+0.8550AB0.9650AC+0.2075BC+0.9904A^2+0.1579B^2−0.2071C^2
R5	=	40.98−10.81A−1.16375B−3.78C+0.0400AB+0.3175AC−0.1125BC−0.9508A^2−1.17B^2−1.34C^2
R6	=	59.113−15.28A−1.5B−4.88C−0.0100AB+1.41AC−1.59BC−4.26A^2−2.10B^2−1.14C^2
R7	=	82.53−9.81A+0.1425B−3.21C+0.8575AB−0.2700AC−1.78BC−2.62A^2−3.36B^2−2.95C^2
R8	=	93.79−6.95A−0.4238B−1.42C+0.5350AB−0.2825AC+0.4875BC−1.62A^2−1.84B^2−0.4808C^2

Prediction of optimized formulation of fast-dissolving caffeine oral film

The final optimized formulation for the fast-dissolving caffeine oral film was obtained through statistical analysis using Design Expert software, achieving a desirability of 0.799. This formulation met all target attributes, including optimal swelling index, adhesion duration, mucoadhesive strength, and rapid drug release. Based on the estimated values, the films were developed and evaluated.

As shown in Table 4, the evaluation results demonstrated a strong similarity between predicted and observed cumulative

Table 3: Observed response of the optimization batches of fast-dissolving oral film produced by Box-Behnken design

Batch No.	Polyox N80% (A)	Polyox N1105% (B)	HPMC E5% (C)	Swelling index % (R1)	Adhesion time min (R2)	Mucoadhesive strength N (R3)	Percentage cumulative drug release				
							1 min (R4)	5 min (R5)	10 min (R6)	15 min (R7)	30 min (R8)
COF 1	3.75	1.25	2.0	125.34	1.45	0.0454	12.88	41.52	59.72	82.22	93.45
COF 2	5.00	1.25	2.5	142.55	1.70	0.0756	05.17	24.17	35.37	64.32	84.16
COF 3	2.50	1.50	2.0	112.75	1.05	0.0183	18.91	48.28	66.32	85.96	97.25
COF 4	3.75	1.00	1.5	125.45	1.35	0.0413	16.58	42.86	61.34	78.54	94.79
COF 5	5.00	1.50	2.0	141.25	1.70	0.0710	06.95	26.72	36.23	68.12	83.35
COF 6	5.00	1.25	1.5	140.32	1.66	0.0684	08.22	31.58	41.00	69.92	86.38
COF 7	2.50	1.25	1.5	108.03	1.12	0.0177	24.10	53.83	74.88	89.05	98.65
COF 8	2.50	1.25	2.5	116.25	1.24	0.0228	17.19	45.15	63.59	84.53	97.56
COF 9	3.75	1.00	2.5	128.53	1.43	0.0470	11.23	36.01	53.46	74.30	89.78
COF 10	3.75	1.25	2.0	125.54	1.45	0.0448	12.78	40.73	58.65	82.36	94.16
COF 11	5.00	1.00	2.0	138.65	1.53	0.0658	07.45	29.36	39.19	65.42	82.34
COF 12	3.75	1.25	2.0	125.00	1.44	0.0451	13.00	40.68	58.97	83.00	93.75
COF 13	2.50	1.00	2.0	109.12	1.16	0.0159	22.83	51.08	69.24	86.69	98.38
COF 14	3.75	1.50	1.5	126.23	1.41	0.0435	14.03	41.15	61.45	81.68	92.18
COF 15	3.75	1.50	2.5	132.23	1.44	0.0507	09.51	33.85	47.23	70.33	89.12

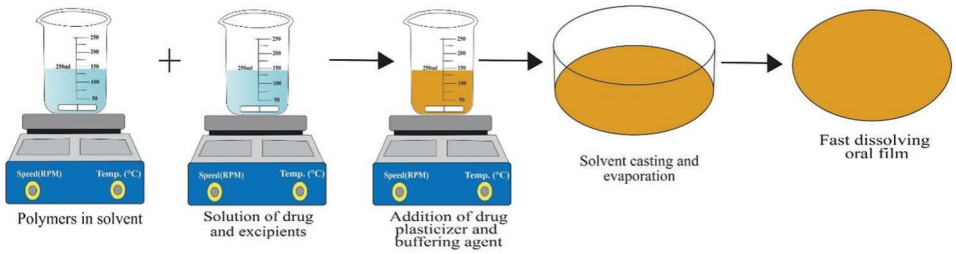


Figure 1: Schematic overview of the formulation of fast-dissolving oral film by solvent casting

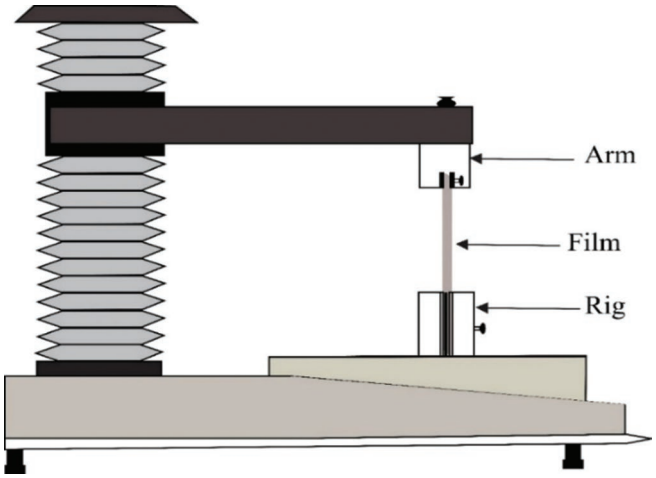


Figure 2: Schematic representation of the texture analyzer

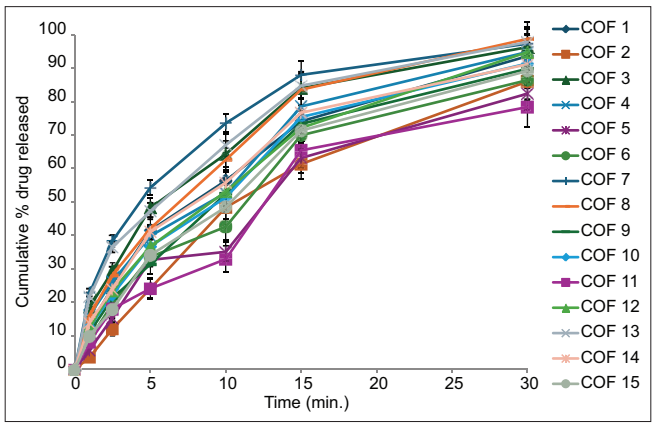


Figure 3: Cumulative % drug release profile of fast dissolving oral film formulation batch COF1-COF15 (All results shown as average ± SD; *n* = 3)

% drug release values. Figure 13 illustrates the drug release profiles' statistical correlation for both the predicted and actual batches of the optimized fast-dissolving caffeine oral film. A linear regression analysis was also conducted to evaluate the relationship between predicted and observed profiles, as shown in Figure 14.

Surface pH

The surface pH of the film was evaluated to assess its potential impact on the oral mucosa. The optimized oral film exhibited a pH of 6.74, which is close to neutral and considered appropriate for the oral environment, as it does not irritate. This suggests that the film pH is compatible with the oral mucosa and is unlikely to produce any discomfort upon administration.[31]

Film weight and thickness

A fast-dissolving oral film with uniform thickness and weight ensures consistent drug distribution across the entire film. The optimized caffeine oral film exhibited a thickness of 0.210 mm, which is considered ideal for oral films. If the film is too thick, it may not dissolve properly, leading to delayed drug release, whereas films that are too thin may dissolve too rapidly, potentially failing to deliver a sufficient drug dose for therapeutic effectiveness.[6] The optimized fast-dissolving caffeine oral film, measuring 2 cm × 2 cm, had a recorded weight of 1082.28 mg, which indicates uniformity and is suitable for application to the oral mucosa, ensuring content homogeneity.[22]

Folding endurance

High folding endurance is an important attribute for oral films, as it prevents them from breaking or shifting from the site of application during administration. The optimized fast-dissolving caffeine oral film exhibited a folding endurance of 285 folds, demonstrating excellent mechanical strength and durability.[32]

Tensile strength and extensibility

For effective oral administration, films must combine softness with durability to withstand the repetitive mechanical forces exerted by jaw movement. In the case of the optimized fast-dissolving caffeine oral film, a tensile strength of 81.70 N and extensibility of 26.69 mm were recorded, as shown in Figure 15. The strong tensile properties resulted from the higher proportion of HPMC E5, whereas the flexibility and elongation were influenced by the presence of Polyox N80. These mechanical properties support observations previously reported in studies on caffeine oral films.[33] The fast-dissolving oral film demonstrated enhanced mechanical strength, evident from its elevated breaking strength

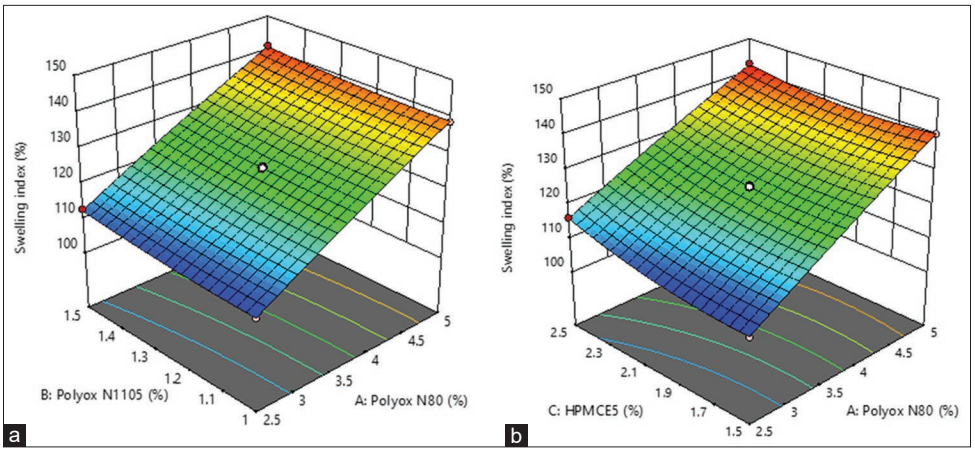


Figure 4: 3D response surface plots depicting the influence of (a) Polyox N80 and Polyox N1105, (b) Polyox N80 and HPMC E5 on swelling index

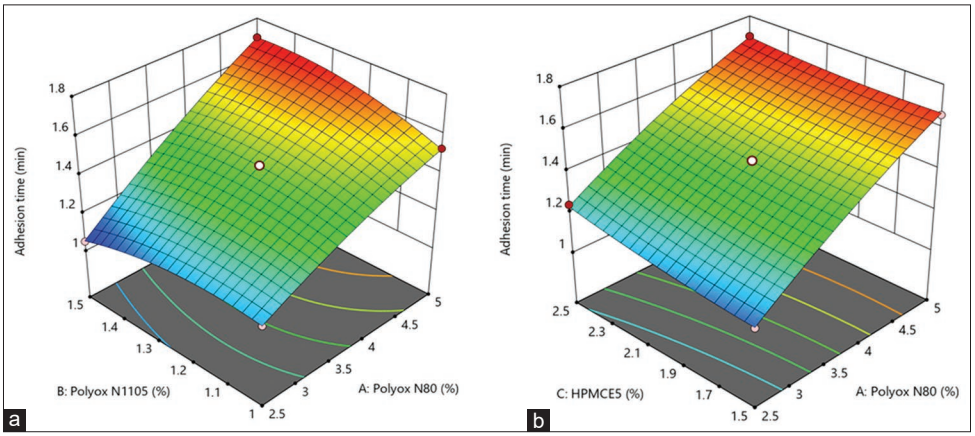


Figure 5: 3D response surface plots depicting the influence of (a) Polyox N80 and Polyox N1105, (b) Polyox N80 and HPMC E5 on adhesion time

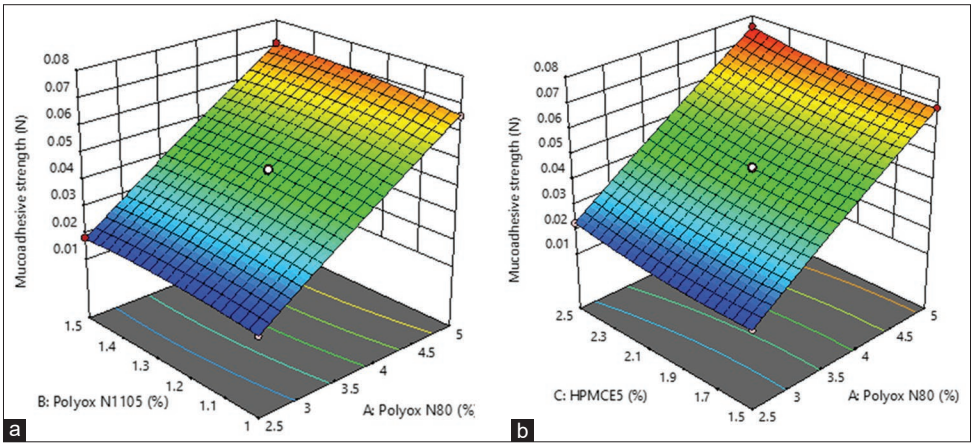


Figure 6: 3D response surface plots depicting the influence of (a) Polyox N80 and Polyox N1105, (b) Polyox N80 and HPMC E5 on mucoadhesive strength

and superior flexibility, along with its ability to elongate without breaking, as reflected by its high extensibility. These characteristics indicate improved structural integrity and mechanical performance, making the film a strong and reliable candidate for oral drug delivery.[34]

Swelling index

The swelling index plays a crucial role in drug delivery via fast-dissolving oral films, as it influences the drug release rate. When the film absorbs water, the resulting swelling

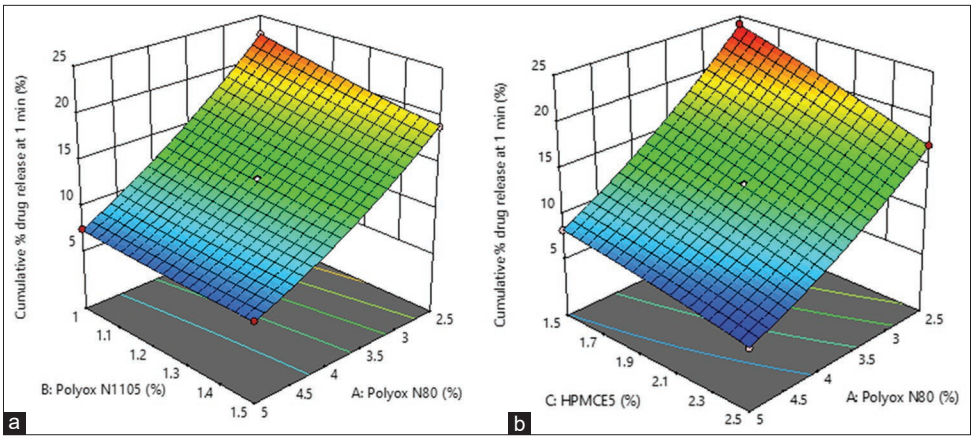


Figure 7: 3D response surface plots depicting the influence of (a) Polyox N80 and Polyox N1105, (b) Polyox N80 and HPMC E5 on % cumulative drug release at 1min

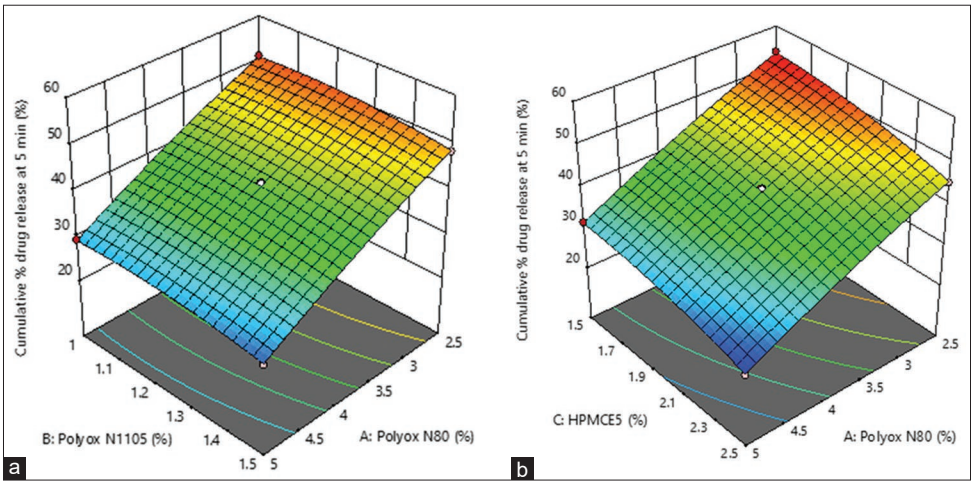


Figure 8: 3D response surface plots depicting the influence of (a) Polyox N80 and Polyox N1105, (b) Polyox N80 and HPMC E5 on % cumulative drug release at 5 min

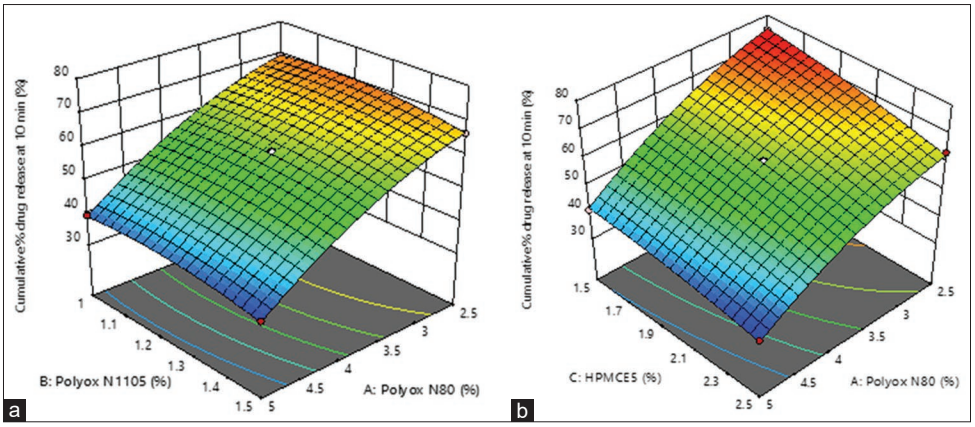


Figure 9: 3D response surface plots depicting the influence of (a) Polyox N80 and Polyox N1105, (b) Polyox N80 and HPMC E5, on % cumulative drug release at 10 min

causes the initially entangled, stretched, or twisted bio-adhesive polymers to relax. This relaxation leads to the quick separation of individual polymer chains and the formation of a defined macromolecular network.[6] The swelling index for all batches ranged between 108.03% and 142.55%, as presented in Table 3. The 3D response surface plots shown in Figure 4 illustrate how the independent variables influenced the swelling index across the formulations. It was observed that increasing the concentrations of HPMC E5 and Polyox N80, both hydrophilic polymers, led to a rise in swelling

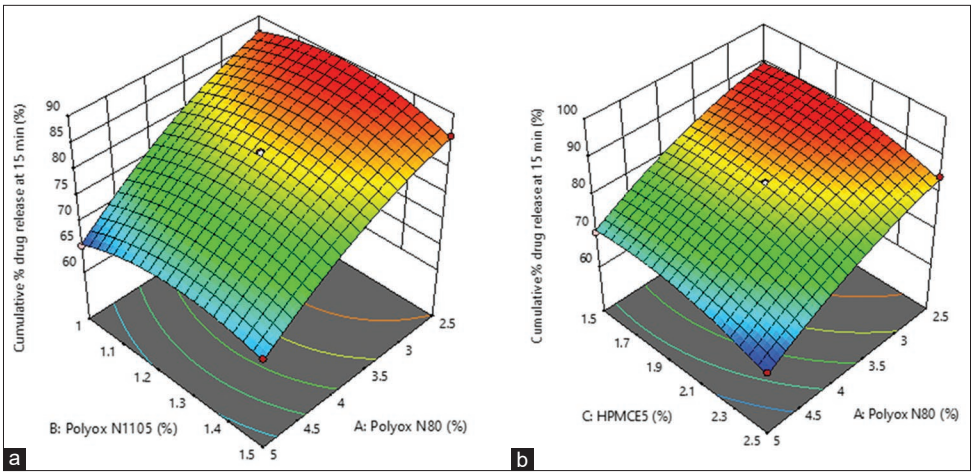


Figure 10: 3D response surface plots depicting the influence of (a) Polyox N80 and Polyox N1105, (b) Polyox N80 and HPMC E5 on % cumulative drug release at 15 min

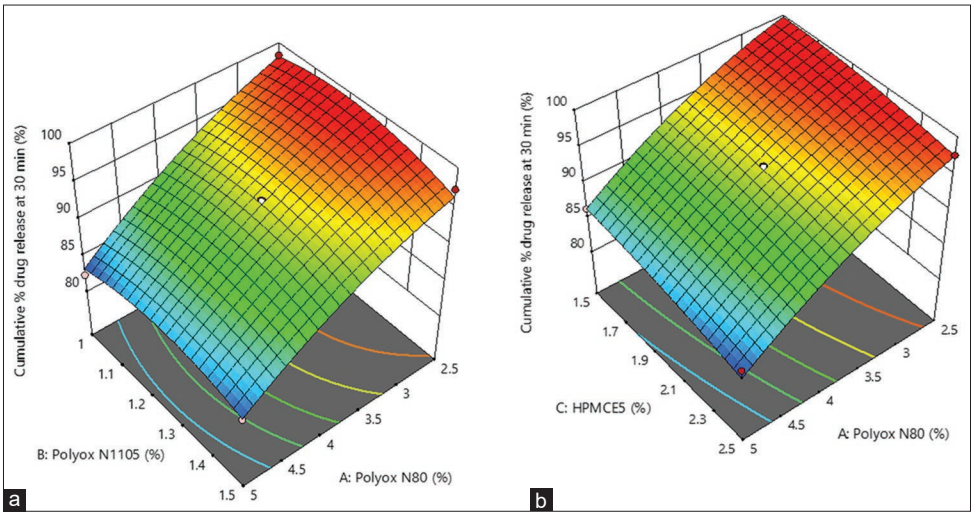


Figure 11: 3D response surface plots depicting the influence of (a) Polyox N80 and Polyox N1105, (b) Polyox N80 and HPMC E5 on % cumulative drug release at 30 min

Table 4: Predicted composition of optimized formulation

S. No.	Independent variables	Composition (%)	
1.	Polyox N80	2.80	
2.	Polyox N1105	1.19	
3.	HPMC E5	1.50	
S. No.	**Response variables**	**Software predicted**	**Experimentally observed**
1.	Swelling index	112.35	108.45
2.	Adhesion time	1.21	1.16
3.	Mucoadhesive strength	0.024	0.023
5.	Cumulative % drug release at 1 min	22.14	22.28
6.	Cumulative % drug release at 5 min	51.45	53.25
7.	Cumulative % drug release at 10 min	72.85	72.87
8.	Cumulative % drug release at 15 min	87.95	84.93
9.	Cumulative % drug release at 30 min	99.04	95.86

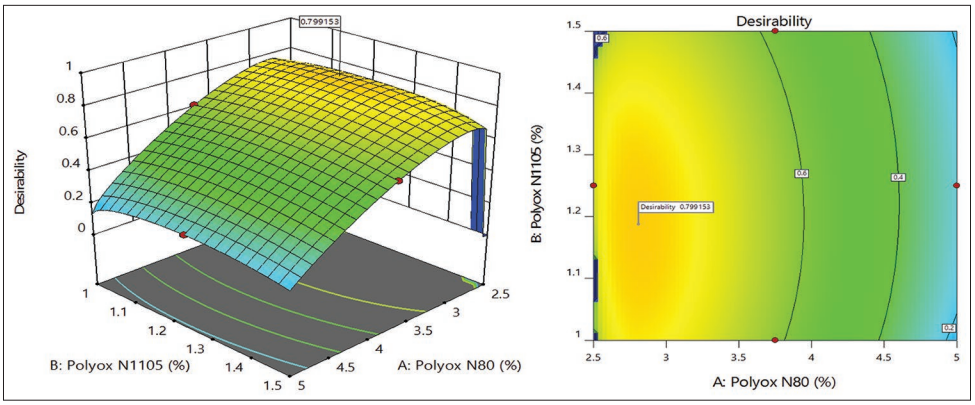


Figure 12: 3D-response and 2D-contour plots presenting the maximum desirability of the developed formulation

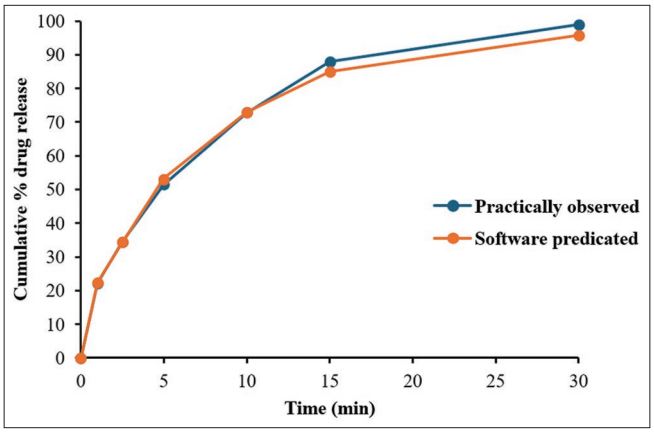


Figure 13: Statistical correlation between predicted and observed values

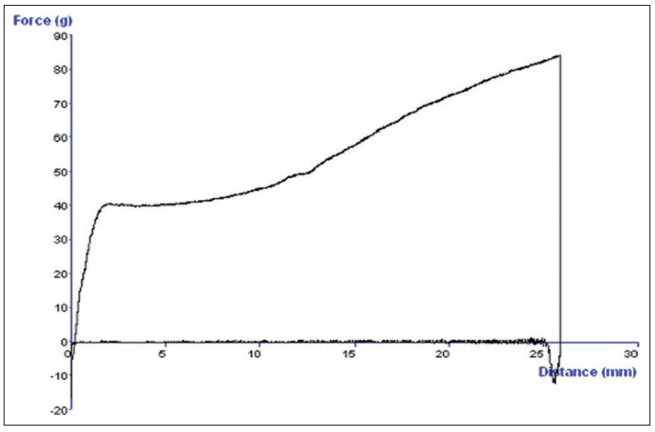


Figure 15: Tensile strength and extensibility study of the optimized oral film

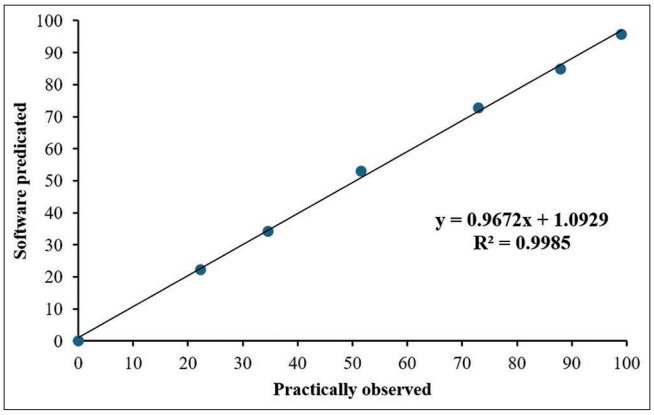


Figure 14: Linear plot between software-predicted and practically observed values of cumulative % drug release

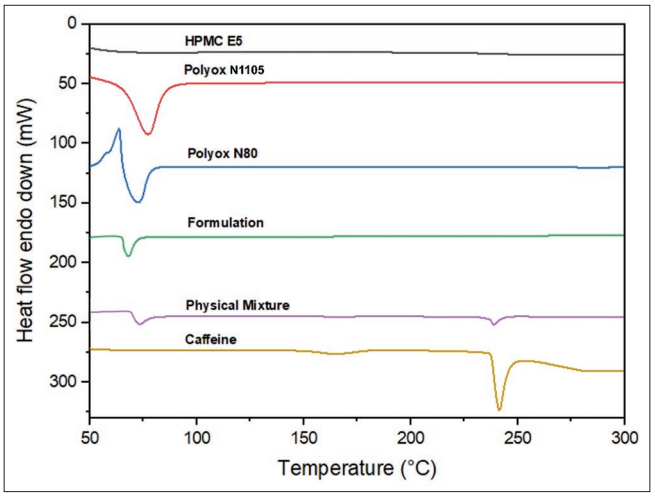


Figure 16: DSC thermograms of caffeine fast dissolving oral film, caffeine, HPMC E5, Polyox N80, and Polyox N1105 samples

index. This occurs because these polymers absorb moisture from the surrounding environment, causing the film to expand in size and volume. However, Polyox N1105 did not show any notable impact on the swelling index. The optimized fast-dissolving caffeine oral film exhibited a swelling ratio of 142.55%, suggesting a slower drug release profile, as a higher swelling index typically correlates with delayed drug release, whereas a lower index indicates faster release. These findings demonstrate that the developed film possesses a higher swelling index compared to caffeine thin films previously reported in the literature.[35] A high swelling index promotes a slower drug release profile and improved mucoadhesive strength, indicating that the fast-dissolving caffeine oral film demonstrates superior water uptake and

film consistency. In contrast, caffeine films reported in earlier studies tend to disintegrate quickly and release the drug more rapidly.

Adhesion time

Adhesion time reflects the efficiency of a film's mucoadhesive characteristics and plays a crucial role in determining both the rate and duration of drug release. Extended adhesion time supports slower drug delivery, whereas shorter adhesion time leads to faster release.[36] As shown in Table 3, all formulation batches demonstrated an adhesion time of approximately 1.05 to 1.70 min. The 3D response surface plots in Figure 5 depict the impact of independent variables on adhesion time. An increase in the concentrations of HPMC E5 and Polyox N80 led to a longer adhesion time. This can be attributed to the gel-forming nature of HPMC E5, which enhances film retention, and the ability of Polyox N80 to increase surface charge, thereby improving film adherence to the mucosal surface. In contrast, changes in the concentration of Polyox N1105 did not significantly influence adhesion time. The optimized fast-dissolving caffeine oral film showed an adhesion time of around 1.16 min, indicating strong mucoadhesion and a sustained drug release effect. Compared to the 0.5–1 h adhesion times reported for caffeine orodispersible tablets and other mucoadhesive films in the literature, the developed formulation demonstrates enhanced mucoadhesive behavior.[37] This improved adhesion leads to enhanced efficacy and patient compliance.

Mucoadhesive strength

Mucoadhesive strength refers to the adhesive force between a mucoadhesive oral film and the mucosal surface. For all the tested batches, the mucoadhesive strength ranged from 0.0159 N to 0.07564 N, as detailed in Table 3. The 3D response surface plots in Figure 6 demonstrate the effect of independent variables on mucoadhesive strength across the formulations. The results revealed that increasing concentrations of HPMC E5 and Polyox N80 led to enhanced mucoadhesive strength.[38] This is because HPMC E5 enhances the mechanical strength and flexibility of the film, whereas Polyox N80 raises the surface charge, promoting stronger interactions with negatively charged mucosal tissues and forming a firmer bond. In contrast, the concentration of Polyox N1105 showed no significant effect on mucoadhesive strength. The optimized fast-dissolving caffeine oral film exhibited a mucoadhesive strength of 0.049 N, which is greater than that of caffeine wafers and film formulations previously reported in the literature. This improved adhesion helps maintain a higher local drug concentration, prevents film displacement, ensures more efficient drug delivery, and improves patient compliance and convenience by reducing the need for frequent dosing.[39]

Drug content uniformity

Uniformity of drug content is a crucial parameter in pharmaceutical quality control to confirm even distribution of the drug within the formulation.[40] The optimized fast-dissolving caffeine oral film showed a drug content of 98.43%, indicating uniform dispersion of caffeine throughout the film with minimal and acceptable standard deviation.

Differential scanning calorimetry

The thermal analysis of fast-dissolving oral film of caffeine, caffeine, Polyox N80, Polyox N1105, HPMC E5, and physical mixture (caffeine + Polyox N80 + Polyox N1105 + HPMC E5) was performed using a differential scanning calorimeter (Perkin Elmer DSC 6000, USA). The analysis was performed on 3–4 mg samples sealed in standard aluminium pans.The sample was scanned at the rate of 20◦C/min in the range of 25 to 300◦C. The thermogram obtained is shown in figure 16.[41]

DSC analysis was conducted to determine the thermal behavior of the drug and excipients and to detect any drug-excipient compatibility issues. Caffeine showed a sharp endothermic peak at 238.62°C. Polyox N80 showed an endothermic peak at 67.94°C.[42] Polyox N1105 showed a sharp endothermic peak at 66.65°C. Physical mixture of the drug with excipients showed peaks at their respective melting points. Whereas no peak at the melting point of the drug was found in the formulation, showing the amorphous nature of the formulation.

Microscopic evaluation of oral film

The optimized batch (COF-F) was performed microscopically using an optical microscope (Leica DM 1000) at ×40 magnification. The optimized oral film batch was studied under microscope and a smooth, homogeneous polymer matrix with evenly dispersed needle shaped caffeine crystal was observed.[43] The uniform crystal distribution and controlled void formation likely enhance water uptake and rapid disintegration, whereas the small crystal size minimizes diffusion path length despite residual crystallinity as shown in figure 17.

In vitro evaluation of drug release

In vitro drug release testing of the formulated batches was performed using a dissolution apparatus with phosphate buffer (pH 6.8) serving as the dissolution medium. As detailed in Table 3 and depicted in Figure 3, the cumulative drug release ranged from 5.17% to 24.10% at 1 min and from 82.34% to 98.65% at 30 min. All batches exhibited a characteristic initial burst release of caffeine, followed by a rapid release phase. The extent of the initial burst varied according to the

viscosity of the polymers used. Figures 7-11 illustrate the 3D response surface plots showing the effect of independent variables on cumulative drug release at various time points. It was found that increasing concentrations of HPMC E5 led to a reduction in drug release, likely due to the formation of a polymeric matrix that encapsulates the drug and slows its diffusion.[44] A slight reduction in drug release was observed with increasing concentrations of Polyox N80 and Polyox N1105. This is likely because Polyox N80 absorbs water and swells, which can impact the rate of drug release from the film, whereas Polyox N1105, being a pH-sensitive polymer, modifies the release profile of caffeine. The *in vitro* drug release study for the optimized batch of the fast-dissolving caffeine oral film revealed a drug release profile of 95.86% within 30 min, as illustrated in Figure 18. These findings suggest an initial burst release followed by an immediate and rapid release phase. Unlike pure drug solution formulations that offer either a quick onset or a rapid release alone, the developed fast-dissolving oral film successfully delivers both, distinguishing it as a more efficient drug delivery system.[45]

Ex vivo adhesion time

The optimized fast-dissolving caffeine oral film exhibited an *ex vivo* adhesion time of approximately 1.16 min, aligning well with findings from earlier studies on fast-dissolving oral films. This can be attributed to the characteristics of HPMC E5, a hydrophilic polymer that swells considerably upon water absorption and remains structurally stable despite changes in hydration, thereby supporting sustained drug release. The higher viscosity of HPMC E5 also leads to the formation of a surface gel that persists for an extended period, enhancing the film's adhesion time. In addition, an increased concentration of Polyox N80 raises the surface charge of the film, improving its interaction with negatively charged mucosal tissues and resulting in a better adhesive property.[15,46,47]

Ex vivo permeation study

Ex vivo permeation studies were performed to evaluate the drug absorption kinetics across a biological membrane, as illustrated in Figure 19. The findings revealed that the optimized film exhibited a twofold increase in drug permeation (1.36 mg or 47.08%) compared to the pure drug solution (0.58 mg or 27.19%) within 30 min as shown in figure 20. The optimized film demonstrated an enhanced drug permeation rate (91.64%) compared to the pure drug solution (72.42%) within the same time frame. This enhanced permeation can be attributed to the swelling capacity of HPMC E5, the increased surface charge provided by Polyox N80, and the pH-responsive behavior of Polyox N1105. Various studies have reported the *ex vivo* permeation of pure drug solutions. However, fast-dissolving caffeine oral

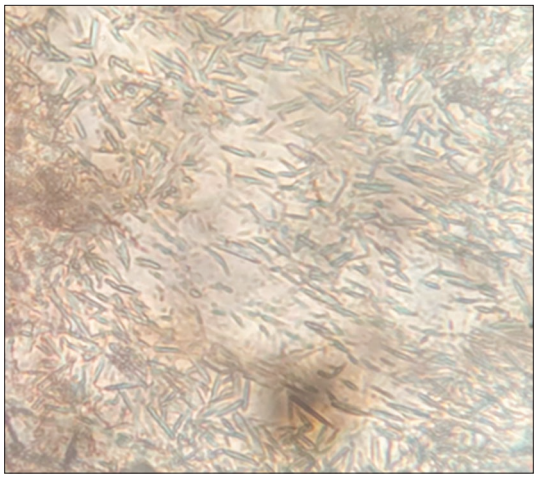


Figure 17: Microscopic view of optimized oral film formulation

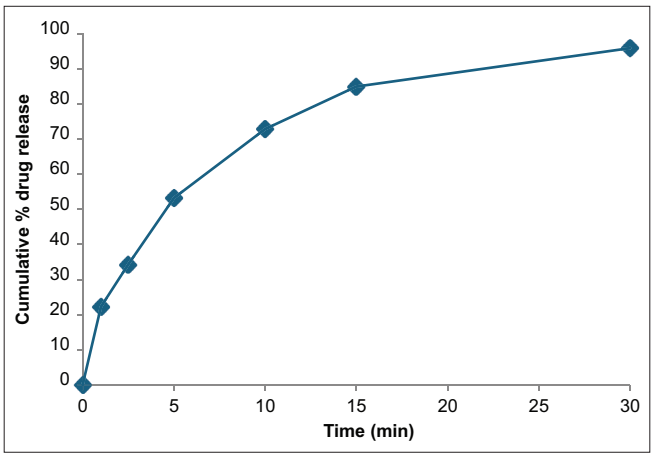


Figure 18: *In vitro* drug release profile of the optimized fast-dissolving caffeine oral film (values are expressed as mean ± SD; *n* = 3)

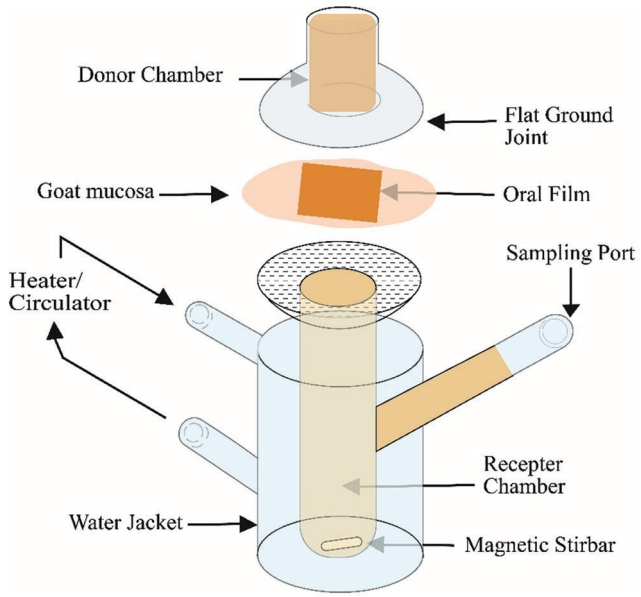


Figure 19: Schematic representation of *ex vivo* permeation study using the Franz diffusion cell

films offer a distinct advantage over pure drug solutions by providing higher drug delivery efficiency across biological membranes.[34]

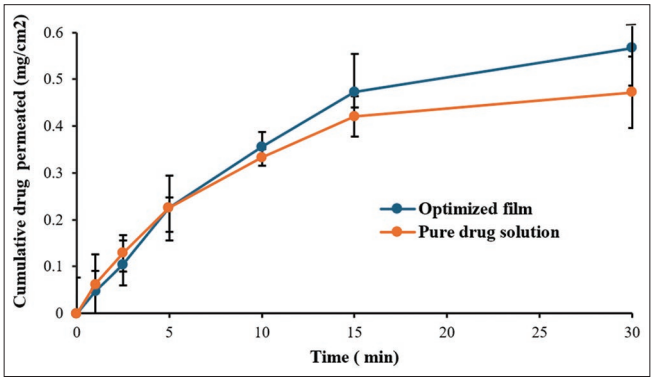


Figure 20: Cumulative drug permeation profiles of optimized caffeine oral film versus pure drug solution (values are expressed as mean ± SD; *n* = 3)

Kinetics model fitting assessment

The *in vitro* drug release data of the optimized fast-dissolving caffeine oral film were evaluated using various kinetic models, including zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell.[25,48,49] The model showing the best fit was determined based on the highest regression coefficient (R^2). Among these, the first-order model exhibited the best fit, with the highest R^2 value of 0.993, as presented in Table 5 and illustrated in Figure 21. This suggests that the drug release from the film follows a diffusion-controlled mechanism, in which the release rate is dependent on the surface area exposed for dissolution, leading to a quick onset and immediate drug release. These findings align with earlier studies on fast-dissolving films and caffeine-based fast-dissolving tablets, which individually demonstrated either a quick onset of action or immediate release. In contrast, the formulated fast-dissolving caffeine oral film integrates

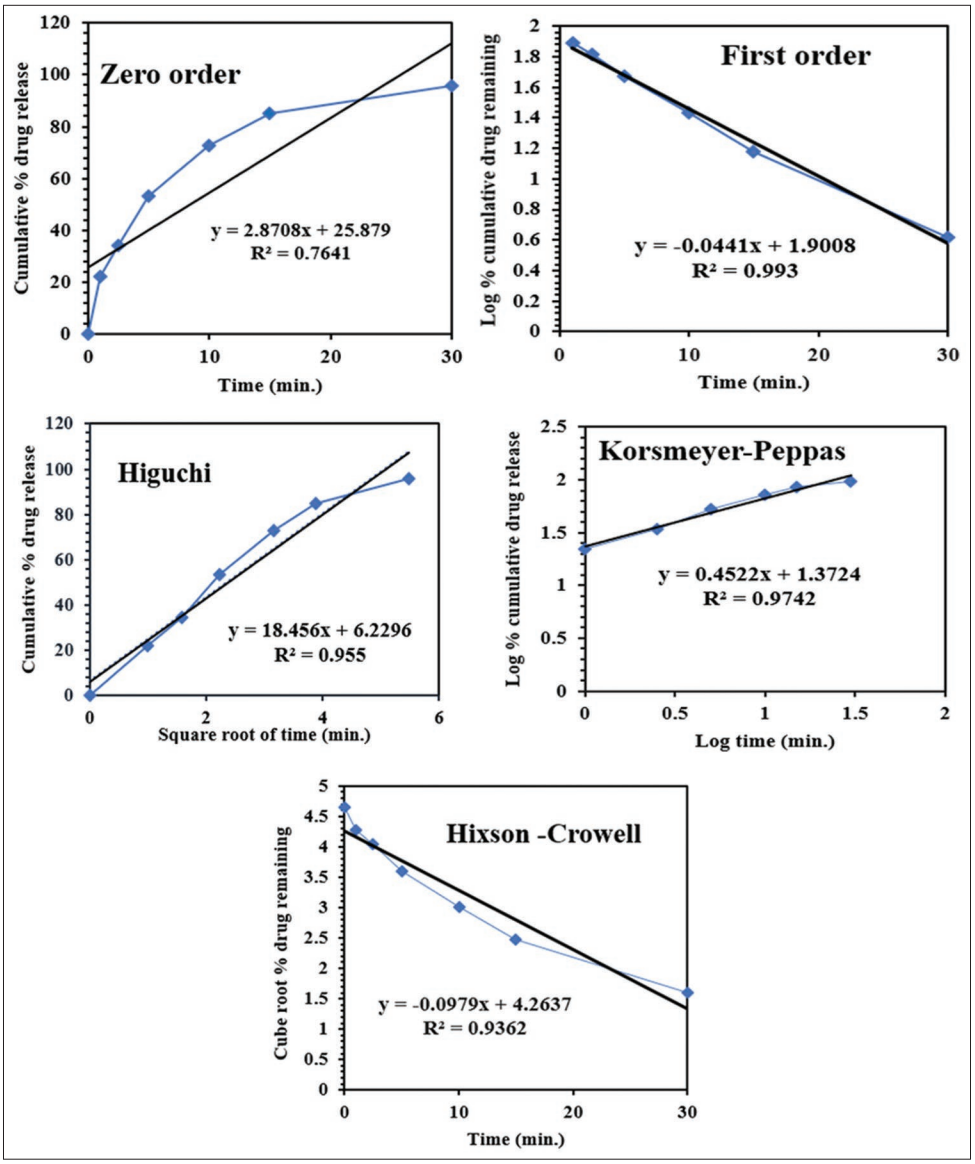


Figure 21: Kinetic modeling of drug release from fast-dissolving oral film

Table 5: Kinetic modeling of drug release from optimized oral film

S. No.	Kinetics models	Equations	R^2
1.	Zero order	$Q_0 - Q_t = k_0 t$	0.764
2.	First order	$\log Q = \log Q_0 - kt/2.303$	0.993
3.	Higuchi	$Q_0 - Q_t = kt^{1/2}$	0.955
4.	Korsmeyer-Peppas	$\log (Q_0 - Q_t) = \log k - n \log t$	0.936

Where Q0=initial drug amount, Qt=remaining drug amount, k0=rate constant, t=time

both advantages, showing better efficiency in drug release profiles.[50]

CONCLUSION

In the present study, the fast-dissolving caffeine oral film was formulated by the solvent casting method and optimized by Box–Behnken experimental design. The film was tested for parameters including swelling index, adhesion time, mucoadhesive strength, and percentage cumulative drug release. The effect of formulation variables on these responses was analyzed using three-dimensional response surface plots and polynomial regression. Higher concentrations of HPMC E5 and Polyox N80 improved swelling, adhesion, flexibility, and mucoadhesive strength, whereas Polyox N1105 had little effect on swelling but, with Polyox N80, influenced pH-sensitive drug release. Overall, increased polymer levels slowed the drug release rate. An optimized formulation, selected based on the evaluation and targeted response limits, showed the highest desirability. It provided sustained adhesion and effective contact with the oral mucosa, ensuring fast onset and rapid release. *In vitro* results indicated 95.86% of the drug was released within 30 min. The *ex vivo* evaluation of the formulated fast-dissolving caffeine oral film demonstrated a two-fold increase in oral mucosal permeation compared to the pure caffeine drug solution. Fast-dissolving oral films are gaining prominence as an effective drug delivery system owing to their rapid disintegration, improved dissolution characteristics, and swift onset of action. They offer convenient dosing, making them especially advantageous for pediatric and geriatric populations. These films can be delivered through oral or buccal routes and are well-suited for administering both medications and health supplements.

ACKNOWLEDGMENT

The authors are grateful toM/s.Alkem Laboratories Pvt. Ltd., Mumbai, India, for providing the gift sample of HPMC E5, Polyox N80, and Polyox N1105.

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Source of Support: Nil. **Conflicts of Interest:** None declared.