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FORMULATION AND EVALUATION OF MUCOADHESIVE IN-SITU BUCCAL GEL OF CHOLINE SALICYLATE AND CURCUMIN

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ABSTRACT

Background: Periodontitis is a chronic inflammatory disease of the periodontium that often requires localized therapeutic intervention for effective management. The buccal delivery of drugs using in-situ gels provides a promising approach due to its ability to enhance drug residence time, improve patient compliance, and enable sustained drug release at the site of action. **Objective:** This study aimed to formulate and optimize mucoadhesive in-situ buccal gel containing Curcumin and Choline Salicylate for the localized treatment of periodontitis usi ng a systematic Box–Behnken Design (BBD) approach. **Methods:** Twelve batches (F1–F12) were developed using varying concentrations of Poloxamer 188 and Carbopol 934. The gels were evaluated for physical appearance, pH, gelation temperature and time, spreadability, viscosity, mucoadhesive strength, drug content, and in vitro drug release. Statistical optimization was performed targeting gelation temperature (~37 °C), viscosity (<1000 cP), ≥40% drug release at 1 hour, and ≥90% release in 4–7 hours. Drug release kinetics were analyzed using mathematical models. The optimized batch was further subjected to a 3-month stability study under refrigerated conditions. **Results:** Among all formulations, batch F9 demonstrated optimal performance, showing a gelation temperature of 37 °C, viscosity of 947 cP, mucoadhesive strength of 11.33 dynes/cm², and sustained drug release over 7 hours (Curcumin: 81.31%, Choline Salicylate: 89.80%). The release followed non-Fickian diffusion, indicating a combination of diffusion and erosion mechanisms. Stability studies

confirmed the formulation's physical and chemical stability over the test period. **Conclusion:** The optimized in-situ buccal gel formulation of Curcumin and Choline Salicylate exhibited favorable physicochemical and mucoadhesive properties along with sustained drug release, indicating its potential as an effective localized therapy for the treatment of periodontitis.

KEYWORDS: Periodontitis, Buccal Drug Delivery, In-Situ Gel, Curcumin, Choline Salicylate, Thermoreversible Gel, Mucoadhesion, Box–Behnken Design.

INTRODUCTION

Periodontitis is a chronic inflammatory disease affecting the supportive structures of teeth, including the periodontal ligament, alveolar bone, and gingival tissues. It is initiated by dysbiotic microbial biofilms that disrupt host-microbial equilibrium, leading to progressive tissue destruction.[1] Globally, periodontitis imposes a significant health burden, with approximately 1.1 billion cases of severe periodontitis reported, ranking it among the most prevalent causes of disability.[2] If untreated, the disease may result in tooth loss and systemic complications, including cardiovascular diseases, diabetes mellitus, and adverse pregnancy outcomes.[3]

Pathogenesis involves bacterial infiltration from dental plaque, stimulating an excessive host immune response that culminates in degradation of connective tissues and alveolar bone.[4] Conventional treatment includes mechanical debridement, such as scaling and root planing, supplemented in some cases with systemic antibiotics.[5] However, systemic antimicrobial therapy has limitations, including inadequate drug concentration at the infection site, patient non-compliance, and the global crisis of antibiotic resistance.[6] Alarmingly, the World Health Organization estimates that antimicrobial resistance contributes to 700,000 deaths annually, with projections reaching 10 million by 2050.[7]

To address these concerns, localized drug delivery systems for periodontal pockets have been explored to enhance site-specific therapy and minimize systemic exposure.[8] Among these, in-situ gel systems have gained considerable attention. These formulations exist as liquids at room temperature but undergo gelation in response to physiological stimuli such as temperature, pH, or ion concentration, enabling controlled drug release at the site of infection.[9] Thermo-responsive systems containing polymers like Poloxamer 188 and Carbopol 934 have demonstrated excellent biocompatibility, mucoadhesive properties, and patient acceptability.[10]

Despite advancements, the clinical use of many active agents in periodontitis remains limited due to pharmacokinetic constraints. For instance, curcumin — a polyphenolic compound derived from *Curcuma longa* — possesses significant anti-inflammatory, antioxidant, and antimicrobial activity, yet suffers from extremely low aqueous solubility and instability under environmental stress.[11] These limitations compromise its therapeutic efficacy and necessitate protective delivery strategies. On the other hand, choline salicylate, a non-steroidal anti-inflammatory drug, exerts analgesic and anti-inflammatory effects via inhibition of prostaglandin synthesis, making it suitable for oral mucosal conditions.[12] However, its efficacy is curtailed by rapid clearance from the site due to salivary washout and mechanical stress within the oral cavity.[13]

This combination of natural and synthetic agents offers potential synergistic benefits in the treatment of periodontitis. Yet, a clear gap exists in the literature regarding their co-delivery via in-situ gel systems, especially those designed for buccal application. Biodegradable and mucoadhesive polymers such as Carbopol 934 can enhance drug residence time, while thermo-sensitive polymers like Poloxamer 188 facilitate gelation at oral temperature.[14] These polymers, when used together, may offer a stable delivery platform that overcomes individual drug limitations while maximizing therapeutic outcomes.

Therefore, this research aims to formulate and evaluate a mucoadhesive in-situ buccal gel incorporating curcumin and choline salicylate for the treatment of periodontitis. By addressing solubility, bioavailability, and mucosal retention challenges through innovative formulation strategies, the study seeks to establish a clinically viable alternative to conventional therapies.[15]

MATERIALS AND METHODS

Choline salicylate (ChS) solution BP was obtained from Shreenath Chemicals, Boisar, Mumbai, and curcumin was procured from Chemdyes Corporation, Rajkot, Gujarat. Poloxamer 188 was purchased from Yarrow Chem Products, Mumbai. Carbopol 934P and polyethylene glycol-400 (PEG-400) were obtained from Research Lab Fine Chem Ltd., Mumbai. All other chemicals and solvents used in the study were of analytical grade.

Instruments and Software Required for the Work

Ultraviolet (UV)-visible double beam spectrophotometer (manufactured by Shimadzu, Japan); Fourier transform infrared spectroscopy (FTIR) spectrophotometer (manufactured by

Shimadzu, Japan); Franz diffusion cell (manufactured by Borosil Glass Works Ltd., Mumbai) and electronic analytical balance, AUX 220 model (manufactured by Shimadzu, Japan) were used for experimental analysis.

Additional routine laboratory glassware, including beakers, measuring cylinders, volumetric flasks, and pipettes, were also utilized throughout the study. All glassware used was of analytical grade and manufactured by Borosil Glass Works Ltd., Mumbai.

Software required for research work

Design-Expert® software, version 13 (Stat-Ease Inc., USA – trial version) was employed for statistical optimization and formulation design.

Analytical UV-Visible Method Development and Validation

A simple UV-visible spectrophotometric method was developed for the estimation of Curcumin and Choline Salicylate (ChS) in the formulation, the procedure given below.

1. Curcumin

A primary stock solution of Curcumin was prepared by dissolving 200 mg of Curcumin in 100 mL of PEG-400, resulting in a concentration of 2000 µg/mL. From this, 5 mL was transferred into a 100 mL volumetric flask and diluted with ethanol to obtain a secondary stock solution of 100 µg/mL. Aliquots of 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 mL were withdrawn and individually diluted to 10 mL with ethanol to yield working standards of 5, 10, 15, 20, 25, and 30 µg/mL, respectively. Each standard solution was scanned between 400–800 nm using a UV-visible spectrophotometer, and the maximum absorbance (λmax) was observed at 428 nm.

2. Choline Salicylate (ChS)

Choline Salicylate BP solution (containing 50% w/v, equivalent to 1000 mg of ChS) was used to prepare a primary stock. 2 mL of this solution was accurately transferred into a 100 mL volumetric flask and diluted with phosphate buffer saline (PBS, pH 6.8) to obtain a stock concentration of 10 mg/mL. From this, 1 mL was further diluted to 100 mL with PBS (pH 6.8) to prepare a secondary stock solution of 100 µg/mL. Aliquots of 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 mL from this secondary stock were each diluted to 10 mL with PBS to obtain final concentrations of 5, 10, 15, 20, 25, and 30 µg/mL, respectively. Absorbance of each concentration was measured at λmax 292 nm, using PBS as blank.

Preparation and Optimization of Thermo-Reversible Mucoadhesive In-Situ Gel[16]

The solutions of Poloxamer 188 and Carbopol 934 were prepared using the cold method. For this purpose, a pre-measured volume of distilled water was cooled to approximately 4 °C, and each polymer was gradually sprinkled into the chilled water with continuous stirring to avoid clumping. The resulting polymeric dispersions were refrigerated and allowed to hydrate for 12 hours, ensuring the formation of clear, uniform solutions.

After complete hydration, the two polymeric solutions were combined and stirred thoroughly to ensure homogeneity. Sodium benzoate was added as a preservative to the mixed dispersion. The formulation was maintained at a low temperature until a transparent and consistent solution was achieved.

In the final step, accurately prepared drug solutions of Curcumin and Choline Salicylate were slowly incorporated into the polymeric blend under aseptic conditions, with continuous gentle stirring to facilitate uniform distribution. The final formulation was then aseptically transferred into pre-sterilized glass vials and securely sealed for further evaluations.

Statistical Optimization Using Box–Behnken Design

The in-situ gel formulation was optimized using Box–Behnken Design (BBD) to evaluate the effect of two formulation variables—Poloxamer 188 (X_1) and Carbopol 934 (X_2)—on critical quality attributes. The dependent responses selected were viscosity (Y_1), mucoadhesive strength (Y_2), and in vitro drug release at 6 hours (Y_3).

Table 01: Independent and Dependent Variables Used in Box–Behnken Design.

Variable Type	Code	Parameter	Level -1	Level 0	Level +1
Independent Variable	X_1	Poloxamer 188 (g)	3.0	3.2	3.4
Independent Variable	X_2	Carbopol 934 (mg)	40	50	60
Dependent Variable	Y_1	Viscosity (cP)	–	Target: <1000	–
Dependent Variable	Y_2	Mucoadhesive Strength (dynes/cm²)	–	Higher desired	–
Dependent Variable	Y_3	In vitro Drug Release at 6h (%)	–	Higher desired	–

The design generated **12 experimental runs**, allowing for modeling and response surface analysis to identify an optimal formulation with suitable syringe-ability, adhesion, and sustained drug release characteristics.

Effect of Formulation Variables on Dependent Responses

- **Viscosity (Y_1)**

Increased significantly with rising **Carbopol 934** concentration due to its swelling capacity; **Poloxamer 188** also contributed moderately via micelle formation.

- **Mucoadhesive Strength (Y_2)**

Enhanced with higher **Carbopol 934** levels, promoting stronger polymer–mucin interactions.

- **In Vitro Drug Release at 6h (Y_3)**

Showed an inverse relationship with viscosity; higher polymer levels slowed release, promoting prolonged drug availability at the site.

Evaluation of In-Situ Gel Formulations[17,18]

All twelve batches (F1–F12) of the prepared mucoadhesive in-situ buccal gels were evaluated for the following physicochemical and performance parameters.

1. Appearance and Clarity

Formulations were visually inspected against white and black backgrounds to assess clarity, color, and homogeneity. Any turbidity, precipitation, or phase separation was noted.

2. pH Determination

The pH of each gel was measured using a digital pH meter (calibrated with standard buffer solutions) by directly inserting the electrode into the sample at 4 °C. Each measurement was performed in triplicate, and the mean value was recorded.

3. Viscosity Measurement

Viscosity was measured using a Brookfield viscometer (Model LVDVE) fitted with spindle No. 01 at 20 rpm. Readings were taken at 4 °C (sol phase) and 37 °C (gel phase) for each formulation. Approximately 25 mL of each sample was analyzed in triplicate, and the average viscosity was reported in centipoise (cP).

4. Syringeability

Each formulation (1 mL) was loaded into a 5 mL syringe fitted with a 21-gauge needle. The ability of the formulation to be smoothly expelled under manual pressure was evaluated. Formulations that passed without resistance were marked as “Pass”; those requiring excessive force or showing clogging were marked “Fail.”

5. Gelation Temperature and Time

The sol–gel transition temperature was determined by the test tube inversion method. 2 mL of each sample was placed in a test tube and immersed in a water bath. The temperature was gradually increased, and at 2-minute intervals, the tube was tilted to 90°. Gelation temperature was defined as the point where flow ceased upon inversion. Gelation time was also recorded from the initiation of heating until gel formation occurred.

6. Spreadability

Spreadability was measured using the glass plate method. A 1 g sample was placed between two glass plates (20 × 20 cm), and a 200 g weight was applied for 5 minutes. The diameter of the spread area was measured, and spreadability was calculated using the formula:

$$S = \frac{ML}{T}$$

Where M = applied weight, L = distance moved, T = time taken.

7. Mucoadhesive Strength

A modified two-beaker assembly using freshly excised goat buccal mucosa was used. 1 g of gel was placed between two mucosal tissues affixed to inverted beakers. Water was added to a suspended beaker until detachment occurred. The weight of water at detachment was recorded as the mucoadhesive strength (in grams). All tests were conducted in triplicate using freshly prepared SGCF (Simulated Gingival Crevicular Fluid, pH 7.4).

8. Drug Content Determination

To determine the drug content of Curcumin and Choline Salicylate in the gel, 1 mL of formulation was dispersed in 50 mL PEG-400 and volume made up to 100 mL with ethanol. The solution was filtered and analyzed using a UV-Visible spectrophotometer at λmax 292 nm (Choline Salicylate) and 428 nm (Curcumin). Drug content was expressed as a percentage of theoretical drug concentration. All samples were tested in triplicate.

9. In Vitro Drug Release

In vitro drug release was evaluated using a Franz diffusion cell with egg membrane as the diffusion barrier. 1 mL of formulation was placed in the donor compartment; PBS (pH 6.8) was used as receptor medium, maintained at 37 ± 0.5 °C. At hourly intervals, 1 mL of receptor fluid was withdrawn and replaced with fresh buffer to maintain sink conditions. Samples

were diluted and analyzed at λmax 292 nm (ChS) and 428 nm (Curcumin) using a UV spectrophotometer. The cumulative drug release (%) was calculated as:

$$\text{Amount of Drug} = \frac{\text{Concentration} \times \text{Volume Taken} \times D.F}{1000}$$

$$\% \text{ Drug Release} = \frac{\text{Amount of Drug Release}}{\text{Drug Dose}} \times 100$$

Drug release kinetics were analyzed using Korsmeyer–Peppas and Fickian diffusion models. All tests were performed in triplicate (n = 3).

RESULTS

Evaluation of In-Situ Gel Formulations (F1–F12)

The prepared mucoadhesive in-situ gel formulations (F1–F12) were systematically evaluated for key physicochemical parameters, including appearance, pH, gelation temperature and time, spreadability, viscosity, and mucoadhesive strength.

The compiled results are shown in **Table No. 02.**

Batch Code	Color & Clarity	pH	Gelation Temp (°C)	Gelation Time (s)	Spreadability (g·cm/s)	Viscosity (cP)	Mucoadhesive Strength (dynes/cm²)
F1	Yellow Clear	7.2	34.0	82	11.2	712	9.45
F2	Yellow Turbid	6.8	35.6	74	10.5	728	9.68
F3	Light Yellow Clear	6.7	33.9	70	12.1	735	9.82
F4	Pale Yellow Turbid	6.9	36.0	55	10.8	754	10.02
F5	Yellowish	6.4	36.5	45	10.1	768	10.18
F6	Yellowish	7.0	35.0	34	11.5	880	10.94
F7	Yellow Clear	7.1	35.9	45	11.0	910	10.86
F8	Yellow Clear	6.9	34.4	58	11.8	920	10.76
F9	Yellow Transparent	6.8	37.0	79	12.9	947	11.33
F10	Yellow Clear	7.0	34.7	83	10.6	899	10.67
F11	Yellow Transparent	6.9	36.0	81	10.3	870	10.43
F12	Yellow Turbid	7.4	34.0	79	11.4	890	10.18

DISCUSSION AND BATCH SELECTION

Appearance & Clarity

Most batches exhibited acceptable clarity; however, F2, F4, and F12 were found slightly turbid. The clarity of F8, F9, and F10 was satisfactory.

pH Values

The pH ranged from 6.4 to 7.4, suitable for buccal application without causing mucosal irritation.

Gelation Temperature & Time

F9 gelled close to body temperature (~37 °C), indicating optimal thermal responsiveness. F8 showed rapid gelation (58 s), while F10 gelled in 83 s, which is acceptable.

Spread-ability and Viscosity

F8 and F9 had favorable spread-ability and high viscosity, indicating excellent syringe-ability and prolonged mucosal contact.

Mucoadhesive Strength

All selected batches showed strong mucoadhesive strength (F8–F10 ranged from 10.67 to 11.33 dynes/cm²), confirming suitability for buccal retention.

Selected for Further Study

- **F8** – Good viscosity, spreadability, mucoadhesion
- **F9** – Optimal gelation temperature, strong bioadhesion
- **F10** – Clear appearance, acceptable gelling behavior

Rejected Batches

F1–F7 and F11–F12 were excluded based on suboptimal performance in clarity, mucoadhesion, or gel behavior.

Drug Content Analysis (F8, F9, F10)

Table 03: Percentage Drug Content of Selected Batches.

Batch Code	Curcumin Drug Content (%)	Choline Salicylate Drug Content (%)
F8	96.58	95.35
F9	98.94	97.66
F10	99.15	97.92

All three batches exhibited drug content within the acceptable range (≥95%), indicating uniform distribution in the gel matrix.

In Vitro Drug Release

Table No. 04: Cumulative % Drug Release of Curcumin and Choline Salicylate.

Time	Curcumin (%)			Choline Salicylate (%)		
	F8	F9	F10	F8	F9	F10
0	0	0	0	0	0	0
1	12.10	14.35	11.80	20.30	22.85	18.90
2	21.35	27.20	20.25	33.15	37.70	30.80
3	29.80	35.45	28.70	45.60	52.40	43.25
4	40.40	47.60	39.60	61.45	69.80	62.15
5	54.60	61.55	52.20	73.95	81.20	76.35
6	66.30	72.40	65.85	82.25	88.55	85.25
7	71.22	81.31	73.20	86.39	89.80	87.10

Interpretation

Batch F9 exhibited the highest drug release: 81.31% for Curcumin and 89.80% for Choline Salicylate at 7 hours. These results confirm F9 as the optimized formulation, selected for drug release kinetics and stability analysis.

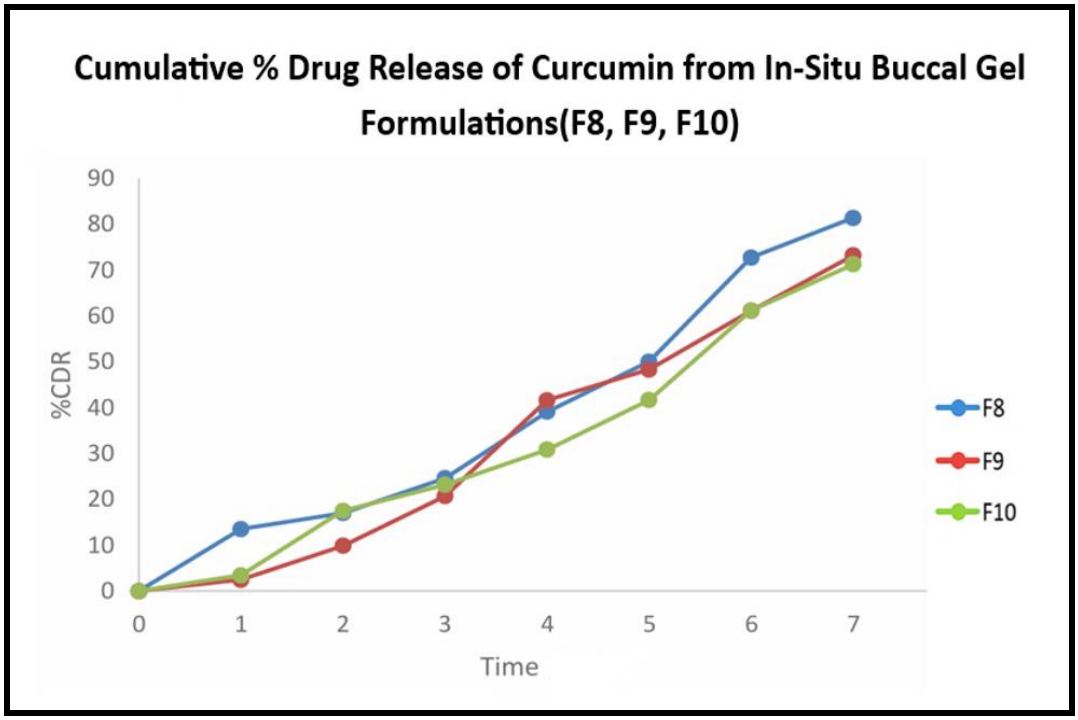

Figure No. 01: Cumulative % drug release of Curcumin.

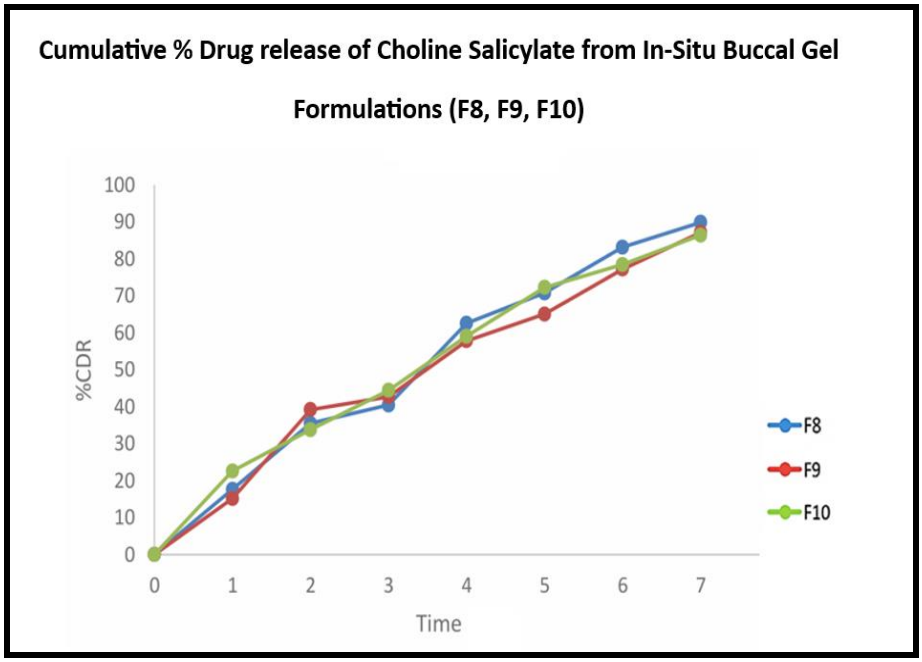

Figure No. 02: Cumulative % drug release of Choline salicylate.

Kinetic Analysis (Batch F9)

To elucidate the mechanism of drug release, the in vitro data of batch F9 were fitted into four mathematical models. The Korsmeyer–Peppas model was used to interpret the diffusional mechanism.

Table No. 05: Kinetic Drug Release of Batch F9.

Drug	Zero Order (R^2)	First Order (R^2)	Higuchi (R^2)	Korsmeyer–Peppas (R^2)	n Value	Release Mechanism
Curcumin	0.962	0.892	0.701	0.748	0.61	Non-Fickian diffusion
Choline Salicylate	0.978	0.935	0.846	0.683	0.68	Non-Fickian diffusion

Conclusion of Kinetics

Batch F9 followed **zero-order kinetics** with **non-Fickian diffusion**, suggesting a combination of diffusion and erosion mechanisms governing drug release.

Stability Studies

The optimized formulation **F9** was selected for stability assessment to evaluate its physicochemical integrity over time. The stability study was conducted under **refrigerated storage conditions (4 ± 2 °C)** for a period of **three months**, following ICH guidelines for semi-solid formulations.

Throughout the storage period, the formulation was monitored for changes in **clarity, viscosity, gelation temperature and mucoadhesive strength.**

OBSERVATIONS

- The gel **retained its clarity** with no signs of phase separation, precipitation, or microbial growth.
- A **slight decrease in viscosity** was observed, which may be attributed to polymeric structural rearrangement upon prolonged storage at low temperatures.
- A **minor reduction in gelation temperature** was also recorded; however, it remained within the acceptable physiological range.

CONCLUSION

The present study successfully formulated and optimized a thermoreversible mucoadhesive in-situ buccal gel incorporating Curcumin and Choline Salicylate for localized treatment of periodontitis. Using a Box–Behnken Design, twelve formulations were developed with varying concentrations of Poloxamer 188 and Carbopol 934. Comprehensive physicochemical evaluation identified batch F9 as the optimized formulation based on ideal gelation temperature (~37 °C), acceptable viscosity, high mucoadhesive strength, and superior spreadability.

In vitro drug release studies confirmed that batch F9 achieved sustained release of both Curcumin (81.31%) and Choline Salicylate (89.80%) over a 7-hour period, with release kinetics following non-Fickian diffusion behavior. The optimized formulation also demonstrated uniform drug content, excellent syringeability, and appropriate gelation behavior under physiological conditions. Stability testing over a three-month refrigerated period revealed no significant changes in physical appearance or drug release performance, indicating strong formulation robustness.

Overall, the optimized in-situ buccal gel provided an effective platform for dual-drug delivery, offering localized therapeutic action, enhanced mucosal adhesion, and controlled drug release. These findings support its potential clinical application in managing periodontitis through improved patient compliance, targeted drug action, and reduced systemic side effects.

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