Ind. J. Pharm. Edu. Res., 2026; Krupapharmacon:42-53.
https://www.ijper.org

Original Article

Formulation and Evaluation of *in situ* Oral Gels Containing Chlorhexidine Gluconate and Curcumin for Periodontitis

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ABSTRACT

Background: Periodontitis is a chronic inflammatory disease associated with bacterial plaque accumulation, and its treatment is often limited by the inadequate retention of antimicrobial agents within periodontal pockets. Thermo-responsive *in situ* gels offer a promising strategy for localized and sustained drug delivery. **Objectives:** To formulate and evaluate thermo-reversible *in situ* gels containing Chlorhexidine Gluconate (CHX) and Curcumin (CUR) for periodontal therapy and compare their performance with commercially available formulations. **Materials and Methods:** Thermo-sensitive hydrogels were prepared using the cold method with Poloxamer 407 as the primary polymer, along with Hydroxypropyl Methylcellulose (HPMC) and polyethylene glycol 400 (PEG 400). Following overnight hydration at 4ºC, CHX or CUR was incorporated into the polymeric matrix. The formulations were evaluated for gelation temperature, pH, viscosity, drug content, *in vitro* drug release, and antimicrobial activity using the agar well diffusion method. The optimized formulations were compared with Hexigel® and Curenext® gel. **Results:** The optimized formulation (P4) exhibited suitable gelation temperature, viscosity, and uniform drug loading. The CHX-loaded gel demonstrated sustained drug release, achieving 74.2% release over 49 hr, whereas the CUR-loaded gel released 98.18% of the drug within 24 hr. Antimicrobial studies revealed that the CHX gel showed the highest inhibitory activity, outperforming Hexigel®, while the CUR gel exhibited greater efficacy than Curenext® gel. **Conclusion:** The developed thermo-responsive *in situ* gels showed superior sustained-release characteristics and antimicrobial efficacy compared with commercial formulations. These findings suggest that CHX- and CUR-loaded *in situ* gels are promising candidates for effective localized management of periodontitis.

Keywords: Antimicrobial Activity, Chlorhexidine Gluconate, Curcumin, *In situ* Gel, Periodontitis, Poloxamer 407, Sustained Drug Release.

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INTRODUCTION

Driven primarily by the accumulation of microbial plaque biofilms and the subsequent host immune-inflammatory cascade, periodontitis is a chronic inflammatory disorder that systematically destroys the supportive structures of the teeth, including the alveolar bone, cementum, periodontal ligament, and gingiva. Left unmanaged, this condition culminates in attachment loss, the development of periodontal pockets, and eventual tooth loss. This disease represents a substantial global healthcare challenge; epidemiological data indicates that moderate periodontitis impacts more than 40% of the adult population, whereas its severe manifestation afflicts approximately 11%.[1]

The etiology of this condition is highly complex and multifactorial. It is characterized by a dysbiotic shift in the oral microbiome prominently involving pathogens such as *Aggregatibacter actinomycetemcomitans, Tannerella forsythia*, and *Porphyromonas gingivalis* which interacts with systemic and environmental variables. These include tobacco consumption, genetic predisposition, psychological stress, socioeconomic disparities, and systemic disorders like diabetes mellitus.[2] Crucially, the clinical relevance of periodontitis extends beyond the oral cavity due to its established correlations with systemic pathologies, including adverse pregnancy outcomes, respiratory tract infections, diabetes, and cardiovascular diseases, emphasizing the urgency for advanced therapeutic protocols.

Standard clinical interventions focus on scaling and root planning, frequently paired with the administration of local or systemic antimicrobial agents. Nonetheless, the therapeutic success of these traditional strategies is severely compromised by rapid crevicular fluid clearance, inadequate local retention of active agents within the pocket, and the rising threat of antimicrobial resistance.[3]

DOI: 10.5530/ijper.krupapharmacon.22

In situ Hydrogels

Representing an innovative class of drug delivery, *in situ* gels are fluid systems that solidify into a matrix upon interaction with physiological conditions such as ionic environment, temperature, or pH. This dual-phase nature allows for straightforward application, followed by enhanced localized retention and extended drug release at the target site. Polymer chemistry frequently utilizes agents like ion-sensitive sodium alginate, pH-responsive Carbopol, and thermo-sensitive Poloxamer 407 to formulate delivery platforms for ophthalmic, periodontal, vaginal, injectable, buccal, and nasal routes.[4] Their ability to restrict drug action to a specific site and provide sustained kinetics makes them ideal for managing chronic disorders like periodontitis.

Chlorhexidine Gluconate

Chlorhexidine Gluconate (CHX) is a widely established biocidal agent renowned for its high water solubility and superior substantivity. Deployed clinically at strengths between 0.2% and 4%, it serves as a cornerstone for plaque mitigation and supportive periodontal therapy. Its delivery formats include local matrices, rinses, and gels, alongside applications in dermatological and pre-operative antisepsis. While CHX offers a broad spectrum of activity, low systemic absorption, and prolonged retention, its clinical use is sometimes limited by external tooth staining, gustatory alterations, and inactivation by anionic excipients. Nonetheless, its definitive efficacy against periodontal microflora underlines its vital role in plaque management.[5]

Curcumin

Curcumin is a bioactive polyphenolic compound extracted from *Curcuma longa* that offers multi-target benefits, including antimicrobial, antioxidant, and anti-inflammatory mechanisms advantageous for periodontal healing. It downregulates the inflammatory cascade by inhibiting TNF-α, NF-κB, and COX-2, while simultaneously neutralizing free radicals through its antioxidant properties. Microbiologically, it exerts clear inhibitory effects against major pathogens like P. gingivalis. The systemic utility of curcumin is severely hampered by deficient water solubility and rapid metabolism; however, incorporating it into localized *in situ* gels circumvents these barriers, enhancing local persistence and bio efficacy within the periodontal pocket.[6]

Study Objective

Consequently, this research aimed to formulate thermo-responsive *in situ* gels containing chlorhexidine gluconate / curcumin. A comprehensive comparative assessment was performed to evaluate their physicochemical properties, *in vitro* release dynamics, and antibacterial profiles against standard commercial periodontal formulations.

MATERIALS AND METHODS

Materials

The active pharmaceutical ingredients used in this study included chlorhexidine gluconate, provided as a complimentary sample by Group Pharmaceuticals Ltd., (Bengaluru, India), and curcumin, gifted by Navashakthi Herbal Labs (Bengaluru, India). The primary thermo-responsive polymer, Poloxamer 407, was supplied by Yarrow Chem (Mumbai, India). The remaining auxiliary polymers and reagents were obtained from standard laboratory supplies and commercial manufacturers, including HPMC E15 from Central Drug House Ltd., (New Delhi, India), PEG 400 from Loba Chemie Pvt Ltd., (Mumbai, India), and analytical-grade methanol from Thermo Fisher Scientific (Mumbai, India).

Pre-formulation studies

Preformulation testing was carried out to investigate the physicochemical properties of chlorhexidine gluconate and curcumin, both individually and in combination with excipients. The objective was to provide useful information for the development of a stable and effective *in situ* gel.

Determination of melting point

To ascertain the melting point of curcumin, a capillary-based approach was implemented. A minimal amount of the sample was introduced into a sealed capillary tube, which was subsequently positioned inside a digital melting point analyzer. The liquefaction temperature, representing the point at which the solid matrix transitioned entirely into a liquid state, was recorded. The assay was conducted in triplicate ($n = 3$) to guarantee the reliability of the collected data.

Solubility determination

The solubility of chlorhexidine gluconate and curcumin was assessed in distilled water, ethanol, methanol, acetone, and Phosphate Buffer (pH 6.8). Excess drug was added to 10 mL of each solvent and shaken for 24 hr to reach equilibrium. The mixtures were then filtered to remove undissolved particles. Solubility in the filtrate was measured spectrophotometrically and expressed in mg/mL.

Analytical method by UV Spectrophotometry

Determination of λ_{max} and Construction of Calibration Curve of Chlorhexidine Gluconate

Quantification of chlorhexidine gluconate was achieved spectrophotometrically by preparing a 100 mg/100 mL (1000 µg/mL) primary stock in distilled water. From this stock, an intermediate dilution of 100 µg/mL was obtained, which was then utilized to formulate a concentration gradient of standard working solutions ranging from 5 to 25 µg/mL. The spectral profile of the 100 µg/mL matrix was evaluated within a 200-400 nm scanning

window on a Shimadzu UV-visible spectrophotometer to establish the λ_{max}, using distilled water blank for baseline correction. The optical response for each standard solution in the 5-25 µg/mL range was subsequently recorded at the determined λ_{max} of 255 nm. Finally, a linear regression plot mapping absorbance as a function of analyte concentration was constructed for drug quantification.[7]

Determination of λ_{max} and Construction of Calibration Curve of Curcumin

Quantitative determination of curcumin was done by dissolving 100 mg of CUR in a sufficient volume of methanol, adjusting the total volume to 100 mL to yield a 1 mg/mL primary stock solution. A secondary working stock was then formulated via a 50-fold dilution, transferring 2 mL of the primary solution into 100 mL of distilled water. This preparation underwent spectrophotometric analysis across a scanning range of 400-600 nm to identify the characteristic λ_{max} of curcumin. Appropriate volumes of the secondary stock were then diluted to produce a series of linearity standards spanning 2 to 12 µg/mL. Finally, the absorbance values for these solutions were determined at the established λ_{max}, and a linear regression profile was generated by plotting absorbance against concentration.[8,9]

Compatibility study by FTIR

FTIR analysis was carried out using a Bruker Alpha II spectrophotometer with ATR to assess drug-excipient compatibility. Pure drug, excipients, and physical mixtures were scanned over 4000-400 cm^{-1}. Spectra were compared for peak shifts or changes indicating possible interactions.[10]

Formulation Protocol for Thermo-Sensitive Hydrogels

Based on the definitive composition profiles (optimized through initial screening of HPMC E15 and PEG 400 combinations), a cold preparation method was deployed (Figure 1).[11] The process initiated with the dispersion of HPMC E15 in refrigerated distilled water (4°C) using a magnetic stirrer set to 100 RPM for a duration of 30 min, after which the dispersion was stored under refrigeration overnight for full hydration. Poloxamer 407 was subsequently added to the hydrated cellulose base under identical agitation conditions (100 RPM for 30 min). To yield a clear, fully dissolved solution, this blend was allowed to sit overnight at 4°C. Concurrently, chlorhexidine gluconate and curcumin were solubilized in the PEG 400 matrix either separately or sequentially for the combined delivery system under continuous magnetic stirring at 100 RPM. To finalize the formulation, these active phases were slowly introduced into the chilled polymer vehicle under mild magnetic agitation at 50 RPM, resulting in the production of completely homogenous, transparent *in situ* hydrogels.

Table 1: Absorbance of standard solutions of Chlorhexidine Gluconate in water at 255 nm.

Sl. No.	Conc. (µg/mL)	Absorbance ± Std. deviation (at 255 nm)
1.	4	0.127 ± 0.020
2.	8	0.243 ± 0.023
3.	12	0.413 ± 0.032
4.	16	0.575 ± 0.035
5.	20	0.767 ± 0.034

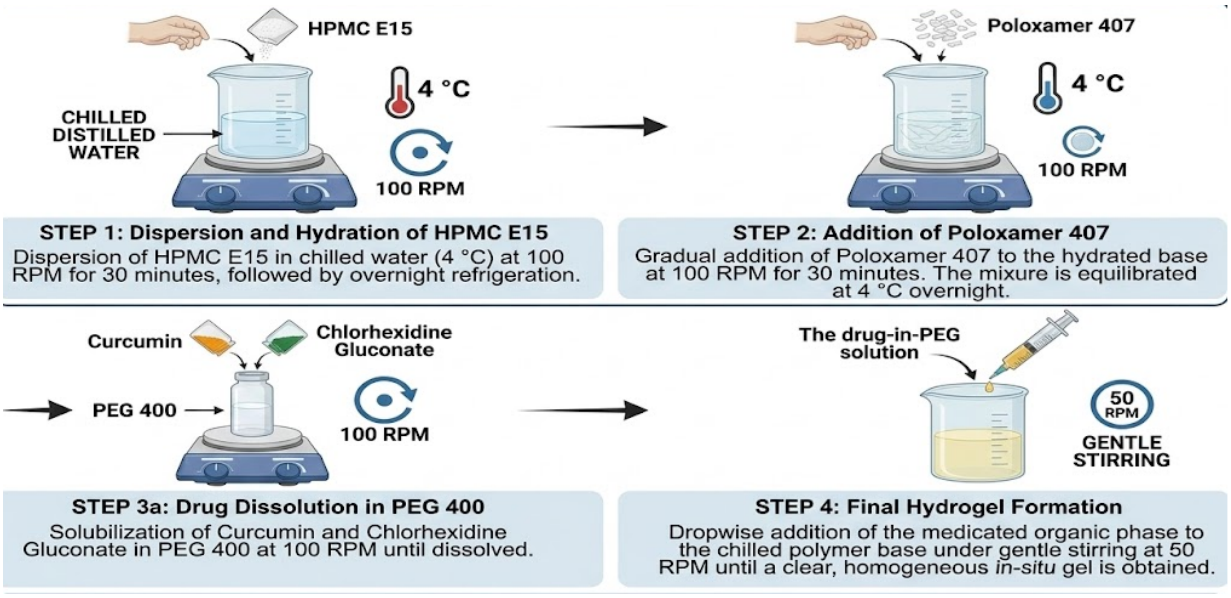

Figure 1: Procedure of Preparing *in situ* gel.

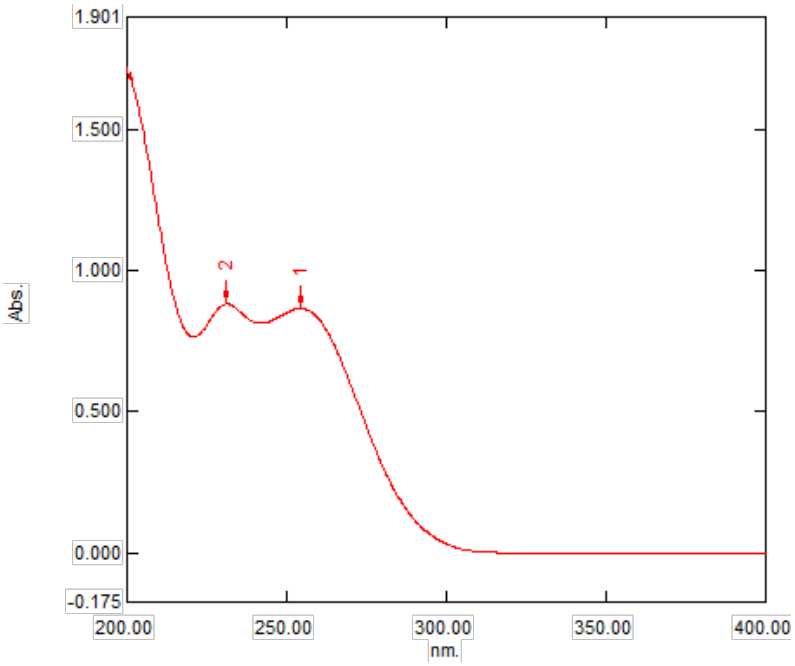

Figure 2: UV Spectra of Chlorhexidine Gluconate in water.

Table 2: UV Absorbance of Curcumin in water at 422 nm.

Sl. No.	Conc. (µg/mL)	Absorbance ± Std. deviation (at 422 nm)
1.	2	0.139±0.009
2.	4	0.275±0.022
3.	6	0.424±0.049
4.	8	0.566±0.055
5.	10	0.733±0.082
6.	12	0.854±0.085

In vitro Drug Release Studies

Assessment of drug release behavior was conducted in a phosphate buffer medium adjusted to pH 6.8 via a membrane-contained diffusion model. A washed and equilibrated regenerated cellulose membrane, (approx 25 µm thickness with a molecular weight cut off 10000 to 12,000 Daltons) served as the passive transport boundary separating the formulation from the receiver phase. 1 mL of either the active *in situ* gel or the reference drug solution was securely enclosed within this hydrated cellulose envelope and exposed to 100 mL of the stirring release environment. At scheduled temporal intervals, a 5 mL volume of the release medium was taken for analysis, with an equal volume of blank buffer introduced back into the system to prevent saturation limits. The drug concentrations within these samples were quantified spectrophotometrically at their respective peak wavelengths, establishing the cumulative percentage of released drug. These kinetic pathways were then mapped comparatively to evaluate how effectively the thermo-sensitive polymeric framework extended drug delivery relative to the free drug solutions.[12]

Antibacterial Assay Protocol

Evaluation of the formulations' inhibitory potential against *Streptococcus mutans* was conducted via a modified cup-plate agar diffusion method. Under sterile conditions, the target microflora (S. mutans) was inoculated into a molten nutrient agar base, which was then distributed into Petri plates and left to cool. Aseptically, vertical wells measuring 6 to 8 mm in diameter were punched into the inoculated agar beds. The prepared wells were subsequently filled with the designated concentrations of the test solutions and combination hydrogels. To allow sufficient thermal diffusion of the active antimicrobials alongside microbial growth, the plates were incubated under appropriate physiological conditions. The resulting therapeutic efficacy was determined by measuring the clear circular zones of inhibition that developed around the perimeter of each well.[13]

Evaluation of Formulated *In situ* Systems

Visual Properties and Micromorphology

Gels were characterized for transparency, clarity, and coloration. Microscopic scanning was performed across multiple fields of view to confirm the complete absence of crystal aggregates, particulate clusters, or gritty structures, validating batch uniformity.

Background Contrast Clarity Analysis

To check for underlying turbidity, a secondary optical inspection was carried out. Samples were illuminated and viewed against contrasting black and white backdrops to detect any faint precipitate or optical cloudiness.

Centrifugal Stress Stability

The physical integrity of the hydrogels was tested under centrifugal forces. Formulations sealed inside 10 cm x 1 cm test tubes were processed at 2000 RPM for intervals up to 1 hr (specifically at 5, 15, 30, and 60 min) to evaluate long-term resistance to phase separation and settling.

Digital pH Evaluation

Formulation pH was monitored using a calibrated glass electrode digital pH meter. Triplicate experimental runs were completed for each batch, and the data was expressed as mean values.

Viscosity and Thixotropic Recovery

Brookefield viscometer was used to measure the viscosity of the gel, spindle 3 was used at RPM 5 for collection of the data.

Thermal Gelation Thresholds

The phase-inversion point (sol-to-gel temperature) was evaluated via a systematic tube-tilting technique. The required gelling latency was quantified as the exact time required for stable matrix immobilization to occur at body temperature.[14-16]

RESULTS AND DISCUSSION

Physical description

- Chlorhexidine Gluconate: Colourless to pale yellow solution.
- Curcumin: Yellow-orange crystalline powder.

Standard graph of CHX

Spectrophotometric responses for the serial dilutions of chlorhexidine gluconate were recorded at the peak wavelength of 255 nm (Figure 2), and the empirical data points are detailed in Table 1. The resulting calibration plot displayed strong concentration-dependent linearity, demonstrating that the analyte complies perfectly with Beer's law within the working limits of 4-20 µg/mL. The standard curve demonstrated an exceptional linear relationship, defined by the regression model y = 0.0363x and a correlation coefficient (R2) of 0.9959 across the 0-20 µg/mL range. This mathematical compliance confirms that the developed UV-visible spectrophotometric method possesses adequate reliability and precision for the routine quantification of the active drug during hydrogel characterization.

Standard graph of curcumin in water at 422 nm

The absorbance of Curcumin standard solutions was measured at its λ_{max} of 422 nm, and the corresponding data are summarized in Table 2. The calibration plot showed good linearity, with Beer's law followed in the concentration range of (2- 12) µg/ mL (Figures 3 and 4).

FTIR Studies

FTIR spectroscopy was utilized to assess the molecular integrity of the free drugs and monitor any underlying chemical interactions resulting from their incorporation into the thermo-sensitive polymer bases. Figure 5 depicts the collected transmission profiles of the various experimental arms: free chlorhexidine gluconate (Spectrum 1), free curcumin (Spectrum 2), mono-loaded CHX gel (Spectrum 3), mono-loaded curcumin gel (Spectrum 4), and the dual-agent combination hydrogel (Spectrum 5).

FTIR spectra of pure Chlorhexidine Gluconate (CHX), curcumin, their individual gels, and the combination gel confirmed the preservation of all major functional groups. Pure CHX showed characteristic N-H, C-H, C=N, C-N, C-O, and C-Cl peaks, while pure curcumin exhibited typical O-H, C=O/C=C, aromatic C=C, and C-O vibrations.

Table 3: Formulae of Chlorohexidine in situ gels.

FORMULATION Code	POLOXAMER 407 (%)	PEG 400 (mL)	HPMC E 15 (mg)	CHX (mL)	DISTILLED WATER (q.s 10 mL)
P1	15	0.1	-	0.1	10
P2	16	0.1	30	0.1	10
P3	17	0.1	-	0.1	10
P4	18	0.1	30	0.1	10

Table 4: Formulae of curcumin in situ gels.

FORMULATION Code	POLOXAMER 407 (%)	PEG 400 (mL)	HPMC E 15 (mg)	CUR (mg)	DISTILLED WATER (q.s 10 mL)
G1	15	1	-	100	10
G2	16	1	30	100	10
G3	17	1	30	100	10
G4	18	1	30	100	10

Table 5: Gelation temperature and viscosity of prepared gels.

Formulation	Formulation Code	Gelation Temperature (°C)	Viscosity (cP) at 25 oC
CHX Insitu gels	P1	No gel formation	—
	P2	35	1320
	P3	27	1260
	P4 (Optimized)	37	2150
CUR Insitu gels	G1	No gel formation	—
	G2	33	1300
	G3	37	1820
	G4 (Optimized)	37	1980

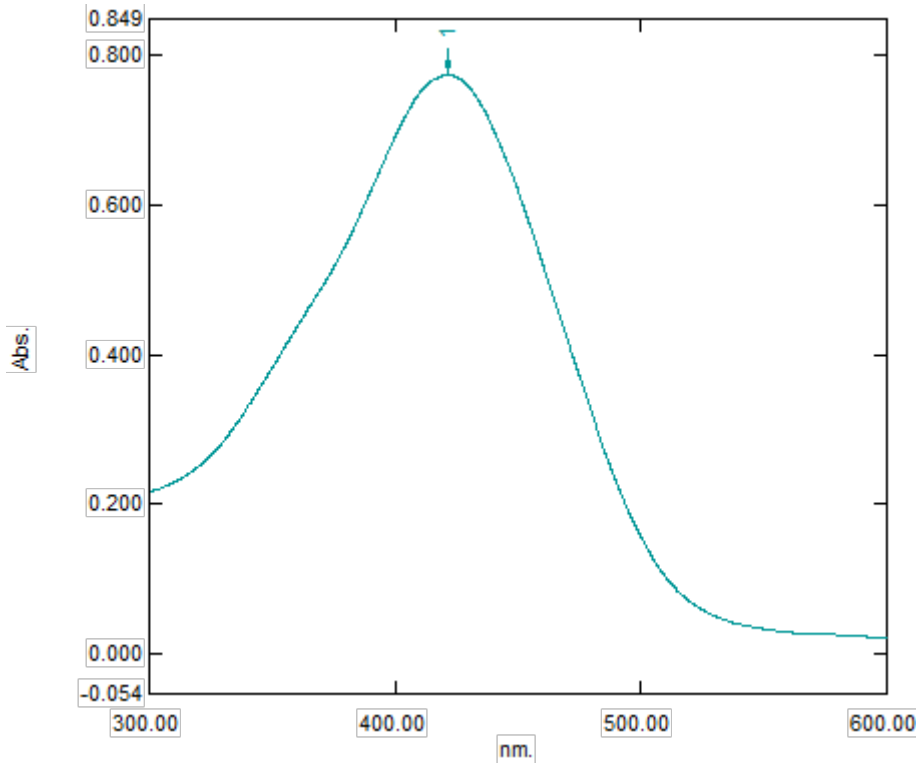

Figure 3: UV Spectra of Curcumin in water.

Both CHX gel and curcumin gel retained these essential peaks with only slight broadening due to hydrogen bonding with the polymer matrix, indicating no chemical interaction or degradation. The combination gel displayed superimposed peaks of both drugs without the appearance or loss of any characteristic bands.

Overall, FTIR confirmed that CHX, curcumin, and excipients are chemically compatible, and the gel formulations maintain the structural integrity of the active compounds.

In Vitro Release studies results and discussion

The exact composition profiles of the in situ gels are outlined in Table 6. The selection of the definitive formulations from each experimental group was governed strictly by thermal gelation kinetics suitable for in vivo application:

Chlorhexidine Monotherapy: Out of the four evaluated batches (P1-P4), formulation P4 was isolated as the optimal candidate. Its thermal phase-inversion point occurred at exactly 37°C, rendering it suitable for localized retention without premature gelation at room temperature.

Curcumin Monotherapy: For the G1-G4 experimental cohorts, batch G4 demonstrated superior rheological properties, displaying a targeted sol-to-gel transition at the physiological temperature benchmark of 37°C.

Comparative evaluation of the cumulative percentage drug release data highlights distinct kinetic properties between the experimental matrices and standard marketed formulations:

Chlorhexidine Gluconate Delivery Systems: The optimized *in situ* gel formulation P4 successfully minimized initial burst release, maintaining a highly regulated, sustained delivery curve that culminated in 74.2 CDR at 49 hr. This prolonged release profile aligns closely with the performance of the commercial comparator, Hexigel, which steadily discharged around 81% of its drug payload over a 48-50 hr period, confirming that the experimental polymer matrix provides a reliable, long-acting localized repository. Curcumin Delivery Systems: The experimental curcumin-loaded hydrogel (G4) followed a accelerated kinetic pathway, achieving an efficient localized release of 98.18% within 24 hr. Conversely, the commercial formulation Curenext gel failed to demonstrate measurable drug availability, exhibiting a practically flatline release profile. This negligible liberation behavior strongly

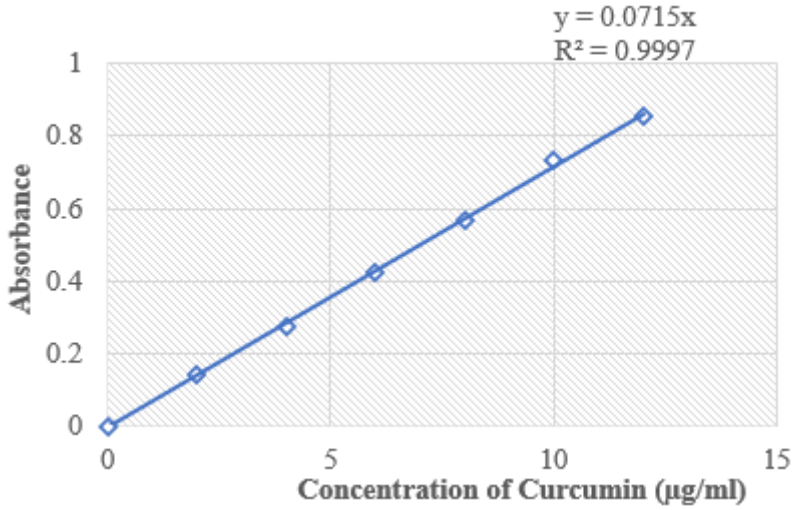

Figure 4: UV Calibration curve of Curcumin in water at 422 nm.

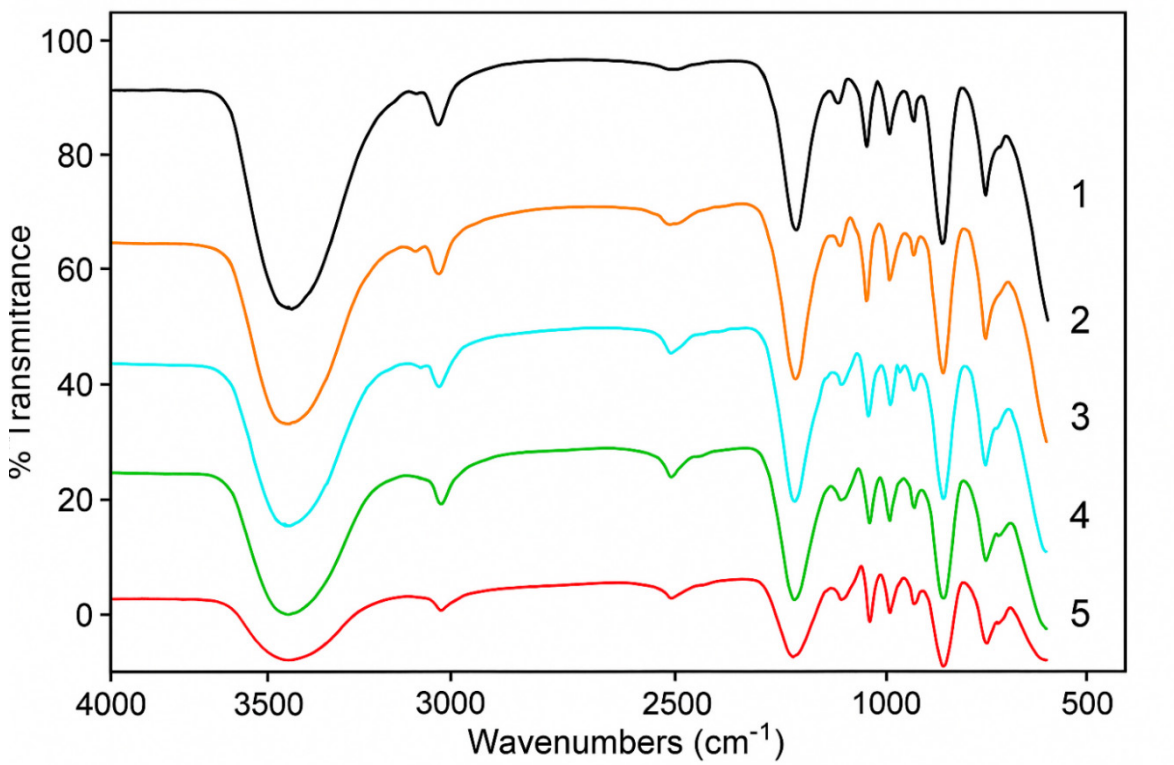

Figure 5: 1 = FTIR spectra of Pure Chlorhexidine Gluconate
2 = FTIR spectra of Pure Curcumin
3 = FTIR spectra of Chlorhexidine Gluconate Gel
4 = FTIR spectra of Curcumin Gel
5 = FTIR spectra of Combination Gel (Curcumin + Chlorhexidine Gluconate)

Table 6: Comparative *In vitro* Cumulative Drug Release Profiles of Formulations P4 and G4.

Sl. No.	Time (hrs)	% CDR Chlorhexidine gluconate *in situ* gel	% CDR Curcumin *in Situ* Gel
1.	0.25	-	4.37 ± 0.73
2.	0.5	-	7.78 ± 1.84
3.	1	1.8 ± 1.13	15.29 ± 1.42
4.	2	5.2 ± 0.99	25.30 ± 1.52
5.	3	8.7 ± 1.12	36.95 ± 2.21
6.	4	12.6 ± 2.77	51.08 ± 0.72
7.	5	17.1 ± 4.75	57.20 ± 0.38
8.	23	46.2 ± 3.97	-
9.	24	49.8 ± 3.03	98.18 ± 1.02
10.	25	52.3 ± 2.28	-
11.	26	54.6 ± 1.6	-
12.	30	57.9 ± 0.75	-
13.	47	70.8 ± 1.41	-
14.	48	72.8 ± 1.0	-
15.	49	74.2 ± 0.69	-

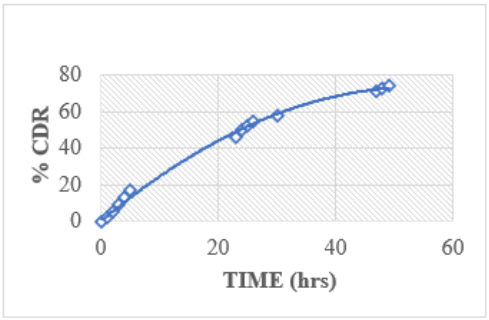

Figure 6: *In vitro* cumulative drug release profile of the optimized chlorhexidine

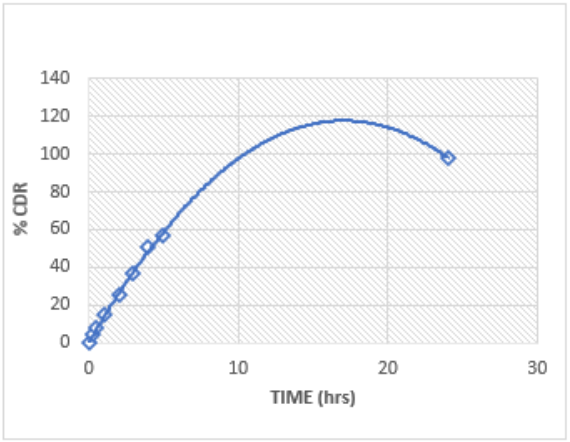

Figure 7: *In vitro* cumulative drug release profile of the optimized curcumin *in situ* gel formulation (G4) as a function of time.

Table 7: *In vitro* Cumulative Drug Release Profile of Chlorohexidine from commercial Hexigel product.

Sl. No.	Time (hrs)	% CDR
1.	0.25	6.47 ± 0.40
2.	0.5	8.63 ± 0.12
3.	1	17.47 ± 0.25
4.	2	24.33 ± 1.25
5.	3	26.67 ± 1.89
6.	24	55.00 ± 2.45
7.	25	61.67 ± 1.25
8.	26	64.67 ± 0.47
9.	27	63.33 ± 1.25
10.	46	78.00 ± 0.82
11.	48	81.00 ± 0.82
12.	50	81.33 ± 1.25

implies low drug availability and compromised localized efficacy in the commercial formulation, validating the therapeutic potential of the experimental G4 hydrogel as a superior vehicle for site-specific delivery. The drug release data are presented in Tables 6, 7 and Figures 5-7.

Antibacterial Activity

The results of anti-bacterial activity are presented as Table 8 and Figures 8-13.

From the Figures, CHX gel elicited a potent response, Hexigel (commercial product) produced a moderate response, and the CUR gel showed mild inhibition. The *in vitro* antibacterial performance of the formulated hydrogels, commercial comparators, and control standards against Streptococcus mutans was determined via agar well diffusion, as summarized in Table 8. The representative zones of inhibition for each treated arm (Samples A through F) are structurally illustrated across

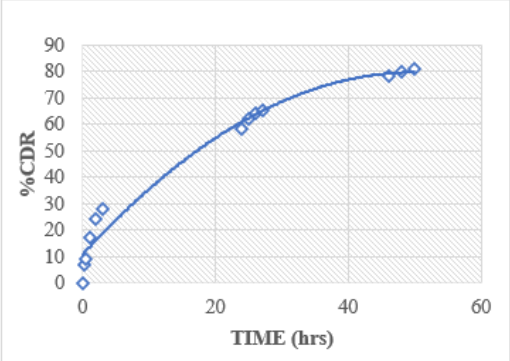

Figure 8: *In vitro* cumulative drug release profile of Chlorohexidine gluconate from commercial product Hexigel as a function of time.

Table 8: Anti-bacterial activity of the best prepared gels and commercial gels.

Sl. No.	Sample	Concentration µg/mL	Zone of Inhibition (mm) *Mutants*
1.	Control	-	-
2.	Standard Streptomycin	1 mg/mL	25
3.	Sample A- Hexigel (commercial product)	100µL	15
		200 µL	20
4.	Sample B- Curenext (commercial product)	100 µL	01
		200 µL	02
5.	Sample C-Curcumin Gel	100 µL	08
		200 µL	10
6.	Sample D -Combination CHX + CUR	100 µL	20
		200 µL	25
7.	Sample- E Chlorohexidine Gluconate gel	100 µL	19
		200 µL	23
8.	Sample- F Placebo	100 µL	01
		200 µL	02

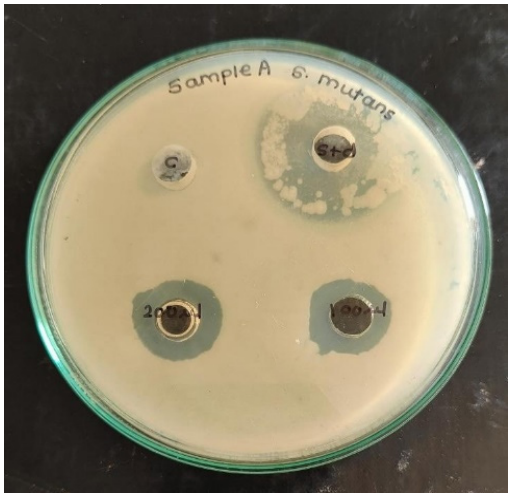

Figure 9: Sample A – Hexigel.

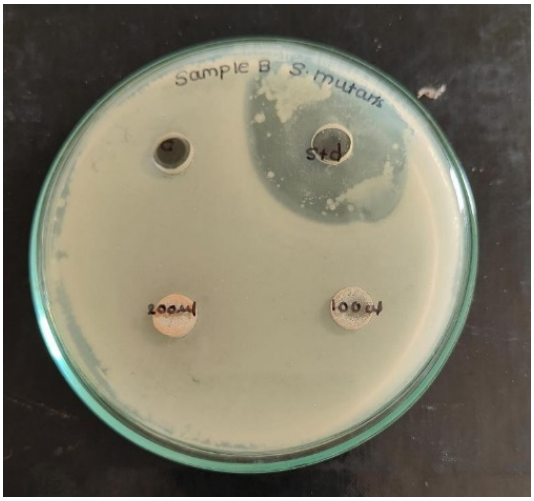

Figure 10: Sample B- Curenext.

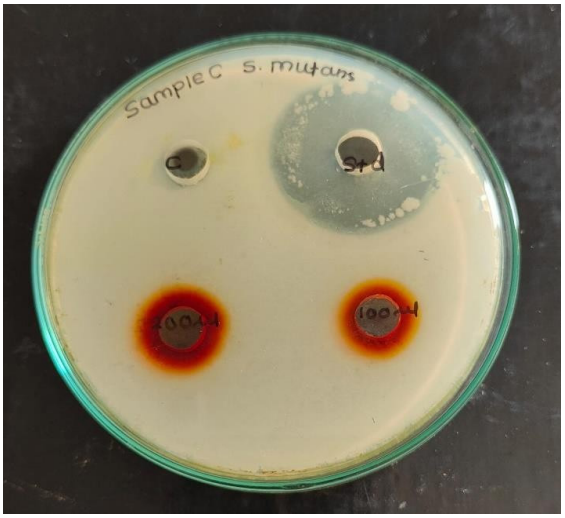

Figure 11: Sample C- Curcumin Gel.

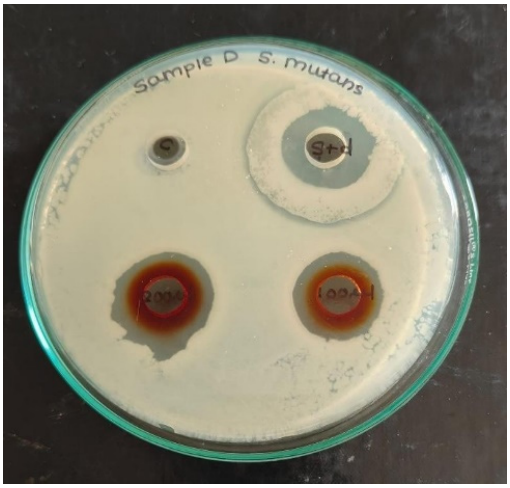

Figure 12: Sample D- Combination Gel

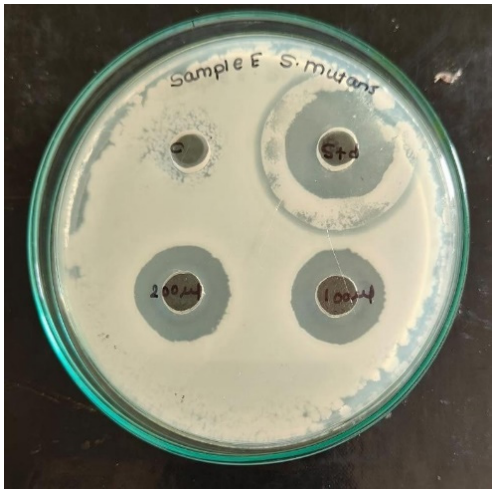

Figure 13: Sample E- Chlorhexidine.

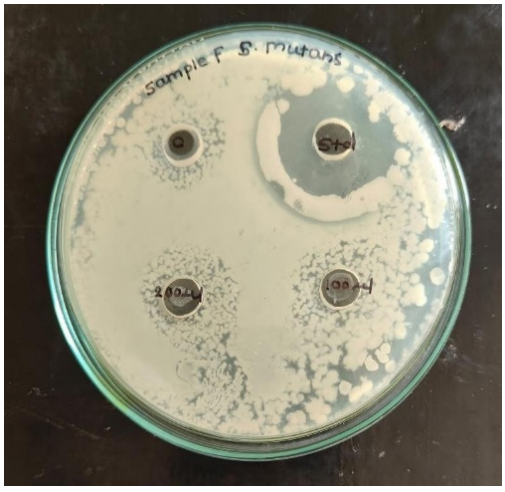

Figure 14: Sample F- Placebo.

Figures 8 to 13. The experimental formulations demonstrated a prominent, dose-dependent inhibitory response. Unformulated placebo matrices (Sample F) and negative controls elicited negligible activity (1-2 mm), confirming that the blank polymer framework does not possess inherent bactericidal properties. Because the combination system (Sample D) recorded higher inhibition zones than the single-drug matrices (Samples C and E) combined at equivalent volume fractions, these results verify a significant cooperative synergy. This ensures that even though curcumin release remains slow and controlled within the combined base, its physical presence effectively potentiates the membrane-disrupting action of chlorhexidine gluconate against *S. mutans* (Figure 14).

CONCLUSION

The study successfully formulated thermosensitive *in situ* gels of Chlorhexidine Gluconate and Curcumin using Poloxamer 407 and HPMC E15, achieving suitable gelling temperature, viscosity, and consistency for periodontal application. Optimized formulations of both drugs showed acceptable physicochemical properties and sustained release profiles. The combination gel demonstrated feasible dual-drug loading with stable gelation behavior and promising antimicrobial testing activity. Overall, the developed *in situ* gels show potential as localized delivery systems for periodontitis management. Future studies should include stability evaluation, *in vivo* performance assessment, and long-term therapeutic investigation

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Research Highlights

What is the current knowledge?

Periodontitis Management Limitations

The conventional treatment of periodontitis, a major chronic inflammatory disease, is limited by rapid drug clearance from the periodontal pocket, resulting in insufficient drug retention and reduced therapeutic efficacy.

Promise of *In situ* Gels

The use of thermosensitive ***in situ*** gels (often using Poloxamer 407) is a promising strategy for localized drug delivery. These systems are current knowledge because they offer a liquid formulation that transforms into a semi-solid gel upon contact with body temperature, ensuring prolonged drug residence and sustained release at the target site.

Dual-Drug Therapeutic Potential

Current knowledge validates the potent combination of:

Chlorhexidine Gluconate (CHX)

The gold-standard antimicrobial agent.

Curcumin (CUR)

A natural compound with strong anti-inflammatory and antioxidant properties, which also addresses the need for overcoming its poor water solubility through specialized formulation.

Superior Formulation Performance

The developed *in situ* gel formulations demonstrate a key advancement:

The optimized Chlorhexidine ***in situ*** gel achieved a controlled and prolonged drug release profile, which is superior to the rapid clearance seen with conventional or marketed products (e.g., Hexigel).

The combination of Chlorhexidine and Curcumin exhibited a significant synergistic effect, leading to an antimicrobial efficacy comparable to that of standard antibiotics (like streptomycin), thus suggesting a highly effective, localized, and potentially resistance-mitigating therapeutic approach.

What is new here?

- **Synergistic Combination:** Developed a novel **Chlorhexidine and Curcumin** gel that showed a powerful **synergistic antimicrobial effect**, matching the efficacy of a standard antibiotic (streptomycin).
- **Extended Release:** The formulation achieved **controlled and prolonged drug release** (up to 49 hr), which is more effective for chronic disease management than the fast clearance of existing commercial gels.

- **Superior to Marketed Products:** The developed gels were found to be **significantly better** than marketed alternatives (Hexigel and Curenext), specifically in terms of stability, drug content, and sustained release.

ACKNOWLEDGEMENT

I would like to express my sincere gratitude to Dr. Raman Dang, Principal of Krupanidhi College of Pharmacy, for providing the essential infrastructure and research facilities that made this work possible. My heartfelt thanks also go to Group Pharmaceuticals Ltd., Bengaluru, for providing the necessary chemicals for the successful completion of my project. Additionally, I am grateful to the Head of Department and faculty members of the Department of Pharmaceutics for their continuous guidance and encouragement throughout the completion of my research.

ABBREVIATIONS

CHX: Chlorhexidine gluconate; **CUR:** Curcumin; **HPMC:** Hydroxypropyl methylcellulose; **PEG:** Polyethylene glycol; **FTIR:** Fourier-transform infrared spectroscopy; **ATR:** Attenuated total reflectance; **CDR:** Cumulative drug release; **RPM:** Revolutions per minute; **λmax:** Wavelength of maximum absorbance; **UV:** Ultraviolet.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

No external funding was received for this research.

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Cite this article: Nithyasri J, Deepika T, Maddi EG. Formulation and Evaluation of *in situ* Oral Gels Containing Chlorhexidine Gluconate and Curcumin for Periodontitis. Indian J of Pharmaceutical Education and Research. Krupapharmacon 2026:42-53.