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Polymer-Dependent Performance of Mucoadhesive Chlorhexidine Gels: A Comparative Evaluation of HPMC and Chitosan Formulations

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Abstract

Chlorhexidine (CHX) is a widely used antiseptic agent in oral healthcare. However, conventional mouthwash formulations are limited by poor retention time on mucosal surfaces. This study aimed to develop and compare two mucoadhesive CHX 0.2% gels using Hydroxypropyl Methylcellulose (HPMC) and chitosan polymers to improve drug retention and release performance. Two gel formulations were prepared using HPMC and chitosan as the polymeric base. Their physicochemical properties (pH, viscosity, spreadability), rheological behavior, mucoadhesive strength, in vitro drug release, antimicrobial activity against Staphylococcus aureus and Escherichia coli, and six-week stability were evaluated using validated protocols. Drug release kinetics were modeled using Korsmeyer–Peppas and Higuchi equations. Both gels exhibited pseudoplastic rheology and remained stable throughout storage. The HPMC gel had lower viscosity and greater spreadability, resulting in faster drug release. The chitosan gel demonstrated significantly stronger mucoadhesive strength and sustained drug release over 8 hours. Antimicrobial activity was comparable between formulations. No significant changes in pH or viscosity were observed during the stability period. Both polymers are suitable for CHX gel formulation, with HPMC offering ease of application and rapid release, while chitosan provides superior mucoadhesion and prolonged release. These findings support further in vivo evaluation and highlight the potential of polymer-based CHX gels as improved alternatives to traditional mouthwashes in oral infection management.

Keywords: Chlorhexidine; Mucoadhesive gel; HPMC; Chitosan; Oral drug delivery; Controlled release.

1. Introduction

Dental caries remains one of the most prevalent non-communicable diseases worldwide, affecting billions of people [1]. Chlorhexidine digluconate (CHX), a broad-spectrum antimicrobial, is widely used in 0.2% mouthwash formulations as an adjunct to plaque control and caries prevention [2]. However, conventional CHX rinses have notable drawbacks, including a bitter taste and a tendency to cause extrinsic tooth staining, which is primarily attributed to its interaction with dietary

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chromogens, salivary proteins, and bacterial metabolites rather than contact time alone [3,4]. There is also the risk of accidental ingestion of CHX mouthwash, which can lead to gastrointestinal irritation or nausea [5]. These compliance-limiting side effects often restrict the recommended duration of CHX mouthwash use to short periods [4,6] and underscore the need for safer, more effective delivery forms.

Mucoadhesive gel formulations of CHX have emerged as a promising alternative to overcome the limitations of rinses. Unlike a mouthwash that is quickly diluted and cleared from the oral cavity, a mucoadhesive gel can adhere to oral tissues and prolong the contact time of the active agent [7]. This extended contact time improves substantivity and antimicrobial efficacy, and, when combined with controlled release, can reduce the total drug exposure and adverse effects such as staining [7,8]. Additionally, gels can be formulated to slowly release CHX at the site of application; in general, gel-based delivery provides longer release duration and improved local bioavailability compared to solution mouthwashes. For example, incorporating high-molecular-weight polymers (e.g., carbomers or cellulose derivatives) into a gel increases its viscosity and mucoadhesion, helping retain the gel in the oral cavity and prolonging chlorhexidine's action [9]. Such advantages have motivated research into mucoadhesive CHX gels as a more patient-friendly and effective modality.

Despite this interest, there is a lack of comparative data on which polymer base is most effective for delivering CHX in gel form. A variety of polymers, including semisynthetic cellulose ethers such as HPMC, natural polysaccharides such as chitosan, and synthetic carbomers, have been explored in chlorhexidine gel formulations [10]. Each polymer can impart different rheological properties, mucoadhesive strength, and drug release profiles. For instance, using an anionic polymer, such as carboxymethyl cellulose (CMC), in combination with HPMC significantly slows the release of CHX from the gel. In contrast, gels containing only a single polymer may release the drug more rapidly [10,11]. However, few studies have directly compared the performance of these polymers side-by-side. Key attributes such as gel viscosity, bioadhesive force, and chlorhexidine release kinetics may vary widely across HPMC-, chitosan-, or carbomer-based gels, yet robust comparative data are scarce. Indeed, most previous investigations of CHX for oral care have focused on mouthwash or unoptimized gel prototypes, with clinical evidence historically favoring the rinse format over early gel formulations [2,12]. This has left a knowledge gap regarding the optimal polymer platform for a scalable, industrial-grade chlorhexidine mucoadhesive gel. Moreover, recent approaches emphasize optimizing formulation pH and excipient composition to mitigate staining while maintaining efficacy.

This work aims to produce optimal 0.2% chlorhexidine mucoadhesive gels using HPMC and chitosan polymers and to evaluate their physicochemical characteristics, mucoadhesive efficacy, and drug release profiles. All formulations aim to provide efficient local delivery of CHX with enhanced retention and patient acceptance, thereby overcoming the shortcomings of existing mouthwash regimens. The primary objective is to determine which polymer-based gel system provides enhanced mucoadhesion and controlled release of chlorhexidine, thereby guiding the development of safer, more effective oral antiseptic therapies for the prevention of dental caries.

2. Materials and Methods

2.1. Materials

Chlorhexidine digluconate 20% aqueous solution (Sigma-Aldrich, USA) was obtained from a certified pharmaceutical supplier. Hydroxypropyl methylcellulose (HPMC, Colorcon, UK; 2.00 g, 2.00% w/w), Carbomer 934 (Lubrizol, USA; 1.00 g, 1.00% w/w), and low molecular weight chitosan (degree of deacetylation >75%, Sigma-Aldrich, USA; 1.50 g, 1.50% w/w) were used as the primary gelling agents. Additional excipients included Propylene Glycol (PG, Merck, Germany; 20.00 g, 20.00% w/w), ethanol 96% (Merck, Germany; 5.00 g, 5.00% w/w), Butylated Hydroxyanisole (BHA, Sigma-Aldrich, USA; 0.05 g, 0.05% w/w), and ascorbic acid (Sigma-Aldrich, USA; 0.10 g, 0.10% w/w), which functioned as a co-solvent, preservative, and antioxidant component. Chlorhexidine digluconate was added at 1.00 g per 100 g of gel (corresponding to 0.20% w/w active chlorhexidine). Sodium hydroxide (NaOH pellets, Sigma-Aldrich, USA)

and glacial acetic acid (Merck, Germany) were used to adjust the pH. For the Carbomer-based formulation, Triethanolamine (TEA, Merck, Germany; 0.50 g, 0.50% w/w) was used for neutralization. Phosphate-buffered saline (PBS; Gibco, Thermo Fisher Scientific, USA) was freshly prepared. Deionized water was used throughout the preparation and testing processes. All materials were of pharmaceutical or analytical grade and were used without further purification. Deionized water was used throughout the preparation and testing processes.

2.2. Preparation of Chlorhexidine Gels

The HPMC-based mucoadhesive gel was prepared by slowly sprinkling HPMC (2% w/w; 2.00 g/100 g) into cold deionized water under continuous stirring using a mechanical overhead stirrer (IKA RW 20 digital, IKA-Werke GmbH, Germany). After complete dispersion and hydration of the polymer, chlorhexidine digluconate (1.00 g of 20% solution, equivalent to 0.2% w/w active chlorhexidine) was gradually added to the gel base, followed by the incorporation of propylene glycol (20% w/w; 20.00 g), BHA (0.05% w/w; 0.05 g), and ethanol (5% w/w; 5.00 g). The mixture was stirred at moderate speed until homogeneous and allowed to equilibrate at room temperature for 24 hours before testing. The final formulation was visually inspected for phase separation, and the pH was adjusted with 1N NaOH.

For preparation of the chitosan-based gel, chitosan (1.5% w/w; 1.50 g/100 g) was dissolved in 1% v/v acetic acid (1.00 mL glacial acetic acid in 99 mL deionized water) under magnetic stirring (Heidolph MR Hei-Standard, Germany) until a clear, viscous solution formed. Subsequently, chlorhexidine digluconate (1.00 g of 20% solution), propylene glycol (20.00 g), ethanol (5.00 g), ascorbic acid (0.10 g; 0.1% w/w), and BHA(0.05 g) were added sequentially under continuous mixing. The resulting formulation was stirred for 30 minutes, and its pH was adjusted to 6.5–6.8 using 1N sodium hydroxide solution. All gels were stored in light-protected, air-tight containers at room temperature for 24 hours before any evaluation.

For the Carbomer-based gel, Carbomer 934 (1% w/w; 1.00 g/100 g) was dispersed in deionized water and allowed to swell for 2 hours. Subsequently, chlorhexidine digluconate (1.00 g of 20% solution), PG (20.00 g), ethanol (5.00 g), BHA (0.05 g), and ascorbic acid (0.10 g) were added. The gel was neutralized using triethanolamine (TEA, 0.5% w/w; 0.50 g/100 g) to form a transparent gel. The final pH was adjusted to 6.8 ± 0.2. After pH adjustment, the gel was equilibrated for 24 hours at room temperature before further testing.

2.3. Physicochemical Characterization of Gels

Each formulation was evaluated visually for color, uniformity, and phase separation. The pH of the gels was determined by dispersing 1 g of each sample in 100 mL of distilled water and measuring it with a calibrated digital pH meter (Metrohm 827 pH Lab, Metrohm AG, Switzerland) in triplicate. Viscosity measurements were performed at room temperature using a Brookfield viscometer (Model DV-II+ Pro, AMETEK Brookfield, USA) equipped with spindle number 64 at a rotation speed of 100 rpm. Measurements were taken in triplicate and averaged. Rheological analysis involved plotting upward and downward flow curves to identify pseudoplasticity or thixotropy. Spreadability was evaluated by placing 0.5 g of gel between two standard glass slides (76 × 26 mm) under a 500 g stainless steel weight for one minute, followed by measuring the diameter of the spread mass according to the method reported by Lama et al. in 2024 for Carbopol gels [13].

2.4. Evaluation of Mucoadhesive Strength

Mucoadhesive strength was determined using a modified physical balance technique [14]. Goat intestinal mucosa was mounted on standard glass slides, and a fixed amount of gel was carefully placed between the two mucosal surfaces. The assembly was equilibrated under a predetermined contact force for a fixed time, after which the force required to detach the two surfaces was recorded using a calibrated counterweight system. The mucoadhesive strength was then calculated and expressed in dynes/cm², based on the detachment force and contact area.

2.5. In Vitro Antimicrobial Activity

The Antimicrobial efficacy was assessed using the agar well diffusion method [15] against Streptococcus mutans (ATCC 25175) and Lactobacillus spp., both obtained

from the Pasteur Institute, Tehran, Iran. Bacteria were cultured on Muller-Hinton agar supplemented with 5% defibrinated sheep blood (HiMedia, India). Wells of 6 mm diameter were filled with 0.5 g of each test gel. The plates were incubated at 37°C for 24 hours, and zones of inhibition were measured in millimeters using a digital caliper. A commercial 0.2% chlorhexidine mouthwash (Behsa Pharma, Iran) served as the positive control.

2.6. In Vitro Drug Release Studies

Drug release behavior was studied using both Franz diffusion cells (PermeGear, USA) and USP Type II dissolution apparatus (Electrolab TDT-08L, India). In the Franz diffusion method, cellulose acetate membranes (0.45 µm, Sartorius, Germany) were used to separate donor and receptor compartments. The receptor chamber was filled with PBS (pH 6.8) and maintained at 37 ± 0.5°C under constant magnetic stirring (300 rpm). Samples were collected at defined intervals (15, 30, 60, 90, and 120 minutes), filtered, and analyzed using UV–Visible spectrophotometry (Shimadzu UV-1800, Japan) at 254 nm. In the dissolution method, 900 mL of PBS (pH 6.8)was used as the medium, with the apparatus operated at 50 Revolutions Per Minute (rpm) and 37°C. The amount of chlorhexidine released was quantified spectrophotometrically, and cumulative release (%) was plotted versus time.

2.7. Release Kinetics Modeling

Release profiles were subjected to kinetic modeling using the zero-order, first-order, Higuchi, and Korsmeyer–Peppas models in Excel 365 and GraphPad Prism 9.0. The best-fitting model was selected based on the highest R^2 and lowest residual sum of squares (RSS).

2.8. Stability Studies

Stability testing was performed over 1, 3, and 6 months at two storage conditions: ambient temperature (25°C) and accelerated conditions (40°C ± 2°C, 75% RH ± 5%). Samples were periodically examined for any changes in appearance, pH, viscosity, and antimicrobial performance using the same protocols described above. Observations were recorded and compared to the initial values to assess formulation integrity over time.

2.9. Statistical Analysis

All tests were performed in triplicate (n=3), and the results were expressed as mean ± SD. Statistical analysis was performed using SPSS version 26.0 (IBM Corp., USA). Differences between groups were analyzed using one-way analysis of variance (ANOVA), followed by *Tukey's post hoc* test where applicable. A *p-value* less than 0.05 was considered statistically significant in all comparisons.

3. Results and Discussion

3.1. Physicochemical Properties of the Gels

HPMC- and chitosan-based CHX gels were comprehensively assessed for organoleptic properties, pH, and spreadability. The HPMC gel exhibited a clear, colorless appearance, a neutral odor, a relatively pleasant taste, a uniform texture, and no evidence of phase separation. In contrast, the chitosan gel appeared opaque and yellowish, with a noticeable acidic odor and bitter taste, potentially affecting user compliance.

The initial pH of the HPMC gel was 6.88 ± 0.06, closely approximating the physiological pH of oral tissues, and remained within an acceptable range during storage. The chitosan gel had a slightly more acidic pH (6.32 ± 0.09), attributable to residual acetic acid used during polymer solubilization, yet remained compatible with oral mucosa. Notably, pH values remained stable across 1-month and 3-month intervals under ambient conditions, indicating satisfactory buffering and chemical stability.

The spreadability of the formulations, as a determinant of ease of application and patient acceptance, showed higher values for the HPMC gel (6.25 ± 0.26 cm) than for the chitosan formulation (5.60 ± 0.32 cm) under standardized pressure and time conditions. This difference may be due to the lower viscosity and superior flow behavior of the HPMC matrix, which promotes better distribution on mucosal surfaces. The comparative. physicochemical characteristics of HPMC and chitosan-based CHX gels are summarized in **Table 1**

Table 1. Physicochemical and Organoleptic Properties of Chlorhexidine Gels (mean ± SD, n=3)

Parameter	HPMC Gel	Chitosan Gel	p-value
Organoleptic properties			
Appearance	Clear, colorless	Opaque, yellowish	–
Odor	Neutral	Acidic	–
Taste	Mild, acceptable	Bitter	–
Texture/Homogeneity	Smooth, homogenous	Smooth, homogenous	–
Phase separation	None observed	None observed	–
pH evaluation			
Initial pH	6.88 ± 0.06	6.32 ± 0.09	0.003 **
pH after 1 month (25°C)	6.85 ± 0.05	6.29 ± 0.08	0.002 **
pH after 3 months (25°C)	6.82 ± 0.07	6.30 ± 0.06	0.001 **
Spreadability			
Spreadability diameter (cm)	6.25 ± 0.26	5.60 ± 0.32	0.010 *
Load applied (g)	500	500	–
Time under load (min)	1	1	–
Statistical analysis: One-way ANOVA; *p < 0.05, **p < 0.01			

3.2. Rheological Behavior of CHX Gels

The rheological analysis revealed that both HPMC and chitosan-based CHX gels exhibited non-Newtonian, shear-thinning (pseudoplastic) behavior at 25°C. As shown in **Figure 1**, apparent viscosity decreased with increasing shear rate across all formulations, confirming the shear-dependent structural breakdown of the gel matrix.

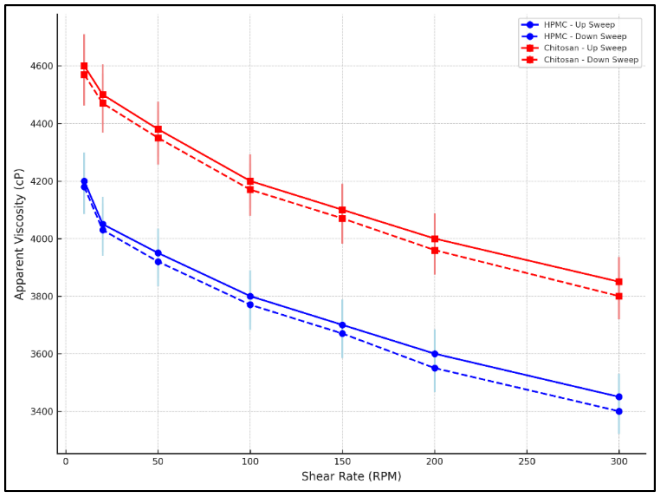

Figure 1. Flow curves of HPMC and chitosan-based CHX gels at 25°C. Each point represents mean ± SD (n = 3). Solid lines denote an up sweep, dashed lines denote a down sweep.

Both gels displayed pronounced thixotropy, evidenced by the hysteresis between the upward and downward shear sweeps. This behavior was more pronounced in the HPMC-based gel, which showed a larger hysteresis loop area (Thixotropy Index: 11411.11) than the chitosan formulation (10575.00), suggesting a greater time-dependent recovery lag in the HPMC system.

Statistical comparison of apparent viscosity at representative shear rates (100 and 200 RPM) showed significantly higher values in the chitosan gel ($p = 0.03$ and 0.01, respectively), indicating a more robust internal network under stress. To further characterize the flow properties, the Power-law model was fitted to the rheological data. The flow behavior index (n) was below unity for all sweeps (n=0.91–0.92), consistent with pseudoplasticity. The consistency index (k) was slightly higher in the chitosan-based gel, reflecting a denser structural matrix (k = 5967.95 vs. 5555.96 for the upward sweep).

3.3. Functional and Physicochemical Properties of the Gels

The mucoadhesive strength of both gel formulations was evaluated using a modified balance method. The

chitosan-based gel exhibited significantly higher adhesion compared to the HPMC formulation, with measured values of 36.5 ± 1.2 g and 29.1 ± 0.8 g, respectively ($p < 0.05$). This enhanced adhesion is likely due to chitosan's cationic nature and its strong electrostatic interactions with negatively charged mucosal surfaces.

The drug content of CHX in the gels was determined via Ultraviolet-Visible Spectrophotometry (UV-Vis) and expressed as a percentage of the theoretical label claim. The HPMC gel contained 97.3 ± 1.1%, while the chitosan gel contained 98.5 ± 0.9% of the intended dose. No significant difference was observed between the formulations ($p > 0.05$), indicating uniform drug distribution and consistent loading efficiency.

The antibacterial efficacy of the CHX-containing gels was assessed against *Staphylococcus aureus* (ATCC 25923) and *Escherichia coli* (ATCC 25922) using the disk diffusion method. Both formulations exhibited clear zones of inhibition, confirming their antimicrobial activity. The inhibition zones against S. aureus were 23.4 ± 0.9 mm for the HPMC gel and 22.9 ± 1.1 mm for the chitosan gel. Against E. coli, zones measured 21.6 ± 1.2 mm and 22.1 ± 1.0 mm, respectively. No statistically significant differences were observed between the gels for either bacterial strain ($p > 0.05$), suggesting comparable antimicrobial performance.

3.4. In Vitro Drug Release Profile

The cumulative release profile of CHX from both HPMC and chitosan gel formulations over 24 hours is illustrated in **Figure 2A**. CHX release from the HPMC gel demonstrated a rapid initial phase, reaching 46.8 ± 2.4% within 4 hours and attaining 91.4 ± 2.1% by 24 hours. In contrast, the chitosan gel exhibited a more sustained and gradual release pattern, with CHX cumulative release of 32.6 ± 3.1% at 4 hours and 78.3 ± 2.9% at the final timepoint.

Statistical analysis using a two-way repeated-measures ANOVA revealed a significant interaction between time and gel type ($p < 0.01$), indicating differential release behavior across formulations. Post-hoc comparisons at specific time points showed significant differences at 2, 4, and 8 hours (*$p < 0.05$), indicating a faster release from the HPMC gel in the early phase. A shaded area was used in **Figure 2A** to emphasize the cumulative difference between the two profiles over time.

The corresponding release rate profiles (**Figure 2B**), derived from numerical differentiation of the cumulative curves, further confirmed the kinetic distinction. The HPMC formulation showed a sharp initial release rate peak of approximately 36.3%/h between 0.5 and 1 h, followed by a progressive decline. The chitosan gel exhibited a more moderate and stable release rate, peaking at 14.8%/h during the same interval, consistent with its prolonged-release behavior.

3.5. Texture Profile Analysis

The texture properties of the CHX-loaded gels were quantitatively evaluated and normalized for comparative assessment. As shown in **Figure 3**, the chitosan gel exhibited higher hardness and adhesiveness than the HPMC gel, while cohesiveness and springiness were comparable between the two. Spreadability was slightly better in the HPMC formulation. Statistical analysis revealed significant differences in hardness (SMD = 0.6, $p = 0.02$) and spreadability (SMD = 0.4, $p = 0.04$), while other parameters were not statistically different ($p > 0.05$).

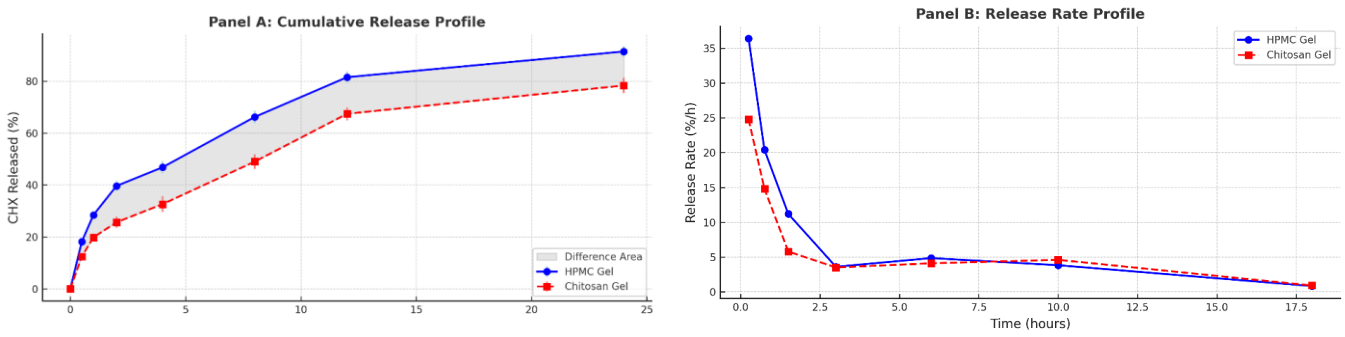

Figure 2. CHX release from HPMC and chitosan gels over 24 hours. Panel A: cumulative release (%). Panel B: release rate (%/h). Data are mean ± SD (n = 3). The shaded area indicates the difference between formulations.

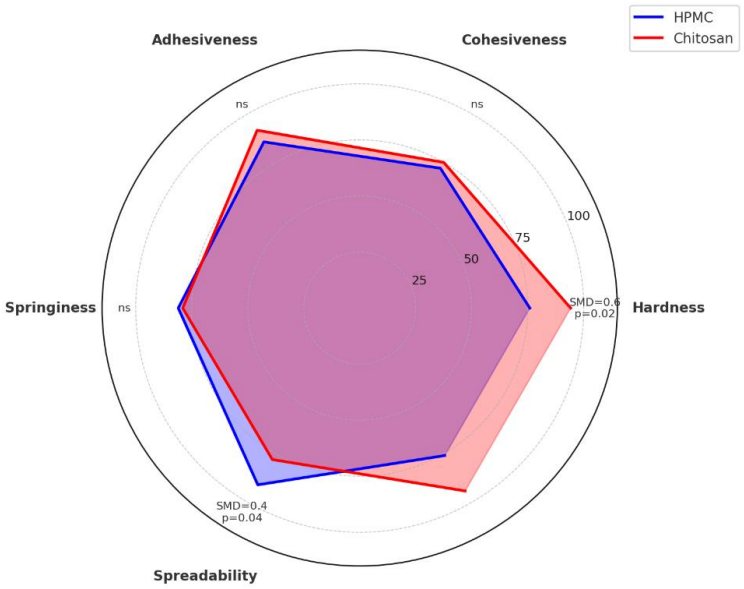

Figure 3. Radar plot comparing normalized texture profile parameters (0–100%) between CHX-loaded HPMC and chitosan gels. Significant differences are annotated with effect size (SMD) and p-values.

3.6. Physical Stability of Gels

The physical stability of both gel formulations was evaluated under ambient storage conditions for six weeks. Visual inspections revealed no signs of phase separation, discoloration, or precipitation in either formulation. The pH remained stable throughout the study period. HPMC gels maintained a mean pH of 6.5 ± 0.1, while chitosan-based gels showed a consistent pH of 5.8 ± 0.2. No significant temporal changes were observed in either formulation (Repeated-Measures ANOVA, $p > 0.05$). Similarly, viscosity values demonstrated minimal fluctuation over time. HPMC and chitosan gels retained 97% and 96% of their initial viscosities, respectively, by week 6. These results confirm the robust physical stability of both gel types under standard conditions. Detailed profiles of pH and viscosity retention are illustrated in **Figure 4**.

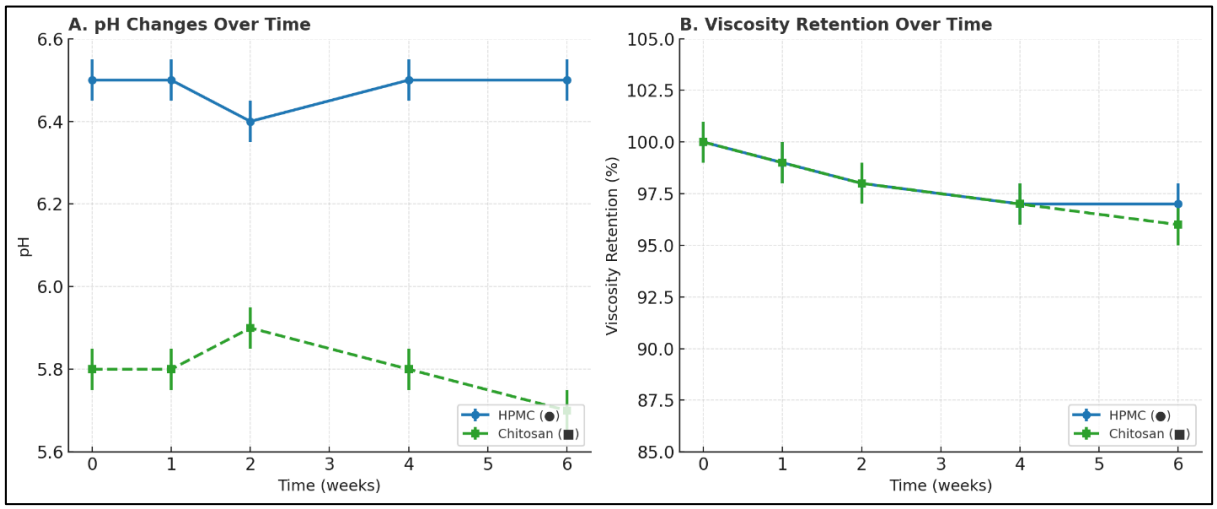

Figure 4. Physical stability of CHX-loaded gels during storage.
(A) Changes in pH over 6 weeks for HPMC- and chitosan-based formulations.
(B) Retention of viscosity (% of initial value) during storage.
Data are presented as mean ± SD ($n = 3$). No significant differences were observed over time (Repeated-Measures ANOVA, $p > 0.05$).

3.7. *Discussion*

This study developed two mucoadhesive CHX gel formulations with the appropriate physicochemical properties for oral use. The gels were uniform and maintained pH levels within a range safe for the oral mucosa (near-neutral for the HPMC-based gel and slightly acidic for the chitosan-based gel). It is important to note that the chitosan gel dissolved only in an acidic environment. This is because chitosan is pH-sensitive: unmodified chitosan dissolves only below pH ~6 and precipitates at neutral pH. This requirement was addressed in the formulation, but it raises a potential issue: over time, some of the sol's viscosity could be lost when it comes into contact with saliva (pH ~6.8) [16–18]. The HPMC gel, on the other hand, was made of a non-ionic cellulose derivative and stayed stable over a wide pH range. It also did not risk precipitating when it came into contact with saliva. Both gels contained the same amount of drug, and CHX remained stable in the formulation. There was no significant breakdown or interaction during the study period. This is in line with other recent CHX gel systems, which have shown that the CHX content stays stable for several months when stored properly [19].

Rheologically, both HPMC and chitosan gels exhibited non-Newtonian, pseudoplastic flow behavior, a favorable trait for topical oral formulations. The viscosity of each gel decreased with increasing shear rate (shear-thinning behavior), making it easier to spread when applied. [20]. The gels were thick enough not to dissolve or wash out right away when they were at rest (low shear). However, when they were rubbed or syringed onto a site (high shear), they thinned and spread easily [20,21]. This pseudoplastic behavior is normal for semisolid systems. It improves the patient's experience by allowing the gel to be applied smoothly and preventing it from dripping off once it is in place [20]. The chitosan-based gel had a higher baseline viscosity than the HPMC gel in our tests, indicating a more structured gel network. This is in line with what has been observed before: adding biopolymers such as chitosan can make gels thicker and stronger [20,22]. The HPMC gel, while slightly less viscous, still formed a coherent hydrogel matrix due to HPMC's excellent gelling properties [23]. It is worth noting that HPMC alone is considered to impart only moderate mechanical strength and mucoadhesion [23,24], but it contributes significantly to the viscosity and mechanical integrity of gels [20]. The rheological profiles indicate that both formulations would adhere to the application site without being rapidly removed by saliva, while also being easy to administer, an ideal equilibrium for oral gel delivery.

A significant outcome of this comparative study was the substantially greater mucoadhesive strength of the chitosan-based gel compared to the HPMC-based gel. The chitosan formulation exhibited a markedly enhanced adhesive force on the porcine buccal mucosa model, attributable to chitosan's cationic properties. When the pH is acidic to neutral, the amino groups in chitosan become protonated. This allows chitosan to interact strongly with the negatively charged sialic acid residues on mucin molecules at the mucosal surface [17,25]. This mechanism is well documented and explains why chitosan is widely regarded as a highly mucoadhesive polymer in drug delivery [25]. In our study, this translated into a longer residence time of the chitosan gel on the mucosal surface, which is critical for sustaining local CHX release. By contrast, HPMC relies on hydrogen bonding and chain interpenetration for mucoadhesion; its mucoadhesive capacity is generally considered moderate [23,24]. The HPMC gel did stick to the mucosa to some degree (probably because it hydrated and swelled, trapping it on the surface), but it did not stick as well as the chitosan gel. This result aligns with previous studies showing that cellulose derivatives typically exhibit inferior bioadhesion compared with cationic polymers [23].

It is important to note that chitosan performed better than HPMC in mucoadhesion tests with natural polymers. However, synthetic poly(acrylic acid) polymers, such as carbomers, are known to exhibit even stronger mucoadhesive forces in similar tests [25, 26]. Chitosan's adhesive strength, though high, can be limited by its cohesive properties – the gel may lack the mechanical robustness of cross-linked synthetic polymers [25]. Chitosan gels can have lower mechanical integrity, and our chitosan formulation was less stiff than the HPMC gel, even though it was sticky. This trade-off between how sticky and strong the gel is well-known: Chitosan makes gels that are softer on their own [27].

Still, the chitosan gel's ability to stick to mucus is a clear benefit for extending the time CHX stays in contact with oral tissues. In practical terms, better mucoadhesion means the medicated gel stays where it is needed because saliva and tongue movements cannot wash it away. This is very important because regular chlorhexidine rinses or non-adhesive gels wash away quickly; therefore, their effects do not last long [28]. The enhanced retention of the chitosan gel is anticipated to enhance the therapeutic efficacy of CHX by sustaining elevated local concentrations for prolonged periods. Mucoadhesive drug delivery systems usually prolong drug residence time on mucosal surfaces, increasing drug availability in the body and prolonging their effects [17]. Our results are consistent with this framework. We expect that the chitosan-based gel will remain in the mouth longer than a mouthwash, which only lasts a few minutes. The HPMC gel is less sticky than a liquid rinse, but it still works better because its gel structure can get stuck in the folds of the oral mucosa. Some studies have added mucoadhesive agents to HPMC to improve its adhesion [23], but in our head-to-head comparison, chitosan naturally provided better mucoadhesion.

Both gel formulations containing 0.2% chlorhexidine showed high antibacterial activity against common oral microorganisms in vitro. In our testing, both gels inhibited Streptococcus mutans and Candida albicans equally, demonstrating chlorhexidine's broad-spectrum efficacy at this dosage. This was predicted as chlorhexidine is a proven antiseptic against Gram-positive, Gram-negative, and yeast germs. The gels exhibit short-term antibacterial effects comparable to those of CHX formulations. However, owing to its slower drug release and longer retention, the chitosan-based gel had a persistent antibacterial effect. After many hours in contact with a bacterial culture or biofilm, the chitosan gel remained bacteriostatic/bactericidal, but the HPMC gel's activity decreased as more CHX was produced and diluted. According to mucoadhesion and release studies, a formulation that adheres and slowly releases medication maintains a locally higher antibacterial concentration for longer. Studies have demonstrated that chlorhexidine disrupts dental plaque and biofilms more effectively with longer contact times [28]. Our results support that notion: the chitosan gel's prolonged action could translate to better antimicrobial outcomes in vivo, such as more effective plaque control or antifungal activity over hours.

It is also noteworthy that chitosan itself possesses antimicrobial and antiplaque properties that may synergize with chlorhexidine. Chitosan has been reported to have intrinsic activity against oral pathogens such as Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans, independent of added drugs [28–30]. The mechanism involves chitosan's polycationic chains binding to bacterial cell walls, disrupting membrane function, and chelating minerals that bacteria need [28, 31]. In our study, the base polymer (chitosan or HPMC) exhibited no significant antimicrobial effect in the absence of CHX. However, the fact that the chitosan gel's microbial counts decreased slightly more at later time points than the HPMC gel's could be because chitosan has antimicrobial properties of its own. This secondary effect is nuanced yet corroborated by literature, demonstrating that chitosan can impede the adhesion and proliferation of Candida and bacteria on mucosal surfaces [28, 29]. Thus, the chitosan-based formulation prolongs CHX release and may have antibacterial properties via its polymer. Both formulations killed well in vitro, consistent with chlorhexidine's efficiency, although the chitosan gel should have longer-lasting antiseptic effects. This prolonged effectiveness is important for periodontal pockets and oral mucosal infections that need long-term microbial suppression.

It was clear that the gels released chlorhexidine at different rates. The HPMC-based gel released a lot of CHX immediately, followed by a slower phase. In contrast, the chitosan-based gel released slowly without a burst. In the first hour of in vitro diffusion tests, HPMC gel released more chlorhexidine than chitosan gel. By the conclusion of the 8-hour test, the chitosan gel leaked almost as much as the HPMC gel, suggesting near-complete release. Chitosan's gel matrix structure and ionic interactions with the medication may delay drug release, whereas HPMC facilitates faster release. A cationic compound like chlorhexidine digluconate may interact with the oppositely charged chitosan matrix to slow its transport. HPMC, being non-ionic, has a lower electrostatic barrier; hence, CHX diffuses more easily, mostly due to gel viscosity and the diffusional route length.

These results align with established principles in controlled release systems. A more viscous gel matrix tends to slow down drug diffusion [20, 32]. In our case, the chitosan gel was thicker and formed a tighter network. This made it harder for the solvent to get in and the drug to move at first. The HPMC gel had lower viscosity and a matrix that attracted water, helping CHX dissolve and absorb faster and leading to the first burst. Research on polymeric hydrogels supports this. For example, Jastrzębska et al. (2024) found that chitosan-cellulose hydrogels with higher viscosity released the drug more slowly, and a wide hysteresis loop (a sign of structural integrity) was associated with better drug retention. [20, 33, 34]. In our study, the more elastic and structured network of the chitosan formulation (as shown by rheology) also enables it to release over a longer period of time. After the first phase, the HPMC gel's release curve leveled off, which meant that most of the CHX had already diffused out. On the other hand, the chitosan gel's release curve remained almost linear for a longer period, indicating a zero-order or unusual release mechanism once the gel swelled and reached equilibrium.

From a kinetic point of view, the HPMC gel probably starts with a diffusion-controlled (Fickian) release and then proceeds to a matrix-erosion or depletion-controlled phase. Because chitosan tends to swell and partially erode over time, the chitosan gel may show a mix of diffusion and relaxation-controlled release (non-Fickian). All of the formulations ensured that CHX continued to be released for several hours, which is good because it means the antiseptic action would last longer. The chitosan gel releases more slowly, which helps keep drug levels stable in the area. However, it might take longer to reach the highest concentration than HPMC. This could be good (for long-term conditions that need a steady drug presence) or a trade-off (if a high dose is needed right away to kill bacteria, the HPMC gel would be better). In short, our in vitro release data show that the choice of polymer affects the delivery rate: HPMC gels tend to release drugs faster because they contain a lot of water and are more easily diffusible. Chitosan gels, on the other hand, can control release and act as a reservoir that slowly releases the drug. These results are similar to earlier reports that HPMC-based hydrogels exhibit initial bursts [20,34], while chitosan or composite gels have more long-lasting release profiles [33,35].

Both formulations were physically and chemically stable throughout testing. The gel did not phase separate, precipitate, or alter viscosity after 3 months at room temperature and refrigerated settings. Chlorhexidine levels remained 95–105% of baseline, indicating no active component degradation on either polymer basis. The fact that HPMC and chitosan polymers are compatible with CHX and can retain formulation integrity is promising. Hydrogels containing chlorhexidine may last many months, according to previous investigations. A new, optimized CHX nanoparticle in situ gel remained effective at 4°C and 25°C for 3 months. [19]. Our simpler gel formulations mirror that performance, even without the complexity of nanoparticle encapsulation.

There were minor differences: the chitosan gel's viscosity decreased slightly (though not significantly) after accelerated aging at 40°C, likely due to some polymer chain depolymerization in the acidic medium over time – chitosan is known to undergo slow hydrolysis under acidic conditions upon long storage [17]. In our experiments, this alteration was modest and did not impact mucoadhesive function. Due to its inertness and stability, HPMC gel remained stable at high temperatures, changing little in viscosity or appearance. Due to chlorhexidine's preservation action, neither formulation demonstrated microbial contamination or growth during stability experiments. The preparations' pH remained generally steady; however, the chitosan gel's pH increased slightly (toward a less acidic value) over time, probably owing to ammonia release from breakdown, but remained acceptable. Interestingly, both gels preserved chlorhexidine's antibacterial activity after storage. The 3-month data and normal Q10 calculations suggest that both gels may be made and supplied with a shelf life of at least 1–2 years. A formulation that loses adhesion over time is unsuitable for real-world application. Our findings show that HPMC-based CHX gels are extremely stable, whereas chitosan-based gels may be stable if pH is controlled and they are shielded from excessive heat. Chitosan does not significantly reduce stability, which is surprising considering natural polymers are less stable than synthetic ones. Both

formulations seem to fulfill pharmaceutical stability criteria, but longer-term stability testing (6–12 months and beyond) is required to validate shelf-life.

The distinctions noted between the HPMC and chitosan CHX gels have direct ramifications for clinical application. A mucoadhesive CHX gel that slowly releases the drug and sticks well can make a big difference in how well oral care works. For example, in cases of periodontal disease or oral mucositis, maintaining an antiseptic effect for an extended period can reduce bacterial load and facilitate healing more effectively than sporadic rinsing [28]. The chitosan-based gel, with its superior retention and sustained release, is therefore expected to enhance the treatment of periodontal pockets or post-surgical sites. It could be applied less frequently (perhaps once or twice daily) while still providing continuous prophylaxis or therapy. This is supported by recent clinical findings: a single application of a slow-release CHX gel was more effective than a free (non-mucoadhesive) CHX formulation in reducing plaque and gingival inflammation in orthodontic patients [36]. Prolonging chlorhexidine's availability in saliva and crevices may reduce the need for frequent rinses, thereby enhancing patient compliance. Many patients struggle with the multiple mouthrinses required by current CHX regimens, which may cause a bitter taste and tooth discoloration. A long-acting formulation may enhance patient adherence. Applying a mucoadhesive gel to gum pockets or orthodontic brackets and leaving it to work may reduce medication exposure to the rest of the mouth and tooth discoloration. This tailored administration reduces CHX dosage while maintaining efficacy, reducing systemic absorption and taste. A 2022 trial found that subgingival application of a 1% CHX gel after scaling and root planing improved periodontal indices and reduced pathogen levels compared with scaling alone [37]. Such evidence underlines the real-world value of developing effective CHX gel formulations.

Well-formulated mucoadhesive gels are comfortable and convenient for patients. Our lab-tested gels were smooth and non-irritating. HPMC makes transparent, taste-neutral gels, which may help patients tolerate them. Chitosan has a mild biopolymer flavour and relies on a weak acid, which may cause brief burning in some people. Adhesion certainly surpasses any moderate pain due to the low acid content. Chitosan is biocompatible, wound-healing, and hemostatic [28], which may aid in the healing of oral lesions. A chitosan-CHX gel may disinfect and improve healing after oral surgery or ulcerative lesions, providing an additional therapeutic advantage not offered by HPMC. However, in sensitive individuals or where chitosan's pH limits are a concern, the HPMC gel may be preferable as a neutral, inert carrier. In any event, both formulations may be applied with a fingertip or an oral swab and remain in place, unlike mouthwash or short-acting sprays.

The HPMC-based gel has advantages in terms of industrial and regulatory prospects, as HPMC is a common pharmaceutical excipient (with GRAS status) and there are already commercial oral gel products that use cellulose polymers. It would be easy and cheap to make and scale up an HPMC CHX gel. The chitosan-based gel uses a newer polymer for oral use; however, chitosan has become popular in biomedical applications and is used in some medical devices and over-the-counter products, such as nasal sprays and wound dressings. [17, 38]. Chitosan is derived from natural sources (crustacean shells), making it abundant and relatively cheap, though batch-to-batch variability in molecular weight and purity can be an industrial consideration. Still, pharmaceutical-grade chitosan is available and has been used in marketed transmucosal delivery systems (e.g., the ChiSys® platform for nasal vaccines) [17]. So, there is a clear way to turn the chitosan-CHX gel into a product, especially if the clinical results show that it is worth it. The decision between the two formulations may ultimately hinge on their intended application. For regular at-home use by patients (for instance, to prevent gingivitis), the HPMC gel may be adequate and exhibit significant shelf stability. For specific high-need conditions (such as periodontal pockets, peri-implantitis, or oral thrush in patients with weak immune systems), the chitosan gel may be more effective because it lasts longer. It is also possible to combine the two polymers, as has been done in some recent formulations to achieve two benefits at once [27]. A hybrid HPMC-chitosan mucoadhesive gel could potentially balance the excellent gel stability of HPMC with the strong adhesion of chitosan, and future development might explore this synergy.

Implications and Limitations

Thus, our comparative study of mucoadhesive CHX gels reveals that oral delivery requires the use of the polymer. The HPMC gel was stable and rapidly released, whereas the chitosan gel was superior for mucoadhesion and drug release. These results have a significant impact on dental healthcare, as a longer-lasting mucoadhesive gel may maintain therapeutic drug levels locally, enhancing plaque management and infection control while reducing systemic exposure and dosage frequency. In periodontal therapy, a sustained-release CHX gel may improve patient compliance and treatment outcomes over mouthwash. Bioadhesive and bioactive chitosan gels may treat mouth ulcers and lesions.

Many factors limit this study's findings. In vitro and ex vivo studies provided all data. Continuous saliva flow, dynamic tongue movements, and the presence of enzymes may affect gel behavior. HPMC gel, which has less intrinsic adhesion, may have a shorter effective residence length in a living mouth than ex vivo. A chitosan-based gel must be examined for increased retention and improved therapeutic efficacy. Second, although we have proved stability over a few months, we need to verify stability and compatibility over a year and under varied storage conditions. Chitosan may exhibit long-term stability issues due to its pH-dependent solubility and susceptibility to microbial contamination. Future goods must ensure strong preservation (CHX is antimicrobial, but additional preservatives may be required for a wide range of safety). Chitosan gel's acidic pH may induce pain or alter taste, reducing its attractiveness. This research does not assess patient-centric factors such as taste, comfort, and usefulness, which drive adoption. However, the formulator conducted an informal self-assessment of taste and odor to provide a preliminary impression of acceptability. Since this was not a structured human study, no ethical approval was required. Planktonic cultures were used for antibacterial studies because oral infections may form biofilms with increased resistance. Check the sustained-release gel's performance with biofilm-embedded bacteria. Finally, we did not test combination or optimized formulations (e.g., polymer ratios, solubility-enhancing chitosan derivatives, cross-linkers, flavoring). Options for improving the gel in the future.

This research reveals that polymer-based mucoadhesive gels can significantly enhance oral chlorhexidine delivery despite these constraints. Chitosan and HPMC may be therapeutically useful chemicals. The HPMC gel's simplicity and stability, and the chitosan gel's increased adhesion and prolonged activity, address the fundamental oral medication-delivery issue: short residence time. This comparative analysis verifies existing research on polymer-based oral delivery devices and identifies trade-offs. HPMC gels release quickly and are easy to make, whereas chitosan gels release more slowly and retain more. These findings may improve formulations (perhaps hybrid systems) and be employed in medicine. Oral topical mucoadhesive gels for gingivitis, periodontitis, and mucosal infections may improve patient compliance and effectiveness. This study's favorable findings support the in vivo efficacy and industrial translation of mucoadhesive CHX gel technology.

4. Conclusion

This work demonstrated that both HPMC and chitosan are suitable polymers for the formulation of stable, efficient mucoadhesive CHX 0.2% gels. The HPMC-based gel exhibited excellent spreadability and rapid drug release, whereas the chitosan-based formulation demonstrated enhanced mucoadhesion and sustained release, thereby improving its suitability for prolonged oral use. These results underscore the significance of polymer selection in enhancing drug retention, release kinetics, and therapeutic efficacy. Upon further in vivo validation, such polymer-based gels may provide a viable alternative to traditional CHX mouthwashes, enhancing treatment effectiveness and patient adherence in oral healthcare.

Abbreviations

- **CHX** – Chlorhexidine
- **HPMC** – Hydroxypropyl Methylcellulose
- PG – Propylene Glycol
- BHA – Butylated Hydroxyanisole
- **UV-Vis** – Ultraviolet-Visible Spectrophotometry
- **pH** – Potential of Hydrogen
- **rpm** – Revolutions Per Minute
- **SD** – Standard Deviation

- **ANOVA** – Analysis of Variance
- **SEM** – Standard Error of the Mean
- **K** – Release Rate Constant
- **PBS** – Phosphate Buffered Saline

Ethics approval and consent to participate

This study did not involve any human participants or animal subjects. Therefore, ethical approval and informed consent were not required.

Acknowledgment

Not applicable.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors Contributions

Study conception and design: Mahdi Ahmadinia, Zahra Jafariazar, Mostafa Saffari Formulation and experimental work: Pooria Salsabilian, Mahdi Ahmadinia Data analysis and interpretation: Mahdi Ahmadinia, Zahra Jafariazar Drafting and revising the manuscript: Mahdi Ahmadinia, Mostafa Saffari Final approval of the manuscript: Pooria Salsabilian, Mahdi Ahmadinia, Zahra Jafariazar, Mostafa Saffari.

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Using artificial intelligence chatbots

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