Original Research Article

Development and Assessment of Bio-adhesive Formulations Containing Chlorhexidine Gluconate

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ABSTRACT

This study focuses on the development and optimization of a mucoadhesive buccal film incorporating chlorhexidine gluconate to enhance oral health outcomes. Recognizing the limitations of conventional oral drug delivery systems, this research explores mucosal drug delivery as an alternative, ensuring localized and sustained antimicrobial activity. The work includes an in-depth analysis of mucoadhesive mechanisms, pharmaceutical formulation strategies, and key evaluation parameters. The experimental framework assesses film properties, covering aspects such as swelling index, drug content, antimicrobial activity, and surface morphology using scanning electron microscopy. This study aims to contribute to effective oral healthcare solutions, emphasizing bio-adhesive drug delivery for improved therapeutic benefits.

Introduction

Oral afflictions, such as gingivitis, periodontitis, and oral ulcers, are widely prevalent and can significantly impact a patient's quality of life. Conventional oral medications often have systemic side effects and may fail to provide adequate localized drug concentration at the site of infection. To overcome these limitations, localized drug delivery systems have gained increasing attention in recent years [1-2,59].

Chlorhexidine gluconate is a widely used antimicrobial agent known for its effectiveness against bacteria, fungi, and viruses. It plays a crucial role in oral care by aiding in prevention and treatment of conditions such as gingivitis, mouth sores, and plaque buildup. Additionally, its antiseptic properties make it valuable for disinfecting the skin before surgical procedures. Available in multiple forms such as mouthwash, toothpaste, gels, soaps, and solutions,

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Chlorhexidine gluconate is a versatile option for maintaining hygiene and preventing infections. [3-4,59].

Mucoadhesive Dosage Forms in Drug Delivery

Mucoadhesive dosage forms are designed to adhere to mucosal surfaces in the body, including the oral cavity, gastrointestinal tract, and nasal passages. These formulations employ polymers with mucoadhesive properties, enabling prolonged retention at the site of action and controlled drug release [5-6]. The primary goal of mucoadhesive drug delivery is to extend the residence time of the dosage form at the targeted site, enhancing therapeutic efficacy and improving patient compliance [7-8].

Chlorhexidine's Mechanism of Action

Chlorhexidine exhibits robust antimicrobial properties, effectively targeting pathogenic bacteria, fungi, and select viruses. Its mechanism of action involves disrupting microbial cell membranes, leading to structural degradation and cell death. Due to its high efficacy at low concentrations, chlorhexidine remains an essential component in various clinical applications, including oral healthcare and antiseptic formulations [9-10].

Objective of the Study

The primary objective of this study is to develop and optimize a mucoadhesive buccal film loaded with chlorhexidine, ensuring enhanced antimicrobial efficacy while minimizing potential irritancy and toxicity. The results can contribute significantly to advancing drug delivery strategies for patients requiring prolonged antimicrobial therapy, particularly in oral, nasal, or gastrointestinal applications [11-12,59].

Introduction of Mucosal Buccal Film

Mucosal buccal films have revolutionized drug delivery by enabling targeted and prolonged release of therapeutic agents within the oral cavity. Utilizing mucoadhesive polymers, these films securely adhere to the buccal mucosa, facilitating efficient drug absorption while significantly reducing systemic exposure and associated side effects [13-14].

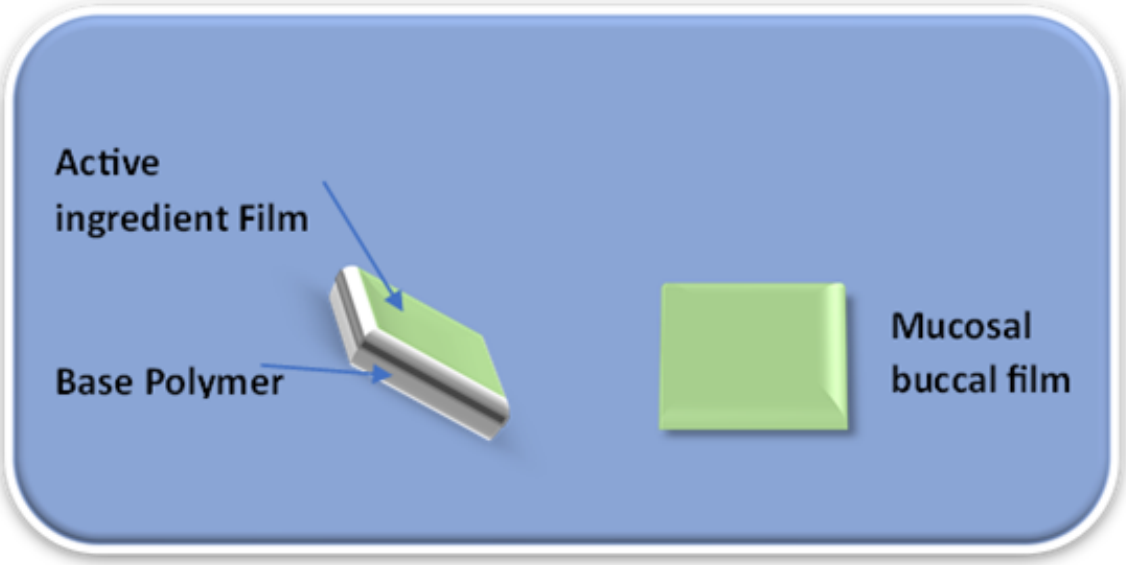


Figure 1: Structure of mucosal buccal film

Mucoadhesive buccal films offer optimized drug delivery, combining high bioavailability with reduced systemic toxicity, making them a promising alternative to conventional oral formulations. Their targeted approach, leveraging the oral cavity's vascularization and accessibility, enhances therapeutic efficacy while improving patient compliance. By

prolonging drug residence time at the application site, these films maximize localized treatment and ensure controlled systemic absorption, creating a more effective and user-friendly dosage form [15-16,59].

Mucoadhesive Drug Delivery Systems

A mucoadhesive dosage form is a specialized drug delivery system designed to adhere to mucosal surfaces within the body, such as the oral cavity, nasal passages, and gastrointestinal tract [17]. The primary objective of these formulations is to extend the drug's residence time at the site of application or absorption, thereby enhancing therapeutic efficacy [18-19]. Mucoadhesive dosage forms are available in different formulations, such as tablets, patches, gels, and solutions. These systems rely on bioadhesive polymers that interact with the mucus layer, ensuring prolonged drug retention at the absorption site for the optimized bioavailability and sustained drug release [20,59].

Mechanism of Mucoadhesive Dosage Form

The mucoadhesion process involves multiple sequential stages to ensure that the dosage form adheres effectively to the mucosal membrane, thereby facilitating prolonged drug retention at the application site. The mechanism can be categorized into the following steps:

Step 1: Wetting and Swelling (Contact Stage)

Upon administration, the mucoadhesive polymer begins to spread and hydrate over the mucosal surface, establishing intimate contact. The polymer components exhibit a high affinity for water, leading to swelling and activation of functional groups responsible for adhesion [21-22,59].

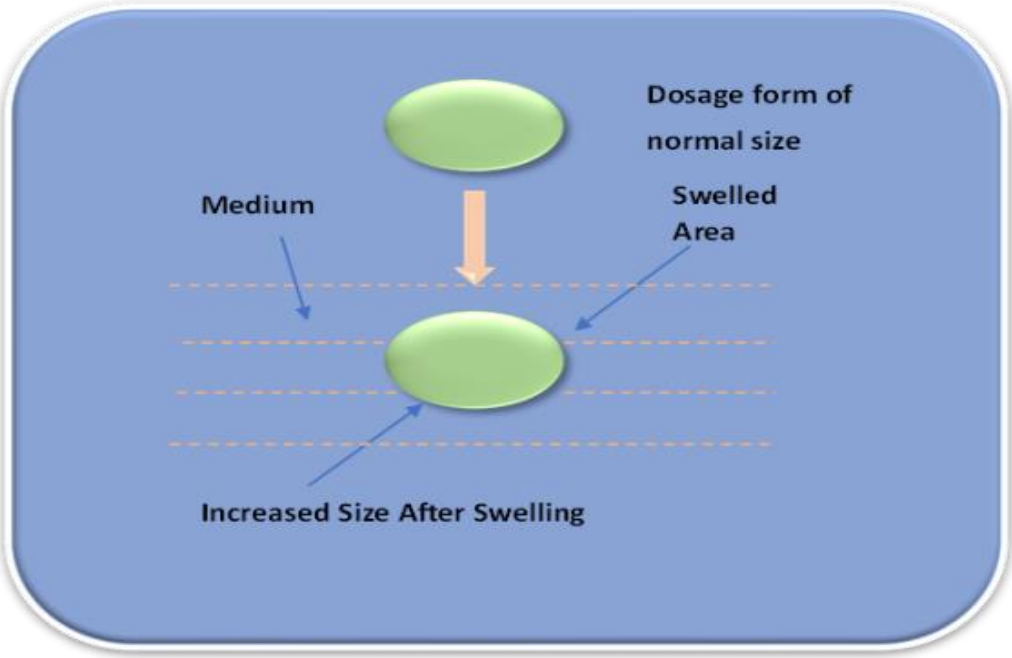


Figure 2: Swelling process of a dosage form

Step 2: Polymer-Mucin Interpenetration (Consolidation Stage)

During this stage, mucoadhesive polymer chains interact with mucin glycoproteins, leading to intermingling and entanglement, ultimately forming adhesive bonds. The complex adhesion process occurs as polymer chains penetrate the mucus layer, establishing strong connections with the mucosal surface.

Key Mechanisms Contributing to Mucoadhesion

Hydrogen Bonding: Interaction between hydroxyl (-OH), carboxyl (-COOH), and amine (-NH2) groups of the polymer and mucin.
Ionic Interaction: Electrostatic attraction between charged mucin components and polyelectrolyte polymers.
Hydrophobic Interaction: Lipophilic segments of the polymer interact with non-polar mucin domains, strengthening adhesion.
These interactions reinforce mucoadhesion, ensuring prolonged drug retention at the targeted mucosal site and enabling controlled drug release for optimal therapeutic efficacy [23,59].

Step 3: Formation of bond between the entangled chains (Final Consolidation Stage)

Primary Bonds: Covalent bonds-stronger, but rare in pharmaceutical mucoadhesion.
Secondary Interactions: Van der Waals forces-weak but contribute to polymer adhesion, hydrogen bonding-formed between hydrophilic functional groups in the polymer and mucin, along with London dispersion forces-temporary interactions supporting adhesion.
Physical Entanglement: The interwoven polymer-mucin network enhances film stability.
These interactions stabilize the mucoadhesive complex, ensuring effective drug release and prolonged therapeutic action at the target site [24-26].

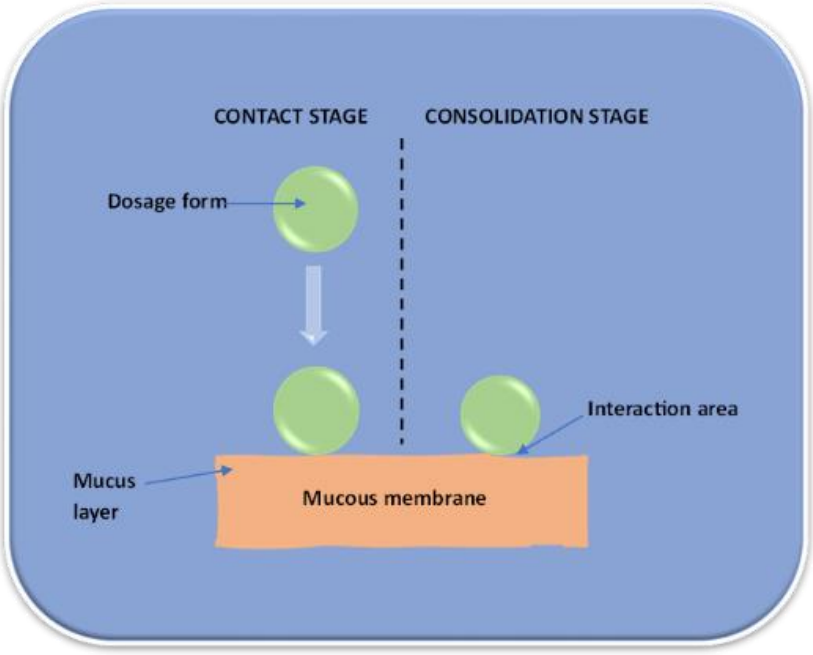


Figure 3: Hydration and expansion of a buccal film

Mucoadhesive Theories

The mechanisms governing mucoadhesion are complex and multifaceted, with several theories attempting to explain the interactions between mucoadhesive polymers and mucosal surfaces.
Wetting Theory
This theory primarily applies to liquid-based mucoadhesive systems, describing how dispersion affects the adhesion strength. Key factors include:

Contact Angle: Smaller contact angles lead to stronger adhesion due to increased contact area.
Spreadability Coefficient: Determines how effectively the liquid spreads over the mucosal surface.
Work of Adhesion: Depends on the surface energies of both the liquid and the mucosal layer, as well as their interfacial energy [27].

Higher Surface Energy: Greater adhesive strength at the interface occurs when individual surface energies are high [28-29].

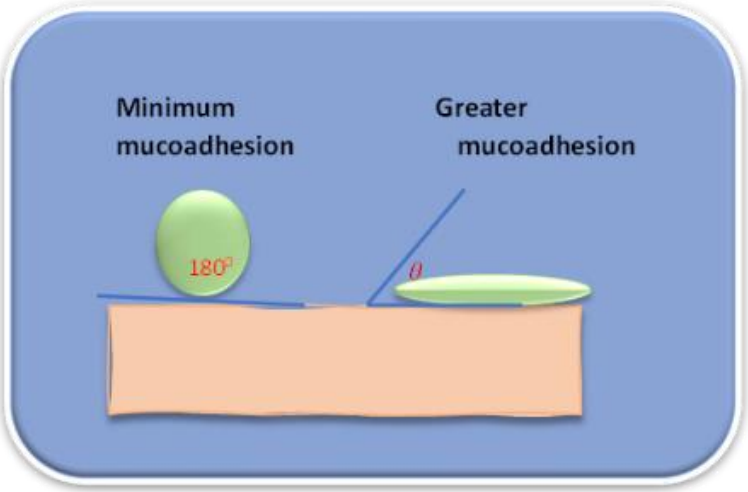


Figure 4: Wetting theory and polymer swelling dynamics

Diffusion Theory

The depth of penetration of mucoadhesive polymers into the mucus layer depends on polymer diffusion coefficient, mucin chain flexibility and mobility, polymer-mucus contact time, mutual solubility, and chemical structure compatibility facilitate polymer diffusion across the interface, strengthening adhesion [30-31,59].

Fracture Theory

Adhesive strength is linked to the force required for detaching two surfaces.
It does not involve polymer interpenetration but measures how much energy is needed to break the bond.
It is primarily applicable for rigid or semi-rigid bioadhesive materials like films and tablets [34,40].

Electronic Theory

Mucoadhesive materials and mucosal membranes carry surface charges.
When these charged surfaces interact, the electron transfer creates an electrical double layer at the interface. This electrostatic attraction contributes to mucoadhesive strength [41].

Adsorption Theory

Mucoadhesion occurs through intermolecular forces, including hydrogen bonding, van der Waals interactions, and hydrophobic interactions, while each interaction is individually weak, their combined effect results in a strong adhesive bond, ensuring prolonged drug retention [42].

Applications of Mucoadhesive Dosage Forms

Mucoadhesive dosage forms provide targeted and sustained drug delivery, making them valuable across various therapeutic applications. They improve drug retention, bioavailability, and patient compliance, especially in conditions requiring localized treatment or systemic absorption.

Oral Health Applications

Treatment of Oral Infections: Used for managing gingivitis, periodontitis, and oral candidiasis.
Pain Management: Provides localized relief for oral ulcers, canker sores, and dental procedures.
Dental Caries Prevention: Enables fluoride

delivery and other anti-caries treatments for improved dental health [43].

Systemic Drug Delivery Applications

Hormone Replacement Therapy: Buccal films assist in delivering estrogen, progesterone, and testosterone.
Antihypertensive Medications: Used in managing high blood pressure, ensuring controlled drug release.
Antiviral Treatments: Helps in targeted drug delivery for HIV and herpes simplex virus infections [44].

Other Pharmaceutical Applications

Nicotine Replacement Therapy: Supports smoking cessation by delivering controlled doses of nicotine.
Bioavailability Enhancement: Improves absorption rates for drugs with poor solubility.
Local Anaesthesia: Facilitates pain relief during dental procedures or minor surgeries [44-45].

Advantages of Buccal Film Mucosal Dosage

Mucoadhesive drug delivery systems provide several key benefits compared to conventional dosage forms, making them highly effective for localized and systemic therapies.
Targeted Drug Delivery
Ensures direct drug application to specific tissues or organs, reducing systemic exposure. It minimizes side effects by limiting drug distribution to non-target areas.

Expedited Absorption

Immediate contact with mucosal surfaces allows rapid drug uptake facilitates fast onset of action, making it effective for pain management and infections.

Bypassing Hepatic Metabolism

It avoids first-pass metabolism in the liver, enhancing bioavailability, and ensures higher drug concentrations reach the systemic circulation.

Enhanced Patient Compliance

It is convenient, painless administration, ideal for patients with swallowing difficulties, and discreet dosage form and improves the acceptance for long-term therapies.

Optimized Bioavailability

Certain drugs exhibit better absorption via mucosal membranes compared to oral tablets, and improve effectiveness of drugs with poor solubility or limited permeability.

Reduced Systemic Side Effects

Targeted local delivery decreases unwanted effects on non-target organs and ensures safer administration for sensitive populations.

Suitable for Drugs with Poor Oral Bioavailability

Mucoadhesive systems enhance absorption for low-permeability drugs and improve therapeutic effectiveness.

Ideal for Sustained-Release Formulations

Enables gradual drug release prolongs therapeutic effects over extended durations and steady drug levels improve efficacy while minimizing dose fluctuations.

Challenges in Mucosal Drug Delivery Systems

Developing mucoadhesive dosage forms presents several challenges across formulation, physiological factors, manufacturing, regulatory compliance, and patient usability. Formulation complexities arise in selecting appropriate mucoadhesive polymers for optimal adhesion, ensuring drug stability in mucosal environments, and controlling release kinetics for sustained therapeutic efficacy. Additionally, enhancing bioavailability is crucial to overcome absorption barriers and maximize drug effectiveness. Physiological factors further contribute to the complexity, as variations in mucosal thickness, pH levels, and enzyme activity affect adhesion, and drug retention. Moreover, mucociliary clearance and enzymatic

degradation pose hurdles, affecting the consistency of drug delivery. On the manufacturing side, scaling up production while maintaining sterility and stability is a significant challenge, requiring robust quality control methods to ensure uniformity. Regulatory challenges further complicate the process, as navigating complex approval frameworks involves compliance with clinical trials and securing intellectual property rights. Lastly, patient-centric considerations play a crucial role in successful mucoadhesive dosage forms. Ensuring convenient dosing, minimizing irritation, and aligning the formulation with patient preferences are essential for improving adherence and therapeutic outcomes. Addressing these challenges is critical for optimizing mucoadhesive drug delivery systems for practical and clinical applications.

Future Prospects and Development, Advancements in Mucosal Dosage Forms

The future of mucosal drug delivery systems is poised for remarkable advancements, driven by cutting-edge research, technological innovation, and evolving healthcare demands.

Short-Term Developments

In recent years, the development of advanced mucoadhesive polymers has been significantly progressed, which improves bioavailability and adhesion properties. The controlled release systems and nanoparticle-based drug delivery mechanisms will further enhance therapeutic efficacy. Additionally, 3D printing technology plays a crucial role in formulating customized mucosal dosage forms, enabling complex geometries and precise drug-loading capacities [46-48].

Innovations by 2030

By 2030, biological therapies, personalized medicine, and digital health integration will reshape the field of mucosal drug delivery. Biologics, vaccines, and gene therapies administered via mucosal routes will gain traction due to their non-invasive nature and targeted delivery capabilities [41,47,49]. Moreover, microbiome-targeted therapies will emerge as a revolutionary approach, addressing the interplay between the human microbiome and disease mechanisms [50-51].

Long-Term Vision

Looking further ahead, stem cell-based therapies, RNA-based drugs, and synthetic biology will transform drug design and administration, providing highly personalized and regenerative treatments. Point-of-care manufacturing will facilitate on-demand production of tailored mucosal dosage forms, making treatment more accessible and individualized.

Industry Impact and Market Growth

Pharmaceutical companies, biotechnology firms, research institutions, and regulatory agencies will continue to drive innovation and commercialization in this sector. The market for mucosal drug delivery is expected to expand, fuelled by growing demand, increased investment in R&D, and expanding applications across various therapeutic areas [52].

Comparative Discussion of Bioadhesive Drug Delivery System,

Buccal drug delivery systems have gained significant attention due to their ability to bypass first-pass metabolism and provide localized treatment. Among these, mucoadhesive buccal films offer distinct advantages over other bioadhesive formulations. Mucoadhesive patches and oral disintegrating films are two widely studied buccal drug delivery systems. Mucoadhesive patches adhere to the buccal mucosa, ensuring sustained drug release over an extended period, while oral disintegrating films dissolve rapidly upon contact with saliva, providing immediate drug action. The selection between these systems depends on therapeutic goals, drug properties, and patient compliance. Research comparing these approaches suggests that mucoadhesive patches are preferable for drugs requiring prolonged exposure, whereas oral

disintegrating films are more proper for formulations designed for rapid relief.

Bioadhesive and floating drug delivery systems serve different purposes in pharmaceutical applications. Bioadhesive systems ensure localized drug delivery, improving retention at the site of action, while floating systems prolong gastric retention, making them ideal for drugs that require extended absorption in the stomach. Buccal films benefit from bioadhesion, ensuring direct drug absorption through the mucosa without first-pass metabolism. Studies have shown that bioadhesive systems are more effective for oral cavity treatments, while floating systems are better suited for gastrointestinal drug delivery.

The polymers selection plays a crucial role in the performance of bioadhesive formulations, influencing adhesion strength, drug release, and patient compliance. Hydroxypropyl methylcellulose (HPMC) enhances mucoadhesion and controlled drug release, while polyvinyl alcohol (PVA) improves film flexibility and drug stability. Additionally, polymers such as Carbopol and chitosan increase bioadhesive strength, ensuring prolonged contact with the buccal mucosa. Research suggests that polymer selection significantly affects drug retention, release kinetics, and patient comfort, making it a critical factor in the development of effective buccal drug delivery systems.

Drug-Polymer Interactions

Chlorhexidine gluconate is a widely utilized antimicrobial agent, and its interaction with different polymers plays a crucial role in determining the effectiveness of bioadhesive formulations. The polymers selection impacts adhesion strength, drug release kinetics, and overall stability of the dosage form.

Interaction of Chlorhexidine Gluconate with Polymers

Chlorhexidine gluconate possesses cationic properties, which influence its compatibility with different polymers. Research suggests that anionic polymers may reduce its antibacterial activity due to ionic interactions, potentially leading to precipitation or diminished drug efficacy. On the other hand, neutral or cationic polymers tend to enhance its stability and bioavailability. For instance, polyvinyl alcohol (PVA) and hydroxypropyl methylcellulose (HPMC) have been found to improve mucoadhesion and controlled drug release, ensuring prolonged contact with the buccal mucosa. Additionally, studies reveal that carbopol-based formulations may exhibit incompatibility with chlorhexidine due to ionic interactions, affecting its antimicrobial potency.

Mucoadhesive Properties of Key Polymers

Hydroxypropyl methylcellulose (HPMC): Enhances mucoadhesion, allowing sustained drug release and improved retention at the application site.

Polyvinyl alcohol (PVA): Provides film flexibility and stability, ensuring uniform drug distribution.

Hydroxyethyl cellulose (HEC): Improves hydration and swelling properties, optimizing drug release over time.

Chitosan: A natural polymer with excellent bioadhesive properties, promoting prolonged drug contact with mucosal tissues.

Carbopol: Frequently used in bioadhesive formulations but may interact with chlorhexidine, potentially reducing its antimicrobial effectiveness.

Scanning Electron Microscopy (SEM) Analysis

SEM imaging is a valuable tool for evaluating polymer-drug interactions at a microscopic level. Studies have used SEM to analyse the surface morphology of chlorhexidine-loaded bioadhesive films, revealing insights into drug dispersion, polymer network formation, and adhesion strength. These images help confirm the uniformity of drug distribution and the effectiveness of the polymer matrix in sustaining drug release. Additionally, SEM analysis can provide information on film porosity, swelling behaviour, and degradation patterns, which are critical for optimizing bioadhesive formulations.

Additional Considerations for Formulation Optimization

pH Effect: The pH of the formulation can significantly impact chlorhexidine stability and solubility. Maintaining an optimal pH range ensures maximum antimicrobial activity.
Moisture Content: Controlling moisture levels in bioadhesive films is essential for drug stability and adhesion properties.
Drug Release Mechanism: The interaction between chlorhexidine and polymers affects diffusion-controlled or swelling-controlled drug release, influencing therapeutic efficacy.
Compatibility with Other Excipients: Ensuring that additional excipients, such as plasticizers and stabilizers, do not interfere with antimicrobial action of chlorhexidine is crucial for formulation success.

Chlorhexidine Gluconate: A Key Antimicrobial for Infection Control

Chlorhexidine is a potential antimicrobial agent widely utilized in healthcare and personal care applications due to its effectiveness against a broad spectrum of microorganisms, including bacteria, fungi, and certain viruses. Its versatility allows for incorporation into oral hygiene products such as mouthwashes and toothpastes, surgical scrubs and skin cleansers for pre- and post-operative care, as well as wound care formulations and medical equipment disinfectants. The mechanism behind its antimicrobial action involves disrupting microbial cell membranes, leading to cell damage and microbial death, which ensures rapid onset of action, sustained antimicrobial activity, and relatively low toxicity. However, certain limitations exist—soap can inactivate chlorhexidine, reducing its efficacy, while high concentrations may produce an unpleasant taste and potential surface staining, particularly on teeth and fabrics. Despite these considerations, chlorhexidine remains a cornerstone in infection prevention and control, contributing significantly to healthcare-associated microbial management [2,6,44,51].



Figure 5: Effect on mucoadhesion and drug administration

Benefits and Applications of Chlorhexidine Gluconate

Chlorhexidine is a highly effective antimicrobial agent widely used in healthcare and personal hygiene due to its broad-spectrum activity and low toxicity. Its primary applications include:
Oral Hygiene: Incorporated into mouthwashes and toothpastes for preventing gingivitis, periodontitis, and oral infections.
Surgical and Skin Cleansing: Used in pre- and post-operative scrubs to reduce the risk of infections.
Wound Care: Essential in antiseptic solutions for treating skin injuries and preventing bacterial contamination.
Medical Equipment Disinfection: Ensures sterility in hospital environments by disinfecting surgical tools and medical instruments.

Despite its advantages, chlorhexidine has limitations, such as potential inactivation by soap, unpleasant taste at high concentrations, and risk of surface staining. However, with proper use and awareness, its benefits can be fully optimized to ensure continued effectiveness in various healthcare and hygiene applications [23,54].

Applications of Mucoadhesive Drug Delivery in Oral Health

Mucoadhesive dosage forms play a critical role in oral healthcare, providing targeted drug delivery and prolonged therapeutic effects. They are widely used for managing various oral conditions, improving patient compliance and treatment outcomes.

Oral Mucositis: Used in chemotherapy and radiation therapy to reduce inflammation and discomfort in mucosal tissues.

Aphthous Ulcers (Canker Sores): Facilitates localized pain relief and accelerated healing.

Gingivitis and Periodontitis: Delivers antimicrobial agents for controlling bacterial infections and gum inflammation.

Halitosis (Bad Breath): Helps in neutralizing odour-causing bacteria, improving oral hygiene.

Oral Lichen Planus: Provides anti-inflammatory treatment, aiding in symptom management.

Dental Implant Maintenance: Supports infection control and healing post-impact placement.

Pharmacokinetics of Chlorhexidine Gluconate

Chlorhexidine gluconate exhibits distinct pharmacokinetic properties, as it is primarily intended for topical application with limited systemic absorption. Its behaviour within the body is governed by four key phases, such as absorption, distribution, metabolism, and excretion, each playing a crucial role in determining its therapeutic effectiveness and potential interactions.

Absorption

Topical Application

Chlorhexidine is primarily absorbed through the skin and mucosal surfaces, such as the oral cavity, wounds, and skin. The rate and extent of absorption depend on several factors, as follow:

Formulation Type: Gels, mouth rinses, creams, or solutions may exhibit different absorption rates.

Concentration: Higher concentrations can prolong contact time with tissues, affecting absorption efficiency.

Application Site: The mucosal lining (such as the buccal or nasal mucosa) generally allows faster absorption compared to intact skin.

Swallowing & Gastrointestinal Absorption

When accidentally ingested, chlorhexidine undergoes limited gastrointestinal absorption due to its high molecular weight and polarity, which prevents efficient transport across intestinal walls. Studies indicate that the majority of the orally ingested drug is excreted unchanged via feces, reflecting minimal systemic bioavailability.

Distribution

Systemic Distribution

Once absorbed, chlorhexidine exhibits restricted distribution, remaining primarily in local tissues at the application site. It is found in saliva, mucosal surfaces, and blood in minimal concentrations, with negligible penetration into vital organs like the liver and kidneys.

Tissue Accumulation and Prolonged Activity

Chlorhexidine can bind to proteins within tissues, resulting in gradual release over time. It particularly accumulates in keratinized tissues such as skin—leading to extended antimicrobial action even after initial application; hair and nails—providing a reservoir effect for sustained protection; as well as oral mucosa and dental plaque—enhancing its efficacy against oral pathogens through prolonged contact.

Metabolism

Chlorhexidine undergoes minimal metabolism within the body. Unlike many drugs that require hepatic enzymatic modifications, chlorhexidine

remains largely unchanged post-absorption. This characteristic contributes to its long-lasting antimicrobial activity, as metabolism does not rapidly degrade the drug.

Excretion

Renal Elimination

A small fraction of absorbed chlorhexidine is excreted via the kidneys in urine, but due to its limited systemic absorption, renal clearance is not a major pathway of elimination.

Fecal Excretion

The primary route of elimination for orally ingested chlorhexidine is through feces. Since intestinal absorption is low, most of the drug is directly excreted without undergoing metabolic processing, preventing systemic accumulation [48,50,59].

Clinical Implications and Summary

Localized Drug Action: Chlorhexidine works at the application site, avoiding unnecessary systemic exposure.
Prolonged Effect: Due to tissue binding, its antimicrobial efficacy extends beyond initial application.
Minimal Metabolism: Being chemically stable, chlorhexidine does not require enzymatic breakdown for elimination.
Fecal Excretion Dominates: After oral ingestion, it is largely excreted unchanged in feces, limiting systemic distribution.

Factors Affecting Pharmacology

The chlorhexidine pharmacokinetics is affected by multiple factors, impacting its absorption, distribution, and interaction potential. Since systemic absorption is minimal, understanding these factors is crucial to optimizing therapeutic efficacy while minimizing risks.

Formulation Type

The dosage form plays a significant role in determining absorption and distribution: Mouthwash & Oral Rinses—Primarily localized action with minimal systemic absorption. Gel-Based Formulations—Prolonged mucosal contact leads to sustained release. Buccal Films & Patches—Enable controlled drug delivery, enhancing bioavailability.

Application Site

Oral Mucosa: High vascularization allows efficient local absorption.
Skin and Wounds: Absorption depends on skin permeability and tissue integrity. Gastrointestinal *Tract (if swallowed)*: Limited intestinal absorption, most is excreted unchanged.

Concentration Influence

Higher concentrations may increase absorption but could also heighten taste intensity and staining risks. Low-concentration formulations provide gentler antimicrobial action with reduced adverse effects.

Co-Administration Effects

Interaction with other drugs or substances can modify its pharmacokinetics.
Soap and Anionic Surfactants: Inactivate chlorhexidine, reducing efficacy. Alcohol-Based *Solutions*: May enhance penetration but alter stability.
Chlorhexidine mainly functions at its site of application, with minimal systemic effects. However, repeated or high-dose use necessitates careful monitoring for potential interactions and tissue accumulation.

Materials and Methods

Active Ingredient: Chlorhexidine Gluconate
Polymers: Hydroxypropyl Methylcellulose (HPMC), Polyvinyl Alcohol (PVA), and Polyvinyl Pyrrolidone K30 (PVP K30)
Plasticizer: Propylene Glycol
Solvents: Ethanol, Distilled Water
Others: Benzalkonium chloride

Equipment Needed

- Beakers (various size)
- pH meter
- Viscometer
- Stirrer
- UV-Vis spectrophotometer
- Analytical balance
- Micropipettes
- Hot plate
- Petri plates
- Diffusion Cell Apparatus
- Aluminum foil
- Magnetic stirrer

Formulation of Buccal Film

Preparation of polymer solution

Heat a specific volume of distilled water and gradually add polyvinyl alcohol (PVA) in concentrations of 3% and 2% (w/v) while stirring continuously until fully dissolved.
Add polyvinyl pyrrolidone k30 (PVP K30) in concentration of 1.2% and 0.8% (w/v) to the PVA solution while stirring.

Incorporation of solvent

Once the polymer solution in homogeneous, add 10 mL of ethanol and stir until well mixed.
Introduce hydroxypropyl methylcellulose (HPMC) at ambient temperature while stirring to obtain a clear solution.

Addition of Plasticizer and Preservative

Add 3 mL of propylene glycol as the plasticizer and 0.01 mL of benzalkonium chloride as the preservative to the polymer solution, ensuring uniform distribution.

Drug Loading

Gradually add 702 mg of chlorhexidine gluconate to the solution drop-wise while stirring continuously. The final concentration of the drug in the film will be 10.8 mg per square cm.

Film Casting

Pour the drug loaded solution into a petri plate and allow it to dry completely at ambient temperature overnight.
After initial drying, place the Petri dish in an oven at 40 ^{o}C for further drying until the film is fully set.

Film Removal and Cutting

Carefully remove the dried film the petri plate using a sterile cutter, cut circular film with a diameter of 1 cm.

Table 1: Formulation table of buccal film for various G series and batches

Pharmacopeial Name	G1			G2		
	F1	F2	F3	F4	F5	F6
Chlorhexidine gluconate	792.06 mg	792.06 mg	792.06 mg	792.06 mg	792.06 mg	792.06 mg
Polyvinyl alcohol	900 mg	600 mg	300 mg	800 mg	500 mg	700 mg
Polyvinyl pyrrolidone (K 30)	360 mg	240 mg	120 mg	320 mg	200 mg	280 mg
Hydroxypropyl methyl cellulose	540 mg	300 mg	200 mg	400 mg	250 mg	350 mg
Benzalkonium chloride	0.01 ml	0.01 ml	0.01 ml	0.01ml	0.01ml	0.01ml
Ethanol	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml
Propylene glycol	3 ml	3 ml	3 ml	3 ml	3 ml	3 ml
Water	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Quantity of Gel	30 ml	30 ml	30 ml	30 ml	30 ml	30 ml

Experimental Design for Bio-Adhesive Buccal Films of Chlorhexidine

The development of bio-adhesive buccal films incorporating chlorhexidine gluconate followed

a systematic approach to optimize formulation parameters and ensure therapeutic efficacy.

Polymer Selection and Formulation Strategy

Initially, various mucoadhesive polymers were selected based on their ability to enhance adhesion and drug retention: Polyvinyl Alcohol (PVA) – provides film-forming properties and structural integrity. Polyvinyl Pyrrolidone K30 (PVP K30) – enhances drug solubility and stabilization. Hydroxypropyl Methylcellulose (HPMC) – improves mucoadhesion and controlled drug release.

The films were prepared using a solvent-casting technique, where the chosen polymers were dissolved in a proper solvent mixture, and chlorhexidine was incorporated to achieve the desired drug concentration and uniform distribution.

Optimization of Film Properties

Multiple formulations were created, varying the proportions of polymers and plasticizers such as propylene glycol, which enhanced film flexibility and adhesion. To ensure the films met the necessary pharmaceutical standards, key parameters were evaluated, including weight uniformity – ensuring consistent drug content across all samples; thickness measurement – maintaining structural integrity for effective muco-adhesion; surface pH analysis – preventing mucosal irritation and maintaining biocompatibility; swelling index – measuring water uptake and polymer expansion for optimal adhesion; and folding endurance – assessing film flexibility to prevent breakage upon application.

This comprehensive experimental framework ensured that the mucoadhesive buccal films met essential criteria for sustained drug delivery, optimizing therapeutic efficacy and patient compliance.

Evaluation of Buccal Film Properties

Weight Uniformity

To ensure consistent drug content and formulation integrity, the weight homogeneity of buccal films was assessed. An analytical balance was used to determine the average weight of multiple samples, verifying uniformity across various films.

Thickness Measurement

A computerized vernier caliper was employed to measure the film thickness at three separate locations, ensuring accuracy and reproducibility. The average thickness was then calculated and documented for quality control purposes.

Surface pH Analysis

Since the surface pH is crucial in determining mucosal compatibility, the films were hydrated in warm isotonic phosphate buffer (pH 6.8) placed in a petri dish at room temperature. The surface pH swollen of the film was assessed using pH paper, ensuring the formulation remained biocompatible and non-irritating upon application [55,57,59].

Table 1: Evaluation on pH

Formulation	pH Value
F1	6.8
F2	7.7
F3	6.68
F4	6.56
F5	7.02

F6	6.9

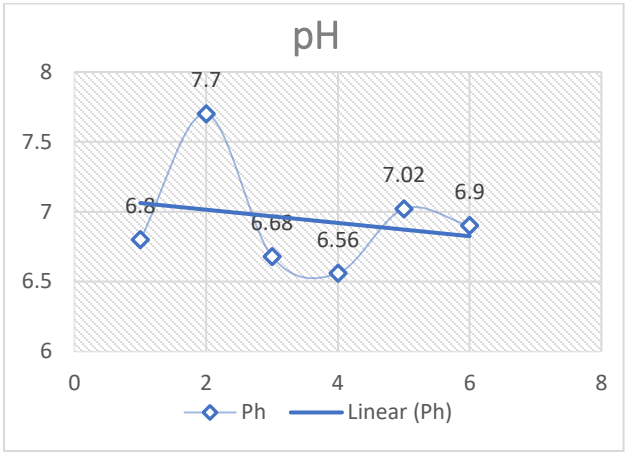


Figure 6: pH Evaluation Graph:Effect on polymer behavior and mucoadhesion

Swelling Index

The films were allowed to swell on an ager plate held at 37 °C in an incubator, with measurements taken at one-hour intervals. The % increase in swelling was calculated using the formula:

$$\textit{Percentage swelling} = \left(\frac{x_t - x_0}{x_0}\right) \times 100$$

Where,
x_t = Weight of the swollen patch after time t
x_0 = Original patch weight at zero time

Folding Endurance Test

The folding endurance test evaluates the mechanical flexibility and durability of mucoadhesive films, ensuring they maintain integrity during handling and storage. Films were physically bent up to 300 times or until they snapped at the same location. The number of successful folds before splitting was recorded, and the mean value was documented as an indicator of film strength and elasticity [51-52].

Folding endurance = $F = log_{10} d$

Where,
F = folding endurance, and
d = number of double folds

Drug Contents Uniformity

Drug content uniformity is a crucial parameter in pharmaceutical formulations, ensuring that each dosage unit contains the intended amount of active pharmaceutical ingredient (API). In the case of chlorhexidine gluconate buccal films, maintaining uniform drug distribution is essential for consistent therapeutic efficacy. The evaluation of drug content uniformity involves dissolving the drug-loaded films in phosphate buffer (pH 6.8), followed by filtration using Whatman filter paper. After appropriate dilution, the extract is analyzed using a UV-spectrophotometer at 254 nm to determine the actual drug concentration [20,53].

$$\textit{Drug Content Uniformity} = \frac{\textit{Measured Drug Content}}{\textit{Theoretical Drug Content}} \times 100$$

Where,
Theoretical drug content is based on the intended drug loading per film.
Measured drug content is obtained from spectrophotometric analysis.

Table 1: Concentration and content of drug on each buccal film

Formulation	Absorbance (254 nm)	Conc. (mg/mL)	Drug Content (%)
F1	0.686	8.6	86.0%
F2	0.702	8.8	88.2%
F3	0.673	8.4	84.0%
F4	0.581	7.3	73.6%
F5	0.641	8	80.0%
F6	0.593	7.4	74.6%

Mucoadhesion Assessment

To evaluate mucoadhesive strength, a modified assembly setup was used, ensuring controlled adhesion and detachment measurement. The experimental process involved:

Adhesion Setup: Buccal films were affixed to a microscope slide using cyanoacrylate glue for a stable attachment.

Hydration Process: The adhered films were hydrated by exposing them to phosphate buffer (pH 6.8) at 37±1 °C for 30 seconds, mimicking physiological conditions.

Detachment Force Measurement: A second slide was positioned in contact with the film, and incremental weight was applied to measure the force required for detachment.

Strength Calculation: The mucoadhesive force of the buccal films was recorded in grams, providing a quantitative measure of their adhesive efficiency [1,54,59].

$$Force\ of\ adhesion\ (N) = \frac{bioadhesive\ strengh\ (g) \times 9.8}{1000}$$

$$Bond\ strength = \frac{force\ of\ adhesion}{surfece\ area}$$

Anti-Inflammatory Activity via Protein Denaturation Inhibition

The anti-inflammatory potential of chlorhexidine gluconate was evaluated through its ability to inhibit protein denaturation, a key marker in inflammation.

Experimental Procedure

A reaction mixture was prepared using: 4.5 mL of 1% aqueous bovine serum albumin (BSA), 0.5 mL of chlorhexidine gluconate, Hydrochloric acid for pH adjustment.

The samples underwent controlled incubation and heating at 37 °C for 20 minutes—initial stabilization phase at 51 °C for another 20 minutes to induce protein denaturation.

After cooling, turbidity was measured spectrophotometrically at 660 nm, allowing calculation of the percentage inhibition of protein denaturation, which serves as a direct indicator of chlorhexidine's anti-inflammatory efficacy [55,59].

$$Percentage\ inhibition = \frac{Abs(control) - Abs(sample)}{Abs(control)} \times 100$$

Where,

Abs (control) = Absorbance of a solution without the drug/extract (water), and

Abs (sample) = Absorbance of a solution with chlorhexidine gluconate

Percentage Moisture Loss (MPL)

To assess internal moisture, the film was placed in a desiccator containing calcium chloride. After three days, the film was removed and weighed again to determine the percentage moisture loss using the following formula:

$$Percentage\ Moisture\ Loss\ (PML) = \frac{Initial\ Weight - Final\ Weight}{Initial\ Weight} \times 100$$

In Vitro Drug release study

The in vitro drug release was conducted using a franz diffusion device with phosphate buffer (pH 6.8) as the dissolving medium at 37±0.5 °C. A cellophane membrane served as the semi-permeable diffusion membrane. Mucoadhesive films of 1 cm^2 were placed on the diffusion membrane and continuously hydrated with phosphate buffer. At each hour, 1 mL of sample was removed from the receptor compartment for UV spectrophotometric analysis [1,56,59].

Table 1: Solvent and its solubility

Solvent	Solubility (mg/mL)
Ethanol	112
Distilled Water	2.56
Phosphate Buffer (6.8) to (7.8)	565

Determination of Antimicrobial Activity

The *in vitro* antimicrobial efficacy of the developed mucoadhesive buccal films was evaluated using the agar diffusion technique, a widely accepted method for assessing bacterial inhibition.

Experimental Procedure

Bacterial Suspension Preparation: A suspension of *Staphylococcus aureus* was uniformly spread over the surface of nutrient agar, ensuring even bacterial distribution.
Buccal Film Placement: The mucoadhesive films were carefully positioned on the agar surface, allowing direct interaction with bacterial colonies.
Incubation Conditions: The plates were incubated at 37 °C for 24 hours, providing the optimal conditions for bacterial growth and drug diffusion.

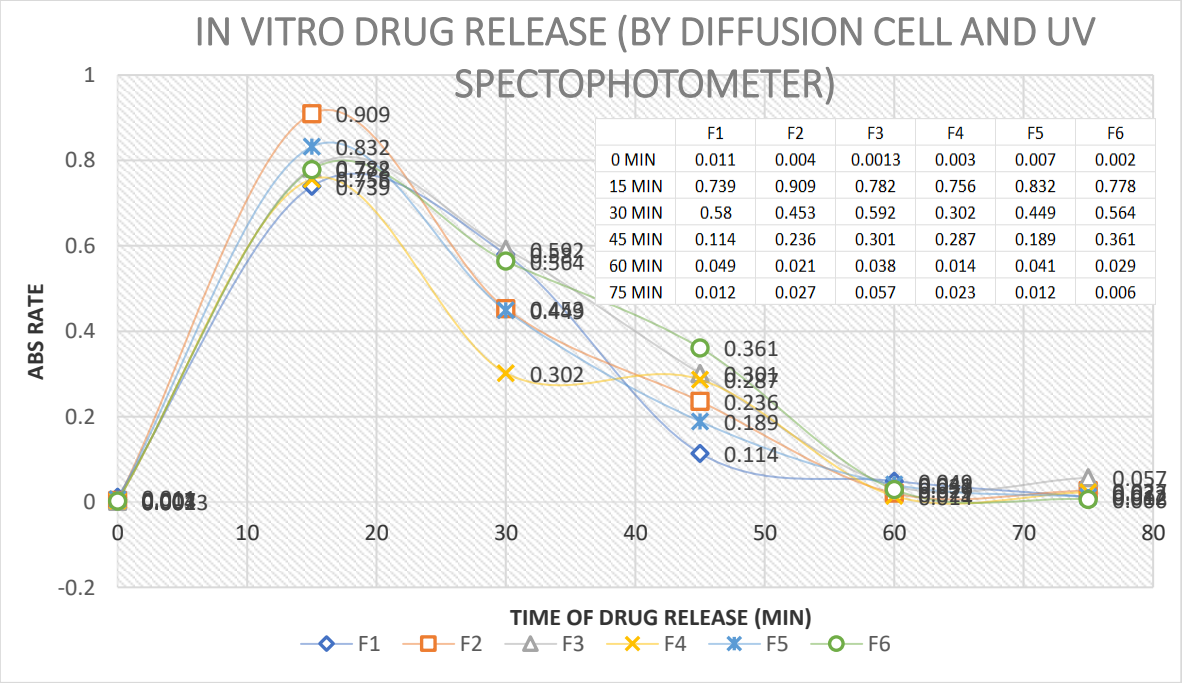
Measurement of Antimicrobial Activity

Zone of Inhibition: Following incubation, the diameters of inhibition zones around each film were measured, indicating the extent of bacterial suppression.
Quantitative Analysis: The inhibition zones served as a measure of chlorhexidine's antimicrobial potency, confirming its effectiveness in controlling bacterial proliferation [56,58].

Evaluating the antimicrobial activity of chlorhexidine gluconate in bio-adhesive buccal films is essential for assessing its effectiveness in bacterial suppression. The zone of inhibition method is commonly used for this purpose, where films containing the antimicrobial agent are placed on agar plates inoculated with *Staphylococcus aureus* (*S. aureus*). After a controlled incubation period, the diameter of the inhibition zone around each film is measured, indicating the extent of bacterial suppression. This quantitative assessment verifies the potency of chlorhexidine gluconate in limiting bacterial growth and preventing microbial colonization.

Ethical Compliance in Antimicrobial Studies

Using bacterial cultures such as *S. aureus* in laboratory testing requires compliance with ethical guidelines and biosafety standards. Researchers must obtain formal approval from an institutional review board (IRB) or an ethics committee, ensuring that the study adheres to responsible microbiological practices. Laboratories conducting antimicrobial evaluations must follow standard safety protocols, including sterile handling techniques, appropriate waste disposal, and contamination prevention measures. Additionally, the utilized bacterial strains should be acquired from certified repositories or approved clinical sources to maintain research integrity and regulatory adherence.



	F1	F2	F3	F4	F5	F6
0 MIN	0.011	0.004	0.0013	0.003	0.007	0.002
15 MIN	0.739	0.909	0.782	0.756	0.832	0.778
30 MIN	0.58	0.453	0.592	0.302	0.449	0.564
45 MIN	0.114	0.236	0.301	0.287	0.189	0.361
60 MIN	0.049	0.021	0.038	0.014	0.041	0.029
75 MIN	0.012	0.027	0.057	0.023	0.012	0.006

Figure 8: *In vitro* drug release graphical expression



Figure 7: Diffusion cell apparatus

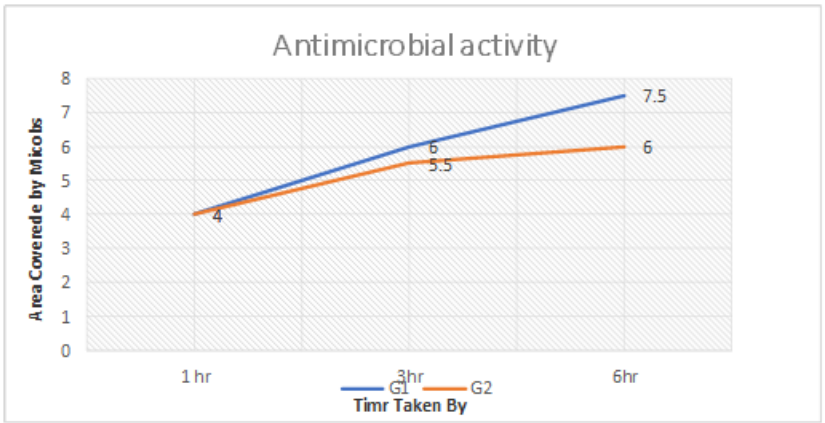


Figure 9: Graphical expression indcating antimicrobial activity

Where,
On Y axis; zone of inhibition, and
On X axis; time taken by microbes.

Microscopic Examination of Buccal Film Surface

The surface morphology and texture of the mucoadhesive buccal films were analysed using a light microscope, providing insights into film uniformity, polymer distribution, and structural integrity. The films were carefully positioned on glass slides, and observations were conducted at different magnifications to evaluate surface smoothness, particle dispersion, and any visible irregularities. This technique provided a basic qualitative assessment, serving as a preliminary step before employing advanced imaging methods for more detailed structural analysis [32,59].

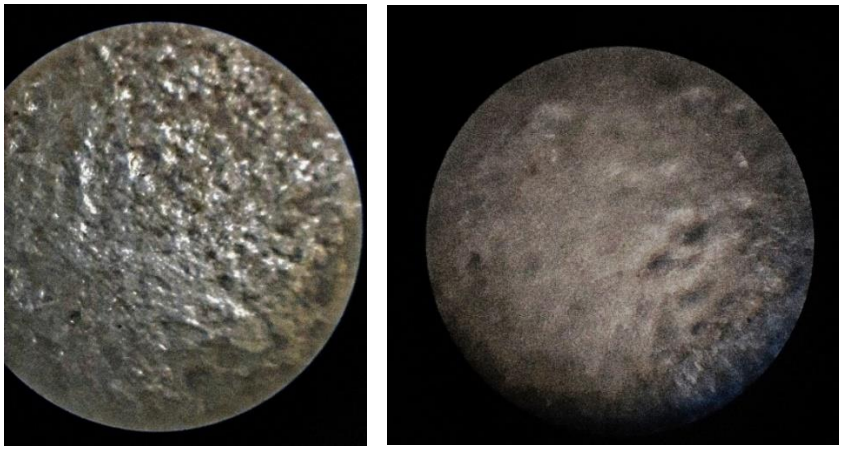


Figure 10: Microscopic scan of buccal film

Table 1: Evaluation table of chlorhexidine gluconate buccal film (between G1 and G2 batch)

Sr./ No.	Evaluation Tests	Batch Details					
		G1			G2		
		F1	F2	F3	F4	F5	F6
1	Weight (mg)	0.40	0.38	0.42	0.41	0.40	0.39
2	Thickness (mm)	0.32 ±120	0.30 ±143	0.32 ±102	0.33 ±168	0.33 ±126	0.32 ±164
3	Surface pH	6.8	7.7	6.68	6.56	7.02	6.9
4	Swelling Index (%)	90	86.84	83.33	65.85	77.5	76.92
5	Folding Index (Double Fold Per Time)	56	62	58	62	61	59
6	Dissolution Uniformity (mg/mL)	0.686	0.702	0.673	0.581	0.614	0.593
7	Mucoadhesive of Film (N)	0.117	0.068	0.137	0.107	0.117	0.096
8	Antimicrobial Activity	4	6	7.5	4	5.5	6
9	Percentage Moisture loss (PML) (%)	5	3	4.2	7	5	4.61
10	*In Vitro* Drug Release (maximum) (mg/mL)	0.739	0.909	0.782	0.756	0.832	0.778
11	Anti-inflammatory Activity (%)	8	12.2	6	27	14.6	19

Results

Based on the evaluation parameters conducted for chlorhexidine gluconate mucoadhesive buccal films, the following findings were observed across the F-series formulations (F1 to F6):

Weight uniformity remained consistent, ensuring accurate film dosage.

Thickness measurements confirmed uniformity, with minor variations among formulations.

Surface pH analysis exhibited F2 had a balanced pH (7.7), minimizing mucosal irritation.

Swelling index was highest in F1 (90%), ensuring prolonged hydration, while F2 maintained an optimal level (86.84%).

Folding endurance values ranged from 56 to 62 double folds, demonstrating good film flexibility.

Mucoadhesive strength was sufficient across all films, supporting extended contact time.

Drug content uniformity exhibited F2 had the highest drug retention (88.2%), indicating efficient incorporation into the film matrix.

In vitro drug release was highest in F2 (0.909 mg/mL), suggesting improved drug permeability.

Anti-inflammatory activity was strongest in F4 (27%), but with lower drug release efficiency.

Antimicrobial activity was most effective in F3 (7.5 mm inhibition zone), confirming bacterial inhibition properties.

Moisture loss (PML) was lowest in F2 (3%), improving stability during storage.

Discussion

Based on the evaluation parameters conducted for chlorhexidine gluconate mucoadhesive buccal films, several key findings were observed across the F-series formulations (F1 to F6):

Optimized Batch Selection

Among all formulations, F2 demonstrated the most favorable characteristics, exhibiting:

Highest drug content uniformity (88.2%)

Superior swelling index (86.84%), ensuring prolonged adhesion

Good mucoadhesive strength (0.068 N)

Balanced surface pH (7.7), minimizing mucosal irritation

The maximum *in vitro* drug release (0.909 mg/mL), confirming efficient drug delivery

Formulation Performance

Weight uniformity was maintained across all batches, ensuring consistency in film thickness.

Swelling index varied across the formulations, with F2 and F1 exhibiting better hydration properties essential for bio-adhesion.

Folding endurance values were within an acceptable range, demonstrating good film flexibility.

Mucoadhesive strength was sufficient across all films, supporting prolonged attachment.

Antimicrobial activity was strongest in F3 (7.5 mm inhibition zone), suggesting effective bacterial inhibition.

Drug Release and Stability

F2 exhibited the highest dissolution uniformity and drug release rate, supporting its role as the optimized formulation.

Moisture loss (PML) was lower in F2 (3%), indicating good stability under storage conditions.

Anti-inflammatory activity was most significant in F4 (27%), but with lower drug release efficiency.

Conclusion

The F2 formulation is the optimized batch for bio-adhesive buccal films containing chlorhexidine gluconate, as it maintains high drug content uniformity, strong mucoadhesive properties, efficient swelling behavior, and superior drug release profile. The study confirms that the selected polymer combination and solvent casting technique effectively produce stable, therapeutically viable buccal films for prolonged drug delivery.

Abbreviations

CHG: chlorhexidine gluconate; **BuF**: buccal film; **HPMC**: hydroxypropyl methylcellulose; **PVA**: polyvinyl alcohol; **HEC**: hydroxyethyl cellulose; **SEM**: scanning electron microscopy; **UV**: ultraviolet spectroscopy; **FTIR**: fourier transform infrared spectroscopy; **HPLC**: high-

performance liquid chromatography; **CFU**: colony-forming units (used in antimicrobial testing); **PBS**: phosphate buffer solution; **irb**: institutional review board (for ethical clearance); **API**: active pharmaceutical ingredient.

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Authors' Contributions

1. Mr. Aditya Sanjay Yewale: Conceptualization, methodology, investigation, data curation, writing—original draft, and supervision—review and editing.
2. Mr. Ajay Ramesh Sapkal: Formal analysis, validation, writing
3. Mr. Ganesh Suresh Khandare: Resources, software, visualization.
4. Mr. Mohit Pravin Zanwar: Investigation, data collection, validation.
5. Mr. Nitin Baban Kalasker: Literature review, writing—original draft preparation.
6. Mr. Faisal A. Shaikh: Supervision, project administration, critical review.
7. Dr. R. H. Kale: Supervision, validation, final approval of the manuscript.

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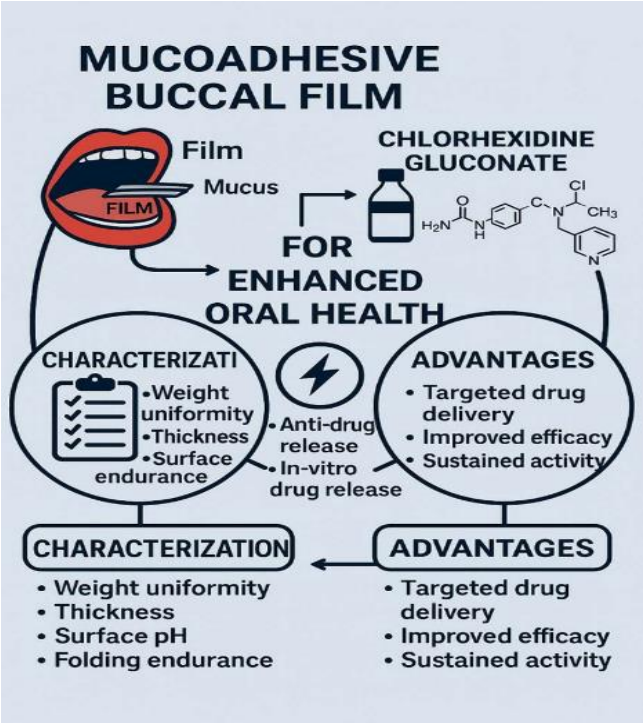
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