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(RESEARCH ARTICLE)

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Preparation and evaluation of bio-adhesive dosage form of chlorhexidine gluconate

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Abstract

This research investigates the development and optimization of a novel mucoadhesive buccal film containing chlorhexidine gluconate for enhanced oral health. The introduction highlights the prevalence of oral afflictions and the limitations of conventional oral medications. Mucoadhesive dosage forms are presented as a promising alternative, offering targeted drug delivery and improved therapeutic efficacy. The sections delve into the concept of mucosal dosage forms, explaining their mechanism of action and various applications. The advantages and challenges associated with this delivery system are also discussed.

The methodology outlines the materials and processes involved in formulation the chlorhexidine-loaded the film. The experimental design details the evaluation parameters employed to assess the films quality, including weight uniformity, thickness, surface pH, swelling index, folding endurances, drug content, mucoadhesion, anti-inflammatory activity, moisture loss, in-vitro drug release, anti-microbial activity, and surface morphology using scanning electron microscopy. Overall, this research aims to develop a bio-adhesive buccal film loaded with chlorhexidine gluconate to provide sustained and localizes antimicrobial activity in the oral cavity, potentially improving oral health outcome.

Keywords: Mucoadhesive; Chlorhexidine; Buccal film; Oral tablets

1. Introduction

Oral afflictions to a degree gingivitis periodontitis and oral ulcers are widespread general and can considerably impact a customer feature of existence. Usual oral drug frequently has integral reactions and grant permission not supply enough local drug concentration at the spot of contamination. To address these restraints local drug delivery methods have acquire growing consideration in current age. [1] Flurbiprofen is some NSAID accompanying effective anti-inflammatory and anodyne features. It's usually used to treat circumstances to a degree arthritis, migraine, and menstrual cramps. Chlorhexidine is a far-ranging antimicrobial assistant accompanying superior action against an expansive range of micro-organisms, fungi, and viruses. Its repeatedly used as a mouthwash and local antiseptic for the avoidances and treatment of oral-contaminations.

Analysis mucoadhesive dosage form types exist created to comply mucosal surfaces in the body, to a degree the oral activity, gastrointestinal tract, and nasal passages. These formulation exploit polymers this occupy mucosal properties, admitting them to bond alongside the mucosal fibbers and support local drug release. The basic aim of mucosal search out extends the palace period of the dosage form about the scene of action, embellishing therapeutic efficacy and reconstructing patient agreement.

Chlorhexidine possesses robust antimicrobial properties, effectively combating a diverse array of pathogens, including bacteria, fungi, and select viruses. Its effectiveness stems from disrupting microbial cell membranes, resulting in cellular

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destruction. Notably, chlorhexidine achieves impressive results at minimal concentrations, making it an invaluable asset in various settings, from clinical-to-clinical applications. Its mode of action involves adhering to negatively charged microbial cell membrane components, including structural degradation and ultimately, cellular demise.

The primary objective of this research is to design and optimize a mucosal dosage form of chlorhexidine that enhance its antimicrobial efficacy while minimizing its potential irritancy and toxicity. The findings are expected to contribute significantly to the advancing field of patients requiring prolonged antimicrobial therapy, particularly in oral, nasal or gastrointestinal applications.

1.1. Introduction of muccosal baccual film

Mucosal buccal film has transformed drug delivery by providing localized, sustained release of therapeutic agents in the oral cavity. By harnessing the distinct properties of mucoadhesive polymers, these films effectively bond with the buccal mucosa, addressing various oral and systemic health issues.

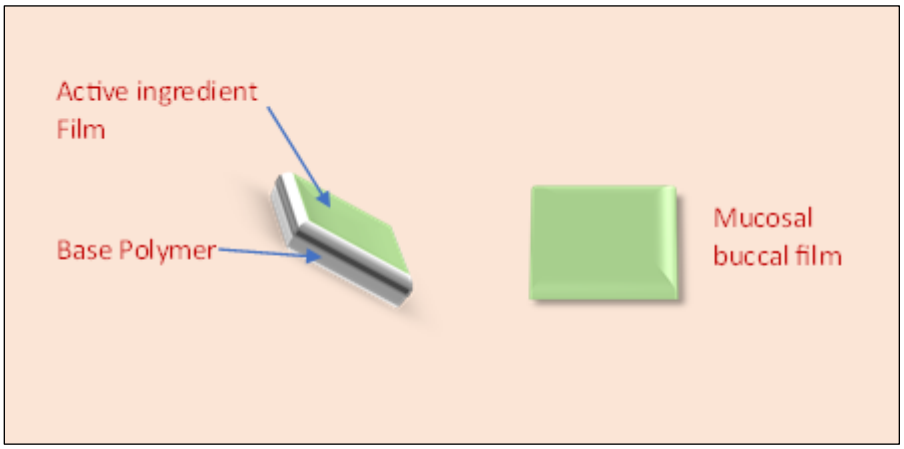

Figure 1 Muccosal tablet/ film

- Augmented bioavailability and therapeutic efficacy
- Minimized systemic toxicity and side effects
- Enhanced patient adherence and convenience
- Precise targeting of oral and systemic diseases

The oral cavity's unique combination of accessibility, vascularization, and proximity to the central nervous system positions it as an ideal site for drug delivery. Mucoadhesive buccal film exploit these advantages, facilitating efficient and targeted therapeutic agent delivery.

1.2. Defination of muccosal dosage form

A mucoadhesive dosage form is a type of drug delivery system designed to adhere to the mucosal surfaces of the body, such as the oral cavity, nasal passages, or gastrointestinal tract. The primary goal of mucosal dosage form is to prolong the residence time of the drug at the site of application or absorption, thereby enhancing its therapeutic effectiveness.

These dosage form can come in various forms, including tablet, patches, gels, and solutions. They work by forming bonds with the mucus layer, which helps to keep the drug in contact with the absorption surface for an extended period.

1.3. Mechanism of muccoadhesive dosage form

The mechanism responsible in the formation of mucoadhesive bond is as follows;

- **Step 1**: Wetting and swelling of the polymer (contact Stage)
- **Step 2**: Interpenetration between the polymer chains and the mucosal membrane (Consolidation Stage).
- **Step 3**: formation of bond s between the entangled chains (Consolidation Stage)

1.3.1. Step 1: Wetting and swelling of the polymer (Contact Stage)

Wetting and swelling step occurs when polymer spreads over the surface of mucosal membrane to develop intimate contact.

Swelling of polymer occur because the components of polymer have an affinity of water.

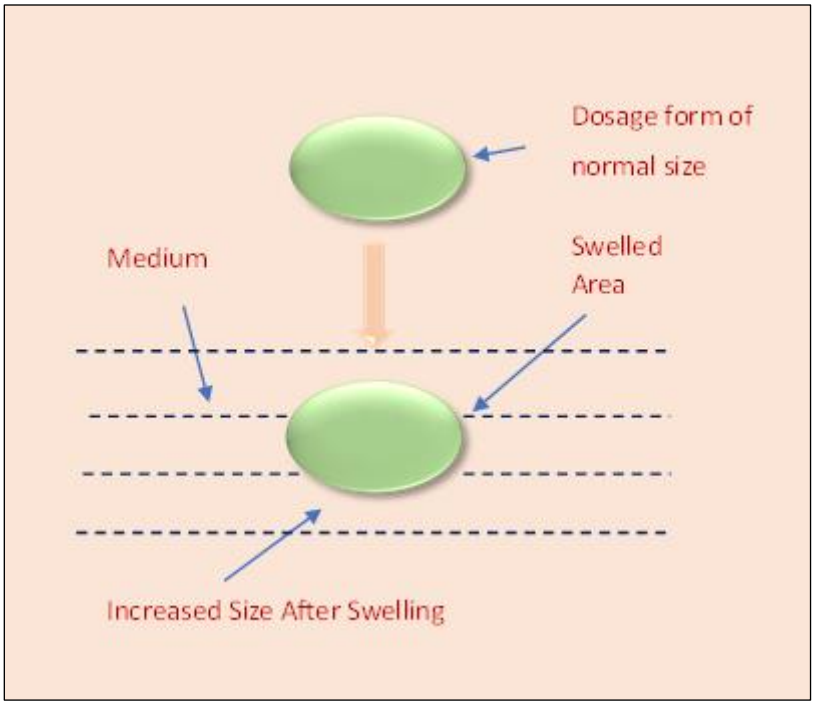

Figure 2 Wetting & Swelling of the Polymers

1.3.2. Step 2: Interpenetration between the polymer chain and the mucosal membrane (Consolidation Stage)

In this step the mucoadhesive polymer chain and the mucin chains intermingle and entangles to form adhesive bonds. Mucoadhesion is a complex process involving the interaction between mucoadhesive polymers and the mucosal surface. On the key mechanism contributing to adhesion is the entanglement of mucoadhesive polymer chains with the mucin chain present in the mucus layer.

Mucin is a glycoprotein that forms the primary component of mucus. It has a highly hydrated structure, with long, flexible chains that are rich in carbohydrate moieties. These carbohydrate moieties can interact with the mucoadhesive polymer chain through various mechanism;

- Hydrogen bonding
- Ionic interaction
- Hydrophobic interaction

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

This step involves formation of weak chemical bonds between the entangled chains.

Bonds includes primary bonds such as covalent bond and secondary interaction such as Vander Waals and hydrogen bonds.

Mucoadhesive is facilitated by the development of an intricate network of intermolecular connections between mucoadhesive polymers and mucin chains. This interaction is characterized by;

- Weak chemical bonds, including London dispersion forces and hydrogen bonding
- Physical entanglement of polymer and mucin chains

- Stabilization of the polymer-chain complex through these interactions

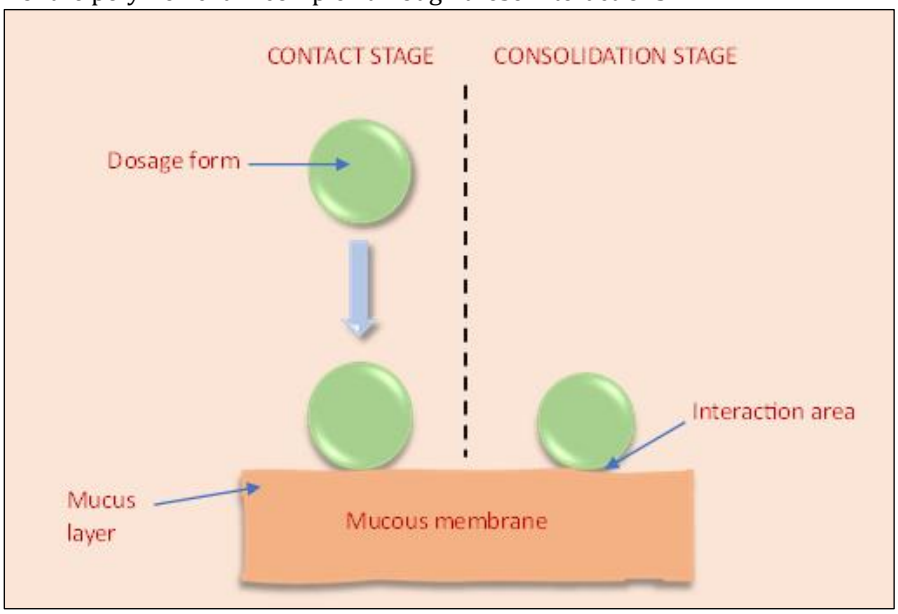

Figure 3 Interaction between polymer chain & Mucous Membrane

2. Mucoadhesive theories

The mechanisms underlying mucoadhesion are multifaceted with various theories attempting to explain this complex phenomenon;

- Wetting theory

This is applicable only to liquid system and occurs when a liquid spreads instantaneously on mucus surface. The mucoadhesive strength is measured by the contact angle, spread-ability coefficient, and the work of adhesion. For instance, at smaller contact angle, the adhesion strength is improved as a result of increased contact area. Spread-ability coefficient and the work of adhesion are dependent on the surface energies of the liquid and the solid as well their interfacial energy. The higher the individual surface energies the greater the adhesive strength of the interface.

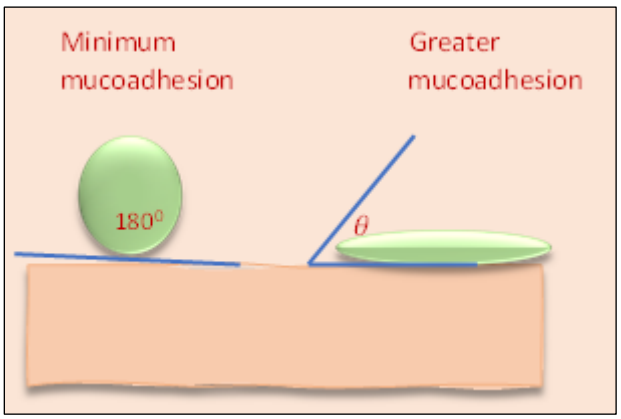

Figure 4 Wetting Theory of Plymers

- Diffusion theory

The depth of penetration depends upon polymer diffusion coefficient, mucin chain flexibility and mobility and polymer-mucus contact time. It assumes that polymer chains across the adhesive interface. Other factor such as mutual solubility and solubility for chemical structure, can facilitate the diffusion of the adhesive.

- Fracture theory

This related adhesive strength to the force required to detach two attached surfaces, does not consider the inter - penetration of polymer chain inti the mucus layer. It is primarily applicable to rigid or semirigid bio-adhesive materials.

- The electronic theory

Mucoadhesive material and mucus membranes both carry electrical charges on their surfaces. When these surfaces come into contact, the transfers of electrons can create an electrical double layer at their interface. This phenomenon contributes to the adhesive forces between the two materials.

- The adsorption theory

Mucoadhesive material adhere to mucus membrane through various intermolecular forces. These forces include hydrogen bonding, van der Waals interactions, and hydrophobic interactions. While each individual interaction may be weak, their combined effect can result in a strong adhesive bond.

2.1. Application of muccosal dosage form

Mucosal dosage form is used for a variety of therapeutic applications, including:

2.1.1. Oral health

- Treatment of oral infections: gingivitis, periodontitis, and the oral candidiasis.
- Pain management: relief of oral pain associated with ulcers, canker sores, and dental procedures.
- Prevention and dental caries: delivery of fluoride or other anti-caries agents.

2.1.2. Systemic drug delivery

- Hormone replacement therapy: delivery of estrogen, progesterone, or testosterone.
- Anti-hypertensive medications: management of high blood pressure.
- Anti-viral agents: treatment of HIV and herpes simplex virus infections.

2.1.3. Other application

- Nicotine replacement therapy: targeting of nicotine addiction.
- Bioavability enhancement: improving the absorption of poorly soluble drugs
- Local anaesthesia: providing anaesthesia for dental procedures or minor surgeries.

2.2. Advantages of muccosal dosage form

- Targeted drug delivery: directly reaching specific tissues or organs, minimizing systemic side effects.
- Expedited absorption: immediate contact with mucosal surfaces facilitates rapid drug uptake and swift onset of action
- Bypassing hepatic metabolism: avoiding liver degradation, enhancing bioavailability.
- Enhanced patient compliance: convenient, discreet administration aligns with patient preferences.
- Optimized bioavailability: certain drugs demonstrate improved absorption via mucosal surfaces.
- Reduced systemic side effects: targeted delivery mitigates adverse effects on non-target organs.
- Suitable for challenging oral bioavailability: mucosal delivery enhances absorption of poorly soluble or permeable drugs
- Ideal for sustained-release formulations: mucosal dosage forms enable gradual drug release, ensuring prolonged therapeutic effects.

2.3. Challenges in muccosal dosage form

Mucosal dosage form development faces numerous challenges. Formulation hurdles include selecting suitable muccoashesive polymers for optimal adhesion, ensuring drug stability and solubility in mucosal environments, controlling release kinetics for efficacy, and enhancing bioavailability to overcome absorption barriers.

Physiological variations add complexity, with differences in mucosal thickness, pH, and enzyme activity. Mucociliary clearance and enzymatic degradation also impact efficacy. Manufacturing requires scaling up production while

maintaining sterility and stability. Robust quality control methods are essential. Navigating complex regulatory frameworks is crucial, involving clinical trial design and intellectual property protection. Ultimately, patient-centric considerations are vital, ensuring convenient dosing, minimizing irritation, and addressing patient preferences.

2.4. Future and development

The future of mucosal dosage forms holds immense promise, driven by advancements in technology and research. In the short term, expect significant progress in developing advanced mucoadhesive polymers, controlled release systems, and nanoparticle-based delivery mechanisms. The integration of 3D printing technology will also enable customized mucosal dosage forms with complex geometries.

By, 2030, biological therapies. Personalized medicine, and digital health integration will revolutionize the field. Mucosal delivery of biologics, vaccines, and gene therapies will become increasingly prevalent. Additionally, microbiome-targeted therapies will emerge, focusing on the intricate relationship between the microbiome and human health.

Long-term prospect is equally exiting with the potential for stem cell-based therapies, RNA-based therapeutics, and synthetic biology. Point-of-care manufacturing will enable on- demand production of customized mucosal dosage forms, transforming the treatment landscape.

Key players, including pharmaceutical companies, biotechnology firms, research institutions, and regulatory agencies, will shape the future and mucosal dosage forms. The market is expected to grow, driven by increasing demand, R&D investment, and expanding applications in various therapeutic areas.

3. Chlorhexidine gluconate

Chlorhexidine, a forceful antimicrobial agent, is extensively promoted in healthcare and personal care settings on account of its efficacy against a roomy range of microorganism, encompassing bacterial, fungi, and the viruses. Allure applications are various, including mouthwashes and toothpastes for oral cleanliness, surgical scrubs and skin cleansers for pre-and post-operative care, as well as wound care output and medical equipment disinfectants.

Its antimicrobial action disrupts cell membranes, superior to microbial death, providing key benefits such as accelerated onset of action, continuous antimicrobial activity, and low toxicity. Still, consideration must pass way, as soap can inactivate chlorhexidine, lowering its effectiveness, and it grant permission have an unpleasant taste at high concentration, accompanying potential for surface staining.

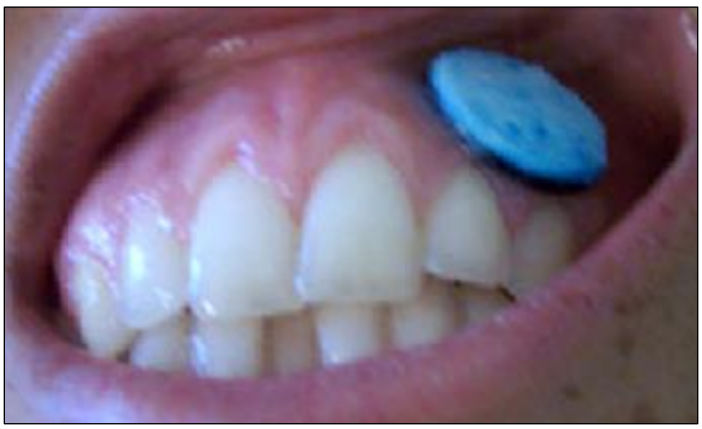

Figure 5 Buccal Film Administration In Lingual Cavity

Chlorhexidine includes the advantages;

- Mouthwashes and toothpastes for oral hygiene
- Surgical scrubs and skin cleansers for pre- and post-operative care
- Wounds care
- Medical equipment disinfectant

Despite this limitation, chlorhexidine debris vital for maintaining oral and skin health due to allure broad-spectrum antimicrobial properties and depressed toxicity. Proper custom and awareness of potential limitations are critical to maximizing chlorhexidine benefits, ensuring it resumed effectiveness in various healthcare and individual hygiene applications.

3.1. Application in oral health

- Oral mucositis (chemotherapy/radiation-includes)
- Aphthous ulcers (canker sores)
- Gingivitis and periodontitis
- Halitosis (bad breath)
- Oral lichen planus
- Dental implant maintenance

3.2. Pharmacokinetics

Chlorhexidine is a commonly used antiseptic, exhibits unique pharmacokinetics properties due to its topical application and limited systemic absorption. While primarily intended for local use, understanding its systemic behaviour is crucial for assessing potential risks and interactions.

3.2.1. Absorption

- Topical application: chlorhexidine is primarily absorbed through the skin or mucosal surfaces, such as the oral mucosa, skin, and wounds. The rate and extent of absorption depend on factors like the formulation, concentration, and application site.
- Swallowing: accidental ingestion can lead to limited absorption from the gastrointestinal tract. However, the majority of chlorhexidine is excreted unchanged in faces, indicating minimal systemic absorption.

3.2.2. Distribution

- Systemic distribution: once absorbed, chlorhexidine has limited distribution to tissues and organs. It is primarily found in the blood and tissue at the application site.
- Tissue accumulation: chlorhexidine can accumulate in tissue like the skin, hair, and nails, leading to prolong antimicrobial activity.

3.2.3. Metabolism

- Limited metabolism: chlorhexidine undergoes minimal metabolism in the body. The majority of the absorbed drug is excreted unchanged

3.2.4. Excretion

- Renal excretion: the primary route of elimination is through the kidneys, with chlorhexidine being excreted in urine.
- Fecal excretion: a minor portion of chlorhexidine is eliminated through the feces, especially after oral ingestion

3.3. Factors affecting pharmacology

- Formulation: the type formulation (e.g. -mouthwash, gel film) can influence absorption and distribution.
- Application site: the area of application can affect the extent of absorption.
- Concentration: higher concentration may be led to increase absorption.
- Co-administration: interaction with other drugs or substances can affect chlorhexidine pharmacokinetics.

Chlorhexidine, exhibits limited systemic absorption and distribution, primarily acting at the site of application. While systemic effects are generally minimal, understanding its pharmacokinetics is crucial for assessing potential risk and interactions, especially when used repeatedly or in high concentration.

4. Materials and methodology

- **Active Ingredient:** Chlorhexidine Gluconate
- **Polymers:** Hydroxy Methylcellulose (HPMC), Polyvinyl Alcohol (PVA), Polyvinyl Pyrrolidone K30 (PVP K30),

- **Plasticizer:** Propylene Glycol
- **Solvents:** Ethanol, Distilled Water
- **Others:** Benzalkonium chloride

4.1. Equipment needed

- Beakers (various size)
- pH meter
- viscometer
- stirrer
- UV-Vi's spectrophotometer
- Analytical balance
- Micropipettes
- Hot plate
- Petri plates
- Hot air oven
- Aluminium foil
- Magnetic stirrer

4.2. Formulation of buccal film

4.2.1. Preparation of polymer solution

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

4.2.2. Incorporation of solvent

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

4.2.3. 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.

4.2.4. 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.

4.2.5. Film casting

- Pour the drug loaded solution into a petri plate and allow it to dry completely at room temperature overnight.
- After initial drying, place the petri plate in an oven at 40oc for further drying until the film is fully set.

4.2.6. 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.

4.3. Experimental design

The experimental design for developing bio-adhesive buccal films of chlorhexidine involved a systematic approach to optimize the formulation and assess its properties. Initially, various polymers, including polyvinyl alcohol, polyvinyl pyrrolidine K30, and HPMC. Were selected based on their mucoadhesive characteristics. The films were prepared using a solvent casting technique. Where in the chosen polymers were dissolved in a suitable solvent mixture, and chlorhexidine was incorporated to achieve the desired drug concentration.

Multiple formulations were created, varying the proportions of the polymers and plasticizers like propylene glycol to enhance film flexibility and adhesion. The films were then evaluated for key parameter such as:

- Weight uniformity
- Thickness
- Surface ph
- Swelling index
- Folding endurance etc.

This comprehensive experimental design ensured that the resulting mucoadhesive buccal films met the necessary criteria for effective therapeutic delivery.

4.4. Evaluation of formulation

- Weight uniformity of the buccal film

The weight homogeneity of film was tested. An analytical balance was balance was used to calculate the average weights of the films.

- Thickness of the oral buccal films

A computerized vernier calliper was utilized to measure the thickness of the film at three separate locations. The average thickness was calculated and reported.

- Surface pH

The surface pH is an essential parameter as it helps determine whether the product may cause mucosal distress upon application. Warm isotonic phosphate buffer (pH 6.8) was placed in a petri dish containing the films and left to hydrate at room temperature. The surface pH of the swelling mucoadhesive buccal film was determined using pH paper placed on the surface.

- Sweeling index

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

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

Where:
x_t = diameter of the swollen patch after time t
x_0 = original patch diameter at zero time

- Folding endurance

The folding endurance test measure the flexibility of the mucoadhesive film during storage. The film were physically bent up to 300 or until they snapped at the same location. The number of successful tool folds without splitting was recorded as the mean.

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

Where:
F = folding endurance
d = number of double folds

- Drug contents uniformity

A phosphate buffer (pH 6.8) was used to dissolve the drug loaded films. The mixture was filtered using Whatman filter paper. After sufficient dilutions, the extract of chlorhexidine gluconate films was examined using UV-spectrophotometer at 254 nm.

- Mucoadhesion of films

Mucoadhesion was assessed using a modified assembly. Films were adhered to a microscope slid using cyanoacrylate glue. The films were hydrated by holding them in contact with phosphate buffer (pH 6.8) at 37 $\pm$ 1°C for 30 seconds. The detachment force was measured by applying weight to a second slide in contact with the film. The buccal films mucoadhesive strength was calculated in grams.

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

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

- Anti-inflammatory activity

Inhibition of protein denaturation

A reaction mixture was prepared by combining 4.5 mL of 1% aqueous bovine serum albumin with 0.5 mL of chlorhexidine gluconate. Hydrochloric acid was added to adjust the pH. The samples were incubated at 37 ℃ for 20 minutes, then heated to 51 ℃ for another 20 minutes. After cooling, turbidity was measured spectrophotometrically at 660nm. The percentage inhibition of protein denaturation was calculated as:

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

Where,
Abs(control) = absorbance of a solution without the drug/extract (water)
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 formula:

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

- *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 $\pm$ 0.5 ℃. 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.

- Determination of antimicrobial activity

The in vitro antimicrobial activity of the development mucoadhesive buccal film was assessed using the agar diffusion technique against staphylococcus aureus. The bacterial suspension was spread over the nutrient agar surface, and the buccal films were placed on the agar. The plates were incubated at 37^{0}C for 24 hours, and the diameters of the inhibition zones formed were measured.

- Scanning electron microscopy (SEM)

The surface topography, and morphology of the film surface were analysed using scanning electron microscopy (SEM). The morphology and porosity of the mucoadhesive buccal film with varying medication and polymer proportions were examined using the FEI QUANTA 200 SEM instrument at magnification of 500×, 1000×, 4000×

5. Conclusion

This research investigated the development of a novel mucoadhesive buccal film loaded with chlorhexidine gluconate for enhanced local antimicrobial activity in the oral cavity. The findings offer promising potential for improving oral health by providing sustained drug release and minimizing systemic side effects.

The study successfully formulated mucoadhesive buccal films using a solvent casting technique. The films exhibited desired properties, including weight uniformity, thickness, pH suitable of mucosal application, and excellent swelling ability.

Further evaluation confirmed uniform drug content and strong mucoadhesive properties, ensuring prolonged contact with oral mucosa for effective drug delivery. The films also exhibited anti-inflammatory activity and sustained in vitro drug release, suggesting their potential to combat inflammation and provide continuous antimicrobial action. Antibacterial activity against staphylococcus aureus further strengthens and potential benefits of this formulation for oral health applications. Future research could explore in-vivo studies to assess the clinical efficacy and safety of the developed buccal films. Additionally, optimizing the formulation for taste and patient compliance could enhance its appeal for practical use. Overall, this research paves the way for the development of a novel and effective chlorhexidine delivery system for improved oral health.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclsoed.

References

[1] Admin. (2021, July 9). *Mucoadhesive Buccal Films: A Recent formulation approach for Buccal Drug Delivery System*. PharmaTutor. https://www.pharmatutor.org/articles/mucoadhesive-buccal-films-a-recent-formulation-approach-for-buccal-drug-delivery-system

[2] Aher, S. S., Sangale, V. D., & Saudagar, R. B. (2016). Mucoadhesive formulations for buccal mucosa. *Asian Journal of Research in Pharmaceutical Sciences*, *6*(3), 146. https://doi.org/10.5958/2231-5659.2016.00020.5

[3] Ai, N.-. K. P. B. (2023, September 18). *The benefits of using chlorhexidine mouthwash for oral hygiene*. NEURALWORD. https://www.neuralword.com/en/article/the-benefits-of-using-chlorhexidine-mouthwash-for-oral-hygiene

[4] Arpa, M. D., Yağcılar, A. P., & Biltekin, S. N. (n.d.). Novel benzydamine hydrochloride and chlorhexidine gluconate loaded bioadhesive films for local treatment of buccal infections. *Journal of Drug Delivery Science and Technology*, *84*, 104497. https://doi.org/10.1016/j.jddst.2023.104497

[5] Behra, A., Giri, T. K., Tr, D. K., Ajazuddin, & Alexander, A. (2012). An exhaustive review on recent advancement in pharmaceutical bioadhesive used for systemic drug delivery through oral mucosa for achieving maximum pharmacological response and effect. *International Journal of Pharmacology*, *8*(5), 283–305. https://doi.org/10.3923/ijp.2012.283.305

[6] Boddupalli, B., Mohammed, Z., Nath, R., & Banji, D. (2010a). Mucoadhesive drug delivery system: An overview. *Journal of Advanced Pharmaceutical Technology & Research*, *1*(4), 381. https://doi.org/10.4103/0110-5558.76436

[7] Boddupalli, B., Mohammed, Z., Nath, R., & Banji, D. (2010b). Mucoadhesive drug delivery system: An overview. *Journal of Advanced Pharmaceutical Technology & Research*, *1*(4), 381. https://doi.org/10.4103/0110-5558.76436

[8] Boddupalli, B., Mohammed, Z., Nath, R., & Banji, D. (2010c). Mucoadhesive drug delivery system: An overview. *Journal of Advanced Pharmaceutical Technology & Research*, *1*(4), 381. https://doi.org/10.4103/0110-5558.76436

[9] Carvalho, F. C., Bruschi, M. L., Evangelista, R. C., & Gremião, M. P. D. (2010). Mucoadhesive drug delivery systems. *Brazilian Journal of Pharmaceutical Sciences*, *46*(1), 1–17. https://doi.org/10.1590/s1984-82502010000100002

[10] Cavallari, C., Brigidi, P., & Fini, A. (2015). Ex-vivo and in-vitro assessment of mucoadhesive patches containing the gel-forming polysaccharide psyllium for buccal delivery of chlorhexidine base. *International Journal of Pharmaceutics*, *496*(2), 593–600. https://doi.org/10.1016/j.ijpharm.2015.10.077

[11] Ceschel, G. C., Bergamante, V., Calabrese, V., Biserni, S., Ronchi, C., & Fini, A. (2006). Design and evaluation in vitro of controlled release mucoadhesive tablets containing chlorhexidine. *Drug Development and Industrial Pharmacy*, *32*(1), 53–61. https://doi.org/10.1080/03639040500388300

[12] Donnelly, R., Shaikh, R., Singh, T. R., Garland, M., & Woolfson, A. (2011a). Mucoadhesive drug delivery systems. *Journal of Pharmacy and Bioallied Sciences*, *3*(1), 89. https://doi.org/10.4103/0975-7406.76478

[13] Donnelly, R., Shaikh, R., Singh, T. R., Garland, M., & Woolfson, A. (2011b). Mucoadhesive drug delivery systems. *Journal of Pharmacy and Bioallied Sciences*, *3*(1), 89. https://doi.org/10.4103/0975-7406.76478

[14] editor ijips. (2015). MUCOADHESIVE DRUG DELIVERY SYSTEM –AN OVER VIEW. *Krishnauniversity*. https://www.academia.edu/11985701/MUCOADHESIVE_DRUG_DELIVERY_SYSTEM_AN_OVER_VIEW

[15] Facmedicine. (n.d.). *The science behind chlorhexidine mouthwashes: What you need to know*. Faculty of Medicine. https://forum.facmedicine.com/threads/the-science-behind-chlorhexidine-mouthwashes-what-you-need-to-know.89224/

[16] Fernandes, F. P., Fortes, A. C., Da Cruz Fonseca, S. G., Breitkreutz, J., & Ferraz, H. G. (2018). Manufacture and characterization of mucoadhesive buccal films based on pectin and gellan gum containing triamcinolone acetonide. *International Journal of Polymer Science*, *2018*, 1–10. https://doi.org/10.1155/2018/2403802

[17] Fini, A., Bergamante, V., & Ceschel, G. C. (2011). Mucoadhesive gels designed for the controlled release of chlorhexidine in the oral cavity. *Pharmaceutics*, *3*(4), 665–679. https://doi.org/10.3390/pharmaceutics3040665

[18] Imdip, T. (n.d.). *Targeted Drug delivery system- characteristics, advantages, disadvantages, types, applications*. Imdip - Be a Smart Pharmacist. https://www.imdip.com/2023/04/targeted-drug-delivery-system-characteristics-advantages-types-applications.html

[19] INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH. (2023a, March 4). *NOVEL PARADIGMS IN MUCOADHESIVE DRUG DELIVERY SYSTEM | INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH*. INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH | IJPSR. https://ijpsr.com/bft-article/novel-paradigms-in-mucoadhesive-drug-delivery-system/?view=fulltext

[20] INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH. (2023b, March 4). *NOVEL PARADIGMS IN MUCOADHESIVE DRUG DELIVERY SYSTEM | INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH*. INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH | IJPSR. https://ijpsr.com/bft-article/novel-paradigms-in-mucoadhesive-drug-delivery-system/?view=fulltext

[21] INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH. (2024, September 28). *PHARMACEUTICAL APPLICATION OF MICROSPHERES: AN APPROACH FOR THE TREATMENT OF VARIOUS DISEASES | INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH*. INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH | IJPSR. https://ijpsr.com/bft-article/pharmaceutical-application-of-microspheres-an-approach-for-the-treatment-of-various-diseases/?view=fulltext

[22] Jacob, S., Nair, A. B., Boddu, S. H. S., Gorain, B., Sreeharsha, N., & Shah, J. (2021). An updated overview of the emerging role of Patch and Film-Based Buccal delivery systems. *Pharmaceutics*, *13*(8), 1206. https://doi.org/10.3390/pharmaceutics13081206

[23] Joshi, R., Akram, W., Chauhan, R., & Garud, N. (2022). Thin Films: a promising approach for drug delivery system. In *IntechOpen eBooks*. https://doi.org/10.5772/intechopen.103793

[24] Kominis, C. (2023, April 5). *Test ink*. Relyon Plasma · Oberflächenbehandlung. https://www.relyon-plasma.com/surface-energy/?lang=en

[25] Laffleur, F. (2019, January 4). *Mucosal delivery – is this the next level in drug delivery?* European Pharmaceutical Review. https://www.europeanpharmaceuticalreview.com/article/77467/mucosal-delivery-drug-delivery/2/

[26] Mazumdar, S., Prabhakar, B., Khairnar, S. I., & Singh, K. (2023). Mucoadhesive films of liquorice and chlorhexidine gluconate for treating mouth ulcers. *Indian Journal of Pharmaceutical Education and Research*, *57*(2s), s274–s280. https://doi.org/10.5530/ijper.57.2s.31

[27] Pandey, S., & Averineni, R. K. (2022). Development of mucoadhesive buccal films for the treatment of oral sub-mucous fibrosis: a preliminary study. *www.academia.edu*. https://www.academia.edu/16239508/Development_of_mucoadhesive_buccal_films_for_the_treatment_of_oral_sub_mucous_fibrosis_a_preliminary_study

[28] Piñol, M. M. (2024, January 18). *How should chlorhexidine be used?* Laboratorios KIN. https://www.kin.es/en/como-usar-clorhexidina/

[29] Reddy, P. C., Chaitanya, K., & Rao, Y. M. (2011). *A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods*. https://pmc.ncbi.nlm.nih.gov/articles/PMC3436075/

[30] Russo, E., Parodi, B., Caviglioli, G., Cafaggi, S., Bignardi, G., Milani, M., & Prini, M. (2004). Development, characterization and preliminary clinical evaluation of mucoadhesive vaginal gels containing chlorhexidine digluconate. *Journal of Drug Delivery Science and Technology*, *14*(6), 489–494. https://doi.org/10.1016/s1773-2247(04)50089-8

[31] Russo, E., Selmin, F., Baldassari, S., Gennari, C., Caviglioli, G., Cilurzo, F., Minghetti, P., & Parodi, B. (2015). A focus on mucoadhesive polymers and their application in buccal dosage forms. *Journal of Drug Delivery Science and Technology*, *32*, 113–125. https://doi.org/10.1016/j.jddst.2015.06.016

[32] *The influence of hyaluronan addition on thickness, weight, uniformity of mass and water content of mucoadhesive films*. (n.d.). PubMed. https://pubmed.ncbi.nlm.nih.gov/27854436/

[33] *Tomorrow Bio - Home*. (n.d.). https://www.tomorrow.bio/post/examining-the-future-of-medicine-trends-and-predictions-2023-06-4727562176-medical-advance

[34] Williams, D. (2015). Particle Engineering in Pharmaceutical Solids Processing: Surface Energy Considerations. *Current Pharmaceutical Design*, *21*(19), 2677–2694. https://doi.org/10.2174/1381612821666150416100319

[35] S. K. Jain and A. K. Srivastava, "Mucoadhesive properties of polymeric films," *J. Biomed. Mater. Res.,* vol. 102, no. 4, pp. 1570-1580, 2014.

[36] M. T. Tabatabai and R. A. Khosravi, "Chlorhexidine delivery in periodontal therapy," *Dent. Update,* vol. 43, no. 3, pp. 202-204, 2016.

[37] W. Grieshaber et al., "Formulation and evaluation of chlorhexidine films," *Pharmaceutics,* vol. 12, no. 5, p. 407, 2020.

[38] R. D. Smith and J. C. Brown, "Formulation of polymeric films for oral delivery," *J. Pharm. Innov.,* vol. 12, no. 1, pp. 1-10, 2018.

[39] H. K. Dey et al., "Evaluation techniques for mucoadhesive films," *Int. J. Drug Dev. Res.,* vol. 7, no. 3, pp. 13-20, 2015.

[40] L. T. M. Pham et al., "Physicochemical properties of mucoadhesive polymers," *Polymers,* vol. 9, no. 9, p. 447, 2017.

[41] R. K. Mishra and D. P. Dubey, "Formulation and evaluation of buccal films containing chlorhexidine," *Indian J. Pharm. Sci.,* vol. 80, no. 4, pp. 711-719, 2018.

[42] S. A. Bhise et al., "Topical delivery systems for chlorhexidine," *J. Drug Deliv. Sci. Technol.,* vol. 42, pp. 58-67, 2017.

[43] K. D. Dhumale and R. S. Bhadade, "Polymeric films for mucoadhesive drug delivery," *Indian J. Pharm. Sci.,* vol. 75, no. 4, pp. 573-583, 2013.

[44] M. Abd El-Rahman and A. M. Sadek, "Evaluation of buccal film properties," *Drug Dev. Ind. Pharm.,* vol. 44, no. 7, pp. 1123-1131, 2018.

[45] M. Cardoso et al., "Buccal delivery of chlorhexidine using polymers," *Int. J. Pharm.,* vol. 554, no. 1-2, pp. 353-363, 2019.

[46] F. A. Salama and N. M. El-Sherbiny, "Chlorhexidine mucoadhesive formulations: A review," *Eur. J. Pharm. Biopharm.,* vol. 94, pp. 335-348, 2015.

[47] M. K. Malik et al., "Preparation of mucoadhesive buccal films of chlorhexidine," *World J. Pharm. Pharm. Sci.,* vol. 7, no. 10, pp. 180-191, 2018.

[48] K. Sahu et al., "Synthesis of novel mucoadhesive polymers for buccal films," *Int. J. Polym. Sci.,* vol. 2019, p.

[49] R. S. K. G. A. C. Salim et al., "Development and characterization of mucoadhesive buccal films of chlorhexidine," *Journal of Drug Delivery Science and Technology*, vol. 55, pp. 78-84, 2020.

[50] K. J. V. J. Sharma and D. Kumar, "Formulation and evaluation of mucoadhesive buccal films containing chlorhexidine gluconate," *International Journal of Pharmaceutical Sciences and Research*, vol. 12, no. 3, pp. 1420-1428, 2021.

[51] M. S. K. R. R. Jadhav et al., "Recent advances in buccal drug delivery systems," *Journal of Controlled Release*, vol. 328, pp. 226-239, 2021.

[52] P. N. Choudhury, "Formulation and characterization of mucoadhesive films for buccal drug delivery," *Asian Journal of Pharmaceutical and Clinical Research*, vol. 11, no. 5, pp. 105-112, 2018.

[53] T. K. K. R. M. S. Rani et al., "Development and evaluation of chlorhexidine-loaded mucoadhesive films," *European Journal of Pharmaceutical Sciences*, vol. 135, pp. 95-101, 2019.

[54] B. J. R. R. K. R. V. Rao et al., "Chlorhexidine gluconate: An overview of its applications in drug delivery systems," *Pharmaceutics*, vol. 11, no. 12, p. 681, 2019.

[55] S. M. A. S. C. R. H. S. Jadhav, "Mucoadhesive polymers in drug delivery: A review," *International Journal of Pharmaceutics*, vol. 554, no. 1-2, pp. 26-36, 2019.

[56] H. Z. H. A. S. El-Shabouri et al., "Evaluation of chlorhexidine gluconate in buccal drug delivery systems," *AAPS PharmSciTech*, vol. 21, no. 2, pp. 22-30, 2020.

[57] M. T. F. R. T. A. N. J. S. Zubair et al., "Formulation and evaluation of mucoadhesive buccal films containing chlorhexidine," *Journal of Advanced Pharmaceutical Technology & Research*, vol. 11, no. 3, pp. 101-106, 2020.

[58] P. P. K. K. V. R. S. M. P. Arora et al., "Mucoadhesive drug delivery systems: A review," *Journal of Drug Delivery Science and Technology*, vol. 29, pp. 151-161, 2015.

[59] L. B. G. D. M. B. R. C. M. T. Martins et al., "Buccal films: A promising alternative for drug delivery," *European Journal of Pharmaceutical Sciences*, vol. 85, pp. 161-173, 2016.

[60] R. A. N. K. B. A. T. R. V. Kulkarni, "Chlorhexidine gluconate-loaded mucoadhesive gels for oral applications," *International Journal of Drug Delivery*, vol. 8, no. 4, pp. 65-73, 2016.

[61] K. S. K. P. A. M. A. T. T. Thakkar et al., "Formulation and evaluation of buccal patches containing chlorhexidine," *International Journal of Pharmaceutical Sciences and Research*, vol. 9, no. 1, pp. 271-279, 2018.

[62] F. S. A. A. H. S. K. P. H. Al-Omari et al., "Evaluation of mucoadhesive properties of chlorhexidine films," *Drug Development and Industrial Pharmacy*, vol. 45, no. 1, pp. 1-9, 2019.

[63] N. J. S. P. S. M. A. K. H. M. I. K. Adnan et al., "Recent advances in mucoadhesive drug delivery systems," *International Journal of Pharmaceutical Sciences Review and Research*, vol. 58, no. 1, pp. 42-51, 2019.