

Development of Mucoadhesive Buccal Film Containing Herbal Extracts (Tulsi, Neem and Clove) for Antifungal Therapy

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ABSTRACT

Oral fungal infections, particularly oral candidiasis, represent a common clinical problem that mainly affects immunocompromised individuals, elderly patients, and denture wearers. Conventional antifungal therapies, although effective, are often associated with limitations such as poor retention in the oral cavity, systemic side effects, frequent dosing, and the emergence of drug resistance. These challenges have encouraged the development of alternative localized drug delivery systems that can provide sustained antifungal action with improved patient compliance. Mucoadhesive buccal films have emerged as a promising platform for oral drug delivery due to their ability to adhere to the buccal mucosa, prolong residence time, and deliver drugs directly at the site of infection. Herbal antifungal agents have gained significant attention in recent years owing to their safety, biocompatibility, and broad-spectrum activity. Medicinal plants such as Tulsi (*Ocimum sanctum*), Neem (*Azadirachta indica*), and Clove (*Syzygium aromaticum*) are well known for their antifungal, anti-inflammatory, and antimicrobial properties, primarily attributed to bioactive constituents such as eugenol, flavonoids, and terpenoids. The incorporation of these herbal extracts into mucoadhesive buccal films offers a synergistic therapeutic approach by combining the advantages of natural antifungal agents with advanced drug delivery technology. This review highlights the pathophysiology of oral fungal infections, limitations of conventional antifungal therapies, and the potential of mucoadhesive buccal films as an effective alternative. Emphasis is placed on formulation strategies, polymer selection, evaluation parameters, antifungal efficacy, and safety considerations of polyherbal buccal films containing Tulsi, Neem, and Clove extracts. The review also discusses current challenges, future perspectives, and the scope for clinical translation and commercialization of herbal mucoadhesive buccal films for antifungal therapy.

Keywords: Mucoadhesive buccal films; Oral candidiasis; Herbal antifungal therapy; Tulsi (*Ocimum sanctum*); Neem (*Azadirachta indica*); Clove (*Syzygium aromaticum*); Localized drug delivery; Polyherbal formulation

INTRODUCTION

Oral fungal infections are common disorders that affect the oral mucosa, especially in immunocompromised individuals, elderly patients, denture wearers, and those receiving prolonged antibiotic or steroid therapy. Among these conditions, oral candidiasis is the most frequently reported, predominantly caused by *Candida albicans*, although other species such as *Candida tropicalis* and *Candida glabrata* may also be involved. Clinically, oral fungal infections manifest in various forms, including pseudomembranous candidiasis, erythematous candidiasis, denture stomatitis, and angular cheilitis.

These infections are often associated with discomfort, burning sensation, inflammation, difficulty in eating or speaking, and impaired oral health, thereby negatively impacting the quality of life of affected individuals. The management of oral fungal infections commonly relies on conventional antifungal therapies, including topical formulations and systemic antifungal drugs. While systemic antifungals are effective, their use is frequently limited by undesirable side effects such as gastrointestinal irritation, hepatotoxicity, and potential drug interactions. Additionally, long-term or repeated use of synthetic antifungal agents has contributed to the

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growing problem of antifungal resistance, particularly among *Candida* species. Topical antifungal preparations, although safer, often suffer from poor retention in the oral cavity due to salivary washout and continuous oral movements, resulting in reduced efficacy and the need for frequent dosing, which ultimately affects patient compliance.

These limitations have highlighted the need for an alternative therapeutic approach that can provide effective and sustained antifungal action at the site of infection. Localized drug delivery to the oral cavity offers a significant advantage by delivering the therapeutic agent directly to the affected area, ensuring higher local drug concentrations while minimizing systemic exposure and adverse effects. Such targeted delivery is particularly beneficial for oral fungal infections, where prolonged contact between the antifungal agent and the infected mucosa is crucial for successful treatment. In this context, mucoadhesive buccal films have gained considerable attention as a novel and patient-friendly drug delivery system. These thin polymeric films adhere to the buccal mucosa and remain in place for extended periods, allowing controlled and sustained release of the active ingredient. Compared to conventional oral dosage forms, mucoadhesive buccal films offer improved residence time, accurate dosing, ease of application, and enhanced patient acceptance. Furthermore, they bypass first-pass metabolism and reduce dosing frequency, making them highly suitable for oral antifungal therapy.

Alongside advancements in drug delivery technologies, there is increasing interest in the use of herbal antifungal agents as safer and more sustainable therapeutic alternatives. Medicinal plants such as Tulsi (*Ocimum sanctum*), Neem (*Azadirachta indica*), and Clove (*Syzygium aromaticum*) have long been valued in traditional medicine for their antifungal, antibacterial, anti-inflammatory, and antioxidant properties. These plants contain a wide range of bioactive phytoconstituents, including eugenol, flavonoids, and phenolic compounds, which have demonstrated significant inhibitory activity against *Candida* species. The incorporation of these herbal extracts into mucoadhesive buccal films combines the therapeutic benefits of natural antifungal agents with the advantages of an advanced delivery system.

Therefore, the development of mucoadhesive buccal films containing Tulsi, Neem, and Clove extracts represents a promising and innovative approach for the effective, safe, and patient-compliant management of oral fungal infections.

2. Oral Fungal Infections: Pathophysiology and Current Treatment Approaches

Oral fungal infections primarily arise due to an imbalance in the normal oral microflora, allowing opportunistic fungi to proliferate and invade the oral mucosa. Under healthy conditions, fungal organisms such as *Candida* species exist as commensals in the oral cavity without causing disease. However, factors such as immunosuppression, diabetes mellitus, poor oral hygiene, xerostomia, nutritional deficiencies, smoking, prolonged use of antibiotics or corticosteroids, and continuous denture wear can disrupt the natural defense mechanisms of the oral mucosa. This disruption facilitates the transition of fungi from a harmless yeast form to a pathogenic hyphal form, leading to tissue invasion, inflammation, and infection.

The pathogenesis of oral fungal infections involves multiple virulence factors, including adhesion to epithelial cells, biofilm formation, secretion of hydrolytic enzymes, and evasion of host immune responses. Biofilm formation, particularly on denture surfaces and oral mucosa, plays a crucial role in disease persistence and resistance to antifungal therapy. Once established, fungal biofilms act as a protective barrier, reducing drug penetration and increasing tolerance to conventional antifungal agents, thereby making treatment more challenging.

Among the various fungal species implicated in oral infections, *Candida albicans* is the most commonly identified pathogen. It is responsible for the majority of oral candidiasis cases due to its strong adhesion capacity and ability to switch between yeast and hyphal forms. Other non-*albicans* species such as *Candida tropicalis* and *Candida glabrata* are increasingly reported, particularly in immunocompromised patients. These species are of clinical concern as they often exhibit reduced susceptibility or resistance to commonly used antifungal drugs, contributing to treatment failure and recurrent infections.



Current treatment strategies for oral fungal infections mainly involve the use of topical and systemic antifungal agents. Common topical dosage forms include mouthwashes, gels, creams, ointments, lozenges, and oral suspensions, while systemic therapy typically consists of azole antifungals such as fluconazole or itraconazole. Although topical formulations are generally safer than systemic drugs, they suffer from several drawbacks, including poor retention in the oral cavity, rapid clearance by saliva, and the need for frequent application. Systemic antifungal agents, while effective in severe cases, are associated with adverse effects such as gastrointestinal disturbances, hepatotoxicity, and drug interactions, and their prolonged use may promote the development of antifungal resistance.

Given these limitations, there is a growing need for sustained local antifungal therapy that can maintain effective drug concentrations at the site of infection for an extended period. Sustained local delivery not only enhances therapeutic efficacy but also reduces dosing frequency, improves patient compliance, and minimizes systemic side effects. Such an approach is particularly beneficial in managing biofilm-associated infections and recurrent oral candidiasis. Therefore, the development of advanced localized drug delivery systems capable of providing prolonged antifungal action within the oral cavity has become an important focus in contemporary pharmaceutical research.

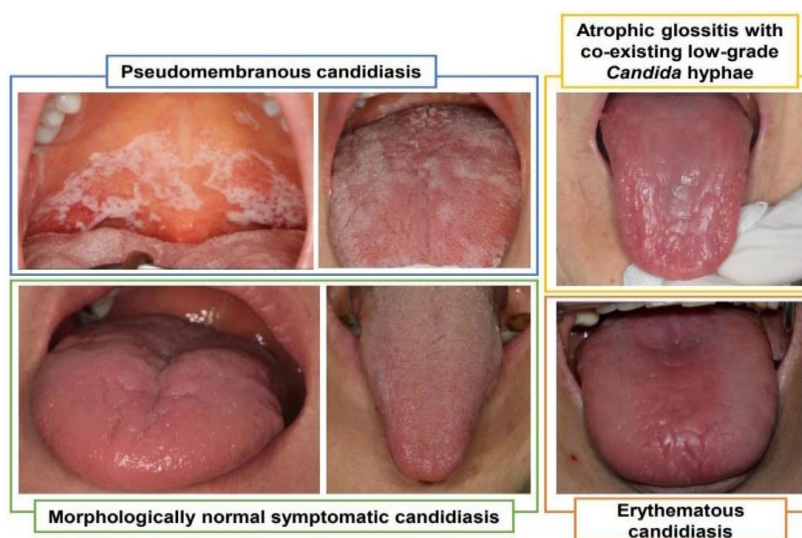


Diagram 1: Pathogenesis of Oral Fungal Infections

3. Mucoadhesive Buccal Drug Delivery System

Mechanism of Mucoadhesion

3.1 Concept and Mechanism of Mucoadhesion

Mucoadhesion generally occurs in three major steps:

Concept of Mucoadhesion

- Mucoadhesion refers to the ability of a dosage form to adhere to the mucosal surface for an extended period.
- In buccal drug delivery, mucoadhesive systems stick to the inner cheek mucosa, allowing prolonged drug contact with the tissue.
- This adhesion helps improve drug absorption, retention time, and therapeutic effectiveness.

1. Initial Contact (Wetting Stage)

- The formulation comes in contact with the mucosal surface and spreads over it.
- Hydration of polymers helps initiate adhesion.

2. Interpenetration Stage

- Polymer chains penetrate into the mucus layer.

- Physical entanglement between polymer and mucin molecules occurs.

3. Bond Formation Stage

- Secondary bonds such as hydrogen bonding, van der Waals forces, and electrostatic interactions stabilize adhesion.

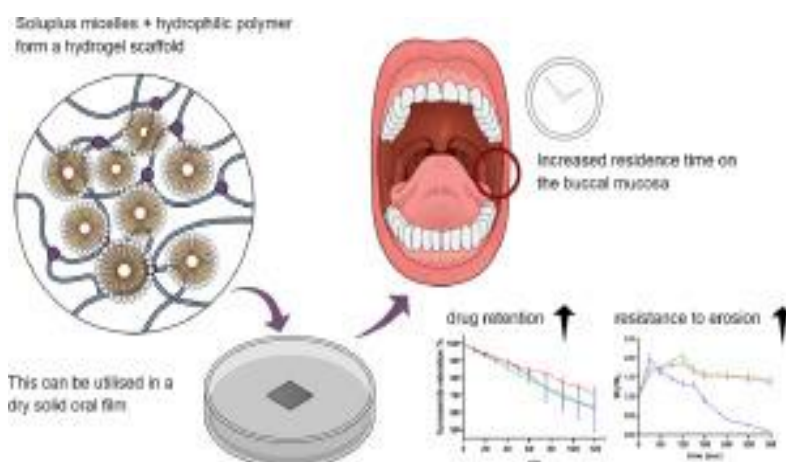


Diagram 2: Mechanism of Mucoadhesive Buccal Film

Theories of Mucoadhesion

1. Wetting Theory

- Suggests that better spreading and intimate contact between polymer and mucosa enhance adhesion.
- Polymers with good wettability show stronger mucoadhesive properties.

2. Diffusion Theory

- Describes the interpenetration of polymer chains into mucin networks.
- Greater chain mobility and flexibility result in stronger adhesion.

3. Electronic Theory

- Proposes that electron transfer occurs between mucosa and polymer.
- Formation of an electrical double layer leads to attractive forces.

4. Adsorption Theory

- Suggests adhesion occurs due to secondary chemical bonds such as hydrogen bonding and hydrophobic interactions.
- These bonds help maintain prolonged attachment to the mucosal surface.

Advantages of Buccal Drug Delivery

- Provides direct drug delivery to the site of infection.
- Avoids first-pass hepatic metabolism.
- Enhances drug bioavailability.
- Allows sustained and controlled drug release.
- Reduces systemic side effects.
- Improves patient compliance due to ease of application.
- Enables rapid onset of action.
- Suitable for both local and systemic therapy.

3.2 Buccal Films as Drug Delivery Platforms

Definition



- Buccal films are thin, flexible polymeric strips designed to adhere to the buccal mucosa and release drugs in a controlled manner.

Types of Buccal Films

1. Single-Layer Buccal Films

- Composed of a single polymer layer containing the drug.
- Simple design and easy to fabricate.
- Suitable for immediate or sustained release.

2. Multilayer Buccal Films

- Consist of two or more layers (drug layer + backing layer).
- Backing layer prevents drug loss into saliva.
- Provides unidirectional drug release and prolonged action.

Comparison with Other Buccal Dosage Forms

Buccal Tablets

- Rigid structure and lower comfort.
- Risk of dislodgement during speaking or chewing.
- Less flexible compared to films.

Buccal Patches

- Thicker and less comfortable.
- May cause irritation due to rigidity.
- Limited flexibility compared to films.

Buccal Gels

- Poor retention due to saliva washout.
- Requires frequent application.
- Less controlled drug release.

Buccal Films (Advantages Over Others)

- Thin and flexible.
- Better adhesion and comfort.
- Sustained drug release.
- Precise dosing and better stability.

Patient Compliance and Clinical Advantages

- Easy to apply and remove.
- Non-invasive and painless.
- Comfortable during speaking and eating.
- Reduced dosing frequency.
- Improved therapeutic outcomes.
- Higher patient acceptance compared to conventional forms.

4. Polymers Used in Mucoadhesive Buccal Films

Natural Polymers

1. Chitosan

- Biodegradable and biocompatible.
- Exhibits strong mucoadhesive properties.
- Enhances permeation and antimicrobial activity.

2. Sodium Alginate

- Hydrophilic polymer with good film-forming ability.
- Provides swelling and controlled release properties.
- Safe and non-toxic.

3. Guar Gum

- Natural polysaccharide with high viscosity.
- Improves adhesion and film flexibility.
- Cost-effective and eco-friendly.



Semi-Synthetic Polymers**1. Hydroxypropyl Methylcellulose (HPMC)**

- Excellent film-forming capability.
- Provides sustained drug release.
- Widely used in buccal film formulations.

2. Hydroxypropyl Cellulose (HPC)

- Improves flexibility and mechanical strength.
- Enhances drug diffusion and swelling behavior.

3. Sodium Carboxymethyl Cellulose (Sodium CMC)

- High mucoadhesive potential.
- Improves viscosity and hydration properties.
- Enhances film stability.

Criteria for Polymer Selection

- Biocompatibility and non-toxicity
- Mucoadhesive strength
- Film-forming ability
- Mechanical strength and flexibility
- Swelling capacity
- Drug compatibility
- Stability and shelf life
- Cost-effectiveness

Role of Plasticizers

Plasticizers are added to improve film flexibility and mechanical properties.

Functions

- Increase film elasticity
- Prevent brittleness and cracking
- Improve tensile strength
- Enhance patient comfort

Common Plasticizers

- Glycerol
- Propylene glycol
- PEG-400
- Sorbitol

Role of Permeation Enhancers

Permeation enhancers improve drug penetration across the mucosal membrane.

Functions

- Increase membrane permeability
- Enhance drug absorption
- Reduce lag time

Common Permeation Enhancers

- Menthol
- DMSO
- Oleic acid
- Tween-80
- Herbal essential oils (clove oil, eucalyptus oil)



Table 1: Polymers Used in Mucoadhesive Buccal Films

Polymer	Type	Role in Formulation
Chitosan	Natural	Mucoadhesion, permeation enhancement
Sodium alginate	Natural	Film formation, swelling
Guar gum	Natural	Adhesion, viscosity
HPMC	Semi-synthetic	Film strength, sustained release
Sodium CMC	Semi-synthetic	Hydration, adhesion

5. Herbal Extracts Used for Antifungal Therapy

Herbal medicines have gained renewed interest in antifungal therapy due to their broad-spectrum activity, safety profile, and reduced risk of resistance. Several medicinal plants traditionally used in oral healthcare possess potent antifungal properties, making them suitable candidates for incorporation into mucoadhesive buccal films. Among these, **Tulsi, Neem, and Clove** are well-documented for their effectiveness against oral fungal pathogens.

5.1 Tulsi (*Ocimum sanctum*)

Phytochemical Constituents

- Tulsi is rich in a wide range of bioactive compounds.
- Major phytoconstituents include **eugenol, ursolic acid, rosmarinic acid, flavonoids**, and **phenolic compounds**.
- These constituents are responsible for its antimicrobial, anti-inflammatory, and antioxidant activities.

Antifungal Mechanism of Action

- Eugenol disrupts the fungal cell membrane by altering membrane permeability.
- Ursolic acid inhibits fungal enzyme systems and interferes with cell wall synthesis.
- Flavonoids generate oxidative stress within fungal cells, leading to cell damage and death.

- Tulsi also inhibits fungal adhesion and biofilm formation on mucosal surfaces.

Evidence of Activity Against *Candida* Species

- Several in-vitro studies have demonstrated the inhibitory effect of Tulsi extracts against *Candida albicans*.
- Tulsi has shown antifungal activity comparable to standard antifungal agents in laboratory studies.
- Its ability to reduce fungal colonization makes it suitable for oral antifungal formulations.

5.2 Neem (*Azadirachta indica*)

Active Constituents

- Neem contains potent bioactive compounds such as **nimbin, nimbidin, azadirachtin, quercetin**, and **limonoids**.
- These constituents contribute to its antifungal, antibacterial, and immunomodulatory properties.

Antifungal and Immunomodulatory Properties

- Neem inhibits fungal cell growth by disrupting cell wall integrity and metabolic pathways.
- It reduces fungal adhesion and prevents biofilm formation on oral tissues and dentures.
- Neem enhances host immune response by stimulating macrophage activity and improving local defense mechanisms.



- Its anti-inflammatory effect helps reduce oral mucosal inflammation associated with fungal infections.

Use of Neem in Oral Care Formulations

- Neem has been widely used in traditional oral hygiene practices such as chewing sticks and herbal toothpastes.
- Modern formulations include neem-based mouthwashes, gels, lozenges, and oral sprays.
- Its proven safety and efficacy support its incorporation into mucoadhesive buccal films for antifungal therapy.

5.3 Clove (*Syzygium aromaticum*)

Eugenol as the Principal Bioactive Compound

- Clove is primarily known for its high content of **eugenol**, which accounts for most of its therapeutic effects.
- Eugenol exhibits strong antimicrobial and antifungal properties.

Antifungal, Anti-inflammatory, and Analgesic Actions

- Eugenol damages fungal cell membranes and inhibits enzyme activity, leading to fungal cell death.
- Clove reduces inflammation by inhibiting prostaglandin synthesis.
- Its analgesic action helps relieve pain and discomfort associated with oral infections.
- Clove also exhibits antioxidant properties that aid in tissue healing.

Synergistic Effects in Oral Infections

- Clove enhances the antifungal efficacy of other herbal extracts when used in combination.
- Synergistic interaction with Tulsi and Neem improves antifungal spectrum and therapeutic outcomes.
- Combined use reduces the likelihood of resistance development and provides comprehensive oral care.

Table 2: Herbal Extracts and Their Antifungal Properties

Plant	Active Constituents	Antifungal Mechanism
Tulsi (<i>Ocimum sanctum</i>)	Eugenol, ursolic acid, flavonoids	Cell membrane disruption
Neem (<i>Azadirachta indica</i>)	Nimbin, azadirachtin, quercetin	Inhibits biofilm formation
Clove (<i>Syzygium aromaticum</i>)	Eugenol	Membrane damage, analgesic action

6. Formulation Strategies for Herbal Mucoadhesive Buccal Films

- **Extraction methods for herbal drugs:** Herbal materials such as Tulsi, Neem, and Clove are first cleaned, dried, and powdered. The active constituents are commonly extracted using aqueous or hydroalcoholic solvents through methods like maceration or Soxhlet extraction. The extracts are then filtered, concentrated, and dried to obtain a stable extract suitable for formulation.

- **Solvent casting technique:** Solvent casting is the most widely used method for preparing buccal films. In this process, selected polymers are dissolved in an appropriate solvent, followed by uniform incorporation of the herbal extract and other excipients. The resulting solution is poured onto a flat surface and dried to form thin, flexible films, which are then cut into the desired size.
- **Optimization of polymer–extract ratio:** The ratio of polymer to herbal extract is optimized to achieve good film-forming ability, adequate mucoadhesive strength, and controlled drug

release. Excess extract may weaken film integrity, while insufficient extract may reduce antifungal efficacy, making optimization essential.

- **Incorporation of taste masking agents and sweeteners:**

Since buccal films remain in the oral cavity for extended periods, taste masking agents and

sweeteners such as mannitol, saccharin sodium, or flavors are added to improve palatability and patient acceptance without affecting therapeutic performance.

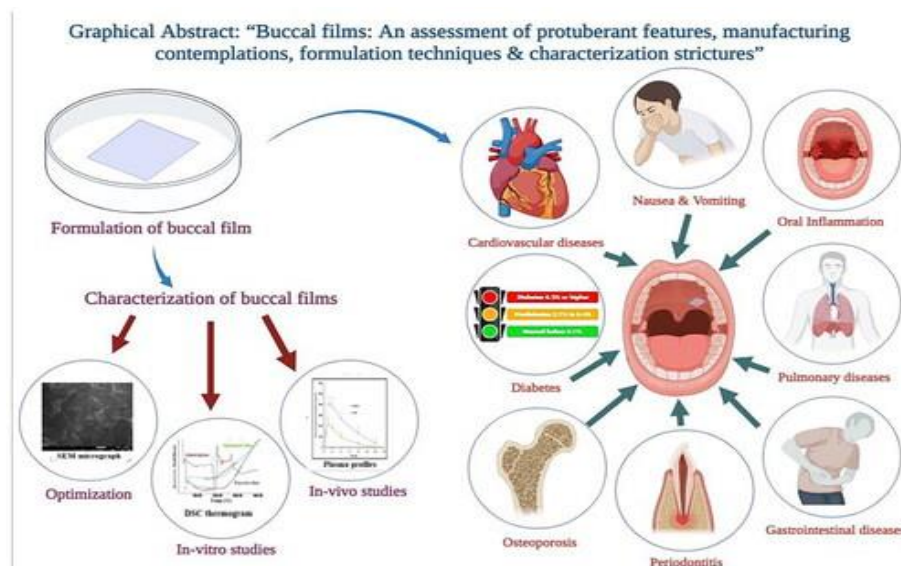


Diagram 3: Formulation Strategy of Herbal Mucoadhesive Buccal Film

7. Evaluation Parameters of Mucoadhesive Buccal Films

7.1 Physicochemical Evaluation

- **Thickness and weight uniformity:** Ensures dose accuracy and uniformity of the buccal films.
- **Folding endurance:** Indicates flexibility and resistance to breaking during handling.
- **Surface pH:** Measured to confirm compatibility with the oral mucosa and avoid irritation.

7.2 Mechanical and Mucoadhesive Properties

- **Tensile strength:** Reflects the mechanical stability of the film.
- **Percentage elongation:** Indicates elasticity and flexibility of the formulation.

- **Mucoadhesive strength and residence time:** Determines the ability of the film to adhere to the buccal mucosa for prolonged periods.

7.3 In-Vitro and Ex-Vivo Studies

- **Drug content uniformity:** Confirms even distribution of herbal extracts within the film.
- **In-vitro release studies:** Evaluate the drug release pattern over time.
- **Ex-vivo permeation studies:** Assess drug permeation through buccal mucosa.
- **Stability studies:** Examine physical and chemical stability during storage.

Table 3: Evaluation Parameters of Buccal Films

Evaluation Test	Purpose
Thickness & weight	Dose uniformity
Folding endurance	Flexibility
Surface pH	Mucosal compatibility



Evaluation Test	Purpose
Tensile strength	Mechanical stability
Mucoadhesive strength	Retention ability
In-vitro release	Drug release profile
Antifungal assay	Therapeutic efficacy

8. Antifungal Evaluation of Herbal Buccal Films

- **In-vitro antifungal assays:** Used to assess antifungal activity against fungal strains.
- **Zone of inhibition studies:** Measure the effectiveness of the formulation against *Candida* species.
- **MIC determination:** Establishes the minimum inhibitory concentration against *Candida albicans*.
- **Comparative analysis:** Antifungal activity is compared with standard antifungal drugs to evaluate efficacy.

9. Safety and Toxicological Considerations

- **Mucosal irritation studies:** Performed to ensure the formulation does not irritate oral tissues.
- **Biocompatibility of polymers:** Confirms safety of polymers used in buccal films.
- **Safety of herbal extracts:** Tulsi, Neem, and Clove are generally regarded as safe for oral use with minimal toxicity.

10. Challenges and Limitations

- Variation in phytochemical content of herbal extracts.
- Difficulties in standardization of herbal formulations.
- Stability and shelf-life concerns due to natural components.
- Regulatory challenges related to herbal drug approval.

11. Future Perspectives

- Translation of herbal buccal films into clinical use.
- Development of advanced and multifunctional polymeric systems.
- Exploration of nano-herbal buccal films for improved efficacy.
- Potential role in personalized therapy for oral fungal infections.

CONCLUSION

Polyherbal mucoadhesive buccal films offer a promising approach for the management of oral fungal infections by providing sustained local drug delivery with improved patient compliance. The combination of **Tulsi, Neem, and Clove** offers synergistic antifungal, anti-inflammatory, and safety benefits. With further research, optimization, and clinical validation, such formulations have strong potential for future pharmaceutical development and commercialization.

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