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Review Article

Polyherbal Mucoadhesive Gel: A Promising Approach for the Treatment of Oral Candidiasis

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Abstract

Oral candidiasis represents a prevalent opportunistic fungal infection in the mouth, primarily triggered by *Candida albicans*. It commonly impacts immunocompromised patients, denture users, individuals with diabetes, and those on extended antibiotic or corticosteroid treatments. Standard antifungal treatments like nystatin, clotrimazole, and fluconazole are commonly employed, yet their long-term application brings drawbacks such as antifungal resistance, systemic adverse effects, low adherence, and frequent relapses. These issues have sparked growing exploration of novel treatment options. Polyherbal mixtures featuring essential oils and plant-based active compounds deliver wide-ranging antifungal, anti-inflammatory, antioxidant, and tissue-repair benefits with minimal toxicity. Integrating these botanicals into mucoadhesive gel formulations boosts effectiveness by extending contact time at the infection site, enabling controlled release, and enhancing localized absorption. Gels formulated with polymers like Hydroxypropyl Methylcellulose (HPMC) and Carbopol offer superior mucosal adhesion and shield irritated tissues from additional harm. Essential oils such as lemongrass, oregano, clove, and tea tree exhibit strong anti-*Candida albicans* effects via mechanisms like membrane disruption, biofilm prevention, and oxidative damage to fungi. This review covers the disease's pathophysiology, shortcomings of traditional therapies, the value of mucoadhesive delivery platforms, the promise of polyherbal strategies, and the role of essential oils in treating oral candidiasis. Ultimately, it posits that polyherbal mucoadhesive gels offer a safe, reliable, and potent option for targeted therapy of oral fungal infections.

Keywords: Oral candidiasis, Mucoadhesive gel, Polyherbal formulation, Essential oils, *Candida albicans*, Antifungal therapy.

Introduction to Oral Candidiasis

Oral candidiasis, commonly referred to as oral thrush, is an opportunistic fungal infection of the oral mucosa predominantly caused by *Candida albicans*, a dimorphic microorganism capable of existing in yeast as well as hyphal forms. Under typical physiological circumstances, *Candida* species exist as harmless commensals within the oral cavity, gastrointestinal tract, and genitourinary system. However, when there is a disruption in host immune defences or alterations in the local oral environment, these organisms can undergo a pathogenic transformation, leading to infection. About 30–50% of healthy people, 50–65% of denture wearers, 65–88% of long-term institutionalized people, and 90–95% of immunocompromised people have Candida albicans (C. albicans) in their mouths.[1] Predisposing factors such as immunosuppression (including conditions like HIV/AIDS and patients undergoing cancer chemotherapy), prolonged use of broad-spectrum antibiotics or corticosteroids, uncontrolled diabetes mellitus, xerostomia (dry mouth), poor oral hygiene, and denture usage significantly contribute to the overgrowth of *Candida* species. [2]

The pathogenicity of *Candida albicans* is attributed to several virulence factors, including its strong ability to adhere to epithelial surfaces, transition from yeast to invasive hyphal forms, and secrete hydrolytic enzymes such as proteases and phospholipases that facilitate tissue invasion. One of the most critical factors contributing to its persistence and resistance is its ability to form biofilms on oral tissues and prosthetic surfaces. These biofilms act as protective barriers, reducing the penetration and efficacy of antifungal agents and shielding the organism from host immune responses.[3]

Clinically, oral candidiasis manifests as creamy white, curd-like lesions on the tongue, buccal mucosa, palate, and oropharyngeal region, which can often be wiped away to reveal erythematous and inflamed mucosa underneath.[4-5] Patients may experience symptoms such as burning sensation, pain, difficulty in swallowing (dysphagia), and altered taste perception. While the condition is generally manageable in healthy individuals, it can pose significant health risks in immunocompromised patients. If left untreated, the infection may spread beyond the oral cavity to the oesophagus and even enter the systemic circulation, leading to severe complications.[6-7]

The current treatment of oral candidiasis primarily involves the use of conventional antifungal agents such as nystatin, clotrimazole, and fluconazole. Although these medications are effective, their use is often associated with certain limitations, including unpleasant taste, frequent dosing requirements, drug intolerance, and potential adverse effects such as hepatotoxicity and gastrointestinal disturbances.[8] Moreover, the increasing incidence of antifungal resistance, particularly among *Candida* species, has become a major clinical concern. Resistance mechanisms such as efflux pump activity, alterations in drug targets, and biofilm-associated protection significantly reduce the efficacy of these drugs, leading to recurrent and persistent infections. [9]

In light of these challenges, there is a growing interest in developing alternative therapeutic strategies that are safe, effective, and capable of overcoming resistance. Herbal and polyherbal formulations, especially when incorporated into advanced drug delivery systems such as mucoadhesive gels, offer a promising approach for the management of oral candidiasis by enhancing local drug retention, providing sustained release, and utilizing multiple mechanisms of antifungal action. [10]

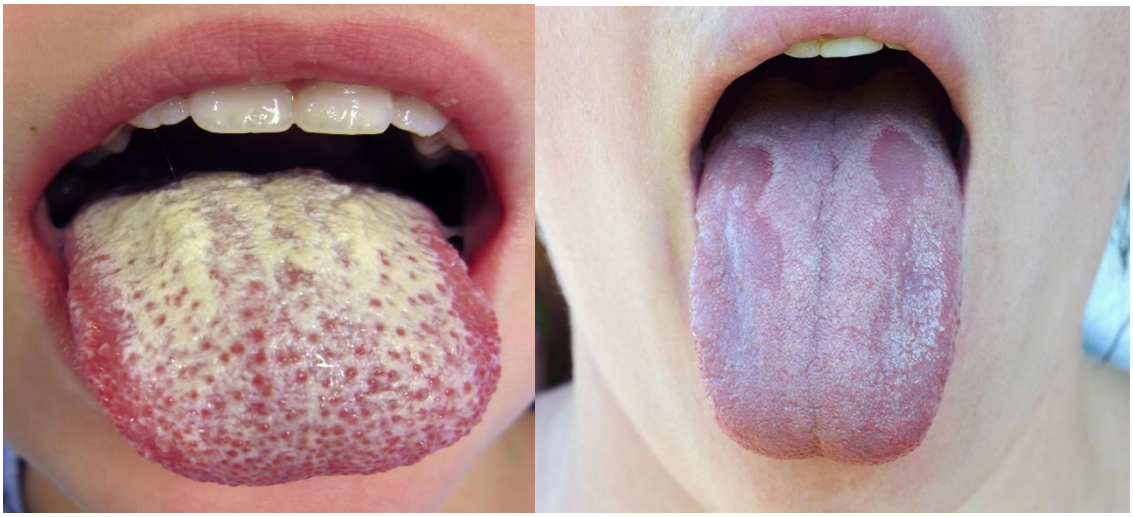


Figure 1: Pictures of oral Candidiasis

Pathophysiology of Oral Candidiasis

Candida albicans is an opportunistic fungal pathogen capable of adhering to epithelial cells and transforming from yeast to hyphal forms. The pathogenicity of *Candida* is associated with several virulence factors including:

- Adhesion to oral epithelial surfaces
- Hyphal transformation
- Biofilm formation
- Secretion of hydrolytic enzymes
- Resistance to host immune responses.[11]

Biofilm formation is one of the most critical virulence factors. Biofilms are structured microbial communities enclosed within an extracellular matrix that protects fungal cells from antifungal drugs and immune defences. These biofilms commonly develop on oral tissues and denture surfaces, resulting in persistent and recurrent infections.[12]

The host immune system plays a major role in controlling *Candida* colonization. Immunosuppression caused by HIV/AIDS, cancer chemotherapy, organ transplantation, diabetes, and corticosteroid therapy weakens host defences and facilitates fungal invasion. [13]

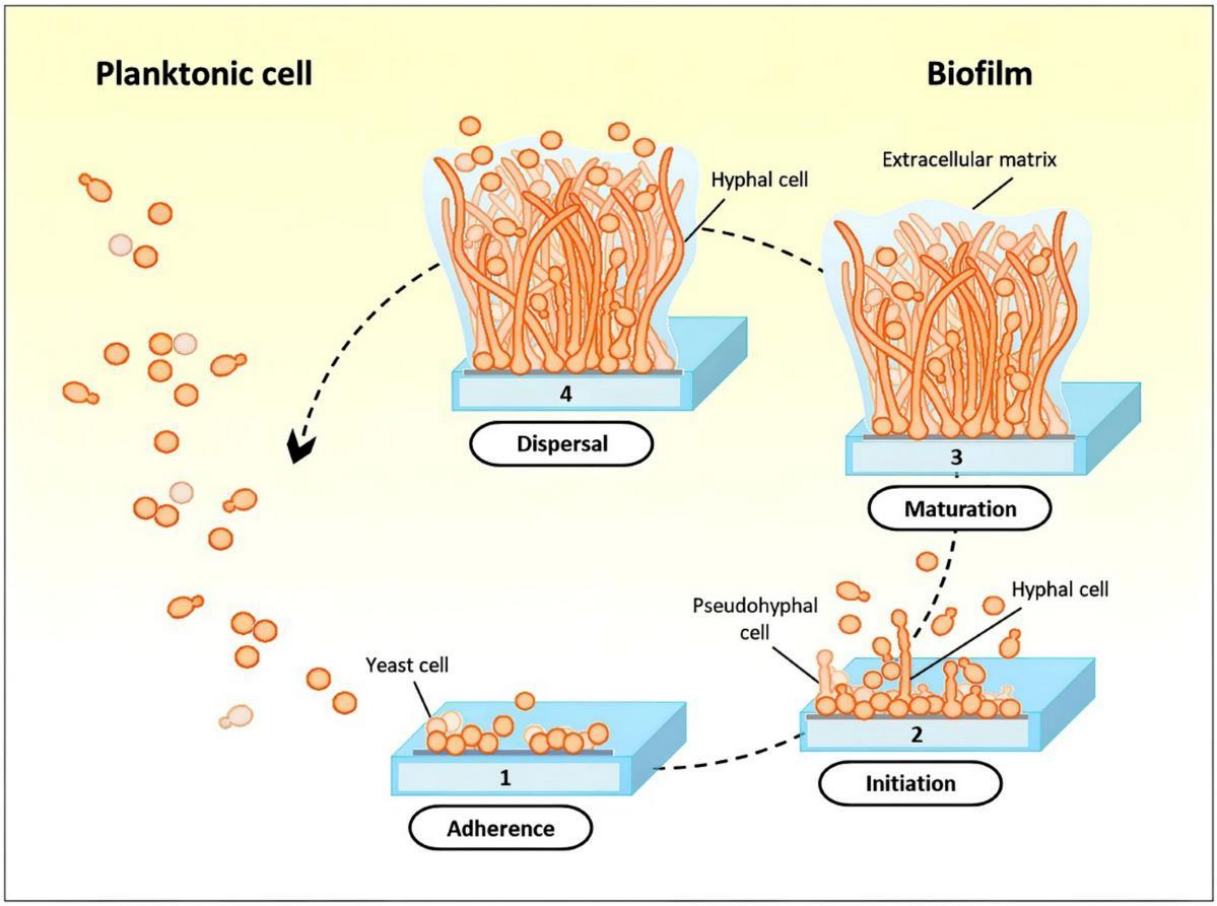


Figure 2: Pathophysiology of Oral Candidiasis

The pathophysiology of oral candidiasis begins with colonization of the oral mucosa by *Candida albicans*, which normally exists as a commensal organism in healthy individuals. Under predisposing conditions such as immunosuppression, diabetes mellitus, prolonged antibiotic therapy, xerostomia, poor oral hygiene, or denture use, the fungus undergoes transformation from its harmless yeast form into the invasive hyphal form. [14] The organism adheres strongly to epithelial surfaces and produces hydrolytic enzymes including proteases and phospholipases that facilitate tissue invasion. Simultaneously, *Candida albicans* forms biofilms on oral tissues and prosthetic surfaces, providing protection against host immune responses and antifungal drugs. This leads to inflammation, epithelial damage, erythema, and formation of characteristic white pseudomembranous lesions associated with oral candidiasis.[15]

Harmfulness and Clinical Significance

Oral candidiasis is not merely a superficial fungal infection but represents a clinically significant condition with both local and systemic implications, particularly in vulnerable patient populations. It typically presents as creamy white, curd-like plaques on the tongue, buccal mucosa, palate, gingiva, and oropharyngeal region. These pseudomembranous lesions can often be gently wiped away, revealing an underlying erythematous, inflamed, and sometimes bleeding mucosal surface.[16] In addition to this classical presentation, other clinical forms such as erythematous (atrophic) candidiasis, hyperplastic candidiasis, and angular cheilitis may also be observed depending on the severity and chronicity of the infection. Patients suffering from oral candidiasis frequently report symptoms such as a persistent burning sensation, oral discomfort or pain, dryness of mouth (xerostomia), altered or metallic taste (dysgeusia), and difficulty in swallowing (dysphagia).[17] These symptoms can significantly interfere with normal oral functions including eating, speaking, and maintaining oral hygiene. As a result, patients may reduce their food intake, leading to nutritional deficiencies, weight loss, and a general decline in health status. In elderly individuals and debilitated patients, this can further contribute to weakness and delayed recovery from other illnesses. [18]

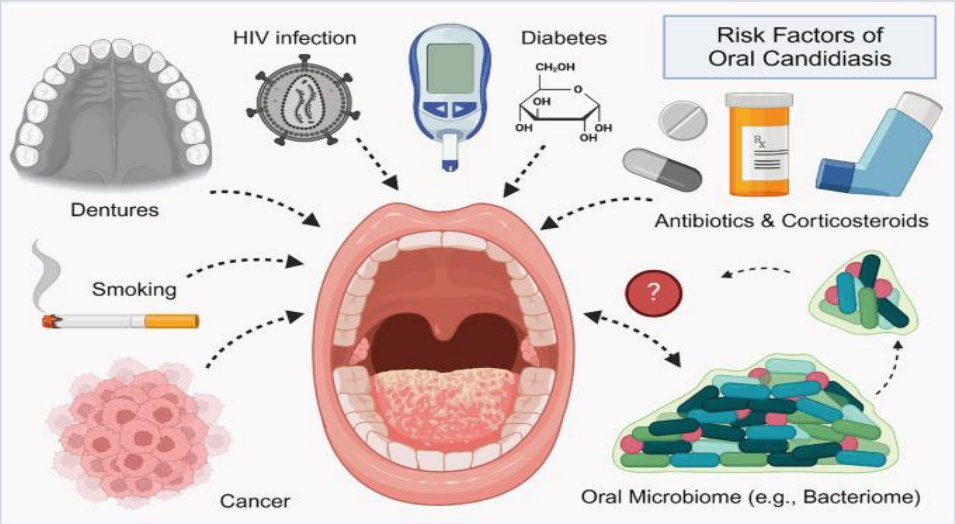


Figure 3: Harmfulness and Clinical Significance

In immunocompromised individuals, such as those with HIV/AIDS, patients undergoing chemotherapy or radiotherapy, organ transplant recipients, or individuals on long-term corticosteroid therapy, oral candidiasis can progress beyond the oral cavity. The infection may extend into the oesophagus, resulting in oesophageal candidiasis, which is characterized by severe pain during swallowing (odynophagia) and can further impair nutritional intake. In rare but serious cases, particularly when host immunity is severely compromised, *Candida* can enter the bloodstream and cause systemic candidiasis (candidemia), a life-threatening condition associated with high morbidity and mortality.[19] Another important clinical aspect of oral candidiasis is its role as a diagnostic indicator of underlying systemic diseases. The presence of recurrent or persistent candidal infection often signals compromised immune function and may be one of the early clinical manifestations of conditions such as HIV infection or poorly controlled diabetes mellitus. In diabetic patients, elevated glucose levels in saliva create a favourable environment for fungal growth, while in HIV patients, reduced CD4+ T-cell counts impair immune defence mechanisms, facilitating opportunistic infections like candidiasis.[20]

Furthermore, the increasing emergence of antifungal resistance has become a major concern in the management of oral candidiasis. Prolonged or repeated use of antifungal agents, particularly azole drugs such as fluconazole, has led to the development of resistant *Candida* strains. The resistance mechanisms include overexpression of efflux pumps that actively expel the drug from fungal cells, alterations in the target enzyme (lanosterol 14α-demethylase), and the formation of protective biofilms that significantly reduce drug penetration. Biofilms not only enhance resistance but also contribute to persistent and recurrent infections, making treatment more challenging. [21] The chronic and recurrent nature of oral candidiasis, combined with drug resistance and systemic involvement, can substantially reduce the quality of life of affected individuals. It imposes both physical discomfort and psychological distress, especially in patients already dealing with underlying chronic illnesses. Therefore, oral candidiasis should be considered a clinically significant condition requiring timely diagnosis, effective management, and the development of safer and more efficient therapeutic alternatives. [22]

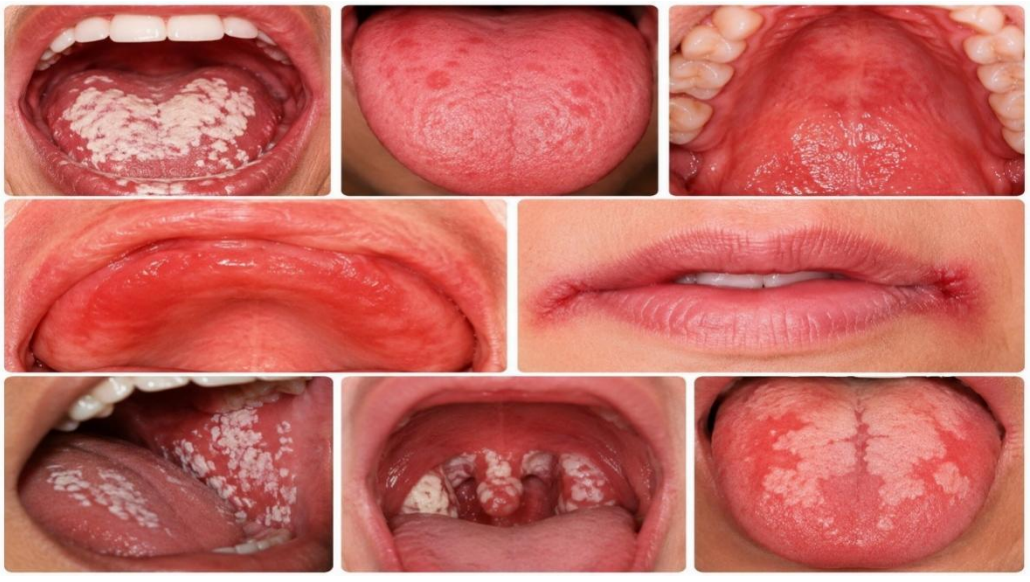


Figure 4: Clinical forms of oral candidiasis

Conventional Treatment and Its Limitations

The conventional management of oral candidiasis primarily relies on antifungal agents such as nystatin, clotrimazole, miconazole, and systemic fluconazole, which are available in various dosage forms including oral suspensions, lozenges, troches, and tablets. These antifungal drugs exert their therapeutic action mainly by targeting the fungal cell membrane. Polyene antifungals like nystatin bind to ergosterol, a key component of the fungal cell membrane, leading to pore formation and leakage of intracellular contents, ultimately causing cell death. On the other hand, azole antifungals such as fluconazole and miconazole inhibit the enzyme lanosterol 14α-demethylase, thereby blocking ergosterol synthesis and compromising membrane integrity and function.[23] Despite their well-established efficacy, the use of these conventional antifungal therapies is associated with several significant limitations that can affect treatment outcomes. One of the major challenges is the development of antifungal resistance, particularly with prolonged or repeated use of azole drugs like fluconazole. Resistance mechanisms in *Candida* species include the overexpression of efflux pumps that actively remove the drug from the fungal cell, mutations in the target enzyme that reduce drug binding, and the ability to form biofilms on oral surfaces and prosthetic devices. Biofilms act as protective barriers, significantly reducing drug penetration and shielding fungal cells from both antifungal agents and host immune responses, thereby contributing to persistent and recurrent infections. [24]

Another important limitation is the requirement for frequent dosing, especially in the case of topical formulations such as nystatin suspension or clotrimazole lozenges, which need to be administered multiple times a day. This frequent dosing schedule can lead to poor patient compliance, particularly among elderly patients, children, and those with chronic illnesses. Additionally, many of these formulations have an unpleasant taste or texture, further reducing patient acceptability and adherence to the treatment regimen. Adverse effects associated with conventional antifungal therapy also pose a concern.[25] Topical agents may cause local irritation, burning sensation, or allergic reactions, while systemic antifungals like fluconazole are associated with potential side effects such as hepatotoxicity, gastrointestinal disturbances (nausea, vomiting, abdominal pain), and drug-drug interactions, especially in patients on multiple medications. These safety concerns limit their long-term use and necessitate careful monitoring.[26]

Furthermore, conventional dosage forms often fail to maintain adequate drug concentration at the site of infection due to rapid clearance by saliva and mechanical actions such as swallowing and tongue movement. This results in reduced contact time between the drug and the infected mucosal surface, leading to suboptimal therapeutic efficacy. Consequently, higher doses or prolonged treatment durations may be required, which can further increase the risk of side effects and resistance.[27] In addition, recurrence of infection is commonly observed after discontinuation of therapy, particularly in patients with underlying predisposing conditions. This highlights the inability of conventional treatments to completely eradicate the infection or prevent re-colonization. Overall, these limitations underscore the need for alternative approaches, such as mucoadhesive drug delivery systems and polyherbal formulations, which can provide prolonged drug retention, improved efficacy, reduced side effects, and better patient compliance. [28]

Mucoadhesive Gel Drug Delivery System

Mucoadhesive drug delivery systems represent an advanced and highly effective approach for the localized treatment of oral infections, particularly oral candidiasis. A mucoadhesive gel is a semi-solid formulation designed to adhere firmly to the mucosal surface of the oral cavity, thereby significantly increasing the residence time of the drug at the site of infection. This prolonged contact enhances drug absorption and ensures sustained therapeutic action. Unlike conventional dosage forms that are rapidly washed away by saliva, mucoadhesive gels remain attached to the mucosa, providing a controlled and localized drug delivery system.[29] The mechanism of mucoadhesion is based on a series of physicochemical interactions between the polymeric components of the gel and the mucin layer covering the oral mucosa. Initially, the gel comes into contact with the mucosal surface and undergoes hydration and swelling. This is followed by interpenetration of polymer chains with the glycoprotein chains of mucin, leading to the formation of a strong adhesive bond. The adhesion is further strengthened by secondary chemical interactions such as hydrogen bonding, van der Waals forces, and electrostatic attraction. These interactions collectively result in firm attachment of the gel to the mucosal surface, resisting dislodgement by saliva and mechanical movements within the oral cavity. [30]

Polymers such as Hydroxypropyl Methylcellulose (HPMC) and Carbopol are widely used in the formulation of mucoadhesive gels due to their excellent swelling capacity, biocompatibility, and strong adhesive properties. HPMC forms a viscous gel upon hydration and provides sustained drug release, while Carbopol, being a polyacrylic acid derivative, exhibits strong bioadhesion due to the presence of carboxyl groups that form hydrogen bonds with mucin. The combination of these polymers can further enhance the gel's consistency, adhesion strength, and drug release profile.[31] One of the major advantages of mucoadhesive gel systems is their ability to provide sustained and controlled drug release at the site of infection. This ensures that a consistent therapeutic concentration of the drug is maintained over an extended period, reducing the need for frequent application. Additionally, localized drug delivery minimizes systemic absorption, thereby reducing the risk of systemic side effects and drug interactions. Improved bioavailability is another key benefit, as the drug is directly delivered to the target site without significant loss.[32]

Furthermore, mucoadhesive gels enhance patient compliance by reducing dosing frequency and providing ease of application. They are non-invasive, comfortable to

use, and can be easily applied to the affected area. In the case of oral candidiasis, where the infection is localized to the mucosal surface, this delivery system is particularly advantageous as it ensures prolonged contact between the antifungal agent and the infected tissue, leading to improved therapeutic outcomes.[33-34] In addition, mucoadhesive gels can act as protective barriers over the infected mucosa, reducing irritation and promoting healing. They can also be formulated with additional agents such as penetration enhancers, preservatives, and flavouring agents to improve stability and patient acceptability. Overall, mucoadhesive gel drug delivery systems provide a targeted, efficient, and patient-friendly approach for the management of oral infections, making them an ideal platform for incorporating polyherbal antifungal agents. [35]

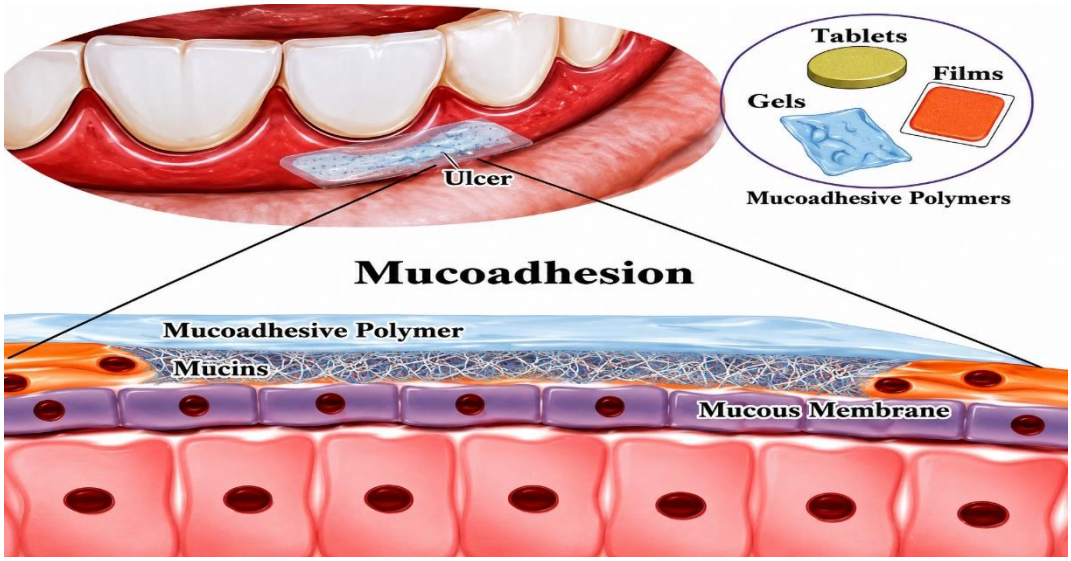


Figure 5: Mucoadhesive Gel Drug Delivery System

Mechanism of Mucoadhesion

The mechanism of mucoadhesive gel drug delivery involves a series of sequential physicochemical interactions between the mucoadhesive polymer and the mucosal surface. These interactions ensure prolonged retention of the formulation at the site of application, leading to sustained drug release and improved therapeutic efficacy. [36]

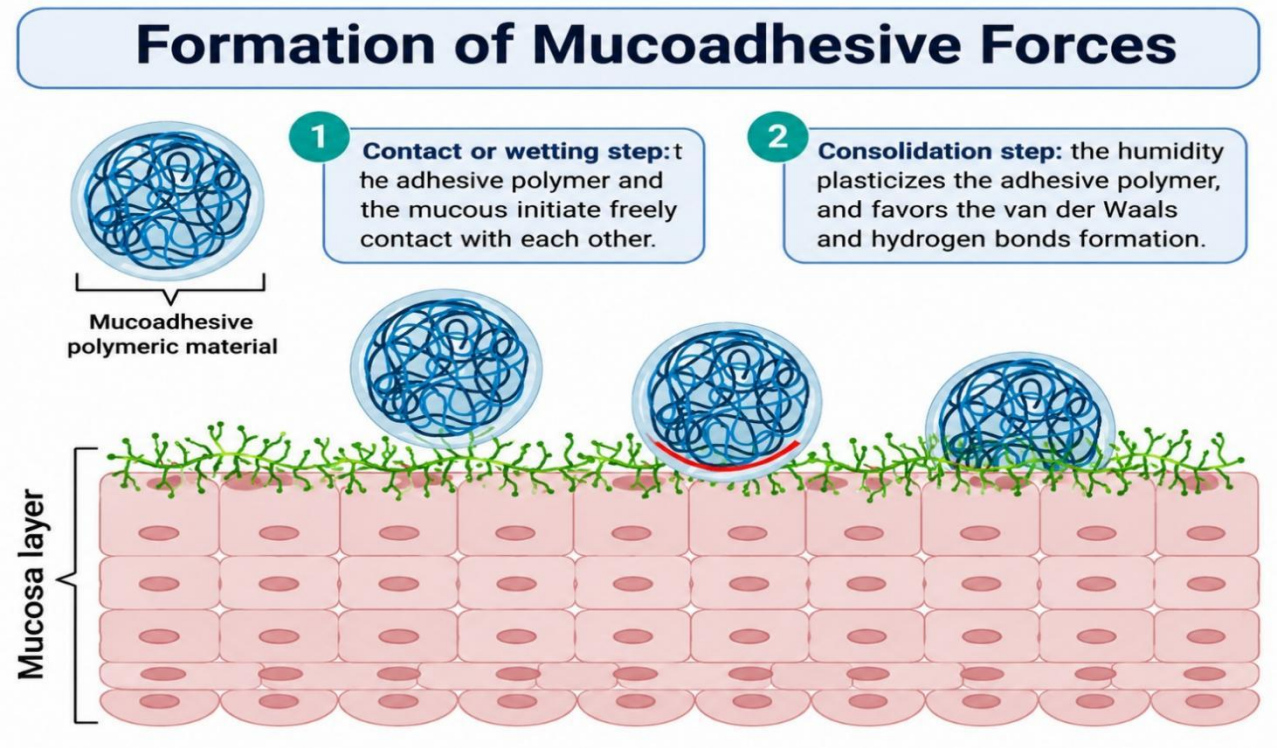


Figure 6: Mechanism of Mucoadhesion

Step 1: Contact Stage

In the first stage, the mucoadhesive gel comes into close contact with the oral mucosal surface. The gel spreads over the mucosa and wets the tissue surface. Adequate hydration allows the polymer chains to become flexible and interact with mucus glycoproteins.

Step 2: Wetting and Swelling

After contact, the hydrophilic polymers present in the gel absorb saliva and swell. Swelling increases the surface area available for interaction and promotes intimate contact between the polymer and mucosal layer.

Step 3: Interpenetration of Polymer Chains

The swollen polymer chains interpenetrate with mucin glycoprotein chains present in the mucus layer. This interdiffusion forms a semi-permanent adhesive network between the gel and mucosal surface.

Step 4: Formation of Adhesive Bonds

Strong adhesive bonds are formed through:

- Hydrogen bonding
- Van der Waals forces
- Electrostatic interactions
- Hydrophobic interactions

These interactions result in firm adhesion of the gel to the oral mucosa.

Step 5: Sustained Drug Release

Once attached, the gel slowly releases the incorporated drug or herbal constituents over an extended period. This maintains a therapeutic drug concentration at the site of infection and improves treatment effectiveness. [37-38]

Advantages of Mucoadhesive Drug Delivery System

1. Prolonged Residence Time

Mucoadhesive formulations adhere firmly to the mucosal surface, allowing the drug to remain at the site of application for an extended period. This improves therapeutic effectiveness.

2. Sustained and Controlled Drug Release

The drug is released slowly from the formulation over time, maintaining a constant therapeutic concentration and reducing fluctuations in drug levels.

3. Improved Bioavailability

Direct contact with the mucosal surface enhances drug absorption and minimizes drug loss caused by saliva washout and swallowing.

4. Reduced Dosing Frequency

Because of prolonged retention and sustained release, repeated administration is minimized, improving patient convenience and compliance.

5. Enhanced Patient Compliance

Mucoadhesive gels are easy to apply, non-invasive, and comfortable for patients, especially in oral conditions like candidiasis.

6. Localized Drug Action

The drug acts directly at the infected site, producing high local drug concentration while reducing systemic exposure.

7. Reduced Systemic Side Effects

Minimal systemic absorption lowers the risk of adverse effects and drug interactions commonly associated with oral or systemic antifungal therapy.

8. Protection of Mucosal Surface

Mucoadhesive gels form a protective layer over inflamed or ulcerated mucosa, reducing irritation and promoting healing.

9. Better Therapeutic Efficacy

Prolonged contact between the drug and mucosa improves penetration and enhances antifungal activity against pathogens like *Candida albicans*.

10. Suitable for Herbal Formulations

Mucoadhesive systems are highly suitable for incorporating herbal extracts and essential oils, improving stability and retention of natural bioactive compounds. [39-40]

Polyherbal Approach in Treatment

The polyherbal approach in treatment is based on the principle of combining two or more herbal ingredients in a single formulation to achieve enhanced therapeutic efficacy through synergistic action. Unlike single-drug therapy, which typically targets a specific pathway or mechanism, polyherbal formulations act on multiple biological targets simultaneously. This multi-targeted approach is particularly beneficial in managing complex infections such as oral candidiasis, where the pathogen exhibits diverse virulence mechanisms including adhesion, biofilm formation, and enzyme-mediated tissue invasion. By acting on several pathways at once, polyherbal systems not only improve overall effectiveness but also significantly reduce the likelihood of resistance development.[41] One of the key advantages of polyherbal formulations is the concept of synergy, where the combined effect of multiple herbal constituents is greater than the sum of their individual effects. In antifungal therapy, this means that different phytochemicals can work together to disrupt fungal cell membranes, inhibit enzyme systems, prevent biofilm formation, and interfere with fungal metabolism. For instance, one herbal component may enhance membrane permeability, allowing another component to penetrate more effectively and exert its action. This synergistic interaction leads to improved antifungal activity even at lower concentrations, thereby minimizing potential toxicity. [42]

Another important aspect of polyherbal therapy is its safety profile. Herbal formulations are generally considered safer compared to synthetic drugs due to

their natural origin and long history of traditional use. They tend to produce fewer side effects and are better tolerated, especially for long-term use. This is particularly relevant in conditions like oral candidiasis, which may require prolonged or repeated treatment. Additionally, herbal ingredients often possess multiple pharmacological properties such as anti-inflammatory, antioxidant, antimicrobial, and wound-healing activities. These combined effects not only help in eliminating the fungal infection but also aid in reducing inflammation, relieving symptoms like burning and pain, and promoting faster healing of the damaged mucosal tissues.[43] In the context of oral candidiasis, polyherbal formulations offer a comprehensive therapeutic approach. The antifungal components directly inhibit the growth of *Candida* species, while anti-inflammatory agents reduce mucosal irritation and swelling. Antioxidants help in neutralizing free radicals and protecting the mucosal cells from oxidative damage, and wound-healing agents promote tissue regeneration. This holistic action ensures not only the eradication of the infection but also restoration of normal oral mucosal health.[44] Furthermore, polyherbal formulations are less likely to induce microbial resistance due to their complex composition and multiple mechanisms of action. Unlike synthetic antifungal drugs that target a single enzyme or pathway, herbal compounds exert a broad-spectrum effect, making it difficult for microorganisms to develop adaptive resistance. This is a significant advantage in the current scenario where antifungal resistance is a growing concern. [45]

In addition, polyherbal formulations can be effectively incorporated into advanced drug delivery systems such as mucoadhesive gels. This combination further enhances their therapeutic potential by ensuring prolonged retention at the site of infection, controlled drug release, and improved patient compliance. The pleasant taste and natural origin of herbal ingredients also contribute to better acceptability among patients. Overall, the polyherbal approach represents a rational and effective strategy for the treatment of oral candidiasis, offering synergistic action, improved safety, reduced resistance, and comprehensive therapeutic benefits. [46]

Role of Essential Oils in Antifungal Therapy

Essential oils are concentrated, volatile, and aromatic compounds extracted from various parts of plants such as leaves, flowers, stems, bark, and roots. In recent years, they have gained significant attention in pharmaceutical research due to their potent antimicrobial properties, particularly their antifungal activity against pathogens like *Candida albicans*. Their natural origin, broad-spectrum activity, and multi-target mechanisms make them promising alternatives or adjuncts to conventional antifungal agents, especially in the management of infections like oral candidiasis. The antifungal activity of essential oils is primarily attributed to their complex chemical composition, which includes terpenes, terpenoids, phenols, aldehydes, and alcohols. These bioactive compounds are highly lipophilic, allowing them to easily penetrate the lipid-rich fungal cell membrane. [47] Once inside, they disrupt the structural integrity of the cell membrane by interacting with ergosterol, an essential component of fungal membranes. This disruption leads to increased membrane permeability, causing leakage of vital intracellular components such as ions, proteins, and nucleic acids, ultimately resulting in fungal cell death. [48]

In addition to membrane disruption, essential oils interfere with various intracellular processes. They inhibit key enzymes involved in fungal metabolism, energy production, and cell wall synthesis. Some essential oil components can also induce oxidative stress within fungal cells by generating reactive oxygen species (ROS), which damage cellular proteins, lipids, and DNA. This multi-faceted mode of action makes essential oils highly effective against fungal pathogens and reduces the likelihood of resistance development, as the organism would need to adapt to multiple simultaneous targets. One of the most important advantages of essential oils in antifungal therapy is their ability to inhibit biofilm formation.[49] Biofilms are structured communities of fungal cells enclosed within a protective extracellular matrix, which significantly enhances resistance to antifungal drugs and host immune responses. Essential oils can disrupt biofilm formation by preventing initial adhesion of fungal cells to surfaces, inhibiting hyphal development, and degrading the extracellular matrix. This property is particularly valuable in oral candidiasis, where *Candida* forms biofilms on mucosal surfaces and dentures.[50] Furthermore, essential oils exhibit additional therapeutic properties such as anti-inflammatory, antioxidant, and analgesic effects. These properties help in reducing inflammation, relieving pain and burning sensation, and promoting healing of the affected mucosal tissues. This holistic therapeutic action makes essential oils highly suitable for incorporation into topical formulations such as gels, mouthwashes, and sprays. [51]

Another key advantage of essential oils is their synergistic potential when used in combination with other essential oils or antifungal agents. When combined, different components can enhance each other's activity, resulting in improved antifungal efficacy at lower concentrations. This not only increases effectiveness but also minimizes potential toxicity and side effects. In the context of drug delivery, essential oils can be effectively incorporated into mucoadhesive gel systems for the treatment of oral candidiasis. The mucoadhesive nature of the gel ensures prolonged contact of the essential oils with the infected mucosa, enhancing their penetration and therapeutic action.[52] Additionally, the controlled release of essential oils from the gel maintains an effective concentration at the site of infection for an extended period. Overall, essential oils represent a powerful and versatile class of natural antifungal agents with multiple mechanisms of action, including membrane disruption, enzyme inhibition, oxidative damage, and biofilm inhibition. Their safety profile, synergistic potential, and additional therapeutic benefits make them an excellent choice for developing innovative formulations such as polyherbal mucoadhesive gels for the effective management of oral candidiasis. [53]

Mechanism of Antifungal Action of Essential Oils

Essential oils contain bioactive phytochemicals such as terpenes, terpenoids, phenols, aldehydes, and alcohols that exhibit potent antifungal activity against *Candida albicans, etc*. Their lipophilic nature enables them to penetrate fungal cell membranes and disrupt vital cellular functions through multiple mechanisms. [54]

1. Disruption of Fungal Cell Membrane

Essential oils interact with ergosterol, a major structural component of the fungal cell membrane. This interaction damages membrane integrity and destabilizes the lipid bilayer.

Effect:

- Structural damage to membrane
- Loss of membrane stability
- Leakage of cellular contents

2. Increased Membrane Permeability

After membrane disruption, the permeability of the fungal membrane increases significantly. This causes uncontrolled movement of ions and intracellular molecules.

Effect:

- Leakage of proteins and nucleic acids
- Loss of potassium ions
- Cellular dehydration
- Cell death [55]

3. Induction of Oxidative Stress

Certain essential oil components stimulate excessive production of reactive oxygen species (ROS) inside fungal cells.

Effect:

- Oxidative damage to proteins
- Lipid peroxidation
- DNA damage
- Mitochondrial dysfunction

4. Inhibition of Fungal Enzymes

Essential oils inhibit enzymes involved in:

- Ergosterol biosynthesis
- Energy metabolism
- Cell wall synthesis

Effect:

- Impaired fungal growth
- Reduced metabolic activity
- Inhibition of fungal replication

5. Prevention of Biofilm Formation

Essential oils interfere with adhesion and hyphal formation, thereby preventing biofilm development on oral mucosa and denture surfaces.

Effect:

- Reduced fungal colonization
- Improved susceptibility to antifungal agents
- Prevention of recurrent infection [56]

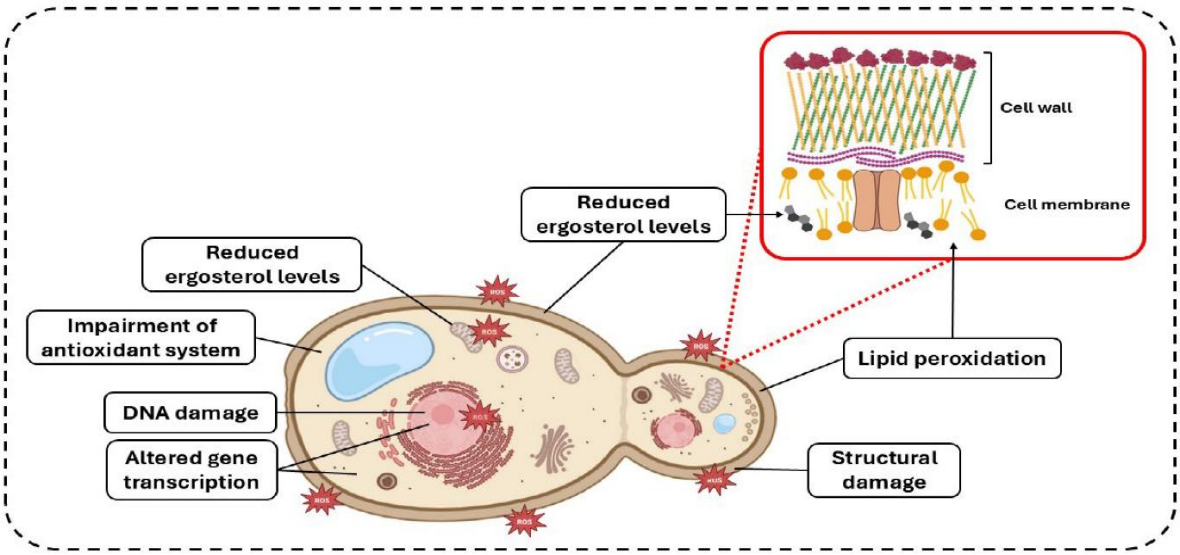
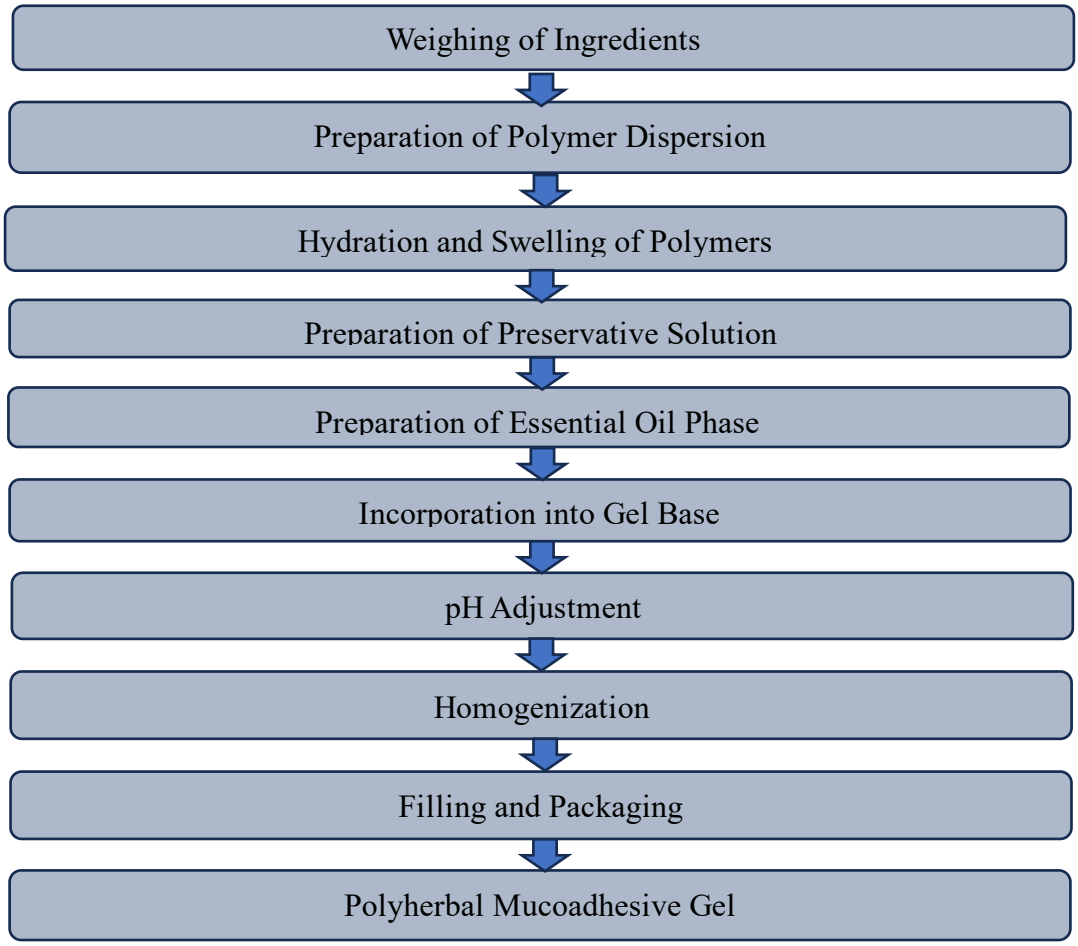


Figure 7: Mechanism of Antifungal Action of Essential Oils

Method of Preparation of Polyherbal Mucoadhesive Gel for Oral Candidiasis



Evaluation Parameters of Mucoadhesive Gel

The prepared gel formulations are evaluated using the following parameters:

Table 1: Evaluation Parameters of Mucoadhesive Gel

Evaluation Parameter	Significance
Physical appearance	Colour, homogeneity, consistency
pH	Compatibility with oral mucosa
Spreadability	Ease of application
Viscosity	Gel consistency
Mucoadhesive strength	Retention ability
Drug content	Uniformity of active constituents
In-vitro drug release	Sustained release profile
Antifungal activity	Efficacy against *Candida albicans*
Stability study	Shelf-life determination

Future Perspectives

The rapid emergence of antifungal resistance among *Candida* species has become a major global healthcare concern and has significantly challenged the effectiveness of conventional antifungal therapies. Extensive and repeated use of azole antifungal drugs such as fluconazole has resulted in the development of resistant fungal strains through mechanisms including efflux pump overexpression, alteration of drug target enzymes, and biofilm-mediated protection. In addition, conventional antifungal treatments are often associated with adverse effects, frequent dosing requirements, poor patient compliance, and recurrent infections. These limitations have created a growing demand for safer,

more effective, and patient-friendly therapeutic alternatives.

In this context, polyherbal mucoadhesive gels have emerged as a highly promising strategy for the management of oral candidiasis. These formulations combine the therapeutic advantages of herbal medicines with advanced mucoadhesive drug delivery systems, offering a multi-functional approach for localized antifungal therapy.[57]

Natural Origin and Better Safety Profile

One of the most important future advantages of polyherbal formulations lies in their natural origin. Herbal ingredients and essential oils are generally considered safer and more biocompatible compared to synthetic antifungal agents. Medicinal plants have been used for centuries in traditional systems of medicine and are associated with fewer toxic effects when used appropriately.[58]

Essential oils such as lemongrass oil, oregano oil, clove oil, cinnamon oil, and tea tree oil possess potent antifungal properties along with anti-inflammatory, antioxidant, analgesic, and wound-healing activities. Because these natural compounds act locally at the site of infection, systemic exposure is minimized, thereby reducing the risk of hepatotoxicity, gastrointestinal disturbances, and drug interactions commonly associated with systemic antifungal drugs. [59]

Furthermore, herbal formulations are better tolerated during long-term use, making them suitable for recurrent oral candidiasis and chronic oral fungal infections.

Multi-Target Antifungal Mechanisms

Unlike conventional antifungal drugs that usually target a single metabolic pathway, polyherbal formulations act through multiple mechanisms simultaneously. This multi-target action is highly beneficial in overcoming fungal resistance and improving therapeutic efficacy.

The bioactive constituents present in essential oils and herbal extracts exert antifungal activity through:

- Disruption of fungal cell membranes
- Inhibition of ergosterol synthesis
- Leakage of intracellular components
- Induction of oxidative stress
- Inhibition of fungal enzymes
- Prevention of adhesion and biofilm formation

Because several phytochemicals act together on multiple fungal targets, microorganisms find it more difficult to develop adaptive resistance. This broad-spectrum and synergistic activity makes polyherbal therapy a promising alternative in the era of increasing antifungal resistance.[60]

In future pharmaceutical research, combinations of different herbal extracts may be optimized to achieve maximum synergistic activity against resistant *Candida* strains.

Improved Patient Compliance

Patient compliance plays a crucial role in successful treatment outcomes, especially in chronic and recurrent infections. Conventional oral antifungal formulations such as mouthwashes, suspensions, and lozenges often require frequent administration due to rapid clearance by saliva and swallowing. This frequent dosing schedule can reduce adherence to therapy.

Mucoadhesive gel systems significantly improve patient compliance by:

- Prolonging retention time in the oral cavity
- Providing sustained and controlled drug release
- Reducing dosing frequency
- Enhancing comfort during application
- Improving taste and acceptability

The semi-solid gel formulation adheres firmly to the oral mucosa and ensures prolonged contact of herbal actives with infected tissues. This localized and sustained action enhances therapeutic effectiveness while improving convenience for patients. [61]

Future formulations may further incorporate flavouring agents, nano emulsions, and advanced bioadhesive polymers to improve patient acceptability and comfort.

Reduced Adverse Effects

Another important future advantage of polyherbal mucoadhesive gels is the reduction of adverse effects associated with conventional antifungal therapy. Systemic antifungal drugs may cause hepatotoxicity, nephrotoxicity, gastrointestinal irritation, and drug-drug interactions, particularly in immunocompromised patients receiving multiple medications.

Localized delivery through mucoadhesive gels minimizes systemic absorption and concentrates the therapeutic action directly at the site of infection. This targeted drug delivery approach reduces the risk of systemic toxicity while maintaining effective antifungal activity.

Additionally, herbal ingredients often possess anti-inflammatory and antioxidant properties that help reduce mucosal irritation, pain, and tissue damage, thereby improving the healing process.

Conclusion

Oral candidiasis remains a significant opportunistic fungal infection, particularly among immunocompromised individuals. Conventional antifungal therapies, although effective, are associated with several drawbacks including resistance, adverse effects, and poor retention in the oral cavity. Polyherbal mucoadhesive gels offer an innovative and promising alternative by combining the synergistic therapeutic benefits of herbal agents with the advantages of localized mucoadhesive drug delivery systems. Essential oils possess potent antifungal, anti-inflammatory, antioxidant, and biofilm inhibitory properties that contribute to effective management of oral candidiasis. Mucoadhesive gels further enhance therapeutic efficacy

by prolonging residence time, improving drug bioavailability, and reducing dosing frequency. Therefore, polyherbal mucoadhesive gels may serve as a safe, effective, and patient-friendly approach for the treatment of oral candidiasis.

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