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Azole Antifungal Lozenges for Oral Candidiasis: Mechanism, Efficacy, and Emerging Resistance.

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ABSTRACT:

Lozenges are an effective pharmaceutical form for delivering medications to treat conditions affecting the mouth and throat. These solid preparations dissolve slowly, providing both local and systemic effects. First conceptualized by James Lofthouse in 1865, lozenges have evolved into a convenient remedy for infections, coughs, and sore throats. Their advantages include prolonged drug action, ease of administration, and improved absorption, though they may cause inconsistent drug distribution and accidental swallowing. Commonly, lozenges incorporate agents such as antibiotics, antifungals, and anesthetics. Notably, miconazole and clotrimazole azole-based antifungal agents—are widely used to treat oral candidiasis, a fungal infection primarily caused by *Candida albicans*. Miconazole disrupts fungal cell membranes, while clotrimazole shows high efficacy in immunocompromised individuals, such as HIV patients or those undergoing chemotherapy. However, antifungal resistance is a growing concern, driven by genetic mutations, structural alterations, and increased drug efflux in fungal cells. To counteract this, researchers are exploring advanced drug delivery systems like bioadhesive lozenges, which extend drug contact time within the oral cavity, improving therapeutic outcomes while minimizing systemic exposure.

Keywords: Lozenges, miconazole, clotrimazole, *Candida albicans.*

INTRODUCTION:

Oral candidiasis, commonly called as oral thrush, is a frequent mycotic infection affecting the buccal mucosa, particularly in immunocompromised patients such as those undergoing chemotherapy, radiation, or living with HIV. As its incidence continues to rise, effective and patient-friendly treatments are in demand.

Medicated lozenges have emerged as a promising mode of antifungal drug delivery due to their ability to maintain prolonged contact with buccal tissues, enabling targeted action and better patient compliance. Azole-based medications such as miconazole and clotrimazole have proven efficacy in treating oral candidiasis by inhibition of ergosterol biosynthesis in mycotic cell membranes.

However, recent reports of azole resistance attributed to genetic mutations, efflux mechanism, as well as structural changes in Candida species warrant investigation into more innovative delivery methods.

This review aims to explore the formulation, mechanism, and clinical utility of azole antifungal lozenges, evaluate emerging resistance trends, as well as highlight gaps in current antifungal strategies.

The paper is structured as follows: a review of relevant literature, methodology of formulation approaches, analysis of therapeutic results, discussion of resistance, and a conclusion offering implications, limitations, and future research directions

Lozenges:

Lozenges are solid(1), flavored, medicated dosage forms(2) designed to dissolve or disintegrate slowly in the mouth(3). Typically sweetened(4), these forms often contain one or more active ingredients(5) intended to provide local or systemic therapeutic effects(6). They are primarily used to relieve symptoms such as sore throat or cough by gradually releasing the active medication when sucked or held in the mouth(7). Lozenges are also beneficial for delivering medication via the buccal mucosa, allowing for both local and systemic effects(6). Their slow dissolution provides a sustained therapeutic action, making them a preferred method for treating throat-related discomfort and other conditions(1).

HISTORY:

James Lofthouse was born in Lancaster, England, in 1842. In 1865, he opened a small drugstore in Fleetwood, a busy fishing town on the Fylde coast. Back then, the town was full of fishermen working the North Atlantic, many of them struggling with serious chest and breathing problems from the harsh conditions at sea. Seeing a real need, James came up with a powerful remedy — a strong mix of menthol, eucalyptus oil, capsicum, and liquorice. The idea was to drop it onto sugar and breathe it in to help clear the lungs. But there was a problem: the glass bottles he sold it in kept breaking during rough trips out on the ocean. To fix this, James got a creative idea, he turned the liquid remedy into a solid form — a sugar-based lozenge made with the same ingredients, which was rolled out, cut into pieces, and dried in an oven. It worked perfectly. The fishermen loved it and would often come into his shop asking for “an ounce of the friends” or “a bag of fisherman’s tablets”, and just like that, the “Fisherman’s friend” were developed.(3).

ADVANTAGES:

Increased bioavailability by avoiding first- pass metabolism(1,5–7).

Reduction in gastric vexation compared to oral tablets(1,6).

Ease of administration for pediatric, senior, and dysphagic cases(2,3,5,7).

Immediate onset of action with dragged medicine exertion(2,6).

Original and systemically good through buccal mucosa immersion(3,5).

No need of water for administration(7).

Inflexibility in expression to suit case requirements(7).

Pleasant taste achieved with sweeteners and flavors(3,7).

Cost-effective with minimum product time and outfit(2,7).

Medicine pullout option if necessary during use(7).

Advanced case compliance due to convenience and taste masking(3,7).

DISADVANTAGES:

Non-uniform drug distribution in saliva for local therapy(5,7,8).

Possible drug drainage to the stomach with saliva(5,7).

Risk of accidental swallowing of the entire dosage form(7).

Potential confusion with candy, requiring caution and secure storage(3,8).

Unsuitability of some drugs (e.g., benzocaine) with aldehyde candy bases(3).

Heat stability and minimal bitterness are critical for drug selection(3).

Lozenges are generally safe for children aged 6 and above(3).

CLASSIFICATION:

Lozenges can be classified into several categories on grounds of different methods, as follows:

❖ **According to the Site of Action**
➢ **Local Effects**
- Example: Antiseptics, Decongestants, Antibiotics

➢ **Systemic Effects**
- Example: Vitamins, Nicotine

❖ **According to Texture and Composition**
▪ **Hard Lozenges**
- Example: Hard candy lozenges

▪ **Compressed Lozenges**
♦ Example: Compressed tablet lozenges
▪ **Soft Lozenges**
▪ **Chewy or Caramel-Based Medicated Lozenges**
▪ **Center-Filled Lozenges**(1,2,5,7)

❖ **Based on Purpose**
➢ **Medicated Lozenges**
- Examples: For local or systemic action (e.g., antiseptics, vitamins)

➢ **Non-Medicated Lozenges**
- Examples: Sugar candies, lollipops(6)

MEDICATIONS:

Medications Delivered Through Lozenges

Drug candidates that can be incorporated into lozenges belong to the following categories:

➢ **Antiseptics** – Used to kill or inhibit the growth of microorganisms, providing protection against infections.
➢ **Local Anesthetics** – Provide pain relief by numbing the affected area.
➢ **Antibiotics** – Treat bacterial infections localized in the throat or oral cavity.
➢ **Antihistamines** – Alleviate symptoms of allergies such as itching, swelling, and irritation.
➢ **Antitussives** – Suppress coughing, providing relief from persistent cough.
➢ **Analgesics** – Relieve pain and discomfort.
➢ **Decongestants** – Reduce nasal or sinus congestion.
➢ **Antifungals** – Treat and prevent fungal infections.
➢ **Demulcents** – Soothe irritation or inflammation of mucous membranes by forming a protective film.

These categories cover a wide range of therapeutic applications for lozenges, making them an effective delivery method for localized and systemic treatments(1,2,8).

ORAL CANDIDIASIS:

Fungal infections are veritably usual amid individualities in diurnal healthcare services(9). Topical treatments for fungal infections are recognized to be desirable than systemic treatment among different individualities(10). Still, certain drawbacks for accepted topical curatives such as limited mucosal time of contact and repeated administration are noted(11). Different types of lozenges became actuality for advancing the API conveyance at the point of activity(12). Achievement of appropriate blood concentration within a destined timeline is thought to be confirmation of clinical effectiveness of technical lozenges. Still, it must be flashed back that conveyance too incorporates the part of case literally ingesting the drug in an unbridled form. Therefore there's requirement of intuitive, accessible lozenge formulation(13). Fungal infections could be managed by using anti-fungal medicines similar to Miconazole, It can be given in the form tablets that enhances the residence duration in oral depression(14). The recent disquisition is aimed to ameliorate patient conformity(6)**.**

Fungal infections, like oral candidiasis, can be managed by antifungal drugs like Miconazole(15). When formulated as lozenges, these medications can enhance the duration of contact with the oral cavity, improving efficacy and potentially boosting patient compliance(6).

Oral candidiasis, or oropharyngeal candidiasis, is a fungal infection affecting patients with compromised immune systems(16). It is commonly observed in individuals with conditions such as AIDS, denture stomatitis, as well as a side effect of cancer chemotherapy or radiotherapy. The chief causative agent is *Candida albicans*.(17) While *Candida* species can exist harmlessly on the skin and mucous membranes, they can transform into a pathogenic form, invading tissues and developing acute as well as chronic diseases to the patient.(18)

The buccal opening is often the initial site of infection, with candidiasis potentially spreading towards the esophagus as well as gastrointestinal tract(19). The key factor triggering the transformation of commensal *Candida* into its pathogenic form is a weakened immune system, which may result from aging, malnutrition, chemotherapy, immunosuppressive therapies, or severe diseases such as HIV or cancer.(18)

Symptoms of oral candidiasis vary widely, ranging from asymptomatic cases to those with a sore or painful mouth, burning sensations on the tongue, and difficulty swallowing, particularly when the hypopharynx is affected(20). This condition can significantly impair quality of life, reducing food and fluid intake. Left untreated, oral candidiasis may lead to progressive colonization, causing discomfort and increasing the risk of more severe infections, such as esophageal candidiasis.(18)

Oral candidiasis is primarily occurring by an rampant abundance of yeast-like fungi, including more than 20 species of *Candida*(21). Amid these, *Candida albicans* is the most common microbe, though other species like *C. tropicalis*, *C. stellatoidea*, *C. guilliermondii*, *C. krusei*, *C. lusitaniae*, *C. glabrata*, *C. pseudotropicalis*, and *C. parapsilosis* can also be responsible. Under favorable conditions, *C. albicans* thrives and transitions into its pathogenic hyphal form, leading to the development of oral thrush(4).

AZOLE ANTIFUNGALS:

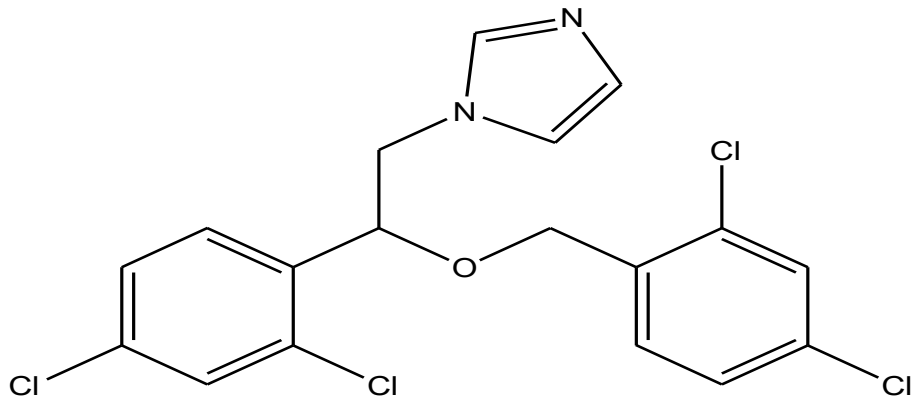
Azole antifungal drugs are the cornerstone in the treatment of mycosis and are classified into two main groups: imidazoles and triazoles(22). The key structural difference lies in their azole rings—imidazoles possess a two-nitrogen azole ring, while triazoles have a three-nitrogen azole ring. Both groups undergo a similar mode of action, inhibiting the fungal cytochrome P450 enzyme 14-α-sterol-demethylase, a crucial enzyme in ergosterol synthesis.(23) This disruption compromises the integrity of the fungal cell membrane, resulting in the deprivation of internal cell structure and ultimately fungal cell death(24). However, some azoles further engage with mammalian P450 enzymes, potentially developing adverse effects and drug interactions(23).

Imidazoles, including clotrimazole, miconazole, and ketoconazole, are primarily used in topical formulations for surface mycosis due to the risks related to parenteral regime(25). In contrast, triazoles, such as itraconazole, fluconazole, and posaconazole, are preferred for systemic infections because of their greater selectivity for fungal enzymes over mammalian enzymes, making them safer for systemic use(26). Triazoles also exhibit a broader antifungal spectrum and higher potency, which has led to increased research into advanced drug delivery strategies for this class of antifungals.(23)

Despite their efficacy, many azole antifungals face challenges related to their hydrophobic nature and low aqueous solubility(27). Drugs like miconazole, ketoconazole, itraconazole, and posaconazole are sparingly dispersible or indissoluble at neutral pH, which can limit oral bioavailability and negatively impact antifungal efficacy, side effects, and pharmacokinetic consistency. On the other hand, fluconazole and voriconazole exhibit much higher aqueous solubility, enhancing their bioavailability(28). Addressing solubility issues is critical to improving the therapeutic effects of azoles as well as minimizing the risk of drug resistance(23,28).

Clinically, the effectiveness of azole antifungal drugs depends not only on their inherent antimycotic action, expressed in their minimum inhibitory concentration (MIC), but also on their bioavailability, penetration to the site of infection, and the host's immune response(29). Because of their superior safety profile, broader activity range, and potency, triazole antifungals remain the focus of ongoing research into innovative drug delivery methods to optimize their therapeutic potential(23,29).

MICONAZOLE:



1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-1H-imidazole

Figure 1: STRUCTURE OF MICONAZOLE

First synthesized in 1969 by Janssen Pharmaceutics in Belgium(30), miconazole is a substituted 1-phenetylimidazole nitrate. Its therapeutic spectrum includes activity against various yeasts and Gram-positive bacteria, highlighting its versatility in clinical applications.(31)

Miconazole nitrate is a widely utilized antifungal agent for the management of oral candidosis, a mycotic infection predominantly developed by *Candida albicans*(32). Localized management with miconazole minimizes systemic adverse effects as well as ensures higher drug concentrations at the infection site, thereby reducing the treatment duration(17). The drug can be formulated in various delivery modes, including oral gel, cream, pessary, coated tampons, intravenous solution, and Scherer capsules, making it suitable for treating both mucosal and systemic candidoses.(24)

Unlike systemic administration, topical application of miconazole results in minimal systemic absorption. Its effectiveness extends beyond fungi, showing activity against Gram-positive bacteria like *Staphylococcus aureus*(33). This property makes it particularly valuable in treating angular cheilitis(24,34) of polymicrobial origin, where bacteria and fungi act together to exacerbate the condition. Studies have demonstrated that miconazole cream is highly effective in managing such lesions, inhibiting the growth of *Staphylococcus aureus*, *Candida albicans*, and *Streptococcus agalactiae* at concentrations as low as 50 µg/ml(24).

Another advantage of miconazole is its suitability for empirical treatment, especially in cases where microbiological diagnostics are unavailable or infeasible. Emerging applications include its incorporation into chewing gum for prolonged drug delivery, a method currently under clinical investigation. While occasional cases of resistance to miconazole and related azoles have been reported, such instances remain rare given the extensive use of these drugs(24).

TABLE 1: PROPERTIES OF MICONAZOLE

PROPERTY	**DESCRIPTION**
CHEMICAL FORMULA	$C_{18}H_{14}Cl_4N_2O$
CATEGORY	ANTI-FUNGAL
BRAND NAME	Oravig
NATURE	Lipophilic
DOSE	50 mg
ABSORPTION	Systemic absorption 10-20%
DISRTIBUTION	In plama,liver,skin and mucosal tissues
METABOLISM	Hepatic
PROTIEN BINDING	Approximately 90%
HALF LIFE	20 to 24 hours
PEAK BLOOD CONCENTRATIONS	1 ug/ml
SPECTRUM OF ACTIVITY	BROAD SPECTRUM

MECHANISM OF ACTION	Lanosterol 14-alpha demethylase (Yeast)
ACTS AGAINST	Candida albicans

MECHANISM OF ACTION:

Miconazole (MCZ) is an antimycotic medication which acts by interfering with the ergosterol biosynthesis which is an essential unit of mycotic cell membrane(35). It targets enzyme CYP450 in the fungus that is responsible for converting lanosterol into ergosterol. Thereby acting as ergosterol biosynthesis inhibitor (EBI)(35,36). At low doses, MCZ slows down the growth of the fungus by preventing the biosynthesis of ergosterol. At higher doses, it damages the cell membrane, ultimately killing the fungus.(37)

In addition to blocking ergosterol, MCZ causes the buildup of harmful Reactive Oxygen Species (ROS) within the mycotic cell(38). This happens because it affects enzymes that normally protect the fungus from oxidative damage. These ROS can damage important parts of the cell, like organelles and the actin cytoskeleton, leading to cell death. This oxidative damage is one of the reasons MCZ is so effective at killing fungi, and it also helps prevent the fungus from developing resistance to the drug. Unlike other similar antifungal medications, MCZ can increase ROS levels even without depleting ergosterol, making it a strong treatment option.(35)

Besides its effect on ergosterol, MCZ may also mess with other aspects of the fungus's function. For example, it might alter the mycotic cell membrane permeation or stop the fungus from taking in the building blocks needed for DNA and RNA(39). It may also stop certain enzymes from working, causing toxic peroxide compounds to build up inside the fungus, adding to its destructive effect.(40)

By blocking ergosterol production, damaging the fungal membrane,(41) and increasing ROS, MCZ takes a multi-layered approach to fighting infections.(42) This makes it especially effective against fungi like *Candida albicans* and dermatophytes. It shows the importance of targeting processes specific to fungi, reducing the chance of resistance, and improving the overall effectiveness of the treatment.(35).

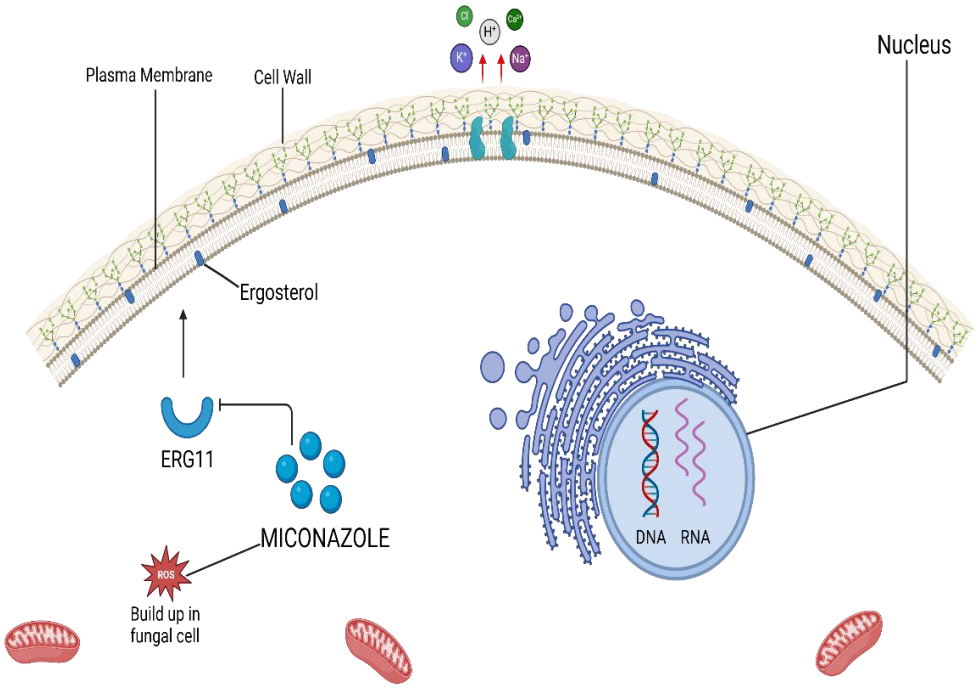


FIGURE 2: Mechanism of Action of Miconazole

FORMULATION AS LOZENGES:

Bioadhesive lozenges containing miconazole nitrate were formulated to maintain effective salivary levels of the drug over an extended period, with a preferred dosage range of 5–10 mg to minimize product bulkiness. Two lozenge formulations were created: Type A, incorporating 5 mg of miconazole nitrate from powder A with improved dissolution properties, and Type B, combining 5 mg of miconazole nitrate with 2.5 mg of chlorhexidine acetate (powder B) to achieve optimal antagonism towards *Candida*. Both formulations included flavoring agents in the upper layer for better taste.(43)

Each lozenge consisted of two layers. The upper layer, designed for modified release, encompassed miconazole nitrate in a dehydrated form blended with Acacia and Cremophor® RH40, responsible for enhancing drug solubility. The lower layer, designed for bioadhesion, was made from rotary dried waxy maize starch and Carbopol 980 to ensure effective adherence to the buccal lining. This two-layer structure was designed to maximize drug delivery and adhesion, providing targeted therapeutic benefits(23).

Formulation Procedure:

The formulation of lozenges involved several systematic steps. Initially the required ingredients were accurately measured according to the formulation specifications, the measured materials were then passed through sieve #40, collected into a polybag and mixed thoroughly to ensure uniform blending. The sifted materials were subjected to dry mixing in a V-cone blender for 5 minutes or a planetary mixer for 10 minutes at optimal speed. To enhance solubility PEG either individually or in combination was combined with Methylene Chloride that served as a solvent too. The dried powder mixture then was transferred into a high shear mixer where the solution of binder was gradually added and fully incorporated. The coarse granules were dried in a tray dryer for the first 10-15 minutes and then further dried at 55°C till the Loss On Drying

(LOD) was attained up to 23. Finally the dehydrated particles were passed against sieve #16 as well as any oversized particles were resized with the use of a multi-mill with a 2 mm screen to achieve the desired particle size.(6)

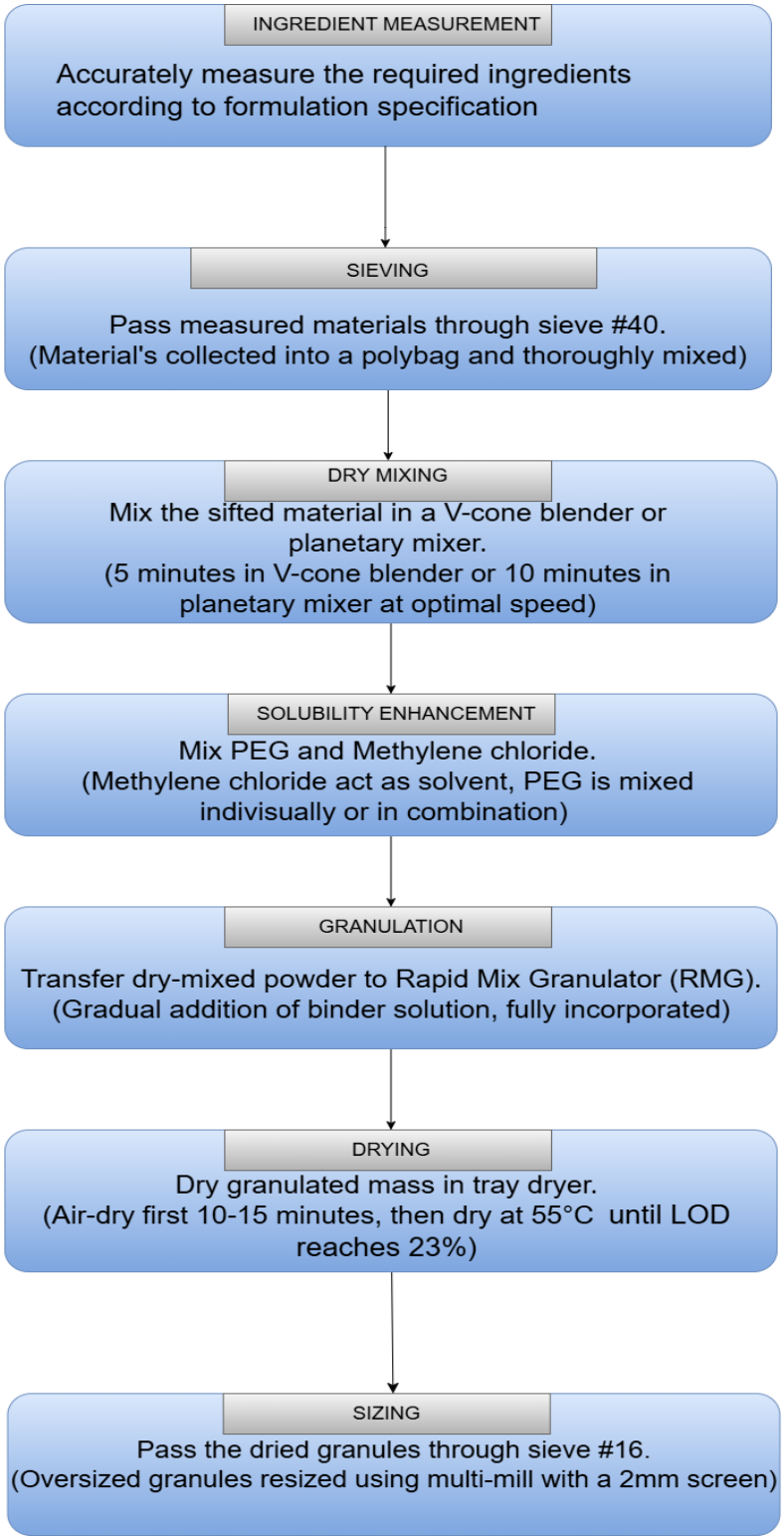


Figure 3: FORMULATION PROCEDURE

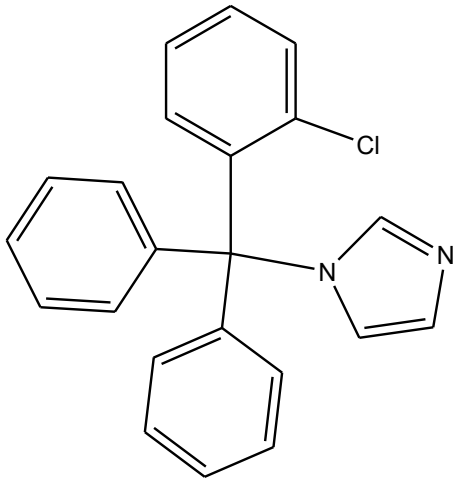
USE IN IMMUNOSUPPRESSED PATIENTS:

Oropharyngeal and esophageal candidiasis are common complications among individuals living with HIV(44). The shift of *Candida albicans* from a innocuous variety organism into a highly infective microbe within vulnerable person is a delicate process driven by its ability to selectively express a wide range of virulence factors(45). These consist of thigmotropism, hyphal development, adhesion to mucosal surfaces, aspartyl proteinase production, and phenotypic flipping(46).

For infected person undertaking radiotherapy for cancer of head or neck, clinically significant stomatitis is almost universal(47,48). It is the leading cause of pain during treatment and significantly affects quality of life. Although *Candida* species colonization and infection tend to increase during radiation therapy, research suggests that yeast colonization itself does not directly contribute to the development of mucositis.(49)

Clinically noticeable oropharyngeal candidiasis is an usual problem for individuals undertaking chemotherapy for solid tumors, lymphomas, as well as leukemias(50). Positive cultures of *Candida albicans* from the oral mucosa frequently confirm this disease. Miconazole, which is taken as a 250 mg pill quadruple, daily and dissolves slowly in the mouth before being eaten, has proven to be an extremely effective treatment(51). Even with shorter treatment periods than alternatives like nystatin or amphotericin B, miconazole has the highest rates of clinical and mycological cure(52). Its absorption from the gastrointestinal system, which neither nystatin nor amphotericin B share, may be one reason for its better performance(53). Its ability to cure deeper infections as well as local ones may be improved by this systemic absorption(51).

CLORTIMAZOLE:



1-[(2-chlorophenyl)diphenylmethyl]-1H-imidazole

Figure 4: STRUCTURE OF CLOTRIMAZOLE

First discovered in late 1960s, Clotrimazole (CLM) is another synthetic imidazole antimycotic agent(54)which possess a widespread action more specifically against mycosis developed due to Candida albicans,(55) dermatophytes, and even other different fungi. Although frequently, it is used for the management of vaginal and cutaneous infections, it can also

be applicable in treating oral infection caused by Candida spp., Trichophyton spp., Microsporum spp., and Malassezia furfur (Pityrosporon orbiculare)(56). Clotrimazole is said to exert fungistatic action and is well-tolerated, showing good anticandidal and antistaphylococcal activity(57). Clinically, clotrimazole has some activity against gram-positive bacteria and, at very high concentrations, acts against Trichomonas spp., including metronidazole-resistant ones.(55)

TABLE 2: PROPERTIES OF CLOTRIMAZOLE

PROPERTY	**VALUE**
CHEMICAL FORMULA	$C_{22}H_{17}ClN_2$
CATEGORY	ANTI-FUNGAL
BRAND NAME	Mycelex
NATURE	Lipophilic
DOSE	10 mg
ABSORPTION	Salivary ranges arise inside 3 hours
DISRTIBUTION	Secreted in breastmilk in animal studies.
METABOLISM	Hepatic (metabolized to inactive metabolites).
PROTIEN BINDING	98%
HALF LIFE	3.5 and 5.5 hours
PEAK BLOOD CONCENTRATIONS	1 ug/ml
SPECTRUM OF ACTIVITY	BROAD SPECTRUM
MECHANISM OF ACTION	Lanosterol 14-alpha demethylase (Yeast)
ACTS AGAINST	Candida albicans

MECHANISM OF ACTION:

Clotrimazole exhibits the antifungal activity similar to the miconazole that is by changing the permeability of fungal cell membranes(58)**,** mainly by inhibiting biosynthesis of ergosterol, a vital unit of mycotic cell membranes, clotrimazole produces its antifungal effects.(56) It inhibits 14-α-lanosterol demethylation, an essential step in the ergosterol biosynthesis, by binding to lanosterol 14-demethylase (CYP51), a cytochrome P450 (CYP450)-dependent enzyme(59). Due to the subsequent depletion of ergosterol and buildup of 14-α-methylsterol, the integrity of the membrane is compromised, which results in changes to membrane permeability, fluidity, and enzyme activity, increased leakiness of the cell wall, and the intracellular potassium loss and other vital components**.**(54) In contrast to polyene antibiotics like amphotericin B, its activity is less reliant on the membrane's sterol content**.**(58) Fungal cell function is further impacted

by clotrimazole, which inhibits sarcoplasmic reticulum Ca^{2+}-ATPase, depletes calcium present intracellularly, as well as blocks calcium-dependent potassium channels and voltage-dependent calcium channels(56)**.**

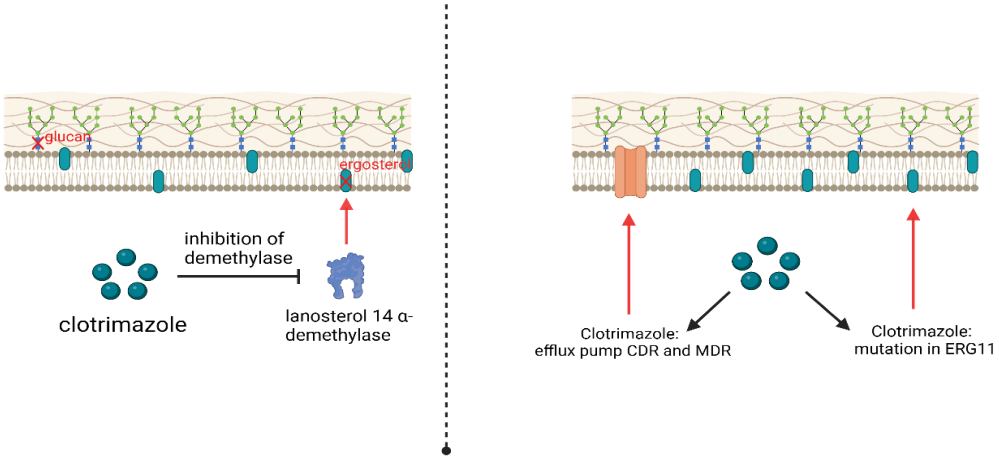


Figure 5: Mechanism of Action of Clotrimazole

FORMULATION AS LOZENGES:

The intended use of clotrimazole lozenges is to alleviate oropharyngeal symptoms produced on by local infections(60). If taken orally or through the buccal lining, they may also have systemic effects**.**(56) Slowly dissolving in the mouth, these lozenges, which usually contain 10 mg of clotrimazole, are administered five times a day for 14 days for treatment of oral candidiasis. For immunosuppressed patients, the dosage is lowered to 10 mg three times a day for the immunosuppressive treatment period as a preventative measure(54,58)**.**

These medicinal lozenges are made by dispersing clotrimazole in PEG 6000 (1:1 weight ratio) and then heating and congealing the mixture. On a hot plate at 150°C, sucrose is dissolved in deionized water while being constantly stirred. Dextrose is then added to create a plastic mass. After cooling, flavoring and coloring ingredients are added, along with hydrophilic gelling agents such sodium alginate, methylcellulose, or chitosan, and citric acid. After that, the mixture is put into molds, allowed to air dry up to 60 minutes, and then covered with aluminum foil. Nine formulations in all, weighing two grams each, were created using different proportions of gelling agents**.**(55)

Formulation Procedure:

The medicated lozenges were made by boiling and congealing 10 mg of Clotrimazole solid dissipated in PEG 6000 (weight ratio 1:1) in each. With the use of demineralized water and constant swirling on a magnetic stirrer on a hot plate at temperature of 150°C, the necessary amount of sucrose was dissolved. With constant stirring, sucrose syrup was mixed with dextrose till mass of plastic nature was created. The solid dispersion medication, citric acid, and hydrophilic gelling agents such as sodium alginate, methylcellulose, or chitosan were added to the plastic mass after the temperature was lowered. After adding a flavoring and coloring ingredient, the material was casted in molds, allowed to dry for sixty minutes, and then covered with aluminum foil(61)

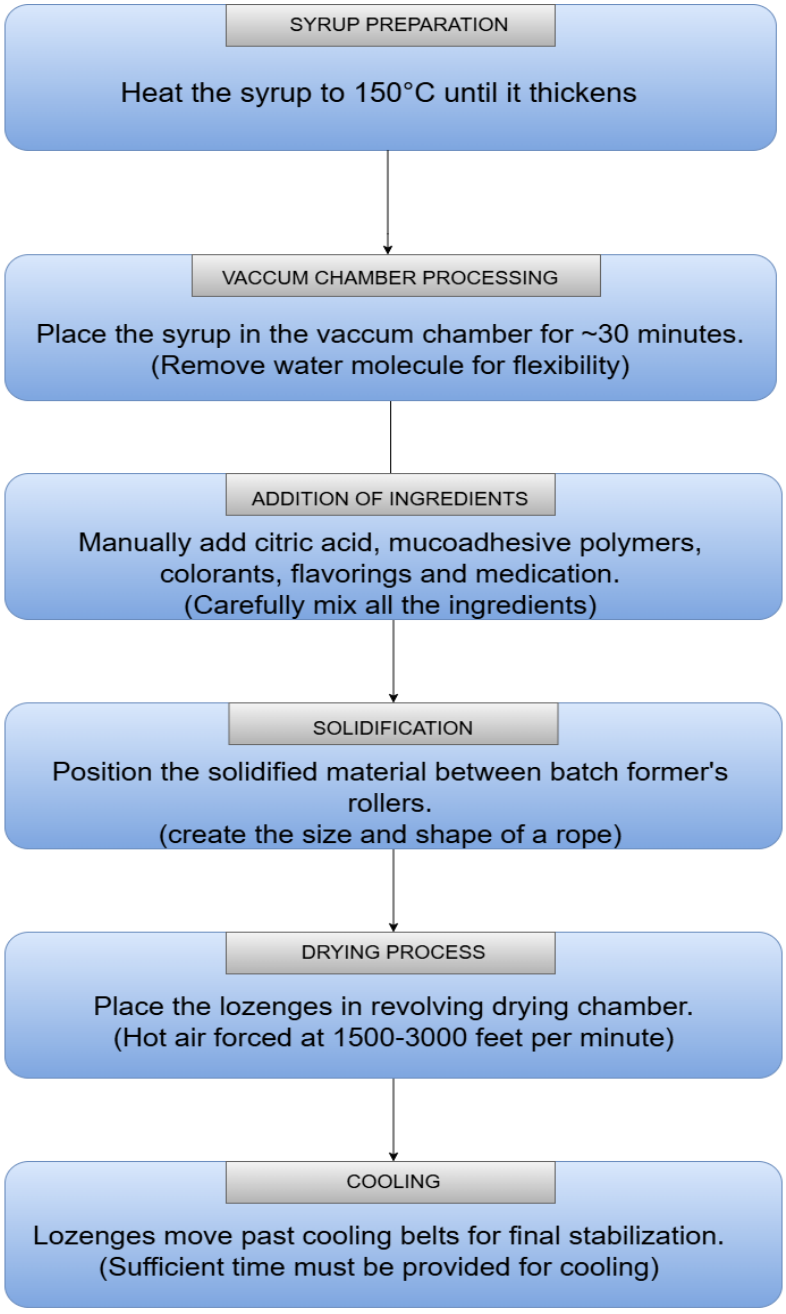


Figure 6: FORMULATION PROCEDURE

USE IN IMMUNOSUPPRESSED PATIENTS:

Radiation-induced mucositis is a frequent and distressing complication for people undertaking radiotherapy for cancers of head and neck (62). This condition results in painful inflammation of the mouth's mucosal lining, making it difficult to eat, speak, and swallow, thereby impacting the patient's overall well-being. The seriousness of mucositis resides on the radiation range and can sometimes restrict cancer treatment(63). However, recent studies indicate that using antibacterial and antifungal lozenges may help reduce the severity, duration, and onset of mucositis, potentially enhancing patient comfort and treatment success.(64)

Oropharyngeal candidiasis, commonly developed due to *Candida albicans*, is a widespread opportunistic buccal mycosis in individuals with HIV(65,66), affecting the majority of people at a point during their infected state. It frequently emerges during early stages of HIV and becomes more prevalent as immune function declines(65,67)**.** Thrush, the most recognizable variant of oropharyngeal candidiasis, is an important clinical marker of HIV progression and is included in most classification systems for the disease(68). In some cases, it has also been linked to the acute phase of HIV infection, underscoring its role in disease monitoring.(69)

Oral candidiasis-related lesions can cause significant discomfort, leading to problems with eating, speaking, and even severe weight loss, which can further weaken the patient's health. Managing this condition is essential(70), and both topical and systemic antifungal treatments are available to help control symptoms(69)**.** Prompt diagnosis and appropriate treatment can effectively enhance quality of life for HIV patients, highlighting the importance of oral healthcare in their overall disease management(65).

Clotrimazole lozenges are an effective and widely used treatment for thrush in HIV-infected individuals(69)**.** These 10 mg oral lozenges are developed to disintegrate slowly in the buccal cavity five times daily, providing localized antifungal action(44,66)**.** While side effects are generally minimal, patient compliance can be challenging due to the frequent dosing schedule and the gritty texture of the medication. Additionally, the presence of dextrose in the formulation raises concerns about dental caries, also person suffering from AIDS-related xerostomia may struggle while dissolving the lozenges(69,71)**.**

Beyond HIV-related oral thrush, clotrimazole is found useful as a prophylactic therapy for person with leukemia undergoing chemotherapy(69). Studies indicate that administering clotrimazole lozenges five times daily effectively treats mild to moderate oropharyngeal candidiasis (OPC)(72) in early-stage HIV infected people and also individuals experiencing initial episodes of candidiasis related to neoplastic diseases(44). Some research suggests that taking the lozenges three times daily may help prevent oral candidiasis in leukemia patients undergoing chemotherapy(67)**.**

Clotrimazole is a topical imidazole antifungal available as a 10 mg troche under the brand name (Mycelex). Each troche should be held in the mouth for 15–20 minutes to ensure proper absorption(73). While usually well accepted, adverse effects include nausea, vomiting, and pruritus. Due to its glucose content, careful consideration should be given to its use in patients at risk for dental issues(65,67).

AZOLE RESISTANCE:

Azoles are among the most frequently prescribed antifungal medications; nevertheless, its effectiveness is limited due to their absence of fungicidal activity with the development from clinical sensitivity(74). This has not yet been established whether the pathogen uses azole transformation as an immunity strategy. Azole resistance in yeast is caused by a number the processes, involving polymorphisms or excess production of the enzyme of interest, the steroid lanosterol 14-α-

demethylase, alterations within complexity structure of membrane sterols that and expression of genes encoding drug evacuation pumps(75). These alterations decrease the effectiveness of azole antifungals making treatment tougher(41). Resistance to fungi might develop in a number of ways(46).

One such method is the substitution of an azole-resistant strain of Candida albicans or an azole-sensitive strain with a species that is naturally resistant to azoles, such as Candida glabrata or Candida krusei(76–79). Another method is temporary or epigenetic resistance, in which azole susceptibility is momentarily decreased by changes in gene expression(80). Only when the drug is present does this resistance last, and when the drug is taken away, it returns to sensitivity(81). Permanent genetic resistance—where durable resistance is conferred by irreversible mutations—is the most worrisome mechanism(82). These resistant strains provide a significant clinical issue because they can spread among people and endure even after drug discontinuation(46)**.**

Azole antifungals work by attaching themselves to lanosterol 14-α-demethylase and stopping the ergosterol synthesis, a crucial unit of mycotic cell membranes. Without ergosterol, the fungal membrane's durability is compromised, which prevents growth and replication. This route is encoded by the ERG11 gene family, which includes Cyp51A and Cyp51B(83). Mutations in these genes result in azole resistance by altering the enzymatic structure and reducing binding of drug(84). The resistance of Candida albicans to azole antifungals has been extensively studied, and one of the primary resistance mechanisms involves point mutations in ERG11(85). It has been discovered that the Erg11p protein has three distinct "hot spot" sites with amino acid alterations that significantly reduce the susceptibility. After azole treatment, fungal cells may continue to exist because of these changes, which hinder the medication's ability to attach to the intended enzyme.(86)

To sum up, azole resistance in Candida albicans is a complex issue caused by changes in sterol biosynthesis, efflux pump overexpression, and genetic mutations(87,88). Understanding these pathways is essential for creating novel treatment approaches to successfully treat fungal infections while antifungal resistance keeps increasing(41)**.**

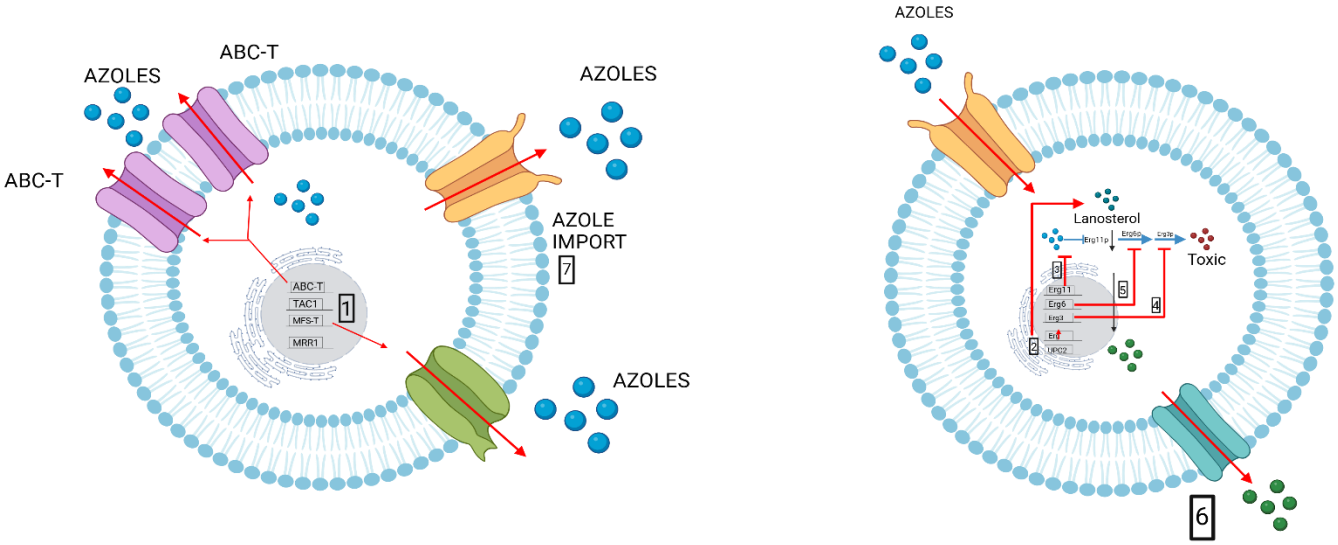


Figure 7: MECHANISM OF AZOLE RESISTANCE

DISSCUSSION:

The therapeutic efficacy of azole antifungal lozenges, particularly miconazole and clotrimazole, for treating oral candidiasis is consistently supported by clinical studies. Miconazole has exhibited high local bioavailability with minimal systemic absorption, making it a favorable option for immunocompromised individuals(31)·(89). Similarly, clotrimazole has shown broad-spectrum antimycotic activity and can be effectively implemented in treating as well as for prophylaxis of oral candidiasis(54).

However, recent studies have highlighted several challenges and contradictions regarding their long-term effectiveness. Emerging resistance to azole medications, particularly among *Candida albicans*, is becoming a significant clinical concern. Mechanisms such as ERG11 gene mutations, increased expression of efflux pumps (e.g., CDR1, CDR2, MDR1), and alterations in sterol biosynthesis pathways reduce the binding affinity and efficacy of azoles(83)·(86). These mechanisms of resistance limit the use of miconazole and clotrimazole in persistent or recurrent cases of candidiasis.

Interestingly, resistance to fluconzole is widespread, research show that miconazole and clotrimazole can remain effective in certain resistant strains due to differing binding mechanisms and lipophilicity (88). For instance, Whaley et al. (2017) observed that clotrimazole retained antimycotic activity in strains resistant to fluconazole, suggesting that azoles are not universally cross-resistant and should be evaluated individually.

In terms of formulation advancements, bioadhesive lozenges have emerged as a promising delivery system. These formulations, often designed with dual layers, enhance drug retention time in the oral cavity as well as ensure longer adherence to the site of infection. Studies by Piérard et al. (2012) and Yang et al. (2008) have confirmed that bioadhesive polymers like Carbopol and hydrophilic gelling agents markedly improve treatment outcomes in contrast to conventional lozenges. This approach addresses one of the primary drawbacks of traditional lozenges—short residence time and drug dilution via saliva.

Despite these benefits, contradictory findings persist regarding patient adherence. Crowley & Gallagher (2014) reported that the gritty texture, frequent dosing schedule (5x/day), and greater sugar content of clotrimazole lozenges negatively impact user compliance. Additionally, in patients with AIDS-related xerostomia, proper dissolution of lozenges becomes problematic, limiting efficacy(69).

The discussion around sugar-free formulations and chewing gum-based delivery represents ongoing research aimed at improving both compliance and antifungal action. As resistance continues to rise and patient adherence remains a challenge, these innovations will play a crucial role in redefining oral antifungal therapy.

Ultimately, while azole antifungal lozenges remain a cornerstone in the treatment of oral candidiasis, their future utility depends on formulation innovation, surveillance of resistance trends, and individualized treatment strategies based on patient profiles and fungal susceptibility**.**

CONCLUSION:

Azole antifungal lozenges especially those containing miconazole and clotrimazole represent a targeted and effective approach to managing oral candidiasis, particularly in immunocompromised patients. Their ability to deliver medication locally within the oral cavity provides therapeutic advantages over systemic formulations, reducing side effects while maintaining efficacy. However, increasing resistance among *Candida* species, driven by genetic and biochemical mechanisms, poses a growing threat to treatment success.

Bioadhesive lozenges have shown promising results in enhancing drug retention and mucosal absorption, offering a potential solution to these challenges. This review reinforces the need for continued innovation in formulation strategies and more comprehensive resistance surveillance to optimize antifungal therapy.

Implications:
The findings highlight the clinical benefits of azole lozenges in treating oral candidiasis. Their ease of administration and reduced systemic absorption make them suitable for diverse patient populations, including pediatrics and geriatrics. Enhanced formulations may improve adherence and outcomes.

Limitations:
This review is based on secondary literature and does not include new clinical trials or patient data. The conclusions drawn depend on the quality and scope of available studies, and there may be variability in results due to differing methodologies.

Future Research Directions:
Future investigations should focus on developing sugar-free and prolonged-release lozenge formulations, evaluating real-world adherence in immunosuppressed patients, and exploring synergistic drug combinations to counteract resistance. More clinical trials are needed to validate in vitro findings and ensure sustained effectiveness.

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