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Novel drug delivery approaches for the management of oral candidiasis

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ABSTRACT

Candidiasis is a fungal infection due to any type of Candida. Infections of the mouth are most common among children, the elderly, and those with weak immune systems. On average around 30-50% of world's population carries Candida albicans as a normal element of oral microflora. The spores of Candida are harmless but become invasive and virulent when there is a disturbance in normal flora and in debilitation of the host immune status which plays a major role in pathogenesis. There are approximately 200 species in genus Candida. The most contagious and virulent among these is Candida albicans, which is isolated most frequently and accounts for about 75% of Candida infection. The diagnosis is based upon clinical examination of signs and symptoms in conjunction with thorough medical history. Mild incidences of oral candidiasis respond to topical therapies, while if relapses occur more quickly, then oral systemic antifungal therapy is recommended. Novel drug delivery systems are designed to achieve continuous delivery of drugs in a predictable manner with reproducible kinetics over an extended period of time.

Key words: Antifungal agents, Candida, Candida albicans, Oral Candidiasis, Novel drug delivery system.

INTRODUCTION

Oral Candidiasis is the most common opportunistic fungal infection of oral mucosa and tongue caused by mycosis of *Candida* species predominantly with *Candida albicans*. It is commonly associated with white patches or plaque on the tongue and oral mucous membranes. Around 30-50% of world's population carries *Candida albicans* as a normal element of oral microflora[1]. Candidiasis encountered in mouth or throat is called thrush or oropharyngeal candidiasis. Candidiasis in the genital area is referred to as a vulvovaginal or genital candidiasis. When *Candida* species enter the bloodstream and spread throughout the body then it is called as invasive candidiasis or candidaemia.

Causative organism:
In the past two decades, the increasing frequency of candidaemia has been reported throughout the world[2]. Various species of *Candida* have been isolated from oral cavity(Table 1) having major medical Importance (in decreasing order of incidence of causing infection)[3,4].

Table 1: Principal Candida species in Oral candidiasis

Principal Candida spp. in Oral candidiasis
Candida albicans
Candida tropicalis
Candida glabrata
Candida parapsilosis
Candida krusei
Candida kyfer
Candida stellatoidea
Candida famata
Candida rugosa
Candida geotrichium
Candida dubliniensis
Candida guilliermondii
Candida lusitaniae
Candida inconspicua
Candida norvegensis

There are approximately 200 species in genus *Candida*. The most important and virulent among them is C. *albicans*, which is isolated most frequently and accounts for about 75% of *Candida* infections[5,6].Candidiasis caused by non-albicans *Candida* species are associated more with cancer patients, immunodeficiency, surgical patients and nurslings. For example, C. *dubliniensis* and C. *geotrichium* become pathogenic in immune-compromised patients [7]. About 35-65% of candidaemia in patientpopulation iscaused by non-albicans candida species. As far as the virulence and pathogenicity of non-albican candida species is concerned, it appears to be less virulent, but in general these have equal or greater virulence in man, when compared with C. *albicans*[8].

Factors affecting susceptibility to oral candidiasis:
Major factors that regulate the growth of infection in patients' body are their immune status, oral mucosal environment and Strain of *Candida albicans*[9].The main host related predisposing factors which are responsible for increasing the susceptibility of oral candidiasis can be divided into: Local host factors, Systemic host factors and Iatrogenic factors (Table 2)[10].

Local Host Factors:[10-13]
1. Altered oral mucosal barrier
2. Salivary secretion: Qualitative, quantitative and flow rate
3. Xerostomia
4. Denture wearing
5. Poor oral hygiene
6. Temporal variation
7. Supression of oral microflora
8. High carbohydrate diet
9. Smoking

Systemic Host Factors:
1. Immuno-compromised patients e.g., AIDS
2. Extremes of age: infant or old age
3. Endocrine disorders e.g. Cushing syndrome, Diabetes mellitus
4. Immunosuppression
5. Nutritional deficiencies e.g. Vitamin and Iron deficiency
6. Organ transplantation (liver, kidney)
7. Malignancies
8. Prolonged hospitalization
9. Hemodialysis
10. Acute/chronic renal failure
11. Granulocytopenia

Iatrogenic factors:
1. Antibiotic therapy
2. Corticosteroid therapy
3. Cytotoxic and Irradiation therapy

Table 2: Host Susceptibility factors and their effect on oral candidiasis

Host Susceptibility Factors	Effect on oral candidiasis
Local Factors	
• **Mucosal barrier**	
▪ Healthy superficial mucosa	Inhibit
▪ Atrophy, hyperplasia or dysplasia	Stimulate
• **Saliva**	
▪ Salivary glucose	Stimulate
▪ IgA component	Inhibit
▪ lysozyme, lactoperoxidase, lactoferrin and histidine-rich polypeptides	Inhibit
▪ Burning mouth syndrome	Stimulate
▪ Acidic pH	Stimulate
▪ Xerostomia	Stimulate
• **Temporal variation**	
▪ During sleep	Stimulate
▪ Eating and Tooth brushing	Inhibit
• **Smoking**	Stimulate
• **Oral Microflora**	
▪ Suppressed	Stimulate
Systemic Factors	
• Immunocompromised (alterations in phagocytic or lymphocytic cells)	Stimulate
• Malignancy	Stimulate
• Cytotoxic and immunosuppressive drugs and radiotherapy	Stimulate
• **Endocrine disorder**	
● Diabetes, Cushing Syndrome, Hyperparathyroidism	Stimulate
• **Hospitalized Patients**	
• Elder / infant patients and Denture wearer	Simulate
• **Nutrition deficiency (Vitamins/Iron)**	Stimulate
• **Physiological factors**	
● Infancy and old age	Stimulate
Iatrogenic Factors	
I. Antibiotic therapy	Stimulate
I. Corticosteroid therapy	Stimulate
I. Cytotoxic/irradiation therapy	Stimulate

Pathophysiology:

Candida fungus was first isolated from the sputum of a tuberculous patient in 1844[13]. *Candida* is a Latin word which means “white”. *Candida albicans* is a dimorphic fungus having three different morphologies in which it can grow: Yeast, Pseudohyphae and Hyphae [14].The spores of *Candida* become invasive and virulent upon disturbance in normal flora and in debilitation of the host immune status [15].*Candida* can cause superficial infection most frequently on moist mucosal surface in the individuals suffering from mild sapping of immunity while systemic infection is encountered in severe immune-compromised patients [11]. The transition of *Candida* from a harmless commensal to a pathogenic organism is associated to environmental changes that lead to imbalance between *Candida* colonisation and host defence mechanism [16] that can be expressed by several virulence factors (Table 3) [17].

Table 3: Virulence factor of *Candida albicans*

Virulence factors	Attributes
Polymorphism	a) Grow either as ovoid-shaped budding yeast or as parallel-walled true hyphae. b) The hyphal form is more invasive than the yeast form. c) Frequent changes in cell surface through antigenic modification by phenotypic switching. d) Several factors can cause a change in morphology such as change in pH and temperature, carbon dioxide levels, starvation, and quorum-sensing molecules (farnesol, tyrosol, and dodecanol)
Adhesin	a) Surface hydrophobicity of cell facilitates the non-specific adherence. b) The agglutinin-like sequence (ALS) genes encode glycosylphosphatidylinositol (GPI)-linked cell surface glycoproteins that allow it to adhere to the specific surfaces.
Invasin	a) Induced endocytosis and Active penetration are two different methods of invasion into host cells. b) For induced endocytosis, the fungus expresses specialized proteins on the cell surface (invasins Als3 and Ssa1) that mediates binding to host ligands (such as E-cadherin on epithelial cells and N-cadherin on endothelial cells). c) Active penetration requires viable C. *albicans* hyphae as it is a fungal-driven process.
Biofilm formation	a) Capability to form biofilms on abiotic or biotic surfaces like dental prosthesis and mucosal surface respectively. b) Formation of biofilms is a sequential process including adherence and proliferation of yeast cells to the surface followed by development of hyphae cells in the upper part of the biofilm. c) Mature biofilm are more resistant to antimicrobial agents and host immune response. d) Biofilm formations are controlled by several transcription factors including Bcr1, Tec1 and Efg1. e) According to recent studies biofilms protect C. albicans colonization from neutrophil attack and prevent the formation of reactive oxygen species [18].
Secreted hydrolases	a) It facilitates active penetration into host cells and enables the uptake of extracellular nutrients from environment. b) C. *albicans* secrete 3 main classes of hydrolases: proteases, phospholipases and lipases.
Metabolic adaption	a) C. *albicans* are usually found in the gastrointestinal microbiome of healthy person. b) Fungus can quickly undergo metabolic adaption such as glycolysis, gluconeogenesis, and starvation responses.

Classification of oral candidiasis:

Lehnerin 1964proposed one of themost commonly used traditionalclassifications of oral candidiasiswhich described as*acute forms* and *chronic forms*with further subdivisions(Table 4) [19]. However, this is not an efficient way to classify the oral candidiasisas it involves the mixture of both clinical and pathological conditions which create discrepancy and confusion e.g. subdivision of chronic hyperplastic candidiasis generate protrusions that either localized in oral cavity or may cause mucocutaneous candidiasis[20]. According toHolmstrup and Besserman study, pseudomembranous candidiasis is not always acute but may be chronic and last for several months in immune-compromised patients and also the term atrophic used to describe erythematous areas (redness of oral mucosa) is limited as it may be caused by increased vascularity with or without reduced thickness of epithelium[21].

Table 4: Traditional classification of oral candidiasis

I.	**Acute candidiasis:**
•	Pseudomembranous candidiasis (oral thrush)
•	Atrophic candidiasis (*Erythematous*)
I.	**Chronic candidiasis:**
•	Atrophic candidiasis*(Denture Sore MouthandAngular Cheilitis)*
•	Hyperplastic candidiasis
a)	Chronic oral candidiasis (Candida leukoplakia)
b)	Candidiasis endocrinopathy syndrome
c)	Chronic localized mucocutaneous candidiasis
d)	Chronic diffuse candidiasis

Axell *et al*. recently proposed clinically more appropriate reclassification of oral candidiasis on the basis of clinical rather than pathologic conditions (Table 5). Thus it comprises of *primary oral candidiasis*, where the condition is confined to the mouth and perioral tissues, and *secondary oral candidiasis*, where there is involvement of mouth in addition to other parts of the body [22].

Table 5: Revised classification of oral candidiasis

Primary oral candidiasis	Secondary oral candidiasis
I. Acute forms • Pseudomembranous Candidiasis • Erythematous Candidiasis	Oral manifestation of mucocutaneous candidiasis (by means of diseases such as thymic aplasia and candidiasis endocrinopathy syndrome)
I. Chronic forms • Pseudomembranous Candidiasis • Erythematous Candidiasis • Hyperplastic Candidiasis ✓ nodular ✓ plaque-like	-
I. *Candida*-associated lesions • Denture-induced stomatitis • Median rhomboid glossitis • Angular cheilitis	-
V. Keratinized primary lesions superinfected with *Candida* • Leukoplakia • Lichen planus • Lupus erythematosus	-

Host oral defence against candida infection:

Oral candidiasis is known as "a disease of the diseased" occurring most commonly in infants, old age and sick patients. During infection an immune response is initiated by recognition of conserved chemical structures named pathogen-associated molecular patterns (PAMPs) of the invading pathogen by pattern recognition receptor (PRRs).Various steps are involved in *Candida* infection, starts with *Candida* sensing, phagocytosis, killing then cytokines stimulation followed by induction of adaptive specific immune responses[23].

The primary defence mechanisms which play a significant role in preventing colonization of candida species in oral cavity include [24,12]

- The physical barrier of oral epithelium prevents the entry of organism and acts as a site for cell mediated immune response.
- Secretory Immunoglobulin A (IgA), which aggregate *candida* and assist in clearance by preventing its adherence to the epithelial surface.
- Salivary factors like flow rate, salivary pH and other secretory molecules such as lysozyme, lactoperoxidase, lactoferrin, salivary glycoprotein and histidine-rich polypeptides have mechanical clearance and candidacidal properties.
- Competition and inhibition of *candida* species by the oral flora are also important in limiting the overgrowth of fungi.

Various immune factors also play an important role in host defence against *candida* infection.

- Neutrophils are granulocytes which facilitate phagocytosis. The candidacidal activity of human neutrophilshas been shown to be enhanced independently by immune interferon (IFN-a) and tumornecrosis factor (TNF)[25,26].
- *Candida* infections are frequently seen when cell-mediated immunity is depressed. Both granulocytes and macrophages have limited intrinsic candidacidal capability, and full expression of their effect is dependent on augmentation by cytokines synthesized or induced by T-cells [25].
- The growth of C. *albicans* is affected by serum antibodies. The IgA is a specific immunologic factor in saliva, which provides a primary defence against oral candidiasis by fungal aggregation and prevention of their adherence to mucosal epithelium[27].

Both humoral and cell-mediated immunity to C. *albicans* may comprise a second line of defence when penetration of mucosa or systemic infection occurs.

Diagnosis and Laboratory testing Techniques:

The diagnosis is based upon clinical examination of signs and symptoms in conjunction with thorough medical history. Smears, swabs and oral rinse samples are the common specimens to diagnose candidiasis [28].

When the clinical diagnosis is not clear, additional tests are performed for it. Each test has its own specifications, advantages and disadvantages so decision about the test should be made very carefully depends upon the nature of lesion to be examined(Table 6)[15,29].

1. Exfoliative cytology - Oral smears are collected from lesions in oral cavity with a sterile metal spatula or wooden tongue blade on to a sterile glass slide. It gives best results with the pseudomembranous form of candidiasis, in which there are greater numbers of fungal hyphae[30].

2. Culture- Oral swabs scraped over the suspected area are collected and cultured to detect presence of *candida* species[31].
3. Biopsy- Predominantly essential for diagnosis of chronic hyperplastic candidiasis[32].

Table 6: Laboratory diagnostic techniques

Isolation Technique	Advantages	Disadvantages	Reference
Smear	• Simple to use • Widely used • Need not to relay on culture media	• Viable cells not determined • Difficult to identify the species • Less sensitive	[33]
Swab	• Simple to use • Viable cells isolated • Site specificity for infection	• Difficult to standardize the technique	[33]
Biopsy	• Recommendedfor chronic hyperplastic candidiasis	• Made excisional or incisional • not suitable for other forms of candidiasis	[34]
Imprint Culture	• Isolate viable cells • Site specific	• Some sitesare unapproachablee.g. whenlesion are not evident	[35]
Paper Points	• Facilitate sampling from subgingival flora or from gingival tissues of acute periodontal abscesses	• Culture media also facilitates survival of facultative and anaerobic bacteria	[36,37]
Culture of whole saliva	• Viable counting technique	• Problems may occur with collection of sample • Not site specific • Time consuming	[38]
Concentrated oral rinse	• Quantitative Technique • Viable cells isolated	• Some patients have difficulty in using rinse • Not site specific	[39]
Commercial Identification Kit	• Useful when microbiology laboratories are not within easy access • High Sensitivity	• Uneconomical • Less efficient than other laboratory techniques	[34]

Management:

In order to achieve the reduction in load of *Candida* in oral cavity various physical and chemical means are used including good oral hygiene practices including tooth brushing and use of antimicrobial mouthwashes. Electrical tooth brushing has ability to remove the *Candida* biofilms from inaccessible sites because of its ability to produce high shear force over the surface[40]. Several mouth rinses demonstrate the anti-candidal activity including benzydamine hydrochloride, benzydamine hydrochloride with chlorhexidine gluconate, triclosan with sodium fluoride, sodium bicarbonate. They produce such response by affecting candida count and salivary flow rate[41]. Essential oils such as tea tree oil [42], cinnamon, manuka, thymol, grapefruit and eucalyptus oil exhibit *in-vitro* anti-candidal activity through cell membrane disruption and enzyme inhibition[43].

The principles of treatment of oral candidiasis are based on the following premises [44]:

a) Diagnosis of the infection;
b) Improving the predisposing factors responsible for increasing the susceptibility of underlying diseases;
c) Consider the type of Candida infection;
d) Use suitable antifungal agents by evaluating the efficacy / toxicity ratio.

There are different treatment modalities to manage oral candidiasis using antifungal agents. Several topical and systemic antifungal medications are used in treatment of oral candidiasis (Table 7). Mild incidences of oral candidiasis respond to topical therapies, which are effective for treatment of uncomplicated candidiasis while if relapse occur more quickly, than oral systemic antifungal therapy is recommended[45].

Topical antifungal agents are also known as the primary line treatment used for mild, superficial and localized *Candida* infection. In early 20th century gentian violet (an aniline dye),carbol-fuschin paint, Potassium permanganate, Whitfield's ointment were used as topical antifungal agents, but due to their non-specific action and side effects, these were replaced by a polyene antifungal agents, nystatin a most widely used topical antifungal agent, discovered by Hazen and Brown in 1950 [46] and amphotericin B, discovered by Gold *et al.*in 1956. They both act by binding to ergosterols present in the cell membrane of fungi, and, alter the membrane permeability which induce leakage of cytoplasmic contents leading to fungal cell death [47,48]. The polyenes have limited utility as they have poor absorbance through the gut; therefore topical application is the principal mean of administration in oral candidiasis. The major limitation of use of amphotericin B is the substantial adverse effects such as fever, chills, vomiting, electrolyte abnormalities and nephrotoxicity [49].

Unlike the polyenes, azoles are another class of antifungal agents. Unlike polyenes, they are fungistatic in nature [50]. They act by inhibiting the enzyme lanosterol demethylase that is a cytochrome P-450 3-A dependent enzyme involved in the synthesis of ergosterol [51]. Miconazole is an imidazole used for local application in mouth but is having limited use due to its potential side effects like skin irritation, diarrhoea and vomiting. Clotrimazole and ketoconazole are other drugs belong to the same class [52,53].

Systemic antifungal agents are used for more generalized candidiasis or for immunocompromised patients where chances of relapse are high [54]. In 1990, two triazoles fluconazole and itraconazole represented a considerable progression in antifungal therapy. A high level of fluconazole is secreted in saliva making the agent particularly suitable for treating oral infection [55].However, the use of fluconazole is affected by its narrow spectrum of activity and development of drug resistance while the use of itraconazole is limited due to absorption problems [56]. The new triazol antifungal voriconazole and pozoconazole are potent antifungal agents and are use alternatives for invasive infections **[**57,58]**.**Recently, another class of antifungal have emerged as an alternative to azoles and polyenes is echinocandins [59]. These large lipoprotein molecules having fungicidal activity against *Candida* that acts by inhibition of the D-glucan synthase, an enzyme required for the synthesis of the fungal cell wall which leads to osmotic instability and death of the fungal cell [60]. Echinocandins such as caspofungin, micafungin, and anidulafunginare well tolerated and safest class of antifungal agents. The use is somewhat limited by their large molecular size that dictates the need for intravenous injection[61].The echinocandins are semisynthetic lipopeptides produced via chemical modification of natural products of fungi.[62,11].

Table 7: Topical and Systemic antifungal drugs for the management of oral candidiasis

Antifungal Drug	Mechanism of action	Side effects	Route of Administration	Dosage form
POLYENES • Nystatin • Amphotericin B	Disrupts fungal cell membrane by binding to ergosterol	• Rarely shows nausea, vomiting, gastrointestial effects. • Nephrotoxicity.	• Topical route • Topical route	• Cream, pastille, oral suspension • Lozenges, oral suspension
AZOLES • Fluconazole • Miconazole • Ketoconazole • Clotrimazole • Itraconazole • Posaconazole • Voriconazole	Inhibit the biosynthesis of ergosterol	• Nausea, vomiting, abdominal pain. • Skin irritation, burning, nausea, diarrhoea • Abdominal pain, nausea, vomiting, liver damage • Nausea vomiting, increase liver enzyme • Nausea, neuropathy and rashes • Nausea, vomiting, diarrhoea, abdominal pain, headache, rash. • Blurred vision; headache; nausea; vomiting, diarrhoea	• Systemic route PMC, AEC, CHC • Topical route CEC • Topical/systemic route PMC, AEC, CHC • Topical route CEC • Systemic route PMC, AEC, CHC • Systemic route • Systemic route	• Tablet, suspension • Oral Gel • Gel, Tablet, Suspension • Gel, Tablet • Capsule • Solution, tablet, intravenous formulation
ECHINOCANDINS • Caspofungin • Micafungin • Anidulafungin	Inhibits D-glucan synthase enzyme	• Very fewer side effects compare to other classes.	• Intravenous route • Intravenous route • Intravenous route	

Post-antifungal Effect (PAFE):

Suppression of fungal growth that persists after limited exposure to antifungal agents. Antifungal agents with longer PAFE could be administered less frequently with longer dosing intervals without any effect of efficacy of dosing [63].

There are three most common mechanisms by which antifungal agents produce PAFE on fungal cell are[64]:

i. Exposure time of the drug at the microbial binding site.
ii. Recovery from drug induced damage to cell structures.
iii. Time require for synthesis of new proteins and enzymes before regeneration of cell growth.

For example, the polyenes disrupt the fungal cytoplasmic membrane in *Candida* species by binding to ergosterol and alter the permeability, the cell would take relatively prolonged period of time to recover before active multiplication could initiate, and thuspolyenes elicit a lengthy PAFE [65].

Novel Drug Delivery Systems:

The design and development of formulations and method of delivery for therapeutic agents is dependent on several variables. Novel drug delivery systems are designed to achieve a continuous delivery of drugs in predictable manner with reproducible kinetics over an extended period of time. The routes other than that for which the antifungal agents were designed have been utilised in attempts to provide advanced drug therapy, reduce adverse effects and improve drug penetration into selected infection site (Table 8).

Table 8: Novel approaches for antifungal therapy

Antifungal agent	Novel formulations	Benefits	References
Nystatin	a) Particulate Toothpaste (contained beads, micro and nanoparticles)	• Enhances the effective absorption of nystatin through particulate system. • It shows slowest release which provides highest inhibitory effect of *Candida albicans* for prolonged period.	[66]
	b) Solid Lipid Nanoparticles	• It delivers the active substance to the target organ at therapeutically significant levels. • Absorption-increasing effects. • Controlled-release properties. • Accommodate high amount of drug. • Negligible side effects.	[67]
	c) Liposomal Gel	• Excellent vehicle for topical delivery of drug as it increases the drug permeation.	[68]
	d) Nanoemulsion	• Avoiding undesirable side effects • Prevent toxicity of potential systemic absorption of drug.	[69]
	e) Niosome	• Increases the efficacy and safety of nystatin. • Use as an alternative to liposomes. • Niosomal encapsulation provide means for parenteral administration	[70]
	f) Liposome	• Increase efficacy • Useful in prophylactic perspectives	[71]
	g) Doubled-layer mucoadhesive tablet	• Such mucoadhesive tablet releases nystatin quickly initially from outer layer and then in a sustained manner. • Swelling-diffusion process modulates the release of nystatin from sustained release layer. • Increase contact time of drug	[72]
Amphotericin B	a) Stealth nanoparticles	• Improve the oral bioavailability. • Feasible, effective and improved alternatives for oral delivery of amphotericin B.	[73]
	b) Nano-emulsions	• Cost effective, non-nephrotoxic and thermodynamic stable. • Nanoemulsion formulation has potential antifungal activity than commercial formulations.	[74]
	c) Solid Lipid Nanoparticles	• Increase in percent relative bioavailability and half-life in comparison to the plain drug. • Provide successful oral administration. • Controlled release property.	[75]
	d) Liposomes	• Lower incidence of infusion-related adverse events and nephrotoxicity. • It improve efficacy of drug.	[76]
Fluconazole	a) Bioadhesive Films	• Act as a controlled release carrier of fluconazole. • Localized delivery at the site of infection. • Reduces dose-related toxicities.	[77]
	a) *In situ* Gel	• Effectively delivers the drug for an extended duration of time in controlled release manner. • Improve therapeutic efficacy.	[78]
	b) Niosomes	• Sustained release of drug • Greatly enhance retention of drug over the surface.	[79]
	c) Ethosomes	• Enhance antifungal activity by enhancing the permeation of drug.	[80]
	d) Microspheres	• High entrapment. • Effective drug release for an extended period of time.	[81]
	e) Microemulsions	• Provide thermodynamic stability. • Enhance drug solubility.	[82]
Itraconazole	a) Microparticles	• Increase rate of drug release. • Stable formulation.	[83]
	b) Transferosomes	• High entrapment efficiency. • Enhance permeation. • Sustained drug release.	[84]

	c) Buccal adhesive *in-situ* gel	• Controlled release of drug. • Better bioavailability • Longer residence time over the applied surface.	[85]
	d) Muccoadhesive Tablets	• Sustain the drug release. • Improved oral bioavailability. • Enhanced the dissolution rate of itraconazole.	[86]
	e) Solid lipid nanoparticles	• Improve the therapeutic efficacy. • Reduction of toxicity of this broad spectrum antifungal agent. • Targeting potential.	[87]
	f) Gastroretensive tablets	• Increase mean residence time of tablet in gastrointestinal tract. • Enhance the solubility of drug. • Controlled release of drug for prolonged period of time.	[88]
	g) Niosomes	• Increase permeation compare to itraconazole solution. • Stable formulation.	[89]
	h) Nanosuspension	• Increases the aqueous solubility of itraconazole. • Higher drug release. • Increase oral absorption of drug.	[90]
Ketoconazole	a) Magnetic nanoparticles	• Attractive strategy for drug delivery.	[91]
	b) Microemulsion	• Enhances microbiological activity to avoid the systemic side effects. • Good solubilizing capacity.	[92]
	c) Niosomal Gel	• Reduces toxicity. • Modify pharmacokinetic and bioavailability. • Can increase the residence time of drug at the site of absorption.	[93]
	d) Lipidic nanoparticles	• Minimizing the adverse side effects. • Providing a controlled release. • Increase the drug stability. • Enhance the drug solubility and permeability.	[94]
	e) Liposomes	• Improve therapeutic response. • Higher entrapment efficiency.	[95]
Miconazole	a) Cubosomal Gel	• Enhanced flexibility for product development. • Exhibit sustained release effect. • Overcome problems like leakage of drug and aggregation.	[96]
	b) Solid lipid nanoparticles and Nanostructured lipid carrier	• Provide sustained release effect. • High entrapment efficiency. • Improved stability profile.	[97]
	c) Nanoemulsion	• Thermodynamically stable. • Facilitate significant drug release.	[98]
	d) Buccal Patches	• Improved uniform and effective level of miconazole in buccal cavity. • Better patient compliance. • Avoid the tolerance formation of Miconazole nitrate.	[99]
	e) Mucoadhesive tablet	• Sustained local release of drug for prolonged period of time.	[100]
Cotrimazole	a) Polymeric Nanoparticles	• Significantly higher anti-fungal activity then conventional formulations.	[101]
	b) Solid lipid nanoparticles	• Prolonged release of drug. • Successfully localize the drug in the skin for to treat topical fungal infections.	[102]
	c) Nanofibres	• Release drug in a predetermined way for prolonged period of time. • Reduce frequency of drug administration.	[103]
	d) Mucoadhesive tablets	• Increase its solubility by complexation with β-cyclodextrin. • Improve the bioavailability of drug through buccal mucosa.	[104]
	e) *In-situ* Gels	• Control drug release and protect the medicaments from a hostile environment. • Represent sustained release behaviour.	[105]
Voriconazole	a) Self-emulsifying drug delivery system	• Improved solubility and bioavailability profile. • Attain sustained activity.	[106]
	b) Niosomes	• Slow and sustained release of drug.	[107]
	c) Floating tablets	• Decrease dosing frequency. • Increased and more effective absorption for drugs which have specific absorption sites.	[108]

		• Enhance oral bioavailability.	
	d) Microemulsion	• Enhance the drug permeation. • Acts as a promising vehicle for topical delivery of voriconazole.	[109]
	e) Sustained release tablets	• Release drug at predetermined rate. • Increase the therapeutic efficacy of drug. • Prevent drug fluctuation.	[110]

CONCLUSION

Oral candidiasis has been recognised for a long time and a considerable amount of progress has been made in the understanding of *Candida* and oral candidiasis during the last few decades when its incidence increased greatly with the advent and escalation of the immunodeficiency diseases. Greater emphasis has been given for reliable isolation and identification of *Candida* species from human clinical samples by using appropriate techniques. The specific nature of determinant of virulence factors of *Candida*, and the response of host tissues towards them have been studied in considerable detail with great emphasis on host susceptibility factors associated with this infection. Due to the increasing incidence of non-albican Candida species in oral infection and the development of resistance against some of the traditionally used antifungal agents, there is a constant need for research to get new and effective agents to treat oral candidiasis. Novel Drug delivery systems for antifungal therapy have less toxic effects and more antifungal activity compared to conventional drug delivery systems. During the last two decades, a lot of research has been carried out on different drug delivery systems and routes of administration of the drugs to overcome the problems like poor aqueous solubility of highly lipophilic drug compounds, adverse effect of the antifungal agents, low bioavailability of drugs, low onset of action, lower efficacy, high cost and poor patient acceptability. Microparticulate drug delivery systems are one of the most acceptable and safer products for the commercial production of antifungal agents.

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