https://doi.org/10.33472/AFJBS.6.5.2024. 7495-7504

African Journal of Biological Sciences

Sustained Local Drug Delivery System for Oral Candidiasis.

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Article History
Volume 6, Issue 5, 2024
Received: 15 May 2024
Accepted: 22 May 2024
Published :07 Jun 2024
doi:*10.33472/AFJBS.6.5.2024. 7495-7504*

ABSTRACT

Oral candidiasis or oral thrush is an infection of the oral cavity most commonly caused by Candida albicans generally occurring secondary to immune suppression. The incidence varies on age and also associated with certain predisposing factors which include salivary gland dysfunction, drugs, dentures, high carbohydrate diet, smoking and diabetes mellitus. Various anti-fungal drugs are available for effective treatment of oral candidiasis. Different conventional oral formulations (Gels, oral solution, suppositories, lozenges, toothpaste, muco-adhesive tablets, tablets, troches, suspensions, pastilles, mouth washes.) for oral candidiasis(OC) are available today. But they have a limited efficacy because of lesser residence time on oral epithelium due to self-cleansing action saliva of oral cavity.Taking into account the high toxicity and the threat of drug resistance of systemic anti-fungal treatment, the Local drug delivery System has been used widely introduced. With local drug administration and controlled drug release of the anti-fungal agents, Drug Delivery system (DDS) could provide higher curative Potential with lesser adverse effects. In this review, we will focus on the application of anti-fungal drugs and oral Biomaterials inspired formulation approaches for the treatment of oral candidiasis.

KEYWORDS: Oral candidiasis, Drug Delivery System, Nano-carriers, Anti-fungal agents, Hydrogels, dendrimers, Muco-adhesive drug delivery, Polymeric materials.

INTRODUCTION

Oral candidiasis is the most common opportunistic infection of oral cavity which is caused by *Candida albicans*.[3] The existence of *Candida* in oral mucosa are considered as normal commensals and hence, the *Candida* isolation in the absence of clinical symptoms should exclude oral candidiasis.[5]. It can also result from the other fungal species such as *Candida glabrata, Candida tropicalis, and Candida krusei*.[1].The common predisposing factors for the candida lesions are Salivary gland dysfunction conditions ,Long term use of Ill – fitting denture (mucosal trauma),Topical corticosteroid therapy, Smoking ,Over use of Broad–spectrum antibiotics and Immunosuppressive therapy ,Radiotherapy for head and neck cancer, Iron /folic acid/vitamin C and A deficiency and Endocrine dysfunction diseases. Adherence of *candida species* over the epithelial cells of oral cavity is mainly prevented by Saliva, which has various anti-candida proteins thereby providing immune mediated mucosal- host-defence. The biopharmaceutic classification system (BCS) elaborates four main sections of drugs that are mainly focused on their solubility and permeability of drugs [10] a) high solubility does not limit dissolution of drugs, so it enhances absorption, b) high permeability enables the drugs to be completely absorbed through small intestine, and c) gastric emptying step provides absorption of drugs with high solubility and permeability.[13]

On considering the nature of drug particle and the drug interactions, a Protective vehicle to circumvent the gastrointestinal destruction of the drug is facilitated, which significantly improves the rate of drug absorption. To compensate the limitations associated with the conventional drug delivery system, the "nanoparticle formulations" are being established in the field of nano-medicine which Encapsulates and protects the nature of the drug. The two different patterns of drug release currently used are continuous and sustained spatial controlled drug release. Evolution of nanomedicine has gradually led to the increases in drug specificity, efficacy, tolerance and therapeutic index. An ideal nanocarrier should be stable, non-toxic or minimally toxic, anti-thrombogenic effect, non-immunogenic, non-inflammatory, biodegradable and should be delivered in smaller proportions, proteins, vaccines or nucleic acid elements.

HISTORICAL ASPECTS

In 1771, *Rosen von Rosenstein* discovered an invasive form of oral candidiasis [7] *Berkhout* renamed the species as the current genus nomenclature as Candida [7] . Nanotubes, Nanowires and other organic and inorganic nanoparticles have been developed for every industry including medicine[12] .In 1952, *Smith Klein Beecham* introduced the first sustained form drug

release formulation that were capable of controlling the drug release kinetics and has the ability to attain 12-hour effectiveness .Controlled release formulations are type of drugs which has sustained release, time based release, extended release and others. Among all the terms "sustained release" is more commonly used in medicine.

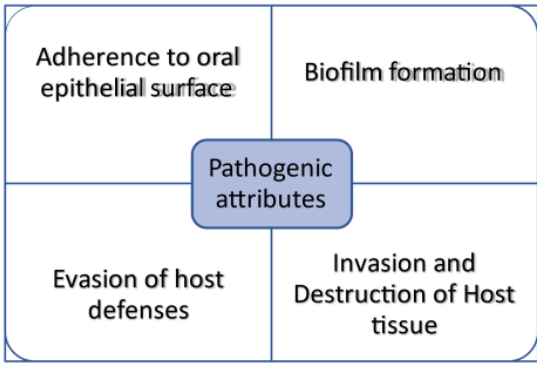
CANDIDAL COLONIZATION ASPECTS:

C.albicans colonizes in multiple sites of oral mucosa, but more commonly it is reported to be present over the dorsal surface of tongue .Host factors are frequently associated with increased candida growth rates which includes: less salivary flow rate, reduced salivary Ph ,O blood group , chemicals from tobacco smoking and increased salivary glucose concentration.[6]. The components of the cell surface allows a commensal yeast strain to escape the immune surveillance and promotes the initiation of oral candidiasis. Changes in cell surface protein glycosylation will induce the formation of hydrophobic protein components which in turn affects the adherence properties of the drug. IgE-mediated immune tissue reactions from the candida antigens leads to certain hypersensitivity reactions in chronic mucocutaneous form of candidiasis.[19]

POTENTIAL PATHOGENIC ASPECTS:

The transitional change from the saprophytic candida to the parasitic form is mainly depended on the predisposing factors associated with the disease. Biofilms are mucosa associated micro-organism embedded over the extra-cellular matrix which are considered to have a multifaceted role [21] (table 1). After the bio-film formation, the Candida virulence increases along with the susceptibility to anti-microbials and progressive decrease in phagocytic immune mechanism. The systemic drugs such as antibiotics, anti-cancer, immunosuppressive, interacts with oral candidiasis and inhibits the growth of organism [5]

(Table 1)[Pathological factors]



CLINICAL AND DIAGNOSTIC ASPECTS:

There are various clinical appearance and types for this disease, yet the simpler form of all these are comprised in (table 2)[3] .Diagnosis is based mostly based on the clinical presentation and risk factors associated with the lesion. Oral candidiasis targets the intra-oral structures, pharynx, and peri-oral structures. Acute pseudomembranous and chronic atrophic candidiasis should be diagnosed based on the culture test, imprint cultures and sensitivity tests which are usually performed, if the initial therapy does not respond well. Acute atrophic and chronic hyperplastic type will mimic various other type of lesions and hence a biopsy is advised along with empirical therapy to rule out malignant lesions[2].Identification of yeast species should be evaluated based on the following features : morphological , bio-chemical immunological and genetic test [19]In order to further confirm, the plaques should be introduced in culture test in which the gram staining presents a large, ovoid, gram-positive yeast as a diagnostic feature.

(Table 2) [clinical classification][3]

ACUTE	**CHRONIC**	**OTHER LESIONS**
Pseudomembranous	Pseudomembranous	Angular cheilitis
Erythematous	Erythematous	Denture – associated erythematous
	Hyperplastic	Median rhomboid glossitis

THERAPEUTIC ASPECTS

The pharmacological management of oral candidiasis are introduced by two routes. Topical medications, which are preferred for superficial infections and for lesions which has invaded in

multiple sites and are uncontrolled by topical drug therapy are treated well with systemic medications.

TREATMENT APPROACHES FOR ORAL CANDIDIASIS:

Promotion of appropriate oral hygiene and frequent follow-up of the patient at a regular interval helps in controlling the factors which are known to precipitate the candida infection[3].The following parameters are taken in consideration while selecting an ideal anti-fungal medication: Immunological status of the patient, characteristic features of the lesion such as clinical presentation, etiological factor, susceptibility to antifungal medications, site of the lesion and dissemination .In addition to it, the pharmacodynamic and pharmaco-kinetic parameters of the drugs should be strictly considered. The most commonly used anti-fungal group of drugs are polyenes, Echinocandins, Azoles which are usually administered in the form of tablets, solutions or suspensions and has certain potential limitations such as lesser bioavailability, increased dose frequency, and resistance to drug on prolonged usage. [11,3]

MECHANISM OF ACTION OF SEVERAL ANTI- FUNGAL DRUGS:(FUNGAL TARGETS)

The foremost action of anti-fungal agents such as ergosterol (azoles) or echinocandins leads to inhibition of the molecular component of the fungus and porous formation thereby altering the integrity and permeability of the cell wall .Polyenes and echinocandins have fungicidal action whereas azoles has fungistatic for *Candida* at their therapeutic doses.[8] Fluconazole has the site-specific action towards Oral candidiasis and has been reported with several drug interactions including oral Hypoglycaemics, Anti-hypertensives, cyclosporin, coumarin-type anticoagulants etc. In 2016, the Infectious Diseases Society of America gave their clinical practice guidelines for oral candidiasis [11,42] .Their recommendations enumerated that for diseases of mild stage with miconazole embedded muco-adhesive buccal tablet 50-mg once daily to be taken for 7-14 days or, for mild disease include nystatin suspension (100,000 U/mL, 4-6 ml, four times daily) or 1-2 pastilles, 200,000 U each, four times daily for 7-14 days).The World Health Organization have formulated the topical treatment with nystatin suspension or with pastilles for oropharyngeal candidiasis in HIV-positive patients[11].

MECHANISM OF RESISTANCE AGAINST ANTI FUNGAL DRUGS:

1.Reduced intracellular accumulation of drug

2.Decreased target affinity of drug

3.Counter-action of effectiveness of drug.[8]

WHERE DOES THE DRUG GETS DELIVERED?

The mucosa of the oral cavity acts as a barrier between the soft tissue and environment which retains all oral tissue fluids in it. It has two different defined layers: a thick, stratified squamous epithelium, and a rich blood supply over the layer of mesodermal origin. The barrier of permeability is located exactly over the middle third of the epithelium [16] Drug movement or transport is mainly dependant on the variations in mucosal thickness, the degree of keratinization and their lipid composition.

NOVEL DRUG DELIVERY SYSTEMS THAT OFFER THE LOCALIZED TARGETED DRUG DELIVERY:

Drug delivery through oral cavity membrane is by three broad categories: 1. Buccal delivery: the drug is administered through the buccal mucosal lining, the vestibular region and upper and lower lips region to the systemic circulation. 2. Sublingual delivery: Administered into the mucosal lining of floor of the mouth and directly enters the systemic circulation. 3. Local delivery: is the route of drug delivery to periodontal, gingival and for the local treatment of ulcers, microbial infections and periodontal disease. The prior benefit of local delivery of drugs includes (i)decreased side effects(ii) enhanced delivery of drugs in smaller proportions to avoid the entry in systemic circulation(iii)Targeted specific local delivery of drug. The dynamic conditions in oral cavity such as alteration in pH levels, masticatory abrasion, slippery mucosa acts as a hinderance for adherence of the drug [16] . Some of the nanoparticulate like Polymers (polymeric microsphere) are resistant to harsh environment of the oral cavity and provide a sustained-release of drug.

Drug delivery systems (DDS) are carriers which have both transport and release of therapeutic agents and bio-active materials to the specific targeted sites .DDS could provide higher curative effects with lesser adverse effects [4] . Targeting is usually accomplished by drug accumulation at the site of interest with vesicular or colloidal forms of carriers. The lipid micro environment bounded around the drug prevents the drug degradation. some of the novel carrier systems such as micro/nano sphere, nano fibres, nano capsules, hydrogel, dendrimer acts as depot system and facilitate the sustained and controlled drug release over a specific period of time and helps in reduction of dosage and provides high patient compliance. some of the common drug carrier system which has their application in dentistry 1) vesicular drug delivery

2) Nano-particulate based drug delivery.3) drug delivery systems.4)colloidal carriers.5)In-situ gelling systems[4]

POLYMERIC MATERIALS:

Chitosan is one of the commonly used natural polymeric component as they are biodegradable, biocompatible, fungicidal, anti-microbial and has anti-tumour property. Low molecular weight chitosan solution is one of the components in denture cleansing solution and mouthwashes, which is used in eradication of biofilms formed over polymethylmethacrylate in denture. Polyhexamethylene guanidine hydrochloride induces a complete elimination of fungal species within few minutes of contact with dentures without affecting their property.

MICRO/NANOPARTICLES:

Micro or nanoscale particles were reported to be a common carrier of anti-bacterial drugs for oral infectious diseases.[4]Among those, Selenium ,a pH-responsive nanoparticles responded to the acidic oral environment and has been reported to inhibit the C.albicans in the bio-film by the process of adherence with the biofilm[9].At a concentration of 25 ppm these nanoparticles have reduced a total fungal burden of around 50%.Nanofibers/nanofiber mats embedded with CPC (cetyl-pyridinium chloride) provided inhibition of microorganism for an extended period of time. And thus CPC along with polymeric nanofibers provided the benefit of functioning as a controlled release system and at lower dose it has antiseptic property [9] .

HYDROGELS:

Hydrogels are water-soluble, porous structural component and has a cross-linked net like structures which gets swollen in aqueous state and shows imbibition in oral tissue fluid which later forms a stable gel matrix structure [4] .Hydrogel DDS when used as a topical bio-adhesive drug material over the oral mucosa showed sustained release of drug .At the site of drug absorption over the Oro-mucosal region, the matrix gel prolongs the residence period of the drug [4]. Various bio-adhesive carriers are used in application of clotrimazole, nystatin, miconazole in the form of lozenges, tablets etc. Application of 50 mg of miconazole once daily with gel matrix showed increased benefits in treatment of pseudo-membranous candidiasis effectively [4].

DENDRIMERS:

Nystatin-loaded nano-emulsion, dendrimers loaded with Clotrimazole PAMAM-NH2 G2 has increased antifungal property than the pure form of clotrimazole[10].Miconazole nitrate in the form of nano lipid gel showed prolonged release of drug in oral mucosa. Amphotericin B

micelles drug preparation which has slow 8-hour release, reduced its cytotoxic nature with enhanced anti-biofilm action in oral membrane. Curcumin-loaded polymeric nanoparticles showed improved antimicrobial characteristics in patients with oral candidiasis [4,9]

MUCOADHESIVE DRUG DELIVERY:

Fixed and controlled release of drug over the targeted site is essentially facilitated by the muco-adhesion. The steps involved in the muco-adhesive bond formation are the spreading, wetting, and dissolution of the polymer followed by the mechano-entanglement of polymer to the tissue surface which results in the chemical van-der wall's interaction of the molecules [15] Advantages of mucoadhesive drug delivery: 1. Provides adequate retention time 2. The therapeutic efficacy of the drug is increased by improved absorption 3. Enhanced accessibility. 4. Higher incidence of patient compliance 5. Faster onset of action. [18].

CONCLUSION

Oral cavity is a unique component with a complex micro-ecological system. With the recent developments, bio-adhesive drug delivery system looks as a promising method to achieve a targeted and sustained drug release and simultaneously maintains the patient compliance. Accessibility of oral mucosa with increased vascularity will serve as a better site for topical delivery of drugs. DDS application has recently taken a step forward in oral medicine, yet a lot of limitations exist in this division. For future clinical co-relations, a long period of in-vivo researches will provide a better treatment approach for management of all the Oro-mucosal lesions.

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