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KETOCONAZOLE LOADED MICROSPHERES: A NOVEL WEAPON FOR ORAL CANDIDIASIS

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ABSTRACT
Ketoconazole is an antifungal medication.Ketoconazole prevents the fungus from growing on the skin. The parameters' affecting the morphology and other characteristics of the resultant products is carried out by Scanning Electron Microscopy (SEM). Drug loaded microsphere has shown that encapsulation and controlled release of Ketoconazole could reduce the side effect while also reducing percutaneous absorption when administered through mucus membrane. The particle size ranged from 30-120µm. The microspheres were incorporated in various concentration of gel formulation and the drug release from these formulations was up to 12 hours. Candidiasis describes a group of yeast like fungal infections involving the skin and mucus membrane. Infection is caused by candida species, typically Candida Albicans. The candidiasis is seen orally in people with altered oral ecology (from dental appliances, hypo salivation or the use of immunosuppressive treatment. Person with HIV or AIDS, or other cellular immune defects) with the high prevalence and opportunistic nature, it is one of the most common infections found in the oral cavity, especially in the geriatrics. Due to asymptomatic nature of the infection and negligence by clinicians during the examination. It is one of the frequently missed pathology. The aim of the review is to enumerate in detail the various type epidemiology and management of oral candidiasis.

KEYWORDS: Ketoconazole, Candidiasis, Scanning electron microscopy, cavity.

INTRODUCTION
Ketoconazole is an antifungal agent applied to treat fungal and yeast infection. It is effective in the treatment of itching, athletes foot, dandruff and also yeast infection caused by candida. Ketoconazole is structurally similar to imidazole, and interfere with the fungal synthesis of ergosterol, a constituent of fungal cell membrane as well as certain enzymes. Resistance to ketoconazole has been observed in a number of clinical fungal isolates, including Candida Albicans.when ketoconazole is administered orally, ketoconazole is best absorbed at highly acidiclevels. So antacids or other causes of decreased stomach acid level will lower the drugs absorption. Ketoconazole is available in tablet form and as a topical agent in creams, foams and shampoos. It is also available in mixture products. The oral form of ketoconazole is used for systemic administration and must be taken at least two hours before any antacids. The high PH of the gastric contents would decrease absorption, so appropriate timing of administration is paramount to its absorption and subsequently efficacy. Adult and pediatric patients with achlohydria should be given ketoconazole tablet with an acidic beverage to decrease pH and allow for optimal absorption. The use of this drug requires a careful risk benefit analysis when selecting ketoconazole as the treatment of fungal infections. Clinicians should avoid using ketoconazole in the treatment of onychomycosis, cutaneous dermatophyte, and candida infections. Ketoconazole is not indicated in the treatment of fungal meningitis because it does not penetrate the cerebrospinal fluid. Some of the off-label uses of ketoconazole include Cushing syndrome and prostate cancer. Ketoconazole works as an antifungal agent by inhibiting the cytochrome P450. This enzyme is responsible for inhibiting the biosynthesis of triglycerides and phospholipids by fungi. More specifically, ketoconazole inhibits the synthesis of lanosterol, a necessary precursor for ergo sterol biosynthesis. Ergo sterol is needed to maintain the integrity of the membrane of fungi.

ADVERSE EFFECTS

- Systemically ketoconazole administration most commonly causesgastrointestinal side effects.
- It also cause nausea, vomiting, constipation, abdominal pain, dry mouth, flatulence and tongue discoloration.
- It can also cause adrenal insufficiency due to its role in the inhibition of enzymes in the steroid synthesis pathway

Side Effects

- Acne.
- Bleeding from sore in the mouth.
- Blistering, crusting, irritation, itching, or reddening of the skin.
- Cracked, dry, or scaly skin.
- Discoloration of the fingernails or toenails.
- Eye dryness, irritation, or swelling.

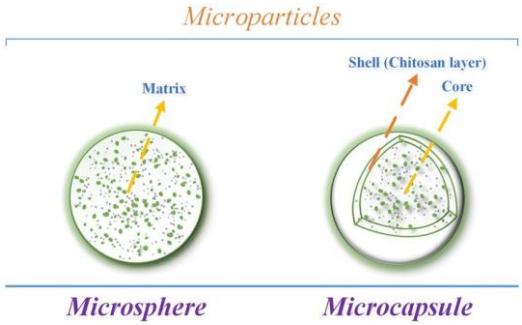
CONTRAINDICATIONS

Ketoconazole is contraindicated in patients with acute or chronic liver diseases due to the association with hepatotoxicity. It is contraindicated in adrenal insufficiency because high doses of ketoconazole inhibit adrenocortical function. Ketoconazole should not be given to patients with a known hyposensitivity reaction. Ketoconazole is contraindicated in patients taking benzodiazepines. It can increase plasma concentration and lead to sedation.

THERAPEUTIC USES

- Ketoconazole is used to treat skin infections such as athlete's foot, jock itch, ringworm, and certain kinds of dandruff.
- This medication is also used to treat a skin condition known as pityriasis (tinea versicolor), a fungal infection that causes a lightening or darkening of the skin of the neck, chest, arm or leg
- It's used to treat skin infections caused by a fungus (yeast). It can also prevent them coming back.

Microspheres are characteristically free flowing powders which consist of proteins or synthetic polymers. These polymers are biodegradable in nature. Microspheres ideally have a particle size less than 200µm. Microspheres can be characterized as solid, approximately spherical particle with a diameter having between 1-1000µm, including dispersed drugs in certain solutions or microcrystalline shape. The microspheres are the one of the novel drug delivery system in which effective therapeutic alternative to conventional or immediate release single unit dosage form. These microspheres prepared and filled in them a hard gelatin or compressed them directly.



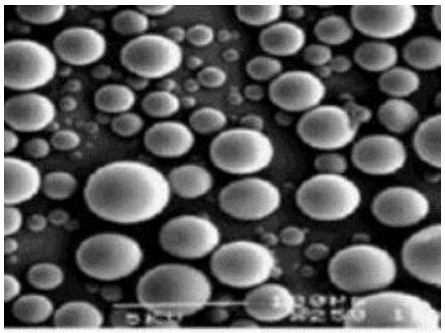


Figure of microspheres.

TYPES OF MICROSPHERES

Microspheres can divided into the following types. They are;

1. **The Magnetic microspheres.**
2. **The Floating microspheres.**
3. **The Polymeric microspheres.**

a. Synthetic polymeric microspheres.
b. Biodegradable polymeric microspheres.

4. **The Bioadhesive microspheres.**
5. **The Radioactive microsphere.**
6. **The Diagnostic microsphere.**
7. **The Muco- adhesive microsphere.**

1. The Magnetic Microsphere

Magnetic microspheres are molecular particles which are tiny enough to move across capillaries without creating an esophageal occlusion (< 4µm) but are extremely sensitive (ferromagnetic) to be trapped in micro-vessels and drawn by a magnetic field of 0.5-0.8 tesla through neighboring tissues. Magnetic microspheres which locate the medication to the site of the disease are very essential.

I. Therapeutic magnetic microspheres.
II. Diagnostic microsphere.

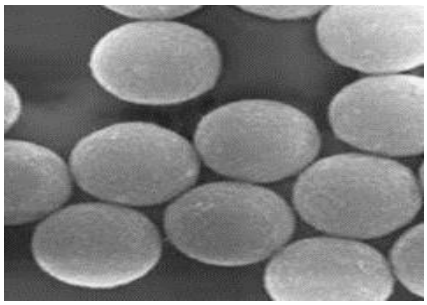


Figure of magnetic microsphere

2. The Floating Microspheres.

Gastro retentive drug delivery methods are floating microspheres on the basis of non-effervescent design. The terminology used synonymously with floating microspheres is hollow microspheres, microballoons or floating micro particles. In a simple sense, floating microspheres are small, hollow objects with no center. These are free flowing cells, varying in scale from 1 to 1000 μm.

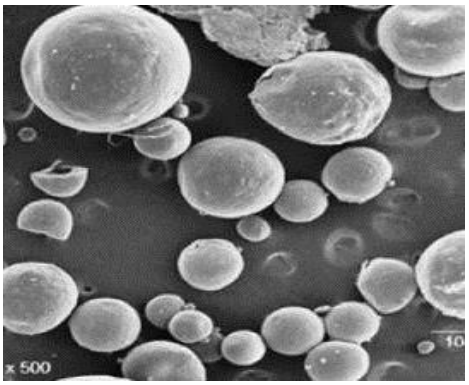


Figure of floating microspheres

3. The Polymeric Microsphere.

The polymeric microspheres can be classified as:

a. Synthetic polymeric microspheres.

The synthetic polymeric microspheres are widely used in the clinical application, moreover that also used as the embolic particles, bulking agent, drug delivery vehicles, fillers etc. & proved to be the safe & biocompatible. But the main drawbacks of these kinds of microspheres are that they tend to migrate away from the injection site & lead to the potential risk, embolism and further damage of organ.

b. Biodegradable polymeric microspheres.

With the concept that they are bioadhesive, biodegradable & biocompatible in nature the natural polymers such as starch are used. The biodegradable polymers prolongs the residence time when they come in contact with the mucous membrane due to its high degree of swelling property withthe aqueous medium thus results in gel formation. By the concentration of polymer & the releasepattern in the sustained manner, the rate & extent of the drug release is controlled. The maindisadvantage is that in clinical use the drug loading efficiency of the biodegradable microspheres iscomplex & it is difficult to control the release of drug.

4. The Bio adhesive microspheres.

Adhesion can be characterized as adherence to the membrane by the use of theSticking the water soluble polymer properties. Bio-adhesive drug delivery system is delivery system uses the bioadhesion property of some of the polymers which become adhering on hydration and can be utilized for prolonged periods of time to direct a medication to a specific area of the body. Thus, the drug's absorption and therefore bioavailability is improved through the decreased dosing frequency resulting in greater compliance with the patient.

5. The Radioactive Microsphere.

The microsphere subgroup that is interacts radioactively and is typically treated in a comparable manner as non-radioactive microspheres. Yet the radioactive microsphere always includes one and sometimes more radio-nuclides, in addition to the matrix material that describes the microsphere and gives it its targeting properties in a particular tissue or organ. Also in low amounts, radioactive microspheres can carry large doses of radiation to a specific region without affecting the natural tissue surrounding them and gives it its targeting properties in a particular tissue or organ.

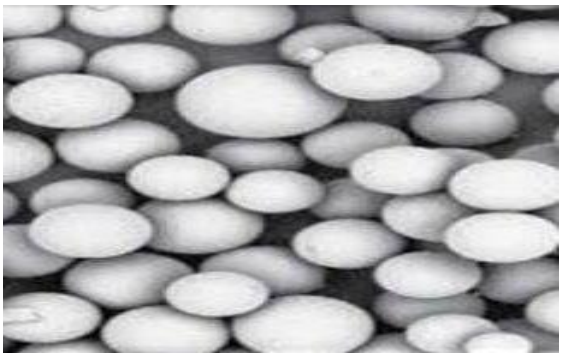


Figure of radioactive microspheres

6. The Diagnostic microsphere.

The magnetic drug transport technique is based on the fact that the drug can be either encapsulated into the magnetic microsphere or it can be conjugated on the surface of the microsphere. The accumulation of the carrier at the site of target allows them to deliver the drug locally.

7. The Mucoadhesive Microsphere.

The mucoadhesive microspheres which are of 1 to 1000mm in diameter & consisting either theentirely of the mucoadhesive polymer or having the outer coating of it & coupling of themucoadhesive properties to the microspheres has the additional advantages. For e.g. The enhanced bioavailability & the efficient absorption of the drugs due to the high surface to volume ratio, themuch more intimate contact with a mucus layer, the specific targeting of the drug to the absorptionsite which is achieved by anchoring the plant lectins, antibodies & bacterial adhesions, etc. on thesurface of microspheres. To adhere to any mucosal tissue the mucoadhesive microspheres can betailored which includes those found in the GIT [gastrointestinal tract], nasal cavity, eye & urinarytract, thus offering the possibilities of the localized as well as the systemic controlled release of thedrugs.

- **METHODS USED IN MICROSPHERE PREPARATIONS**

- Wax coating and hot plate
- Spray Drying Techniques

- Coacervation
- Solvent evaporation
- Precipitation
- Freeze drying
- Single emulsion solvent evaporation technique
- Double emulsification method
- Ionic gelation method

Wax Coating and Hot Melt

Waxused to encapsulate the main components, by dissolving or dissolving or dispersing the product in melted wax. The waxy paste or mixture, such as frozen liquid paraffin, is released by high intensity blending with cold water is heated up for at least an hour. Then the external layer (liquid paraffin) is decanted and the microphages are immersed in a non-miscible solvent and dry air is required to dry. For the surface ingredients, carnauba wax and beeswax can be used and both should be combined to obtain desirable characteristics.

Spray Drying Techniques

This was used to prepare polymer microspheres mixed charged with drug. This requires dispersing the raw substance into liquefied coating liquid, and then spraying the mixture into the air for surface solidification accompanied by rapid solvent evaporation. Organic solvent and polymer solution are formulated andsprayed in various weight ratios and drug in specific laboratory conditions producing microspheres filled with medications. This is fast but may lose crystalinity due to rapid drying.

Coacervation

This method is a straight forward separation of micro molecular fluid into two immiscible types of material, a thick coacervate layer, comparatively condensed in macromolecular fluid into two immiscible types of material, a thick coacervate layer, comparatively condensed in macromolecules, and a distilled layer of equilibria. This method is referred to as basic coacervation, in the presence of just on macromolecules.

Solvent Evaporation

The method of solvent evaporation has also been extensively used to preparation of PLA and PLGA microspheres which contain many various drugs. Several variables where identified that can significantly affect microspheric characteristics, such as solubility of drugs, internal morphology, and type of solvent, diffusion rate, temperature, polymeric composition as well as viscosity and drug loading. The efficacy of solvent evaporation system to create microspheres relies on the effective entanglement of the active substance into the particle, and therefore this procedure is particularly efficient with drugs that are either insoluble or partially soluble in the liquid medium that constitutes the constant phase.

Precipitation

It is a modification of the form of evaporation. The emulsion is polar droplet scattered over a non-polar medium. The use of a co-solvent can extract solvent from the droplet. The subsequent rise in the concentration of polymers induced precipitation to create a microspheres suspension.

Freeze Drying

Freeze drying is effectively used in protein API microsphere preparation. The method is freezing, sublimation, main drying and secondary drying. At the freezing step, account is taken of the eutectic point of the components. During the process, lyoprotectants or cryoprotectants will stabilize API molecules by removing water, creating a glass matrix, lowering intermolecular interaction by forming hydrogen bonds between the molecules or dipole- dipole interactions.

Single Emulsion Solvent Evaporation Techniques

This process requires polymer dissolution in an organic solvent accompanied by emulsification of an aqueous environment containing the emulsifying agent. The resulting emulsion is stirred for several hours in atmospheric condition to allow the solvent to evaporate, which is then washed, rinsed and dried in desiccator's, designed and manufactured drug microspheres with polymers by diffusion evaporation method with emulsion solvent.

Double Emulsification Method

The Doppel- emulsion strategy requires mixing W/O/W or O/W/O processing the double emulsion. The aqueous solution of the product is distributed in a continuous lipophilic organic phase. The continuous step which consists of a polymeric solution eventually encapsulated medication observed in the scattered aqueous layer to form primary emulsion. The microspheres filled with the drugs prolonged the release of the medication 24 hours and where observed to be diffusion and erosion regulated.

Ionic Gelation Method

Ionotropic gelation is depend on the tendency of polyelectrolytes to cross connect to develop hydrogel beads often called gelispheres in the existence of counter ions. Gelispheres are circular cross linked polymeric hydrophilic agent capable of substantial gelation and thickening in model biological fluids and drug release regulated by polymer relaxation via it. The hydrogel beads are formed by dumping a drug –laden hydrophilic compounds .creating a three dimensional lattice the moiety is ionically cross-linked. Biomolecules may also be placed into these gelispheres to maintain their three-dimensional form under moderate condition.

Advantages of Microspheres

- Decrease ofsize contributes to an increasing the surface area and can increase the potency of poorly soluble material.
- Providing a steady quality of medications in the body that can improve patient compliance

- Drug packaging with polymers prevents the drug avoid enzymatic cleavage while making it suitable for drug method delivery system.
- Less duration of dosing contributes to higher patient compliance.
- Effective usage of medication can enhance bioavailability and decrease harmful effects occurrence or severity.
- Helps protect the GIT from opioids irritants.
- Transform liquid into solid shape and block the unpleasant taste.
- Reliable means, if charged, to transmit the medication to the target location with precision and to sustain in the targeted concentration at the targeted site and with no undue impact.
- Reduce central reactivity related to the external world.

Disadvantages of Microspheres

- Variations in the rate of discharge from one dosage to the next.
- Controlled release formulations typically have a higher dose load and so any lack of quality of the release properties of the drug substances can contribute.
- Potentially dangerous.
- These dosing types must not be broken or chewed.
- The changed releases from the formulation
- The release rate of the regulated dose process of release which differs from a number of factors like diet and transfer level through gut.

APPLICATION OF MICROSPHERES

- Microspheres in vaccine delivery
- Microsphere in gene delivery
- Oral drug delivery
- Transdermal drug delivery
- Targeting by using micro particulate carriers
- Monoclonal antibodies
- Intratumoral and local drug delivery
- Other applications
  - Microspheres are used in membrane technology
  - Immuno- sorbent assay
  - Used in cosmetics fragrance

ORAL CANDIDIASIS

The candidiasis is an opportunistic infection commonly affecting the oral cavity. It is often undiagnosed among elderly, particularly in denture wearers and in many cases is avoidable with proper oral hygiene care. It can also be a mark of systemic diseases, such as diabetic's mellitus and is a common problem among the immune compromised. The candidiasis of the oral cavity is caused due to over growth or infection by yeast like fungi candida. The predominant ones are candida albicans, candida glabrata, candida peudotropicalis, candidida lusitaniae. The oral candidiasis is the most common human fungal infection especially in early and later life.Systemic candidiasis carries a mortality rate of 71% to79%. It is important for all the clinicians treating the older patience to be aware of the risk factors , diagnosis and treatment of oral candidiasis.

- **CLASSIFICATION AND TYPES**

There are different types of oropharyngeal candidiasis including acute pseudomembranous,acute atrophic, chronic hyperplastic, denature stomatitis, median rhomboid glossitis and angular cheilitis.

1. Acute pseudomembranous candidiasis(thrush)

They commonly occur as adherent white plaques resembling curdled milk of cottage cheese on the surface of liable and buccal mucosae, hard and soft palates, tongue periodontal tissues and oropharynx. The membrane can be scrapped off with a swab to expose the underline erythematous mucosa.

2. Acute atrophic candidiasis

Acute atopiccandidiasis also known as erythematous candidiasis is commonly associated with burning sensation in the oral cavity or tongue. Clinical appearance of flecks may not be the prominent feature. The tongue may appear to be bright red or give a bald appearance.

3. Chronio hyperplastio candidiasis

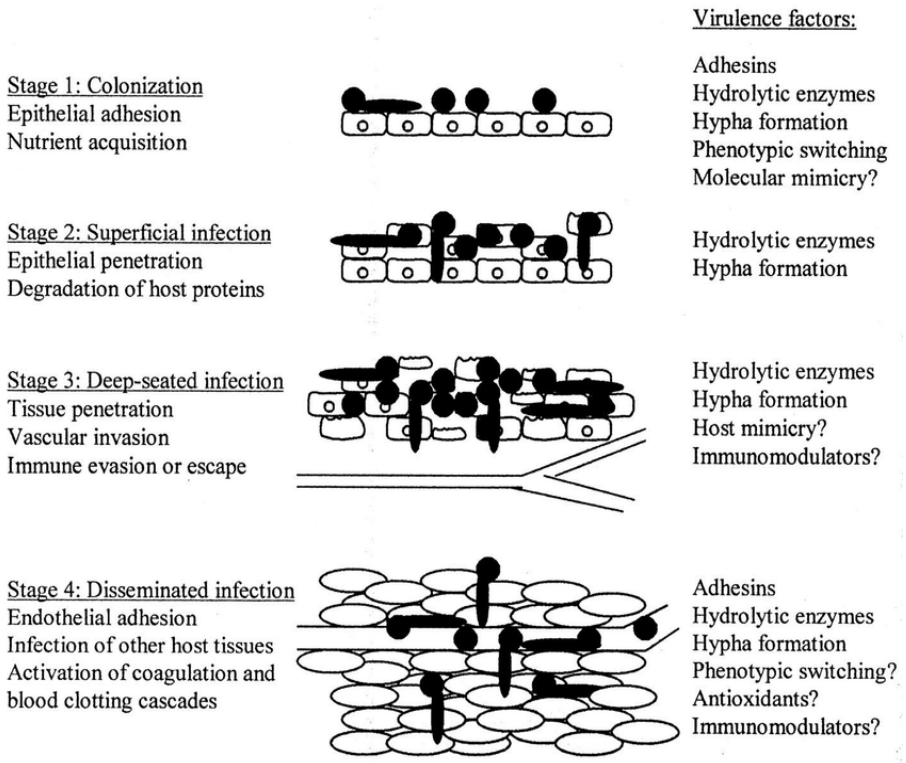
Chronio hyperplastio candidiasis occurs on the buccal mucosa or lateral borders of the tongue as a speckled or homogenous white lesion. It is usually associated with smoking, and complete resolution of the infection seems to be depend on cessation of the habit.

- PATHOPHYSIOLOGY

Candidia albicans is the prominent causal organism of most type of candidiasis. It is a relatively harmless organism inhibitating the oral cavity or almost 50% of the populations.Other species including candida krusei, have been found in immune compromised persons. Candidida glabrata is an emerging cause of oropharygeal candidiasis in patient receiving radiation for head cancer. In patience with HIV infections, new patients, such as candida inconspicua and candidida dubliniensis, have been recognized.

Pathogenesis of oral candidiasis is surface molecules that permit the adherence of the organism to other stuctures (eg , human cells, extracellular matrix ,prosthetic devices). Acid proteases and phospholipase that involove penetration and damage of cell envelopes. Ability to convert to a hyphal form (phernotypic switching).

Oral candidiasis usually occurs in neonates and the elderly. The immature immune mechanism of newborn s and the reduced immune defense in the elderly are the major etiological factors in the pathogenesis of oralthrush. However, other co-factors are also important, such aspoor oral hygiene smoking, and dentures.



Steps in pathophysiology

Risk Factors for Oral Candidiasis

Candida species are normal micro biota components of the oral Cavity, gastrointestinal system, and genitourinary tracts. When there is an imbalance in the normal flora, the overgrowth of candida species may occur, thus producing oral candidiasis. Candida species are present as yeasts in healthy state, but under certain conditions, may transform into a pathologic hyphae form. The predisposing factors of oral candidiasis development include immune dysfunctions, immune suppressant drugs, prolonged antibiotics therapy, diabetes, human immunodeficiency virus(HIV) infection, chemotherapy, radiotherapy, alcohol and tobacco use and dental infections. The risk factors are

Endogenous factors

1. Infancy
2. Old Age
3. Pregnancy
4. Immunocompromised state
5. Diabetes Mellitus
6. Vitamin Deficiencies
7. Poor overall health

Exogenous factors

- Poor nutritional diet
- Use of specified pharmacotherapeutics
- Cigarette smoking
- Chronic local irritation or trauma
- Local radiation
- Malignancy with chemotherapy treatment

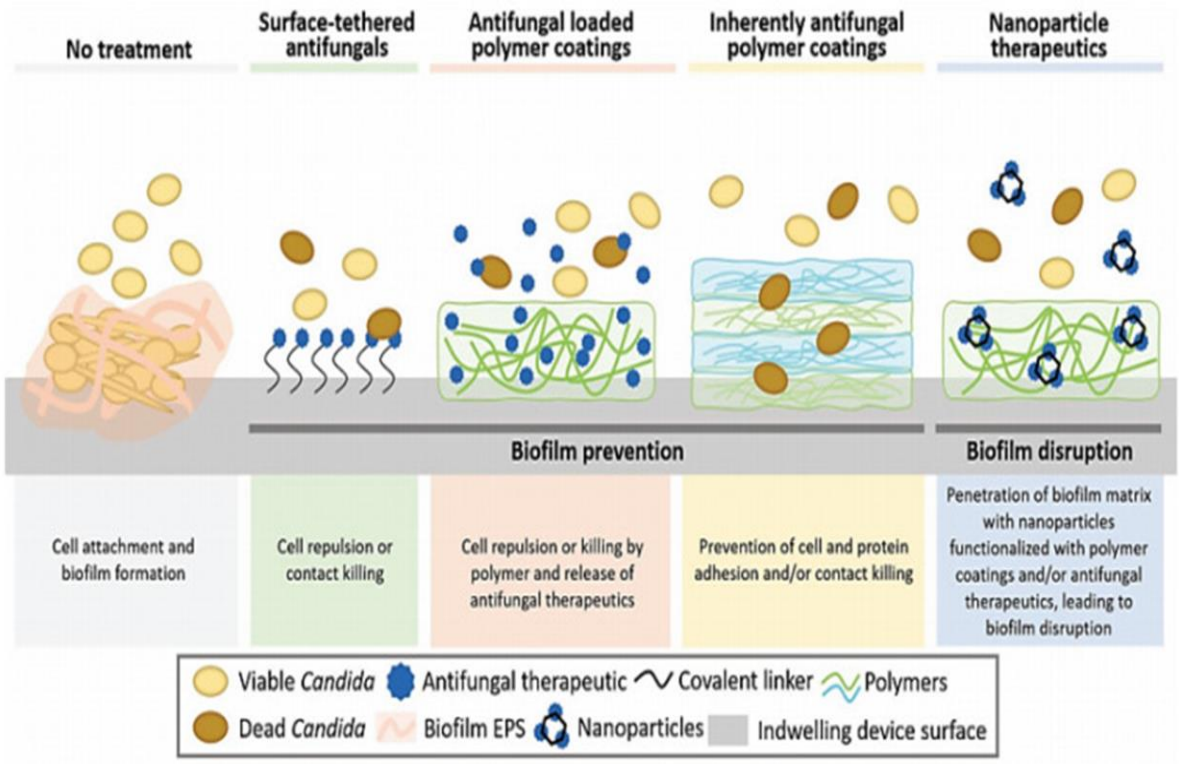
CLASSIC TREATMENT OPTIONS FOR ORAL CANDIDIASIS

In denture wearers, oral candidiasis current management relies on good hygiene practices, close attention to proper denture fit with tissue conditions, and administration of antifungal agents. Immunocompetent patients respond well to topical or oral medications, but there is a high risk of systemic infection in case of the elderly and medically or immunologically compromised patients.

Depending on the type of oral candidiasis, several treatment options can be employed. The most conventional and efficient currently available drugs for treating oral candidiasis are polyenes (e.g. amphotericin B and nystatin) azoles (ketoconazole, clotrimazole, fluconazole). These antifungal agents can be administered either locally or systemically, in various forms ranging from oral suspensions, ointments, creams, gels, and troches, to tablets, pastilles, and even intravenous infusions. However, due to their toxicity, adverse effect, side effect, and acquired resistance, these therapeutics action is often hindered conventional local oral delivery formulations usually exhibit an initial burst release that rapidly decreases to sub therapeutic concentrations. Whereas regular antifungal systemic drugs result in severe side effects. Therefore, novel treatment options must be considered for improving anti candida medicine efficiently while protecting the organism from potentially harmful effects.

NOVEL TREATMENT OPTIONS FOR ORAL CANDIDIASIS

As oral candidiasis current treatment is becoming rather ineffective due to the emergence of resistant strains, there is an increased research interest towards novel treatment options. The investigated strategies include the use of intrinsic anti candida materials, antimicrobial nanoparticles, and natural antifungal essential oils and extracts, replacing traditional prosthesis material and denature adhesive with biomaterials capable of preventing bio-film formation, including regular antifungal agents to targeted and controlled release delivery systems, and combined approaches towards developing the optimum treatment.



MANAGEMENT

Taking a history followed by a thorough examination of the oral cavity, including the hard and soft palates, the buccal mucosa are usually good starting points in case of denture wearers, the examination should be done after they have been removed. Predisposing factors should be identified and resolved followed by an assessment of the type, severity, and chronicity of the infection. The oral hygiene involving scaling of the teeth and regular cleaning dentures. Dentures should be cleaned and disinfected daily and left out overnight or at least 6houres daily. The dentures soaked in a denture cleaning solution such as chlorhexidine has been found to be very effective in eliminating candida than brushing. When rinsing the mouth with topical antifungal, the patient should ensure that the dentures are removed and that entire oral mucosa is coated with antifungal and held in the mouth for few minutes. Oral candidiasis is a treatable disease, and the prognosis is usually positive in the majority of patients. A thorough medical history and appropriate workup are crucial for the successful treatment of patients with oral candidiasis. The likelihood of developing oral candidiasis can be reduced through the elimination of risk factors and maintenance of efficient oral hygiene. Mechanical means to remove heavy candidial plaques from oral lesions is important and can promote antifungal action and speed healing. From the first antifungals, nystatin and amphotericin in the late 1950 to the early 21st centuary, over 60 years, only a small number of antifungal drugs have become available,and most are fungistatic.

BENEFITS

- Increased duration of action
- First pass effect can be avoided
- Reduce toxicity
- Patient compliance is good
- They facilitate accurate delivery of small quantities of potent drug and reduced concentration of drug at site other than the target organ or tissue
- They provide protection for unstable drug before and after administration, prior to their availability at the site of action
- Provide the ability to manipulate the in vivo action of the drug, pharmacokinetic profile, tissue distribution and cellular interaction of the drugs
- Provide constant and prolonged therapeutic effect
- Provide constant drug concentration in blood there by increasing patient compliance
- Reduces the dosing frequency and thereby improving the patient compliance

CONCLUSIONS

To summarize, oral candidiasis can be a life-threatening infection for immunocompromised individuals, requiring strong antifungal drugs. The classic therapeutic approach implies the administration of different polyenes, azoles while prevention is ensured through good hygiene practices and attention to proper denture fit. To avoid Candida species overgrowth and limit the adverse effects associated to traditional antifungal agents, advances have been made for developing anti-Candida biomaterials.

By making use of inherently fungistatic or fungicidal polymeric, inorganic, and natural products, coating functionalizing and or incorporating the drug like ketoconazole loaded microspheres are all considered efficient novel treatment options for oral candidiasis. Besides, delivering classic drugs via controlled delivery systems helps reducing adverse effect without hampering the therapeutic performance.

The review of microspheres is better of drug delivery system than other type of drug delivery system. In upcoming days this microsphere novel drug delivery system which shows more effective in treatment of oral candidiasis. Mainly this formulation gives safety to the active pharmaceutical ingredient and also other excipients used in formulation. Maintenance of good oral and denture hygiene is crucial. It is important to remove dentures overnight, use denture cleanser, or make a new denture if an ill-fitting denture with stomatitis exists. Rinsing the mouth after use of an inhaled steroid is helpful to prevent oral candidiasis.

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