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Novel mucoadhesive formulations for antifungal topical drug delivery

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Abstract
Both the number of fungi that cause systemic diseases and the number of those diseases itself are on the rise. Antifungal agents that are used to treat include the azole group of medications (Ketoconazole, Fluconazole, and Itraconazole), Nystatin, polyene antibiotics (Amphotericin B), and fluoropyrimidines (Flu Cytosine). Innovative drug delivery strategies for topical antifungal treatment, determined by the kind of formulations are categorized as mucoadhesive gels, mucoadhesive emulsions, liposomes, nanospheres and nanoparticles-based systems etc. A new era in the management of fungal infections has been brought about by the development of lipid-based antifungal drugs. Hopefully, developments in liposome technology will lead to antifungal regimens that are less hazardous and more effective. Novel drug delivery systems for antifungal therapy, aiming at reducing the side effects and maximizing the antifungal activity have added a new dimension to the treatment of fungal infections. New Comparing drug delivery systems for antifungal therapy to their parent compounds administered by conventional systems, the former exhibits greater antifungal activity and less toxic effects.

Keywords: Antifungal, topical, drug delivery, nanotechnology, mucoadhesive

Introduction
Fungal infections are most recurrent type of skin disorders and frequently grow in warm and moist areas. There are about 300 types of fungal species which cause infection in humans and among them many species infect skin and mucosal membranes. Normally many types of fungus present on the human body but they do not cause any infection. The fungal skin infections mostly occur in sweaty and poorly aerated body parts or penetrate in side body through any cut or wounds. It is very tough to control fungal infections when it reaches to the blood circulation and severity of such infections vary from patient to patient. Invasive fungal infections are the critical health complications in immuno-suppressed persons such as diabetic patients etc [1]. Different types of drugs that are accepted for first line control of such fungal infections are polyenes derivatives (amphotericin B and nystatin), azoles derivates (fluconazole, voriconazole and posaconazole) and echinocandins (caspofungin, micafungin and anidulafungin). Many fungi have developed drug resistance on the multiple uses of antifungal drugs therefore, some new and effective line of treatment has been explored to maximize the therapeutic efficacy of drugs [2].
To overcome the drawbacks of the conventional drug therapies, now scientists mainly focus their research on the nanotechnology and its applications. By the aid of nanoparticle technology it is possible to increase the solubility of poorly water soluble drugs, improve penetration and absorption through skin or mucosal linings. Thus nanoparticles are used as an important tool in the formulation of controlled and targeted drug delivery systems.
In addition to using the cell membrane, cell wall, and virulence factors as potential antifungal targets, novel delivery systems for approved and experimental compounds are also being developed for the treatment of invasive fungal infections.

Based on the degree of penetration into bodily tissues, fungi known as mycosis that affect people can be categorized into four groups:
1. Fungi that grow only on the skin's or hair's surface are the cause of superficial mycosis.
2. Athlete's foot and ringworm are examples of infections that fall under the category of cutaneous mycosis, also known as dermatomycosis, where growth only happens in the outermost layers of the skin, nails, or hair.
3. Subcutaneous, connective, and bone tissue are all affected by subcutaneous mycosis, which penetrates beneath the skin.
4. Deep or systemic.

Different Types of Mucoadhesive Drug Delivery Systems used in Topical drug delivery

1. Solid Mucoadhesive Systems

These mucoadhesive systems bind to the mucosal membrane by physical and chemical interactions. Different types of mucoadhesive drug delivery systems are:

- **Mucoadhesive Microspheres:** Mucoadhesive microspheres mainly used for the controlled and targeted drug delivery. They make close contact with a large mucosal surface area and thus increase their retention over it for prolonged duration and also delivered the drug to less approachable sites. The mucosal membrane of various organs such as GIT, ocular, vaginal, rectal and nasal are different sites for drug delivery currently being largely investigated for the delivery of the mucoadhesive microspheres [3].
- **Liposomes:** Liposomes are spherical vesicles consisting of phospholipid bilayers. Liposomes have gained a great interest as potential drug delivery systems to maximize drug efficacy [4]. Coating liposomal surface with mucoadhesive polymer may improve the stability of the liposome and also improves their retention at the target site [5]. It is reported that Gum karaya gel based liposomal dispersion provides antifungal effect for long time period and can be utilized for cutaneous drug delivery [6].
- **Mucoadhesive Nanoparticles:** Nanoparticles are nano size range (1to100 nanometer) particles. Mucoadhesive nanoparticles offer many advantages such as longer residence time, decrease mucociliary clearance and improve permeability through epithelium or mucosal surfaces and thus improve bioavailability at the target site [7].
- **Mucoadhesive films/insets:** Insert or film made by mucoadhesive polymers provides higher adhesion or binding of the film over the surface of the mucosa, and increase its residence time. Proper binding of the insert with mucosal lining minimize the skin irritation and increase patient compliance. Different studies had been reported that mucoadhesive inserts are stable drug delivery devices for ocular and transdermal applications. Various mucoadhesive biocompatible and non toxic polymers such as thiolated poly (acrylic acid) are the promising carrier for preparation of ocular inserts [8].
- **Lozenges:** Mucoadhesive lozenges may be used for the delivery of drugs for the local effect. Different classes of drugs such as antimicrobials, corticosteriods, local anaesthics, antibiotics and antifungal can be delivered as mucoadhesive lozenges for better therapeutic efficacy. Controlled and sustained drug delivery in the oral cavity by mucoadhesive lozenges improved bioavailability and better patient compliance [9].

2. Semisolid Mucoadhesive Formulations

- **Gels:** Mucoadhesive gels have been used to increase the binding of the formulation with mucosal surfaces for extended period of the time and provide controlled release of drugs. Gels usually have low viscosity so their retention at the application site can be increased by the use of mucoadhesive polymers such cross-linked polyacrylic acid, carbopol etc. Mucoadhesive nanogels have been extensively used for the effective drug delivery to the eye, oral cavity and vagina [10].
- **Films or Patches:** Flexible films or patches are the drug delivery devices which forms an intimate contact with mucosal membrane. Mucoadhesive films or patches mainly utilized for the drug delivery in to the buccal cavity or eye as their retention is better than non mucoadhesive systems. Zilactin® (Zila) is a marketed mucoadhesive film that is used in the treatment of canker sores, cold sores and lip sores. Transdermal patches consisting of the mucoadhesive polymers HPMC, SCMC and cabomer 934 with terbinafine HCl were found effective for the treatment of nail fungal infection [11].

3. Liquid Mucoadhesive Systems:

High viscosity liquids mainly used to treat mucosal surfaces in form of protectants or as drug delivery systems.

- **Suspensions:** Addition of mucoadhesive polymer in the formulation of liquid suspension increases its viscosity and thus improves absorption through mucosa. Sucralfate suspension used in different type of ulcers acts as protectant and covers the mucosal surfaces within the GIT. Now a day's nanosuspensions are widely explored to improve drug bioavailability and stability at the target site [12].
- **Gel forming liquids:** This type of liquid systems undergoes a liquid gel phase transition and liquid converted in to viscoelastic gel in response to a change in stimulus such as temperature, ionic strength or pH at the delivery site. Various polymers show this type of transition such carbomer become more viscous by the increase in pH, Gellan gum and alginate gum based systems become viscous gel in response to increased ionic strength [13].

Novel Antifungal Formulations

Different types of novel antifungal formulations are summarized in table 1.

Table 1: Some Novel Antifungal Formulations

Formulation	Drugs used	Advantages	Limitations	References
Liposomes	Ketoconazole, Clotrimazole	Suitable both hydrophilic and lipophillic drugs	Drug leakage, poor stability	[14, 15]
Solid lipid Nanoparticles	Ketoconazole, Clotrimazole, Voriconazole	High permeation and penetration in to the deeper skin	Drug leakage, not suitable for hydrophilic drugs and poor drug loading etc.	[16-19]
Niosomes	Ketoconazole Itraconazole, Miconazole, Fluconazole	Higher skin permeation and chemical stablility as comcopared to liposomes	More leaky vasculature as compared to liposomes	[20, 21]
Micelles	Clotrimazole, Econazole	improves drug solubility and high permeation of	Poor loading, poor stability, Skin	[22]

	nitrate, Fluconazole	drugs in the skin	irritation	
Nanogel		Biocompatibile & biodegradable, high permeation	Formulation processing	[23, 24]
Polymeric Nanoparticles	Amphotericin B	High permeation, Biocompatibile & biodegradable,	Poor drug loading	[25]
Microneedle	Miconazole	Painless therapy	Less fluid infusion in to skin	[26-28]
Nanoemulsion	Nystatin, Clotrimazole	Thermodynamically and kinetically stable, suitable for skin permeation of both hydrophilic and lipophilic drug	Poor retention, Skin irritation	[29-33]

Conclusion

In summary, fungal infections are a global problem that can pose a serious threat to an individual with weakened immune system. Many other medications have lost their efficacy in treating fungal infections as a result of our medical system's long-standing over-reliance on antibiotics to combat these infections. As a result, new drug delivery techniques have been developed, including colloidal carriers, nanoparticulate-based drug delivery systems, and miscellaneous delivery systems. These systems primarily aid in decreasing the toxicity and boosting the effectiveness of antifungal medications, thereby enhancing the therapeutic benefit of antifungal medication therapy.

Declaration of interest

The authors were addressing no conflicts of interest.

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