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Antifungal Agents: New Approach for Novel Delivery Systems

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Abstract
The present therapy adopted by physicians for the treatment of fungal includes the systemic administration and topical administration of antifungal agents. A concern in these formulations involves systemic adverse effects and also less concentration of drug at the site of infection. Hence an attention has recently been focused on novel drug delivery of antifungal agents which is the most widely accepted approach.

Key Word: Buccal gel, Transdermal films,, Nanoparticles,, Mucoadhesive tablets, Nanosuspensions, Micoemulsion, Niosomes

INTRODUCTION

The design and development of formulation and method of delivery for therapeutic agents is dependent on several variables. The relationship between the formulations, mode of delivery, pharmacokinetics, toxicity and clinical indication must be carefully balanced to successful development of suitable drug delivery systems. To eliminate fungal infection, antifungal agents should be administered either locally or systemically. dministration of antifungals by routes other than that for which the agent was designed or approved have been utilised in attempts to provide directed therapy, reduce adverse effects and improve drug penetration into selected infection sites, such as the central nervous system, lungs and peritoneum. The most widely investigated agent utilising a novel method of drug delivery is amphotericin B. Dose forms for this agent include topicals (aerosol, nasal spray, irrigations, pastes, absorbable sponges, impregnated bone cement and gelatin), oral dosage forms (solutions, suspensions, tablets and so on) and ophthalmic preparations (drops, ointments and injections). Amphotericin B has been administered by routes such as oral, endobronchial, intrathecal, intracisternal, intra-articular, intraperitoneal, ophthalmic and as an antibiotic 'line lock'. Nystatin has been administered as an aerosol, percutaneous paste and bladder washes. Azoles, such as miconazole, fluconazole, ketoconazole and posaconazole, have been administered by novel methods but to a lesser degree. Most of these reports involve miconazole. The dose forms and routes of administration for azoles have included irrigants (bladder, joint), ophthalmic preparations (eye drops, intraocular injections, ointments), impregnated bone cement, endobronchial and intrathecal administration. Finally, both methylene blue (bladder washes) and flucytosine (peritoneal lavage, ophthalmic eye drops) have also been employed. Adequate evaluations of both the safety and efficacy of these therapies are most often hindered by prior or concomitant antifungal therapies, comorbidities and the lack of controlled clinical trials. In addition, the availability of newer treatment options, which demonstrate significant improvement in drug distribution and treatment-related adverse effects make many such novel modes of administration less practical or necessary. In contrast, the inhalation of antifungal aerosols, such as amphotericin B, is rapidly becoming a viable prophylactic option.

AZOLES AND TRIAZOLE ANTIFUNGAL AGENTS:

Miconazole (developed by Janssen Pharmaceutica) is used for skin infections such as tinea pedis, tinea cruris and vulvovaginitis. It comes in cream, lotion, powder, spray liquid and spray powder, and also in suppository form for vaginal use.

Adverse effects include: increased burning, itching or irritation of the skin or vagina, stomach pain, fever or foul-smelling vaginal discharge.

Products: Micatin, Monistat-3, Monistat-7, Monistat-Derm, Monistat Dual-Pak

S.No	Miconazole containing Novel drug delivery
1.	Buccal gel[1]
2.	Transdermal films[2]
3.	Nanoparticles[3]
4.	Mucoadhesive tablets[4]
5.	Swelling-controlled release system[5]
6.	Nanosuspensions[6]
7.	Microcapsules[7]
8.	Chewing Gum[8]
9.	Niosomes[9]
10.	Solid lipid nanoparticles[10]
11.	Micoemulsion[11]

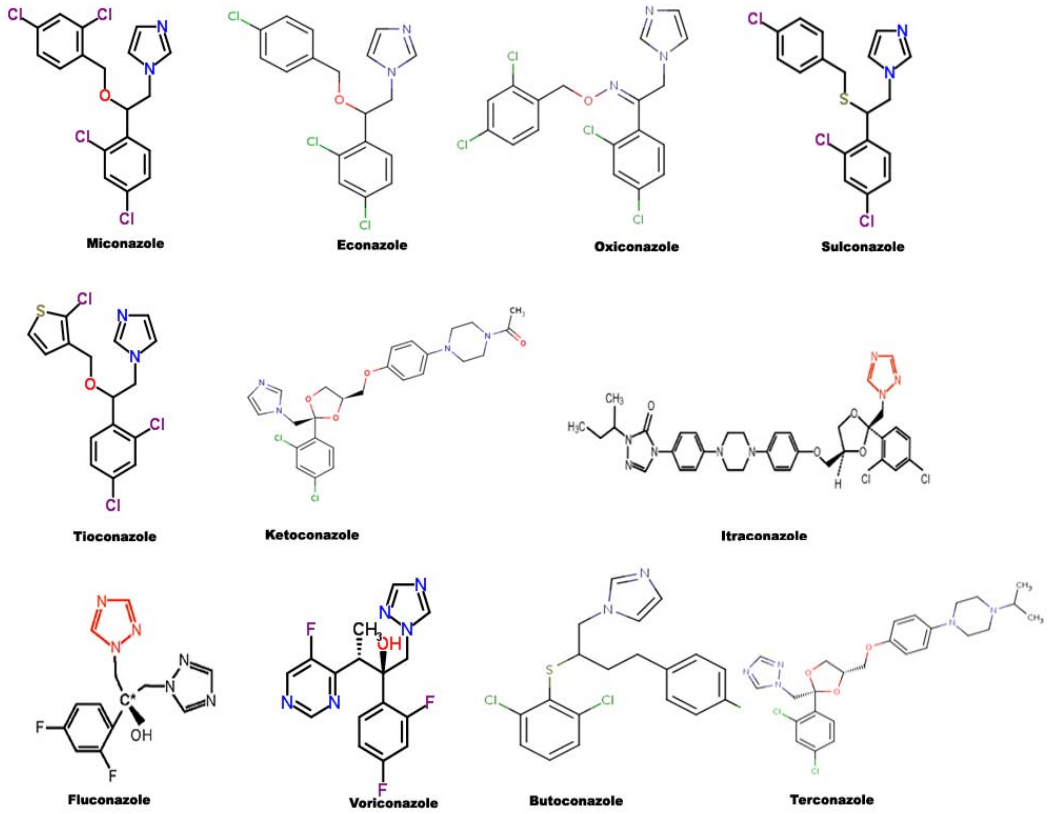

Figure 1: Structure of antifungal agents

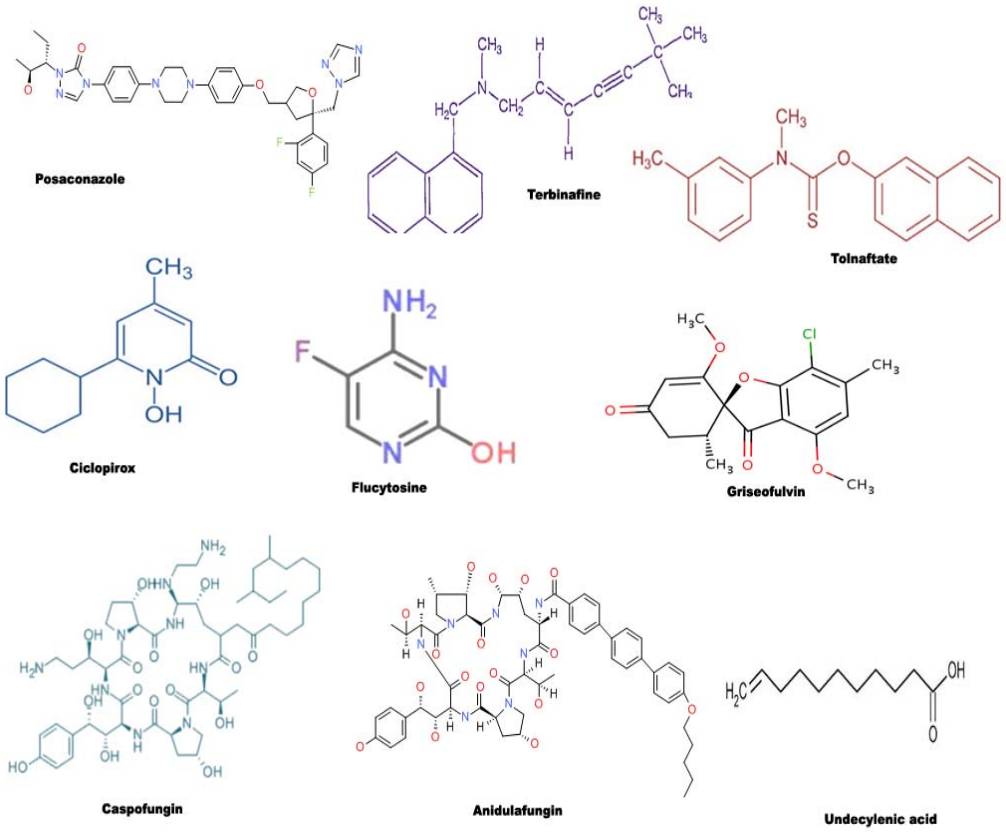

Figure 2: Structure of antifungal agents

Econazole (developed by Janssen Pharmaceutica) is a topical cream applied to the skin to treat fungal infections including: tinea corporis, tinea pedis, tinea cruris, and superficial candidiasis.
Adverse effects include: Burning, itching, stinging, redness and skin rash.
Products: Spectrazole, Ecostatin

S.No	Econazole containing Novel drug delivery
1.	Microemulsion [12,13]
2.	Microemulsion based gel[13]
3.	Solid lipid nanoparticles[14]
4.	Mucoadhesive microspheres[15]
5.	Sustained-release suppositories[16]
6.	Topical aerosol[17]
7.	Microparticles[18]
8.	In-situ gel[19]
9.	Vaginal tablets[20]
10.	vaginal douche[21]
11.	Liposome[22]

Oxiconazole (developed by F. Hoffmann-LaRoche and Siegfried AG) is a cream or lotion applied to the skin in the treatment of tinea corporis, tinea pedis and tinea cruris.
Adverse effects include: Burning, itching, blistering, crusting, dryness or flaking of the skin, scaling, severe redness, soreness, swelling and pain in hairy areas with pus at the root of hair.
Products: Oxistat, Oxizole

S.No	Oxiconazole containing novel drug delivery
1.	Topical lotion[23]

Sulconazole (developed by Syntex Research) is a topical cream or solution to treat tinea corporis, tinea pedis and tinea cruris.
Adverse effects include: Burning, stinging, itching and redness of the skin.
Products: Exelderm

S.No	Sulconazole containing novel drug delivery
1.	Topical powder [24]

Tioconazole (developed by Pfizer U.K.) is a cream to treat tinea corporis, tinea pedis, tinea cruris and cutaneous candidiasis.
Adverse effects include: Burning, itching, redness, skin rash and swelling.
Products: Trosyd AF, Trosyd J

S.No	Tioconazole containing novel drug delivery
1.	Topical powder [25]

Ketoconazole is supplied as a cream or in shampoos at one- or two-percent, for the treatment of tinea pedis, tinea corporis, tinea cruris and cutaneous candidiasis.
Adverse effects include: itching, stinging, skin rash, dry skin, and dry or oily scalp.
Products: Nizoral Cream, Nizoral A-D Shampoo (1%), Nizoral Shampoo (2%)

S.No	Ketoconazole containing Novel drug delivery
1.	Solid lipid nanoparticles[26]
2.	Magnetic nanoparticles[27]
3.	Topical lacquer[28]
4.	Niosomal gel[29]
5.	Transfersomal gel[30]
6.	Mucoadhesive nanoparticles[31]
7.	Microemulsion[32]
8.	Effervescent vaginal tablet[33]
9.	microcapsules tablet[34]

Itraconazole is taken orally in capsule form to treat fungal infections that start in the lungs and spread throughout the body. Itraconazole can also be used to treat fungal infections of the nails, although it is important to point out that treatment of nail fungal infections does not result in healthier looking nails. Normal nail appearance will occur only with new growth, which can take up to six months for full nail growth. Oral solutions of this antifungal agent can be used to treat oral candidiasis.
Adverse effects include: diarrhea, constipation, gas, stomach pain, heartburn, sore or bleeding
gums, sores in and around the mouth, headache, dizziness, sweating, muscle pain, decreased
sexual desire or ability, nervousness, depression and runny nose.
Product: Sporanox

S.No	Itraconazole containing novel drug delivery
1.	Transfersomes[35]
2.	Bioadhesive film[36]
3.	Solid lipid nanoparticles[37]
4.	Gastroretentive tablets[38]
5.	Microparticles[39]
6.	Niosomes[40]
7.	Microemulsion transdermal delivery[41]
8.	Nanosuspensions[42]
9.	Buccal adhesive *in situ* gel[43]
10.	Nanocrystal[44]
11.	Microcapsule[45]
12.	Nanoparticles[46]
13.	Liposome[47]
14.	Mucoadhesive tablet[48]

Fluconazole is a one-a-day tablet or suspension to treat yeast infections of the vagina, mouth, throat, esophagus, abdomen, lungs, blood and other organs. Fluconazole is

also used to treat meningitis and can prevent yeast infections in patients who are likely to become infected due to chemotherapy or radiation therapy before a bone marrow transplant.
Adverse effects include: headache, dizziness, diarrhea, stomach pain, heartburn and changes in the ability to taste food. More severe side effects can include: excessive tiredness, loss of appetite, upset stomach, vomiting, tingling or numbness in the extremities, fever, chills, rash, hives and difficulty breathing or swallowing.
Product: Diflucan

S.No	Fluconazole containing novel drug delivery
1.	*In situ* gel[49-52]
2.	Nanogels[53]
3.	Microemulsion[54]
4.	lipidic nanoparticles[55]
5.	Niosomes[56]
6.	Liposomes[57]
7.	Ethosomes[58]
8.	Transdermal spray[59]
9.	Microspheres[60]
10.	Microemulsion based vaginal gel[61]
11.	Biodegradable implant[62]

Voriconazole is formulated in an oral suspension, tablets or parenteral injection. It is used to treat different kinds of serious fungal infections and may be used in patients who have not responded to other antifungal agents.
Adverse effects include: rash, bloating or swelling of face, arms, hands, lower legs or feet, stomach pain, blurred vision, chills, convulsions, dizziness, dry mouth, headache and muscle pain.
Product: VFEND

S.No	Voriconazole containing novel drug delivery
1.	Microemulsion[63,67]
2.	Drug loaded bone cement[64]
3.	Nanoparticles[65]
4.	Transethosome[66]
5.	*In situ* gel[68]
6.	Microspheres[69]

Butoconazole is a cream suppository used to treat vulvovaginitis. It is used either once or in a seven-day regimen at bedtime.
Adverse effects include: burning or irritation in the vagina when cream is inserted, stomach pain,
fever or foul-smelling vaginal discharge.
Product: Gynazole-1
Terconazole is supplied as a cream or suppository to treat vulvovaginitis. It is usually used daily at bedtime for either three or seven days.
Adverse effects include: headache, missed menstrual periods, burning or irritation in vagina when cream or suppository is inserted, stomach pain, fever, or foul-smelling vaginal discharge.
Product: Terazol 3, Terazol 7
Posaconazole (Schering-Plough) is a novel triazole in Phase II clinical trials to be used as an oral suspension to treat invasive fungal infections caused by Candida and aspergillus. The current clinical trial will conclude in October 2006.

ALLYLAMINES

Terbinafine comes as a tablet to take orally or as a topical cream It is used to treat fungal infections of the nails.
Adverse effects include: headache, dizziness, diarrhea, stomach pain, heartburn and changes in the ability to taste food. More severe side effects can include: excessive tiredness, loss of appetite, upset stomach, vomiting, tingling or numbness in the extremities, fever, chills, rash, hives and difficulty breathing or swallowing.
Product: Lamisil

S.No	Terbinafine containing novel drug delivery
1.	Hydrogels[70]
2.	Microspheres[71]
3.	Liposomes[72]
4.	Solid lipid nanoparticles[73]
5.	Nanolipidgel[74]
6.	Transfersome[75]

Tolnaftate is is a topical cream to treat tinea infections of the skin.
Mechanism of Action: The exact mechanism unknown; however, it has been reported to distort
the hyphae and to stunt mycelial growth in susceptible organisms. Inhibition of squalene epoxidation has also been reported.
Adverse effects are rare. Skin irritation has been reported.
Products: Aftate, Tinactin, Ting, Breezee

MISCELLANEOUS

Ciclopirox is a topical solution used to treat fungal infections of the nails and hair.It is a broad-spectrum antifungal medication that also has antibacterial and anti-inflammatory roperties. Adverse effects: redness, irritation, burning, blistering or swelling at the site of application and discoloration of the nails or surrounding area. Treated nails may become ingrown.
Product: Loprox, Penlac nail lacquer
Flucytosine was synthesized in 1957 as an antitumor agent. It was inactive but it was found to have antifungal activity.
Adverse Effects: GI upset, hepatic involvement seen in the increase in transaminases, Hematologic involvement include anemia, leucopenia. Thrombocytopenia is the major complication of therapy and may be due to low levels of 5-FU circulating.
Product: Ancobon (Roche)
Griseofulvin is an antifungal produced from Penicillium griseofulvin. Therapy must continue until new tissue replaces old diseased tissue. When given orally, plasma-borne griseofulvin becomes incorporated into keratin

precursor cells and ultimately into kearatin that cannot support fungal growth.

Adverse effects: Headache is a common adverse effect. May cause aplastic anemia. Being gradually replaced by newer agents.

Products: Fulvicin-U/F, Grifulvin V, Gris-PEG

Caspofungin acetate is an parenteral injection used in the treatment of invasive aspergillosis in patients refractory to or intolerant of other antifungal therapies. Studies have shown caspofungin to be effective against invasive candidaisis. It is a semisynthetic lipopeptide (echinocandin) derived from a fermentation product of Glarea lozoyensis.

Adverse effects: thrombophlebitis, vein irritation, histamine-related symptoms, anaphylaxis has been reported.

Product: Cancidas

Anidulafungin (Pfizer) has recently been approved to treat infections by Candida.

Adverse Effects: Diarrhea, elevation of liver enzymes.

Product: Eraxis

Undecylenic Acid is widely used topically as the zinc salt in OTC preparations for topical treatment of infections by dermatophytes.

Adverse effects are rare. Skin irritation has been reported.

Products: Desenex, Cruex, Decylenes Powder, Caldesene, Gordochom Solution

CONCLUSION:

Even though the clinical efficacy of systemic antifungal treatment is well established, the potency is decreased by thousand fold when reaches the target site, and also large dose and/or prolonged administration is often necessary to maintain an effective drug concentration. The long-term use of systemic antifungal drugs is associated with potential adverse effects and patient non-compliance and also less drug availability at the site of infection, limits its use. In such condition a safe and effective novel route of drug delivery device, which will reduce the dose and increase the concentration of drug in the targeted organ with low systemic concentration is highly desirable.

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