WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL RESEARCH

Review Article

2025
Volume: 02
Issue: 04
Page: 153-173

A REVIEW - NOVEL DRUG DELIVERY SYSTEMS FOR ANTIFUNGAL TREATMENTS

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Received: 26 February 2025 **Revised: 20 March 2025** **Accepted: 07 April 2025**

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ABSTRACT

Antifungal drugs are commonly used as conventional delivery systemin the treatment of infection. The efficacy of drugs depends on penetration to skin. Noveldelivery system for topical delivery of antifungal drugsincludes ethosomes, liposomes, nanoparticles, nanosuspension, nanosponges, microsponges and emulgel. Therefore, new formulation strategies are used for development of new delivery systems. The various antifungal drugs areAmphotericin B, fluconazole, clotrimazole, itraconazole, miconazole, ketoconazole, voriconazole, bifonazole, oxiconazole, silver salts, terbinafine etc. This review discusses about the antifungal potential of various drugs and provides overview on their novel drug delivery systems.

INTRODUCTION

Fungal infections have undoubtedly increased lately and arestated as a serious emergent condition that threatens millions of lives in the world.[1] Fungi exist everywhere inhouses, hospitals, hotels, gardens, playgrounds, skin, andmucous membranes. The most common isolated organismsare *Candida*, *Fusarium*, and *Aspergillus* species. Trauma,administration of immunosuppressive agents, and AIDs arethe most prevalent risk factors.[2] The most common fungaldiseases are superfcial infections of the skin and nails whichare mainly caused by dermatophytes, causing nails infection,ringworm of the scalp, and athlete's foot.[3, 4] Oral andgenital tracts mucosal infections are also common, especially vulvovaginal candidiasis.[5]

Invasive fungal infections have high mortality rates; however, they have a much lower incidence than superfcial infections.

Antifungal drugs are classifed as either fungistatic or fungicidal based on their mechanism of action. Fungistatic drugs inhibit the growth of the fungi while fungicidal drugs directly kill them.[6] They are divided according to their chemical structure into azole antifungals, polyene antifungals, echinocandin antifungals, allylamine antifungals, and others, as demonstrated . The oldest antifungal drugs are polyenes. They have low rates of resistance, broadspectrum activity, and established clinical records. Nystatin is a polyene antifungal drug that shows outstanding action against a wide range of yeast and fungi. Also, amphotericinB is a polyene antifungal drug that has antifungal activity against *Candida* species.[7]

Azole antifungals are synthetic drugs that act by inhibiting fungal cell membrane synthesis by inhibiting the enzyme which converts lanosterol to ergosterol. This in turn increases fungal membrane fuidity and permeability which inhibits fungal cell growth and replication. Examples of this group are clotrimazole, terconazole, isoconazole, miconazole, butoconazole, econazole, ketoconazole, fenticonazole, and sertaconazole.[8] Echinocandins are antifungal drugs that are efective against *Aspergillus* species. Rezafungin is a novel fungistatic echinocandin drug; however, it is used as secondary therapy with other antifungals.[9]

Antifungal drugs have disadvantages in terms of the spectrum of activity, pharmacokinetics and pharmacodynamics, resistance mechanisms, drug-drug interactions, and compound toxicity. Moreover, they have some limitations regarding clinical efciency due to their physicochemical characteristics such as their hydrophobic property that contributes to low aqueous solubility and also selectivity problems driving from the similarity between fungi and human cells.[10] This arouses the need to create a new delivery system for antifungal drugs owing to minimize or eliminate their drawbacks and improve their efficacy.[11]

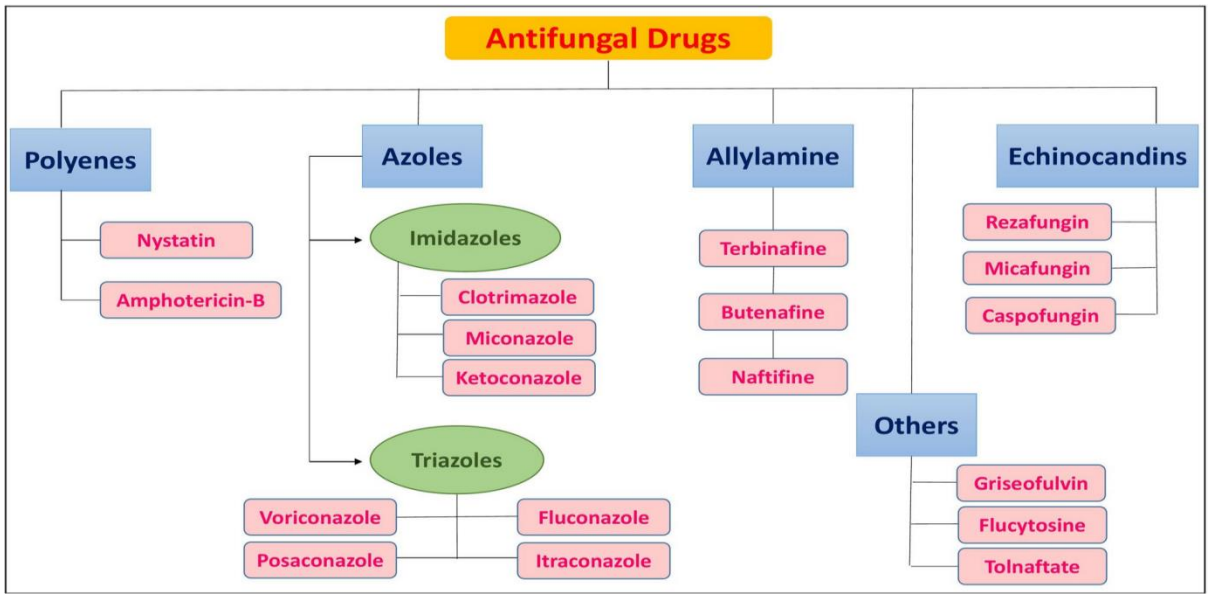

Fig. 1: **Classifcation of Antifungal Drugs.**

❖ **Novel Drug Delivery Systems**

● **SLN (solid-lipid nanoparticles)**

These are nano-lipid carriers where the active therapeutic is dispersed within a lipid core matrix. These are nanoparticle-imprinted matrices composed of lipids & surfactants. Solid lipid nanoparticles can be prepared using high homogenization or through the preparation of microemulsion[12] SLN's are w/o emulsion containing solids lipids as oil phase. The advantages of SLN's include low risk of toxicity (used lipids are physiologically same), hence biocompatible. The smaller size of lipid particles allows close contact with stratum corneum, facilitates dermal penetration of drug and controlled release of drug Their formulation generates a film on the skin and prevent water evaporation. As a result, the skin remains hydrated and barrier function remains intact. The lipid nanoparticles are spherical in shape hence have excellent lubrication behavior preventing skin irritation and allergy. They have high drug entrapping capacity and the release kinetics are well-modulated. The active ingredients are protected from degradation through encapsulation. The commercial sterilization procedure can be employed for versatile range of preparations. The stability is excellent for long-term with bioavailability remaining high. However, SLN's suffer from few limitations like limited numbers of drugs soluble inappropriate lipid.[13] SLNowing to their high lipid content shows increased drug payload, exhibiting slow and controlled drug release properties, particularly for azole drugs. SLNs comprising of Compritol and co-surfactant (PEG 600) prepared by using hot high-pressure homogenization technique exhibits high encapsulation efficiency of Ketoconazole as high as 70%. However, the type of lipids,

surfactants, their concentration and method of preparation play pivotal role in determining efficacy of encapsulated therapeutics. Lipid nanoparticles with high molecular weight fatty alcohols and straight-chain primary alcohols show poor drug loading capacity and delayed-release behavior due to their highly ordered crystalline structure of lipid matrix, leaving little space for therapeutic molecules. On the other hand, low melting point lipids, triglycerides, partial glycerides and amphiphilic lipids considered suitable for SLNs, offers increased drug loading, improved skin penetration and reduced drug leakage of topically applied anti-fungal drugs. Considering comparative advantages, SLN appears to be a potential formulation for the topical delivery of anti-fungal chemotherapeutics. Souto and co-workers prepared SLNs and nanostructured lipid carriers (NLCs) for the topical delivery of clotrimazole.[14] Developed carriers assure sustained drug release behavior for a period of 10 h, while solid lipid nanoparticles displaying occlusive property, which is desirable for topical formulation . Both SLNs and NLCs protect the encapsulated drug against photo degradation, conferring stability and had comparable antifungal activity to the marketed product against Candida albicans.[15, 16] Sanna and co-workers demonstrated that SLN formulations have enhanced permeation of encapsulated econazole nitrate across impermeable character of stratum corneum after 1 h of its application and have higher penetration of econazole nitrate into deeper layers of skin after 3 h compared to reference gel[17] Passerini et al. compared the therapeutic performance of econazole nitrate loaded SLNs with solid lipid microparticles having similar formulation attributes.[18] It was found that SLN preparations exhibits significantly higher skin permeation of miconazole nitrate against commercial gel preparation. SLN preparations also demonstrate a signifi- cantly higher targeting effect[19] More recently Cassano and co-workers demonstrated that SLNs prepared with PEG-40 stearate and PEG- 40 stearate acrylate containing ketoconazole (KCZ) and clotrimazole (CLT) are found useful in vaginal yeast infections caused by Candida albicans[20] In addition to drug, anti-fungal efficacy of lipid Nanocarriers can beincreased to a great extent using cationic lipids. Cationic lipid known to modulate antifungal activity through various mechanisms includes disruption of endosomal membranes, form complexes with DNA and enhanced cell permeability. Recently Debora and co-workers suggested that cationic lipids like dioctadecyldimethylammoniumbromide (DODAB) and hexadecyltrimethylammonium bromide (CTAB) shows excellent anti-fungal activity against Candida albicans. Nonetheless, cationic lipids induce local toxicity over a therapeutic concentration.[21] Further the size of SLNs played an important role in the treatment outcome of cutaneous mycosis. In a current study the impact of SLNs size on skin penetration was assessed by Zahra and co-workers,

result indicated that SLNs size in the range 50–200 nm easily penetrates into the cutaneous layer whereas sizes between 200 and 400 nm accumulate in the dermis, thereby recommended as appropriate regimens for treating fungal skin infections.[22] In spite of advantages SLNs have been suffering from few limitations like low drug pay-load and uneven drug release. NLCs are second-generation nano-lipid carriers consisting of both solid and liquid lipids have the capacity to hold wide variety of drugs. In a comparative study between NLC and SLNs on encapsulation performance for Ketoconazole, it is found 62.1 and 70.3 percentage encapsulation for SLN and NLC respectively. Further NLC has successfully improved the light stability of Ketoconazole compare to SLNs.[23] Moreover, NLC due to low fatty acid triglycerides shows better drug solubility and grater skin permeability compare to SLNs. Gratieri and co-workers in their study concluded that NLC exhibited high encapsulation efficiencies of voriconazole and improving cutaneous delivery compare to SLNs and plain drug.[24] Recently lipid carriers based topical gel were designed to overcome potential limitations of lipid nano-carriers like poor retention at application site, low drug payload, poor storage stability and possibility of drug expulsion. Recently Shaimaa and co-workers studied the therapeutic potential of Fluconazole-loaded SLNs Cremophor RH40 and Poloxamer 407 topical gel against Pityriasis Vesicolor. The results showed entrapment efficiency between 55.49% to 83.04%. Clinical studies demonstrated 1.4-fold greater clinical response against marketed cream.[25] Although nano-lipid preparation have exhibits improved safety and higher therapeutic performance and to treat critical fungal disorders. However poor storage stability, particle size, size distribution, poor drug payload, high manufacturing cost.

- **Liposomes**

These are bilayer phospholipid spherical vesicles composed of amphiphilic lipids (phospholipids and cholesterol). They can accommodate a wide variety of drugs including both hydrophilic and lipophilic drugs. They may trap hydrophilic molecules in their aqueous core and lipophilic drugs in their lipid bilayer.[26, 27] Amphiphilic phospholipid and ultra flexible character of liposomes protect the drug from degradation and increase skin permeability. Due to their ability to alter the biodistribution profile of entrapped drug, these are considered suitable for topical drug delivery. They can be either adsorbed on the outermost skin surface or penetrate into deeper layers. Drug release profile, liposome morphology and skin retention plays a crucial role in deciding the therapeutic performance of liposomal formulation. Amphotericin-B has a broad-spectrum antifungal activity but due to

its ability to bind mammalian cell cholesterol produce unwanted toxicity. Liposomal Amphotericin B can reduce the toxicity, due to its ability to form complex with Amphotericin. Liposomes with different surface properties and morphology have been investigated for topical antifungal drug delivery including conventional, deformable, mucoadhesive liposomes. Liposomal gel of ketoconazole show higher drug retention in the skin as compared to the gel and cream formulations.[28] The therapeutic effects of two marketed econazole formulations i.e. econazole nitrate cream, econazole liposome gel have been investigated on both uninfected and infected reconstructed human epidermis. Toxicological findings suggested that the single application of the cream showed higher acute skin toxicity compared to the liposome gel. It was also observed that liposomal formulation completely eliminated Candida albicans induced specific pathological alterations like hyperkeratosis, dyskeratosis, and parakeratosis.[29] Liposomes can be prepared from different techniques using a variety phospholipids. Deformable or elastic liposomes represent a new class of phospholipids vesicles designed to improve dermal and cutaneous antifungal drug delivery. Ultra-deformable liposomes prepared with Tween 80 as edge activator showed 107 8nm diameter, PDI of 0.078 and -3 0.2mV zeta potential displayed 40 times higher accumulation of drugs compared to AmBisome. In addition to lipid composition, liposome morphology and surface properties also play a crucial role in determining drug permeability and dermal accumulation. Verma and co-workers reported liposomes with 120 nm size resulted higher skin permeation compared to larger ones.[30] In an ongoing effort to improve antifungal activity cationic liposomes have been found advantageous. AmB-loaded cationic liposome exhibited size range of 400–500 nm and zeta potential between 40–60 mV, exhibited higher antifungal activity compared to plain drug. However, clinical application of cationic liposome is limited due to its toxicity of cationic components. Irrespective of advantages, major complications related to the liposomal formulations include drug-drug-carrier compatibility complex, drug expulsion, scale-up procedures, and stability.

- **Microemulsion**

These are stable, translucent and isotropic dispersions of oil in water stabilized by surfactants and co-surfactants for topical and transdermal administration of drugs with a droplet size of 0.1–1.0 μm. These have been reported very promising delivery system of anti-fungal agents due to their unique ability to enhance drug solubility. The antifungal spectrum of many azole drugs is compromised due to their low aqueous solubility. In a recent study by Ashara and co-workers determined the solubility of voriconazole in a microemulsion system developed

by using Neem oil Acrysol™K-150 and PEG as oil phase, surfactant and cosurfactant respectively. Results indicated the solubility of voriconazole in Neem® oil microemulsion was found to be 7.51 0.14 mg/g against 2.7 0.12 mg/g of plain drug characterized by a significant increase in MIC values.[31]

They offer the advantages like increasing drug solubility, high thermal stability, high permeability, easy manufacturing, optical clarity, and low cost. They show excellent biocompatibility because microemulsions are the appropriate delivery system for topical and transdermal systems. The presence of oils and surfactants in microemulsion formulation facilitate drug permeability across stratum corneum.[32, 33, 34, 35] A microemulsion gel containing fluconazole seems to be effective for thetreatment of invasive fungal infections.[36] Similarly Radwan and co-workers in their study reported enhanced skin retention of sertaconazole in 0.5% Carbopol 934 gel. Sertaconazole loaded microemulsion Carbopol gel showed higher drug retention (1086.1 µg/cm2) compared to marketed formulation "Dermofix® cream" (270.3 µg/cm2).[37] Microemulsion due to reduced interfacial tension and low particle size can be easily designed into gel. Microemulsion topical gel not only improves stability but also enhances their antifungal activity, further gel formulation helps to reduce the local toxicity accounted due to high content of surfactant in microemulsion. Accordingly Kumari and Kesavan studied the antifungal effect of chitosan-coated microemulsion containing clotrimazole. In vitro anti-fungal study results demonstrated chitosan-coated microemulsion revealed higher antifungal activity compared to plain microemulsion due to its controlled release behavior of encapsulated drug and intrinsic fungicidal activity of chitosan.[38] Several researchers further confirmed the ability of microemulsions to increase percutaneous permeability of fluconazole.[39] The same results were obtained with microemulsion formulae of ketoconazole, itraconazole, voriconazole, and econazole.[40, 41, 42, 43, 44, 45] Microemulsion based hydrogel containing clotrimazole showed higher skin permeation, retention and better in vitro antimicrobial activity against C. albicans compared to the reference cream.[46] Patel and co-workers had investigated the therapeutic performance of ketoconazole loaded microemulsion prepared by using lauryl alcohol, Labrasol and ethanol as oil phase, surfactant and co-surfactant respectively. Experimental findings suggested that the developed microemulsion shows superior percutaneous absorption of ketoconazole. Further it has been found that the skin permeation of ketoconazole has been increased with increasing the quantity of lauryl alcohol and with decreasing the surfactant/co-surfactant ratio in the microemulsion. The optimum formulation was chosen based on their

activity against Candida albicans. The results indicated that microemulsion formulation shows higher zone of inhibition compared to reference ketoconazole cream. Histopathological analysis on the rat skin revealed no sign of toxicity . Microemulsion formulations need high concentration of surfactant and co-surfactants combination to cover wider interface, complete emulsifi- cation of the ingredients and long-term stability. However, the undesirable residues on the substrate may cause local skin toxicity on prolonged use, hence local toxicity must be taken into account, particularly when they are intended to be used for a longer period.

- **Nanoemulsion**

It is a single phase, stable and isotropic dispersion consists of emulsified oil phase, water and amphiphilic molecules with droplet size ranging from 5-200nm.[47] These are thermodynamically and kinetically stable. Nanoemulsion because of high concentration of surfactants are considered suitable for skin permeation of both hydrophilic and lipophilic drugs. Recently Soriano and co-workers evaluated the skin flux and antifungal efficacy of Clotrimazole loaded nanoemulsion using both human and porcine skin. The result indicated optimized nanoemulsion provided a sustained release, higher skin permeation, and antifungal efficacies than commercial references.[48] Nanoemulsion has immense potential to improve the solubility of lipophilic drugs. A study by Sosa et al., 2017 showed that AmB loaded nanoemulsion formulation accounted for higher solubility and higher antifungal effect with very little systemic absorption.[49] Nanoemulsion based topical formulation are often selected to enhance the therapeutic efficacy and tolerability of locally applied anti-fungal drugs. Further, these have ability to improve solubility of low soluble drugs and also help to protect the drugs from chemical & enzymatic degradation, makes them a suitable topical vector for antifungal drugs.[50, 51, 52] Nystatin loaded nanoemulsion was prepared with the objective of decreasing undesirable side effects of encapsulated drug as systemic absorption. Permeability studies revealed that the retained amount of drug was enough to ensure desired antifungal activity with no sign of systemic absorption.[53] Moreover, nanoemulsions possess lot of commercial potentials owing to their reduced skin toxicity as they can usually be prepared using significantly less surfactant than microemulsion.

- **Ethosomes**

Ethosomes are high alcohol-containing vesicular carriers consisting of hydroalcoholic phospholipid.Ethosomes may contain diferent phospholipids like phosphatidylglycerol,

phosphatidylcholine, hydrogenatedphosphatidylcholine, phosphatidylinositol, phosphatidic acid, phosphatidylserine, and phosphatidylethanolamine in addition to alcohol, water, and propylene glycol.[54] Studies showed that ethosomes have a great ability to permeate through human skin due to their high fexibility. They can transport diferent types of drugs more efciently across the skin barrier; therefore, ethosomes are mainly used topically.[55] Ethosomes are composed of natural phospholipids, so purity may be an issue.[56] They may clump together causing precipitation; also, a high concentration of alcohol may cause irritation to the skin.[57]

Girhepunje et al. prepared ethosomes for the treatment of cutaneous *Candida* infections by enhancing dermal deliv- ery of ciclopirox olamine.[58] Ethosomes were prepared using diferent concentrations of Lipoid S PC-3 and ethanol. The optimum ethosomal formulation of ciclopirox olamine showed a higher encapsulation efciency and a stable pro- fle. Transmission electron microscopy showed unilamel- lar spherical shape vesicles. The ciclopirox olamine loaded ethosomes highly accumulated inside the skin which tar- geted the drug to the epidermal and dermal sites. These out- comes showed that ethosomes are a great carrier for trans- dermal delivery and more topical applications of ciclopirox olamine in the treatment of fungal infections.

Also, amphotericin-B ethosomal gel was formulated by Kaur and Maurya, and antifungal activity was evaluated.[59] The formulation was prepared using the cold method. The study included in vitro antifungal assessment which showed that the ethosomal gel had a higher zone of inhi- bition against *Candida albicans* than marketed liposomal gel. Also, ethosomal gel formulation had signifcant efcacy in treating *Candida* infections induced rat mycosis model compared to drug solution and marketed liposomal gel of the drug. These results ensured the therapeutic potential efectiveness in the treatment of dermal mycosis caused by *Candida albicans*. Results recommended that ethosomal gel can be the most capable carrier system for dermal and trans- dermal delivery of amphotericin-B to treat dermatomycoses.

- **Transethosomes**

Transethosomes are innovative vesicular systems that are similar in composition to ethosomes with an extra edge activator or penetration enhancer. They have the advantages of transferosomes and ethosomes.[60] Transethosomes are highly fexible vesicles with a high fux rate and high skin permeability compared to other vesicular systems. They are highly stable, biocompatible, and bio-degradable with high patient compliance.[61] However, the drugs'

molecular size must be reasonable to be absorbed percutaneously. Also, since transethosomes contain high alcohol concentration they may cause skin dermatitis as ethosomes .

Song et al. formulated voriconazole-loaded transetho- somes to treat skin fungal infections.[62] Transethosomes were formulated applying thin flm hydration method con- taining Lipoid S100 and diferent types of edge activators. Voriconazole-loaded transethosomes had spherical morphol- ogy. They had high skin deposition of the drug in the dermis and epidermis area compared to liposomes, ethosomes, and polyethylene glycol drug solution.

Ahmed et al. prepared ketoconazole loaded transetho- somes for the ophthalmic treatment of fungal infections.[63] Vesicles were prepared using thin flm hydration method, containing different ratios of l-α-phosphatidylcholine, Tween 80, and stearyl amine with ethanol and propylene gly- col. The formulated transethosomes were spherical, highly fexible, and with high entrapment efciency. Draper–Lin small composite design was used to evaluate the studied factors and select the optimum formulation. Ketoconazole antifungal activity of the optimum formulation was signif- cantly enhanced, and formulations were safe for the cor- nea. Transethosomes vesicles penetrated the posterior eye segment. In a conclusion, ketoconazole transethosomes are considered a promising system for the ocular treatment of deep fungal eye infections.

- **Transferosomes**

Transferosomes are biocompatible and biodegradable vesic- ular carriers that were presented by Cevc et al. in the 1990s.[64] They are composed of phospholipids and edge activa- tor. The presence of an edge activator in the structure of transferosomes gives the vesicles ultra- deformable charac- teristics called self-optimizing deformability. This additional feature allows the transferosomes to change their fexibility and pass through the skin pores naturally, as well as, the very narrow pores.[65] Therefore, transferosomes are pre- ferred to be used for topical and transdermal administration. However, transferosomes have some limitations such as low purity of natural phospholipids, and high production cost; also, they are slightly unstable chemically.

Qushawy et al. prepared a transferosomal gel using miconazole nitrate for the treatment of *Candida* skin infec-tions.[66] Miconazole nitrate-loaded transferosomes were prepared using a thin lipid flm hydration technique applying 23 factorial design, using three independent

factors: type of surfactant, total lipids, and the phospholipid: surfactant ratio. They had high drug encapsulation and small particle sizes. Also, the drug transferosomal gel showed superior antifungal activity than Daktarin® cream 2%. Miconazole nitrate transferosomes also showed a high ability to penetrate the skin.

- **Niosomes**

Niosomes are composed of hydrating mixture of non-ionic surfactants and cholesterol with the formation of vesicles. It increases the drug efficacy as compared to free drug that is not encapsulated. These are preferred over liposome because they exhibit high chemical stability. The vesicular systems in cosmetics and therapeutic uses may offer several advantages.[67] Percutaneously absorption of Fluconazole increases with niosomes.[68] Terbinafinehaving minimum adverse effect and improved the adherence.[69] Methods for preparation of niosomes include Film hydration technique, Sonication Reverse phase evaporation technique or Ether injection method, bubble method and micro fluidization.[70]

- **Nanosponge**

Nanosponges having three dimensional networks whose backbone is long length polyester. It is mixed with solution of small molecules called as cross linkers. The spherically shaped molecules are filled with cavities where drug is stored. The polyesters are biodegradable that breaks down easily in body[71]. Cyclodextrininclude both hydrophilic and lipophilic drugs and they release drug at the target site in controlled manner.[72]

- **Dendrimers**

Dendrimers are branched, spherical large molecules having tree like structure. The name comes from Greek word Dendron. A dendrimeroften adopts a spherical three-dimensional structure. Tomaliawas the person who synthesized the first family of dendrimers. The dendrimers having diameter in the range of 1 to 10nm.[73] AmphotericinB, Niclosmide, Prulifloxacinand econazole as a PAMAM dendrimersincrease the solubility.[74,75,76] Sulfamethoxazole release rate was increased with the penetration enhancer concentration and Dithranolincreased permeation.[77,78] Dendrimers can be Synthesized by Divergent growth and Convergent growth methods.[79]

❖ **Novel Antifungal Drugs with Novel Delivery System**

No.	Antifungal drug	Delivery system	Site of application	Reference
1.	Amphotericin B	Dendrimer,ethosomes, Ttransfersomes	Intravenous	[80,81,82]
2.	Sulfamethoxazole	Dendrimer	Topical	[83]
3.	Ketoconazole	Dendrimer	Topically	[84]
4.	Voriconazole	micro emulsion,Gel	Topically	[85,86]
5.	Itraconazole	Micro emulsion,Emulgel, Emulsion	Topically	[85,87,88,89]
6.	Miconazole	LiposomesNano emulsion, Nano suspension	Topically	[85,90,91,92]
7.	Econazole Nitrate	Liposomes	Topically	[85]
8.	Fluconazole	Liposomes, Ethosomes, Gel, Niosomes, Micro sponge	Topically	[85,93,94,95]
9.	Terbinafine	Nanostructure, Gel, Niosomes, Dendrimers	Topically	[96,97,98,99]
10.	Nystatin	Dendrimers	Topical	[100]
11.	Clotrimazole	Ointments, Ethosomes	Topical	[101,102]
12.	Oxiconazole	Gel	Topically	[103]
13.	Bifonazole	Micro emulsion,organogel	Topical	[104,105]
14.	Hydroxypropyl-β-Cyclodextrin	Nail lacquer	Topical	[106]
15.	Ciprodoxacin Hydrochloride	Nano particles	Topical	[107]
16.	Croconazole	Microemulsion, Liposomes	Topical	[108]
17.	Amorol	Nano particles	Topical	[109]
18.	Cyclodextrin	Nano sponge	Topical	

CONCLUSION

Fungal infections remains a continuous and growing threat to human health. Inappropriate and irrational use of antifungal chemotherapeutics resulted in the development of multidrug resistance fungal pathogens, unwanted toxicity, and low therapeutic efficacy. current literature evi-dence suggested that new and alternative drug delivery systems are currently focusing on various research activities. In this case, the formulation of topical carriers play an important role in skin penetration of the drugs and overall therapeutic performance. Continuous growth in the field of nanotechnology proposes a new approach to the treatment of fungal skin infections. Prolonged use of anti-fungal drugs are related with potential side effects, patient non-compliance and lower bioavailability at target site limits its clinical potential. To solve this issue, safe and effective novel drug delivery systems, which will reduce the dose with increase in concentration of drug in the targeted organ having low sys temic concentration, is highly desirable.

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