



Review article

Recent advances in topical carriers of anti-fungal agents

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ARTICLE INFO

Keywords:

Solid-lipid nanoparticles
Liposomes
Niosomes
Microneedle
Microsponge gel
Nanogel
Materials science
Nanomaterials
Materials application
Microbiology
Infectious disease
Pharmaceutical science

ABSTRACT

Fungal skin infections are the most common global issue for skin health. Fungal infections are often treated by topical or systemic anti-fungal therapy. Topical fungal therapy is usually preferred because of their targeted therapy and fewer side effects. Advanced topical carriers because of their distinct structural and functional features, overcome biopharmaceutical challenges associated with conventional drug delivery systems like poor retention and low bioavailability. Literature evidence indicated topical nanocarriers loaded with anti-fungal agents display superior therapeutic response with minimum toxicity. Nanocarriers often used for topical anti-fungal medication includes Solid-Lipid nanoparticles, Microemulsions, Liposomes, Niosomes, Microsponge, Nanogel, Nanoemulsion, Micelles etc. This review summarizes recent advances in novel strategies employed in topical carriers to improve the therapeutic performance of anti-fungal drugs.

1. Introduction

Fungal infection is one of the major burden of skin disease worldwide. The reported prevalence of fungal infection is about 40 million people in developing & underdeveloped countries. Fungi usually attack the skin surface during the initial phase and later invade into the deeper layer by desquamation. Candida species is one of the fungi which are most superficial cutaneous infection [1, 2, 3, 4, 5]. Fungal infection expressed in deeper layer of skin called cutaneous mycoses". Cutaneous fungal infections are commonly known as "Dermatophytes". Fungi commonly involved in different dermatomycoses include Tinea corporis, Tinea pedis and Tinea cruris [6, 7, 8]. Once, fungal infection further penetrates deeper skin tissue is known as "Subcutaneous mycosis". [9]. Anti-fungal chemotherapy is used in the treatment of both superficial and deep fungal infection. Figure 1 show fungal infections commonly seen in the different layers of skin.

Topical delivery of anti-fungal drugs is perhaps the best route against major skin dermatophytes, ensuring its direct access and higher retention rate at the target. Topical delivery further contributes to reduced systemic toxicity and avoid pre-systemic metabolism. Various drugs like

ketoconazole, itraconazole, clotrimazole are used as topical administration to skin by spreading or rubbing [10, 11, 12]. Advantages of topical delivery further include site specific drug delivery, reduce systemic toxicity, increase patient compliance, increase the efficacy of treatment and improve bioavailability [13]. On the other hand, topical delivery of anti-fungal drugs can cause adverse skin reactions like allergic reaction and itching [14, 15, 16]. Further, conventional formulation needs high dose and repeated administration, associated with an increased risk of both local and systemic toxicity. For this reason, novel drug delivery system is envisaged with an objective to reduce local side effects and increase their therapeutic efficacy. The present review deals with the advanced topical nanocarrier approaches for cutaneous administration of anti-fungal agents. Novel drug delivery systems (NDDS) is one of the widely investigated topical formulation in pharmaceutical research. NDDS because of its unique ability to control release kinetics of encapsulate drugs, encapsulate a wide array of drugs and increase disease specific localization, reduces dosing frequency and enhance clinical efficacy. However, when implementing an appropriate topical formulation, one needs to understand the detail mechanism of antifungal therapeutics for maintaining adequate therapeutic performance. Ergosterol is likely to

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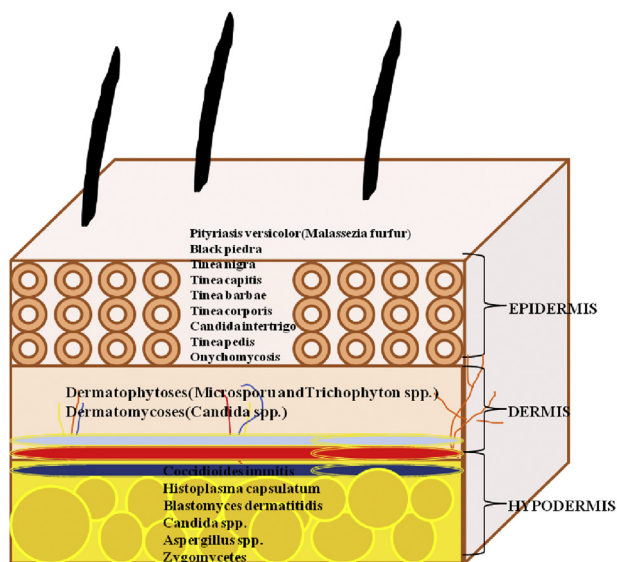


Figure 1. Layers of skin with fungal infections.

play an important role in maintaining fungal cell membrane fluidity and integrity. Attenuation of the 14 α -demethylase causes down-regulation of ergosterol synthesis results deposition of 14-methylated sterols that inhibit the demethylation of lanosterol into ergosterol [17, 18, 19]. Ergosterol serve as a growth factor for fungal cells, which promote growth [20, 21, 22]. The anti-fungal activity of azoles is related to its ability to block the synthesis of ergosterol. Lipid formulation appears to be highly efficient carriers to improve fungicidal activity of azole drugs. Solid lipid nanoparticles of PEG stearate acrylate loaded clotrimazole shows considerable low MIC (Minimum inhibitory concentration) against *Candida albicans* compare to plain drug, attributed to its higher permeation and retention potential. Similarly, high skin penetration of topical antifungal formulations ought to be an important feature for effective treatment of cutaneous dermatophytosis. Particle size, surface charge, and lipophilicity play an important role in determining penetration depth into different skin layers. It is believed that negatively charged nanostructured lipid carriers ranging in size between 200-300nm shows higher penetration into deep skin layers to treat cutaneous dermatophytosis. The polysaccharide-rich layer composed of chitin and glucan plays an integral role in the maintenance of cellular integrity of fungal pathogen and making it highly retardant to lipophilic antifungal drugs. Topical preparation containing boric acid or acetic acid acts against the biofilm and hyphal growth of *C. albicans* by neutralizing their virulence power. On the other hand, undecylenic acid and secondary bile acids inhibit the morphological plasticity to lower their pathogenic potential. The Literature reveals that plant essential oils like tea tree, rosemary, eugenol, cardamom, clove bud, cinnamon leaf, citronella, geranium bourbon, ginger, oregano, and winter savory oils appeared to be most potent substitutes inhibiting activity of fungal Cytochrome P450. The terpenes/terpenoids constituent give the lipophilicity character to them and with small molecular weights, they get easily penetrate the fungal mycelium. The presence of aforementioned component in topical formulations may act synergistically via increased membrane permeability and breaking of membrane integrity. They have other vital properties like blocking the fungal cell wall formation, mitochondria dysfunction, and efflux pumps inhibition. However, the fungistatic or fungicidal property, anti-biofilm property needs careful evaluation at their corresponding concentration of use. Recently Massa and coworkers investigated the antifungal potential of different essential oils against resistant strain to azole drugs (*Candida glabrata*). Results demonstrated that Oregano and winter savory oils exhibit significant fungicidal activity and medium-high levels of toxicity against human keratinocytes [23]. Similarly, cinnamon oils microemulsion containing

fluconazole shows increased antifungal activity owing to their higher drug solubility, Cytochrome inhibition, and permeability. Similarly, metal nanoparticles owing to their high surface area, large complexation constant and high surface charge denature fungal signaling protein leads to fungal cell death. Fungistatic or fungicidal activity of metal nanoparticles has not been understood clearly. Few studies reported that metal nanoparticles cause oxidative stress of essential biomolecules includes the deoxyribonucleic acid, proteins, and lipids via reactive oxygen species, leads to cell death. Recent work demonstrate that the combination of nanometal with antifungal drugs increases antifungal activity. Ahmad and coworkers investigated the antifungal activity of conjugate system of Amphotericin B and nanometal, demonstrated enhanced antifungal activity owing to intrinsic antimicrobial activity of silver nanoparticle against the experimental strain (*C. albicans* and *C. tropicalis*) [24]. In addition to this, silver changes membrane permeability enhances drug penetration eventually leads to cell death thus may offer an alternative therapeutic strategy to tackle resistant fungal infections. Understanding anatomy physiology of skin and potential therapeutic targets is also necessary for creating effective topical formulations. Different targets for antifungal agents are shown in (Figure 2) and list of Anti-fungal drugs with their potential target in dermatophytes are presented in Table 1 [25].

Different anti-fungal drugs act through different targets for eg: - Azoles (Ketoconazole, Itraconazole, Fluconazole, and Posaconazole) block the synthesis of ergosterol. Antifungal medication like Morpholines and Terbinafines inhibits the conversion of lanosterol to ergosterol. Since the therapeutic target (squalene epoxidase) is a lipid, therefore lipids in nanoparticles like solid lipid nanoparticles and liposomes will improve the permeability of drug to skin. Polyenes antibiotics (Amphotericin B and Nystatin) form complex with ergosterol and modulate the membrane permeability of fungal cell causes leakage of the cellular contents leads to cell death. Glucans are the major components involve in the integrity of fungal cell wall. Glucan synthase present in fungal cell add glucose monomers to preexist glucan, thereby contribute in maintaining the cell integrity. Inhibition of glucan synthase weaken the cell membrane and causes cell lysis. Drugs like Flucytosine inhibits nucleic acid synthesis, converted 5-fluorouracil to 5-fluorouridylic acid through a cascade process involving cytosine deaminase and UMP pyrophosphorylase. Further, 5-fluorouridylic acid is phosphorylated and inserted into m-RNA, causing inhibition of fungal protein synthesis, leads to fungal cell lysis [26].

1.1. Biofilm formation and anti-fungal drug resistance

A biofilm represent a structured microbial group attached to a substrate and present within a self-produced complex organic matter [27]. Biofilms constitute distinct protection against external threats [28, 29, 30]. Fungal biofilm formation results through a series of biochemical events comprising of cell adhesion to a suitable substrate, proliferation, production of matrix components, maturation, and dispersion. The cell density within the biofilm matrix and types of microorganism are critical factors that influence the antifungal resistance. *Candida* spp. is the most prevalent fungal species associated with biofilm formation [30, 31]. Apart from *Candida* other filamentous fungi including *Malassezia*, *Saccharomyces*, *Histoplasma*, and *Trichosporon* also suggested to develop biofilm [27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39]. Some of these pathogen are ubiquitous and it is assumed that biofilm play an important role to their survival under adverse conditions [40, 41]. Microtiter plate model is frequently used to study fungal biofilm. Biofilm formation in case of *C. albicans* depends on morphogenetic conversions, growth conditions, cell density and type of interactions with extracellular matrix. As the biofilm matures, the entire event is finely tuned and controlled by complex regulatory network [42, 43] Current reports revealed liposomal formulations of Amphotericin B exhibit excellent anti-fungal performance against resistant strain of *C. albicans* [44]. Cytosine permease represent the crucial enzyme involved in the cellular uptake of 5-fluorocytosine (5-FC), afterwards it undergoes enzymatic hydrolysis to release the

owing 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 [50]. 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 [50]. 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*. [51, 52] 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 [53] Passerini *et al.* compared the therapeutic performance of econazole nitrate loaded SLNs with solid lipid microparticles having similar formulation attributes [54]. It was found that SLN preparations exhibits significantly higher skin permeation of miconazole nitrate against commercial gel preparation. SLN preparations also demonstrate a significantly higher targeting effect [55] 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* [56] In addition to drug, anti-fungal efficacy of lipid Nanocarriers can be

increased 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 dioctadecyldimethylammonium bromide (DODAB) and hexadecyltrimethylammonium bromide (CTAB) shows excellent anti-fungal activity against *Candida albicans*. Nonetheless, cationic lipids induce local toxicity over a therapeutic concentration [57]. 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 [58]. 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 [59]. Moreover, NLC due to low fatty acid triglycerides shows better drug solubility and grater skin permeability compare to SLNs. Gratiere 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 [60]. 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 Versicolor. The results showed entrapment efficiency between 55.49% to 83.04%. Clinical studies demonstrated 1.4-fold greater clinical response against marketed cream [61]. 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, and

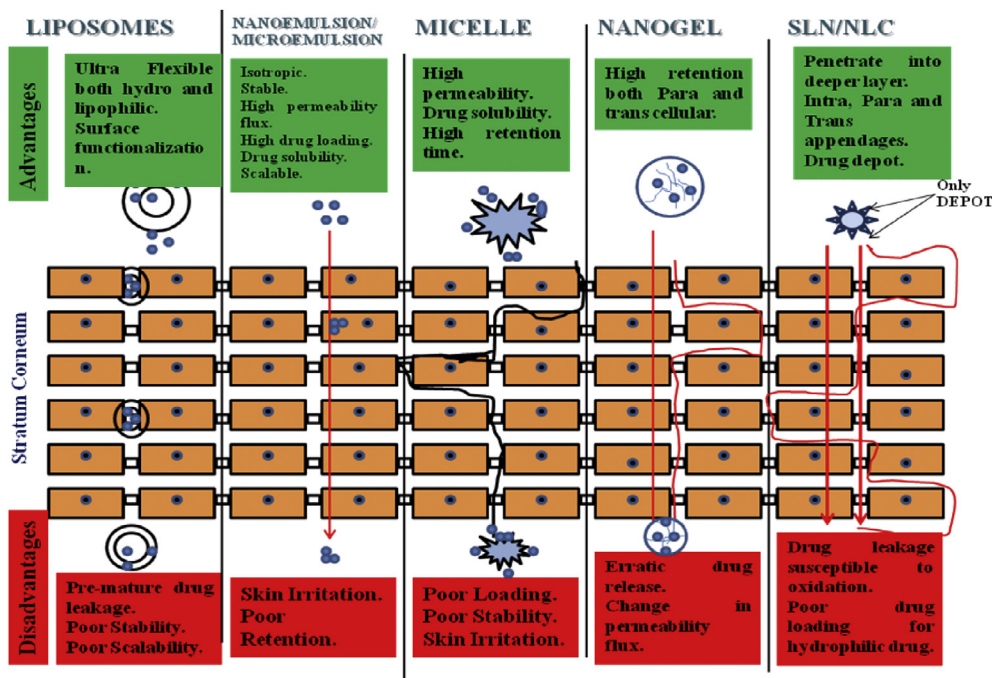


Figure 3. Schematic representation of the stratum corneum showing the mechanism of penetration of different topical drug carriers.

Table 2. Application of various nanoparticles against fungal infections of the skin.

Nanomaterial	Name of fungi causing skin Infections	Skin infections caused by Fungus	Percutaneous Penetration		Antimicrobial	Clinical		Outcome	Refs.	
			Skin of animal/human	Result	Assay Method	Result	Study			Result
Solid Lipid Nanoparticles	Candida spp.	Vaginal infection and skin candidiasis.	—————	—————	CLSI standard protocol against <i>C. albicans</i> (ATCC24433)	—————	—————	Sustained release of KTZ in SLN/ Dextran hydrogel with no irritation in rabbit skin study	[52]	
			Ex-vivo in pigskin	Higher lipid content results in increased diffusional distance and slower drug release	—————	—————	5 Caucasian female 26 ± 6 years forearm	Low lipid conc. Increase the penetration of ECN in the upper skin	Rapid penetration through the SC in 1 h and improved enhanced diffusion after 3 h in the deeper layer	[53]
Liposomes	<i>C. albicans</i>	Cutaneous candidosis	Reconstructed human epidermis EpiDerm™ EPI100	Distribution was more intense on the surface of stratum corneum hence CA specific surface damage was less	—————	—————	—————	Due to the liposome formulation of econazole hyperkeratosis, focal thickening of the <i>stratum-corneum</i> , dyskeratosis, and parakeratosis are totally eliminated.	[65]	
Niosomes	<i>C. albicans</i>	Skin candidiasis, Superficial mycosis.	Ratskin	Initially high but slowed later due to vesicular formation	—————	—————	—————	Sustained drug release and enhancement cutaneous retention of drug Fluconazole	[70]	
Microemulsion	<i>C. albicans</i>	Superficial mycosis, Swelling	Female mice abdomen	2 to 3 times more retention compared to the method liquid microemulsion	Agar diffusion	Antifungal activity of clotrimazole microemulsion was better compared to the cream form	Clinical evaluation with 10 Female and 3 Male	Clinical efficacy was 92.31% for topical fungal diseases	No toxic effect on the skin even after a longer contact.	[89]
			Ratskin	KTZ in ME form has more penetration compared to the aq. solution	Cup plate method against <i>C. albicans</i> (ATCC10231)	—————	—————	—————	Mean zone of inhibition was larger than the reference standard	[84]
Micelles	<i>C. albicans</i>	Skin candidiasis	Porcine and Human skin	Significant high drug (Econazole and	—————	—————	—————	Higher drug deposition	[107]	

(continued on next page)

Table 2 (continued)

Nanomaterial	Name of fungi causing skin Infections	Skin infections caused by Fungus	Percutaneous Penetration		Antimicrobial		Clinical		Outcome	Refs.
			Skin of animal/human	Result	Assay Method	Result	Study	Result		
				Fluconazole) deposition compared to the market						
Microneedles	C. albicans, E. coli, Staphylococcus cocci	Skin candidiasis	Porcine skin	Penetration was up to the stratum corneum layer	Agar plate method against C.albican (ATCC90028)	Voriconazole modified microneedle gave a significant growth inhibition	—————	—————	Microneedles with inkjet deposited antifungal drug coatings may serve as TDDS vehicles for antifungal applications.	[113]
					Agar plating method	Significant growth of inhibition with miconazole-loaded GantrezAN 169 BF microneedles	—————	—————		[114]
Silver nanoparticles	Candida albicans, Malassezia furfur, Trichophyton rubrum	Skin candidiasis, Athlete's foot, Superficial mycosis and Rashes			XTT reduction assay against C. albican biofilm	Safe Conc. Of AgNPs showing effect against the film	Cytotoxicity assay with HepG2 cells	Membrane damaging activity at fungicidal conc. Is not interfering with mammalian membrane	Potent inhibitors and have good therapeutic potential	[136]
					Disc diffusion method	Maximum activity against T. rubrum followed by C. albicans, C. tropicalis, and M. furfur	—————	—————		[139]
Gold Nanoparticles	Candida Albicans	Athlete's foot, rashes, Swelling and skin candidiasis			Disc diffusion method against NCIM and MTCC microbes		—————	—————	Potent inhibitors	[141]
Chitosan Nanoparticles	Candida Albicans	Skin candidiasis			Microdilution susceptibility testing against C. albican ATCC 14053	Improve the liposome residence time and therapeutic effect	—————	—	High drug loading and potent inhibitors	[142]
Chitosan-silver nanoparticles composite	Candida albicans, Candida spp.	Skin candidiasis			Liquid growth inhibition assay	Fungal growth inhibition was significantly high	—————	—————	Potential alternative for antifungal chemotherapy.	[129]
Zinc oxide Nanoparticles	Microsporium canis, Trichophyton verrucosum	Ringworm, Athlete's foot			Disc diffusion against T. mentagrophytes (MTCC7687) and M. canis(MTCC3270)	Significant antidermatophytic activity compared to KTZ	—————	—————	Possess significant anti-dermatophytic activity against M. canis	[131]
Ketoconazole Nanoparticles	Malassezia furfur	Folliculitis, Seborrheic Dermatitis and dandruff			Kirby-Bauer disc diffusion method	Good antimalassezial activity(26mm) compared to the positive control of methanol having no effect	—————	—————	Significant activity against M. furfur	[133]

poor scalability remains constant challenge for transition into clinical set-up.

2.2. 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 [62, 63]. 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 [64]. 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 [65]. 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 ± 8 nm diameter, PDI of 0.078 and -3 ± 0.2 mV 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 [66]. 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.

2.3. Niosomes

These are a kind of spherical lipid vesical prepared by non-ionic surfactants [67]. They interact with the stratum corneum, resulting in the reduction of transepidermal water loss [68] Its skin permeation depends on the types of surfactant, properties of drug used and morphological characteristics of niosomal preparations [46, 69]. The therapeutic activity of ketoconazole was found to be increased in niosomal preparations. Niosomes of itraconazole and miconazole were also found to be effective, proving themselves to be effective carrier systems for antifungal drugs. Fluconazole-loaded niosomes prepared using different surfactants (Span 40, Span 60, and Brij 72) revealed prolonged localized and sustained effects of fluconazole [70] Another group has attempted to prepare and optimized a niosomal gel containing naftifine hydrochloride,

in which drug loaded niosomal preparation was incorporated into a hydroxyethyl-cellulose gel to improve physical drug stability and drug loading [71]. These are a kind of bilayer lipid structure with non-ionic surfactants [67]. They interact with the stratum corneum, resulting in reduction of transepidermal water loss [68] The degree of skin permeation depends on the interaction between niosome and skin, nature of drug, composition and morphology of niosome [46, 69] Niosomes owing to their stable bilayer structure protect encapsulated therapeutic agent from proteolytic enzymes, surrounding pH and osmotic agents, thereby increasing the product stability. However, niosome exhibits relatively leaky vasculature compared to liposomes. Irrespective of comparable features, niosomes provide several distinct merits over liposomes includes higher skin permeation, making it suitable for the treatment of dermal and cutaneous mycosis, higher chemical stability increases product shelf life and lower costs. Further niosomes due to their unique amphiphilic properties can entrap wide variety of therapeutics. Further shape, size, fluidity, and surface functionalization of niosomal preparation can be easily tailored by changing in formulation composition and method of preparation. The antifungal activity of ketoconazole was found to be increased by encapsulating it into niosomes. Niosomes of itraconazole and miconazole were also found to be effective for the treatment of fungal infection. Niosomal formulation containing Fluconazole prepared by using different surfactants (Span 40, Span 60, and Brij 72) showed enhanced skin permeation and drug accumulation following topical application [70]. Similarly, another study demonstrated that niosomal gel exhibits approx. 6.5 times higher drug localization in the skin when compared with plain carbopol gel indicating better target accumulation of niosomal gel. Charge inducers such as anionic (diacetyl phosphate and lipoamine acid) or cationic (sterylamine and cetyl pyridinium chloride) components are often incorporated in formulation to increase the stability of the vesicles. It acts by inhibiting the aggregation of vesicles due to net repulsive forces [72]. Negatively charged niosomes incorporated in hydroxyethyl cellulose gel shows higher physical and chemical stability compared to plain niosomal formulations [71]. Unique features of niosomes allow for usage through various topical routes like vaginal, mucosal, ocular, etc. Ning and co-workers investigated antifungal activity of clotrimazole loaded niosomal gel. Results indicated sustained and controlled release pattern with good tolerability on tissue level in rat for suitable local vaginal therapy [73]. Apart from above-mentioned advantages, niosomes exhibit some challenges which include aqueous niosomal suspensions may undergo fusion, leakage of encapsulated therapeutics, and drug may undergo hydrolysis that leads to limited stability.

2.4. 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 μ m. 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 manyazole 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 co-surfactant 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 [74].

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*. [75, 76, 77, 78] A microemulsion gel containing fluconazole seems to be effective for the

treatment of invasive fungal infections [79]. 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 ($1086.1 \mu\text{g}/\text{cm}^2$) compared to marketed formulation "Dermofix® cream" ($270.3 \mu\text{g}/\text{cm}^2$) [80]. 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 [81]. Several researchers further confirmed the ability of microemulsions to increase percutaneous permeability of fluconazole [19, 82]. The same results were obtained with microemulsion formulae of ketoconazole, itraconazole, voriconazole, and econazole [83, 84, 85, 86, 87, 88]. Microemulsion based hydrogel containing clotrimazole showed higher skin permeation, retention and better *in vitro* antimicrobial activity against *C. albicans* compared to the reference cream [89]. 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 [84]. Microemulsion formulations need high concentration of surfactant and co-surfactants combination to cover wider interface, complete emulsification 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.

2.5. 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 [90]. 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 [91]. 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 [92]. 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 [93, 94, 95]. 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 [96]. 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.

2.6. Microsponge gel

It is a unique drug delivery system provides better control of encapsulated drug release, composed of microporous pellet with a size range from 10-25 μm . These are small artificial particles composed of natural or synthetic polymers with high drug loading capacity equal to their own weight. This is considered as biocompatible, non-irritating, non-allergic, and safe for human skin make them suitable for topical drug delivery. This is advantageous because it improves stability and enhances formulation flexibility [97, 98, 99]. Microsponges are tiny porous microparticles capable of entrapping a wide range of active ingredients, interconnecting pores ensure the prolonged release of encapsulated drug over time. Unlike liposomes and lipid carriers where premature leaching is a major disadvantage, Microsponges based drug delivery systems show no premature release of encapsulated therapeutics. Fluconazole has excellent activity against fungi but suffered clinically because of skin irritation following topical application. Fluconazole loaded microsponge formulation were developed by liquid-liquid suspension polymerization using different polymers (styrene and methyl methacrylate). Further, the developed microsponge was entrapped in carbopol 940 and examined for in-vitro drug release using Franz diffusion cell. Results revealed 67.81 % cumulative drug release at 12 h from the composite gels. Similarly Bothiraja and co-workers in their study demonstrated that eberconazole nitrate loaded microsponge in ethyl cellulose gel indicated controlled drug release, no sign of skin irritation and higher antifungal potential compared to commercial cream [100]. The microsponge proved to be excellent formulation for controlled release of fluconazole. Recently, Carac cream contains 0.5% fluorouracil is used for the treatment for multiple actinic or solar keratoses. Carac is a patented porous microsponge system wherein the drug is incorporated into a porous microbead. Further, the porous particles containing drug are suspended in a emulsion cream base. In another study, a microsponge formulation for retinoic acid was prepared and analysed for drug release and anti-acne activity [101, 102]. One example is Itraconazole and Econazole as active agents in the Microsponge drug delivery system for the application of sustained release of actives [103]. In addition to abovementioned applications, numerous reports have confirmed that microsponge carriers are non-irritating, reduced side effects and improved stability however the traces of residual monomers left at the time of microsponge synthesis may cause toxicity and hazardous to health.

2.7. Micelles

It is a cluster of surfactant molecules in nanometer scale dispersed in a liquid with a lipophilic core and hydrophilic shell. They are usually preferred as for hydrophobic drugs. Advantages of polymeric micelles as topical delivery including improve drug solubility; increase partitioning of both hydrophilic and hydrophobic drugs in the skin, drug accumulation into the hair follicles and skin. These were reported to be promising carriers for delivering topical antifungal drugs [104, 105, 106]. Bachhav and coworkers investigated the antifungal activity of new aqueous micellar dispersions of different antifungal drugs clotrimazole, econazole nitrate, and fluconazole. The micelles were developed using novel amphiphilic block copolymers (methoxy poly (ethylene glycol) -hexyl substituted polylactide). These micelles, which were in the nanometer range, showed superior entrapment for econazole nitrate [107, 108]. The report also indicated that surfactant types also play an important role in determining the clinical efficacy of micellar systems. In general, micellar system from nonionic surfactants is less toxic and better compatible compare to anionic and cationic surfactants. Anionic surfactants like sodium lauryl sulfate have ability to solubilize lipids and soluble proteins present in skin via chemical interaction causes release of small molecular

weight soluble proteins and peptides and ultimately leads to denaturation. Nonionic surfactant likes Polyoxyethylene, Poloxamer, poloxamine, polysorbates polyoxyethylenes, and polysorbate binds to skin proteins via weak hydrophobic interaction and thus did not change in skin physiology.

2.8. Microneedle

These are designed to be painless therapy in a way to restore the skin function without affecting the epidermis. These are prepared by several techniques include micro-molding, microfabrication, photolithography, and micro shaping. It has many potential benefits including avoidance of presystemic metabolism, rapid onset of action, suitable for a wide variety of pharmaceuticals, countering needle phobia and ease of drug administration. This technology provides opportunities to overcome limitations associated with conventional formulations like poor aqueous solubility, low permeability, low bioavailability of hydrophilic drugs, repeated administration and systemic side effects [109, 110, 111]. Gill and co-workers studied the effect of microneedle dimension on pain and compared with conventional hypodermic needles. Microneedles of all specification exhibited significantly less painful (5%–40%) compared to conventional hypodermic needle. Microneedle geometric like width, thickness, and tip angle had no significant effect on pain. However, needle length and number play an important role in determining pain sensitivity and intensity. It was noted that decreasing the density and length of the microneedles significantly reduced the pain intensity. The pain score increased by just over 2 fold with 10 fold increase in the density of microneedles. Similarly the pain score increased by 7 fold with a three-fold increase in the length of microneedles [112]. Piezoelectric inkjet dispensing with microneedle provide opportunity to improve drug formulation. Boehm and coworkers prepared biodegradable polymer microneedles consisting of polyglycolic acid coated with voriconazole by using piezoelectric inkjet printing method and the antifungal potential of the developed formulation was compared with conventional microneedles against different experimental micro-organisms (*Candida albicans*, *Escherichia coli* and *Staphylococcus aureus*). The prepared microneedles shows superior antifungal activity against *Candida albicans* while unmodified devices were found ineffective against the experimental strains. Piezoelectric inkjet printing method found effective to enhance drug loading of poorly water-soluble drugs onto microneedles [113]. Piezoelectric inkjet printing technology was successfully used to load miconazole onto polymeric microneedles (poly (methyl vinyl ether-co-maleic anhydride) created from Gantrez® AN 169 BF. In this process, Dimethyl sulfoxide was selected as a solvent to improve antifungal drug penetration. The developed miconazole-loaded Gantrez® AN 169 BF Microneedles showed good antifungal potential against *Candida albicans* [114]. Although solid microneedle is the simplest form of microneedle for transdermal drug delivery it requires skin pretreatment prior to microneedle treatment. On the other hand, hollow microneedle suffers from one major limitation as it allows less volume of fluid that can be infused into the skin which can be overcome by partial retraction of skin prior to the drug treatment.

2.9. Electroporation

This is a biophysical phenomenon used to enhance the transdermal permeation of drugs by applying intermittent electric pulses that cause transient changes in cell membrane permeability. Increasing the permeability of chemotherapeutics or DNA molecules across the skin using high voltage electrical pulses, known as “electrochemotherapy” [115]. Electroporation is particularly an exciting alternative to improve drug permeability. More recently Novickij and co-workers investigate the skin permeation effects of pulsed electric fields (2.5–25 kV cm⁻¹) with fluconazole, terbinafine, and naftifine at a pH range of 3.0–9.0. Pulsed electric fields produced higher inactivation of *C. albicans* at low pH and increased sensitivity to terbinafine and naftifine to which the strain was

initially resistant [116]. Similarly, in another by the same group of researchers suggested that the electric field pulses of 50 μ s and 100 μ s generated in bursts of 5, 10, and 20 results in the full inactivation of *T. rubrum* and *C. albicans* colony. Although electroporation technique shows great potential to increase skin permeability. However, it has difficulties in manipulating the targeted cells and in delivering therapeutics to those cells into post-electroporation steps. In order to overcome that difficulties microcapillary electroporation may be used with the help of micropipette or it may be combining with specific physical, chemical or biological support to improve specificity and clinical potential.

2.10. Iontophoresis

This is a method used to enhance penetration of drugs into the skin by application using low intensity electric current. The drug is placed under an electrode having the same charge as of drug, so that the repulsive force between the like charges acts as a driving force to increase drug penetration across the skin [117]. This technique is driven by the application of electric potential which gives characteristic property to it. Thus, making it suitable for the controlled dosage form [118]. Recently Kalkanci and coworkers investigated voriconazole penetration and anti-fungal potential in the fungal keratitis model assisted by iontophoresis. The result shows that the Iontophoresis-assisted group demonstrated the better antifungal activity against the experimental strains *F. solani* keratitis (4-log reduction) and *C. albicans* keratitis (5-log reduction) compared with native drug followed by topical ocular application. Further voriconazole levels were also found to be the highest in corneal tissue in animal groups received iontophoretic treatment [119]. Further iontophoresis in combination with permeation enhancers found to be effective in eradicating deep skin fungal infection. Accordingly recently Monti and coworkers studied the potential of iontophoresis in translingual permeation of nystatin with and without permeation enhancers like cetylpyridinium chloride and Polyoxyethylene sorbitan monooleate. The result indicated that iontophoresis in addition to cetylpyridinium chloride produced a 5-fold rise in the permeability of the bovine hoof membrane to the drug compares to plain iontophoresis [120]. In spite of the number of potential implications of transdermal iontophoresis, there are still limitations need to be addressed for successful clinical applications like the selection of drug based on skin surface electric potential, that supports cationic drugs. Secondly, skin irritation remains a major issue that needs resolution for long term applications.

2.11. Nanogel

Nanogel is defined as nanoparticles made of cross-linked hydrophilic polymer ranging from 20–200nm. They can be administered through different routes i.e. oral, topical, vaginal, ocular etc. Due to their smaller size and soft materials, they show better skin permeation and diffusion based swelling allowed desired drug release behavior. In general they have an excellent biocompatibility and high payload of hydrophilic drugs [121, 122, 123]. Some nanogels possess a hydrophilic nature which limits good encapsulation property of hydrophobic drugs [124]. Advantages of nanogel include high biocompatibility, high biodegradability, enhanced permeation capability, capability to cross the blood-brain barrier and nanogel is found to be appropriate to administer a wide variety of drugs including hydrophilic and lipophilic drugs [124, 125]. The most common limitations of nanogel includes it is difficult to separate the surfactant and the solvent from the finished product even though the nanogel processing is not very pricey [126, 127].

2.12. Metal nanoparticles

Metal nanoparticles have received much popularity because of their distinct structural and functional properties. They are small cluster of metal atoms with a size range of 10–100nm and has distinct optical and

functional properties. The optical properties of metal nanoparticles have clearly shown in case of gold nanoparticle wherein the gold nanoparticles in the size range between 5–20nm has a red ruby color whereas size in the 100–200 nm range have bluish color. The nanoparticles due to their high aspect ratio make diffusion faster even below the critical temperature. The optical properties of gold, silver, lead, platinum nanoparticle arise from resonant oscillation of their free electrons in the presence of light, also known as Localized surface Plasmon resonance (LSPR). The advantages of metallic nanoparticles include strong plasma absorption, biological system imaging, determine chemical information on metallic nanoscale substrate, Surface-enhanced Raman scattering. Disadvantages of metallic nanoparticles include impurity, difficulty in synthesis, particle instability, biologically harmful. Preferably, metallic nanoparticles should be prepared by a suitable method that is easily reproducible, available and economical with use minimum number of reagents that ay control the particle size. These are formed by physical, chemical and biological methods. Stabilization of metallic nanoparticles is done by electrostatic stabilization and Steric stabilization. Between 10–100nm of different shapes, sizes of gold, nickel, silver, iron metallic nanoparticles have been checked out as drug delivery systems. **Figure 3** showing the mechanism of penetration of different topical drug carriers through stratum corneum.

An overview of topical nanocarriers used against different dermatophyte is presented in **Table 2** [128, 129, 130, 131, 132, 133, 134, 135].

3. 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 evidence 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 systemic concentration, is highly desirable.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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