



Nanomaterials for skin antifungal therapy: An updated review

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ABSTRACT

Topical diseases are treated with oral and conventional topical formulations till date. Both oral and topical routes face many challenges such as poor absorption, high metabolism, toxicity, and drug-drug interactions. Conventional topical dosage forms like creams, lotions, and gels have failed to show controlled drug release. Literature reports indicated that more than 1.5 lakh (approximate) people lost their lives due to fungal infections and several lakhs of the population are affected. Even then, it is a neglected subject by public health authorities, and while most of the deaths from fungal diseases can be stopped. Globally, it is estimated that over 30 lakh cases of pulmonary *Aspergillosis*, 7 lakh cases of *Candidiasis*, 2.5 lakh cases of *Aspergillosis*, 5 lakh cases of *Pneumocystis jirovecii* pneumonia, and many more occur annually. Nanomedicines play a key role in reducing the number of patients coming up with fungal infections. A small-sized drug can easily penetrate the micropores of the skin and show desirable results. Nanomedicines rely on various nanomaterials (lipidic carriers, metal nanoparticles, carbon nanotubes, quantum dots, etc.) for their therapeutic efficacy. Nanomaterials can facilitate efficient topical drug delivery by increased penetration, enhanced safety and efficacy, and sustained and targeted release of drugs. The review summarizes the basics of nanomedicine with respect to topical delivery and various nanomaterials for better therapeutics of the fungal infections of the skin.

INTRODUCTION

Nanomedicine is an area of science and nanotechnology that is used in prognosis, medication, and prevention of diseases and injuries (Patil *et al.*, 2008). Generally, nanomedicine may be defined as an application of nanotechnology in devices and products, prepared with the aim to repair and cure damaged tissues (such as muscle, bone, and nerves). The purpose of nanomedicine is to utilize nanotherapeutic and nanodiagnostic products for patient benefits (Ventola, 2012). For example, Verigene is a nanodiagnostic product that can rapidly identify various irresistible pathogens (Dodémont *et al.*, 2014; Verigene System, 2018). Nanotechnology has revealed its potential to fight against different skin disorders such as atopic dermatitis and psoriasis (De Jong and Borm, 2008; Hafner *et al.*, 2014).

Generally, the success in the cure of skin fungal infections is limited using conventional treatment strategies. Nanotechnology has shown significantly improved therapeutic

efficacy in the treatment of these fungal infections. Globally, 2 lakh cases of *Cryptococcal meningitis* complicating HIV/AIDS, 30 lakh cases of chronic pulmonary *Aspergillosis*, 7 lakh cases of invasive *Candidiasis*, 2.5 lakh of invasive *Aspergillosis*, 5 lakh cases of *Pneumocystis jirovecii* pneumonia, 1 lakh case reports of disseminated *Histoplasmosis*, over 100 lakh case reports of fungal asthma, and around 10 lakh case reports of fungal *Keratitis* occur annually (Bongomin *et al.*, 2017).

Nanomedicine has solved several problems associated with medical research having poor solubility and lack of target specificity intended for therapeutic compounds (Poirot-Mazères, 2011). Nanotechnology has improved the efficacy and safety of conventional therapeutics; for example, it targets directly on specific the site having a drug with low bioavailability (Bawa, 2011). Micelles, lipid nano particles (NPs), microemulsions, vesicular delivery systems, nanoemulsions, polymeric NPs, carbon nanotubes, and fullerenes and dendrimers are various nanomaterials that have attracted attention toward theranostics and nanovectors in nanomedicine (Kralj and Pavelic, 2003). Nanomedicine broadly focuses on three areas: Nanoinstruments and nanomaterials, which can be utilized as biosensors, help in the treatment and act as drug transporter, the awareness of molecular medication in the fields of proteomics and microorganisms (modified or synthetically

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produced), and the application of nanotechnology is intended for the repair of genetic material, cell surgery, and the betterment of natural physiological functions. Nanomedicines based on various nanomaterials with a specific application in skin fungal infections are incorporated in this review.

Topical delivery of nanocarriers through skin barrier

Pharmaceutics and drug delivery are still facing a lot of problems in the topical administration of drugs such as absorption of drugs in different skin layers before getting to the targeted site. Successful topical drug delivery system has been limited because of the penetration barrier provided by skin (Brown *et al.*, 2006). The two main layers that affect the penetration of skin are “epidermis and dermis.” The epidermis is the outmost layer of the skin. It is further differentiated into five layers, i.e., stratum corneum (SC), stratum granulosum, stratum spinosum, stratum lucidum, and stratum basale. It protects the skin from micron-sized particulates, pathogens, hydrophilic chemicals, and water retention (Palmer and DeLouise, 2016). SC and stratum granulosum form a water-tight junction which enables to permeate hydrophilic antifungal drugs or drug molecules having a molecular weight of more than 500 kDa, such as amphotericin B (Uchechi *et al.*, 2014). The hydrophilic nature of the drug results in reducing effectiveness against pathogens; thus, the topically drug applied must be lipophilic in nature as it forms a reservoir on SC, and the drug permeates slowly in the epidermis and the dermis. The release rate of the lipophilic drug is controlled by nanocarriers/nanotechnology to achieve greater bioavailability and prolonged pharmacological effect. Thus, recent nanocarriers having properties such as less than 500 kDa molecular weight of drug enhances a flux through skin or lipid coating of drug which makes ease in permeation of drug through SC (Bos and Meinardi, 2000).

Penetration of nanomaterials through skin involves three main pathways such as intercellularly around corneocytes, intracellularly through corneocytes, and dermal structures like sebaceous or sweat glands, and hair follicles (Filon *et al.*, 2015).

NANOMEDICINE IN SKIN FUNGAL INFECTIONS

Fungal infection

Fungi are the most infectious organisms affecting the skin and the mucosal layer of internal organs (Kim, 2016). It is reportable that the human population of approximately 20%–25% shows the incidence of skin fungal infections (Gupta *et al.*, 2005). Fungal skin infections are highly contagious, which generally spread through infected bathroom floor and usage of contaminated towels, clothing, and other household items. The identification of fungal infection can be done simply by visual symptoms of skin changes like cracking, redness, peeling, and itching. Yeast infection, ringworm infection, jock’s itch, athlete’s foot, and so on are the various common fungal infections (Bseiso *et al.*, 2015). There are three types of fungal infections such as subcutaneous, superficial, and cutaneous. The microorganism causing disease and their examples are shown in Figure 1.

Poor skin penetration and the high dose of hydrophilic antifungal medication diminish their productivity against contagious skin pathogens (Akhtar *et al.*, 2015). The antifungal drugs should be lipophilic in nature for effective topical drug delivery as lipophilic medications demonstrate excellent skin penetration to the skin layer (Kircik, 2016; Kyle and Dahl, 2004).

Nanocarriers build their approach merely toward hair follicles and tend to accumulate among corneocytes and lipids present within the skin (Firooz *et al.*, 2015). Nanocarriers possess the potential to prolong the release of drugs and thereby reduce the dose of antifungals and dose-related side effects (Kaur and Kakkar, 2010). Multiple drug resistance in antifungals has turned out to be the most significant global drawback, resulting in adverse health effects and reduced life quality (Nigam, 2015). Biofilms have a vital role in the development of yeast infections (Sanglard, 2016). Antifungal resistance due to biofilms increases its metabolic activity, reflecting a maturation of biofilms, which shows the emergence in antifungals drug resistance (Baillie and Doublas, 2000; Chandra *et al.*, 2001; Wnorowska *et al.*, 2015).

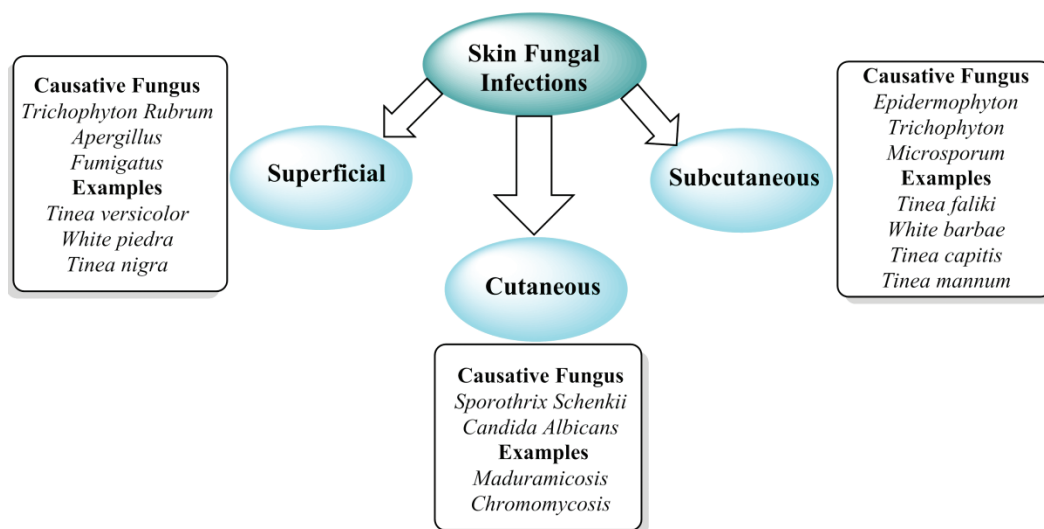


Figure 1. Types of skin fungal infections.

Significant antifungal activity against dermatophytes has been shown by metal NPs [e.g., gold (Au) and silver (Ag)] and metal oxide NPs like zinc oxide (ZnO), titanium dioxide (TiO₂), iron oxides (Fe), and copper oxide (CuO). Silver compounds are familiar with their antimicrobial activity since history. The smaller the dimensions, the stronger will be the antimicrobial activity of the NPs (Higa *et al.*, 2013). AgNPs aid in the treatment of fungal infection as antimicrobial agents. The AgNPs penetrate into the plasma membrane of fungi by disrupting and binding to the sulfur-containing protein moieties of the plasma membrane (Lara *et al.*, 2015). AgNPs exhibited antifungal activity against various fungi causing skin infections, such as *Microsporum canis*, *Trichophyton mentagrophytes*, *Candida albicans*, *Trichophyton rubrum*, *Candida tropicalis*, *Candida glabrata*, and *Malassezia furfur*, and also used in numerous cosmetics that facilitate in preventing skin infections (Aghamoosa and Sabokbar, 2014; Gupta *et al.*, 2013; Kim *et al.*, 2008; Mohamed *et al.*, 2014).

Nanomaterials used in fungal infections

Most nanomaterials are used in fungal infections are in nanoscale, i.e., from 1 to 1,000 nm. The nanomaterials acquire some unique characteristics such as increased strength and hardness, superparamagnetism, strong surface adsorption capacity, quantum properties, and chemical reactivity. These are specially considered to facilitate the delivery of diagnostic or therapeutic agents acting through the biologic barriers, which is primarily aimed to (i) ease out the administration to molecules; (ii) regulate molecular-interactions; and (iii) perceive molecular changes in a sensitive manner. Nanomaterials have a variety of different size, shape, chemical composition, and surface characteristics such as solid or hollow structures (Doll *et al.*, 2013; Fröhlich, 2012; Xia *et al.*, 2009; You *et al.*, 2012) and are capable of adjoining into new drug-delivery vehicles, diagnostic devices, and contrast agents (Peer *et al.*, 2007). For UV protection, zinc oxide (ZnO) and titanium dioxide (TiO₂) NPs are commonly used on cellulose fabrics (El-Hady *et al.*, 2013; Farouk *et al.*, 2013). In addition, TiO₂ and ZnO NPs are usually used in sunscreen cosmetic products (Nohynek *et al.*, 2008; Schmid and Riediker, 2008) collectively with nanosilver, nanogold, and other inorganic nanostructured materials to achieve the desired antibacterial activity (Hebeish *et al.*, 2013; Selvam *et al.*, 2012). Recent studies suggest that the application of nanotechnology in medicine enhances the stability, solubility, biocompatibility, permeability, targeting, and sustained release of drugs as well as vaccines (Sanglard, 2016). Several nanocarriers are discussed further in this review that has been investigated by researchers to permeate antifungal drugs for topical application (Dastjerdi and Montazer, 2010).

Properties of nanomaterials

Nanomaterials primarily consist of nonmetal and metal atoms or their combinations, and these are named as organic, metallic, semiconducting particles, respectively. For the improvement of biocompatibility and direct targeting of biologic molecules, nanomaterials are generally encapsulated with polymers and bio-recognition molecules. However, the size and shape of the nanomaterials are based on the salt and surfactant. Several conditions should be maintained during the

synthesis of nanomaterials, such as reaction temperatures, reactant concentrations, and solvent conditions (Niemirowicz *et al.*, 2017a). Factors for a nano-based delivery system are as follows:

1. Particle size, zeta potential, and size distribution: molecular shape and size of systems are affected by their physical stability, drug release, and cellular uptake of nanoparticulates. Particle size distribution is influenced by the rate of stirring, type and amount of the dispersing agent, temperature, and viscosity. Zeta potential is important for measuring the surface charge of dispersion to maintain its stability.
2. Surface properties: Surface charge of the molecule affects the binding of NPs to the cell membrane. The surfaces of nanomaterials can be modified to make them less harmful to health.

Types of nanomaterials

The nanocarriers which are utilized commonly for the treatment of fungal infections are discussed below:

Vesicular delivery systems

Liposomes

Liposomes are phospholipid vesicles, consisting of one or more lipid bilayers in water with a hydrophilic head and a lipophilic tail. They possess hydrophilic compartments between the membranes and lipophilic compartments within bilayer membranes (Grath and Uitto, 2008). Liposomal drug delivery system encapsulating antibiotics can resist the microbial activity against drug-resistant strains as liposome protects the drug from degrading enzyme via isolation process and also promotes diffusion across bacterial envelope (Elzainy *et al.*, 2003; Foldvari *et al.*, 1990). Liposomes are biodegradable and biocompatible in nature. Liposomes are absorbed on the skin surface via lipid-rich channels after that they form occlusive films, increasing drug penetration and skin hydration into SC (Bseiso *et al.*, 2015).

Ethosomes

Ethosomes are nanocarriers having a high concentration of ethanol, water, and phospholipids content in them and are used for transdermal delivery of the drug. It may contain 2%–5% phospholipids and 20%–40% ethanol (Grath and Uitto, 2008). Drug penetration through the skin is higher in the case of ethosomes as compared to liposomes due to the ability of ethanol to fluidize the membrane lipids of SC (Akhtar *et al.*, 2016; Blume *et al.*, 1993; Romero and Morilla, 2013). The addition of ethanol increases the particle size of ethosomes, and a decrease in size was observed by maintaining a constant concentration of phospholipid (Campani *et al.*, 2016). The ethanol presence in ethosomes additionally offers a negative charge on its surface, thereby increasing its colloidal stability (Mbah *et al.*, 2014). Ethosomes infuse through the SC barrier and increase the transdermal flux. The combination of phospholipids and high alcohol content in nanocarrier results in deeper distribution and penetration into the skin (Uchechi *et al.*, 2014).

Researchers studied the voriconazole-loaded ethosomes to increase their deposition in the skin. The developed ethosomal formulation exhibited enhanced permeation of drug

in the rat abdominal skin in comparison to voriconazole in the hydroethanolic solution (Faisal *et al.*, 2016).

Transfersomes

Transfersomes are ultra-flexible vesicles with a bilayer structure and penetrate into the skin easily by passing intracellularly through the lipidic membrane of the SC. It mobilizes from the dehydrated SC to a deep-sited hydrated SC layer via an osmotic gradient. The surfactant present in the transfersomes helps to solubilize the lipid present in SC and allows the higher permeation of the drug through vesicles (Qushawy *et al.*, 2018). They showed enhanced skin penetration in comparison to conventional liposomes because of their increased deformability (Hussain *et al.*, 2017). These are more hydrophilic than other conventional lipid vesicles bilayer and swell more so that they can easily pass from the skin membrane.

Topical antifungal transfersomal formulations loaded with miconazole nitrate showed reduced toxicity along with enhanced antifungal activity in comparison to liposomal formulations and free drug solutions (Pandit *et al.*, 2014). Recently, researchers developed transfersomes loaded with amphotericin B with enhanced antibacterial activity (40-fold) as compared to a marketed liposome formulation of amphotericin B (AmBisome) (Verma and Utreja, 2018).

Transethosomes

Transethosomes are vesicular nanocarriers and possess the merits of both transfersomes as well as ethosomes. Their structure is the same as that of the ethosomes including a penetration enhancer (Kumar *et al.*, 2016). One of the studies developed voriconazole-loaded transethosomes with enhanced *in vivo* skin deposition of voriconazole within a viable layer. These proved to be better than other nanocarriers like conventional liposomes, deformable liposomes, ethosomes, and polyethylene glycol drug solution (Song *et al.*, 2012).

Niosomes

Niosomes are bilayer vesicular systems composed of single alkyl chain nonionic surfactants (Hamishehkar *et al.*, 2013). Structurally, the hydrophilic heads of the surfactant oriented toward the exterior and interior of the bilayer, whereas the hydrophilic tail orients inside the bilayer (Handjani-Vila *et al.*, 1979). Therefore, both hydrophilic and hydrophobic drug molecules can be encapsulated in niosomes. Various surfactants employed in the niosome formulation are Spans, Tweens, polyglycerol alkyl ethers, polyoxyethylene alkyl ethers, and so on (Thakkar and Brijesh, 2016). Later on, Alomrani *et al.* (2015) formulated the niosomal formulations of itraconazole using nonionic surfactants for improved transdermal delivery of drugs.

Spanlastics

Spanlastics are vesicular carrier systems, named as “modified niosomes” because it contains spans along with edge activators like Tweens. Kakkar and Kaur (2011) reported ketoconazole spanlastics vesicles using Span 60 and Tween 80 for its ocular delivery. Farghaly *et al.* (2017) reported the topical delivery of fenopropfen calcium via nanovesicular spanlastics. Elsherif *et al.* (2017) estimated spanlastics incorporating

terbinafine hydrochloride for treatment of nail fungal infection specifically onychomycosis.

Oleic acid vesicles

Oleic acid is the most-used penetration enhancer for the delivery of different bioactive molecules through the skin. Oleic acid enhances skin penetration via subcutaneous lipid fluidization and phase separation. It is revealed that these fatty acids, e.g., oleic acid and linoleic acid tend to form vesicular structures in the aqueous environment (Verma *et al.*, 2014).

Fatty acids consist of a carbon atom chain having polar and nonpolar parts. Zakir *et al.* (2010) formulated oleic acid vesicles incorporating fluconazole with efficient drug delivery through SC. Verma and Utreja (2018) investigated clotrimazole oleic acid vesicles for cutaneous *Candidiasis* treatment in guinea pigs. The oleic acid vesicles showed higher skin permeation and skin retention in animal skin. *In vivo* study revealed the capability of drug-loaded with oleic acid vesicles to give sustain release of the drug. Therefore, vesicular nanocarriers minimize the drawbacks of antifungal drugs due to their unique properties like high biocompatibility, ease of surface modification, and their small size. These vesicular nanocarriers proved effective in treating skin fungal infections associated with immunosuppressive diseases like AIDS, as these exhibited controlled drug release behavior which does not activate the immune system of the patient. Above all, these vesicular nanocarriers lead to improve the stability of antifungal drugs within infected tissues, thereby enhancing the antifungal efficacy (Verma *et al.*, 2014).

Lipid NPs

Solid lipid nanoparticles (SLNs)

“SLNs” provide a solid lipid core matrix that helps to solubilize lipophilic molecules, and the lipid core is stabilized with surfactants. Examples of lipids are monoglycerides, diglycerides, triglycerides, steroids, fatty acids, and waxes. SLNs provide physical stability, excellent tolerability to drug molecules, and can be used for controlling the drug release (Voltan *et al.*, 2016).

Nanostructured lipid carriers

Nanostructured lipid carriers are the second generation of lipid NPs and possess a mixture of solid lipids and liquid lipids (Bseiso *et al.*, 2015). Both solid lipid NPs and nanostructured lipid carriers are the best choice for the treatment of topical skin infections, mainly for antifungals as they are lipophilic in nature. These nanostructured lipidic carriers are associated with a low risk of toxicity. The small size of nanocarriers ensures its close contact with SC and enhances the dermal penetration of the drug (Voltan *et al.*, 2016).

Nanoparticles (NPs)

NPs are nanoparticulate dispersions having a particle size of 10–1,000 nm. Active moiety is entrapped, attached, dissolved, or encapsulated into a matrix. Researchers reported NPs as a good choice for an antifungal drug because ampicillin encapsulated with chitosan showed antifungal activity against *C. albicans*. In addition, amphotericin B entrapped into Poly lactic-co-glycolic acid (PLGA) NPs showed increased bioavailability and

decreased side effects in systemic amphotericin B therapy (Gratieri *et al.*, 2010). A study reported the fungicidal activity of MgO NPs against soilborne *Phytophthora nicotianae* and *Thielaviopsis basicola*. The NPs inhibited fungal growth, spore germination, and impede sporangium development more efficiently (Chen *et al.*, 2020).

Polymeric NPs

Polymeric NPs are colloidal systems in which a drug is entrapped, dissolved, coated, encapsulated, or dissolved having a diameter of less than 1 μm . Polymeric NPs are categorized as nanocapsules and nanospheres. Nanocapsules are vesicular systems in which the drug is entrapped inside an aqueous or oily cavity surrounded by a polymeric membrane, whereas nanospheres are the matrix systems in which the drug is physically and uniformly dispersed in the matrix. They possess cytotoxicity of a polymer as a problem is raised by the use of organic solvents in the production of polymeric NPs. Thus, the development of solid dosage forms of NPs is of potential interest in research to overcome side effects (Jijie *et al.*, 2017).

Micelles

Micelles are spherical in shape and aggregates of surfactant molecules dispersed in a liquid colloidal system. These aggregates are prepared in an aqueous solution due to the hydrophilic head of surfactant mounts toward the outer surface and hydrophobic tail sequestering toward the center of the micelle (Kumar *et al.*, 2014). Abd-Elsalam (2018) formulated polymeric mixed micelles incorporating terconazole and enriched with cremophor EL. These micelles are of promising potential for topical drug delivery and result in the successful local treatment of skin fungal infections. The efficacy and specificity of micelle-based drug delivery are improved by the use of thermosensitive, ultrasound-sensitive, light-sensitive, and pH-sensitive polymers or block copolymers /or attachment of targeting moieties/ligands to micelles.

Microemulsions and nanoemulsions

Microemulsions are thermodynamically stable, a mixture of oil and water which is stabilized by the use of surfactants and cosurfactants. They are used widely as they enhance the solubility of the drug, thermodynamically stable, ease of permeation, and low cost. The oil and surfactant used in microemulsion act as a penetration enhancer for SC (Palmer and DeLouise, 2016). Nanoemulsions are stable dispersions composed of two immiscible phases, i.e., continuous and dispersed phase. It is characterized by its stability and clarity. These can be incorporated in different dosage forms: creams, gels, foams, sprays, and liquids. They show a broad-spectrum activity against fungi and bacteria. These nanocarriers are the best choice of antifungal agents due to their lipophilicity (Güngör *et al.*, 2013).

Quantum dots (QDs)

QDs refer to semiconductor nanocrystals which consist of 10–50 atoms and have size ranging from 2 to 10 nm. From the last 20 years, QDs are used in optics and electronics, but now they are of special interest in nanomedical research. The application

of QDs in nanomedical research includes QDs containing cadmium telluride (CdTe), cadmium selenide (CdSe), indium arsenide (InAs), and indium phosphide (InP). They possess unique electronic, optical, remarkable photostability, and surface properties. These properties make QDs to be useful as luminescent probes, fluorescent which emits light over a broad range, and for optical imaging (Jha *et al.*, 2018; Taylor and Webster, 2011). They have molar extinction coefficients, i.e., 10–50 times higher than organic dyes, which made them brighter and increased blood circulation times during *in vivo* studies (Sajja *et al.*, 2009; Zambom *et al.*, 2019). QDs have a larger surface area for binding of chemical agents, and due to small size, it is used in the diagnosis of cancer, targeting at neoplastic sites. QDs are used for targeted drug delivery, tissue engineering, and *in-vivo* imaging (including angiogenic vessel mapping, lymph node, and cell subtype isolation). Other uses of QDs are light-activated therapies, image-guided surgery, and diagnostic tests. Surface coatings facilitate to enhance the fluorescent yield and surface fine-tunability QDs. It also decreases the adverse effects such as hepatotoxicity that may be induced by QDs containing selenium (Se), cadmium (Cd), and arsenic (As). Presently, the research of QDs is prohibited to animal studies due to the toxicity caused by these heavy metals (Veloso *et al.*, 2018).

Diagrammatic representation of various nanocarriers is shown in Figure 2. Various nanocarriers studied for the treatment of skin fungal infections have been summarized in Table 1.

PATENT LITERATURE

Various antifungal compositions based on nanocarriers containing different antifungal agents and other excipients have been investigated against different strains of fungi. A summarized relevant patent literature is depicted in Table 2.

FUTURE PERSPECTIVE

The current era has witnessed extraordinary growth in research in the area of nanomedicine. The use of nanocarrier's concept in these topical preparations offers various advantages as compared to conventional topical preparations. The use of nanomaterials for skin cancer, tissue replacement, and faster recovery of skin diseases is the future of skin healthcare. In recent studies, nanomaterials have proved to be much effective in skin tissue engineering. The benefits of using nanomedicine-based preparations include high therapeutic effects because of better skin penetration, targeted and controlled drug delivery. The treatment of various topical infections like psoriasis, acne, eczema, impetigo, pustular acne, and dermatitis is still the most challenging field for researchers because of the lack of efficacy and effectiveness of different conventional anti-infective treatments. The emergence of new drug-resistant microorganisms like *Methicillin-resistant Staphylococcus aureus* and penicillin-resistant *Pseudomonas aeruginosa* further increases the challenges in the skin-related treatment. The use of nanotechnology in anti-infective skin treatments can act as a major driving force to enhance the efficacy and effectiveness of the treatment. Though the regulation and safety of nanomedicines are debatable, this area of research will continue to evolve with the advances in nanomedicine technologies.

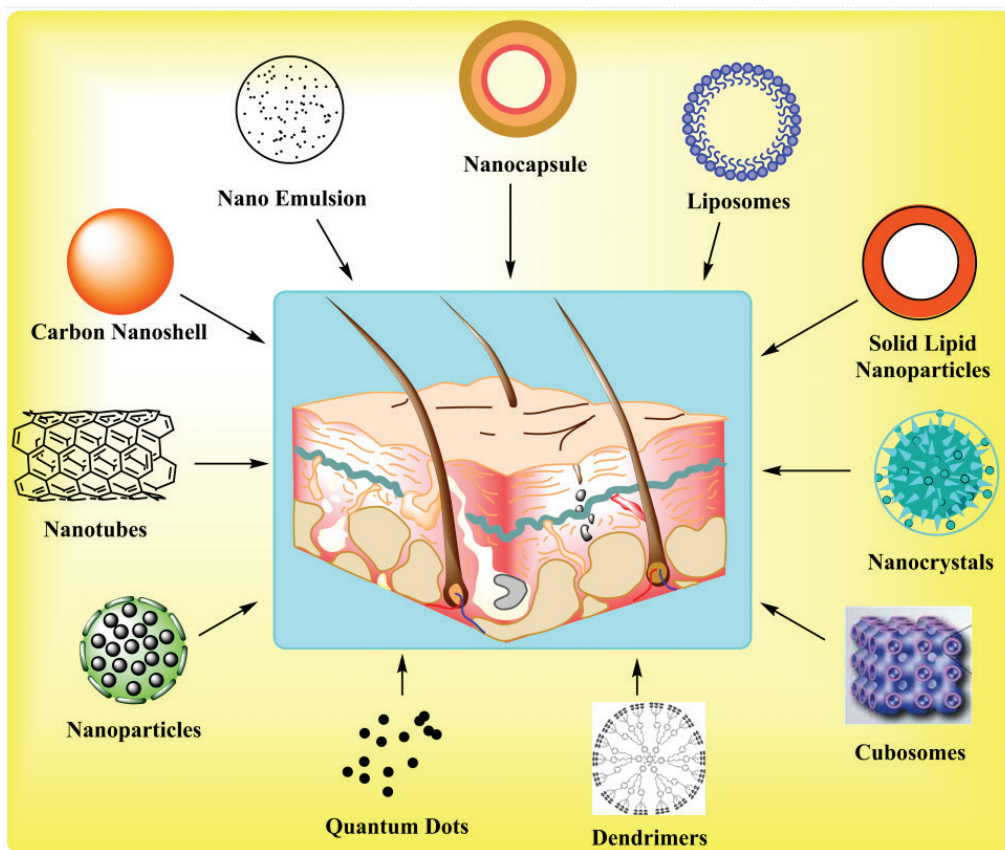


Figure 2. Various novel carriers in the treatment of skin fungal infections.

Table 1. Various research reports on nanocarriers along with antifungal drug, target microorganism, and their use.

Microorganism	Drug	Drug carrier	Use	Reference
<i>C. albicans</i>	Histatin 5	Liposome	Oral <i>Candidiasis</i>	Zamboni <i>et al.</i> , 2019
<i>C. albicans</i>	voriconazole	Liposome	Fungal infection	Veloso <i>et al.</i> , 2018
<i>Aspergillus</i>	Amphotericin B + Dectin 1	Liposome	Fungal infection	Ambati <i>et al.</i> , 2019
<i>C. albicans</i>	ketoconazole	Liposome	Fungal infection	Guo <i>et al.</i> , 2015
<i>Penicillium expansum, Aspergillus niger, Penicillium herquei, Fusarium graminearum, Aspergillus flavus</i>	Garlic extract	Liposome	Antifungal	Pinilla <i>et al.</i> , 2019
<i>Aspergillus</i>	Amphotericin B	Liposome	Burn patients	Laurent <i>et al.</i> , 2019
<i>C. albicans</i>	Oxiconazole nitrate	Ethosomal gel	Contagious diseases	Khan <i>et al.</i> , 2019
<i>A. flavus</i>	Voriconazole	ethosomes	Topical fungal infections	Faisal <i>et al.</i> , 2016
<i>A. niger</i>	Fluconazole	Ethosomal + liposomal gel	Fungal skin disorders	Rathore <i>et al.</i> , 2015
<i>C. albicans</i>	fluconazole	Niosomal gel	Corneal fungal infections	Fetih, 2016
<i>C. albicans</i>	oxiconazole	Niosomal gel	Fungal treatment	Rasheed <i>et al.</i> , 2018
<i>Candida species</i>	Miconazole nitrate	Spanlastics	Ocular fungal infections	Mohanta <i>et al.</i> , 2017
<i>C. albicans</i>	Itraconazole	Spanlastics	Ocular fungal infections	ElMeshad and Mohsen, 2016
<i>C. albicans</i>	Clotrimazole	Oleic acid vesicles	Antifungal agent	Verma <i>et al.</i> , 2014
<i>C. albicans</i>	Terbinafine hydrochloride	Nanostructured lipid carriers	fungal infections	Gaba <i>et al.</i> , 2015
<i>C. albicans</i>	Terbinafine hydrochloride	Solid lipid NPs	Onychomycosis	Tiwari <i>et al.</i> , 2014
<i>C. albicans</i>	Bifonazole	Solid lipid NPs	Antifungal agent	Garse <i>et al.</i> , 2015
<i>A. niger</i>	Gold	NPs	Antifungal agent	Sojinrin <i>et al.</i> , 2017
<i>A. niger + Penicillium</i>	Zinc	NPs	Antifungal agent	Aldosari <i>et al.</i> , 2019

(Continued)

Microorganism	Drug	Drug carrier	Use	Reference
<i>A. niger</i>	Clove essential oil	NPs	Fungicide	Hasheminejad <i>et al.</i> , 2019
<i>Aspergillus, Candida, Fusarium, Penicillium</i>	Hassalidins	NPs	Antifungal	Humisto <i>et al.</i> , 2019
<i>C. albicans</i>	Itraconazole	NPs	Antifungal	Alhowyan <i>et al.</i> , 2019
<i>C. albicans</i>	LL-37 Peptide + Ceragin CSA-13	NPs	Antifungal	Niemirowicz <i>et al.</i> , 2017b
<i>Candidiasis + Cryptococcosis</i>	Miltefosine	NPs	Antifungal	De Castro Spadari, 2019
<i>C. albicans</i>	Capsfungin + Amphotericin B	Micelles	Antifungal agent	Hsieh <i>et al.</i> , 2017
<i>C. albicans</i>	Amphotericin B	Micelles	Controlled release Antifungal agent	Wang <i>et al.</i> , 2016
<i>C. albicans</i>	Luliconazole	Ethogel + liogel	Antifungal agent	Kaur <i>et al.</i> , 2019
<i>C. albicans & other species</i>	Clove oil	Ethosomal gel	Cutaneous <i>Candidiasis</i>	Shetty <i>et al.</i> , 2019
<i>C. albicans</i>	Terbinafine hydrochloride	Ethosomal topical gel	Onychomycosis	Shruthi <i>et al.</i> , 2018
<i>C. albicans</i>	Miconazole nitrate	Transfersomal gel	<i>Candida</i> skin infections	Qushawy <i>et al.</i> , 2018
<i>C. albicans</i>	fluconazole	Transfersomal gel	Candidial infections	Tejaswini <i>et al.</i> , 2016
<i>C. albicans</i>	Miconazole + farnesol	Polymeric NPs	Vulvovaginal <i>Candidiasis</i>	Costa <i>et al.</i> , 2019
<i>Candidiasis species</i>	nystatin	Polymeric NPs	Oral cavity	Roque <i>et al.</i> , 2018
<i>C. albicans</i>	Amphotericin B	PLGA NPs	antifungal	Li <i>et al.</i> , 2018

Table 2. Patent literature on various antifungal compositions.

Patent no.	Title	Description	References
US 2014/0364440 A1	Topical oil composition for the treatment of fungal infections	Invention discloses the antifungal compositions having antifungal compounds, oil, and excipients. High fatty acids or esters are excluded in the current composition.	Bapat <i>et al.</i> , 2014
AU2014252157B2	Composition and formulation of antimicrobial agents, processes thereof, and methods for treating microbial infection	Current invention comprises antimicrobial compounds and other excipients. The composition includes at least one fatty acid or ester with a carbon chain less than C11, and wherein the fatty acids or esters of more than 10 carbons are not included. These compositions are nanocomposites with a nano-sized particle.	Prasad <i>et al.</i> , 2016
BR102014029027A2	Use of nanoformulations containing 2-aminothiophene derivatives as antifungal agents	Current disclosure investigated the nanoformulations containing thiophene derivatives as antifungal agents, which has been confirmed by evaluating antifungal efficacy <i>in vitro</i> against <i>Candida</i> and <i>Cryptococcus</i> yeast species.	Rabelo <i>et al.</i> , 2016
CA3039485A1	Antifungal dry powders	It relates to dry powder formulations containing homogenous particles of a triazole antifungal agent (itraconazole) in crystalline form, stabilizer, and one or more excipients.	Perry <i>et al.</i> , 2018
WO 2015/035102 A3	Compositions and methods for the treatment of fungal infections	Relates to compositions to treat fungal infections using compounds containing a lipopeptide moiety and a formyl peptide receptor ligand in the treatment of fungal infections caused by <i>Aspergillus</i> or <i>Candida</i> .	Forrest <i>et al.</i> , 2016
WO 2016/205009 A1	Treating infection by a platelet-targeting microbe using NPs	It discloses the methods, combinations, and pharmaceutical compositions for prevention or treatment of infection by a platelet-targeting microbe in a subject, using an effective amount of a nanoparticle comprising a non-cellular material, with an outer coat comprising of a cellular membrane derived from a platelet, and an agent for preventing, treating, diagnosing, and prognosing the said infection.	Zhang <i>et al.</i> , 2018
WO 2018/136778 A1	Telodendrimers with riboflavin moieties and nanocarriers and methods of making and using same.	It relates to compositions and nanocarriers comprising of linear dendritic TD containing riboflavin. The nanocarriers' compositions showed desirable loading properties with stability and are used for efficient <i>in vivo</i> delivery.	Luo <i>et al.</i> , 2015

CONCLUSION

The most attractive and acceptable strategy for the treatment of skin disorders is topical treatment by applying creams/gels directly on the impacted part. This resulted in the highest patient compliance and therapeutic outcomes. The use of nanomedicine for the treatment of skin disorders is a growing area in research to promote the medical and scientific aspects of nanomaterials in skin health and disease. The nano-medicines act by interacting at a sub-atomic level in the skin tissues. Different types of nanocarriers like liposomes, silver NPs, lipidic NPs, dendrimers, and QDs can act as the most promising drug

delivery treatments. All of them have different significance and mechanisms of interactions at barrier membrane interfaces. This uniqueness of interaction at a sub-atomic level in tissues increases the distinctiveness of different niosomal preparations and hence they can be used as per the requirement. In this review, we have discussed all the emerging topical preparations by using nanomedicine based drug delivery systems. We have discussed different challenges, formulation considerations, mechanisms of their action, and their results with some important examples of research articles. The use of nanomaterials for skin cancer, tissue replacement, and faster recovery of skin diseases is the future of

skin healthcare. The use of nanomedicine-based drug delivery system as topical skin infection treatments is more effective as compared to the conventional dosage forms but the results are not to the mark of complete satisfaction and hence a right direction is needed in which efforts and studies need to be performed to win the battle against this global challenge.

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All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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