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A Review on SLN and NLC for Management of Fungal Infections

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Fungal disease is an invasive, serious, and systemic topical infection that affects the mucous membranes, tissues, and skin of humans. Oral medicines, on the other hand, have significant side effects, making topical treatments a viable alternative. Many antifungal medications applied through the skin in various conventional forms (gels or creams) may cause skin redness, erythema, stinging, and burning sensations. A promising approach to overcome the limitation of conventional form is the use of Nanocarriers for the treatment of skin infections since it allows targeted drug delivery, enhanced skin permeability, and controlled release and hence offers a lower risk of side effects. During the last few decades, lipid nanoparticles (LNPs) such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have gained a lot of attention. SLNs were designed to overcome the drawbacks of conventional colloidal carriers, such as emulsions, liposomes, and polymeric nanoparticles, by offering benefits such as a good release rate and drug targeting with high physical stability. NLCs are SLNs that have been modified (Second generation SLN) to improve stability and capacity loading. This review discusses the pathophysiology of the fungal diseases, the application of SLN and NLC, its method of preparation, Characterization, and an overview of clinical trials on SLN and NLC for the treatment of fungal infection.

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1. INTRODUCTION

Fungal infections are becoming more common these days, especially among immunocompromised people. This increase in fungal infection is due to the association of immunodeficiency diseases or overuse of immunosuppressive drugs and may occur also during solid organ transplantation, stem cell transplantation, and neonatology. The coupling of pathogenic fungi has increased in fungal infection, whether superficial or systemic [1]. Examples of fungal infection: Ringworm body (tinea corporis), Athlete's foot (tinea pedis) Jock itch (tinea cruris), Ringworm of the scalp (tinea capitis), Tinea versicolor. Cutaneous candidiasis, Onychomycosis (tinea unguium) [2].

Fungal infections are divided into two types: superficial infections and systemic infections, which affect the entire body. Superficial infections affect the body's skin, eyes, hair, and nails, whereas systemic infections are associated with the human biological system. To treat these fungal infections solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are used as a carrier for the antifungal drug, for effective treatment [2].

In the year 1990, SLN were produced in laboratories as alternatives to liposomes, emulsions because of the biocompatibility of liquid lipids [3]. Drugs loaded with SLNs have shown advantages like reduced toxicity, increased loading capacity, chemical adaptability, the biodegradability of lipids, large-scale production capability [4]. NLC is the second generation of lipid nanoparticles. Unlike SLN, NLC's lipid matrix is made up of a mix of solid and liquid lipids, resulting in a reduced melting point of the lipid and at body temperature, the lipid matrix in the nanoparticles remains solid [5]. A surfactant or a combination of surfactants can also be used to stabilize NLC in aqueous dispersion. The inclusion of oil in the composition prevents the solid lipid from recrystallizing during storage, hence increasing the loading capacity, particularly for lipophilic substances [6]. The average size of SLN and NLC is in the nanoscale range, from 40 to 1000 nm depends on the composition lipid matrix (i.e., lipid and surfactant combination) and the manufacturing technique [3]. The difference between SLN and NLC are shown in Fig. 1.

2. PATHOPHYSIOLOGY OF FUNGAL INFECTION

Fungi infections can be inherited from the environment, or they can be acquired from within the host in rare cases when they are part of the local flora. A frequent method is inhaling pathogenic conidia produced by molds growing in the microenvironment [7]. Some of these molds are found all over the world, while others are only found in places where the environment is conducive to their growth. The disease can only be acquired in the endemic region in the latter instance [8]. When environmental fungi are unintentionally injected across the epidermal barrier, they cause illness. Only a small percentage of fungi present in the environment are pathogenic [8]. Endogenous infections are restricted to a few yeasts, the most prevalent being Candida albicans. These yeasts can colonize by sticking to host cells and infiltrating deeper structures if given the chance [9].

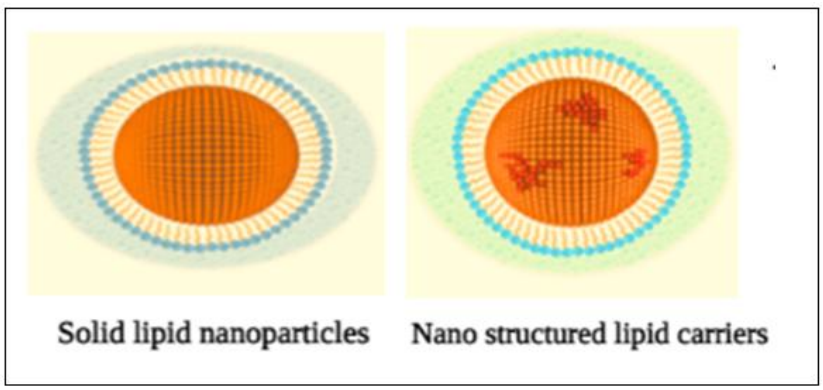

Fig. 1. Schematic representation of SLN and NLC

2.1 Pathogenesis

In comparison to bacterial, viral, and parasitic infections, the pathogenic processes and virulence factors involved in fungal infections are less well understood [10]. The closest comparisons are to bacterial infections because of the enduring popularity of adherence to mucosal surfaces, severity, extracellular secretions, and contact with phagocytes [10,11]. The concepts covered fungal infections in general. The majority of fungi are opportunists, causing significant illness mainly in those who have weak immune systems. Only a few fungi are capable of infecting previously healthy people [12].

2.2 Invasion

Most effective infections must first pass through a surface barrier, such as the skin, mucous membrane, or respiratory epithelium. The mechanical fracture can introduce certain fungus and causes fungal infection (wound) [13]. Sporothrix schenckii infection, for example, usually occurs after a thorn puncture or other visible damage. To get past the upper airway defenses, [14] infectious fungi that infect the lungs must produce conidia that are small enough to be inhaled. Arthroconidia of Coccidioides immitis (2-6 m), for example, can float in the air for a long time before reaching the terminal bronchioles and causing pulmonary coccidioidomycosis [15].

2.3 Trauma is Associated with the Traumatic Injection

Conidia that are small enough may be able to get through airway defenses. A dimorphic fungus in the environment goes through a metabolic shift similar to a heat shock reaction, changing its shape and development to a more invasive form, which is triggered by temperature and maybe other cues [16]. The invasion of the indigenous yeast C Albicans directly via mucosal barriers is also associated with a morphologic alteration, the formation of hyphae. The cause of this transition is unknown, but the new form has the potential to enter and spread [17]. Extracellular enzymes (e.g., proteases, elastases) are associated with the advancing edge of Candida's hyphal form, as well as the invasive forms of a variety of dimorphic and other bacteria [18].

2.4 Injury

There has been little evidence that the extracellular products of opportunistic fungus or dimorphic pathogens harm the host directly during infection in the same way as bacterial toxins do but there is no evidence found for the presence of necrosis and infarction in the tissues of people infected with Aspergillus suggests toxicity such as infection, burns [19]. Exotoxins, also known as mycotoxins, are produced by certain fungi in the environment but not in humans. The fact that circulates widely throughout the body, the structural components of the cell do not have the same effects as Gram-negative bacteria's endotoxin. The circulating products of Cryptococcus neoformans have been proven to suppress immunological activities The damaging characteristics of delayed-type hypersensitivity (DTH) reactions as a result of the immune system's failure to remove the fungus appear to be the primary source of damage caused by fungal infections [20] [21].

3. TOPICAL ANTIFUNGAL

Topical antifungal drug administration is likely the most effective method for combating major skin dermatophytes, as it ensures direct access to the target and a better retention rate. Topical administration also helps to avoid pre-systemic metabolism and reduces systemic toxicity. Various drugs, such as ketoconazole, itraconazole, and clotrimazole, are applied to the skin as a topical application. Table 2 depicts some of the marketed formulations available for the treatment of superficial fungal infections [22-24].

3.1 Antifungal Medication Resistance and Biofilm Formation

A biofilm is a complex organic substance formed by a microbial community adhering to a substrate on its own. Biofilms provide a one-of-a-kind barrier to outside hazards. Cell adhesion is a suitable substrate, proliferation, matrix component synthesis, maturation, and dispersions are the biochemical phases that lead to the formation of fungal biofilms [25]. Antifungal resistance is determined by the cell density inside the biofilm matrix, as well as the bacteria species. The most common fungus found in biofilms is Candida albicans. Other filamentous fungi, such as Malassezia, Saccharomyces, Histoplasma, and Trichosporon, have been implicated in the production of biofilms [26]. Biofilm is thought to be critical to the survival of certain of these illnesses in hostile environments. Fungal biofilms are often studied using the microtiter plate paradigm. Morphogenetic

alterations, growth circumstances, cell density, and the kind of extracellular matrix connections all influence biofilm development in Candida albicans [27,28]. As the biofilm develops, the entire process is carefully regulated and managed by a sophisticated regulatory network. Recent research has found that liposomal versions of Amphotericin B exhibit exceptional antifungal effectiveness against Candida albicans resistant strains [29]. Enzymatic hydrolysis of the enzyme cytosine permease, which is essential for cellular absorption of 5-flurocytosine, releases the active medication 5-fluorouracil. When one or more of the aforementioned enzymes are weak, 5-FC resistance develops [30]. Traditional topical formulations have several disadvantages, including limited permeability and significant adverse effects, making them unsuitable for long-term use. Due to the growing incidence of infections, azole resistance in non-Candida Albicans strains has become a major issue [31]. Azole resistance in Aspergillus fumigatus has been associated with recurring sub-micron dosages and clinical exposure to mutant strains [28].

Several experimental antifungals are now being tested in human trials, with only a few showing results against azole-resistant species. These include drugs that target specific biochemical systems linked to drug resistance, such as ergosterol and -glucan synthesis, making resistance easier to overcome [32]. Because processes linked to fluconazole sensitivity, such as mutations in the ERG11 gene, result in higher levels of lanosterol 14a-demethylase, which is involved in azole metabolic deactivation, resistance to other azoles may develop (e.g., itraconazole, voriconazole) [33, 34].

4. LIPID NANOPARTICLES FOR THE TREATMENT OF FUNGAL INFECTION

Particle size, surface charge, and lipophilicity all have a role in determining the depth of penetration into various skin layers. The smaller size of lipid particles allows for closer interaction with the stratum corneum, allowing for better medication penetration and regulated release [31,35] Because of their ability to alter and improve the pharmacokinetic and pharmacodynamic properties of drugs, nanoparticles have been used in pharmaceutical formulations. This is due to their capacity to improve drug solubility and stability, allow for controlled release, and show biocompatibility with tissues and cells, all of which contribute to an overall increase in therapeutic efficiency. As a result, developing novel biopharmaceutical systems, particularly nanoparticulate carriers, is an effective technique for improving the therapeutic efficacy, safety, and compliance of antifungal agents [36,37]. Table 2 depicts some of the lipid based nanoparticle formulations for antifungal drug delivery.

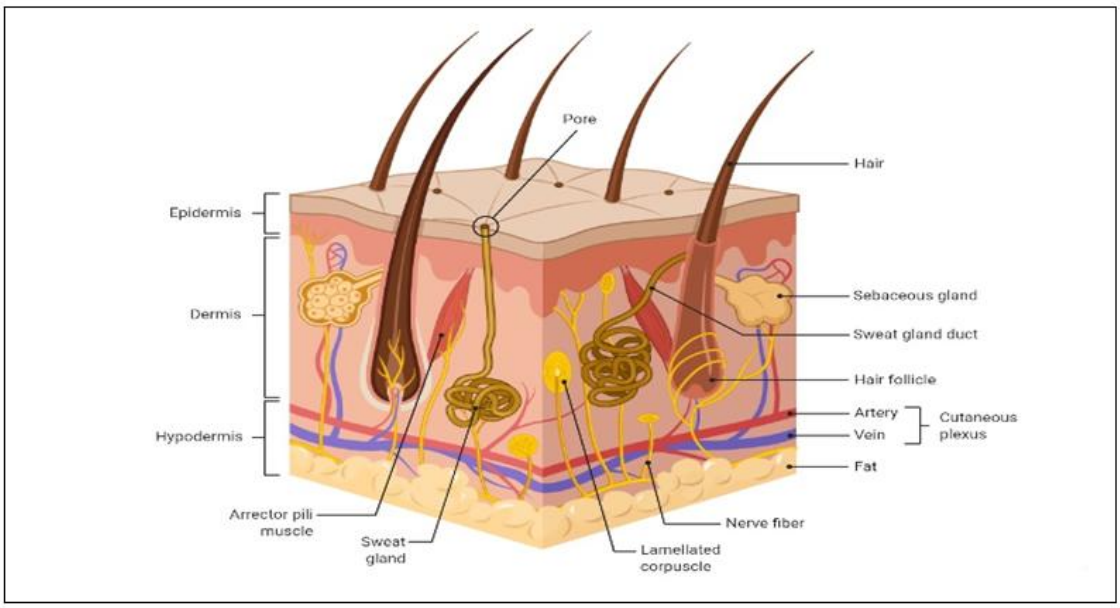

Fig. 2. Different layers of skin

Table 1. Marketed formulations available for the treatment of superficial fungal infections

Drug	Brand name	Dosage form	Manufacturer
Clotrimazole	Lotimin(1%)	Cream	Schering
	Gyne-Lotrimin(1%)	Cream	Schering_Plough
	Mycelex_G(1%)	Cream	Miles
Miconazole	Manistat_ermD(2%)	Cream	Pifzer
	Micatin(2%)	Cream	Ortho_McNeil
Ketoconazole	Xologel(2%)	Gel	Stiefel Labs
	Nizoral(2%)	Cream	Janssen
Econazole	Spectazole(1%)	Cream	Ortho
	Econail(5%)	Nail lacquer	Macrochem- corporation
Sertaconazole	Ertaczo(2%)	Cream	Ortho Neutrogena
Ciclopirox	Laprox(0.77%)	Cream	Hoechst-marrion-Roussel
	Laprox(0.77%)	Gel	Aventis pharma
Terbinafine	Lamisil(1%)	Cream	Merz pharmaceuticals
Fluconazole	Flucomet(0.3%)	Eye drops	Sun
	Syscan(0.3%)	Eye drops	Torrent
	Zocon(0.3%)	Eye drops	FDC
Natamycin	Natacyn(5%)	Ophthalmic Suspension	Alcon
Ciclopirox amine	Only(8%)	Nail lacquer	Cipla
	Penlac(8%)	Nail lacquer	Dermik
	Nailon(8%)	Nail lacquer	Protech biosystem
Amorolfine	Loceryl(5%)	Nail lacquer	Roche lab

Table 2. Lipid Nanoparticles containing antifungal drugs marketed for topical application

Drug	Novel formulation	Findings
Miconazole	Liposome, niosome SLN.	The prepared formulation has good, enhanced permeation properties to the skin [6].
Fluconazole	Liposomes, Niosome, SLN&NLC	SLN formulation shows better localization in dermal and it is sustained released over a day [25]. NLC prepared formulation showed better retention time over the skin and effective targeting properties compared to SLN [35].
Clotrimazole	SLNs and NLCs	NLC showed increased drug entrapment compared to SLNs [38].
Ketoconazole	SLN and NLC	SLN were not stable while NLC were stable while exposed to light [39]

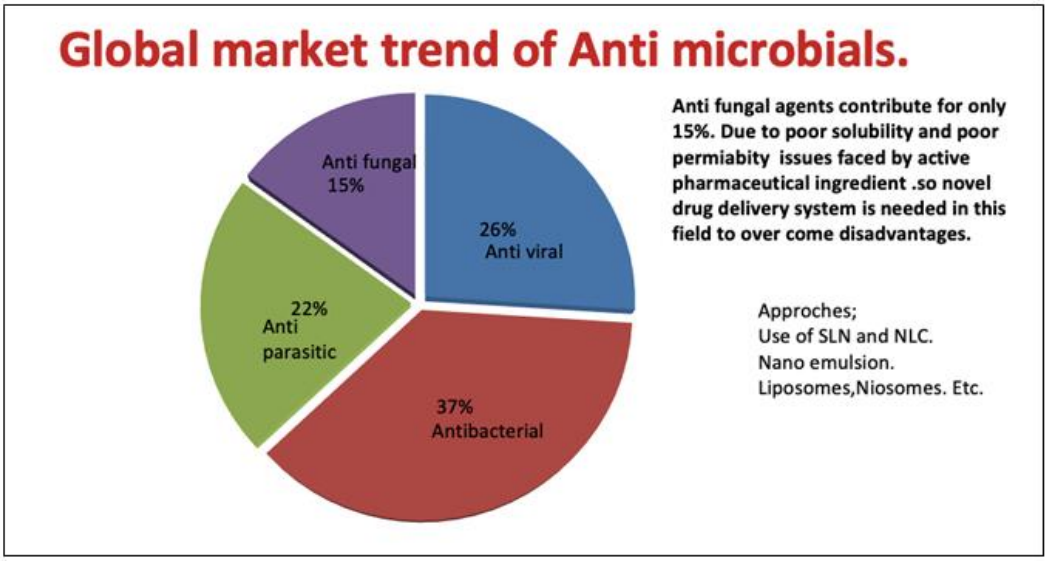

Fig. 3. Descriptive analysis of the use of antimicrobials

5. METHODS OF PREPARATION OF NLC AND SLN

5.1 High-Pressure Homogenization

The SLN and NLC for preparing approach is high-pressure homogenization. This strategy's advantages extend beyond its quick construction time. The strategy likewise permits lab-scale preparation to be effortlessly translated to huge scope creation. Furthermore, the evasion of natural solvents, yielding normal molecule size in the submicron area, and because of the wide range of homogenizer brands and types available at a reasonable price, is a widely used method in many businesses [40]. In any event, because it is a high-energy cycle, it raises the temperature, which is incompatible with heat-sensitive apparatus. This approach entails applying strong pressure to a very small hole (a couple of microns wide). Particles are reduced to submicron size due to high shear pressure and cavitation powers. At both high and low temperatures can be homogenized in high-pressure homogenization for SLN and NLC can be achieved (hot and cold homogenization, individually). In any case, keep in mind that the drug should be dissolved or scattered at a temperature of 5°C above its melting point [41].

The entire interaction is carried out at temperatures over the lipid's liquefying point in hot homogenization. Fast mixing produces a pre-emulsion of the drug layered lipid is softened and the fluid is emulsified (5-10°C above lipid Melting point) (for example Ultra-Turrax). The heated pre-emulsion is later homogenized at a controlled temperature using a high-pressure homogenizer. When the pre-emulsion lipid fixation is in the range of 5-10%, a single homogenization cycle is adequate to produce a hot emulsion with molecule sizes in the range of 250–300 nm [42]. Finally, obtained nano emulsion is cooled to room temperature and recrystallizes, forming SLN and NLC. Emulsion fixation levels of 40% or above can also be homogenized. NLC cannot be formed with lipid contents greater than 30%; instead, unusually considered SLN features must be employed. Regardless, the emulsion lipid fixation will dictate the number of cycles, as the energy required to shear the lipid mass is proportional to its focus in the detail. However, because molecule dynamic energy increases favor mixture, increased order of homogenization cycles usually results in larger molecules [43]. In most cases, three homogenization cycles are recorded in the literature. Advantages: Hot homogenization can be employed in any situation for temperature-sensitive combinations because the hour of exposure to higher temperatures is usually brief. Disadvantages: Especially for temperature-sensitive mixes and hydrophilic mixtures, which can transition from the lipid to the aqueous phase when heated to a high temperature [41, 42].

5.2 Cold Homogenization

This approach is same as that of hot homogenization technique which comprise of

dispersion or dissolving or solubilization of the drug in the melted lipid. Then the drug lipid mixture is rapidly solidified either with the help of liquid nitrogen or dry ice. The drug-loaded solid lipid is milled by using a roller mill or ball mill to a micron size range of 50-micron to 100 micron and further microparticles are dispersed in chilled emulsifier solution to obtain a pre-suspension. Then this pre-suspension is subjected to high-pressure homogenization at room or below room temperature, where the cavitation force is strong enough to break the microparticles to SLN and NLC [44,45].

5.3 Microemulsion Technique

The lipid phase is melted, and the aqueous phase (which contains surfactant) is heated to the same temperature as the lipid (or lipid mix). The lipid phase of the microemulsion is completed by gently mixing in the aqueous solution to form the microemulsion. To prepare lipid nanoparticles, the microemulsion is added to cold water (2-10°C). Finally, the prepared nanoparticle is lyophilized after being rinsed with distilled water, filtered (to eliminate bigger particles), and rinsed again to remove excess water. The limitations, by the way, include the requirement for relatively large surfactant groups, as well as the drug leakage from the molecule suspension caused by the microemulsion being emptied into the water, resulting in a suspension with an exceedingly low drug loading [43]. Advantages: It is easily scalable from lab scale studies to pilot plant studies. Disadvantages: Toxicological problems may cause the complications.

5.4 Emulsification by Solvent Evaporation

The lipid is dissolved in a water-insoluble organic solvent and subsequently emulsified by the aqueous phase in this method. The solvent evaporated at low pressure, allowing lipid precipitation and nanoparticle dispersion in aqueous solutions to occur [41]. This is a fully heat-free process that can make nanoparticles are reduced to 100 nm depending on the employed components. Using an organic solvent, on the other hand, has the drawback of leaving hazardous residues in the sample [41].

5.5 Solvent Injection

The lipid is liquified in a water-miscible solvent before being quickly injected with a micro-injection needle into a stirred surfactant-containing aqueous phase [46]. When it comes to generating lipid nanoparticles, the process is straightforward to apply, versatile, and effective. However, utilizing an organic solvent has several drawbacks [47]. Advantages: This technique does not require low or high temperatures. No need for pH modification, ultrasonication, homogenization, or pressure variations [48].

5.6 Phase Inversion

Magnetic stirring of the formulation contents (lipid matrix, drug, water, and surfactant) and three different temperature cycles (85-60-85-60-85°C) are used in this method to achieve the inversion process(43). The combination is then given a cold distilled water thermal shock, which causes lipid nanoparticles to develop. This process requires no organic solvents and only a brief heating duration. However, it is a lengthy procedure with numerous steps [48].

5.7 Membrane Contraction Technique

This method was developed to mass-produce lipid nanoparticles. In the molten lipid holding matrix the drug is forced into an aqueous phase containing surfactant that is kept at lipid melting temperature (usually with a pore diameter of 0.05 m) through a porous membrane [41]. The lipid creates minute droplets as it travels through the holes, which precipitate as lipid nanoparticles then the preparation is cooled to room temperature. The strategy is straightforward scalable, and the change in particle size is as simple as switching between membranes with varying pore diameters [46].

Advantages: SLN and NLC size can be controlled to an appropriate size [49].

Disadvantages: The main drawbacks of this method are potential metal contaminations and physical instability [50].

6. PHYSICOCHEMICAL CHARACTERI-ZATION OF SLN AND NLC

The physicochemical characteristics of NLC are critical for quality assurance and security to investigate the structure and versatility, various strategies were used, including particle size analysis, zeta potential (ZP), transmission electron microscopy, differential scanning calorimetry (DSC), X-Ray diffraction (XRD), laser diffraction, and field-flow fractionation. These processes reveal the formulation's physical and

chemical stability; the surface charge, in general, determines whether or not the particles will flocculate [51].

6.1 Particle Size

The physical stability of dispersion is dependent on particle size, and as particle size drops, the surface area rises, particle size is a significant parameter in creating control and quality [52]. PCS (Photon Correlation Spectroscopy) is based on laser light diffraction and may be used to examine particles with diameters ranging from 200 nm to 1 m. Rayleigh's theory states that the scattering intensity of particles smaller than 200 nm corresponds to the sixth power of the particle dimension [53].

6.2 Zeta Potential

The electric potential of a particle in suspension is denoted by ZP. It's a metric that may be used to determine the physical stability of colloidal dispersions. The surface charge generates a potential surrounding the particle that is greatest at the surface and diminishes as the particle separates from the medium [54]. The ZP may be calculated by measuring the particle speed in an electrical field (electrophoresis measurement). This procedure may be used to determine the form of the particles that have been created as well as their molecular size [55]. On a sample holder, aqueous Nano lipid carrier dispersions can be applied and dispersed (thin carbon film). The samples are placed inside the magnifying lens' vacuum section, and the air is sucked out of the chamber. Light emission is produced by an electron cannon located at the top of the column. The electrons emitted by the light travel through the lens, which focuses them into a small point and scans the material row by row. The electrons are then collected, and the signals are delivered to an amplifier [56].

6.3 Differential Scanning Calorimetry

DSC is a commonly used method to get information on a formulation's physical and energetic characteristics. It calculates the heat loss or gains as a function of temperature due to physical or chemical changes inside the sample [49]. The degree of crystallinity of the particle scattering is determined by using DSC on powder. The rate of crystallinity is measured by DSC by comparing the bulk material's liquefying enthalpy/g to the scattering's softening enthalpy [57].

6.4 Atomic Force Microscopy

Atomic force microscopy (AFM) is an excellent tool for evaluating extremely small morphological and surface features. AFM uses a very tiny sharp-tipped probe at the free end of a cantilever that is driven with interatomic repulsion or attraction interactions between the tip and the specimen's surface, rather than photons or electrons [58]. While electron microscopy is still commonly used, AFM has various advantages, including real-time quantitative data collection in three dimensions, quick sample preparation times, flexibility in working settings, and effective nanoscale magnifications [59].

6.5 *In vitro* Drug Release

To measure the rate of drug release content from drug products, in-vitro release uses well-established Franz diffusion cells. It entails the administration of a drug to a membrane that separates the donor and receiver chambers (synthetic membrane, excised animal skin, or excised human skin) [60]. In vivo, the receiver chamber duplicates sink conditions. The rate of delivery obtained in these investigations is thought to be comparable to the condition in vivo. The approach has been frequently employed in drug discovery studies to assess formulations and to understand cutaneous drug transport mechanisms. In a systematic flow, the controlled release of drugs from lipid nanoparticles can result in a longer half-life and delayed enzymatic attack. The temperature at which NLCs are manufactured affects the drug release behaviour [61].

7. LIPID NANOPARTICLES FOR TOPICAL ANTI-FUNGAL DRUG DELIVERY

With a surface area of about 2m2, the skin is one of the body's major organs. It has three layers: a thin epidermis on the exterior, a thicker middle layer dermis, and the thickest hypodermis on the interior. It conducts a variety of important functions. The stratum corneum, the epidermis' outermost layer, is made up of keratinized and dead cells [62,63]. Because of their high lipid content, pharmaceuticals with a greater drug payload and delayed, controlled drug release should be able to pass through it, notably azole drugs [64]. SLNs containing compritol and a co-surfactant (PEG 600) were made utilizing a heated high-pressure homogenization method exhibit excellent performance and high encapsulation efficiency of up to 70% for

Ketoconazole [64]. In determining the efficacy of encapsulated medicines, however, the type of lipids, surfactants, concentration, and preparation technique are all critical considerations. Due to the highly organized crystalline structure of the lipid matrix, which leaves limited space for therapeutic molecules, lipid nanoparticles containing high molecular weight fatty alcohols and straight-chain primary alcohols exhibit low drug loading capacity and delayed-release behavior. Low melting point lipids, such as triglycerides, partial glycerides, and amphiphilic lipids, on the other hand, are regarded to be suitable for SLNs because they allow for higher drug loading, improved skin penetration, and less antifungal drug leakage. Based on qualified benefits, SLN is observed to be a feasible formulation for topical delivery of antifungal agents [64,38,65].

Souto et al developed SLNs and NLCs containing clotrimazole for topical delivery. SLN with occlusive features has been produced as carriers that allow continuous drug release behavior over 10 hours, making them appropriate for topical applications [57]. SLNs and NLCs protect the encapsulated drug in formulation from photodegradation, assuring its stability, and have shown antifungal efficacy against Candida albicans comparable to the commercial product [65,66]. Sanna et al found that SLN formulations increased encapsulated econazole nitrate penetration beyond the stratum corneum's impermeable after 1 hour and had better when compared to reference gels, econazole nitrate penetrated deeper layers of skin after 3 hours [67]. Passerini et al. compared the efficacy of econazole nitrate loaded SLNs to solid lipid microparticles with similar formulations in terms of treatment efficacy with characteristics. When compared to commercial gel formulations, SLN preparations demonstrated significantly higher miconazole nitrate skin permeability [68]. The targeted effect of SLN preparations is also significantly greater. Cassano et al have revealed that Candida albicans-causes vaginal yeast infections, SLNs containing ketoconazole (KCZ) and clotrimazole (CLT) prepared with PEG-40 stearate and PEG-40 stearate acrylate are effective. Nanocarriers can penetrate the skin layers and transport topical medicines. SLN, liposomes, niosome, and microemulsion are examples of novel topical formulation techniques are microemulsion, Nano emulsion, etc. [69].

The therapeutic agent is incorporated inside a lipid core matrix in these nano-lipid carriers. High homogenization or microemulsion preparation methods can be used to formulate SLN [70]. SLNs are emulsion-free SLNs with solid lipids as the oil phase. SLNs have low toxicity (the lipids utilized are biologically identical), making them biocompatible. The tiny size of lipid particles permits closer interaction with the stratum corneum, resulting in better permeation of the and regulated release [71,72]. Their composition forms a coating on the skin, preventing water from evaporating. As a consequence, the skin is kept moisturized and the barrier function is preserved. Because the lipid nanoparticles are spherical and have great lubricating properties, which helps to minimize skin irritation and allergies. They have more drug entrapment capacity and well-modulated release kinetics. Encapsulation protects the active components from degradation [70-72]. However, SLNs have a few drawbacks, such as a restricted number of drugs and a lipid SLN grown to a large amount employing cationic lipids. Disruption of endosomal membranes, formation of DNA complexes, and increased cell permeability are all recognized methods through which cationic lipid modulates antifungal action. Debora and colleagues have proposed that cationic lipids, such as dioctadecyl dimethylammonium bromide (DODAB) and hexadecyltrimethylammonium bromide (CTAB), had strong antifungal action against Candida albicans [73] Nonetheless, over a therapeutic dose, cationic lipids cause local toxicity. Furthermore, the size of SLNs influenced the result of cutaneous mycosis therapy. In a recent study, Zahra et al evaluated the impact of SLN size on skin penetration. The results showed that SLNs in the 50–200 nm range readily penetrate the cutaneous layer, whereas sizes larger than 200 nm accumulated in the dermis, so these formulations are used ineffective treatment for fungal infection [74]. Despite their benefits, SLNs have a few drawbacks, such as limited drug-loading and irregular drug release. NLCs are second-generation lipid nanoparticles consisting of a blend of solid and liquid lipids capable of holding a wide range of drugs (72). In research comparing the encapsulation performance of NLC and SLNs for Ketoconazole, it was discovered that SLN and NLC had 62.1 and 70.3 percent encapsulation, respectively. Furthermore, as compared to SLNs, NLC has successfully enhanced Ketoconazole's light stability [39]. Furthermore, NLC has superior drug solubility and skin permeability than SLNs due to lower fatty acid triglycerides. In their investigation, Gratieri et al. found that NLC had higher

Table 3. Recent advances in Lipid nanoparticles of anti-fungal agents

Antifungal drugs (SLN and NLC)	Lipids	Mode of action	Method of preparation	Diseases	Findings	Reference
Fluconazole and FLZ-SLNs	Compritol 888 ATO Precirol ATO5	It acts by preventing production of vital elements in the fungal membrane as ergosterol by inhibiting the fungal cytochrome P-450 enzyme. This inhibition action on cytochrome P-450 enzymes was found to be greater in fungal species in contrast to mammalian enzyme, which improve the safety profile of triazoles	high shear homogenization and ultrasonication method	pityriasis versicolor	superior significant fast therapeutic index in treatment over commercially available CandistanVR cream.	[75]
Ketoconazole-SLN	Tripalmitin	inhibits the transformation of blastospores to invasive mycelial forms	hot homogenization coupled with the ultrasonication method	fungal infections	Improved Bioavailability, enhanced antifungal activity	[76]
clotrimazole (CLZ) and alphalipolic acid (ALA)- SLN	dimethyldioctadecylammonium bromide	CLZ antifungal activity is related to its capability to interfere with the biosynthesis of ergosterol, the major component of the fungal cytoplasmic membrane, with the consequent depletion of ergosterol and its replacement with the aberrant sterol species, 14-a-methylsterol, thus disturbing the membrane permeability and fluidity	phase inversion procedure	Candida albicans mycosis	potential synergistic treatment of topical infection	[77]
Fluconazole-loaded solid lipid nanoparticles	glyceryl monostearate	NA	hot homogenization via an ultrasonic probe	oral candidiasis	local and systemic effect of FZ-loaded SLNs of candidiasis through the buccal mucosa.	[78]
Itraconazole -NLC	Tricaprylin and Compritol 888	inhibition of the P450-dependent lanosterol C14α-demethylase enzyme, which is an essential step for the conversion of lanosterol to ergosterol in the fungus, leading to the disruption of permeability and function of the plasma membrane		Sporotrichosis	improved cutaneous targeting of the drug, demonstrated antifungal efficacy	[79]
econazole-loaded nanostructured lipid carriers	Glycerol monostearate, Capmul MCM	suppressing the growth of dermatophytes in stratum corneum as well as in epidermis	ultrasonication emulsion technique	dermatophytes	enhanced antifungal activity against dermatophytes	[80]
Luliconazole -NLC	Palmitic acid, Oleic acid	inhibiting 14-alpha-lanosterol demethylase (membrane protein of CYP51 class in the cytochrome P450 superfamily of enzymes involved in ergosterol biosynthesis) in the fungal cell wall	hot melt emulsification technique followed by probe sonication	Superficial Tinea infections	Enhanced antifungal activity of Luliconazole NLC compared to cream form	[81]

Antifungal drugs (SLN and NLC)	Lipids	Mode of action	Method of preparation	Diseases	Findings	Reference
Fluconazole-NLC	stearic acid, oleic acid	NA	emulsification/sonication technique	oral candidiasis	improved anti-candidiasis activity	[82]
Luliconazole-NLC	Compritol 888 ATO, Labrafl M 2125	NA	hot emulsification followed by ultra-sonication technique	fungal infections	Enhanced antifungal activity	[83]

Table 4. Patents on lipid nanoparticles for fungal infection

IN202117035651	Targeted nanoparticles and their uses related to fungal infections
AU2021105626	Development and evaluation of luliconazole loaded solid lipid nanoparticles-based gel for topical application
IN1813/DEL/2011	“A novel solid lipid nanoparticle formulation”
WO2020028916	Amphotericin loaded pegylated lipid nanoparticles and methods of use

voriconazole encapsulation efficiencies and improved cutaneous delivery when compared to SLNs and plain drugs [75]. Recently, topical gels based on lipid nano-carriers were developed to alleviate some of the drawbacks of lipid nano-carriers, such as poor application site retention, limited drug loading, unstable during long-term storage, and the likelihood of drug ejection. El-Housin et al., have investigated the therapeutic potential of Fluconazole-loaded SLNs Cremophor RH40 and Poloxamer 407 topical gel in the treatment of Pityriasis Versicolor. Entrapment efficiency ranged from 55.49 percent to 83.04 percent, according to the findings. Clinical trials revealed a 1.4-fold better clinical response when compared to commercial cream. Although nano-lipid preparations have been shown to increase therapeutic effectiveness and safety in the treatment of essential fungal illnesses [76].

Some of Patents for antifungal drug containing lipid nanoparticle given in Table 4.

8. STATUS OF LIPID NANOPARTICLES FOR FUNGAL INFECTION IN CLINICAL TRIALS

Nanoparticles are becoming more popular as a result of medical applications such as diagnosis and therapy and with an increased number of nanomedicines currently in clinical trials. The key advantages of nanoparticles are their ability to control drug release, distribution, and delivery to a specific site in order to reduce toxicity by inhibiting drug access into other parts of the body. Only a few clinical trials involving lipid nanoparticles for the treatment of the fungal infection are discussed.

Clinical Assessment of Oxiconazole Nitrate Solid Lipid Nanoparticles Loaded Gel (ClinicalTrials.gov Identifier: NCT03823040) was conducted by Minia University on Active Comparator: Tinox® group the male patients (12 to 43 years old) including 5 cases tinea pedis, 9 tinea versicolor and treated with oxiconazole nitrate cream 1% and Experimental: Oxiconazole nitrate SLNs loaded gel group 13 males and one female (17 to 50 years old) including 3 cases tinea pedis, 8 tinea versicolor, 3 tinea circinate and treated with oxiconazole nitrate SLNs loaded gel. Both the group treatment was performed by rubbing the gel twice daily for two/ four weeks according to different types of tinea. phase I study for the Oxiconazole Nitrate Solid Lipid Nanoparticles Loaded Gel is completed [84]. The researchers conducted a clinical investigation on over 30 patients with Pityriasis versicolor to test FLZ-SLNs topical gels, the results of which were compared to Candistan cream. In this study, each patient was followed up by a clinical and mycological assessment every week during therapy to examine the clinical efficacy and safety of various treatment regimens. The authors reported that the formulation appeared to be faster and more effective than topical Candistane [75].

9. CONCLUSION

Fungal infections have become a major public health concern due to their high prevalence. The use of a nanodrug delivery system to enhance the treatment effectiveness, safety, and compliance of antifungal medicines is an excellent technique to overcome the limitations of conventional forms such as cream, gel. This system has shown promising results in terms of increased water solubility, efficiency, and stability of antifungal agents. When compared to other colloidal carriers, SLNs is a complex system with evident advantages and limitations. NLCs were developed to overcome the stability and drug leakage issues of the SLN. Because its disordered crystal matrix prevents drug expulsion resulting in high drug entrapment efficiency. Nanotechnology enables the development of formulations that increase not only the treatment's effectiveness but also the patient's quality of life by lowering side effects, particularly during long-term therapy. Even though using lipid nanoparticles for topical administration is a very promising and appealing application field, more research is required to understand the mechanism of penetration and interaction of nanoparticles.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

FUTURE PERSPECTIVE

Skincare products infused with nanotechnology are quickly spreading over the world and have

proven to be very beneficial in the treatment of fungal skin diseases. Because there are no precise restrictions in place at the moment, these medications are fast proliferating in the personal care industry. However, there are environmental and safety problems. there are several adverse effects that need to be addressed. As a result, there is an urgent need for harmonized rules and guidelines for the use of nanoparticles.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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