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Review Article

Niosomes as Nanocarrier for Onychomycosis Infections: A Review

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ABSTRACT

Although skin is a protective barrier and acts as a defence mechanism against various stimuli, it is prone to infections due to bacteria, fungi, and other pathogens. Most skin infections are caused by fungi, which have thick walls and can spread the infection for days. Therapeutic management of such infections is possible by ensuring a consistent plasma concentration of the drug at a steady-state level at the site of action. Oral azoles, commonly used for treating fungal infections pose problems with solubility and permeability. There is a need to administer azoles for an extended period, leading to drug resistance.

The aim of the current review is to strategize niosomes, which have sparked a lot of interest in creating new transdermal delivery systems as an alternative to oral delivery of antifungal drugs. These systems are dosage formulations designed to release the medicament at rates that differ significantly from their corresponding conventional dosage forms. Niosomes are the delivery system where the drug is entrapped in a vesicle using a non-ionic surfactant.

The method used for writing this review was based on online and internet scholarly works related to transdermal and lipidic systems.

This review provides an overview of the fungal infections, emphasizing onychomycosis, treatment, drawbacks of the conventional approaches, various advantages of niosomes for topical fungal infections, composition, and preparation methods along with the characterization and evaluation, research carried out, applications and prospects.

Keywords: Cholesterol, Onchomycosis, Extrusion, Niosomes, Non-ionic surfactant, Stability.

Introduction

People have remained troubled by transmissible diseases all through the past, and the current COVID-19 (Coronavirus disease 2019) virus is a scary recall persisting in present-day humanity. Contagious illnesses continue as one of the leading causes of mortality internationally.[1] The recurrence rate of acquiring microbial, viral, or fungoid infections increases every year due to the ease of transmission among the people.[2] Quick and successful treatment opportunities will help avoid the circulating disease to secondary organs.[3] Fungal infections are the rigid type of infections that can develop effortlessly and are found to continue throughout a period, triggering immense distress to humanity. Annually, around 150 million severe cases of fungal infections occur worldwide, resulting in 1.7 million deaths per year.[4] Some prevalent species are known to cause infections are Aspergillus, Candida, Tinea, Pneumocystis, Cryptococcus, and Histoplasma.[5] A subcategory of fungal infections comprising athlete's foot, finger and toe-nail infections, oral thrush, and ringworm are widely reported around the globe and are common in Asian countries. These infections can even result in systemic and adaptable infections that enter the bloodstream and cause more dangerous diseases, especially in people with foregone immune systems.[6,7]

This review article covers onchomycosis, treatment of onchomycosis using various molecules like azoles, morpholines, alkylamines. It also emphasizes transdermal drug delivery systems, and the role of nanotechnology especially lipid-based systems-niososmes, its formulation strategies, characterization, evaluation, applications, and prospects.

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Materials and Method

The method used for writing this review was based on online and internet scholarly works. The source includes Taylor and Francis, ScienceDirect, Google Scholar, PubMed, ResearchGate, Scopus, and other platforms for information related to the aim of this work. The search terms included Onchomycosis, Treatment of Onchomycosis, Transdermal drug delivery systems, Lipid-based drug delivery systems, Niosomes, Cholesterol, Extrusion, Film method, Niosomes, Non-ionic surfactant, Stability.

Results and Discussion

Onychomycosis

Onychomycosis (OM) is a recurring fungal illness of the nail accounting for 50 percent of all disorders related to nails. Dermatophytes such as Trichophyton rubrum and non-dermatophyte yeasts, mainly *Candida albicans*, cause this illness. This sort of infection is more common in older folks or people with poor peripheral circulation. It is also reported in patients with diabetes and HIV under treatment with immunosuppressant drugs. Though most nail infections are simply cosmetic issues, they can cause substantial problems that stay for a long duration. Sometimes the patient may have difficulty walking if his/her toe-nail is infected severely. At times it may cause pain during standing and while exercising. All these problems may even cause psychological distress and develop a fear in the patient limiting his/her social behaviour/interactions.

OM can be classified into numerous groups based on where the infection originates.

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A. Distal and lateral subungual OM**:** It is a prevalent type of onychomycosis seen in many individuals. The organism enters the nail via the hyponychium and invades the distal nail bed. Then it slowly spreads to the proximal nail bed.
B. Superficial white OM**:** It develops on the exterior side of the nail. Small shallow pale spots with distinctive edges can be seen on the nail plate, slowly progressing. Topical anti-fungal drugs are sufficient to treat the condition.
C. Proximal subungual OM**:** This generally starts when the contributing agent permeates via the eponychium, which is the crucial site for the organism's attack and is rarely reported.
D. Total dystrophic OM**:** It is an advanced type of infection deemed by total devastation of the nail plate.[8]

Treatment of onychomycosis

Both topical and oral agents are used in the treatment of nail infections (Figure 1). Many marketed oral dosage forms are available for the treatment of onychomycosis. Though oral therapy is considered the gold standard in all age groups, significant adverse effects and potential negative drug-to-drug interactions limit its use. Topical anti-fungal has been reported to have minimal adverse effects, but their poor penetrations limit their usage. The two critical chemical classes of anti-fungals used in treating onychomycosis are (i) Azoles, (ii) Morpholines, and allylamines. A brief note on these are as follows:

Azoles

Around 40 drug candidates with azole structures are currently available, categorized into four generations and hybrids.[9]

1st generation azoles

The 1st generation of azoles evolved with the three compounds: clotrimazole (**1**), miconazole (**2**), and econazole (**3**). These preparations were marketed as dermal drugs creating azoles, a lead molecule in anti-fungals. Miconazole exhibited excellent action against candidiasis and tinea.[10] However, its continuous usage is associated with cardiotoxicity.[11] Luliconazole (**4**), the novel azole from the first-generation legalized by USFDA, has a distinctive vinyl-imidazole scaffold. It exhibits broad-spectrum activity against dermatophytes viz., *Microsporum gypseum*, *Trichophyton rubrum*, and *Epidermophyton floccosum.*[12]

2nd generation
In 2nd generation azoles, the significant modifications in the structure improved the safety, pharmacokinetics, and spectrum of action. The vital revolution in the advancement in the structure of azoles was the incorporation of a triazole swapping the former imidazole ring.[13] The first discovered molecule using the triazole ring was fluconazole (5), followed by itraconazole (6). Compared to the first generation, the second-generation (Fig. 3) showed a significant improvement in the spectrum of activity when administered through different routes. Nevertheless, kinetics and safety profiles were still challenging. Subsequently, the next generation of azoles developed upgraded structures of the second generation.

3rd generation
In growing concerns regarding the high frequency of infections, novel drug candidates were developed as triazole moieties or third-generation azoles. In this generation, major structural modifications were made to improve kinetics and safety profiles with an extended spectrum of activity. More prominently, the scientist designed the structure that could combat infection resistance. Efinaconazole (**7**), a triazole used to treat minor to modest nail infections, acknowledged its leading worldwide consent, resulting in better activity than the oral formulation.[14]
Figure 2 depicts structures of azoles. Additionally, a few more innovative compounds are presently in phase-III clinical trials, like genaconazole (**8**) and iodiconazole (**9**). In phase II, saperconazole X, and in phase I, embeconazole X are in the pipeline.[15,16] Several triazole-linked alcohol hybrids are explored, and many novel and identified skeletons assimilated into their moieties are evaluated for their anti-fungal activity.[17–19]

4th generation
Though the prior generations effectively developed and resolved the issues like; potency, resistance, the spectrum of activity, and kinetic difficulties –a major side effect is known as the 'Achilles' heel' was reported in drug-drug interactions instigated likely by inhibition of human cytochrome P450 (CYP3A4) enzyme.[10]
This is a major concern in immunocompromised patients. After subsequent swapping of imidazole moiety with triazole, the selectivity increased, but the drug resistance still subsists. Substitution of low-avid metal-binding tetrazole ring in the place of high-avid metal-binding was further synthesized and reported as potent fourth-generation azoles; these include Quilseonazole (10) and oteseseonazole (11) (Figure 3).[20,21]

Fusion molecules as impending azole family
Standard combinatorial chemistry or current virtual screening methods are yet to bring a revolution in the search for new drug molecules. Molecular hybridization can be adopted to achieve innovation in anti-fungal drug molecules that are inexpensive and can circumvent the development of resistant strains. Molecular hybridization combines pharmacophoric scaffolds of diverse bioactive constituents to produce an innovative hybrid compound with enhanced efficacy and affinity.[22]
Fluconazole (5), a promising anti-fungal drug with worthy *in vivo* and kinetic efficiency, is fascinated by molecular hybridization technique. Fluconazole (5) derivatives were synthesized by swapping the new triazole heterocyclic ring with added possible moieties directly or utilizing appropriate linkers.[23]
The above-mentioned innovative approach to designing structures makes fluconazole hybrids potential leads.

Morpholines and allylamines
Morpholines (Figure 3) are synthetic compounds that have continued as successful molecules in agricultural applications. Amorolfine (12) is the only compound used topically in treating nail infections and superficial mycoses. Nevertheless, neither of its targets has fascinated the current research attention. Terbinafine (13) (Fig.3) is an allylamine that shows excellent in-vitro activity towards Aspergillus spp., Fusarium spp., and other filamentous fungi.[24]
One of the promising routes other than the conventional (oral) approach for treating superficial fungal infection is delivering the drug transdermal.

Transdermal drug delivery systems
Transdermal drug delivery is a non-invasive controlled delivery of drugs through unbroken skin. Skin is the largest and most accessible organ of the body. It mainly functions as an impermeable protective barrier to entering outer or external environmental substances into the body.

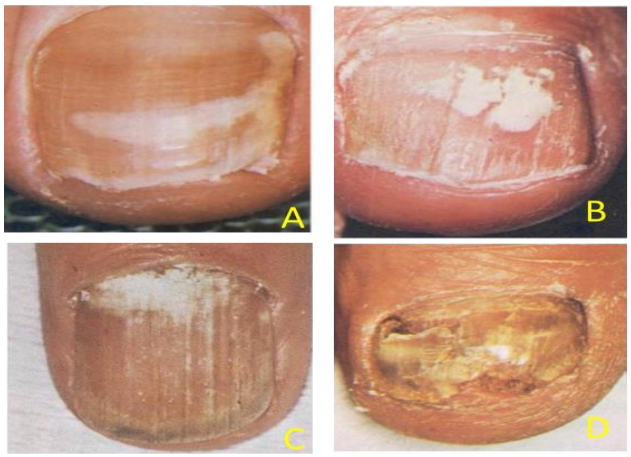

Figure 1: Types of onychomycosis affecting the nails.

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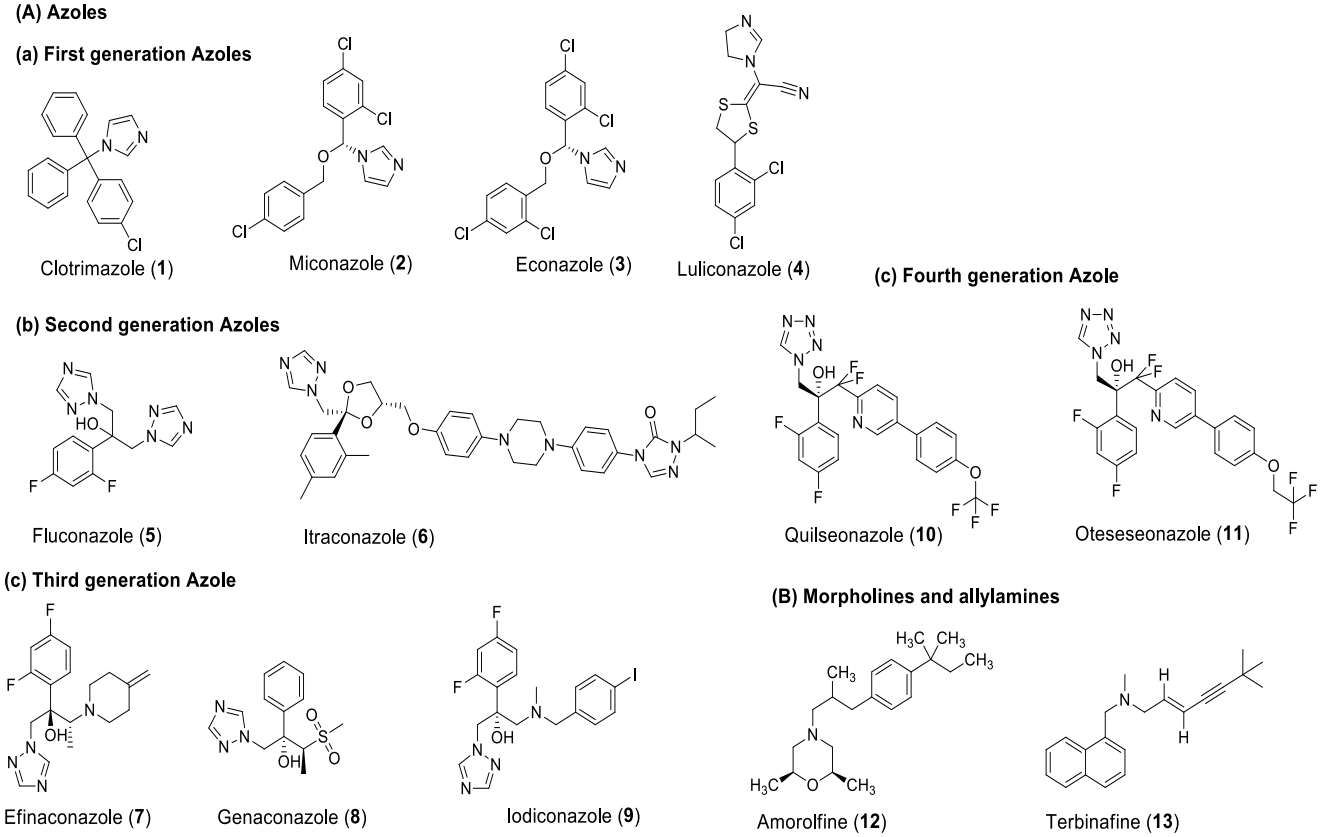

Figure 2: Structures of azoles and other classes of anti-fungals used in onychomycosis.

Transdermal delivery offers many benefits over other dosage forms. These are for zero-order delivery of drugs for many hours to days for chronic conditions where frequent administration is required. Nevertheless, topical anti-fungal preparations such as creams, gels, and lotions may work well. However, side effects such as erythema, redness of the skin, and burning sensation limit their applicability in treating infections.[25] Most anti-fungal drugs are lipophilic and have good skin diffusion ability making them suitable for topical.[26] Hence, delivering the drug topically in a controlled and prolonged manner will help maintain a good level of the drug at the site of infection. However, the anti-fungal drugs have high molecular weight making them challenging to administer topically. One of the importance of topical delivery is that the drugs' molecular weight should be less than 500 Daltons.[27]

Hence nanotechnology is currently being explored by many researchers to address the delivery of such drugs for the topical route. Nanotechnology uses raw material on an atomic or molecular dimension specifically designed to deliver the drugs. When drugs are in nanosized form, entry into the hair follicles is effortless, gets deposited in the layers of the skin, and releases the drug slowly. Apart from the above advantages, it also enhances the drug's stability, availability, and residence time and thereby reduces the dose-related side effects as observed when drugs are administered orally.[28]

In this current review, A sincere effort to present the effectiveness of lipidic nanocarrier systems such as niosomes for the successful treatment of topical fungal infections was made. The review entails its advantages and preparation techniques along with the various evaluation methods used in topical formulation delivery.

The lipid-based nanosystems are considered superior for the topical route compared to polymeric systems due to their ability to release the drug for a prolonged period, apart from their low toxicity, improved bioavailability, and high biocompatibility great drug-loading effectiveness.[29]

The different nanocarrier systems or colloidal carrier systems include microparticles, nanoparticles, polymeric micellar systems, and lipid-based nanosystems.

Lipid-based nanosystems classification

Generally, these systems are divided into three types based on the nature of the state self-emulsifying drug delivery systems, vesicular systems, and non-vesicular systems. The vesicular lipid systems (VS) include liposomes, sphingosomes, niosomes, transfersomes, aquasomes, ufasomes, ethosomes, pharmacosomes, phytosomes, vesosomes, colloidosomes, archaeosomes, and herbosomes.[30]

Vesicular systems are highly ordered structures made of one or more concentric bilayers created because of the self-assembling of amphiphilic structural units arranged when encountering water. These systems were identified in 1965 by Prof. Bingham, also called Bingham bodies. The main advantage of VS is that drug concentration can be localized at the site of actions, and hence drugs reaching the nontargeted organs can be highly reduced.[31] The various advantages of VS are given in Figure 3. Of the various vesicular lipid systems (Figure 4), the role of niosomes in transdermal delivery is being discussed in detail, along with the manufacturing excipients, formulation techniques, characterization, and evaluation techniques.

Niosomes

Niosomes are identified as an excellent vehicle for delivering anti-fungal drugs topically. These systems can solubilize poorly soluble drugs and thereby provide high local concentration serving as a depot in sustaining drug release when used for topical delivery.

Unlike liposomes, niosomes are chemically stable. The other advantages include biocompatibility, low cost, easy handling and storage, and low toxicity.[32]

Basic elements used in the preparation of niosomes

The basic components are cholesterol and non-ionic surfactants, and a charge inducer.

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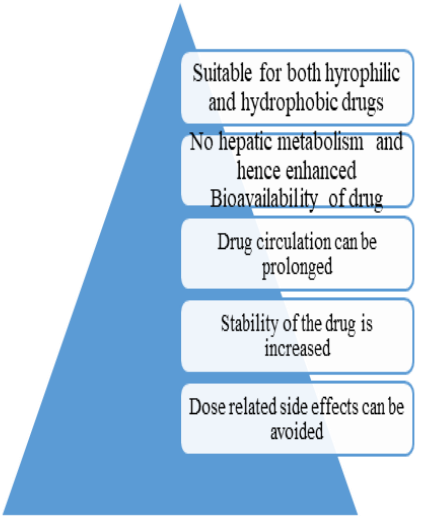

Figure 3: Advantages of Vesicular drug delivery systems.

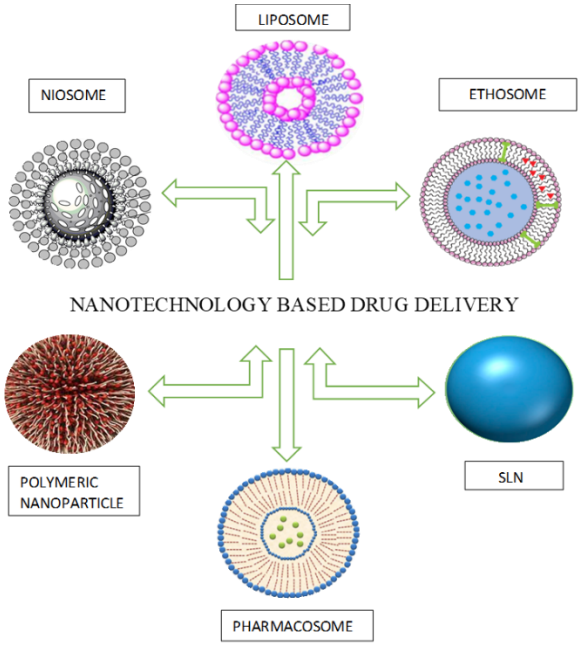

Figure 4: Schematic representation of the various nanotechnology-based drug delivery systems.

Cholesterol**:** Steroids are a key component of the cell membrane. It is mainly used to provide rigid nature with proper shape to the formed vesicles. Their presence affects the layer fluidity and permeability. It is amphiphilic with its OH group orienting in the direction of the aqueous phase and its aliphatic chain in the direction of the surfactants hydrocarbon group. Incorporating cholesterol will inhibit the drug seepage by preventing gel to fluid phase formation.[32]
Non-ionic surfactants**:** These surfactants can form uni and multi-lamellar vesicles and are amphiphilic. Non-ionic surfactants show good biological acceptance. Hydrophilic-lipophilic balance (HLB) value of surfactant plays a significant role in the size of the niosomes. The alkyl chain length is linearly proportional to the size. Non-ionic surfactants include Brij 35(Polyoxyethylene Span 80 (sorbitan monooleate). Tween 80 (Polyoxyethylene sorbitan monooleate) and Tween 20 (Polyoxyethylene sorbitan monolaurate).
These surfactants are considered GRAS grade, very safe, and highly accepted for oral and parenteral, and topical use. Non-ionic or amphoteric surfactants (poloxamer, lecithin, and Tween 80) are commonly employed for formulation design. A pair of surfactants help in controlling the droplet size and enriches the stability of the formulation. The surfactant with a hydrophilic and lipophilic balance (HLB) value of 14 to17 is not ideal for formulation development as it results in low drug entrapment. HLB values 8 have the highest entrapment efficiency.[33]
Charge inducers**:** Adding a charge inducer will improve the strength of the formed vesicles by introducing a charge on the exterior. Charge inducer also prevents the merging of vesicles owing to repellent forces of similar potential on the particles and offers superior zeta potential to the system. Stearyl amine and cetyl pyridinium are used as positive charge inducers, while dicetyl phosphate and the lipoamino acids act as negative charge inducer.[34]

Various formulation approaches are employed for niosomes.
Ether injection
To form vesicles, surfactant: cholesterol ether mixture of approximately 20 mL is slowly injected into 4 mL of aqueous phase (preheated) at 60°C temperature. [35] The ether was removed by evaporation by a rotary evaporator leading to the formation of vesicles.

Handshaking method
The surfactant: cholesterol mixture prepared (10 mL) in diethyl ether was taken in a rotary evaporator; the solvent was evaporated at room temperature to form a thin film. The vesicles were then formed upon hydration with aqueous media.

Ultra-sonication process
In this method, To the aqueous phase, a mixture of surfactant and cholesterol was added, and then probe sonication was performed for 3 to 5 minutes at 60°C. By sonication method, unilamellar vesicles are formed. Sonication can be achieved either by probe or bath sonicator.

Multiple membrane extrusion technique
The surfactant: cholesterol mixture prepared in chloroform is taken into the rotary evaporator, and the solvent is evaporated to form a thin film. The formed film is then treated with aqueous drug liquid and subjected to extrusion using a polycarbonate membrane to form vesicles.

Reverse phase evaporation method
Vesicles are prepared by adding a drug aqueous solution to the blend of ether and chloroform containing cholesterol: surfactant. The mixture is subjected to sonicated at low temperature to form w/o emulsion. The formed emulsion is evaporated under reduced pressure to form a thin film. Phosphate buffer saline (PBS) maintained at 60°C was added to form niosomes.

Micro fluidization method
In this technique, the drug with surfactant solutions interacts at high velocities in the interaction chamber. Because of very high-speed impingement and the energy involvement produces the niosomes. The fundamental benefit of this approach is that it produces homogenous and smaller unilamellar vesicles. Generally, the drug which is not trapped within the vesicles is removed by gel filtration, dialysis, and centrifugation methods.

Characterization and evaluation of Niosomes
The following parameters are evaluated for the formed niosomes, and these are as follows:

Size and morphology
For the size and morphology of the vesicles, various methods such as Dynamic light scattering (DLS), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) are employed. Also, techniques such as freeze-fracture replication-electron microscopy (FF-TEM) and cryo-transmission electron microscopy (cryo-TEM) are employed depending on the availability of the equipment[36]. DLS offers concurrently cumulative data on particle size and valuable information about the uniformity of the solution and particle size. A single quick peak in the DLS profile means the presence of a single population of scatterers. The polydispersity index value of less than

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0.3 indicates a homogenous system. The microscopic methods are primarily used to describe niosomes morphology.

Zeta potential
The surface charge on vesicles is determined by the zeta sizer (Malvern zeta sizer). Overall, charged particles are more stable than uncharged vesicles. [36]

Bilayer characterization
Characterization for bilayer of niosomes vesicles is an important parameter to know the drug entrapment of the loaded drug. Lamellae numbers can be verified by techniques such as Atomic Force Microscopy (AFM), Nuclear magnetic resonance (NMR), and by small-angle X-ray scattering (SAXS). The change of fluorescence probe quantifies the rigidity of the bilayer membrane of the formulations as a function of temperature. Generally, measurement 1,6 diphenyl-1,3,5-hexatriene (DPH; luminous) is combined with the dispersion of niosomes.

Entrapment efficiency (EE%)
It is described as the percentage of drug trapped in niosomes. The unentrapped drug is separated from niosomal formulation by dialysis, gel chromatography, and centrifugation techniques. By adding Triton X-100 of 0.1% or methanol, the vesicles are destroyed, and the amount of drug-loaded is determined either by spectroscopic technique or by high-performance liquid chromatography. [37]

Stability
Generally, the stability of the niosomes is tested by measuring particle size, EE%, and mean vesicle size by storing the formulation under different conditions as per the ICH guidelines for stability testing. At respective time intervals, samples are withdrawn and analyzed for the above, along with the percentage of drug release. [38]

In vitro release
The dialysis tubing method is commonly used for drug release from niosomes. The washed and soaked dialysis bag is filled with formulation and immersed in a buffer solution of respective pH at room temperature, and subjected to stirring or shaking. The withdrawn samples were analyzed for drug content and determined drug release. [39]

Applications
Niosomes have various applications concerning drug delivery to oral, parenteral, and transdermal delivery routes. Many niosomal formulations were patented for dermal applications. Niosomal formulations were reported to treat skin conditions such as psoriasis, vitiligo, inflammation, alopecia, and other cosmetic complications. Applications of niosomes in treating fungal infections and the related research studies are presented in Table 1, along with the study's highlights.

Constraints of Niosomes for topical delivery of drug
In contrast to liposomes, the valuable asset of niosomes is their biochemical stability. These nanocarriers are highly balanced towards oxidation or biochemical degradation and have prolonged stability during storage. [40] Generally, the surfactants employed for niosomes formulation were eco-friendly, non-immunogenic, and biocompatible. No special storage and handling are required for surfactants used in these formulations. Size and surface charge can be manipulated by the method chosen to prepare the same.
It was observed that there could be an aggregation of vesicles during storage, leading to drug leakage. Moreover, the purification of niosomes requires high effort. [41] Techniques such as membrane filtration and heat sterilization are inappropriate for niosomal vesicles. Hence, these fields need extra research work to provide niosomal preparations marketably.

Table 1: Research work reported on niosomal formulations for topical delivery

Name of the drug	Ingredients	Inference
Itraconazole (ITZ)	Cholesterol, span 20,40 and 60 carbopol 940, chloroform and methanol	ITZ niosomal gel was found to increase the drug release and permeation. It also reduced the side effects and improved patient compliance. [42]
Itraconazole	Span 60, cholesterol ethanol & propanol	ITZ formulated niosomes were found to have excellent skin permeation and are efficient in antimycotic activity compared to the marketed formulation. [41]
Ketoconazole (KTZ)	Cholesterol, span 80, tween 80, chloroform, PBS, and distilled water	KTZ-loaded niosomal gel prolonged the drug action compared to Ketoconazole non-niosomal gel and successfully improved the anti-fungal activity. [43]
Econazole (ECZ)	Cholesterol, span 80, chloroform, methanol, triton X	Formulated ECZ niosomes were assessed for drug release, and it was found to extend the release for a day and improve the therapy. [44]
Terbinafine (TBF)	Cholesterol, isopropyl alcohol, citric acid, Tween 60 & 80, Span 60, chloroform, methanol	TBF niosomal gel improves the anti-fungal activity compared with conventional gels. [45]
Oxiconazole (OCZ) nitrate	Span 60, cholesterol, carbopol 934,	OCZ shows maximum drug diffusion and entrapment. The authors reported that niosomal gel was suitable for treating nail infections. [46]

Prospects

In recent years, there has been much interest in developing novel transdermal drug delivery techniques, particularly niosomes, for the treatment of fungal infections. In this research, we looked at many niosomal formulation and development studies for various fungal diseases. Because niosomes are made up of surfactants, formulators must find the exemplary surfactant and surfactant: cholesterol ratio to achieve minimal toxicity, stability, and efficiency. Surfactants that are biocompatible, biodegradable, and low-cost will help niosomal compositions succeed. For even more successful therapy of fungal infections, a focus on enhancing the ability to pass through skin barriers and improving drug penetration is required. More toxicity testing will be required in future preclinical and clinical research. Stability and therapeutic efficiency improvements will pave the way for the commercial manufacture of niosomal drug formulations.

Conclusion

Lipid systems such as niosomes can be considered novel nano-drug carriers to fabricate effective topical anti-fungal drug delivery for conditions such as onychomycosis. They extend a considerable prospect for packing both hydrophilic and lipophilic drugs individually or both drugs simultaneously. Research in this direction is being carried out for many drugs such as anticancer, anti-inflammatory, anti-infective, and many more for various routes of administration along with topical routes. Studies reported that niosomes would enhance the strength of the loaded drug, reduce the drug dose, and target and prolong the drug release at the site. Therefore, niosomes can be considered a promising tool for therapeutics meant for topical delivery.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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