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TREATMENT OF ONYCHOMYCOSIS: CONVENTIONAL AND NOVEL APPROACHES

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ABSTRACT

Onychomycosis, also known as tinea unguium, is a fungal infection of the nail bed or nail plate. It affects approximately 14% of the world's population and accounts for approximately 50% of all nail diseases. Dermatophytes, non-dermatophyte moulds, and yeast are the most common causative organism. It was initially thought to be a cosmetic issue but has recently gained attention due to its persistent nature and difficult treatment with relapses. Onychomycosis is typically treated with oral and topical medications. Although effective, oral antifungal agents are hepatotoxic and cause drug-drug interactions. Topical therapy is more patient-friendly because it does not have these side effects, but it has another disadvantage of improper nail penetration. Efforts have been made for decades to improve topical delivery for the effective treatment of onychomycosis. Mechanical, physical, and chemical methods were used. Despite all efforts, the nail delivery problem remains unresolved. For improved drug permeation and localized therapy, the emphasis has recently shifted to novel drug delivery systems such as nanoparticles, microemulsions, polymeric films, and nail lacquers. This review article discusses both conventional and novel formulation approaches for the treatment of onychomycosis.

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INTRODUCTION

Onychomycosis is a common fungal infection of the nail and accounts for half of all nail infections [1]. Itis reported to influence about 19% of the population across the world[2]. Onychomycosis has a significant impact on patient'squality of life, causing pain, discomfort, and physical impairment. If left untreated, the infection can spread to other nails as well as to other parts of the body [1].It is caused by dermatophytes (e.g., Trichophyton spp.), non-dermatophyte moulds (NDMs, e.g., Scopulariopsis brevicaulis, Acremonium spp., Aspergillus spp., and Fusarium spp.) and yeasts (Candida spp.). Up to 70% of dermatophyte nail infections are caused by Trichophyton rubrum and T. mentagrophytes, but the prevalence and type of infection vary geographically [3].

Onychomycosisis characterized by discoloration and increasing thickness of the nail plate. As the infection progresses, the nail plate becomes brittle and separation of the nail plate from the nail bed may occur [4]. In patients with complicating factors, deformed nails can lead to surrounding tissue damage and leads to secondary bacterial infection. Furthermore, it may lead topsychological, social and occupational limitations thereby affecting the patient's quality of life [5].

The rate of onychomycosis prevalence is frequently determined by the person's age, social class, inclining factor, occupation, living conditions, and climatic conditions, as well as the patient's recurrence incidence [6]. The prevalence is found to be 25% higher in people suffering from HIV or human immunodeficiency virus disease [7]. Researchers in the field have discovered that the disease's prevalence increases with age, which can be explained by the presence of poor fringe course, blood sugar, repeated trauma in the nail region, chronic exposure to pathogenic fungi, poor or low immune system, improper toenail cutting and cleaning, and poor foot cleanliness, wearing of tight fit clothing and shoes [6,7].

Clinically, Onychomycosis is classified as distal and lateral subungual onychomycosis (DLSO), superficial white onychomycosis (SWO), proximal subungual onychomycosis (PSO), endonyxonychomycosis and total dystrophic onychomycosis. Fig 1. shows the classification of onychomycosis[1].

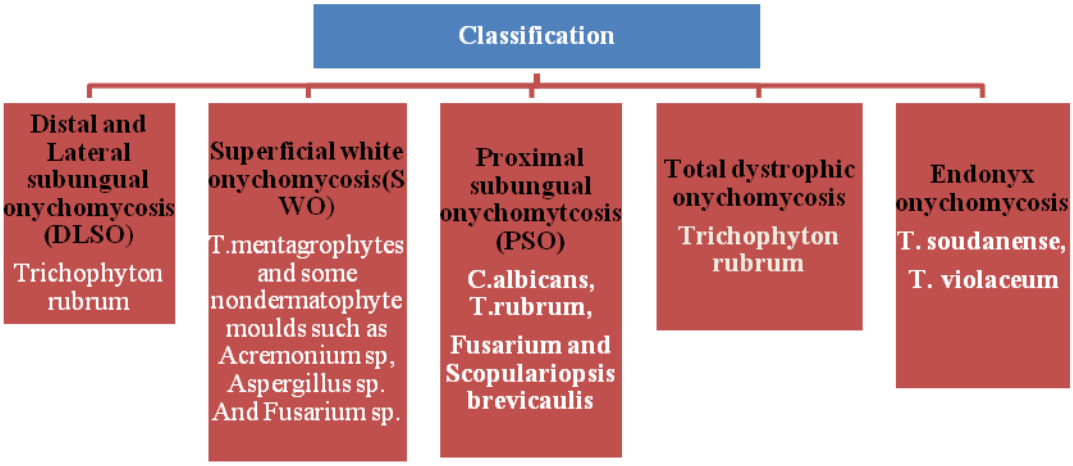

Fig1: Classification of Onychomycosis[1].

Onychomycosis is difficult to treat due to the difficult diagnosis, but a definitive method of diagnosis is required to distinguish it from other nail disorders. Onychomycosis diagnostic procedures include laboratory methods, microscopy, fungal culture, and biopsy. Fungal culture and microscopy are standard diagnostic procedures used to identify and determine the dermatological agent, whereas a biopsy is required to suspect conditions similar to onychomycosis, such as psoriasis. Confocal laser microscopy, dermatophyte test strips, Raman spectroscopy, and fluorescence microscopy are some of the emerging diagnostic techniques for onychomycosis [8].

Onychomycosis is a not life-threatening infection, but if not treated properly can transform into an exasperating problem, which may consume more time to restore its reasonable condition. Onychomycosis is treated with broad categories of antifungal agents, including allyl amines, azoles, benzoxaboroles, and echinocandins [1,9]. The squalene epoxidase is inhibited by antifungal medications in the allylamine class. Terbinafine, Naftifine, and butenafine are all members of this class [10].Azole antifungal medications inhibit CYP450, thus stop the growth of fungi by preventing the conversion of lanosterol into ergosterol by C14-demethylase. Posaconazole, ravuconazole, voriconazole, and ketoconazole are a few examples of azoles antifungal medications used to treat onychomycosis [11]. A 1,3-dihydro-2,1-benzoxaborole lead chemical is the building block of benzoxaborole molecules. The two drugs in this group that are undergoing clinical trials to treat onychomycosis are tavaborole and AN-2718. They provide an alternative method of attacking fungi in onychomycosis because they target protein synthesis. The cell's tRNA stores become unbalanced as a result of their inhibition of the fungal LeuRS tRNA synthetase. In vivo protein production is prevented by this imbalance [12].

This review article provides an overview of conventional and novel formulation approaches for thetreatment onychomycosis.

CONVENTIONAL TREATMENT OF ONYCHOMYCOSIS

1. Systemic therapy

Onychomycosis is typically treated with long-term systemic antifungal therapy. Until the 1990s, the only oral treatment options were griseofulvin and ketoconazole, and the cure rate was extremely low. Fluconazole, itraconazole, and terbinafine are examples of new antimycotics that have improved treatment success [13].

Griseofulvin is approved for use in both adults and children. Griseofulvin is a fungistatic agent that inhibits nucleic acid synthesis, causing cell death. They are reasonably priced. Both fingernail and toenail infections require extensive treatment and have low cure rates. Griseofulvin does not yet have a paediatric formulation. They are not recommended if you have lupus erythematosus, porphyria, or severe liver disease.The main drug interactions are with Warfarin, Ciclosporin, and oral contraceptive pills [14,15].

Terbinafine,an allylamine, inhibits the enzyme squalene epoxidase thus blocking the conversion of squalene-to-squalene epoxide in the biosynthetic pathway of ergosterol, an integral component of the fungal cell wall. Its action results in both depletion of ergosterol and accumulation of squalenewhich causes fungistatic effect and is directly fungicidal. Terbinafine has a very low minimum inhibitory concentration (MIC) of approximately 0.004g ml^{-1}. This is similar to the minimal fungicidal concentration (MFC), indicating that this drug is truly fungicidal in vitro. It is the most active currently available anti-dermatophyte agent in vitro and clinical studies strongly suggest that this is also the case in vivo. It has high cure rates compared with Griseofulvin and Itraconazole. It has short duration of therapy and increased patient compliance. Terbinafine is given at a dose of 250mg daily for 6 weeks for fingernail onychomycosis and 12 weeks for toenail onychomycosis.Side effects include idiosyncratic liver and skin reactions. It has reversible taste disturbance in 1:400 patients. Plasma concentrations of Terbinafine is reduced by rifampicin and increased by Cimetidine [15,16].

Itraconazole has antifungal activity against yeasts, dermatophytes, and some non-dermatophyte moulds. It is not as effective in vitro against dermatophytes as terbinafine.Although it is generally felt to be a fungistatic agent it can achieve fungicidal concentrations, because its MFC is about 10 times higher than its MIC. Itraconazole is either taken 200mg daily for three months or in pulses of 200mg twice daily for a week followed by a three-week break.Monitoring of liver function is required for treatment durations of longer than one month. Itraconazole is contraindicated in pregnancy and not licensed for use in children and has main drug interaction with anticoagulants, antihistamines, anxiolytics digoxin, simvastatin etc [15,17].

Ketoconazole and fluconazole, the two other systemic agents available for oral use, are not approved for nail infection. Ketoconazole may be used in some cases of yeast infection of the nails, but it cannot be prescribed for dermatophyte onychomycosis due to hepatotoxicity concerns [15]. Fluconazole has primarily been used to treat vaginal candidiasis and systemic yeast infections, though it is also effective against dermatophytes. There have been a few published studies on its use in nail infections, but the dose and duration of treatment are still unknown [15].

2. Topical drug delivery

There are several topical antifungal preparations available both as prescriptiononly medicines and on an over-the-counter basis. The active antifungal agent in these preparations is either an imidazole, an allylamine, or a polyene, or a preparation that contains a chemical with antifungal, antiseptic and sometimes keratolytic agents such as benzoic acid, benzyl peroxide, salicylic acid or aundecenoate [10].

Topical therapy seems to be an attractive option due to its non-invasiveness and ability to deliver drugs to the desired site at a faster rate. The advantage of topical therapy includes the absence of systemic adverse events, and drug interactions, enhanced patient compliance and reduced cost of treatment. However, the active drug from the topical formulation must permeate and overcome the highly restrictive barrier properties of the human nail plate [18].

Formulation Options

The process of developing a new chemical entity having the desired pharmacologic/pharmacokinetic profile which allows adequate nail unit penetration is difficult and costly process. Therefore, researchers are more interested in developing a pharmaceutical formulation that would aid in the diffusion of drug molecules through the nail plate, thereby achieving effective drug concentration in the nail bed and matrix.

Formulations like ointments and creams owing to their hydrophobic nature have found limited application in the treatment of nail disorders because nail plate acts as a hydrogel and any formulation that enhances hydration would increase the permeation of the drug through it. As a result, formulations that increase the residence time, increase the hydration level of the nail plate, or provide an occlusive effect are being studied for transungual drug delivery. Because of their occlusive properties, nail lacquers, films, and adhesive patches increase nail hydration, which increases the diffusion of permeating molecules by causing keratin fiber disruption. Gels, on the other hand, improve drug permeation by increasing residence time [18].

2.1. Nail Lacquers

Nail lacquers have been employed as a cosmetic to provide protection to the nails and to decorate the nails. Medicated nail lacquers are a relatively newer type of formulation that has been used for transungual drug delivery. Nail Lacquersconsist of a solution of a film-forming polymer and drug. Upon application to the nail plate, solvent evaporation takes place. The film left behind after solvent evaporation works like a drug reservoir. From this drug store, the drug undergoes release and penetration across the nail for an optimum period. A high diffusion gradient is generated for drug permeation into the nail plate [19]. Film formation on the nail plate also causes a reduction in water loss from the surface of the nail surface into the atmosphere. Hyperhydration of the upper nail plate layers takes place, further assisting in drug diffusion [2]. Table 1 contains commercially available nail lacquer [20].

Table 1: Commercially available nail lacquer [20].

Therapeutic agent	Brand name	Company name
Ciclopiroxamine 8%	Onylac	Dermic, Canada
Ciclopiroxamine 8%	Penlac	Roche lab, Australia
Ciclopiroxamine 8%	Nailon	Protech Biosystem, India
Amorolfine 5%	Loceryl	Protech Biosystem, India
Econazole 5%	Econail	MacrochemCorporation, Lexington

The general nail lacquer contains of solvents, film forming polymer, resin, colouring agent,suspending agents and surfactants. Film-forming agents are an essential component of nail lacquers. Numerousfilm-formingmaterials have been used in nail enamels, like nitrocellulose, cellulose acetate, ethyl cellulose and various other polymers. The purposes of the addition of resins, suspending agents and surfactants to the nail lacquers are to enhance the adhesive property of the film, increase the viscosity of enamel, and improve the drug's wettability and solubility, respectively. Humectants are also a part of nail lacquer composition to improve drug solubility and permeation [21]. The main use of plasticizers in nail lacquer is to increase flexibility, elongate the durability of the film, and decrease its brittleness of the film. The ideal plasticizers have zero volatility, so their effect would persist throughout the life of the film. It should be free from colour,odour, nontoxic and have no effect on the chemical stability of the film forming polymer. It should impart uniform plasticity to the nail enamel over a large range of temperatures [22].

Films formed after the application of nail lacquers are categorized as water-soluble/insoluble films. This classification is mainly based upon the polymer used for film formation. Water-insoluble films, e.g., methacrylic polymers and vinyl resins, provide sustained drug release and are wash-resistant. However, such films require weekly removal either mechanically (nail filing) or with organic solvents; this may adversely affect the surrounding skin [23]. Water soluble films, e.g., hydroxypropyl chitosan, possess a stronger adhesion to and more facilitated drug partitioning/release into nail plates. Hydroxypropyl chitosan-based nail lacquer was shown to improve amorolfine and ciclopirox delivery through bovine hoof membranes as compared to Loceryl® and Penlac® nail lacquers (based on water-insoluble film formers). Hydroxypropyl chitosan has been shown to also accelerate nail growth. This effect helps shorten the treatment period. Water-soluble films are, however, easily washed on exposure to water [24]. To combine advantageous adhesion and drug-release properties of water-soluble films with occlusives and wash-resistance of water-insoluble films, Shivakumar et al. Suggested a bilayered nail lacquer composed of an underlying drug-loaded hydrophilic layer and an overlying hydrophobic layer [25].

Recent time has witnessed the advancement in conventional nail lacquers to improve the penetration of anti-fungal agent into the nail bed. Active agent penetration can be improved further by using penetration enhancers such as thiol compounds, hydrating agents, and keratolytic agents. The incorporation of permeation enhancers in nail lacquer been widely explored to increase drug penetration into the toenail, as a simple and effective technique [26]. Hydrophilic permeation enhancers, such as polyethylene glycols, pantothenic acid, hydroxypropyl-β-cyclodextrin (HP-β-CD) or sodium lauryl sulphate (SLS) has been shown to increase drug penetration across the nail plate by improving the hydration level of the nail plate, forming a porous microchannel, or by decreasing the contact angle between the topical solution and the surface or nail plaque [27].

Traynor et al. used a modified Franz cell to demonstrate the effect of permeation enhancers on two marketed nail lacquers and terbinafine transport across human nail samples in vitro. The permeation enhancing system was found to improve the permeation of both drugs found in nail lacquers and terbinafine through human nails. Furthermore, the ATP assay confirmed that the system improved terbinafine permeation across infected cadaver nails, resulting in decreased levels of ATP equivalent to those of uninfected negative control samples. It was discovered that adding permeation enhancers changes the chemical structure of nails. These enhancers not only improved the therapeutic efficacy of existing topical products, but also initiated terbinafine transungual transport and efficacy [28]. Table 2. Shows examples of Nail Lacquer Reported in the Literature.

Table 2. Examples of nail lacquer reported in the literature.

Drug name	Formulation Components	Outcomes
Luliconazole [29]	HPMC, PEG-400, glycerol, and thioglycolic acid	Formulation stable for 1-month, low drying time, appreciable non-volatile content, and minimal skin irritation with suitable aesthetic coverage.
Terbinafine HCl [25]	Water-resistant film former- poly (4-vinyl phenol) Combination of Eudragit RL 100 (hydrophobic polymer) and Hydroxypropyl cellulose (HPC) LF (hydrophilic polymer)	High permeation and drug retention in the nail plate.
Naftifine HCl [30]	Eudragit RL100, Eudragit RS100, and ethyl cellulose	Release of drug directly proportional to the concentration of Eudragit RL100 in the formulation.
Ciclopirox olamine or clobetasol propionate [31]	Poloxamer 407, methyl-β-cyclodextrin, Nacetylcysteine and hydro-ethanolic mixture	The low concentration of Poloxamer and the use of hydroethanolic mixtures as solvent improved the efficacy of nail lacquer through rapid drying and easy film formation.
Ciclopirox [32]	Solvent-isopropyl alcohol (IPA), alkalizing agent potassium hydroxide, permeation enhancer- urea	Enhanced retention of drug and high permeation compared to marketed formulation.
Terbinafine HCl [33]	Film former-Eudragit RLPO In situ gel-Pluronic® F68	Nail lacquers showed higher retention time as compared to the marketed cream formulation.
14[C]-Ketoconazole [34]	Ethanol, polysilicone-8, panthenol, acrylates copolymer, tocopheryl acetate, phytantriol, butylene glycol, benzophenone-3, and calcium chloride, and fragrance	The cumulative concentrations of ketoconazole achieved using nail lacquers in the deep ventral layer of the nail plate and the nail bed was significantly higher than commercial ketoconazole cream.

Major advantages of topical nail lacquers involve [1]:

1. Nail lacquer prevents reinfection at the beginning of the treatment as it inhibits the adhesion of fungal spores (propagules) on and underneath the nail plate.
2. Nail lacquers form an occlusive lacquer film and increase nail plate hydrations, which ultimately help in enhancing the diffusion of antifungal drug across the nail plate. Hydration enhances antifungal drug diffusion through the nail plate.
3. Additionally, this hydration benefit of nail lacquer helps in the germination of drug-susceptible fungal hyphae and limits the formation and persistence of drug-resistant fungal spores.

2.2. Patches

Nail patches could serve as drug carriers for the topical treatment of nail diseases like onychomycosis. An ideal nail patch should be easy to apply, adhere to the nail plate for the duration intended, release the loaded drug, which can then permeate the nail, be simple to remove cleanly when desired and be aesthetically pleasing. The main benefits of nail patches are that patients do not feel like they are receiving medication, that they are easily removed when needed, and that they improve patient compliance.

A transungual drug delivery patch formulation contains a pressure-sensitive adhesive matrix (PSA), a drug-impermeable backing membrane, a release liner, and other excipients. The release liner and backing layer must be chemically inert, and the backing layer must be aesthetically pleasing and flexible [35].

Typically, the adhesive is a pressure-sensitive adhesive (PSA), which is defined as a material that adheres to a substrate with light pressure and, ideally, leaves no residual adhesive upon removal. It is one of the patch's most important components. The PSA must adhere to the substrate, be biocompatible and compatible with the drug and excipients, be stable and functional once formulated in the patch, provide adequate drug diffusivity, and be acceptable to regulatory authorities. Polyisobutylenes (PIBs), polysiloxanes (silicones), and polyacrylate copolymers (acrylics) are the most commonly used PSAs in skin patches, and there are numerous commercially available options within each of these groups [35,36]

Donnelly et al. developed a 5- aminolevulinic acid bioadhesive patch (ALA). The patch was made from an aqueous mixture of two polymers, tripropylene glycol methyl ether and poly (methyl vinyl ether/maleic anhydride). A 5-h lag time was observed for ALA permeation, followed by an improvement in permeation rate. After 24 and 48 hours of application, drug concentrations of 2.8 and 6.9 mM were found in the ventral layer of the nail, respectively [37].

2.3. In-situ gels

In-situ gels are liquid aqueous solution that turns into gel at physiological conditions [38]. In-situ gels have many advantages, such as ease of administration, reduced dose, improved local bioavailability, increased patient compliance and simple manufacturing procedures [39].Gelation of polymers normally happens due to cross-linkage of the polymer chains. This could be chemical cross-linkage (covalent bond formation) or physical cross-linkage (non-covalent bond formation) [40]. Temperature is the easiest stimulus to manipulate in responsive in-situ gels. The aqueous solutions turn to gel (sol-gel transition) due to an increase in temperature, due to the self-assembly of the polymer chains as a result of hydrophobic interactions. Pluronics ® or poloxamers are the most common example of polymers that change due to temperature modulation [41]

El-sherif NI et al. developed two drug delivery dosage forms, an in-situ gel and a nail lacquer, and tested their ability to deliver TBH encapsulated in spandex carriers to the nail plate. Using the cold method, in-situ gel formulations were prepared using different Pluronics® concentrations and evaluated for sol-gel transition temperature, viscosity, and in-vitro release studies. The nail lacquer formulation was prepared in various concentrations using Eudragit® RLPO as a film-forming polymer and tested for drying time, non-volatile content, water resistance, and in-vitro release studies. Finally, an ex-vivo human cadaver nail permeation study with optimized formulations was used to compare TBH permeation and retention in the nails to a commercially available TBH cream (Lamisil® 1% cream). The optimized in-situ gel formulation G6 demonstrated 51% more retained TBH in the nails (2.050.008 mg/cm^2) than the marketed product Lamisil® cream 1% (1.360.03 mg/cm^2), indicating successful transungual delivery of TBH from the prepared in-situ gels [42].

NOVEL DRUG DELIVERY APPROACHES FOR TREATING ONYCHOMYCOSIS

Oral drug delivery options for the treatment of nail infection have been associated with severe side effects and have the potential for drug-drug interactions which has clear implications for patients' quality of life. Whereas topical antifungal therapy bypasses the systemic side effects of oral antifungal agents, but the efficacy rates are poor for topical therapy as compared to oral therapy and thus requirea long duration of treatment.

The inconvenience of oral and topical therapies and the high relapse rate of the disease call for requirement of the novel therapies. The stability, release and residence time of the drug can be modified by the utilization ofnovel topical preparations comprising colloidal/nano formulations.

1. Microemulsion

Microemulsions are clear, stable, isotropic mixtures of oil, water, and surfactant, which are often combined with a cosurfactant. Microemulsions (ME) are transparent and thermodynamically stable as their droplet size range from 10 to 100 nm and they don't coalesce [43]. It is a promising drug carrier for both transdermal and dermal drug delivery because a large amount of drug can be incorporated in the formulation and the microemulsion ingredients can facilitate drug permeation by lowering the diffusion barrier of the stratum corneum. However, since microemulsions have a low viscosity, their retention in the affected area is quite low. Thus, the addition of gelling agents could increase the viscosity of the microemulsion [44].

Barot BS et al. developed a terbinafine microemulsion gel for the treatment of onychomycosis. D-optimal design was used to optimise the microemulsion components. An optimised formulation with 5.75% oleic acid, 26.87% Labrasol, 26.87% Transcut P, and 40.5% water was chosen. The drug-loaded gel had better skin retention and antifungal activity than the market formulation, the author attributed that this could be due to special characteristics of microemulsion like smaller droplet size, low interfacial tension, and large interfacial area [44].

Chouhan P et al. created a transungual drug delivery formulation of ciclopirox olamine based on microemulsions and a colloidal carrier for the treatment of onychomycosis. Capmul PG8 was chosen as the oil phase, with Cremophor EL and Transcutol P acting as surfactant and cosurfactant, respectively. Pseudoternary phase diagrams were created using various Smix ratios (surfactant:cosurfactant). The phase diagram produced by the 1:3 ratio revealed the largest microemulsion region. D-optimal mixture design was used to further optimise the microemulsion's construction, with oil, Smix, and water as independent variables and globule size, transungual flux, and nail drug loading as response variables. The optimised microemulsion with 2% oil, 40% Smix, and 58% water was mixed into Carbopol 940 gel base and tested for transungual drug permeation. The optimised microemulsion-based gel formulation demonstrated globule size (25.81.2 nm), transungual flux (0.4360.014 g/cm^2 /h), and drug loading in nail plate (82.895.74 g) that were in close agreement with the predicted value of the response variable by the optimization software, i.e., 26.145 mm, 0.431 g/cm^2 /h, and 81.023 g. Based on these findings, the author confirmed that the D-optimal mixture design can be used to successfully design and develop a microemulsion-based formulation of ciclopirox olamine [45].

2. Liposomes

Liposomes have emerged as a promising drug delivery vehicle for increasing the permeation flux of many drugs across the biological membrane**.** Liposomes are colloidal phospholipidic vesicles comprised of lipid bilayers like that of bio membranes existing in humans [46].Among their several possible pharmaceutical applications, they have been widely applied in topical drug delivery.

Tanrverdi et al. developed terbinafine HCl liposome and liposomal gel formulations. Phospholipon 90 G was used as a lipid for preparation of this vesicular system. Because of its added adhesive properties, liposomal poloxamer gel showed better drug accumulation in the nail bed and was easier to apply. This formulation remained on the nail plate for a longer period of time, possibly resulting in a sustained release of terbinafine HCl [47].

Sakshi Singh Chouhan developed Luliconazoleloaded liposomal nail lacquer. Liposome were prepared by modified film hydration technique. Then optimized formulation of liposomal suspension was further used to prepare nail formulation. Among different formulations, the formulation (LF-8) was showed good drug entrapment, average particle size and zeta potential. The optimized formulation of liposomal suspension LF-8 was further used to prepare nail formulation. The luliconazole loaded nail lacquer formulation (LLNLF-4) was showed highest drug release (97.38±3.64), antifungal activity and smoothness in-vitro among the other formulations.The authorconcluded that this techniquecan be used to maximize the topical bioavailability of drug across the nail [48].

3. Nanoparticles

In recent years, there has been a lot of interest in nanoparticles in topical/transungual drug delivery. Nanoparticles in the form of a topical medication can be easily applied to the nail, eliminating the side effects associated with oral medications. Transungual delivery with nanoparticles promotes deeper penetration of the drug into the nail plate, improves retention in the nail plate, and controls drug release, ensuring drug release at the infection site for an extended period of time to maintain the desired therapeutic drug concentration [49].

Ullah KH et al. developed chitosan nanoparticles (CSNP) loaded poloxamer 407 (P407) gel formulation for transungual delivery of terbinafine HCl (TBN) to treat onychomycosis. The developed TBN-CSNP formulation demonstrated good physicochemical properties as well as sustain release. TBN-CSNP loaded P407 gel demonstrated increased sustain release and improved TBN permeation across the nail plate. In addition, CSNP-loaded P407 gel outperformed TBN-loaded P407 gel in terms of nail uptake efficiency. The author concluded that a topical formulation based on prepared polymeric nanoparticles may be a promising candidate for the treatment of onychomycosis, overcoming the issue of frequent application of conventional formulation [49].

Tiwari N et al reported the biological synthesis of zinc oxide nanoparticles (ZnO-NPs) from Rosa indica L. petals extract (rose). Its effectiveness was tested against two dermatophytes that cause onychomycosis, Trichophyton mentagrophytes and Microsporum canis. When antibiotics were tested in combination with ZnO-NPs, their activity against the tested dermatophytes was increased. The authors also developed nanoparticles containing nail paint (nanopaint), and their antifungal activity against T. mentagrophytes and M. canis was tested. ZnO-NPs and nanopaint containing ZnO-NPs both demonstrated significant antifungal activity. The greatest activity was observed against M. canis and the least against T. mentagrophytes. According to the findings of the study, ZnO-NPs can be used as a potential antifungal agent for the treatment of onychomycosis [50].

4. Transferosomes

Transferosomes are a novel type of vesicular carrier. Transferosomes are primarily composed of phospholipids with the addition of sodium cholate as a biocompatible edge activator. Transferosomes high deformability and skin penetration are the most important properties associated with them, in addition to the benefits of their good affinity for skin efficacy and safety. By adding surfactants (such as sodium cholate) to the phospholipid bilayers, traditional liposomes are transformed into transferosomes (TF), also known as ultra-deformable nano-liposomes [51].

TDT-067 is a novel terbinafine formulation in a transferosome particle. Phase II clinical trials have been completed. Because of its hydrophilic surface, transferosomes aid in drug absorption. With a minimum inhibitory concentration ranging from 0.03 to 15 ng/ml, the formulation is effective against Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum. TDT-067 was administered twice daily for 12 weeks in phase II clinical trials. Only 23.5% of patients experienced minor side effects. TDT-067 was found to have more potent antifungal activity against dermatophyte species than naked terbinafine (as used in oral therapy) and commercially available topical terbinafine spray [51].

CONCLUSION

Onychomycosis is difficult to treat due to its invasive and persistent nature. Traditional formulations necessitate a longer treatment duration, which leads to patient noncompliance, adverse effects, and increased costs. The use of nano formulations such as liposomes, nanoparticles, microemulsions, in-situ hydrogels, and transferosomes can help to reduce therapy duration, cost, adverse effects, and relapse rate. These drug delivery systems appear to be promising in terms of drug retention and release. The potential for novel delivery systems to replace traditional methods appears to be quite promising. The future development of nanotechnology will help to meet the various needs and challenges of transungual drug delivery.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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