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REVIEW ARTICLE

Novel Drug Delivery Strategies for the Treatment of Onychomycosis

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Abstract: Onychomycosis accounts for 50% of all nail disease cases and is commonly caused by dermatophytes. It was primarily considered a cosmetic problem but has been garnering attention lately due to its persistent nature and difficult treatment with relapses. With prolonged treatment duration and high cost involved in treating onychomycosis, several attempts have been made in overcoming the rigid nail barrier. The conventional treatment of onychomycosis involves oral and topical therapy. The oral antifungal agents though quite effective, are hepato-toxic and cause drug-drug interactions. Topical therapy is more patient compliant being devoid of such adverse effects but it suffers from another setback of improper nail penetration. Amorolfine and ciclopirox nail lacquers are popular market products. Since decades, efforts have been made to enhance topical delivery for efficiently treating onychomycosis. Mechanical, physical and chemical methods have been employed. Despite all the attempts made, the nail delivery issues are far from being solved. Recently, the focus has shifted to novel drug delivery systems like nanoparticles, microemulsions, polymeric films and nail lacquers for enhanced drug permeation and localized therapy. The research around the world is exploring their potential as effective treatment options. This review intends to further explore the novel delivery strategies to treat a persistent fungal infection like onychomycosis.

Keywords: Nail barrier, nanoparticles, novel strategies, onychomycosis, persistent infection, drug delivery.

1. INTRODUCTION

Onychomycosis was not regarded as a serious infection until quite recently. It started gaining attention after the approval of terbinafine for oral therapy by the US Food and Drug Administration in 1996. This was succeeded by approval of ciclopirox for topical therapy in 1999 [1]. It prevails among around 5% of the total world population and affects toe-nails much more than finger-nails [2]. The incidence of onychomycosis in India ranges from 0.5% to 5% with more prevalence in warm humid climates [3]. Mostly it is caused by dermatophytes, which belong to one of the three genera [Trichophyton, Epidermophyton, and Microsporum], with T. rubrum being the most prevalent of all [4]. Physical manifestations include brittleness of nails, distortion of nail structure and discoloration [5]. Various types of onchycomycosis infections are given in Fig. (**1**).

Treatment options for onychomycosis are quite limited mainly due to deep-seated infection and impermeable nature of nail. The impermeability of nail can be attributed to the highly stable and strong disulfide linkages and hydrogen bonds in

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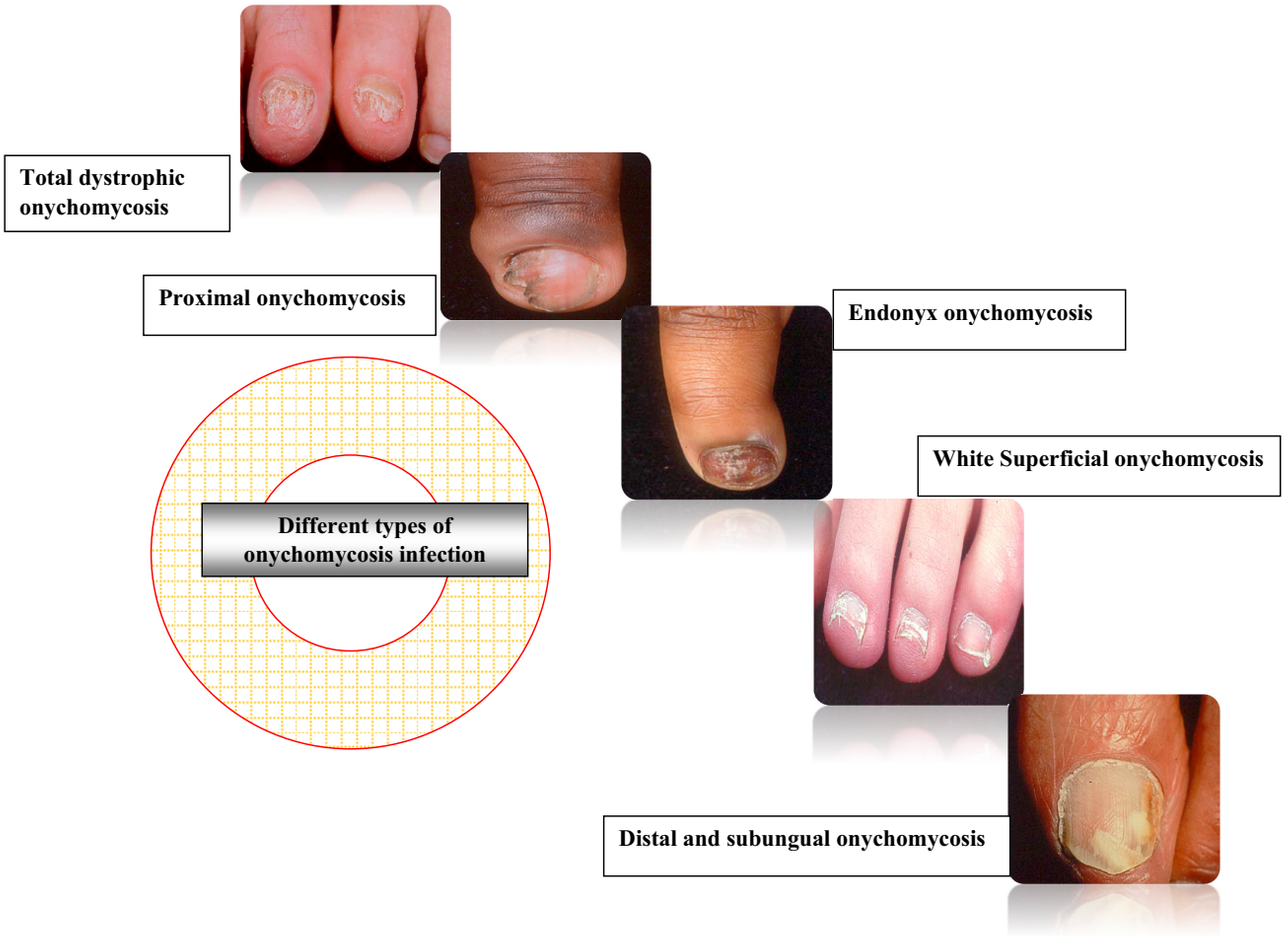

Fig. (1). Various types of onchycomycosis.

keratin network. With hard keratin fibers and globular proteins to hold them tight, nail plate is one of the toughest biological barriers to exist [6]. The oral antifungal therapy for onychomycosis usually lasts long and brings a set of adverse effects, especially hepato- toxicity and drug interactions. With their limited availability at the site of action, the prescribed dose is escalated or the frequency is increased. This not only further increases the associated side effects but also the treatment cost [7, 8]. On the contrary, topical therapy is devoid of such side effects and is convenient to patients but its effect is hampered by rigid keratin structure of the nail which is quite difficult to penetrate. Topical therapy is usually prescribed only in mild cases. Also, the conventional topical formulations get easily removed or washed off from the nail plate while doing chores. Many techniques have been devised to facilitate topical delivery to the nail like mechanical, physical and chemical. Generally, these techniques involve applying topical formulations after therapy to enhance permeation. The mechanical therapy involves complete nail avulsion or nail abrasion with filing the affected part of the nail. The physical treatment modalities include high-end techniques like iontophoresis, phonophoresis, photodynamic therapy or laser therapy. The chemical treatment involves the addition of chemical penetration enhancers to the topical formulation which interferes with the chemical bonding in nail structures and facilitates permeation by breaking the existing bonds. Sometimes the combinations of these techniques with oral or topical therapy are prescribed. But every technique comes with its own set of issues and there still does not exist a method in the market which can provide the desired result in less time [7]. This leaves a lot of space for developing novel strategies to bring about not only efficient drug delivery but also patient compliance. The focus

has shifted from nail lacquers and painful surgical nail removal to nanotechnology for facilitating delivery. Nanoparticles not only promote deeper nail penetration but also drug retention and controlled release. Nanoparticles can ensure site-specific drug release over prolonged duration to maintain the desired therapeutic drug concentration. Encapsulation of oral antifungal drugs in nanoparticles is also capable of reducing the toxicity issues. Apart from nanoparticles, research work on other novel systems have also been carried out like *in situ* gels, microemulsion, polymeric films *etc*. Such novel systems delivered through an appropriate dosage form will serve as useful vehicles for nail drug delivery. This review will focus on discussing such novel strategies which hold a lot of potential for treating persistent issue like onychomycosis [9, 10].

2. CONVENTIONAL THERAPY

For the treatment of onychomycosis, the current therapeutic options are oral and topical drug delivery. But the topical drug delivery, in turn, can be enhanced using mechanical, physical and chemical methods. Cure rate with oral antifungal drugs is high but they are not suitable for use in patients like the elderly or immune-compromised [11]. Longer duration of therapy with oral antifungals causes serious adverse effects like hepatotoxicity, cardiac and gastric disturbances [12]. Drug-drug interactions and regular liver tests are a big inconvenience [13]. On the contrary, topical antifungal agents bypass the systemic circulation and cause little or no side effects. They offer easier application with non- invasive nature and more compliance [14]. They are suitable for geriatric, pediatric and pregnant patients and in the case when the nail matrix is not involved [15]. But the main issue with topical therapy is improper penetration through nails with a higher frequency of infection relapse [16]. Also, topical therapy gives direct and localized therapy which provides minimum inhibitory concentration required to act against dermatophytes. The challenges faced in treating onychomycosis are listed in the Fig. (**2**). Drugs can be administered topically or transungually in the form of nail lacquers, solutions and gels [17]. Nail lacquers offer a new exciting platform for topical delivery [18]. They are applied easily like nail polish and form a film over the nail plate [19].

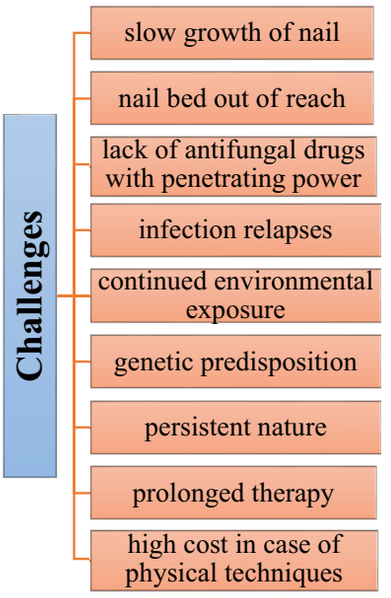

Fig. (2). Challenges faced in treating onychomycosis.

No matter how cosmetic a problem like onychomycosis seems, it still requires treatment, especially in case of diabetics in which it cause complications like cellulitis and gangrene. Oral antifungal drugs are considered the first line treatment for onychomycosis. The conventional treatment usually involves terbinafine or itraconazole as possible oral therapy options. Terbinafine is administered in the dose of 250mg daily for 6 weeks in case of fingernail onychomycosis and 12 weeks in case of toenail onychomycosis. Itraconazole is either administered 200mg daily for 3 months or given in pulses at 200mg twice daily for a week followed by a break of 3 weeks [20]. Such treatment involves 2 pulses for fingernail onychomycosis and 3 pulses for toenail onychomycosis. Another oral drug is fluconazole which is not used usually due to moderate success rates and longer therapy required. Many other novel oral antifungal drugs are being designed specifically for onychomycosis like luliconazole, ravuconazole, posaconazole, *etc*. They are listed in the table. The topical therapy, on the other hand, involves the use of solutions and nail lacquers. The recommended topical therapy involves Ciclopirox 8% and amorolfine 5% nail lacquers with the regimen of amorolfne being 1 to 2 times a week upto 6 months which can extend up to a year. Ciclopirox nail lacquer involves daily application for at least 4 months [21]. Through the therapy sessions, it has been observed that topical therapy alone does not

Table 1. Current therapy available for onychomycosis.

Mode of Therapy	Drug	Dosage Regimen	Advantages	Disadvantages	Contraindications	References
Oral	Terbinafine	250 mg per day for 6 weeks (fingernails) and 12 weeks (toenails) alone or in combination with amorolfine	More effective, less relapses, safer for diabetic patients	Hepatotoxicity, less effective in non- dermatophyte onychomycosis, affects taste and smell, toxic dermal necrolysis	Impedes metabolism of tricyclicAntidepressants, beta blockers selective serotonin reuptake inhibitors and monoamine oxidase inhibitors, should be avoided in breast- feeding mothers.	[12-15]
Oral	Itraconazole	200 mg twice a day for 1 week or pulse treatment of 2 courses for fingernails and 3-4 courses for toenails alone or in combination with amorolfine	Wider spectrum of antifungal activity, more effective in mixed infections, better for Candida onychomycosis	Absorption issues, peripheral Neuropathy, hepatotoxicity	Negative inotropic effects, prohibited in patients with congestive heart failure, drug- drug interations especially with warfarin- like and coumarin- like drugs, should be avoided by breast-feeding mothers.	[16-18]
Topical	Amorolfine	Till the desired results are obtained	Lower minimum inhibitory concentration, better retention in nail plate	Cleaning and abrasion required prior to application, itching, redness, irritation	Not approved for treatment in North America.	[19, 20]
Topical	Ciclopirox	Till the desired results are obtained	Good nail permeability, less resistance development	Nail abrasion is absolutely necessary, complete removal of previous layer is required	Only used when less than half of the nail is affected or oral therapy is prohibited.	[21-23]

offer much benefit. In fact it should not be employed if half of the nail has already been consumed with fungus. But combination treatment gives good results due to synergistic antifungal action of drugs. For example, Lecha *et al.* showed that the combination therapy of 200mg oral itraconazole for 3 months with amorolfine nail lacquer for 6 months gave a good clinical rate of 94% [22]. Even oral terbinafine with amorolfine nail lacquer has delivered good results [23]. Sometimes combination therapy also includes mechanical methods like complete nail removal or nail abrasion along with oral antifungal drugs. Novel physical treatment options have also been designed now, like iontophoresis, laser therapy, photodynamic therapy or ultrasound mediated delivery which enhances topical penetration of drugs [24, 25]. The current therapy available for treating onychomycosis is mentioned in Table **1** and the current penetration enhancement techniques are mentioned in Table **2**.

3. NOVEL DRUG DELIVERY STRATEGIES FOR TREATING ONYCHOMYCOSIS

The chances of relapse in the onychomycosis cases are very high. Current oral therapy poses the risk of hepatotoxicity and drug-drug interactions whereas topical therapy suffers from extremely longer duration of treatment. Both of these situations are inconvenient to patients as well as ineffective due to frequent relapses [49]. This calls for better and effective therapies leading to extensive research in this area. Various novel drug delivery systems like nanoparticles, microemulsions, hydrogels *etc*. have been tried in research across

Table 2. Penetration enhancing techniques for treating onychomycosis.

Category	Technique	Specifications	Procedure	Advantages	Disadvantages	Reference
Mechanical	Nail avulsion	Complete separation of nail plate from other units,	Anesthesia followed by Surgical (physical removal) or chemical (application of urea ointment)	No side effects or long term complications.	Postoperative nail deformity, pain.	[24-26]
	Nail abrasion	Filing or debriment of nail plate so as to increase penetration of topical antifungal drug	Sanding of the nail plate with sandpaper number 150 or 180 attached to dermabrader device	Decreases the critical fungal mass and aids the penetration, better patient acceptability, no complications.	Better efficacy is obtained in combination with topical antifungal agents. Also requires expert help.	[27, 28]
Chemical	Addition of penetration enhancing chemical compounds	Keratolytic agents, enzymes, organic solvents, thiols, mercaptans, hydrophobins	These are added in the topical formulation as penetration enhancers	Enhanced nail permeation, non-invasive, convenient.	Itching, irritation at the site of application.	[28]
Physical	Iontophoresis	Comprises of two electrodes and a power source	Application of small electric current (0.5 mA.cm-2) to enhance penetration	Does not affect nail structure, affordable, patient compliant.	Inappropriate intensity of current, cutaneous side effects.	[28-31]
	Laser therapy	Includes Nd:YAG short pulse and Q switch 1064 nm and the diode 870, 930, and 980 nm	Avulsion/ abrasion of the nail plate followed by laser treatment at 5000W/cm2 power density or applying CO_2 laser beam with daily topical antifungal drug	Bypasses systemic toxicity, non- invasive, no teratogenic risks, no photo- ablation.	Tissue damage, photoageing, too many parameters to be controlled for desired results, less specificity, less information, high cost.	[32-34]
	Photodynamic	Employs a light source to excite the photo-sensitizer to create reactive oxygen species which destroys fungal structure	Delivered in combination with methyl-aminolevulinic acid (three sessions, with 15 days interval) or 5-aminolevulinic acid (once a week)	No relapses, no hepatotoxicity, no interactions with drugs.	Teratogenic risks, slight pain, restriction in exposure to direct sunlight or heat for at least 2 days, improper penetration (for which either urea is employed or microabrasion is done).	[35-38]
	Ultrasound	Low frequency ultrasonic waves improve penetration by forming micropores in the nail structure	400 and 600 kHz frequencies and duration of 120 seconds were found most efficient for application	Enhanced and controlled rate of penetration, no systemic side effects.	Complicated device, expert help necessary, costly.	[39-48]

the field. The same will be discussed following in the review.

3.1. Nanoparticles

Nanoparticles in topical/ transungual drug delivery have gained a lot of attention in recent years. Nanoparticles in the form of a topical medication can be easily applied on nail and also dodge the adverse effects associated with oral drugs. The inclusion of nanoparticles improves drug targeting and also enhances the drug profile and permeation [50]**.** Below are some of the nanoparticles which have been tried for treating onychomycosis.

3.1.1. Nanocapsules

Nanocapsules are nanosized drug delivery carriers that have a core comprising a solid or liquid bound by a polymeric shell on the outside. The core is usually a lipophilic solvent like oil which is employed for enclosing lipophilic/ hydrophobic drugs. Synthetic polymers like poly[lactic acid] [PLA] and poly[lactide-co-glycolide] [PLGA] are usually involved in the preparation of nanocapsules. Encapsulating antifungal drugs in nanocapsules ensures sustained release, antifungal efficacy and enhanced permeation. Some research studies showing the use of nanocapsules delivering antifungal drugs for onychomycosis are discussed below [51].

Flores *et al.* [2013], developed and evaluated nanocapsules and nanoemulsions containing *Melaleuca alternifolia* essential oil [tea tree oil] in an onychomycosis model. The *in vitro* antifungal activities were evaluated against *Trichophyton rubrum* species by two onychomycosis models. The diameter of the fungal colony was measured in both the cases. It was found that the nanocapsules containing tea tree essential oil performed better in reducing the growth of *T. rubrum*. It was also found to facilitate better permeation into the fungal cells [52].

In another study, Flores *et al.* [2016] developed Tioconazole-loaded nanocapsule suspensions with a coating of a cationic polymer for transungual drug delivery. It presented a size of 155 nm for uncoated nanoparticles and 162 nm for those with the cationic coating. The formulations demonstrated good *in vitro* antifungal activity against C. albicans. Pullulan nanobased nail formulation demonstrated good viscosity which is essential for nail application. The nanocapsule suspensions and Pullulan nanobased nail formulation also demonstrated lesser irritancy than free drugs and commercial formulations. Pullulan nano-based nail formulation was found promising for the treatment of onychomycosis [9]. This work has been further extended to the addition of *in vitro* release tests [IVRT] and *in vitro* permeation tests [IVPT]. The effect of nail poration on penetration was also studied. Series of experiments with Nile Red and confocal microscopy utilizing fluorescent marker into the nail plate was employed to observe the pathway and depth of nail penetration. The tioconazole loaded- nanocapsule formulation was found to provide sustained and greater drug release. With the Nile red experiments a penetration depth of 90-160 μm was found to attain after 7 days. Moreover, the nail poration aided in better nail permeation of the nanocapsule formulations [53].

3.1.2. Polymeric Nanoparticles

Since last few years, polymeric nanoparticles have been exploited for novel drug delivery to target various diseases. The reasons behind its success have been biocompatibility, flexible designing, stability and longer duration of action. Polymeric nanoparticles have also found use in treating onychomycosis [54].

For example, Chiu *et al.* [2015], formulated polymeric nanoparticles of poly-[ε-caprolactone] loaded with Nile Red for visualization after topical application. The nails were pretreated with microneedle poration so as to open up pores to facilitate fluorescent probe- loaded polymeric nanoparticles penetration. Laser scanning confocal microscopy was employed to visualize the pathway. Afterwards, two-photon fluorescence and stimulated Raman scattering microscopies were used in combination to further track the Nile Red loaded polymeric nanoparticles and observe their fate. Sustained release of polymeric nanoparticles was clearly observed and the techniques were successful in monitoring the release. Microneedle poration facilitated fluoroscent probe delivery into deeper regions of the nail. The results support the potential of polymeric nanoparticles acting as drug reservoirs in the deeper regions of nail and micronee-

dle poration facilitating drug delivery and deeper nail penetration [55].

A recent research work carried out by Wang *et al.* [2018], demonstrated the potential of ketoconazole-encapsulated crosslinked fluorescent supramolecular nanoparticles as controlled release formulation for treating onychomycosis. The preparation of such novel nanoparticles required a two-stage approach. The nanoparticle delivery was done intradermally *via* tattoo. Nanoparticle characterization revealed good encapsulation efficiency and sustained release of ketoconazole. *In vivo* studies using tattoo were carried out on a mouse model. The results support the use of ketoconazole-encapsulated crosslinked fluorescent supramolecular nanoparticles as an intradermal controlled release solution for treating onychomycosis [56].

3.1.3. Nanoemulsion

Nanoemulsion consists of droplets of a mixture of lipids and surfactants lying within the size range of 10-500nm. It possesses all the characteristics essential for antifungal therapy like stability, improving solubilization issues, enhanced permeation effect and targeted action. They are better alternatives to less stable liposomes [51]. Much research work has been carried out exploiting nanoemulsion for onychomycosis therapy. Many times the nanoemulsion is delivered in the form of gel which has been termed as 'nanoemulgel'. Some studies are delineated below.

Mahtab *et al*. [2016] prepared Ketoconazole nanoemul-gel with the incorporation of permeation enhancer for transungual drug delivery and checked its efficacy in inhibiting the growth of dermatophytes *in vitro*. *In vitro* cumulative drug released at the end of 24 h from formulations NE3, NEG1 and drug suspension were found to be 98.87 ± 1.29, 84.42 ± 2.78% and 54.86 ± 2.19%, respectively. *Ex vivo* transungual permeation studies were performed. The antifungal effect of NEG1 on *Trichophyton rubrum* and *Candida albicans* showed a significant zone of inhibition as compared to drug solution. The results demonstrated enhanced permeation with ketoconazole nanoemulgel [57].

In yet another study done by Kumar *et al.* [2012], nano-emulsion- gel of ciclopirox olamine was developed, evaluated and optimized for treating subungual onychomycosis. The formulation was developed by aqueous phase titration method and was evaluated *in-vitro*. Pseudoternary phase diagrams were constructed and Box Benkhem model [RSM] was employed for optimization. Size and zeta potential were taken as dependent variables and formulation components were taken as independent variables. Series of nanoformulations were developed. Fluorescence microscopy was employed to observe the longer retention capability of the nanoemulsion-gel formulation. So, the study successfully formulated a thermodynamically stable antifungal nanoemulsion gel carrying ciclopirox olamine with prolonged retention capability [58].

3.1.4. Nanovesicles

Vesicular systems have always been fair option while promoting skin penetration. Although vesicles like liposomes, ethosomes, transferosomes have shown their capability as drug delivery systems, yet another new class of vesicles called penetration enhancing vesicles have also shown promise [59]. These nanovesicles have been employed for transungual delivery for nail fungal infections as well. The studies conducted are discussed below.

Bseiso *et al.* [2015], developed and characterized nanovesicles loaded with sertaconazole for transungual delivery. The nano- penetration enhancing vesicles [nPEVs] were prepared using different nail penetration enhancers and characterized. The selected nPEVs formula and the marketed Dermofix cream were compared. N-acetyl-L-cysteine was found to be the optimum nail penetration enhancer for incorporation within vesicles. nPEVs showed high encapsulation efficiency of sertaconazole ranging from 77 to 95%, a size ranging from 38-538nm. Compared to the conventional marketed cream, the selected nPEVs formula showed 1.4-folds higher hydration and drug uptake enhancement into nail clippings and higher zone of inhibition too [6].

Elsherif *et al.* [2016] formulated terbinafine hydrochlo-ride in a spanlastic nano-vesicular carrier that enables and enhances transungual drug delivery. A full factorial design was implemented

to study the effect of different formulation and process variables. An optimized formulation with high entrapment efficiency [62.35 ± 8.91%], average particle size of 438.45 ± 70.5 nm, and 29.57 ± 0.93 was obtained. The release of drug was 59.53 ± 1.73% after 2 and 8 h, respectively. An *ex vivo* study was also conducted in a human cadaver nail plate. The results confirmed that nanovesicular spanlastics exhibit promising results for the trans-ungual delivery of Terbinafine for onychomycosis [60].

3.2. Liposomes

Liposomes are phospholipid bilayered vesicles which consist of an aqueous core and phospholipid outer membrane. The structure is similar to that of natural membrane thereby imparting a unique characteristic for drug delivery. Liposomes have been found suitable for both hydrophilic and hydrophobic drug delivery. Liposomes have been widely employed in topical drug delivery applications due to their advantageous features like biocompatibility, better skin penetration, stability, less toxicity and sustained release. For better stability and controlled release, usually cholesterol is added in liposomes. Moreover, if ethanol is added in lipid vesicles, it becomes ethosomes consisting of phospholipid, ethanol and water. It is believed that liposomes and etho-somes are capable of taking advantage of some lipophilic pathways in the nail which makes them a promising option for nail drug delivery. Several antifungal drugs have already been incorporated in liposomes and ethosomes for topical antifungal therapy [51, 61].

Tanrıverdi and Ozer [2012] conducted a research in which they developed terbinafine loaded liposome and ethosome formulations with their gel forms. Evaluation tests along with *in vitro* and *ex vivo* release studies were also carried out. Nail characterization studies showed changes in the nail surface after application of all the formulations with gel formulations inducing more changes than others. It was found that all the formulations had the potential for efficiently delivering terbinafine to the nail. Moreover, the accumulation studies showed that liposome poloxamer gel formulation was the best regarding better accumulation and easier application to the nail [61].

Tanrıverdi and Ozer continued the research work with others in liposomal formulations for nail delivery by doing another study in 2015. They developed and evaluated a new film formulation of terbinafine hydrochloride loaded liposome. The efficacy of the terbinafine loaded liposome film was compared with terbinafine-loaded liposome, ethosome, liposome poloxamer gel and ethosome chitosan gel formulations. Characterization studies involved drug content estimation, bioadhesive and tensile strength. *In vitro* and *ex vivo* permeation studies were also carried out to identify an optimum film formulation which demonstrated better antifungal activity than the rest. This was done to validate the use of such a novel formulation for treating onychomycosis. It was found that terbinafine-loaded liposome film formulation had better antifungal activity on fungal nails than all other formulations [62].

3.3. Microemulsion

Microemulsion is a thermodynamically stable carrier having low surface tension and droplet size in the range of 10-100nm. It possesses superior qualities like enhanced bioavailability, absorption and permeation. It enhances bioavailability of all kinds of drugs including hydrophilic as well as lipophilic [63]. Undoubtedly, microemulsions have garnered a place for themselves in novel drug delivery systems due to their versatility and ease of preparation. Microemulsions include oil, surfactant, cosurfactant, and water in defined ratios. They have become popular means of delivery for topical and transdermal formulations due to their capacity to hold large amounts of drug and enhancing diffusion across dermal membranes [64].

Barot *et al.* [2011], developed a microemulsion-based gel of terbinafine for onychomycosis therapy. D- optimal design was applied in order to optimize the amount of oil, mixture of surfactant and cosurfactant and water in the microemulsion. The prepared formulations were evaluated for droplet size and drug solubility. The formulation was adapted into gel form with 0.75% w/w carbopol 934P. The optimized gel demonstrated better penetration and retention as compared to commercial formulation. It also showed better antifungal activity against strains of *Candida albicans* and *Trichophyton rubrum*. The optimized microemulsion

based gel showed promising results as potential therapy for onychomycosis [64].

Yet another microemulsion based gels were developed by Kansagra and Mallick [2015] for solubilization and better nail penetration of novel antifungal drug, Luliconazole. The microemulsion was optimized with its components of Olive oil as oil, Capmul MCM as a surfactant and iso propyl alcohol as a cosurfactant. Evaluation tests like particle size analysis, droplet size, spreadability, stability, *in vitro* release studies were conducted. The globule size of the optimized batch was 32.59 nm. The microemulsion based gel demonstrated antifungal activity against *Candida albicans* indicating its efficacy as a formulation in onychomycosis [65].

3.4. Hydrogels/ *In situ* Gels

Hydrogels are hydrophilic polymeric networks which possess the ability to absorb huge amounts of water or physiological fluids. Hydrogels can be synthesized from both natural and synthetic polymers. They have demonstrated good viscosity and bioadhesion without causing any irritation or sensitization. They can be easily washed out and adhere well. Self- assembling type hydrogels are formed in response to some external stimuli like temperature or pH or even concentration. Such systems are called *in situ* gelling systems [66]. The hydrogel solution turns to gel and then to sol [sol-gel transition] due to self- assembly because of hydrophobic interactions. The most common examples of such polymers are Pluronics® or poloxamers which undergo transition due to temperature changes. Such systems offer many advantages like ease of administration, better local availability, simple manufacturing and patient compliance [67]. Hydrogels have been employed in topical drug delivery a lot. The good reputation is due to swelling character, adhesiveness and biocompatibility. Most importantly, incorporation of a drug in hydrogel improves the release kinetics and solubility profile of the drug [68]. Some of the research work targeted at onychomycosis is described below.

Nogueiras-Nieto *et al.* [2013] explored the use of *in situ* gelling hydrogels based on polypseudorotaxanes of Pluronic F- 127 and partially methylated β-cyclodextrin as aqueous nail lacquers. N-acetylcysteine and urea were incorporated as penetration enhancers. The transungual drug delivery of the formulation across human nail was found to be better than a marketed organic lacquer which supports the growing hypothesis that aqueous-based nail lacquers are better drug delivery strategy in nail topical delivery [69].

El-sherif *et al.* [2017] developed two drug delivery dosage forms; the *in-situ* gel and the nail lacquer and evaluated them for their ability to deliver terbinafine hydrochloride [TBH] encapsulated in spanlastic carriers to the nail plate. The optimized *in-situ* gel formulation, showed higher amounts of retained TBH in the nails [2.05 ± 0.008 mg/cm2] compared to the marketed product Lamisil®cream 1% [1.36 ± 0.03 mg/cm2] indicating successful trans-ungual delivery of TBH from the prepared *in-situ* gels [67].

Celebi *et al.* [2014], developed hydrogels and microemulsion -based gel both enclosing terbinafine hydrochloride and assessed their antifungal efficacy. Three different hydrogel formulations were prepared using chitosan, Carbopol 974 and Natrosol 250 polymers. The microemulsion based gel was prepared using Carbopol 974. Comparative release studies were conducted between the formulated gels and the marketed product. The *in vitro* release studies demonstrated that the Natrosol gel exhibited highest drug release, followed by Carbopol gel, chitosan gel, commercial product, and then the microemulsion-based gel. Consequently, Natrosol based hydrogel loaded with terbinafine exhibited highest potential as a topical formulation against fungal infections like onychomycosis.

3.5. Other Novel Strategies

There are many other research studies conducted for developing novel treatment for onychomycosis. Some of these are currently undergoing clinical trials and have shown immense potential in antifungal activity against onychomycosis. These are discussed as follows.

3.5.1. PB-3058

P-3058 is another novel terbinafine transungual solution. Dose finding investigation studies were conducted in patients suffering from mild to moderate onychomycosis with P-3058. P-3058 5%

o.d., 10% o.d. and 10% o.w. gave superior results as compared to P-3058 2% after 24 weeks. A phase IIb still needs to be conducted at a larger scale to determine its efficacy as a formulation [70]. A Multicenter, Randomized, Double-blind, Parallel, Vehicle-controlled Study to Evaluate the Efficacy and Safety of P-3058 10% Nail Solution [NCT02549001] in the treatment of onychomycosis is still being conducted and was expected to complete by October 2018. The study was in Phase III [71].

3.5.2. TDT- 067

TDT-067 is the novel formulation of terbinafine in a transferosome particle. It has completed Phase II clinical trials [72]. Transferosome promotes more drug absorption because of its hydrophilic surface. The formulation is potent against Trichophyton rubrum, T. mentagrophytes, and Epidermophyton floccosum with a minimum inhibitory concentration in the range of 0.03 to 15 ng/ml [42]. Phase II clinical studies involved administration of TDT-067 twice daily for about 12 weeks. Only 23.5% of patients reported mild adverse effects [72]. TDT-067 demonstrated more potent antifungal activity against dermatophyte species than conventional terbinafine formulations [73].

3.5.3. NB-002

Pannu *et al.* [2009], designed NB-002 which is a novel formulation of terbinafine in the form of nanoemulsion. It demonstrated better antifungal activity against major dermatophytes involved in onychomycosis and Candida albicans too. NB-002 includes a penetration enhancer called cetylpyridinium chloride. In a randomized, double-blind, vehicle-controlled trial, sponsored by NanoBio Corporation, participants were administered NB-002 at 0.25% twice daily, 0.5% once daily, 0.5% twice daily or vehicle once or twice daily for 42 weeks. Only mild dermal side effects were noticed. It has completed Phase II clinical trials but the data is not available [74].

3.5.4. Novel Techniques

Novel techniques like device based therapies are gaining a lot of appreciation lately because they circumvent some of the issues associated with oral and topical therapy. These therapies can be used or in combination with antifungal drugs to improve efficacy. The major disadvantage of such techniques is the requirement of a medical assistant throughout the treatment process [75].

Some techniques which have been recently developed are:

Mesoscissioning technology: This technique involves the creation of micro- conduits of 300- 500 microns through the nails. They serve as transporting pathways for drugs across the nail plate.

Nanopatchnail fungus: This involves the application of AC/DC current to facilitate delivery of drugs though nail cuticle. This treatment can be used to target fungus at its source of growth [48, 76].

The recent work done in the field of novel delivery systems for onychomycosis [77-80] is discussed in Table **3**.

CONCLUSION

Onychomycosis remains a persistent and invasive fungal infection with the affected part of nail difficult to reach for treatment. Relapses still happen even after years of therapy and the more technical treatment options come with high cost and requirement of assistance. Moreover, patients are not still comfortable being subjected to iontophoresis or laser therapy no matter how efficient these techniques are. Longer therapies frustrate patients and they have to switch over to the last resort of surgical nail removal. In such a scenario, novel options like nanoparticles, liposomes or transferosomes, seem promising. With negligible side effects, better and deeper drug release and drug retention, these systems have a lot to offer to the antifungal therapy. Coupled with a novel dosage form which can act as an excellent delivery vehicle, novel delivery systems have the potential to replace the conventional therapy in coming years. More attention is being focused on eradicating the long-standing issues associated with onychomycosis and it will not be surprising to assume the solution may well be on its way.

Table 3. Most recent research work done on novel drug delivery strategies for treating onychomycosis.

Category	Year	Novel Formulation	Main Techniques/ Studies	Key Findings	Advantages	References
Nanoparticles	2018	Ketoconazole-encapsulated crosslinked fluorescent supramolecular nanoparticles	Ratiometric mixing, *in vivo* fluorescent imaging, high-performance liquid chromatography, matrix-assisted laser desorption/ ionization mass spectrometry imaging, histology, mouse model, tattoo based delivery.	The nanoparticles showed high encapsulation efficiency, appropriate fluorescence, sustained release and intradermal retention.	Less invasive, localized and controlled release, dodges systemic side effects, can be applied to other diseases as well.	[1]
Nanoparticles	2018	tioconazole-loaded polymeric nanocapsules	Ultrafiltration-centrifugation, *in vitro* release and *in vitro* permeation tests, nail poration, laser scanning confocal microscopy, photon fluorescence, Raman scattering imaging, confocal microscopy.	3 formulations- lacquer, nanocapsule and film were prepared and characterized, almost 100% encapsulation efficiency, were stable, consistent release profile, nail poration provided no leverage, localized therapy observed through Nile Red.	Prolonged release, efficient delivery, greater drug payload, greater penetration.	[2]
Nanoparticles	2017	Voriconazole-loaded nanostructured lipid carriers (NLC)	HPLC, hydration studies, nanoparticles characterization, stability studies, *in vitro* studies with porcine hooves, statistical analysis.	Maximum penetration was obtained with Urea as enhancer, drug release was 78- 86%, formulations were stable, the release kinetics fitted Higuchi model.	Deeper nail penetration, controlled release.	[3]
Nanoparticles	2017	tioconazole Pullulan nano-based nail formulation	Nanocapsule characterization, morphological analysis, Ultrafiltration-centrifugation, *in vitro* release studies, bio adhesion assays, antifungal study, irritant potential through Hen's Egg Test - Chorio allantoic Membrane method.	Homogenous nanoparticles, Newtonian properties, release was bi- exponential, better antifungal activity against *C.albicans*, less irritant potential.	A hydrating formulation so increases permeation easily, better efficacy and deeper nail permeation.	[4]
Nanoparticles	2016	Terbinafine loaded nano-based spanlastic vesicular carriers (nanovesicles)	Ethanol injection method, *in vitro* release studies, 2^4 full factorial design, Differential Scanning Calorimetry, X-ray Diffractometry, *ex vivo* permeation, nail pulverization.	Entrapment efficiency was 8 to 80%, sonication reduce particle size, amorphous, particles were unilamellar and spherical, better drug retention, more drug distribution and deeper nail penetration.	Better drug release and nail penetration.	[5]
Nanoparticles	2016	Ketoconazole loaded nanoemulgel with penetration enhancer	Ultra-performance liquid chromatography (UPLC), Aqueous titration, high-pressure homogenization (HPH), Stress-Stability Studies, Nanoparticle characterization, nanoemulgel evaluation studies, *in vitro* release, tranungual permeation, antifungal activity and histo pathological studies.	Optimized mean droplet size range: 63- 126nm, No phase separation or flocculation occurred, non-Newtonian, pseudo-plastic nature, maximum drug release was approx. 98%, better antifungal activity than drug solution.	Less toxicity and irritant potential, kinetically stable, safe and effective.	[6]

(Table 3) contd…

Category	Year	Novel Formulation	Main Techniques/ Studies	Key Findings	Advantages	References
Spanlastic	2017	Terbinafine loaded spanlastics delivered through novel dosage forms-*in situ* gels and nail lacquer	Ethanol injection method, characterization studies, *in vitro* drug release, 2^3 full factorial experimental design, *ex vivo* nail permeation studies.	Drug permeation was obtained in the order: *In situ* gel> nail lacquer>marketed product.	Greater efficacy, patient compliance, more coverage, no irritation.	[7]
Nail lacquer	2017	Terbinafine delivery *via* liposome-loaded nail lacquer	Thin film hydration technique, quality by design (QbD) technique, liposomes characterization, *In Vitro* Drug Release, Lyophilization, characterization of liposome loaded nail lacquer, *In Vitro* drug permeation, antifungal activity.	Drug permeation was more with liposome loaded nail lacquer than with simple nail lacquer, same antifungal activity as of drug solution, formulations passed all evaluation tests.	Enhanced permeation and more therapeutics efficacy.	[8]
Nail lacquer	2017	Ciclopirox-Based Eudragit RLPO Nail Lacquer	Penetration enhancers screening, 3^3 full factorial design, Physicochemical characterization, *in vitro* release study, *ex vivo* nail permeation, Confocal Laser Scanning Microscopy.	Endopeptidase enzyme was selected as penetration enhancer, better permeation than marketed lacquer, better drug diffusion.	Enhanced permeation, non-invasive, localized therapy.	[9]
Nail lacquer	2017	Terbinafine in polyurethane nail lacquer	Quasi-pre-polymerization method, Fourier Transform Infrared Spectroscopy (FTIR), *In vitro* cytotoxicity assay, Determination of wettability, *In vitro* adhesion test, *in vitro* release study, *in vitro* antifungal activity, positron annihilation lifetime (PAL) measurement.	Contact angle< 90°, no cytotoxicity, better adhesion, lower MIC value, better *in vitro* drug release.	Biocompatible lacquers, Better drug diffusion, hydrophilic nature, nail adhesion.	[10]
Polymeric films	2016	Polymeric films as novel dosage form for onychomycosis	Carboxy methyl cellulose sodium salt (Sod CMC), Chitosan, 2-Hydroxy ethyl cellulose (HEC), (Hydroxy propyl)methyl cellulose (HPMC), Polyvinyl pyrrolidone (PVP), Propylene glycol (PPG) were the polymers used for making films, film characterization, irritation studies, microscopic studies, adhesive studies.	Dry and non-sticky films, no irritation, HEC and HPMC showed swelling, the polymeric films showed stability, flexibility, water resistance and adhesiveness.	Non- invasive, suitable for nail application.	[11]

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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