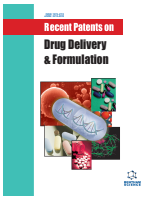
Recent Patents on Drug Delivery & Formulation 2019, *13*, 203-218

REVIEWARTICLE

Recent Patents on Permeation Enhancers for Drug Delivery Through Nails



Tainá Kreutz[1], Sheila Porto de Matos[1] and Letícia Scherer Koester[1,*]

[1]*Graduate Program in Pharmaceutical Sciences, School of Pharmacy, Federal University of Rio Grande do Sul, Av. Ipiranga, Santana, 2752, Porto Alegre, Rio Grande do Sul, Brazil*

ARTICLE HISTORY

Received: August 31, 2019
Revised: October 21, 2019
Accepted: October 24, 2019

DOI:
10.2174/1872211313666191030155837

Abstract: The human nail is a unique barrier with a keratinized constitution that favors protection and fine touch. However, many disorders can affect the nail, among them, are the onychomycosis and psoriasis. Systemic oral therapy has been applied to treat these diseases, even presenting disadvantages, including side effects, drug interactions, contraindications, toxicity, high cost and low patient compliance. A great option to succeed in dealing with the problems associated with oral therapy is the topical administration of drugs. However, nail composition, low diffusion through ungual route and reduced tissue bioavailability for topical treatments are limiting factors. These drawbacks can be overcome by promoting penetration through the nails by employing penetration enhancers. The review focuses on patents that highlight permeation enhancers applied to nail drug delivery for the treatment of onychomycosis and psoriasis. Literature and patent searches were conduced regarding the topic of interest. The substantial literature and patent search revealed that permeation enhancers, especially chemicals, are great strategies for promoting the ungual delivery of drugs. Nail topical therapy containing permeation enhancers is an attractive option for delivering localized treatments.

Keywords: Nail drug delivery, ungual drug delivery, permeation enhancer, patent, onychomycosis, psoriasis.

1. INTRODUCTION

The nail is a unique barrier, constituted by many strands of keratin held together by disulfide bonds, which behaves like a hydrogel and has a compact nature with a particular thickness [1].

Some disorders can affect the nail by altering its coloration and thickness or causing deformation [1, 2]. The conditions with clinical importance are onychomycosis and psoriasis [3]. The first consists of a fungal infection, mostly caused by dermatophytes, with a worldwide prevalence of 5.5%, while the second is an autoimmune disease characterized by an abnormal proliferation and differentiation of keratocytes [4, 5]. Both are persistent diseases whose treatments include mainly oral and topical therapies [6, 7]. The most effective treatment of onychomycosis is orally administered antifungal substances, while psoriasis is effectively treated by systemic steroids [5, 8]. However, oral treatments with antifungal and steroids are often associated with some disadvantages including resistance, long treatment, drug interactions, side effects, contraindications, toxicity, low patient compliance and high cost [3, 9-12]. A great alternative to overcome the drawbacks of oral therapy is to treat these diseases topically, using mechanical, physical, chemical and formulation agents [13]. Despite being the preferred administration route for drug delivery to the nail, topical therapies also have difficulties. Due to its keratinized composition and rigid structure, the diffusion of drugs through the nail plate and tissue bioavailability are reduced, leading to low concentration in the nail bed [14-16]. Moreover, the binding of the drug to the keratin in the nail plate impairs free active drug, diminishing the concentration gradient and limiting the penetration into deeper tissues [17]. In this sense, topical applications fail on delivering an effective concentration of drugs to the affected tissue. Recently, approaches aiming for the enhancement of drug permeation through the nail barrier have been investigated [13].

Permeation enhancers are strategies with the ability to increase the diffusion gradient and permeation through the dense keratinized nail plate by disrupting it mainly by mechanical, physical, chemical and derived from the formulation agents itself [13, 18]. This review brings an overview of the literature and patent search regarding existing and applied permeation enhancers for the treatment of onychomycosis and psoriasis.

2. NAIL ANATOMY AND PHYSIOLOGY

Besides its cosmetic features and social impact, the human nail is an important organ, being analogous to mammalian hooves and claws and acting as a protecting coverage for the

*Address correspondence to this author at the Graduate Program in Pharmaceutical Sciences, School of Pharmacy, Federal University of Rio Grande do Sul, Av. Ipiranga, Santana, 2752, Porto Alegre, Rio Grande do Sul, Brazil; Tel: +55 51 33085278; Fax: +55 51 33085437;
E-mail: leticia.koester@ufrgs.br

2212-4039/19 $58.00+.00

tips of fingers and toes. In addition, it provides the ability to manipulate objects and improves tactile sensation. The most apparent part of the nail apparatus is the nail plate, which varies amongst individuals but normally is presented as a thin, hard, slightly elastic, translucent and convex structure [3].

At first, despite its function and keratinized composition, due to remarkable characteristics as hardness and impermeability, there were attributed differences between the nail and the *stratum corneum* of the skin. The human nail is approximately 100 times thicker than the *stratum corneum*, being the toughest barrier structure of the human body [19, 20]. The molecular structure of the nail plate, comprising keratin molecules interacting through disulfide linkages and the low lipid content gives to this structure a hydrogel-like behavior, distinguishing it from other body barriers [13].

The nail unit is composed of the nail plate, nail bed, nail fold, nail matrix and the hyponychium, presented in Fig. (**1**).

- Nail matrix: located underneath the skin at the proximal end of the nail, is the only living part of the nail apparatus and comprises germinative epithelial tissue, whose cell division gives rise to the nail plate [21];
- Nail bed - very thin epithelium on which the nail plate lies, strongly adheres to and slides over during its growth [1];
- Hyponychium - is the space below the free edge of the nail plate where the latter starts to detach from the nail bed [1];
- Nail folds - proximal and lateral, are skin structures that enclose the nail plate at its lateral and proximal edges. From proximal nail fold, extends the cuticle, which is a physical seal against the entry of exogenous materials [1];
- Nail plate - the most visible part of the nail apparatus, is a thin stratum (0.25-0.6 mm) and is made up of approximately 25 layers of dead, keratinized and flattened cells tightly bond to each other [3];

In general terms, the nail plate is produced by the nail matrix, residing on the nail bed, and is framed and ensheathed by the nail folds and the hyponychium [1, 3, 22].

The hardness and rigidity attributed to the nail plate are especially due to this "sandwich orientation" of the keratin fibers, which are arranged into three layers: dorsal, intermediate and ventral. The dorsal layer is a few cells thick, with skin-type keratin filaments, oriented at the transverse and perpendicular directions to the growth axis. The intermediate nail layer is a softer, more flexible, thicker layer, accounting for the majority of the nail thickness, presenting hair-like keratin filaments, oriented perpendicularly to the growth axis. Meanwhile, the ventral layer is very thin, consisting of a few layers of cells, connecting the nail plate to the nail bed, with keratin filaments similar to the dorsal layer [23]. Hair keratins differ from epithelial keratin (skin-type) by their much higher content of cysteine, which forms numerous chemical cross-links between the filament and the nonfilamentous matrix, increasing keratin stability [24].

In addition, the nail plate is a highly hydrated barrier, which confers its elasticity and mobility [25]. Although there is no consensus on the amount of water comprised in the nail, being between 7-12% [9], 5-30% [25] and 10-30% w/w [18], it is known that this content impacts positively the diffusion of molecules across the nail plate [1]. The nail plate also has the ability to absorb water from the environment, reinforcing the hydrogel feature of the nail. Hydration of the nail plate is an important parameter in nail plate health and for ungual drug delivery [1]. On the other hand, the nail plate has a low lipid content, varying between 0.1-1%, against about 10% for the stratum corneum of the skin, which can be found mostly in the ventral and dorsal layers and are organized in bilayers in parallel to the surface [3, 19]. The nail plate lipids consist of cholesterol sulfate, ceramides, free sterols, free fatty acids, triglycerides, sterol and wax esters, and squalene [26]. In the case of nail disease, the homeostasis of the nail apparatus may be altered, thus modifying the hydration parameters and lipid content [27, 28].

Full fingernail growth occurs in approximately 6 months, whilst the toenail takes about 12 to 18 months to grow completely [3]. The nail growth rate figures about 0.1 mm/day for fingernails and 0.03-0.05 mm/day for toenails, and it can be subject to the influence of several factors, such as gender, age, pregnancy, local and systemic disease, nutrition, trauma/nail biting, hand dominance, weather and chemical exposure [3, 29].

3. NAIL DISEASES AND TREATMENTS

A wide range of diseases and disorders can affect the nail, varying from pigmentation or discoloration to chronic inflammation and fungal infections [30].

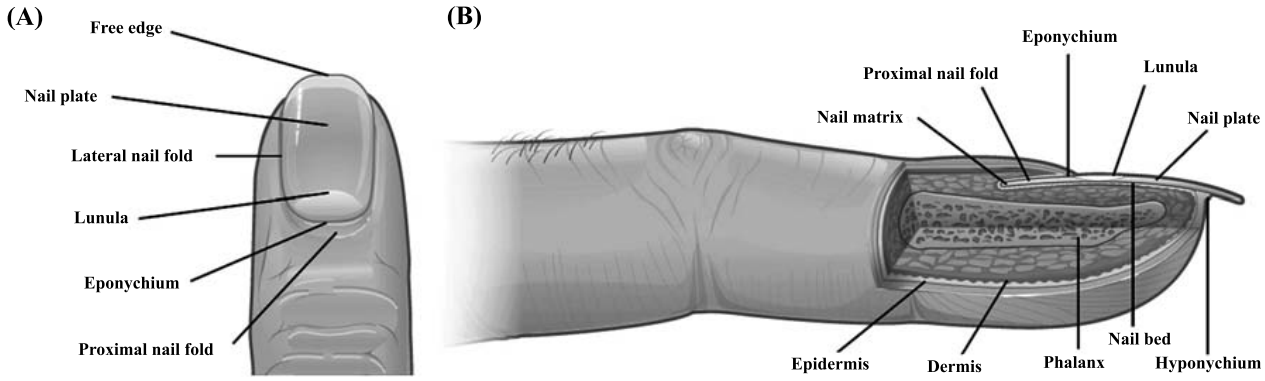


Fig. (1). Top (**A**) and lateral (**B**) view of the nail. Adapted from OpenStax College [CC BY 3.0 (https://creativecommons.org/licenses/by/3.0)]. (*A higher resolution / grayscale version of this figure is available in the electronic copy of the article*).

Mainly, alterations on nails are caused by disorders in the nail plate size and shape, onychomycosis (fungal infections of the nail plate and/or nail bed) and psoriasis [3]. As a result of genetic disorder or birth defects, the nail plate may be totally or partially absent in newborns and children. In other conditions, the nail plate may be excessively long or short, excessively large or small, thickened or hypertrophied, spoon-shaped, with different curvatures, dysmorphic surface and present abnormal color in comparison with the normal ones. All of those disorders are associated to nail plate size and shape and might be related to genetic inheritance, systemic diseases, trauma, nail-biting, occupational hazard, exposure to water and chemicals and infections [1, 30]. Onychomycosis and psoriasis are the most common diseases that affect nails [3]. In this review, those conditions and their associated treatments are approached, mainly because the drug treatments of diseased nails available today have been focused on these two disorders.

3.1. Onychomycosis

Onychomycoses are fungal infections of the nail plate and/or nail bed responsible for almost 50% of all disorders which affect the nail and occur, especially in the elderly population rather than in children [31-33]. Toenail onychomycosis is 4 to 10 times more frequent in comparison with fingernail infection, and requires a longer treatment period [34]. It is caused mostly by dermatophytes, but also by non-dermatophytes and yeast, being the most common nail disorder noticed in clinical practice with a worldwide prevalence of 5.5% [4]. Almost 70% of these infections are attributed to dermatophytes, predominantly *Trichophyton rubrum* (>50%) and *T. mentagrophytes* (about 20%). Other etiologic agents involved in nail infection are *Epidermophyton floccosum*, *Microsporum spp.*, *Aspergillus spp.*, *Fusarium spp.*, *Scytalidium spp.*, and *Candida spp.* [4, 35].

Patients affected by onychomycosis complain of local pain, difficulty in fitting shoes, nail discoloration, nail separation, brittleness or thickening that often worsens with time, becoming a physical and social inconvenience, causing embarrassment and impacting negatively on the quality of life [36].

Onychomycosis can be divided clinically into five categories related to the first location of the infection: a) distal and lateral subungual onychomycosis; b) superficial white onychomycosis; c) proximal subungual onychomycosis; d) endonyx onychomycosis; and e) total dystrophic onychomycosis [3, 4]. The first one is the most frequent type, being characterized by distal onycholysis with hyperkeratosis, nail plate thickening and yellowish to brownish discoloration [4]. The second one is the most common in the pediatric population, usually caused by *T. mentagrophytes*, *Aspergillus spp.* and *Fusarium spp.*, involving the nail plate in localized or wide regions, giving the nail a chalky white appearance and with or without black patches and transverse striate [4, 35, 37, 38]. The third one is a relatively uncommon subtype in which the fungus infects the proximal nail fold and progresses distally, exhibiting lesions containing diffuse patches or transverse striate patterns [4, 39]. The fourth one is commonly caused by *Trichopyton soudanense* and *T. violaceum* characterized by fungal invasion of the nail plate without infection of the nail bed, presenting lamellar nail split and milky patches of the nail plate [4]. Finally, the last one is considered the last stage of onychomycosis with the entire nail plate and bed infected by the fungus characterized by nail plate dystrophic and crumbled aspect [3, 4].

There are basically four treatment protocols for onychomycosis, which consists of oral drugs, topical drugs, a combination of oral and topical drugs and mechanical removal of the nail plate. The last one can be the most effective option in cases of lateral nail plate infection. However, since the introduction of newer treatments, it is rarely indicated to the treatment of severe onychomycosis [6]. Oral systemic treatments with antifungals are highly recommended for patients affected in at least 50% of the distal nail plate, in the nail matrix, or in multiple nails, and for patients whose conditions have not responded after 6 months of topical therapy. The main oral treatments for onychomycosis are terbinafine, itraconazole and fluconazole [8]. Topical monotherapy is indicated for superficial white onychomycosis, and is an interesting alternative in distal subungual onychomycosis, which affects less than 50% of the surface area without matrix involvement [40]. Almost 75% of all onychomycoses fall into this category [6]. Furthermore, it is recommended when a few nails are infected and indicated for children due to the facility [6, 39]. Topical antifungals currently used are mainly ciclopirox and amorolfine [8]. The combination of oral and topical therapies may also be prescribed and is an attractive option for onychomycosis as it can improve prognosis and help in reducing systemic exposure [6].

3.2. Nail Psoriasis

Psoriasis is a chronic, autoimmune and incurable skin disease that impacts significantly on the patient's quality of life and social interactions. The degree of severity varies and is influenced by genetic and environmental factors. Manifestations on the skin are the most characteristic findings in psoriasis, while disorders and symptoms on nails provided from the disease are often neglected [5]. Around 80 - 90% of the patients suffering from skin psoriasis develop nail psoriasis, which brings with it even more pain and aesthetic concerns [41]. Its pathogenesis is associated with the abnormal proliferation and differentiation of keratinocytes due to immune response. Exogenous and endogenous antigens that provoke immune responses activate dendritic cells and the last ones interact with the T cells located in the upper epidermis in perivascular location resulting in the generation of inflammatory response. Once the T cells migrate into the skin, they are now capable of inducing changes within the keratinocytes. $CD8^+$ cytotoxic T cells and type 1 $CD4^+$ T helper cells release large quantities of type 1 cytokines, interleukin-2 (IL-2), interferon-gamma (IFN-γ) and Tumor Necrosis Factor-alpha (TNF-α) that results in keratinocyte hyperproliferation, angiogenesis and inflammatory response associated with the characteristic lesions of psoriasis [5, 42, 43].

The most common nail psoriasis manifestations are pitting, onycholysis, nail bed discoloration, subungual hyperkeratosis, abnormalities of the nail plate and splinter hemorrhages [22].

Regardless of many recent advances in terms of treatments being proposed to skin psoriasis, no "gold standard"

of treatment is recommended and the options for nail psoriasis are still limited [44]. The great difficulty recognized in clinical studies is that the existing treatments have restricted patient compliance and short-lived remissions. As nail psoriasis tends to be persistent and refractory, the treatment depends on patient motivation and compliance and it is often restricted to nail dystrophy [5].

The management of nail psoriasis can be divided into topical, intralesional, radiation, systemic and combined therapies. Systemic therapy is an alternative for patients whose nail disease tend to be resistant to the other therapies and is only indicated to ones that also present skin symptoms [5]. Methotrexate, cyclosporine and acitretin are used as conventional systemic treatment options. New biological agents such as adalimumab, entracept, infliximab and ustekinumab have also been indicated for nail psoriasis therapy [5, 7, 45]. Topical therapy can be a convenient alternative to oral therapy, being supported by the use of 5-fluorouracil, anthralin, tazarotene, cyclosporine, glucocorticosteroids (*e.g.*, betamethasone, clobetasol propionate, fluocinolone acetonide and triamcinolone acetonide) and vitamin D3 [1, 5]. Radiation, such as UVA (ultraviolet A light phototherapy), PUVA (UVA potentiated with psoralen, a photosensitizer), SRT (superficial radiotherapy), Grenz rays, electron beam, UVB (ultraviolet B light) and NB UVB (narrowband UVB) can also be employed in order to treat psoriasis [5, 46]. Intralesional therapy consists of injecting small doses of a corticosteroid directly into or near the region of the nail apparatus that has the nail dystrophy [5]. This kind of therapy has relevant limitations associated with atrophy of the nail plate and the underlying nail bed and bone, hematomas and pain [47, 48]. The most frequently used steroids are triamcinolone acetonide, triamcinolone diacetate, betamethasone, methyl-prednisolone and prednisolone tebutate [5]. Despite the fact that monotherapy can often be a successful approach, many patients frequently require a treatment method that combines the use of two or more treatment modalities in the association, which has the potential of being more successful in managing nail psoriasis [5].

4. LIMITATIONS ON NAIL TREATMENTS

Nail disorders can have various origins, including exposure to chemicals agents, infections, trauma and congenital, hereditary, systemic and local diseases [1]. The appropriate treatment will depend, obviously, on the cause, severity of the disease, patient population and choice, and cost-effectiveness [1, 6]. As aforementioned, the long period of treatment, recurrence in high rates and low compliance of the patients are important remarks in therapeutic conduct [16].

In the case of onychomycosis and psoriasis in nails, the current standard of treatment is oral therapy due to the success rate [7, 11]. However, in systemic treatments several aspects concerning therapeutical safety, such as side effects, drug interactions and risks associated with hepatic injury may limit their desirability, especially in the elderly population that is the most affected by comorbidities, being an obstacle for managing these diseases [3, 10-12]. Furthermore, systemic treatments for onychomycosis have a significant limitation related to poor blood circulation in the nail apparatus, leading to poor drug transport [49]. In this sense, oral therapy has found a restricted success rate due to drug interactions, side effects, contraindications, toxicity and high treatment cost [9].

To overcome the disadvantages associated with oral treatment, topical therapy is desirable especially due to its local effect, resulting in reduced or inexistent adverse systemic events and side effects, as nausea, vomiting and liver dysfunction, and improved treatment compliance [13]. Topical treatment is also appropriate for patients who are reluctant to oral medicines or have swallowing difficulties [6].

Nevertheless, topical nail therapy has been underestimated mainly due to poor penetration of drugs into the nail plate and difficulty in achieving adequate bioavailability of therapeutic agents in the nail [15, 16]. The low efficiency of topical formulations may also be related to patient reduced compliance [12]. To accomplish the pharmacological effect overcoming the disadvantages associated with the nail penetration and to improve patient acceptance, new treatments have been emerging for ungual administration with a focus on altering the nail plate barrier by means of physical and mechanical methods, chemical treatments, formulation characteristics and penetration enhancers [13].

5. PERMEATION ENHANCERS APPLIED TO TOPICAL ADMINISTRATION TO THE NAIL

With regard to the topical nail administration of drugs, many nail diseases can be effectively treated only if the administered drug is able to penetrate through the dense keratinized nail plate [9]. However, there are several aspects that impact in drug transport across the nail plate, such as nail physical conditions (hydration and thickness), physicochemical properties of the drug molecule (shape, conformation, size, charge and hydrophobicity), formulation characteristics (drug concentration and vehicle), presence of permeation enhancers, and interactions between permeant and nail plate keratin network [1, 3, 13]. Most strategies for promoting the ungual delivery of drugs rely on the use of nail permeation enhancers [1]. With absent or few side effects, commonly associated with transitory local rash and sensitivity, most permeation enhancers can be easily removed from the nail if necessary and they are a great alternative over systemic delivery for onychomycosis and nail psoriasis [50, 51]. In order to improve the penetration of drugs through nail, some approaches are proposed, comprising mechanical, physical, chemical and those intrinsic to formulation [13].

5.1. Patent Search Methodology

In order to assess the current status of the development concerning permeation enhancers of drugs across the nail barrier, a patent search was carried out. Patent database Espacenet (worldwide.espacenet.com) was employed in the search, which consisted of a patent survey sort by priority date over a period of 10 years (2008 - 2018). At first, a patent search matching the terms “nail”, “fungal”, “antifungal”, “psoriasis” and “antipsoriasis” with truncation symbol (*) in the title or abstract was performed in order to evaluate the number of patent priority requests over the cited lapse time, from which 244 results were retrieved. Furthermore, a patent search with keywords “nail”, “fungal”, “antifungal”, “psoria-

sis", "antipsoriasis", "enhancer", "permeation" and "penetration" with the truncation symbol (*) in the title or abstract was also made to assess the number of patent priority requests focused on enhancers to nail drug delivery and were disregarded from the patent search the ones out of scope, with missing information or confusing translation. From this search, 31 results were retrieved of which 25 were considered relevant within the subject of the present review. The results are summarized in Tables **1** and **2**.

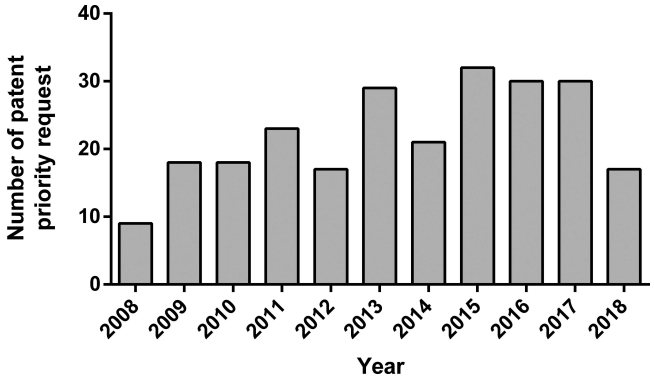


Fig. (2). The number of patent priority requests over 10 years, matching the search terms "nail", "fungal", "antifungal", "psoriasis" and "antipsoriasis" with the truncation symbol. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

As it can be noted in Fig. (**2**), the number of patent priority requests increased gradually over the years, peaking in the last 4 years with about 30 requests each year. The year 2018 presented only 17 patent priority requests, since some patents were still unpublished and, consequently, unlisted. These findings denote the recently increasing interest in developing new ways to treat fungal infections and psoriasis, since these diseases are persistent. The development of new forms to evaluate drug retention in nails and sensitive analytical equipment also influenced this raise over the years [2].

Despite the increasing interest of treatments of nail disorders, this result does not necessarily reflect the interest in the use of permeation enhancers. Fig. (**3**) presents the number of patent priority requests over 10 years containing terms "enhancer", "permeation" and "penetration" with truncation in the patent title or abstract. A decline in the use of these terms in the title or abstract in 2018 in comparison with 2008 is noticeable. This effect may be attributed to the fact that inventors sometimes do not declare in the title or abstract the details of the invention, making it often only possible to find the terms associated with permeation enhancers in the patent body. Even so, it can be noted that permeation enhancers are still in vogue when it comes to treatment against fungal infections and nail psoriasis.

With regard to the number of patent priority requests sorted by the applicant (Fig. **4**), the predominant *stratum* of interest in permeation enhancers for nail drug delivery resides primarily on companies, followed by independent applicants and lastly, the universities. This demonstrates the great interest of private companies regarding the use of permeation enhancers for nail drug delivery.

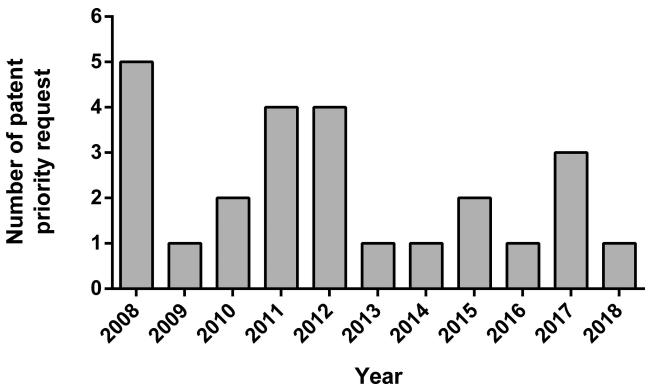


Fig. (3). The number of patent priority requests over 10 years, matching the search terms "nail", "fungal", "antifungal", "psoriasis", "antipsoriasis", "enhancer", "permeation" and "penetration" with the truncation symbol. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

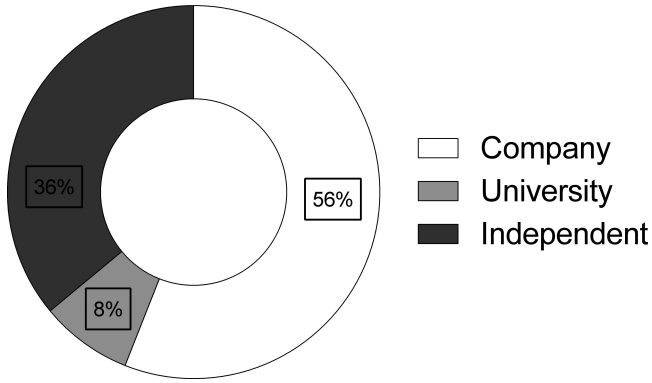


Fig. (4). The number of patent priority requests over 10 years sort by the applicant, matching the search terms "nail", "fungal", "antifungal", "psoriasis", "antipsoriasis", "enhancer", "permeation" and "penetration" with the truncation symbol. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Additionally, the percentage of patent priority requests sorted by country (Fig. **5**) was also evaluated. It is important to highlight the United States of America when it comes to patent filings containing permeation enhancers for nail drug delivery, with almost 50% of patent priority requests. Japan and China also filed significant patent priority applications, with about 30% of the total. Other applicants come from countries of the European and Asian continents. These results denote a hegemony of applicants of the aforementioned continents together with the United States of America. No South American, African, or Oceanian applicants were found.

Moreover, it is noticeable in Tables **1** and **2** a much higher interest in promoting permeation for the treatment of onychomycosis than psoriasis. This fact is believed to be related to the worldwide prevalence of onychomycosis, as aforementioned, being the most common nail disorder in clinical practice [4].

In view of these results, it is imperative to better understand which permeation enhancers are used and how they work.

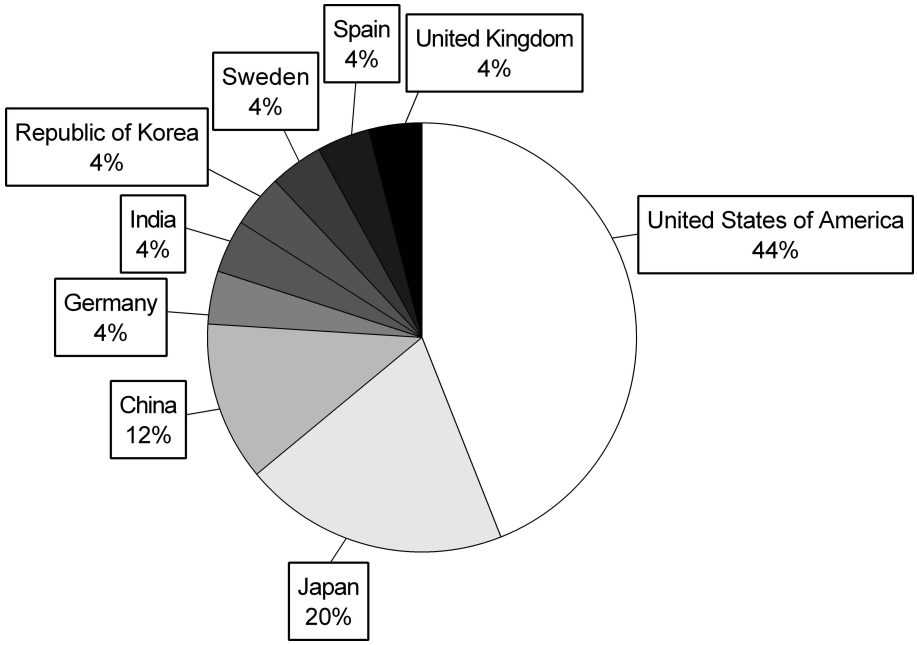


Fig. (5). The percentage of patent priority requests over 10 years sort by country, matching the search terms "nail", "fungal", "antifungal", "psoriasis", "antipsoriasis", "enhancer", "permeation" and "penetration" with the truncation symbol. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

5.1.1. Mechanical Permeation Enhancing Techniques

Mechanical methods to enhance nail penetration include abrasion and nail avulsion. Those methods are invasive and can be extremely painful. The nail abrasion implies in a procedure of thinning the nail plate with sandpaper in order to decrease its thickness or remove it completely and to decrease the fungal mass in cases of onychomycosis. This technique impacts on the aesthetic aspects of the abnormal nail, by improving its contour, and also makes the nail bed more prone to the contact with antifungal chemicals [13, 30]. Furthermore, the nail avulsion is a surgical procedure that involves the total or partial separation of the infected nail plate from the nail bed [13]. No patents were found concerning this approach.

5.1.2. Physical Permeation Enhancing Methods

Physical methods to increase penetration of drugs include iontophoresis, etching, lasers, electropulsation, ultrasound, ultraviolet light, microneedle, hydration and occlusion. These procedures are considered superior to chemical methods in terms of delivering hydrophilic and macromolecular agents [13, 17]. Patent search results comprising physical permeation enhancing methods are shown in Table **1**.

Etching consists of a formation of profuse microporosities allowing the therapeutic agent to penetrate due to roughness and increased surface area [13, 30, 52]. Microneedles are also applied to offer an increased permeation of drugs creating pores and holes in the nail plate, which provides sites that able drugs to penetrate [53]. In order to enhance penetration by promoting pores in the nail, US2014371751A1 patent reflects a device for automatically controlling the drilling through a nail infected with onychomycosis. In this invention, the control system advances the cutter through the nail whilst monitoring the position of the cutter and automatically stops from advancing preventing the entrance on the nail bed, which can cause pain. As the device consists of a physical permeation enhancer, once the cutter has perforated the nail, a suitable antifungal agent can be applied [54]. Moreover, US2018207414A1 patent presents a nail treatment kit for onychomycosis comprising a cap having a 1 mm thickness circular blade and a container with antifungal treatment, removable from each other. When attached, the device can be inverted, contacting the circular blade with the surface of a nail infected with a fungus, rotated, teasing holes in the nail, and the container can be compressed, dispensing the antifungal treatment. The treatment kit can be used in various nails, limiting the application region to the infected parts [55].

Electropulsation technique may enhance drug delivery due to permeabilization caused by structural changes in the dorsal layer of the nail plate, which depends on the voltage, length of electrical pulses and frequency [1]. Furthermore, ultrasound-mediated delivery proposes the drug distribution to the target site by cavitation from a low-intensity ultrasound [1, 56].

Phototherapy by ultraviolet light consists of the incidence of a radiation beam forming craters into the nail by disrupting the molecular bonds through ablation [57]. Besides, lasers and pulsed lasers expose the nail to a specific electromagnetic beam, which may disrupt the integrity of keratin chains removing nail layers, making holes in nails favoring the delivery of the drug on the target site [13]. US2013211481A1 patent is related to a handheld antifungal treatment for onychomycosis comprising a light source that generates visible light which can be directed to an infected area such as a beam of light. The light source can form a beam of light in a range of the electromagnetic spectrum between 100 - 1200 nanometers, including infrared radiation,

Table 1. Physical permeation enhancers.

Title	Publication Number	Priority Number	Priority Year	Propose	Technology	Type of Permeation Enhancer	Description of Permeation Enhancer
Simple device for treating *tinea unguium*	US2011245785A1; US8814837B2 [62]	JP20080292958 20081117 JP20090107244 20090427 JP20090205412 20090907 WO2009JP05808 20091102	2008	Onychomycosis	Device	Physical	Positive pressure
Enchanced trans-keratin drug delivery	WO2010011354A2; WO2010011354A3 [64]	US20080137925P 20080805 US20080135960P 20080725 US20080135984P 20080725 US20080137262P 20080729 US20080135961P 20080725 US20080135983P 20080725	2008	Onychomycosis	Device	Physical	Heat
Controlling drug transport and current in iontophoretic onychomycosis treatment	US2011066134A1 [59]	US20100755989 20100407 US20090167261P 20090407	2009	Onychomycosis	Device	Physical	Iontophoresis
Bubble-type *tinea unguium* treatment implement	JP2012115596A [63]	JP20100270402 20101203	2010	Onychomycosis	Device	Physical	Positive pressure
Medical device for controlled nail penetration	US2014371751A1; US9826983B2 [54]	GB20120000005 20120101 WO2012GB53174 20121218	2012	Onychomycosis	Device	Physical	Electromechanical system and a single use cutting component
Hand held system for antifungal treatment	US2013211481A1; US8888829B2 [58]	US201313766577 20130213 US201261598838P 20120214	2012	Onychomycosis	Device	Physical	Visible electromagnetic radiation
Nail penetration device for delivery of anti-fungal treatments	US2018207414A1 [55]	US201815877759 20180123 US201762449245P 20170123	2017	Onychomycosis	Device	Physical	1 mm-thickness circular blade

with the ability to illuminate and heating the target area. The inventors proposed that the radiation is able to penetrate through the nail without damaging it and heat the fungus to the point that it dies [58].

Iontophoresis is a non-invasive technique that delivers compounds across the nail by applying an electric field [13, 30]. US2011066134A1 patent discloses an iontophoretic treatment system for onychomycosis using drug applicators targeting either nail only or nail and surrounding tissue. Simultaneous iontophoretic delivery with terbinafine administration improved the antifungal concentrations and transfer efficiency to the nail [59].

Meanwhile, hydration and occlusion play an important role on the enhancement of penetration, since hydrated nails

have increased pore size which may be related to transungual penetration, and occlusion reduces water loss, tend to normalize ceramide concentration and water binding capacity, leading to the reconstruction of water and lipid homeostasis in dystrophic nails [60, 61].

Other physical penetration methods are being developed in order to improve topical efficiency [13]. One of them is US2011245785A1 patent consisting of a dome-shaped applicator, constituted by an elastic material, which has an open part provided with a flange for adhesion. The device can be filled with liquid containing antifungal agents under pressure using an injector, which allows drug therapy to penetrate deeply in the nail by positive pressure. As suggested by an inventor it is possible to let the antifungal agent penetrate into a deep part of the nail by merely hermetically bonding the dome-shaped applicator, avoiding evaporation or leakage of the solvent of the liquid antifungal agent. The rubber material constitution may be with polybutadiene-based rubber, butadiene-acrylonitrile-based rubber, chloroprene-based rubber, acryl rubber, acrylonitrile-butadiene rubber, isoprene rubber, silicone rubber and others, preferably butyl rubber [62]. Moreover, JP2012115596A patent demonstrates a bubble-type onychomycosis treatment device consisting of a capsule with a structure in which the antifungal drug is injected and that can be easily released by pressing it. The capsule, having a portion with low bonding strength being constituted of resins such as polypropylene or polyethylene, is inserted in an elastic applicator having the fringe part which hermetically adheres to the nail surface affected by onychomycosis. The content of the capsule is leaked by pressing and pushing the applicator releasing the antifungal agent in the nail, thus allowing the drug to penetrate into the nail [63]. Additionally, WO2010011354A2 patent describes a system and method for enhancing permeation of "anti-infective" agents using heat to improve "trans-keratin drug delivery" through the infected nail in a dark, warm and moist environment and consists of a device in which a holding apparatus attaches a drug delivery mechanism to the digit. The drug delivery mechanism consists of the anti-infective-agent in its pharmaceutical dosage form and a heating device, where the anti-infective agent is in direct contact with the dorsal surface of an infected nail [64].

In addition, there are chemical permeation promoters, which turn drugs able to penetrate by disrupting keratin bonds from nail but maintaining its integrity [1]. These enhancers are the main focus of this review and are best exposed in sequence.

5.1.3. Chemical Permeation Enhancers

Chemical permeation enhancers are chemical substances, which act by destabilizing and weakening the physical and/or chemical bonds of the nail keratin and so increasing penetration of active compounds through the nail plate [2, 65]. Chemical permeation enhancers for ungual delivery are discussed in a few reviews [1, 13, 18], however, there is no consensus among them when it comes to the classification of these permeation enhancers. The ungual penetration enhancers existing up to date were categorized as solvents, keratolytic agents, compounds that cleave the disulfide bonds, enzymes, miscellaneous and etchants [1], and are described below and summarized in Table **2**.

5.1.3.1. Solvents

Solvents as water, dimethyl sulfoxide and methanol have the ability to enhance permeation of drugs to the nail plate [1].

The aqueous pathway plays a leading role in drug penetration through the nail. Since the nail plate has the tendency to hydrate and swell similarly to hydrogels, the increased distance between the keratin fibers due to swelling results in enlarged pores and thus, enabling molecules to diffuse through the nail [3]. After hydration, the nails become more elastic and more permeable to substances applied topically [66, 67]. The increase in nail plate hydration can enhance the drug diffusivity within the nail plate, as previously reported for ketoconazole by Gunt and Kasting [66].

Dimethyl Sulfoxide (DMSO) has been proposed as a nail permeation enhancer after some reports have described its ability to facilitate drug transport as antimycotics and caffeine [68, 69]. Despite its mechanism of action still uncertain, it is proposed that the presence of DMSO alters the lipid concentration of the nail plate improving transungual drug delivery [1].

Methanol proved to be an effective penetration enhancer when employed on formulations. This solvent may induce structural changes on the dorsal nail surface, increasing its roughness, and thus increasing the penetration of caffeine across the nail plate, as demonstrated by Vejnovic and coauthors [68]. Despite being a good solvent for lipophilic drugs, its toxicity limits its use [68].

5.1.3.2. Keratolytic Agents

Keratolytic agents are chemicals with the aptitude of breaking disulphide bonds, which connect keratin strands. In other words, they have the ability to disrupt the tertiary structure and hydrogen bonds in the keratin, destabilizing the keratin network enlarging diffusion pathways and helping on drug permeation [1, 2, 70]. Keratolytic agents are mainly urea and salicylic acid [71]. Quintanar-Guerrero and coauthors studied the influence of keratolytic agents on the *in vitro* permeation of imidazole antimycotics finding that these permeation enhancers can fracture the surface of the nail creating pathways for drug penetration [71].

5.1.3.3. Compounds that Cleave the Disulfide Bonds

Compounds that cleave the disulfide bonds are mainly composed of thiols sulfites and hydrogen peroxide groups [1].

Thiols are a class of compounds that contain sulfhydryl groups (-SH) with a promising ungual penetration potential. Their mechanism of action involves reducing the disulfide bonds in the keratin on the matrix of the nail, destabilizing the fibers and promoting transungual drug delivery [3]. In this sense, permeation enhancement is attributed to the cleavage of disulfide bonds by reduction or oxidation [65]. Some of the chemicals comprised in this group are pyrithione, n-acetylcysteine, cysteine, thioglycolic acid, 2-mercaptoethanol, and N-(2-mercaptopropionyl) glycine [18, 70].

Moreover, sulfites also have the ability to increase the transungual flux by interacting with the nail keratin and re-

ducing the disulphide bonds [2, 18]. They react with the disulfide bonds in proteins or peptides to produce thiols and thiosulphates, and those last ones, after formation, reduce the disulfide bond in the keratin matrix infringing on the barrier property [1]. Sulfites agents are sodium sulfite and sodium metabisulfite [18, 72].

Hydrogen peroxide is also a transungual penetration enhancer, being the only oxidizing agent, whose mechanism is related to oxidizing and cleaving the disulfide bonds, thus enhancing nail permeability [1]. It can be associated with other penetration enhancers to improve permeation through the nail plate [73].

5.1.3.4. Enzymes

Proteases are specific enzymes that may hydrolyze keratin bonds of the nail, leading to impairment of barrier character thereby increasing transungual diffusion through nails [2].

One of them is papain, a plant endopeptidase enzyme that contains highly reactive sulfhydryl groups, which may degrade the surface of the nail and increase permeability for drugs applied topically [71]. Keratinase is another protease, a keratolytic enzyme, which may hydrolyze nail keratins acting on both intercellular matrix and dorsal nail corneocytes, thereby corroding and weakening the nail barrier, favoring transungual drug permeation [74].

5.1.3.5. Miscellaneous Class of Penetration Enhancers

Inorganic salts, hydrophobins and dioxolane are included in miscellaneous class of penetration enhancers [1].

As evaluated by Nair and coauthors, some inorganic salts are able to enhance penetration through nail by increasing the hydration of the nail plate. These salts investigated were ammonium carbonate, calcium carbonate, potassium carbonate, sodium sulfite and sodium phosphate [75].

Hydrophobins are amphiphilic fungal proteins, which are able to reduce the surface tension and adhere to hydrophilic and hydrophobic structures. There are currently three identified hydrophobins, hydrophobin A, B and C, which appear to act as coating and protective agents, promoting permeation of drugs by covering molecules, and acting as a surfactant to increase nail drug delivery [65, 68, 76].

The 2-*n*-nonyl-1, 3-dioxolane, known as SEPA® (soft enhancement of percutaneous absorption), is a compound suggested to exert a plasticizing effect by promoting a film formation, adhering to the nail and contributing to penetration of drugs [77].

5.1.3.6. Etchants

Etching agents are used to modify the nail by disrupting its dorsal surface, causing microporosites within the nail plate, so increasing surface area. Phosphoric acid and tartaric acid are applied as etching agents [78, 79]. Repka and coauthors have shown that phosphoric acid promoted the penetration of ketoconazole in the nail, whereas for tartaric acid, its use to effectively deliver topical treatments is suggested based on studies due to the ability to modify the nail surface [52, 79].

5.1.3.7. Important Patents on Chemical Permeation Enhancers to Nail Drug Delivery

Several patents have been taken over on chemical permeation enhancers for nail drug delivery. Many of them exposed more than one type of enhancer in the same request and for this reason, they are summarized together below. In addition, Table **2** also addresses the patents found.

US2016235847A1 patent consists of the use of a metal chlorite salt (chlorine dioxide, a disinfectant agent) as a penetration enhancer for antifungal agents for the treatment of onychomycosis, with or without applying heat to the infected nail [80].

JP2010126532A patent provides a solution comprising an antifungal agent as terbinafine in combination with a plant essential oil or a component of it as terpenes which may be applied in the area and surrounding area affected by dermatophytes fungi. Terpenes, in this case, are characterized by molecules constituted with 10 carbon atoms (monoterpene) and 15 carbon atoms (sesquiterpene). Plant essential oils comprised in this invention were palmarosa oil, lavender oil, patchouli oil, while components were geraniol, linalool and nerolidol. Inventors proposed that administering plant essential oil or essential oil component combined with an antifungal agent may increase the concentration of the antifungal drug at the infected site [81].

CN102844026A patent discloses a nail composition comprising a proton source in the form of an organic acid (preferably citric acid or acetic acid), which may also present a humectant, a film-forming agent, a penetration enhancer agent (as thioglycolic acid, sodium thioglycolate, potassium thioglycolate, urea or other keratolytic agents) and a solvent, typically water. The formulation may also comprise other excipients, as panthenol and preservative agent, additional solvent and UV inhibitor. As described by the inventors, the formulation developed was more effective against some fungal infections than Loceryl®, a commercially available antifungal, presenting a kill rate of 80% when applied weekly and about 99% when applied daily, against ranges from 75% and 80% at the same periods for Loceryl® [82].

JP2018048159A patent comprises a method of treatment and treatment consisting on an anhydrous or substantially anhydrous pharmaceutical formulation capable of permeating into a nail and treating fungal infection comprising at least one therapeutic agent as iodophor, at least one antifungal agent, dimethyl sulfoxide and a naturopathic substance, such as tea leaf extract. The treatment exhibits good results against nail infections [83].

RU2013136147A patent describes an anhydrous formulation containing allylamino antifungal compound (as terbinafine and naftifine), carboxylic acid or alkyl ester, diol (as propanediol and butanediol) and a complexing agent of amino acetic type. The formulation can also comprise permeation enhancers as urea, sulfhydryl group-containing amino acids and keratin degrading agents. The inventors affirmed the invention provided an increased permeation of the therapeutic agent in the nail, increasing the efficiency of therapy [84].

Table 2. Chemical and intrinsic to formulation permeation enhancers.

Title	Publication Number	Priority Number	Priority Year	Propose	Technology	Type of Permeation Enhancer	Description of Permeation Enhancer	Pharmaceutical Form
Nail fungus treatment and composition	US2016235847A1 [80]	US201615139075 20160426 US20090587495 20091007 US20090387119 20090428 US20080203375P 20081222 US20090207268P 20090210 US20080125790P 20080429	2008	Onychomycosis	Formulation	Chemical	Chlorine dioxide	Non specified
Promotion of antifungal agent absorption	JP2010126532A [81]	JP20080328700 20081128	2008	Onychomycosis	Formulation	Chemical	Plant essential oils as palmarosa oil, lavander oil, patchouli oil, and components of essential oils such as geraniol, linalool and nerolidol	Solution
Penetrating carrier, antifungal composition using the same and method for treatment of dermatophytes	WO2010037089A1 [92]	US20080194508P 20080929	2008	Onychomycosis	Formulation	Formulation	Combination of turpentine (pine oil) and at least one of peppermint oil or mineral oil or one or more essential oil alcohols (such as menthol, eugenol, eucalyptol, cinnamyl alcohol, linalool, charvicol, terpinols anethole, geraneol, and terpinols)	Liquid carrier system
Fungal nail treatment composition	CN102844026A [82]	WO2011GB50379 20110225 GB20100003336 20100226	2010	Onychomycosis	Formulation	Chemical	Thioglycolic acid, sodium thioglycolate, potassium thioglycolate, urea or other keratolytic agents	Solution
Antifungal composition for treatment of skin and nail	JP2018048159A; JP6273065B1 [83]	US201161518709P 20110511 US201261600268P 20120217 US201161627148P 20110919 US201161518689P 20110511 US201161518690P 20110511 US201161457699P 20110516	2011	Onychomycosis	Formulation	Chemical	Dimethyl sulfoxide	Solution

Table (2) contd….

Title	Publication Number	Priority Number	Priority Year	Propose	Technology	Type of Permeation Enhancer	Description of Permeation Enhancer	Pharmaceutical Form
Novel antifungal composition	RU2013136147A; RU2587064C2 [84]	SE20110050107 20110211 WO2012EP52327 20120210	2011	Onychomycosis	Formulation	Chemical	Urea, sulfhydryl group-containing amino acids and keratin degrading agents	Solution
External preparation for treating ringworm and method for applying the same	JP2012162511A [85]	JP20110040790 20110208	2011	Onychomycosis	Formulation	Chemical	N-methylpirrolidone, crotamiton and salicylic acid	Hydrogel or patch containing hydrogel
Film coating agent for treating onychomycosis and preparation method thereof	CN102488702A [86]	CN201110432920 20111221	2011	Onychomycosis	Formulation	Chemical	Lauryl alcohol, azone, borneol, camphor, isopropyl myristate, ethanol, glycerol, isopropanol, polyethylene glycol 400, dodecyl methyl sulfoxide, urea and ethylenediaminetetraacetic acid	Polymeric film
Excipient system for topical delivery of pharmaceutical agents	AU2017272269A1; AU2017272269B2 [87]	AU20170272269 20171207 AU20130227981 20130910 US201261698898P 20120910 US201261698875P 20120910	2012	Onychomycosis	Formulation	Chemical	Alkyl lactate and *Simmondsia chinesis* seed oil	Serum
Topical pharmaceutical compositions comprising terbinafide and urea	EP2664327A1 [88]	EP20120003791 20120514	2012	Onychomycosis	Formulation	Chemical	Dimethyl sulfoxide, urea, N-methyl pyrrolidine and N, N-dimethylacetamide mainly	Cream, gel, suspension, lotion, foam, spray, aerosol and solution
Formulation and evaluation of itraconazole loaded niosomal gel for the treatment of onychomycosis	IN3107DE2013A [93]	IN2013DEL3107 20131018	2013	Onychomycosis	Formulation	Formulation	Niosomes	Gel
Treatment of nail disorders	US2016008274A1 [89]	US201414326186 20140708	2014	Onychomycosis and psoriasis	Device	Chemical	Chemical penetration enhancers like dimethyl sulfoxide, urea, salicylic acid and others	Pad or covering

Table (2) contd….

Title	Publication Number	Priority Number	Priority Year	Propose	Technology	Type of Permeation Enhancer	Description of Permeation Enhancer	Pharmaceutical Form
Nail lacquer composition containing ciclopirox	US2018104227A1 [94]	KR20150043724 20150328 WO2016KR02333 20160309	2015	Onychomycosis	Formulation	Chemical and Formulation	Improvers of hydrophilic property of the film membrane such as polyvinylpyrrolidone and alkyl cellulose, and penetration enhancers such as urea, salicylic acid.	Nail lacquer
Pharmaceutical composition for treating leuconychia	CN105193726A; CN105193726B [95]	CN201510749055 20151108	2015	Onychomycosis	Formulation	Formulation	Vesicle solution	Solution or cream
Nanoparticle compositions and methods for treating onychomychosis	US2017209490A1; US10201571B2 [96]	US201715415562 20170125 US201662286768P 20160125	2016	Onychomycosis	Formulation	Chemical and Formulation	Metal nanoparticles mixed with a penetrating solvent	Solution, cream, lotion, gel, powder, jelly
External preparation for treating trichophytosis unguium	WO2019088005A1 [90]	JP20170209136 20171030	2017	Onychomycosis	Formulation	Chemical	Ethyl lactate	Non specified
Composition for treating onychomycosis	WO2019105793A1 [97]	EP20170204960 20171201	2017	Onychomycosis and topical psoriasis (not ungual)	Formulation	Chemical and Formulation	Microemulsion and Urea	Microemulsion pure or incorporated in nail varnish
Plant extraction formula applied to onychomycosis and *tinea pedis*	CN109303815A [91]	CN201811545147 20181217	2018	Onychomycosis	Formulation	Chemical	Azone, salicylic acid	Paste

JP2012162511A patent demonstrates a pharmaceutical preparation comprising a hydrogel base formed by synthetic or natural water-soluble polymers (as carboxyvinyl polymer, polyvinyl alcohol, guar gum, tamarind seed gum, gellan gum) with dispersed liposomes loaded with antifungal agent (as terbinafine, butenafine, neticonazole) and containing at least one permeation enhancer such as N-methyl pyrrolidone, crotamiton and salicylic acid. The liposomes developed preferably may have 100 nm or less, which can pass through nail pores delivering the antifungal drug. The formulation can be applied as a pure gel or can be served as a patch containing the hydrogel. The inventors indicate that the pharmaceutical preparation exhibited better skin permeability than a commercially available product (Lamisil®) [85].

CN102488702A patent reveals a formulation containing 11 - 30 parts by weight of the therapeutical agent, 3 - 8 parts of plasticizer, 1 - 5 parts of a penetration enhancer, 3- 8 parts of a film-forming agent, and 49 - 82 parts of solvent. The pharmacological agents can be terbinafine, fluconazole, ketoconazole, clotrimazole, ciclopirox, salicylic acid, *etc*., while plasticizer is a mixture of one or more of glycerin, polyethylene glycol-400. Permeation enhancers described are azone, borneol, camphor, ethanol, glycerol, urea, dodecyl methyl sulfoxide, *etc*., while film-formers consists of gelatin, carbomer, corn mash, polyethylene glycol and cyclodextrin, and as the pharmaceutical solvent is proposed ethanol, glycerin, isopropanol and others [86].

AU2017272269A1 patent is related to a pharmaceutical serum comprised of alkyl lactate, *Simmondsia chinesis* seed oil and a pharmaceutical agent, such as antifungal, hormones and others. In accordance with the invention, the antifungal agent is absorbed by and incorporated into the nail matrix by diffusing through the epithelium of the nail bed to reach the nail bed hyperkeratosis, and it also penetrates into the ventral nail plate, making the formulation highly effective against fungal agents [87].

EP2664327A1 patent reflects a topical formulation containing an antifungal agent (as terbinafine), urea and water,

mainly, and which can also comprise other excipients as permeation enhancers. In accordance with inventors, formulations prepared with the constituents described above showed a good penetration into and permeation through the nails, also allowing the delivery for precise dosing to the nail plate [88].

US2016008274A1 patent is associated with a device, such as a pad or covering, that delivers a drug (antifungal or anti-inflammatory) for treating nail disorders, secured to the skin at the nail matrix and extended over the nail plate. To the pad, a liquid or semisolid formulation can be placed with the therapeutical drug. The device may also comprise a chemical permeation enhancer as dimethyl sulfoxide, urea and salicylic acid [89].

WO2019088005A1 patent is linked with a topical formulation containing an antifungal agent as efinaconazole or luliconazole, a volatile component as ethanol, a non-volatile component such as a medium-chain fatty acid triglyceride and a permeation enhancer such as ethyl lactate, and may or may not contain water in low amounts and sodium edetate hydrate as a stabilizer. *In vitro* Franz diffusion permeation with bovine hoofs showed a great improvement in penetration of antifungal agents, as well as *in vivo* efficacy in Hartley guinea pig, which demonstrated a reduction in fungal colony-forming units [90].

CN109303815A patent proposes a pure extract preparation formula for onychomycosis comprised of 70 parts of turpentine, 20 parts of petrolatum, 0.6 parts of chlorhexidine acetate, 2.4 parts of belladonna extract, 1.5 parts of azone, 1 part of salicylic acid, 4.5 parts of sclerotium. In accordance with the authors, the formula presented a good antifungal effect and penetrated the nail surface [91].

5.1.4. Intrinsic to the Formulation

Murdan proposed that optimal drug formulation may be a crucial point to deliver pharmaceuticals to the nail [18]. In this view, several patents related to the intrinsic characteristics of the formulation presented the permeation enhancement profile. These features, often coupled with chemical permeation enhancers, can potentiate the delivery of drugs to the diseased tissue. Patents featuring formulation intrinsic characteristics and those associated with chemical enhancers to favor the delivery of drugs to the nail are described below and summarized in Table **2**.

WO2010037089A1 patent consists of a formulation of a liquid carrier system comprising of combination of turpentine (pine oil) and at least one of the following: peppermint oil, mineral oil, or essential oil alcohols that may enhance lipophilic antifungals (ciclopirox olamine, terbinafine, miconazole, itraconazole, ketoconazole, econazole, tolnaftate and fluconazole) through keratinized tissue, aiming the application of the carrier system directly upon the nail surface [92].

IN3107DE2013A patent comprises a formulation of niosomal gel containing itraconazole for the treatment of onychomycosis. The permeation results showed that the developed formulation with low vesicle size (around 260 nm) can be an effective delivery system. To the inventors, the penetration of the niosomes through the nail can be due to the detachment of the nail plate from the nail bed creating cavities providing the drug delivery from formulation [93].

US2018104227A1 patent discloses a nail lacquer containing at least one antifungal agent, at least one film-forming agent, a solvent, and additives (as hydrophilic promoters and permeation enhancers), which presented penetrating effect of the antifungal drug into the nail, without the inconvenience in removing the film formed when reapplying the drug solution [94].

CN105193726A patent reveals a pharmaceutical formulation composed of weight of 1-15 parts of the fungal agent terbinafine, 1-15 parts of fungal agent bifonazole, 15-60 parts of the capsule (one or a combination of one of sorbitan fatty acid ester, sorbitan monooleate polyoxyethylene ether, cholesterol and oleic acid), 5-50 parts of the hydration medium (one or a combination of sodium cholate and sodium deoxycholate), 10-80 parts of purified water. In another way, the invention combines antifungal agents with excipients to prepare a vesicle solution, which may present fast onset, safety and reliability. On clinical trials, solution or cream from the developed composition applied to the nails showed superior results in comparison to the single terbinafine cream and the bifonazole solution [95].

US2017209490A1 patent provides a nanoparticle composition consisting of spherical and/or coral-shaped metal nanoparticles (such as silver and gold) mixed within a penetrating solvent, which can be employed to treat an infected area in the nail without releasing metal ions. Due to the small size of the nanoparticles, the inventors believe that the particles are able to be absorbed into and move quickly through the nail region. Metal nanoparticles can be lethal to fungal microbes by catalyzing the cleavage of disulfide bonds within a vital protein or enzyme or through the production of active oxygen species, which can oxidatively cleave protein bonds. The penetration can also be facilitated due to a solvent configured to promote the delivery of the nanoparticles, having compounds that are able to enhance penetration, such as dimethyl sulfoxide [96].

WO2019105793A1 patent proposes a pharmaceutical composition in the form of a microemulsion comprising an alcohol ethoxy sulfate, an ethoxylated glyceryl fatty acid ester, an ethoxylated sorbitol or sorbitol anhydride fatty acid ester, urea, and may contain carboxylic acids to adjust pH, biotin to enhance the growth of nails, calcium chloride to harden the nail, antifungal agent. The microemulsion penetrates into the nail and creates an acidic environment, which effectively kills dermatophytes and other pathogenic fungi. Although indicated for the treatment of topical psoriasis, the treatment of nail psoriasis has not been covered [97].

As noted above, many modified delivery systems have been approached to promote the permeation enhancement of drugs in the nail. For skin permeation, this strategy has been applied for enhancing drug skin permeation since these systems penetrate the *stratum corneum* through passive diffusion [98]. Flores and coauthors developed a formulation containing nanocapsules coated with chitosan and loaded with tioconazole to treat onychomycosis [99]. Rocha and coauthors presented a voriconazole-loaded nanostructured lipid carrier capable of promoting drug penetration into

deeper regions of hooves (mimicking the nail), possibly interacting with keratin chains [100]. In general terms, modified systems are able to enhance the delivery of drugs at the place of interest.

These recent researches only reinforce the tendency to employ new modified delivery systems associated with the intrinsic characteristics of the formulations.

CONCLUSION

Topical administration of drugs to the nail containing chemical permeation enhancers is an attractive option as being ideal topical drug delivery systems for localized delivery.

CURRENT & FUTURE DEVELOPMENTS

Onychomycosis and psoriasis are nail disorders that impact significantly on patients' quality of life and often cause embarrassment in social life. Over the last decades, with the development of new formulations to treat these diseases and the advent of new methodologies *in vitro* to predict penetration through the nail barrier and determine the onychopharmacokinetics, the ungual route has gained more emphasis. Topical formulations seemed to be preferred over systemic treatments due to localized action, reduction of systemic side effects and higher patient convenience and compliance. However, poor permeability of drugs through the nail plate has proved to be a drag on drug delivery, not achieving the expected pharmacological activity. As a suggestion to overcome this feature, various studies proposed different methods for permeation enhancement of molecules through the nail barrier, including chemical approaches. Chemical permeation enhancers are being employed even more frequently to topical formulations since they are cost-effective, noninvasive and do not require medical intervention. However, it is challenging to develop topical formulations for proper nail drug delivery in view of its unique dense keratin network. The perspective for topical formulations for the treatment of onychomycosis and psoriasis lies in the association of physical permeation enhancer methodology, providing tiny holes in the nail with an adequate dosage form containing chemical permeation enhancer and a potent drug in an appropriate delivery system (immediate and prolonged release). In this sense, chemical permeation enhancers play a pivotal role in the development of formulations to deliver drugs through the nail.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - CAPES (Finance Code 001).

CONFLICT OF INTEREST

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

ACKNOWLEDGEMENTS

The authors would like to thank CAPES and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for their research fellowships.

REFERENCES

[1] Murthy SN, Maibach HI. Topical nail products and ungual drug delivery. Boca Raton: CRC Press 2013.

[2] Shanbhag PP, Jani U. Drug delivery through nails: Present and future. New Horiz Transl Med 2017; 3: 252-63.

[3] Murdan S. Drug delivery to the nail following topical application. Int J Pharm 2002; 236(1-2): 1-26. [http://dx.doi.org/10.1016/S0378-5173(01)00989-9] [PMID: 11891066]

[4] Lipner SR, Scher RK. Onychomycosis: Clinical overview and diagnosis. J Am Acad Dermatol 2019; 80(4): 835-51. [http://dx.doi.org/10.1016/j.jaad.2018.03.062] [PMID: 29959961]

[5] Jiaravuthisan MM, Sasseville D, Vender RB, Murphy F, Muhn CY. Psoriasis of the nail: Anatomy, pathology, clinical presentation, and a review of the literature on therapy. J Am Acad Dermatol 2007; 57(1): 1-27. [http://dx.doi.org/10.1016/j.jaad.2005.07.073] [PMID: 17572277]

[6] Lecha M, Effendy I, Feuilhade de CM, Di Chiacchio N, Baran R. Taskforce on Onychomycosis Education. Treatment options-development of consensus guidelines. J Eur Acad Dermatol Venereol 2005; 19(Suppl. 1): 25-33. [http://dx.doi.org/10.1111/j.1468-3083.2005.01284.x] [PMID: 16120203]

[7] Joshi M, Sharma V, Pathak K. Nail psoriasis: An updated review of clinical reports on therapy and formulation aspects for topical delivery. J Drug Deliv Sci Technol 2015; 30: 63-73. [http://dx.doi.org/10.1016/j.jddst.2015.09.017]

[8] Gupta AK, Paquet M, Simpson FC. Therapies for the treatment of onychomycosis. Clin Dermatol 2013; 31(5): 544-54. [http://dx.doi.org/10.1016/j.clindermatol.2013.06.011] [PMID: 24079583]

[9] Shivakumar HN, Juluri A, Desai BG, Murthy SN. Ungual and transungual drug delivery. Drug Dev Ind Pharm 2012; 38(8): 901-11. [http://dx.doi.org/10.3109/03639045.2011.637931] [PMID: 22149347]

[10] Warren RB, Griffiths CEM. Systemic therapies for psoriasis: Methotrexate, retinoids, and cyclosporine. Clin Dermatol 2008; 26(5): 438-47. [http://dx.doi.org/10.1016/j.clindermatol.2007.11.006] [PMID: 18755362]

[11] Vlahovic TC. Onychomycosis: Evaluation, treatment options, managing recurrence, and patient outcomes. Clin Podiatr Med Surg 2016; 33(3): 305-18. [http://dx.doi.org/10.1016/j.cpm.2016.02.001] [PMID: 27215153]

[12] Murdan S. Nail disorders in older people, and aspects of their pharmaceutical treatment. Int J Pharm 2016; 512(2): 405-11. [http://dx.doi.org/10.1016/j.ijpharm.2016.05.022] [PMID: 27180233]

[13] Elkeeb R, AliKhan A, Elkeeb L, Hui X, Maibach HI. Transungual drug delivery: Current status. Int J Pharm 2010; 384(1-2): 1-8. [http://dx.doi.org/10.1016/j.ijpharm.2009.10.002] [PMID: 19819318]

[14] Khengar RH, Jones SA, Turner RB, Forbes B, Brown MB. Nail swelling as a pre-formulation screen for the selection and optimisation of ungual penetration enhancers. Pharm Res 2007; 24(12): 2207-12. [http://dx.doi.org/10.1007/s11095-007-9368-3]

[15] Nolting S, Korting HC. Onychomycoses-local antimycotic treatment. Berlin, Heidelberg: Springer Berlin Heidelberg 1990. [http://dx.doi.org/10.1007/978-3-642-75409-8]

[16] Naumann S, Meyer JP, Kiesow A, Mrestani Y, Wohlrab J, Neubert RHH. Controlled nail delivery of a novel lipophilic antifungal agent using various modern drug carrier systems as well as *in vitro* and *ex vivo* model systems. J Control Release 2014; 180: 60-70. [http://dx.doi.org/10.1016/j.jconrel.2014.02.013] [PMID: 24560884]

[17] Narasimha MS, Wiskirchen DE, Bowers CP. Iontophoretic drug delivery across human nail. J Pharm Sci 2007; 96(2): 305-11. [http://dx.doi.org/10.1002/jps.20757] [PMID: 17080425]

[18] Murdan S. Enhancing the nail permeability of topically applied drugs. Expert Opin Drug Deliv 2008; 5(11): 1267-82. [http://dx.doi.org/10.1517/17425240802497218] [PMID: 18976136]

[19] Bronaugh RL, Maibach HI. Percutaneous absorption: Drugs, cosmetics, mechanisms, methodology. Boca Raton: Taylor & Francis Group 2005. [http://dx.doi.org/10.1201/9780849359033]

[20] Chouhan P, Saini TR. Hydration of nail plate: A novel screening model for transungual drug permeation enhancers. Int J Pharm 2012; 436(1-2): 179-82. [http://dx.doi.org/10.1016/j.ijpharm.2012.06.020] [PMID: 22705091]

[21] Christi JM, Aundhia C, Seth A, Shah N, Kondhia D, Patel S. Review on transungual drug delivery system. Indo Am J Pharm Res 2017; 7: 686-706.

[22] Zaias N. The nail in health and disease. Lancaster: MTP Press Limited 1980. [http://dx.doi.org/10.1007/978-94-011-7846-4]

[23] Garson JC, Baltenneck F, Leroy F, Riekel C, Müller M. Histological structure of human nail as studied by synchrotron X-ray microdiffraction. Cell Mol Biol 2000; 46(6): 1025-34. [PMID: 10976860]

[24] Lynch MH, O'Guin WM, Hardy C, Mak L, Sun TT. Acidic and basic hair/nail ("hard") keratins: Their colocalization in upper cortical and cuticle cells of the human hair follicle and their relationship to "soft" keratins. J Cell Biol 1986; 103(6 Pt 2): 2593-606. [http://dx.doi.org/10.1083/jcb.103.6.2593] [PMID: 2432071]

[25] Egawa M, Ozaki Y, Takahashi M. *In vivo* measurement of water content of the fingernail and its seasonal change. Skin Res Technol 2006; 12(2): 126-32. [http://dx.doi.org/10.1111/j.0909-752X.2006.00141.x] [PMID: 16626387]

[26] Helmdach M, Thielitz A, Röpke EM, Gollnick H. Age and sex variation in lipid composition of human fingernail plates. Skin Pharmacol Appl Skin Physiol 2000; 13(2): 111-9. [http://dx.doi.org/10.1159/000029915] [PMID: 10754459]

[27] Jemec GB, Agner T, Serup J. Transonychial water loss: Relation to sex, age and nail-plate thickness. Br J Dermatol 1989; 121(4): 443-6. [http://dx.doi.org/10.1111/j.1365-2133.1989.tb15511.x] [PMID: 2624837]

[28] Krönauer C, Gfesser M, Ring J, Abeck D. Transonychial water loss in healthy and diseased nails. Acta Derm Venereol 2001; 81(3): 175-7. [http://dx.doi.org/10.1080/000155501750376249] [PMID: 11558871]

[29] Scher RK, Daniel CRI. Nail: Diagnosis, therapy, and surgery. 3rd ed. Philadelphia: Elsevier Saunders 2005.

[30] Shanbhag PP, Jani U. Drug delivery through nails: Present and future. New horizons. Transl Med (Sunnyvale) 2017; 5: 252-63.

[31] Scher RK. Onychomycosis is more than a cosmetic problem. Br J Dermatol 1994; 130(Suppl. 43): 15-5. [http://dx.doi.org/10.1111/j.1365-2133.1994.tb06087.x] [PMID: 8186135]

[32] Ghannoum MA, Hajjeh RA, Scher R, *et al.* A large-scale North American study of fungal isolates from nails: The frequency of onychomycosis, fungal distribution, and antifungal susceptibility patterns. J Am Acad Dermatol 2000; 43(4): 641-8. [http://dx.doi.org/10.1067/mjd.2000.107754] [PMID: 11004620]

[33] Debruyne D, Coquerel A. Pharmacokinetics of antifungal agents in onychomycoses. Clin Pharmacokinet 2001; 40(6): 441-72. [http://dx.doi.org/10.2165/00003088-200140060-00005] [PMID: 11475469]

[34] Kumar S, Kimball AB. New antifungal therapies for the treatment of onychomycosis. Expert Opin Investig Drugs 2009; 18(6): 727-34. [http://dx.doi.org/10.1517/13543780902810352] [PMID: 19426118]

[35] Coleman NW, Fleckman P, Huang JI. Fungal nail infections. J Hand Surg Am 2014; 39(5): 985-8. [http://dx.doi.org/10.1016/j.jhsa.2013.11.017] [PMID: 24766830]

[36] Lipner SR, Scher RK. Onychomycosis: Current and investigational therapies. Cutis 2014; 94(6): E21-4. [PMID: 25566580]

[37] Welsh O, Vera-Cabrera L, Welsh E. Onychomycosis. Clin Dermatol 2010; 28(2): 151-9. [http://dx.doi.org/10.1016/j.clindermatol.2009.12.006] [PMID: 20347657]

[38] de Berker D. Clinical practice. Fungal nail disease. N Engl J Med 2009; 360(20): 2108-16. [http://dx.doi.org/10.1056/NEJMcp0804878] [PMID: 19439745]

[39] Singal A, Khanna D. Onychomycosis: Diagnosis and management. Indian J Dermatol Venereol Leprol 2011; 77(6): 659-72. [http://dx.doi.org/10.4103/0378-6323.86475] [PMID: 22016272]

[40] Iorizzo M, Piraccini BM, Tosti A. Aktuelle behandlungsoptionen der onychomykose. JDDG J Ger Soc Dermatology 2010; 8: 875-9.

[41] van der Velden HM, Klaassen KM, van de Kerkhof PC, Pasch MC. Fingernail psoriasis reconsidered: A case-control study. J Am Acad Dermatol 2013; 69(2): 245-52. [http://dx.doi.org/10.1016/j.jaad.2013.02.009] [PMID: 23541759]

[42] Nestle FO, Conrad C. Mechanisms of psoriasis. Drug Discov Today Dis Mech 2004; 1: 315-9. [http://dx.doi.org/10.1016/j.ddmec.2004.11.005]

[43] Bayliffe AI, Brigandi RA, Wilkins HJ, Levick MP. Emerging therapeutic targets in psoriasis. Curr Opin Pharmacol 2004; 4(3): 306-10. [http://dx.doi.org/10.1016/j.coph.2004.02.003] [PMID: 15140425]

[44] Committee for Medicinal Products for Human Use - European Medicines Agency. Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis 2004.

[45] Kyriakou A, Patsatsi A, Sotiriadis D. Biologic agents in nail psoriasis: Efficacy data and considerations. Expert Opin Biol Ther 2013; 13(12): 1707-14. [http://dx.doi.org/10.1517/14712598.2013.851192] [PMID: 24156504]

[46] Sala M, Diab R, Elaissari A, Fessi H. Lipid nanocarriers as skin drug delivery systems: Properties, mechanisms of skin interactions and medical applications. Int J Pharm 2018; 535(1-2): 1-17. [http://dx.doi.org/10.1016/j.ijpharm.2017.10.046] [PMID: 29111097]

[47] Wozel G. Psoriasis treatment in difficult locations: Scalp, nails, and intertriginous areas. Clin Dermatol 2008; 26(5): 448-59. [http://dx.doi.org/10.1016/j.clindermatol.2007.10.026] [PMID: 18755363]

[48] Murthy SN, Vaka SRK, Sammeta SM, Nair AB. TranScreen-N: Method for rapid screening of trans-ungual drug delivery enhancers. J Pharm Sci 2009; 98(11): 4264-71. [http://dx.doi.org/10.1002/jps.21743] [PMID: 19363796]

[49] Kushwaha AS. The screening of permeation enhancers for transnail delivery of terbinafine hydrochloride. J Bioequivalence Bioavailab 2018; 10: 75-7. [http://dx.doi.org/10.4172/0975-0851.1000381]

[50] Akhtar N, Sharma H, Pathak K. Onychomycosis: Potential of nail lacquers in transungual delivery of antifungals. Scientifica 2016; 2016: 1387936. [http://dx.doi.org/10.1155/2016/1387936] [PMID: 27123362]

[51] Täuber A, Müller-Goymann CC. *In vitro* permeation and penetration of ciclopirox olamine from poloxamer 407-based formulations- Comparison of isolated human stratum corneum, bovine hoof plates and keratin films. Int J Pharm 2015; 489(1-2): 73-82. [http://dx.doi.org/10.1016/j.ijpharm.2015.04.043] [PMID: 25895717]

[52] Repka MA, Mididoddi PK, Stodghill SP. Influence of human nail etching for the assessment of topical onychomycosis therapies. Int J Pharm 2004; 282(1-2): 95-106. [http://dx.doi.org/10.1016/j.ijpharm.2004.06.010] [PMID: 15336385]

[53] Chiu WS, Belsey NA, Garrett NL, *et al.* Drug delivery into microneedle-porated nails from nanoparticle reservoirs. J Control Release 2015; 220(Pt A): 98-106. [http://dx.doi.org/10.1016/j.jconrel.2015.10.026] [PMID: 26478016]

[54] Thomas, R.L. Medical device for controlled nail penetration. US2014371751A1 (**2014**).

[55] Napolez, A. Nail penetration device for delivery of anti-fungal treatments US2018207414A1 (**2018**).

[56] Abadi D, Zderic V. Ultrasound-mediated nail drug delivery system. J Ultrasound Med 2011; 30(12): 1723-30. [http://dx.doi.org/10.7863/jum.2011.30.12.1723] [PMID: 22124008]

[57] Neev J, Nelson JS, Critelli M, *et al.* Ablation of human nail by pulsed lasers. Lasers Surg Med 1997; 21(2): 186-92. [http://dx.doi.org/10.1002/(SICI)1096-9101(1997)21:2<186::AID-LSM10>3.0.CO;2-D] [PMID: 9261796]

[58] Ward, A.R., Ward, T.O., McBride, Z. Hand held system for antifungal treatment. US2013211481A1 (**2013**).

[59] Barsness, M., Davis, S., Etheredge, R., Chang, K., Kim, H. Controlling drug transport and current in iontophoretic onychomycosis treatment. US2011066134A1 (**2011**).

[60] Hao J, Li SK. Transungual iontophoretic transport of polar neutral and positively charged model permeants: Effects of electrophoresis and electroosmosis. J Pharm Sci 2008; 97(2): 893-905. [http://dx.doi.org/10.1002/jps.21025] [PMID: 17683062]

[61] Susilo R, Korting HC, Greb W, Strauss UP. Nail penetration of sertaconazole with a sertaconazole-containing nail patch formulation. Am J Clin Dermatol 2006; 7(4): 259-62. [http://dx.doi.org/10.2165/00128071-200607040-00007] [PMID: 16901186]

[62] Inaba, Y. Simple device for treating tinea unguium. US2011245785A1 (**2011**).

[63] Inaba, Y. Bubble-type tinea unguium treatment implement. JP2012115596A (**2012**).

[64] Weinfield, T.A. Enchanced trans-keratin drug delivery. WO2010011354A2 (**2010**).

[65] Gupta AK, Paquet M. Improved efficacy in onychomycosis therapy. Clin Dermatol 2013; 31(5): 555-63. [http://dx.doi.org/10.1016/j.clindermatol.2013.06.010] [PMID: 24079584]

[66] Gunt HB, Kasting GB. Effect of hydration on the permeation of ketoconazole through human nail plate *in vitro*. Eur J Pharm Sci 2007; 32(4-5): 254-60. [http://dx.doi.org/10.1016/j.ejps.2007.07.009] [PMID: 17928205]

[67] Gunt H, Kasting GB. Hydration effect on human nail permeability. J Cosmet Sci 2006; 57(2): 183-4. [PMID: 16758557]

[68] Vejnovic I, Simmler L, Betz G. Investigation of different formulations for drug delivery through the nail plate. Int J Pharm 2010; 386(1-2): 185-94. [http://dx.doi.org/10.1016/j.ijpharm.2009.11.019] [PMID: 19941943]

[69] Stüttgen G, Bauer E. Bioavailability, skin and nailpenetration of topically applied antimycotics. Mykosen 1982; 25(2): 74-80. [http://dx.doi.org/10.1111/j.1439-0507.1982.tb02721.x] [PMID: 7062934]

[70] Kobayashi Y, Miyamoto M, Sugibayashi K, Morimoto Y. Enhancing effect of N-acetyl-l-cysteine or 2-mercaptoethanol on the *in vitro* permeation of 5-fluorouracil or tolnaftate through the human nail plate. Chem Pharm Bull 1998; 46(11): 1797-802. [http://dx.doi.org/10.1248/cpb.46.1797] [PMID: 9845958]

[71] Quintanar-Guerrero D, Ganem-Quintanar A, Tapia-Olguín P, Kalia YN, Buri P. The effect of keratolytic agents on the permeability of three imidazole antimycotic drugs through the human nail. Drug Dev Ind Pharm 1998; 24(7): 685-90. [http://dx.doi.org/10.3109/03639049809082373] [PMID: 9876516]

[72] Malhotra GG, Zatz JL. Investigation of nail permeation enhancement by chemical modification using water as a probe. J Pharm Sci 2002; 91(2): 312-23. [http://dx.doi.org/10.1002/jps.10058] [PMID: 11835191]

[73] Brown MB, Khengar RH, Turner RB, *et al.* Overcoming the nail barrier: A systematic investigation of ungual chemical penetration enhancement. Int J Pharm 2009; 370(1-2): 61-7. [http://dx.doi.org/10.1016/j.ijpharm.2008.11.009] [PMID: 19071202]

[74] Mohorčič M, Torkar A, Friedrich J, Kristl J, Murdan S. An investigation into keratinolytic enzymes to enhance ungual drug delivery. Int J Pharm 2007; 332(1-2): 196-201. [http://dx.doi.org/10.1016/j.ijpharm.2006.09.042] [PMID: 17097244]

[75] Nair AB, Sammeta SM, Vaka SRK, Narasimha MS. A study on the effect of inorganic salts in transungual drug delivery of terbinafine. J Pharm Pharmacol 2009; 61(4): 431-7. [http://dx.doi.org/10.1211/jpp.61.04.0003] [PMID: 19298688]

[76] Vejnovic I, Huonder C, Betz G. Permeation studies of novel terbinafine formulations containing hydrophobins through human nails *in vitro*. Int J Pharm 2010; 397(1-2): 67-76. [http://dx.doi.org/10.1016/j.ijpharm.2010.06.051] [PMID: 20620203]

[77] Hui X, Chan TCK, Barbadillo S, Lee C, Maibach HI, Wester RC. Enhanced econazole penetration into human nail by 2-n-nonyl-1, 3-dioxolane. J Pharm Sci 2003; 92(1): 142-8. [http://dx.doi.org/10.1002/jps.10291] [PMID: 12486690]

[78] Repka MA, O'Haver J, See CH, Gutta K, Munjal M. Nail morphology studies as assessments for onychomycosis treatment modalities. Int J Pharm 2002; 245(1-2): 25-36. [http://dx.doi.org/10.1016/S0378-5173(02)00321-6] [PMID: 12270239]

[79] Mididoddi PK, Prodduturi S, Repka MA. Influence of tartaric acid on the bioadhesion and mechanical properties of hot-melt extruded hydroxypropyl cellulose films for the human nail. Drug Dev Ind Pharm 2006; 32(9): 1059-66. [http://dx.doi.org/10.1080/03639040600683410] [PMID: 17012118]

[80] Swenholt, K.G. Nail fungus treatment and composition. US2016235847A1 (**2016**).

[81] Inoue, S., Abe, S. Promotion of antifungal agent absorption. JP2010126532A (**2010**).

[82] Johnson, N. Fungal nail treatment composition. CN102844026A (**2012**).

[83] Capriotti, J., Capriotti, K. Antifungal composition for treatment of skin and nail. JP2018048159A (**2018**).

[84] Lindahl, A. Novel antifungal composition. RU2013136147A (**2015**).

[85] Sekiya, K., Morikane, S., Morikane, D., Kikuchi, J., Yasuhara, S. External preparation for treating ringworm and method for applying the same. JP2012162511A (**2012**).

[86] Weijun, L. Film coating agent for treating onychomycosis and preparation method thereof. CN102488702A (**2012**).

[87] Rockhill, T., Beeson, W.H. Excipient system for topical delivery of pharmaceutical agents. AU2017272269A1 (**2018**).

[88] Willers, C. Topical pharmaceutical compositions comprising terbinafide and urea. EP2664327A1 (**2013**).

[89] Tausk, F. Treatment of nail disorders. US2016008274A1 (**2014**).

[90] Natori, N., Takabe, H., Ishimaru, T., Iseki, H., Karasawa, K. External preparation for treating trichophytosis unguium. WO2019088005A1 (**2019**).

[91] Zhong, Y. Plant extraction formula applied to onychomycosis and tinea pedis. CN109303815A (**2019**).

[92] Selner, M. Penetrating carrier, anti-fungal composition using the same and method for treatment of dermatophyte. WO2010037089A1 (**2010**).

[93] Nagpal, S., Goyal, A., Narang, R.K. Formulation and evaluation of itraconazole loaded niosomal gel for the treatment of onychomycosis. IN3107DE2013A (**2015**).

[94] Kim, N., Cho, Y., Jeong, S., Bae, B., Lee, J., Lee, J. Nail lacquer composition containing ciclopirox. US2018104227A1 (**2018**).

[95] Lu, H. Pharmaceutical composition for treating leuconychia. CN105193726A (**2015**).

[96] Niedermeyer, W.H. Nanoparticle compositions and methods for treating onychomycosis. US2017209490A1 (**2017**).

[97] Krainbring, V.G.A. Composition for treating onychomycosis. WO2019105793A1 (**2019**).

[98] Touitou, E., Barry, B.W. Enhancement in drug delivery. Boca Raton: CRC Press 2007.

[99] Flores FC, Chiu WS, Beck RCR, da Silva CB, Delgado-Charro MB. Enhancement of tioconazole ungual delivery: Combining nanocapsule formulation and nail poration approaches. Int J Pharm 2018; 535(1-2): 237-44. [http://dx.doi.org/10.1016/j.ijpharm.2017.11.008] [PMID: 29126904]

[100] Rocha KAD, Krawczyk-Santos AP, Andrade LM, *et al.* Voriconazole-loaded Nanostructured Lipid Carriers (NLC) for drug delivery in deeper regions of the nail plate. Int J Pharm 2017; 531(1): 292-8. [http://dx.doi.org/10.1016/j.ijpharm.2017.08.115] [PMID: 28859937]