Review

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Research and Application of Methods for Improving Nail Permeation: A Review

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This review aims to explore the current methods and advancements in nail permeation, with a focus on the potential of ultrashort pulse lasers to enhance drug delivery. The treatment of nail diseases, such as onychomycosis, is particularly challenging due to the dense structure of nails, which hinders drug permeation. We reviewed traditional methods that are used to enhance drug penetration; however, these methods are often limited by discomfort, infection risks, and inadequate drug permeability. Laser therapy offers a novel perspective in enhancing transungual drug delivery by creating channels on the nail surface without damaging the nail root or bed, thus improving drug absorption. However, common lasers (such as CO_2 lasers) may increase the target temperature beyond the thermal denaturation threshold, thus causing thermal damage to the nail bed and underlying tissues. This can also induce cracks and tissue debris, thus potentially spreading fungal pathogens in cases of onychomycosis. We specifically noted the potential of ultrashort pulsed lasers, which operate in the femtosecond range, to produce high peak power with minimal thermal damage to surrounding tissues. These lasers can create micropores on the nail plate via cold ablation, thus making them promising tools for improving the treatment of nail diseases. However, experimental data on this method are limited, and further studies, including histological research, are needed to validate its effectiveness in enhancing local drug permeability. This represents both a challenge and an opportunity for advancing nail disease treatments.

Keywords: nail; drug permeation; nail channels; femtosecond laser

Introduction

Nails, which are situated at the extremities of the human body, exhibit a distinct curvature. As it extends from the nail root toward the distal end, the thickness and density of the nail plate progressively increase, thereby providing protective functions. Despite its mere thickness of approximately 600 µm, the nail plate comprises 80–90 layers of tightly arranged keratinized cells, which form interlocking structures between cells [1]. The proteins within the nail plate maintain a specific three-dimensional structure through stable disulfide bonds, thus increasing the compactness of the nail plate [2]. The nail plate is categorized into three layers: the dorsal side, the middle layer, and the ventral side, with a thickness ratio of 3:5:2 [3]. The permeability of the intermediate layer is the highest, whereas that of the dorsal side is the lowest [4]. Devoid of blood vessels or nerve endings, the nail plate derives its nutrition primarily from surrounding soft tissues and the vasculature and nerves at the extremities [5]. The nail root serves as a pivotal site governing nail growth, with fingernails achieving complete coverage of the nail bed after six months, whereas toenails require approximately twelve months to achieve complete coverage. Furthermore, pathological nail plates can induce diminished growth rates and thickening of the nail plate [6,7]. Despite its protective function, the nail's dense and rigid structure presents significant challenges for drug penetration. Studies have shown that although the nail plate is not entirely impermeable and resembles the surface of the skin, its dense and rigid characteristics significantly affect its permeability. The relatively low permeability of the nail plate may also be attributed to the repulsion that occurs between charged keratin proteins. Consequently, the achievement of complete drug penetration through the nail plate is challenging. This barrier impedes the effective delivery of therapeutic concentrations of topical drugs to the nail bed, complicating the treatment of nail-related diseases such as onychomycosis.

Traditional Methods to Enhance Nail Permeability

Traditional physical and chemical methods have been employed to enhance nail permeability, but each comes with significant limitations (Table 1, Ref. [1,8–22]). These methods aim to overcome the nail plate's inherent barriers, but their effectiveness is often hindered by patient discomfort, incomplete drug penetration, or procedural complexity. Overall, these methods face numerous challenges. Nail abrasion and chemical treatments, for example, often cause

Table 1. Summarizes the disadvantages of traditional methods.

Methods	Disadvantages	Reference
Nail abrasion	Requires experienced operators; improper use may lead to excessive thinning, thus causing contact with the nail bed, bleeding, discomfort, and increased infection risks.	[8]
Nail avulsion	Causes significant patient discomfort; prolonged exposure to the nail bed increases infection risks. Damage to the nail root may hinder nail shape restoration or growth.	[9]
Iontophoresis	Effectiveness lacks substantial clinical support. The process is time-consuming. Higher current for effectiveness increases associated risks.	[10,11]
Microdrilling	Drilling can cause cracks, hinder recovery, and is time-consuming. Maintaining consistent depth is difficult, thus risking nail bed damage.	
Low-frequency ultrasound	Limited penetration effectiveness.	[1]
Intramatricial injection	Requires professional and experienced physicians to perform.	[12]
Chemical methods	Prolonged nail soaking time, with certain chemicals potentially damaging the nail structure.	[13–19]
Medicinal nail polish	It can form a film to reduce nail moisture loss. Excessive use of medicinal nail polish may lead to nail plate oversaturation, serving as a breeding ground for drug-resistant fungi.	[20–22]

discomfort or insufficient penetration of drugs. Other techniques, such as iontophoresis or microdrilling, require specialized equipment and expertise, making them less practical for widespread use.

Limitations and the Need for Innovative Solutions

Given the limitations of traditional methods, more efficient and less invasive techniques are needed. Establishing microchannels directly on the nail surface to facilitate drug diffusion from the nail bed could offer a promising solution. Due to the fact that the nail plate consists of keratinized cells and lacks active repair mechanisms, the microchannels that are created using advanced techniques, such as laser-assisted methods, remain open and effective without posing a significant risk of infection. Laser-assisted approaches provide a minimally invasive alternative, allowing for precise and efficient drug delivery, potentially overcoming the shortcomings of traditional methods. These techniques represent a significant advancement in improving nail permeability and enhancing therapeutic outcomes.

Common Laser Creation of Nail Channels and Thermal Damage

Among the laser types that are utilized for assisted optical perforation, the most prevalent are continuous and pulse lasers [23–25]. Pulse lasers emit energy in pulses, which are characterized by high energy and short duration, thus enabling energy concentrations within a specific range. When common pulse lasers interact with the nail surface, the absorbed laser energy disperses and heats the surrounding tissues, thus resulting in the vaporization and melting of the nail tissue. For example, the fractional CO_2 laser, which employs microneedle array technology to penetrate the nail surface, creates pores on the nail surface. The heat energy that is generated by the laser accelerates drug penetration, thus facilitating drug entry into the interior of the nail plate [12]. Consequently, it is regarded as one of the optimal tools for establishing nail channels. However, prolonged exposure to pulse lasers may increase the target temperature beyond the threshold that is required for thermal denaturation, thus leading to thermal damage and potentially affecting surrounding tissues [26]. The application of this method to the nail plate may induce cracks and tissue fragments, which can introduce nail fungal pathogens into new environments and thereby promote their proliferation. Researchers have reported that holmium:yttrium aluminum garnet (Ho:YAG) and erbium-doped:yttrium aluminum garnet (Er:YAG) lasers can cause noticeable cracks on the nail surface following interaction with the nail plate, with potential failure to penetrate the nail plate. In contrast, as shown in Fig. 1 (Ref. [27]), the pores created by ultrashort lasers remain intact without cracking or melting being observed on the nail surface. Thus, a reduction in the pulse duration of lasers can significantly mitigate the thermal damage caused by laser treatment and minimize the involvement of surrounding tissues.

Ultrashort Laser Development of Nail Channels

Mechanism of Ultrashort Pulse Action

Ultrashort pulse lasers are characterized by their extremely brief pulse durations, which are typically localized in the femtosecond (10^{-15} second) range. These lasers generate high peak power with minimal thermal damage to the surrounding tissue, thus making them suitable for precision applications such as the creation of micropores in the nail plate. As shown in Fig. 2 (Ref. [27]), ultrashort lasers exhibit highly precise cutting effects and minimal trauma, and they are deemed to be safe and predictable. Their primary feature involves the induction of optical breakdown, thus enabling laser energy to be tightly focused within transparent tissues (such as the cornea). When ultrashort lasers interact with target tissues, the free electrons within the target absorb a significant amount of photon energy, which

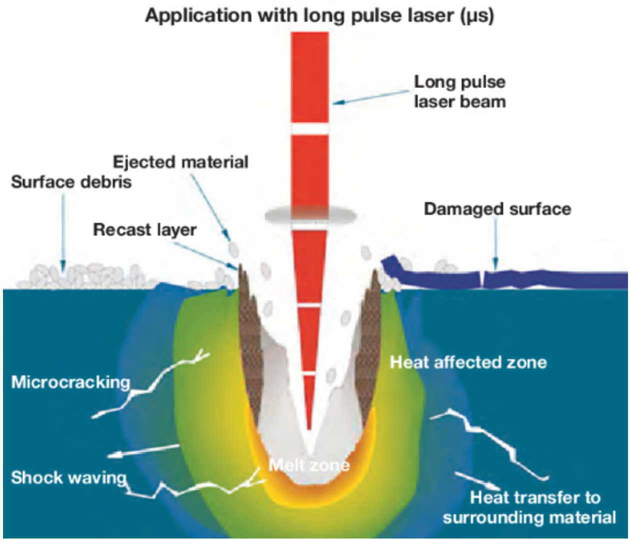

Fig. 1. Schematic diagram of the action of a long pulse laser. Reproduced with permission from Steven Hypsh [27], AM&P Technical Articles; published by ASM International, 2014.

leads to a rapid increase in electron density over a short duration. Upon reaching a critical density of approximately 10^{18}–$10^{20}/\text{cm}^3$, the formation of a plasma occurs at the focal point of the laser beam, which consists of ions and free electrons [28]. This plasma ejects tissue in an outward direction, thus removing it without generating excessive debris that adheres to or penetrates the normal nail surface, while also dissipating almost all of the heat. This occurs as electrons are first ejected, and the repelling ions do not recondense on the pore surface. Furthermore, the airflow that is generated on the tissue surface during laser action aids in the removal of tissue debris, reduces thermal effects, and enhances the efficiency of laser drilling [29]. Patients undergoing femtosecond laser treatment may experience a mild warming sensation or slight tingling during the procedure, which is typically well tolerated. However, the precise ‘cold ablation’ mechanism of ultrashort pulse lasers significantly reduces the risk of pain, thus making them an attractive option for patients with sensitive nails or for those who are at risk for discomfort from heat-based treatments. Compared with conventional pulse laser thermal processing, ultrashort lasers can be used to optimize treatment methods. Femtosecond lasers can gradually ablate the nail layer-by-layer, with each application depth being relatively shallow. This allows practitioners to devise treatment plans based on the thickness of the nail plate. In both the entire nail and a single nail plate, following the opening of nail channels via ultrashort laser application and the subsequent administration of corresponding antifungal drugs, the trauma that is inflicted on the nail tissue is minimal, and compliance is high.

Ultrashort pulse laser technology is not without its limitations. The advantages of establishing nail channels via ultrashort pulses currently remain theoretical and idealistic. Histological studies are needed to further verify whether this method can increase the permeability of topical medications. At present, femtosecond lasers are primarily used in ophthalmology, and the cost of a single treatment is relatively high. However, if this method proves to be beneficial to patients, the development of a femtosecond laser device that is tailored for dermatological treatments can significantly reduce costs, thus making it more accessible to patients. The distinctive feature of femtosecond lasers involves “cold processing”; therefore, it is important to avoid inducing effects on the nail bed to minimize the risks of bleeding and pain.

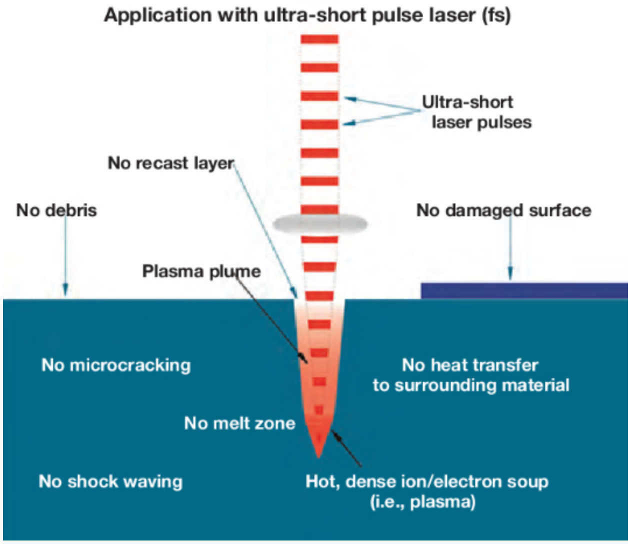

Fig. 2. Schematic diagram of the action of an ultrashort laser. Reproduced with permission from Steven Hypsh [27], AM&P Technical Articles; published by ASM International, 2014.

Factors Influencing the Establishment of Nail Channels via Ultrashort Laser

Laser Parameters

The selection of laser parameters is crucial for optimizing the efficacy of femtosecond lasers in nail treatments. First, the laser wavelength should match the optimal absorption rate of the target tissue to achieve the desired penetration depth. Given that the nail plate is thin with limited light absorption capacity, the selection of a shorter wavelength in the ultraviolet range enhances the cutting precision of femtosecond lasers, thus allowing more concentrated and effective interactions [28]. Second, the pulse width should be close to or shorter than the thermal relaxation time of keratin, which confines thermal damage to the target area and minimizes potential adverse effects on surrounding tissues [30]. Energy density, which determines the amount of energy that is delivered per unit area, influences the penetration depth; however, an excessively high energy density may lead to thermal damage. Therefore, it should be adjusted appropriately based on nail thickness and therapeutic goals. The spot size also affects the energy distribution depth, with adjustments being made to optimize the laser's penetration depth and coverage area. The high irradiance of the femtosecond laser rapidly heats the tissue, thus employing photomechanical forces to disrupt the target tissue (rather than vaporization). This capability allows the laser to create precise cutting planes within the tissue, which is ideal for constructing micropores that increase drug permeability. When these parameters are finely tuned, optical breakdown can occur, thus further improving tissue precision by forming microchannels under laser irradiation and thereby effectively promoting localized drug penetration (Fig. 3).

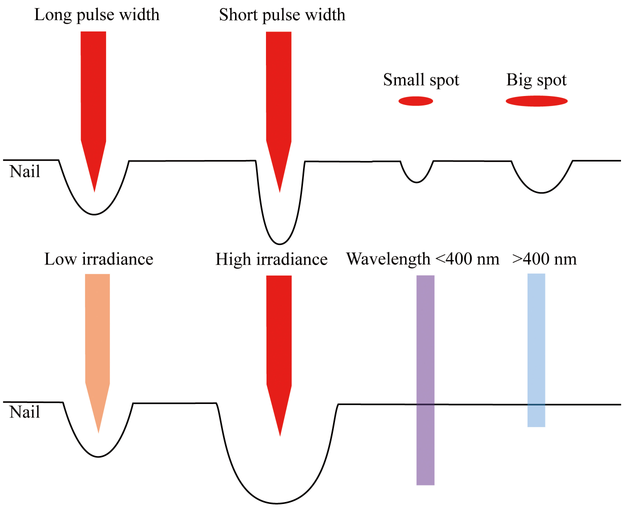

Fig. 3. Diagram of different laser parameters. Drawn by PowerPoint version 2021 (Microsoft Corporation, Redmond, WA, USA).

Nail Conditions

The thickness, hardness, and moisture content of the nail influences the penetration capability and efficacy of the laser. Therefore, it is advisable to direct the laser beam perpendicular to the nail plate for optimal ablation. The maintenance of an appropriate moisture level in the nail is crucial, as high humidity or completely dry conditions may increase the likelihood of nail plate cracking or fracture. Loose protein structures between keratinocytes contribute to increased nail plate flexibility, whereas lipid substances reduce moisture loss [31].

Laser Application Time and Mode

The duration of laser application is a critical factor in determining the depth and extent of nail channel formation, thus directly impacting therapeutic efficacy and potential adverse effects. Extended laser application times allow for deeper and more uniform channel formation across the nail layers, which enhances drug delivery potential by creating expanded pathways that facilitate more effective drug penetration. However, prolonged laser exposure may lead to complications such as nail bed bleeding, delayed healing, and structural changes in the surrounding tissues. Thus, a balance of the application time is essential to maximize the channel depth while minimizing tissue damage. To mitigate the risks associated with prolonged laser exposure, alternative scanning modes can be utilized to manage the thermal load by distributing laser energy more evenly across the nail surface. Techniques such as concentric sequential scanning and alternate line scanning are particularly effective in this regard. In concentric sequential scanning, the laser beam is applied in a spiral pattern, whereby it moves outward from the center of the application area. This approach ensures that each point is revisited at intervals, thus allowing for sufficient cooling time to reduce cumulative thermal effects. Alternatively, alternate line scanning applies the laser in a staggered pattern, which prevents direct overlap of consecutive laser spots. This strategy significantly minimizes thermal accumulation in adjacent areas by spacing out the energy pulses, thus increasing the cooling time and preventing excessive localized heating. Both methods help reduce the risk of thermal damage by extending the cooling intervals between pulses, thus allowing the efficient expulsion of tissue debris and preventing unnecessary heat buildup. Via the careful modulation of the laser duration and scanning mode, clinicians can achieve a balance between effective nail channel formation and controlled thermal management, thus optimizing treatment outcomes.

Laser Treatment Area

In optimizing nail channel formation to enhance drug delivery, the location, extent, and depth of laser application are critical. Direct irradiation of the nail matrix, which governs nail growth, should be avoided to reduce the risk of disrupting nail regeneration and to maintain normal nail growth and recovery. For lesions located in the proximal nail area, focusing the laser energy on the superficial or middle layers of the nail plate (rather than fully penetrating the plate) can improve drug permeation efficiency while minimizing direct laser exposure to the matrix.

External Environmental Factors

Environmental control during treatment is essential for ensuring consistent and safe outcomes. Auxiliary cooling mechanisms, such as rapid air circulation, help to reduce heat accumulation that is generated by the laser. The introduction of cooling gas into the laser scanning area effectively dissipates excess heat, clears tissue debris from the nail surface, enhances visibility and precision, and minimizes the risk of localized overheating.

Individual Variations

Differences in nail characteristics, along with the type of nail fungal infection, contribute to variations in the efficacy of laser treatment. For example, the average water content of normal detached nail plates is 11.90%; however, this value can significantly vary across individuals and conditions [32]. This variation may influence nail permeability and the response to topical treatments. Additionally, older individuals typically have higher cholesterol content in their nails, thus potentially impacting permeability [33]. Individuals with thicker and harder nails may require higher laser parameters for effective penetration, whereas those with thinner and softer nails may need more precise laser parameters to prevent damage to surrounding tissues. Notably, the distal subungual type tends to be more manageable and conducive to recovery than the proximal subungual type and total nail destruction type.

Conclusion

Herein, we specifically focused on laser-assisted nail channel creation, which is an innovative therapeutic approach that has garnered increasing attention. A comparison between conventional pulse lasers and ultrashort pulse lasers reveals that, although conventional lasers can be somewhat effective in creating nail channels, they are not ideal because of their propensity to cause thermal damage and tissue debris. In contrast, ultrashort pulse lasers, with their cold ablation capabilities, offer a more precise, minimally invasive, and predictable treatment option, thus representing a highly promising therapeutic pathway. Furthermore, we discussed various factors that may influence the success of ultrashort pulse lasers in creating nail channels; however additional research is necessary to fully understand their therapeutic benefits.

Availability of Data and Materials

Not applicable.

Author Contributions

HWW conceived this manuscript. HYM conceptualized the review's structure, data collection, and drafting of the manuscript. HWW and HYM contributed to the acquisition of data. HWW contributed valuable intellectual insights, reviewed the final draft, and actively participated in the discussion. Both authors were involved in the drafting and critical revision of the manuscript. Both authors have read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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