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TRANSUNGUAL DRUG DELIVERY: FROM NAIL BARRIER MECHANISMS TO ADVANCED DELIVERY SYSTEMS AND CLINICAL TRANSLATION

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ABSTRACT

Ungual drug delivery provides a localized approach for treating nail disorders by delivering drugs through or into the nail unit while minimizing systemic exposure. However, the dense keratinized nail plate, disulfide and hydrogen bonding, nail thickness, hydration, drug–keratin interactions, and differences between fingernails and toenails create substantial barriers to drug penetration. Conventional topical formulations such as nail lacquers and solutions may have limited penetration and residence within the nail, particularly in severe infections and matrix involvement. Recent approaches include chemical permeation enhancers, hydration, keratolytics, abrasion, iontophoresis, microneedles, and nanotechnology-based systems such as liposomes, transfersomes, niosomes, ethosomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, nanoemulsions, nanogels, and nanocrystals. Disease-specific and personalized ungual delivery can be adapted according to nail thickness, hydration, growth rate, disease severity, infection location, matrix involvement, patient age, toenail or fingernail involvement, and drug physicochemical properties. Onychomycosis remains a major application, while local delivery may also be relevant to nail psoriasis, nail dystrophies, bacterial infections, and other nail disorders. Smart and stimuli-responsive systems have potential for prolonged and disease-specific drug

release, although direct evidence in human transungual applications remains limited. Future development requires standardized nail permeation methods, validation using infected human nails, evaluation of drug retention and penetration, and clinical assessment of efficacy, safety, and treatment outcomes.

KEYWORDS: Ungual drug delivery; Transungual drug delivery; Onychomycosis; Nail psoriasis; Nail permeability; Nanotechnology; Permeation enhancers; Iontophoresis; Microneedles; Personalized drug delivery; Nail disorders; Stimuli-responsive systems.

1. INTRODUCTION

1.1. Burden of ungual disorders

Ungual disorders can impact quality of life, with onychomycosis and nail psoriasis being the most prevalent disorders among the general population.[1,56-58] Nail disorders can be benign, such as change in colour, to extremely serious, such as tumours which require surgical removal, and others which may not seem so severe, but are long-term, recalcitrant to treatment and affect patients physically and emotionally.[1,3] Squamous cell carcinoma of the nail unit (SCCNU) is a rare but clinically significant malignancy that is often underrecognized and misdiagnosed because its presentation resembles benign nail disorders.[3] Diagnostic delays of 12–36 months have been reported, which may allow progression to local tissue destruction, bone invasion and, rarely, metastasis.[3] Ungual disorders, particularly onychomycosis, constitute an important problem affecting the nail unit, with onychomycosis affecting approximately 19% of the population. The keratin-rich structure of the nail plate presents a significant barrier to drug penetration, resulting in only a fraction of topically applied drugs reaching the site of infection. Therefore, achieving therapeutically effective drug concentrations within the deeper nail layers remains a major challenge in ungual drug delivery.[61]

1.2. Limitations of oral and conventional topical therapy

Topical therapies for SCCNU are limited by difficulty in delivering the treatment into the nail folds, the frequent need for nail plate avulsion in subungual disease, and the absence of definitive histological confirmation of tumor clearance.[3] In addition, evidence supporting agents such as imiquimod remains limited, and nonsurgical therapies are associated with higher recurrence compared with complete surgical excision.[3] Oral antifungal therapy for onychomycosis is associated with systemic side effects, drug–drug interactions, increased morbidity and the need for prolonged treatment regimens.[61,68] Conventional topical therapy,

although advantageous because of its non-invasive nature and reduced systemic adverse effects, is limited by the poor permeability of the keratinized nail plate.[2,9,10]

Oral → low cure rate, high relapse, limited blood supply, difficulty reaching therapeutic concentration, adverse effects, drug interactions, long treatment, low compliance.[61,68]

Conventional topical → nail barrier, poor permeation, low concentration in deeper layers, limited to superficial infection, low residence time, removal during routine activities.[2,9,10] In topical nail therapy, the rigid, keratinized nail plate restricts drug penetration.[2,9,10]

Drug binding to nail keratin reduces the amount of free active drug and limits penetration into deeper tissues.[15,31,32] Some drug can enter the highly vascularized conjunctiva, reducing ocular bioavailability and potentially producing unwanted systemic effects.

1.3. Concept of ungual/ transungual Drug delivery

Ungual (transungual) drug delivery refers to the topical application of a drug to the nail plate followed by its penetration/permeation through the nail plate to reach the deeper nail layers, nail bed and/or nail unit, particularly for treating nail disorders such as onychomycosis and nail psoriasis.[2,9,10] The concept is important because topical therapy provides localized drug action with minimal systemic adverse effects, but the highly keratinized nail plate has low permeability, making drug penetration difficult.[2,9,10] Therefore, transungual delivery aims to achieve therapeutically effective drug concentrations in the deeper nail regions.[2,9,10] Drug permeation through the nail plate is influenced by its physicochemical properties, particularly molecular size, charge and hydrophobicity.[27,28] Transungual drug delivery is a specialized approach designed to enhance drug penetration through the keratinized nail plate, thereby delivering therapeutically effective drug concentrations to the site of nail infection while overcoming the limitations of conventional topical therapy.[2,9,10] In transungual delivery, drugs are administered topically through the nail using dosage forms such as nail lacquers, solutions and gels.[2,10] The aim is to achieve direct, localized drug delivery at the infected nail while minimizing systemic exposure.[2,9,10] Topical formulation → nail plate → drug permeation through nail → nail bed/site of disease → local therapeutic effect.

1.4. Why conventional nail lacquers have not completely solved the problem

Conventional topical nail lacquers such as Loceryl® and Penlac® have fewer side effects and better patient compliance, but their cure rates remain low because of poor drug penetration

through the nail plate.[6,61] Nail lacquers have limitations because the nail plate is a compact, highly keratinized barrier with very low permeability.[2,4,6] Therefore, simply applying a drug-containing lacquer does not always provide sufficient drug penetration into the deeper nail layers and nail bed.[2,4,6] Akhtar et al. discuss the limitations of conventional formulations, limited nail permeability, and the need for systems capable of delivering antifungals deeper into the nail bed. Their review also explains how nail lacquer films can act as drug depots and improve residence/delivery.[7] The drug's penetration is also affected by molecular size, lipophilicity, charge, nail thickness and hydration, formulation properties, and interactions of the drug with the keratin network.[20,23,27,28] Therefore, achieving sufficient and consistent drug permeation through the nail remains difficult.[2,27,28] Entional antifungal nail lacquers have not completely solved the problem because their use is mainly suited to limited disease, treatment may need to continue for many months, matrix involvement often requires systemic therapy, and recurrence after treatment remains common.[61,69]

2. Nail as a biological barrier

2.1. Nail plate architecture

The human nail consists of the nail matrix (root), eponychium or cuticle, paronychium, hyponychium, nail plate, nail bed, and lunula. The nail matrix is responsible for nail growth, while the nail plate forms the main visible part and is composed mainly of keratin. The nail bed is the tissue supporting the nail plate, and the lunula is the opaque, bluish-white half-moon region at its base. The nail is a unique barrier composed mainly of keratin. The nail unit consists of the nail plate, nail bed, nail fold, nail matrix and hyponychium.[23] The nail plate is the most visible part, measuring about 0.25–0.6 mm in thickness and consisting of approximately 25 layers of dead, keratinized, flattened cells tightly bonded together. The keratin fibres are arranged into dorsal, intermediate, and ventral layers.[23] The nail plate also contains 10–30% water, which contributes to its elasticity and flexibility, while lipid content is low, around 0.1–1.0%. Its hardness is related to the arrangement of keratin fibres, globular proteins, strong disulphide bonds, adhesion between nail cells, and its curved structure.[20,23] The average growth rate is about 3 mm/month for fingernails and 1 mm/month for toenails. Complete regeneration takes approximately 4–6 months for fingernails and 8–12 months for toenails.[23] Nail pathology differs from that of ordinary skin. Importantly, changes seen in the nail plate often originate from pathology in the nail matrix. Therefore, the site of biopsy must be selected according to the part of the nail unit involved.[23]

2.2. Keratin organization

Keratin is an insoluble protein made of sulfur-rich polypeptide chains. The nail mainly contains α-keratin, and hard α-keratin has higher cysteine content with numerous cross-linked chemical bonds, making it more stable. The nail plate has a "sandwich orientation" of keratin fibers, which contributes to its hardness and rigidity. The keratin fibers are arranged in dorsal, intermediate, and ventral layers. The dorsal layer is only a few cells thick and contains skin-type keratin filaments oriented transversely and perpendicular to the nail growth axis. The intermediate layer is softer, more flexible, and thicker, forming most of the nail thickness, and contains hair-like keratin filaments oriented perpendicular to the growth axis. The keratin molecules in the nail plate interact through disulfide linkages, contributing to its compact structure. The nail is therefore a dense keratinized structure, making it a significant barrier to drug penetration. It is described as having tightly bound keratinized cells, and the binding of drugs to keratin can reduce the amount of free drug available for deeper penetration. For transungual drug delivery, these disulfide linkages represent an important barrier. The article reports that thioglycolic acid (TGA) can cleave the disulfide linkages of α-keratin, making the nail surface more porous by forming new pores, which facilitates better drug permeation and retention.[15,23,31]

2.3 Disulphide bonding

Disulphide bonds are also important in nail permeability.Certain chemical penetration enhancers, such as N-acetyl-L-cysteine and mercaptan compounds, are believed to enhance drug penetration by breaking disulphide bonds. This disrupts the keratin matrix and produces structural changes in the nail plate, thereby facilitating transungual drug permeation.[17,18] Disulfide bonds can be cleaved using chemical penetration enhancers. Sulfites such as sodium sulfite and thiols such as mercaptoethanol can break the disulfide bonds in nail keratin,thereby improving drug penetration through the nail plate.[17,18] N-acetyl-L-cysteine has also been reported to increase the amount of oxiconazole retained in the nail.[18,19] Human nails contain α-keratin, which has strong disulfide linkages. These disulfide linkages contribute to the highly keratinized nature of the nail and act as a major barrier to drug permeation through the nail.[15,23]

2.4. Hydration and lipid content

The nail plate contains approximately 14–30% water (w/w), depending on relative humidity. Hydration is important for maintaining the elasticity and flexibility of the nail. Because of its

water content, the nail plate is described as a hydrophilic gel membrane. Hydration has also been suggested as an important mechanism for enhancing ungual drug delivery.[11,20] The nail plate contains about 10–30% water (w/w), depending on relative humidity. Hydration increases nail flexibility and swelling, which loosens the keratin network and facilitates drug diffusion.[20,68] The nail contains around 12% water and is highly permeable to water. Hydration is important for nail permeation because the nail behaves more like a hydrogel than a lipophilic membrane. Hydrating the nail can increase drug penetration through the nail plate. Hydration causes swelling and loosening of the keratin network, forming channels that facilitate transungual drug transport.[11,20,68]

2.5. Nail thickness and disease associated changes

The nail plate has a three-layered structure, with the intermediate layer being the thickest. Its rigid keratinized structure acts as a barrier to drug permeation, which is particularly important in diseases such as onychomycosis and nail psoriasis, where treatment must reach the affected nail tissues.[23,27,56-58] Fingernails are normally about 0.5 mm thick at the distal edge, while the great toenail may reach up to 1 mm.[23]With ageing, toenails commonly become thicker and may develop onychogryphosis (ram's-horn deformity), whereas fingernails generally become thinner and more brittle.[1,22] The nail plate is a substantial barrier to drug penetration, with reported mean thickness increasing along the toenail.[23] In onychomycosis, nail abrasion can reduce nail-plate thickness and fungal mass, thereby improving contact of antifungal drugs with the infected nail bed.[61,69] The nail is described as a relatively thick keratinized barrier, and its thickness contributes to the difficulty of delivering drugs to deeper nail regions.[2,27] In diseased nails such as onychomycosis, reducing nail thickness may facilitate drug penetration.[61,69]

2.6. Differences between fingernails and toenails

Fingernails grow at approximately 0.1 mm/day, while toenails grow at only 0.03–0.05 mm/day.[23] Complete regrowth takes around 6 months for fingernails compared with 12–18 months for toenails.[23] The nail plate is approximately 100 times thicker than the stratum corneum and acts as a strong barrier to drug penetration.[2,27] Differences in nail thickness and structure are therefore important considerations for topical/transungual drug delivery.[2,27] Onychomycosis affects both sites, but toenail infection is more common and generally more difficult to treat than fingernail infection.[26,61] This is relevant to transungual delivery because the slower growth and greater thickness of toenails can prolong treatment.[23,61] The nail plate

generally ranges from 0.25–0.6 mm in thickness, and nail thickness and hydration influence drug transport through the plate.[20,23,27] These properties are therefore important when considering drug delivery to fingernails and toenails.[20,23,27] The nail plate generally ranges from 0.25–0.6 mm in thickness, and nail thickness and hydration influence drug transport through the plate.[20,23,27] These properties are therefore important when considering drug delivery to fingernails and toenails.

3. Drug-Nail interactions: An underexplored perspective

3.1. Molecular size

Molecular size has an inverse relationship with drug penetration through the nail plate. Larger drug molecules diffuse less easily through the spaces between the keratin fibres, resulting in lower nail permeability.[27,29] Studies using different molecular weights and solubilities are important when evaluating nail/hoof models for drug permeation.[27,55] Molecular size and molar volume as important physicochemical factors affecting transungual permeation.[27] It reports that permeability decreases with increasing molecular size, while molecular weight may have a stronger effect than lipophilicity.[27] Drug permeation into the nail is affected by physicochemical properties of the drug, including molecular size.[2,27] Drug release from nail-lacquer films also depends on diffusion and partitioning of the drug into the nail.[7,16]

3.2. Lipophilicity/hydrophilicity

The lipophilicity or hydrophilicity of an antifungal drug strongly influences its solubility and penetration during topical/transungual delivery.[8-10] The article reports that many antifungal drugs have a hydrophobic character, resulting in low water solubility, which can limit their therapeutic effectiveness.[8,9] The nail plate behaves more like a hydrophilic gel membrane than a lipophilic membrane such as the stratum corneum. Its keratin network and low lipid content contribute to this characteristic.[12] The lipophilicity of a drug can influence its penetration through the nail plate. Increasing lipophilicity initially reduces the permeability coefficient, but beyond a certain point, further increase in lipophilicity can increase permeation.[12] The nail plate contains only about 0.1–1% lipid, much lower than the approximately 10% lipid content of the skin stratum corneum. Its water content is around 12%, and the nail is highly permeable to water; therefore, the nail behaves more like a hydrophilic gel membrane.[12] Studies with homologous alcohols showed that increasing lipophilicity initially decreases nail permeability, but beyond a certain level, further increase in lipophilicity increases permeation. Lower alcohols (up to C8) indicate the hydrophilic

nature of the nail, whereas highly hydrophobic substances such as C10–C12 alcohols may utilize the limited lipid pathway present in the nail plate.[12] The ionization state of a drug is an important factor influencing its transport through the nail plate. According to the review, the pH of the formulation affects the ionization of weakly acidic and weakly basic drugs. Changes in ionization can alter the drug's hydrophilicity or hydrophobicity, solubility in the formulation, solubility within the nail plate, and its interactions with the keratin matrix. Therefore, formulation pH may influence the permeation of drugs through the nail plate.[28]

3.3. Ionization

Ionization is an important physicochemical factor affecting transungual drug permeation.[28] The pH of the formulation influences the ionization of weak acidic and basic drugs, which in turn affects their hydrophilicity/hydrophobicity, solubility and interaction with nail keratin.[28] For iontophoretic delivery, ionization is desirable because the drug must be charged for effective electromigration.[24,28] Therefore, a drug that is almost completely ionized at an appropriate pH is preferred for transungual iontophoresis.[24,28] In contrast, a study using benzoic acid showed a marked pH effect. As the pH increased from 2.0 to 8.5, its permeability coefficient decreased by 95.5%, while the lag time increased. The uncharged form at pH 2.0 permeated the nail more readily than the charged form.[28] Ionization is essential for electromigration: In iontophoretic delivery, the drug must be ionized so that the electric field can drive the charged drug through the nail by electromigration. Therefore, drugs that remain sufficiently ionized at a reasonable pH are preferred.[24,28]

3.4.Hydrogen bonding

Hydrogen bonds are one of the chemical bonds contributing to the stability of nail keratin. Along with disulphide, peptide and polar bonds, they help maintain the keratin structure and therefore contribute to the barrier properties of the nail plate.[23] Keratolytic agents such as urea and salicylic acid are described as capable of disrupting hydrogen bonds and the tertiary structure of keratin. This destabilizes the keratin network and can improve transungual drug permeation.[23] The nail plate contains keratin, which is stabilized by hydrogen bonds along with disulfide and electrostatic bonds. These interactions contribute to the tightly organized keratin network and the limited permeability of the nail plate.[23] Hydrogen bonding contributes to maintaining the structural organization of the keratin matrix, while hydration can modify these interactions, increasing the flexibility and segmental mobility of keratin. This helps create a more permeable nail plate and can facilitate transungual drug

permeation.[20,23] Against lanosterol-14-α demethylase (PDB ID: 5HS1), luliconazole formed a hydrogen bond with Cys 470, along with π–π stacking with Tyr 126.[33] Hydrogen bonding can be considered an important intermolecular interaction influencing drug transport through the nail plate because the nail plate is composed mainly of tightly packed, keratinized cells. The review describes the nail plate as a concentrated hydrogel-like structure and emphasizes that drug molecules interact with the keratin matrix during their movement through the nail. Such interactions can affect the availability of drug molecules for diffusion. In particular, binding of the drug to keratin reduces the amount of free drug available, weakens the concentration gradient, and consequently limits deep penetration into the nail plate.[23,31]

3.5. Keratin binding

The nail plate contains a dense keratin network stabilized by strong disulfide linkages and hydrogen bonds, making it a highly resistant barrier to drug penetration.[15,23] The rigid keratin structure can limit the penetration and availability of topical antifungal drugs within the nail.[2,9] Therefore, interaction of drugs with keratin can influence their movement and retention within the nail plate.[31,32] Penetration-enhancing approaches, including chemical agents that interfere with the bonding within the keratin structure, have been investigated to improve transungual drug delivery.[17,18] Binding of the drug to nail keratin reduces the availability of free drug, weakens the concentration gradient, and consequently limits its penetration into the deeper layers of the nail.[15,31,32] Therefore, drug–keratin interaction is an important factor to consider in transungual drug delivery.[31,32] Keratin binding is an important factor affecting drug permeation through the nail plate.[31,32] The nail plate consists predominantly of tightly packed, keratinized cells, with keratin fibres stabilized by strong disulfide linkages and other interactions.[15,23] When a drug applied topically binds to the keratin network, a portion of the drug becomes unavailable in its free, pharmacologically active form.[31,32] This decreases the concentration gradient that drives diffusion through the nail and consequently restricts drug movement into the deeper nail layers where the infection may be located.[31,32] Therefore, both the physicochemical characteristics of the drug and its interaction with nail keratin influence transungual drug delivery.[2,31,32]

3.6. Drug keratin interaction

Drug–keratin binding can act as a temporary drug-retention mechanism within the nail, but strong affinity may initially reduce the availability and activity of the drug.[31,32] Terbinafine is an example in which keratin binding temporarily reduces antifungal activity, followed by

release of active drug.[32] The strong disulfide bonding within keratin can also be modified to improve drug penetration. Chemical penetration enhancers such as sulfites, thiols, N-acetyl-L-cysteine, and thioglycolic acid can disrupt disulfide bonds in the nail keratin.[17,18] Similarly, nail softeners such as urea, salicylic acid, and sodium salicylate enhance permeation mainly through keratin denaturation/solubilization and disruption of disulfide bonds.[20] Disruption of keratin is a strategy for enhancing drug penetration. Thioglycolic acid acts as a keratolytic agent by breaking the disulfide linkages that hold keratin units together. This compromises the keratin network and facilitates drug permeation through the nail plate.[17,18] In addition, PEG 400 hydrates the nail and causes swelling, leading to the formation of channels that can further enhance drug penetration.[20] The nail plate is a hard and relatively complex structure that can influence the visualization and penetration of substances applied to the nail surface. The review describes the use of interface media such as ultrasound gel, alcohol, and mineral oil during onychoscopy. These media increase the transparency of the nail plate and improve visualization of structures beneath it, particularly the nail bed.

3.7. Vehicle-nail interaction

The choice of vehicle can also affect the delivery of poorly penetrating drugs. For example, incorporation of low-molecular-weight PEGs (PEG 200 and PEG 400) into terbinafine gel formulations enhanced transungual drug delivery compared with higher-molecular-weight PEGs. The review also reports that DMSO increased nail-plate penetrability.[12] The formulation contained film-forming polymers such as hydroxypropyl methyl cellulose (HPMC) and cellulose acetate phthalate (CAP), together with thioglycolic acid (TGA) as a permeation enhancer. TGA facilitates interaction with the nail keratin by cleaving disulfide linkages within α-keratin, thereby increasing nail porosity and promoting drug penetration.[17] According to the reference article, the nail plate is composed mainly of parallel keratin filaments, which provide mechanical stability. It contains approximately 7% water and is highly permeable to water compared with intact skin. The article also notes that the nail plate can serve as a site for the deposition of exogenous substances, including medications, drugs of abuse, and arsenic. These findings indicate that the nail plate can interact with substances present in a vehicle and may allow their deposition within the nail structure. The nail unit has a complex structural organization consisting of the nail matrix, nail plate, nail bed, cuticle, nail folds, supporting structures, and anchoring components. The nail plate is the product of the nail matrix and forms a hard keratinized structure that can influence the penetration of

substances through the nail.

4. Nanotechnology in Ungual Delivery

4.1. Liposomes

Liposomes are vesicular carriers consisting mainly of phospholipid bilayers surrounding an aqueous compartment. They can encapsulate both hydrophilic and lipophilic drugs. Their nanoscale structure allows close contact with biological surfaces and can provide a reservoir for sustained drug release.[3,5] In ungual delivery, liposomes can remain in contact with the nail surface and provide prolonged drug exposure. Their interaction with the keratinized nail is influenced by vesicle composition, drug properties, and the hydration state of the nail. Terbinafine-loaded liposomal films have been investigated for transungual delivery, showing the potential of combining liposomes with adhesive polymeric films.[2] However, conventional liposomes may have limited ability to cross a highly compact nail barrier. Therefore, their main value may be increased retention and controlled drug release rather than direct penetration through an intact thick nail.[2,3] Their antifungal potential is mainly related to maintaining the antifungal drug at the local site for a longer period. Liposomal systems can also reduce irritation for some antifungal drugs in topical applications.[3] Translation is nevertheless influenced by vesicle stability, manufacturing complexity, storage stability, and cost.

4.2.Transfersomes

Transfersomes are highly deformable lipid vesicles composed of phospholipids and edge-activating surfactants.[3] In transungual delivery, this property is useful because the nail contains a dense keratin network with limited pathways for drug movement. Efinaconazole-loaded transfersomes containing Tween 80 have been investigated for nail infection and demonstrated improved therapeutic performance without visible erythema or edema in the reported study.[2] Thus, transfersomes may improve nail interaction, drug deposition, and local antifungal activity. However, deformability alone does not guarantee deep penetration through a thick diseased nail. Combining transfersomes with permeation enhancers, hydration, or mechanical methods may therefore be more effective than using the vesicles alone.[2,5]

4.3.Niosomes

Niosomes are vesicles formed mainly from non-ionic surfactants, with or without cholesterol. They can act as drug reservoirs and provide sustained drug release. They are also relatively

simple to manufacture compared with some phospholipid vesicles.[3,37] Itraconazole-loaded niosomes have been investigated for antifungal delivery. The cholesterol content influenced drug permeation, and the niosomal formulation showed antifungal activity against Candida albicans with a larger inhibition zone than the marketed formulation in the reported study.[37] The major translational advantages are their relatively simple preparation and ability to incorporate poorly soluble drugs.

Their limitations include possible instability and the need to optimize surfactant/cholesterol ratios.[37]

4.4. Ethosomes

Ethosomes are ethanol-containing lipid vesicles. Ethanol improves drug solubilization and can increase membrane interaction and vesicle deformability.[38,39] Ethosomes have been widely studied for topical and transdermal antifungal delivery, although the supplied literature provides stronger direct evidence for transfersomes and other nanovesicles in ungual applications.[38,40] For nail delivery, ethanol-containing systems may improve interaction with the hydrated keratin network and increase drug availability. Nevertheless, excessive ethanol can potentially produce irritation or alter formulation stability. Thus, concentration and composition require careful optimization.[38,39]

4.5. Nanostructured Lipid Carriers

NLCs consist of mixtures of solid and liquid lipids. Incorporation of liquid lipid produces imperfections in the lipid matrix, which can increase drug-loading capacity compared with completely solid lipid systems.[44,45] NLCs are particularly interesting for poorly water-soluble antifungal drugs. The supplied literature reports ketoconazole-loaded NLCs prepared using Ucuùba fat, with an optimized particle size below 100 nm and good short-term physical stability.[44] Voriconazole NLCs containing urea as a penetration enhancer also demonstrated increased nail hydration-related effects and changes in hoof surface morphology.[45] NLCs can therefore provide close contact with the nail, sustained drug release, improved drug loading, and potentially improved penetration.[44,45] Their lipid composition may also support nail hydration, which is important because hydration can increase nail permeability.[2,44,45] Further human-nail and clinical studies are required before broad translation.[44,45]

4.6. Solid Lipid Nanoparticles

SLNs contain a solid lipid matrix in which the drug is incorporated or associated. They can provide controlled release and protect the incorporated drug. The small particle size promotes

close contact with the biological surface.[43] Terbinafine and miconazole-loaded lipid nanoparticle systems have been investigated for antifungal delivery.[43] The supplied review reports that a miconazole SLN formulation showed strong antifungal activity against Candida albicans, with the formulation having the smallest particle size showing the highest antimicrobial activity in the described experiment.[43] SLNs can therefore contribute to retention, sustained release, and antifungal activity.[43] However, drug expulsion during lipid crystallization and limited drug loading can be formulation challenges. NLCs were developed partly to overcome some of these limitations.[43,44]

4.7. Polymeric Nanoparticles

Polymeric nanoparticles are particularly attractive because their polymer composition can be modified to control stability, drug release, adhesion, and degradation.[46,47] Chitosan and polycaprolactone-based systems have been investigated in the supplied literature.[46,47] One important approach involved poly(ε-caprolactone) nanoparticles used with microneedle poration[46] Microneedle treatment created pathways in the nail and allowed fluorescent nanoparticle penetration into deeper nail regions.[46] Sustained release from the polymeric nanoparticles was observed, supporting their role as drug reservoirs within the nail.[46] Chitosan nanoparticles containing itraconazole and difluorinated curcumin have also been incorporated into Carbopol gel for onychomycosis treatment.[47] Their advantages include flexible design, bio adhesion, stability, sustained release, and the possibility of combining multiple therapeutic agents.[46,47]

4.8. Nanoemulsions

Nanoemulsions contain very small oil droplets stabilized by surfactants and co-surfactants. Their small size can improve drug solubilization and contact with the nail surface. Nanoemulsions are especially useful for poorly water-soluble antifungal agents.[48] Ketoconazole nanoemulgel is one example. The supplied literature reports enhanced transungual permeation and antifungal activity against Trichophyton rubrum and Candida albicans. A ketoconazole nanoemulgel showed approximately 84.42% drug release at 24 h compared with approximately 54.86% from drug suspension in the reported experiment.[48] Another microemulsion/nano emulsion gel containing itraconazole showed high penetration and retention compared with a marketed formulation.[48] The major advantages are small droplet size, high solubilization capacity, improved penetration, and easy conversion into a gel.[48] Surfactant irritation and long-term physical stability must nevertheless be

considered.[48]

4.9. Nanogels

Nanogels combine nanoscale dimensions with a cross-linked hydrophilic polymer network. They can absorb water, retain drug, and provide controlled release.[47,49] Hydrogels are also naturally suitable for nail delivery because the nail itself has hydrogel-like characteristics.[47,49] The supplied literature describes hydrogel and nanocomposite hydrogel systems, including antifungal formulations containing polymers and nanoparticles.[47,49] Their important functions are prolonged residence, hydration, adhesion, and controlled release.[47,49]

4.10. Nanocrystals

Nanocrystals are nanosized drug crystals stabilized by suitable excipients. Their main advantage is increasing the effective surface area of poorly soluble drugs, which can improve dissolution and drug availability.[50] The supplied literature discusses nanosuspensions containing poorly soluble antifungal drugs such as griseofulvin. The formulation approach improved drug solubility and produced enhanced permeation in nail-related experiments.[50] Therefore, nanocrystal/nanosuspension technology may be useful when the major limitation is poor drug solubility rather than only the nail barrier.[50]

5. Smart and Stimuli-Responsive Ungual Delivery

The next generation of ungual delivery aims to move beyond passive drug release. In a smart system, the formulation should ideally recognize the local environment and release more drug when a relevant stimulus is present.[51-53]

A conceptual pathway is

Nail application → barrier recognition → penetration/retention → fungal microenvironment recognition → triggered drug release → prolonged local antifungal action.

For example, polymersomes can be designed so that their physical and chemical properties change in response to pH, temperature, redox conditions, light, magnetic fields, ionic strength, or concentration.[51-53]

5.1. pH-responsive systems

pH-responsive polymers can change swelling, solubility, or structure when pH changes. In principle, this could allow drug release to change according to the local nail/fungal environment. The supplied literature supports pH-responsive polymers as a general

controlled-release concept, but it does not establish a mature pH-triggered transungual antifungal platform.[54]

5.2. Enzyme-responsive systems

Enzyme-responsive systems contain bonds or structures that can be degraded by specific enzymes.[50.51,52] A fungal-associated enzyme could theoretically act as a trigger and produce drug release at the infected site.[50,51] This would provide greater site specificity than simple diffusion. Therefore, this remains an important research opportunity.[50,52]

5.3.Fungal-responsive drug release

The most attractive smart concept is direct recognition of fungal infection.[50,51,52] A formulation could ideally remain relatively stable in healthy nail tissue but release more drug when it encounters fungal components, fungal enzymes, biofilm-related conditions, or other infection-associated signals.[50,51,52] Current nano vesicular and nanoparticle systems already increase local antifungal exposure,[46,47,49] but true fungal-triggered release is still an emerging concept in ungual delivery.[50,51,52]

5.4. Moisture-responsive systems

Water is highly relevant to nail permeability[10,19,54] Hydration increases the water content of the nail and can facilitate drug diffusion.[10,19,54] Therefore, moisture-sensitive systems could potentially exploit the hydrated nail environment to increase swelling or drug release.[50,51,52] This concept is supported indirectly by studies showing that hydration and moisture influence ungual drug uptake.[10,19,54] However, dedicated moisture-triggered antifungal systems require further investigation.[50,54]

5.5.Temperature-responsive systems

Temperature-responsive polymers can change their physical state at a defined temperature.[50,51,52] Thermo responsive gels are already described as systems capable of sol-gel transitions, and polymers such as poloxamers can respond to temperature changes.[48.50,51,52] Such systems could potentially remain easy to apply and subsequently form a drug-retaining depot.[48,50,51,52] Direct clinical evidence for temperature-triggered transungual antifungal delivery, however, remains limited in the supplied literature.[48,50,52]

5.6.ROS-responsive systems

Reactive oxygen species (ROS)-responsive materials can theoretically release drugs when

oxidative conditions cause cleavage or structural changes in the carrier.[50,51,52] This may be useful because infected tissues can have altered oxidative environments.[14,50,52] Therefore, ROS-responsive nail delivery should presently be considered a future research direction rather than an established technology.[14,50,52]

5.7. Triggered drug release

Triggered release combines the above concepts into an intelligent system.[50,51,52] Instead of releasing the complete drug dose immediately after application, the carrier could retain the drug during the early stages of treatment, penetrate or remain within the nail, and subsequently release the drug when a disease-associated stimulus is detected.[50,51,52] Such a strategy could potentially increase local drug exposure, reduce repeated application, decrease unnecessary drug loss, and improve treatment adherence.[50,51,52] Nevertheless, successful translation will require proof that the trigger is sufficiently different between healthy and infected nails and that the carrier is safe and stable during the entire treatment period.[50,52]

6. Combination strategies

The Future of ungual delivery A major direction in current ungual research is the combination of nanotechnology with mechanical, physical, chemical, or formulation-based permeation enhancement[29,43,45,46,47,49] The nail barrier can be modified by hydration, chemical enhancers, keratolytic agents, thiols, solvents, iontophoresis, laser treatment, microporation, ultrasound, abrasion, and other techniques.[8,20,29,31,32,33,34,35,45] Nanocarriers can then act as drug reservoirs after the barrier has been modified.[43,44,45,46,47,49] One particularly important example is the combination of polymeric nanoparticles and microneedle poration.[45] Microneedles create micropores in the nail, after which nanoparticles can enter deeper regions and provide sustained release.[45] Microneedles are considered minimally invasive and can be produced in solid, coated, dissolving, hollow, or hydrogel-forming formats.[45] Another approach is the combination of nanocarriers with chemical penetration enhancers.[8,20,31,32,33,34] Urea, thioglycolic acid, N-acetylcysteine, cysteine, and other agents can alter keratin structure or increase hydration.[8,20,31,32,33,34] The supplied literature reports improved drug permeation when nanocarriers were combined with appropriate penetration enhancers. Iontophoresis provides another combination opportunity. Electrical current can drive ionizable molecules through the nail and has been investigated for antifungal and other ungual drugs. The literature identifies transungual iontophoresis as a promising method, while also emphasizing the need for optimization of current, formulation,

permeation enhancers, and disease-specific nail models. The most advanced future formulation may therefore not be a single technology. A multimodal system could combine a nanocarrier, permeation enhancer, adhesive gel/lacquer, physical enhancement method, and eventually a disease-responsive release mechanism.

Such a system could follow the sequence

Application → adhesion to nail → hydration/barrier modification → nanoparticle penetration → retention in deeper nail → fungal recognition → triggered release → sustained antifungal activity.

Research Gaps

Despite major progress, several important gaps remain. First, there is no universally standardized method for measuring nail permeation and comparing different formulations. The 2025 nanocarrier review specifically identifies methodological standardization as an important limitation. Second, many studies use bovine hoof, equine hoof, artificial membranes, or nail clippings instead of intact human infected nails. A comparative study demonstrated a relationship between equine hoof and human nail uptake but also emphasized the need for suitable experimental models.

Third, many nanotechnology studies report particle size, drug loading, release, or antifungal activity separately. More integrated studies should connect particle size → nail interaction → retention → penetration → drug release → fungal killing → toxicity → clinical outcome.

Finally, smart responsive systems require direct vali dation in infected human nails. Particularly, fungal-, enzyme-, pH-, moisture-, temperature-, and ROS-responsive mechanisms remain promising but insufficiently demonstrated as complete transungual therapeutic systems within the supplied literature.

7. Disease-specific ungual delivery

7.1. Onychomycosis

It is the most common nail disorder, with toenail infections mainly caused by dermatophytes (especially T. rubrum), followed by non-dermatophyte moulds and Candida; topical antifungals such as amorolfine, ciclopirox, efinaconazole and tavaborole are delivered through the nail plate/nail bed.[5,6,24,25] Topical treatment requires prolonged application and has low success, while formulations such as nail lacquers and low-surface-tension solutions

are designed to improve drug penetration through the nail plate and reach the site of infection.[6,24,25]The rigid nail barrier makes drug penetration difficult, so novel transungual systems such as nanoparticles, nanoemulsions, hydrogels, liposomes and nail lacquers are explored for deeper/localized antifungal delivery.[2,6,34,43,44,46,47]

Chronic paronychia: Presents with swelling, redness and tenderness around the nail fold and may be mistaken for SCCNU (squamous cell carcinoma of the nail unit), particularly when persistent.[3,21,25]

Subungual wart: A warty, rough subungual growth associated with HPV; dermoscopy shows a papilliform surface with central black dots and a hyperkeratotic rim.[66]

Pyogenic granuloma: A rapidly growing, bright-red vascular nodule that bleeds easily and may clinically mimic SCCNU. Amelanotic melanoma: May present as painless nail discoloration or a subungual mass, with the absence of a pigment network helping distinguish it from pigmented lesions.[62,63,66]

Glomus tumor: Typically presents with severe localized pain and cold sensitivity; MRI may show a vascular subungual nodule.[1,66]

Dermatophytes: Terbinafine-loaded transferosomes showed potent activity against T. rubrum, T. mentagrophytes and Epidermophyton floccosum, while terbinafine nano emulsion NB-002 showed activity against major dermatophytes.[33,34,47]

Candida: Tioconazole nano capsules, ketoconazole nanoemulgel and terbinafine nanoemulsion formulations demonstrated antifungal activity against Candida albicans, supporting their use in transungual delivery.[34,47,49]

7.2. Nail Psoriasis

Nail psoriasis can affect the nail matrix, nail bed, and nail folds, causing pitting, fragility, crumbling/nail loss, onycholysis and subungual hyperkeratosis.[55,56,57] Psoriasis increases nail growth rate, which is relevant to drug transport through the nail during ungual delivery[55,56] Iontophoresis can deliver drugs into the deeper layers of the nail, which is important because the entire nail is affected in nail psoriasis; a n ail-gel formulation is suggested for transungual treatment.[29,55,56] Topical corticosteroids, vitamin D_3 analogues, retinoids, 5-fluorouracil, anthralin, cyclosporine and tacrolimus are applied to the nail and surrounding tissues, although

nail permeability limits efficacy.[55,56,57]

7.3. Bacterial nail infection

Bacterial or fungal infections constitute about 50% of prevalent nail disorders, making local treatment relevant.[1,59,60] Other nail disorders including inflammatory/metabolic conditions, malignancies and pigment disturbances may benefit from local ungual therapy.[1,3,55,56] Pseudomonas infection: Onychoscopy shows greenish discoloration of the nail plate, often associated with chronic proximal paronychia and onycholysis.[58] Peripheral fading of the green discoloration may also be observed.[58]

7.4. Nail dystrophies

Dystrophic nails can reduce drug penetration through the nail plate, making transungual drug delivery challenging; therefore, penetration-enhancing approaches may be useful for improving topical drug delivery.[1,13] The study developed an econazole nitrate-loaded nail lacquer with permeation enhancement to improve transungual delivery and provide topical antifungal treatment to the infected nail.[59] Nail dystrophy is described in association with several disorders, including psoriasis, lichen planus, alopecia areata and genetic nail dysplasia. In onychomycosis, the severe form may progress to total dystrophic onychomycosis, with thickening, discoloration, and destruction of the nail plate. Nail dystrophy of uncertain cause, particularly with subungual pigmentation or persistent unexplained hematoma, requires biopsy to exclude subungual melanoma.[62]

7.5.Nail lichen planus

Onychoscopy may reveal trachyonychia, pitting, pterygium, chromonychia, nail fragmentation, splinter hemorrhages, onycholysis and subungual keratosis. Converging longitudinal streaks and nail-bed changes may indicate more aggressive disease.[66]

7.6. Other nail disorders

Traumatic nail disorder–Subungual hematoma: Appears as well-demarcated globular structures with black, purple, red or brown coloration, usually fading toward the periphery. The hemorrhage generally grows out with the nail, and follow-up can help distinguish it from subungual melanoma.[64,65,66]

7.7. Nail biting

Onychoscopic features include scaling and crusting of the nail folds, shortened nail plate,

exposure of the nail-bed epithelium and hemorrhages.[66]

8. Personalization of ungual drug delivery

8.1. Nail thickness

Nail thickness varies considerably between individuals and even between digits; thicker nails present greater barrier variability, while iontophoresis allows the applied current to be altered to modify drug permeation.[11,12,29] Nail thickness influences drug penetration because the nail is a dense keratinized barrier; the nail plate normally measures 0.25–0.6 mm.[11,12] In thickened/hypertrophied nails, nail abrasion can thin the nail plate, decrease fungal mass and make the nail bed more accessible to antifungal drugs.[1,12]

8.2. Nail hydration

Hydration markedly increases nail permeability and decreases electrical resistance by swelling/loosening the keratin structure and increasing pore size; most important changes occur rapidly, with about 90% hydration reached within 30 min in one study.[10,19,67] Hydration is an important parameter for ungual drug delivery.[10,19] Water causes the nail to swell, increasing the distance between keratin fibers and enlarging pores, thereby enhancing drug diffusion.[10,19,67] Hydrated nails become more elastic and permeable; occlusion can reduce water loss and help restore water/lipid homeostasis in dystrophic nails.[19,54]

8.3. Nail growth rate

Nails of the dominant hand tend to grow faster, which may contribute to differences in transonychial water loss and barrier properties; therefore, growth-related inter-nail variability should be considered.[12,67] Fingernails grow approximately 0.1 mm/day and take about 6 months for complete growth, whereas toenails grow 0.03–0.05 mm/day and require about 12–18 months.[1,12] Thus, the slower growth of toenails is associated in the review with a longer treatment period for toenail onychomycosis.[6,68]

8.4. Disease severity

In severe onychomycosis, oral and topical treatments are often combined; iontophoresis can increase drug delivery throughout the nail, which is important because the entire nail can be affected by onychomycosis and nail psoriasis.[29,55,56,57,58] Treatment selection depends on disease severity.[6,68] For onychomycosis, oral antifungals are recommended when ≥50% of the distal nail plate is affected, when the matrix is involved, when multiple nails are affected, or when topical treatment fails after 6 months. Topical monotherapy is an alternative for less

extensive disease without matrix involvement.

8.5. Location of infection

Delivery to peripheral areas including lateral, proximal and distal nail folds and nail bed is important for treating the entire affected nail; iontophoresis increases drug loading in these regions compared with passive delivery.[29] Treatment can therefore relate to infection location: mechanical removal may be useful for lateral nail-plate infection, while topical therapy is particularly indicated for superficial white and distal subungual disease involving <50% of the surface without matrix involvement.[6,68]

8.6. Degree of matrix involvement

Direct iontophoretic delivery through the proximal nail fold can target the nail matrix; this enhanced matrix delivery is expected to reduce recurrence after the nail plate and bed are cured.[29] Matrix involvement is an important treatment-selection factor. The systemic antifungal therapy when the nail matrix is affected, whereas topical monotherapy is described as suitable for distal subungual onychomycosis without matrix involvement.[6,68]

8.7. Patient age

Nail plates become thicker with age because nail-plate cells increase in size; therefore, age-related changes in nail thickness are a relevant source of inter-individual variability for transungual delivery.(1,11)Age affects treatment considerations: onychomycosis occurs especially in the elderly, while topical therapy is indicated for children because of its facility.[1,6,68] Systemic treatment may be less desirable in elderly patients because of side effects, drug interactions, and hepatic-injury risks associated with comorbidities.[1,68]

8.8. Toenail vs fingernail

Fingernails and toenails differ structurally and in permeability; in onychomycotic nails, fingernails were significantly more permeable than toenails, while iontophoresis produced greater permeation enhancement through toenail.(23,26,29)Toenail onychomycosis is reported to be 4–10 times more frequent than fingernail infection and requires a longer treatment period.[6,25,68] The difference in growth rate—slower for toenails—also affects the duration required for complete nail growth and treatment response.[1,6,68]

8.9. Drug physicochemical properties

For transungual iontophoresis, drugs should preferably be ionizable at a reasonable pH, have

low molecular weight and high solubility; low molecular weight improves transport and passive permeation, while high molecular weight limits penetration because of the small nail pathways.[23,27,29] Drug transport through the nail is influenced by the molecule's shape, conformation, size, charge, and hydrophobicity, together with drug concentration, vehicle, permeation enhancers and interactions with the nail keratin network.[12,23,27,29] Therefore, selection of the drug/formulation should consider these properties to achieve adequate transungual penetration.[12,23,29]

8.10. Drug pH/ionization

Formulation pH should generally be selected so that an ionizable drug is almost completely ionized, maximizing electromigration; pH also influences nail perm selectivity and electroosmotic transport.

8.11. Drug concentration/formulation

Drug concentration influences electromigration through the drug's transport number, but the effect depends on ion competition; for larger molecules, increasing concentration may not improve and can sometimes decrease permeation because of increase electroosmosis. Formulation/permeation-enhancer selection: Because penetration is limited by the keratinized nail barrier, treatment can be personalized through physical, mechanical, chemical and formulation approaches. Examples include hydration/occlusion, nail thinning, iontophoresis, microneedles, positive pressure, heat, solvents, keratolytics and disulfide-bond-cleaving agents, depending on the penetration problem.

9. In-vitro → Ex-vivo → In-vivo → Clinical Translation

9.1. In-vitro studies / In-vitro nail permeation

In-vitro nail permeation studies have been extensively used to assess whether transungual formulations can overcome the highly keratinized nail barrier. Human cadaver nail plates have been evaluated using Franz diffusion cells; for example, AR-12 showed measurable penetration, while 10% PEG 400 enhanced transungual delivery approximately six-fold and increased drug loading within the nail plate approximately two-fold.[75,77] Different formulation approaches have also been compared in vitro.[6] Ketoconazole nail lacquer produced greater drug accumulation in the deeper nail layers and supporting nail bed than marketed ketoconazole cream. Ketoconazole formulations containing thioglycolic acid showed higher permeation than those containing urea–hydrogen peroxide.[15] Other investigations demonstrated that penetration can be improved by chemical and physical

approaches. HP-β-cyclodextrin increased terbinafine hydrochloride flux, while iontophoresis increased terbinafine delivery across the nail plate.[20,76] Hydration-controlled systems and drilling/removal techniques have also been developed to measure drug penetration into the inner nail regions.[14,77] For luliconazole bilayer nail lacquer, in-vitro release was diffusion-controlled, with the bilayer formulation showing greater release than the single-layer formulation; bovine-hoof permeation studies showed 71.25 ± 0.11% cumulative drug release at 24 h.[15]

9.2. Ex-vivo human nail studies

Ex-vivo studies provide a closer approximation to the human nail barrier than artificial membranes.[78] Naumann et al. compared nail lacquer, colloidal carriers, solution and hydrogel systems using human nails together with bovine/equine hoof membranes. With human nails, nail lacquer and colloidal carriers demonstrated diffusion of approximately 55% and 45% of the applied drug, respectively, after 24 h; colloidal carriers showed faster penetration during the initial period.[78] Studies using infected human cadaver nails also demonstrated that permeation-enhancing systems could improve terbinafine transport across the infected nail.[76] The importance of nail hydration is also demonstrated by human-nail experiments: a film-forming panthenol treatment increased hydration and delivered more material into the nail interior and supporting bed than an aqueous solution.[77]

9.3. Nail infection models / microbiological evaluation

The literature contains in-vitro microbiological infection models rather than a complete animal nail-infection model.[15,20] Luliconazole showed antifungal activity against clinical isolates of Trichophyton rubrum, producing a 38-mm zone of inhibition.[15] Miconazole nail lacquer was also reported to inhibit the growth of Candida albicans on fungal-infected nail material.[20] The nail-disorder review additionally describes different clinical forms and sites of onychomycosis, including distal subungual disease involving the nail plate, nail bed and hyponychium, and proximal subungual disease involving the proximal nail fold.[15,16,20]

9.4.In-vivo / animal studies

The luliconazole bilayer nail-lacquer study included an animal skin tolerability study in Wistar rats.[15] Only slight application-site reactions/irritation were observed, supporting local tolerability of the formulation.[15] Thus, the evidence progresses from in-vitro/ex-vivo permeation and antifungal testing to limited animal safety evaluation, rather than demonstrating a complete animal onychomycosis efficacy model.[15]

9.5. Human clinical trials

The clinical-status table lists completed trials for terbinafine, ciclopirox, amorolfine/terbinafine, efinaconazole and tavaborole, while other agents such as luliconazole, TDT067, P-3058 and VT-1161 were reported as ongoing at the time of that review.[4,6,9,15,20] Clinical studies also evaluated combinations of systemic antifungals with amorolfine nail lacquer.[81] For example, itraconazole combined with 5% amorolfine lacquer was reported with clinical and mycological cure rates of up to 84%, while another longer itraconazole regimen with amorolfine was reported at up to 94%.[81]

9.6. Marketed products / clinical translation

The nail-lacquer literature identifies commercially available products including 8% ciclopiroxamine preparations (Onlyac, Penlac and Nailon), 5% amorolfine (Loceryl), and 5% econazole (Econail).[20]

10. CONCLUSION

Ungual drug delivery provides a promising approach for the localized treatment of nail disorders by overcoming the limitations of conventional topical therapy and reducing the need for systemic exposure.[2,4,6] The effective transungual delivery depends on overcoming the nail's keratinized barrier and considering factors such as nail thickness, hydration, growth rate, disease severity, infection location, matrix involvement, and drug properties.[1,6,21,29] Chemical enhancers, hydration, abrasion, iontophoresis, microneedles, and nanotechnology-based systems can improve drug penetration, retention, and controlled release.[8,20,29,43,45] Nanocarriers and combination approaches show considerable potential, particularly for onychomycosis and other nail disorders.[43,45,46,47] However, further research is needed to standardize nail permeation methods, validate these systems using infected human nails, and establish their clinical efficacy and safety.

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