

Pharmacotherapeutic Principles of Ungual Drug Delivery System

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Abstract

Ungual drug delivery (UDD) system bestows upon with the human nail as a hydrophilic barrier which can be used as a novel pathway to drugs used for therapy of nail disorders and also indications which cause those abnormalities. The common aberrations include onychomycosis, nail psoriasis, yellow nail syndrome, paronychia, etc for which UDD can be thought of. The basic requirement of any pathological condition is a drug in its appropriate dosage form. Although the nail barrier has a physiology which restricts drug absorption but certain physical and chemical modifications can be done to corroborate the drug delivery. Nail lacquers, polishes, varnishes and other forms of antifungal drugs are employed to accentuate drug action at sites of mechanical distortion or mycological infections. The electrochemical techniques and surgical procedures required are understood to enhance optimal drug therapy. The present paper studies the various unguinal disorders and ways to treat them using the novel unguinal delivery system.

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INTRODUCTION

A Human Nail epitomizes the barriers which embark upon conjectures of not only external delight but also lay certain endorsements to an individual's overall wellness. The science and technology pertaining to the unguinal part of human body is a microcosm to the development and innovation of a novel dosage form. A simple corollary is drawn out by every medical

practitioner when a patient suffers from any pathological condition such as that of anemia^[1].

Various benign indications such as listed below, are common advents and abnormalities that are correlated to impetuous treatment of various disorders.

1. increased nail thickness
2. horizontal white lines in the nails
3. concavity (spooning)
4. brittle, dry nails and infection^[2]

Table 1: Common unguinal changes^[3]

S. No.	Causative constraint	Ungual implications
1.	Aging	slowed nail growth and brittle, dull, or yellowish nails
2.	Environmental factors (e.g., exposure to chemicals, polishes, or harsh detergents; prolonged water exposure; reaction to adhesives used in artificial nails; use of certain medications)	Nail abnormalities like changes in the shape, size, and nature of the nail physiology.
3.	Injury or trauma (e.g., striking fingers with a hammer, closing fingers in doors, stubbing a toe, wearing ill-fitted footwear, biting nails habitually).	Spooning of nails, dryness, and infections

For establishing a correlation between the human nail and the diseased state, one must contemplate its horn-like envelope covering the dorsal aspect of the terminal phalanges of fingers and toes in humans. The nail plate which acts as a difficult barrier to external haptens provides an atypical ambience for drug penetration which is expended in this drug delivery system. Henceforth it is quintessential to study the various anatomic and physiologic features embodied by this part of our human makeup.

ANATOMY OF THE HUMAN NAIL

Human fingernails and toe nails are made of a tough protein called keratin, as animal’s hooves and horns. These are located on the dorsal aspect of the terminal 40% of the distal phalanx of each finger. The distal phalanx provides bony support for the nail

bed and is fractured in 50% of fingertip injuries^[4]. The nail bed lies protected between the nail plate and the distal phalanx. A smooth nail bed is essential for regrowth of the normal-appearing nail. The entire fingernail unit or onyx consists of the nail plate, the proximal nail fold (eponychium), the lateral nail fold (perionychium), the distal nail fold (hyponychium), and the germinal and sterile matrices ^[5].

Table shows different nail components and their physiology ^[6,7,8]

Nail Structure	Structural significance(Anatomy)	Physiology
Nail Root	The root of the fingernail is also known as the germinal matrix. This portion of the nail is actually beneath the skin behind the fingernail and extends several millimeters into the finger. The edge of the germinal matrix is seen as a white, crescent shaped structure called the lunula.	The fingernail root produces most of the volume of the nail and the nail bed. This portion of the nail does not have any melanocytes, or melanin producing cells.
Nail Bed	The nail bed is part of the nail matrix called the sterile matrix extending from the edge of the germinal matrix, or lunula, to the hyponychium. As the nail is produced by the root, it streams down along the nail bed, which adds material to the undersurface of the nail making it thicker.	The nail bed contains the blood vessels, nerves, and melanocytes, or melanin-producing cells. It is important for normal nail growth that the nail bed be smooth. If it is not, the nail may split or develop grooves that can be cosmetically unappealing.
Nail Plate	The nail plate is the actual fingernail, made of translucent keratin. The pink appearance of the nail comes from the blood vessels underneath the nail.	The underneath surface of the nail plate has grooves along the length of the nail that help anchor it to the nail bed.
Cuticle	The cuticle of the fingernail is also called the eponychium. The cuticle is situated between the skin of the finger and the nail plate fusing these structures together.	It acts as a waterproof barrier.
Perionychium	The perionychium is the skin that overlies the nail plate on its sides. It is also known as the paronychial edge.	The perionychium is the site of hangnails, ingrown nails, and an infection of the skin called paronychia.
Hyponychium	The hyponychium is the area between the nail plate and the fingertip. It is the junction between the free edge of the nail and the skin of the fingertip.	It acts as a waterproof barrier.
Germinal Matrix	The nail root and the sole structure responsible for the formation and growth of the nail plate. The nail root sits beneath the proximal nail fold. The matrix produces the keratin cells which form the nail plate. The matrix determines the shape and thickness of the nail plate.	The epithelium of the germinal matrix, sterile matrix, and eponychial fold contribute to the production of the nail plate through 3 modes of keratinization. The germinal matrix epithelium undergoes onychokeratinization, forming the main substance of the hardened nail plate, which is composed of stratified layers of cornified onychocytes.

Multiple arteriovenous anastomosis and myoneural glomus units are present within the nail bed. Capillaries are abundant in the germinal matrix. An arbor zing arcade of vessels in the distal nail bed communicates with a similar arcade from the palmar pulp vessels. Two large venous channels emerge from the lateral aspect of the nail bed and proceed dorsally to converge with the dorsal venous drainage system of the finger just distal to the distal inter phalangeal joint.

The lymphatic vessels follow the same route and have a similar network. The nerve supply to the nail bed is from the radial and ulnar digital nerves, which parallel the course of the arterial supply to the nail bed^[8].

Nail Growth & Regeneration

The nail plate is approximately 0.5 mm thick in females and 0.6 mm thick in males, and it tends to increase with age. The nail grows at a rate of approximately 1.8-4.5 mm per month or 0.1 mm per day; thus, the average nail can regrow completely in 6-9 months.

1. Periods of stress or illness can detrimentally inhibit nail growth.
2. biting or short trimming of the nail can heighten growth^[9].

The hardness of the nail is dependent on the onychocyte bands, matrix proteins, and the hydration level of the nail. The water content of fingernails varies from 10-30%. Brittle nail plates have lower water contents.

Trauma to the fingertip and nail unit remains the most common of all hand injuries. . Loss of nail-bed integrity can produce a permanent and significantly dysfunctional deformity of the fingernail. A traumatic nail-plate avulsion exposes the underlying nail bed, making it susceptible to the harsh environmental conditions^[10]. Blunt or sharp trauma to the nail compresses the nail bed and can result in lacerations and more complex crush injuries. Avulsion injuries are common and usually signify a greater level of

trauma. Blood and plasma exudate create a scab over this exposed nail bed. The surface epithelium and keratinaceous solehorn invariably remain adherent to the avulsed nail plate^[9].

PATHOPHYSIOLOGY AND PHARMACOLOGY OF THE NAIL

The nail being a complex structure as it is is affected by various disorders which embark upon certain pathophysiological parameters and furthermore help us understand the unguinal drug delivery system. A study of their treatment gives us a clearer picture of the drug disposition and pharmacokinetic parameters needed to be studied.

1. CER NAIL DEFORMITY

Omega nail deformity or trumpet nail deformity or a Pincer nail is a disorder contemplating transverse over-curvature of the nail plate.

Patient suffering from psoriasis, SLE, Kawasaki disease, cancer, end-stage renal disease, and some genetic syndromes have these indications. Although the etiology and pathogenesis of the indication is unknown but is often associated with an ingrown nail whether on hand or on toe ^[11].

Treatment

1. **Phenol matricectomy:** It is a technique in which a local anesthetic (such as lidocaine) is used, the outer edges of the nail are removed and phenol is applied which destroys the cells of the matrix, preventing regrowth of the nail^[12,13].
2. In any treatment of pincer nails, doctors may prescribe an emollient, such as Urea 40, to treat dry, cracked, itchy skin or an antibiotic to fight off or prevent infection^[12].

2. CHOMYCOSIS

Onychomycosis is a fungal infection of the toenails or fingernails. Onychomycosis causes fingernails or toenails to primarily

- a) thicken
- b) discolor

- c) disfigure
- d) Split

And secondary effects include irritation, pain and pressure. The incidence of onychomycosis has been increasing and is related to diabetes, a suppressed immune system, and signs with aging.

Onychomycosis is caused by 3 main classes of organisms: dermatophytes (fungi that infect hair, skin, and nails and feed on nail tissue), yeasts, and non dermatophyte molds. Dermatophytes include mainly *Epidermophyton*, *Microsporum*, and *Trichophyton* species. Yeasts include *candida* species^[14, 15].

The disease is characterized mainly into five types ^[14, 16, and 17]

1. **Distal Lateral Subungual (The Area under the Nail) Onychomycosis (DLSO or DSO):** In this case the fungus spreads from the skin and invades the underside of the nail where the nail meets the nail bed. Inflammation in these areas of the nail is seen.
2. **White Superficial Onychomycosis (WSO)** is usually confined to the toenails. Small white speckled or powdery-looking patches appear on the surface of the nail plate. The nail becomes rough and crumbles easily.
3. **Proximal Subungual Onychomycosis (PSO)** is characterized by an area of white spotting, streaking, or discoloration (leukonychia) develops near the nail fold and may extend to deeper layers of the nail. The nail plate becomes white near the cuticle and remains normal at the end.
4. **Candidal Onychomycosis:** In this the nail fold becomes inflamed (erythematous), or the nail plate separates from its bed (onycholysis). The affected fingers or toes start to look rounded on the ends, like drumsticks, and, sometimes, the entire thickness of the nail becomes infected. The nail bed thickens and hardens (nail bed hyperkeratosis), and inflammation of the

nail fold is observed in chronic mucocutaneous disease (disease of mucous membrane and regular skin).

5. **Endonyx Onychomycosis (EO)** Here the nail plate has a milky white discoloration; the nail does not separate from the bed (no onycholysis). The area under the nail (subungual area) does not thicken or harden (no hyperkeratosis).

Treatment^[18,19,20]

1. **Surgery (nail avulsion or matrixectomy):** Surgical approaches to onychomycosis treatment include surgically or chemically removing the nail.
2. **Newer oral antifungal drugs** terbinafine (Lamisil Tablets) and itraconazole (Sporanox Capsules) have replaced older therapies, such as griseofulvin, in the treatment of onychomycosis.

3. PARONYCHIA

Paronychia is inflammation of the nail fold often caused by localized, superficial infections or abscesses of the area around the nail or the epidermis bordering the nail. The nail plate becomes thickened and distorted with pronounced transverse ridges.

1. **Acute paronychia** is commonly associated with nail biting, aggressive manicuring, artificial nail placement, and trauma. The paronychia area is usually erythematous and tender, and the nail may appear discolored and distorted.
2. **Chronic paronychia** is the reaction of contact irritants or alkali and prolonged moisture exposure to the human nail. Cooks, bartenders, custodians, janitors, health care professionals, and patients with diabetes are at risk for chronic paronychia^[21,22].

Treatment

1. Development of an abscess requires incision and drainage as well as an appropriate oral

antibiotic such as amoxicillin with clavulanic acid to cover aerobes (gram positive and gram negative) and anaerobes^[23].

2. Chronic paronychia is treated with topical antifungal medication such as ketoconazole cream. A mild topical steroid like hydrocortisone may be added to the antifungal medication to help reduce inflammation ^[23].

4. NAIL PSORIASIS

Psoriasis is a skin disorder with signs of patches of raised, red skin with silvery scales. its common indications are clear yellow-red nail discoloring that looks like a drop of blood or oil under the nail plate, little pits in your nails, lines going across the nails (side to side rather than root to tip), thickening of the skin under your nail, areas of white on your nail plate, loosening of the nail, crumbling of the nail, tiny vertical black lines in the nail, redness of the pale arched area at the bottom of your nail, arthritis of fingers with nail changes^[23-27].

Treatment

1. Avulsion therapy by chemical or surgical means can be used as an surgical therapy for psoriatic nail disease.
2. Chemical avulsion therapy includes the use of urea ointment in a special compound to the affected nail under occlusion for 7 days, and the nail is removed atraumatically.
3. Systemic therapy if you have both skin and arthritis symptoms (systemic therapy is medication that spreads throughout your body). It is often in pill or injectable form, including methotrexate tablets, and injectable Enbrel (etanercept), Humira (adalimumab), as well as infusible Remicade (infliximab) ^[23].

5. HERPETIC WHITLOW SYNDROME

Herpetic whitlow is a self-limited disease characterized by is a lesion (whitlow) on a finger or

thumb caused by the herpes simplex virus(HSV-1, HSV-2 Strains are isolated). It is a painful infection that typically affects the fingers or thumbs. Occasionally infection occurs on the toes or on the nail cuticle ^[28-29].

Symptoms of herpetic whitlow include swelling, reddening and tenderness of the skin of infected finger. This may be accompanied by fever and swollen lymph nodes. Small, clear vesicles initially form individually, then merge and become cloudy ^[30].

Treatment

- a. Topical acyclovir 5% has been demonstrated to shorten the duration of symptoms and viral shedding.
- b. Antibiotic treatment should be used in case of chronic conditions ^[30-31].

6. SPOON NAILS (KOILONYCHIAS)

Iron deficiency anemia, trauma from nail biting or chemical solvents, blue-and-white fingers on cold exposure from Raynaud's disease or associated collagen vascular disorders such as Raynaud's phenomena and thyroid disease are some of the conditions that cause spooning of nails. This condition appears as the converse of clubbing. The nail bed is concave with the edges everted similar to a spoon. Multiple transverse grooves can result from several factors, including minor trauma, nail biting, chronic eczema, chronic inflammation, and paronychia.

Their treatment involves mainly use of antifungal drugs and topical preparations as discussed earlier. Further use of urea, vitamins, calcium and other growth regulators is comprehended ^[32].

7. PITTING

Nail pitting is construed as pinpointed pitted spots or defects in the keratin on the nail plate. It is caused by defective superficial layering and incomplete clumps of keratinized cells falling out of the nail plate. Pits

can be scattered in patients with psoriasis, alopecia areata, or trauma.

Dovonex (calcipotriene a synthetic form of vitamin D3) and Tazorac (tazarotene vitamin A derivative) could be used for enhancing the growth kinetics of nail regeneration. Application of a topical cream (corticosteroids) improves pitted nails [33].

8. NAIL PLATE OVERGROWTH (ONYCHOGRYPHOSIS) & NAIL PLATE THICKENING

Infrequent cutting with decreased arterial blood supply or recurrent trauma allows the nails to become thick and lose their surface luster. The nail keratin distally bends around and eventually curves under the toe. Excessive pressure causes subungual hemorrhage, especially in the presence of diabetes

mellitus or peripheral vascular disease. Other types of thickened nails may not have the dramatic changes of onychogryphosis.

Psoriasis causes thickened nails because of abnormal retained hard keratin; other characteristics include pits and small irregular depressions in the nails, distal onycholysis (abnormal thick and separated distal nail plate), and whole-nail dystrophy. Prevention and timely cutting of nails can be done.

Thick nails may be the result of genetic abnormalities, trauma, poor circulation, fungal infection, or inflammatory skin condition such as psoriasis. Thick nails may cause pain and are associated with distal separation, secondary fungal invasion, subungual hemorrhage, and skin breakdown [34].

9. NAIL DISCOLOURATIONS

Nail Color	Etiology	Treatment
Brown-Black ^[35-37,39]	<ol style="list-style-type: none"> 1. Acute subungual hematomas 2. Splinter hemorrhages 3. Hematomas 	Malignant transformation warrants a skin biopsy; the specimen should be taken from the most proximal pigment segment through the nail plate and include nail bed skin.
Green ^[38-39]	<i>Pseudomonas</i> excreting a pyocyanin pigment	Topical application of acetic acid (1%) compress, silver sulfadiazine, or ciclopirox olamine
White ^[39] (Leukonychia)	<ol style="list-style-type: none"> 1. Leukonychia is a white discoloration of the nail plate that can be total, subtotal, transverse, punctuate, or longitudinal. 2. Incomplete keratinization or abnormal vasculature of the nail bed. 	<ol style="list-style-type: none"> 1. Vitamins and calcium salts are given along with iron. 2. Anticoagulants could be given.
Yellow ^[40]	<ol style="list-style-type: none"> 1. Photosensitivity caused by drugs, such as tetracyclines. 2. Drug binding to keratin. 3. Low vascular supply. 4. Protein leakage. 5. Microvasculature effusion 	<ol style="list-style-type: none"> 1. Growth and blood supply is increased. 2. Antifungals are used such as <u>griseofulvin - oral suspension, Grifulvin V</u> 3. <u>itraconazole, Sporanox</u>

METHODS OF DRUG DELIVERY AND ROUTE OF DRUG ADMINISTRATION

The complexity of the nail anatomy and its drug delivery (ungual drug delivery) constitutes a concoction of deficiency in the literature and practical implications of the disorders as discussed earlier. The hurdles that a drug would face in case of unguinal drug delivery can be estimated by the assay of nail's inner drug content.

The following method is a basic test method for unguinal bioavailability and what should be the approaches in drug administration across the nail.

METHOD FOR ANALYZING DRUG CONTENT IN HUMAN NAILS [41-44]

1) Isolation of Human Finger Nail plates

Nail plates are collect from adult human cadavers & stored in a closed container at oC. Before each

experiment nail samples are gently washed with normal saline to remove any contamination, then rehydrate by placing them for 3 hrs on a cloth wetted with normal saline.

2) Preparation of Formulation

The test carrier formulation contains absorption enhancer (DMSO) & other excipients. Normal saline is the control. Concentration of sample in test carrier formulation & in normal saline control is measured. Also pH, pKa values for test, control formulations were measured. A $\mu\text{L}(5)$ aliquot is removed from each vial & radioactivity is measured in a Packard Liquid Scintillation counter (Model 1500).

3) Dosing & surface Washing Procedures

A $\mu\text{L}(5)$ dosing aliquot of the test solution is applied to surface of a nail plate with a micro syringe twice daily. Approximately 8 hrs apart for 7 days, Starting the second the day, each morning before dosing, the surface of the nail is washed with cotton tips.

4) System: Nail Incubation

A Teflon one-chamber diffusion cell is used to hold each nail. A small cotton ball wetted with 0.1ml normal saline is placed in the chamber to serve as a nail bed & provides moisture for the nail plate. The ventral (inner) surface of the nail is placed face down on the wet cotton ball. Hydration of the nail plate & the supporting cotton bed is measured with a relative humidity temperature meter. The cells are placed on a platform in a large glass holding tank filled with saturated sodium phosphate solution. A digital relative humidity/temperature meters is used for monitoring room temperature, the chamber temperature, & humidity. The holding is then covered, thereby monitoring the cells at a constant humidity of 40%.

5) Sampling & procedure

After completion of incubation phase the nail plate is removed from the diffusion cell. The nail plate is transferred to a clean Teflon diffusion cell for processing. The nail plate is inverted so that the

ventral (nail bed) surface faced up & the dorsal (outer) dosed surface faced down. The nail samples are removed as a powder by drilling. The powdered nail sample are transferred into glass scintillation vial & weighed. An aliquot of 5.0 ml Packard toluene -350 is added to the scintillation vial to dissolve the powder. All samples are incubated at 40C for 48 hours followed by the addition of 10 ml scintillation cocktail. The radioactivity of each sample is counted by a liquid scintillation counter.

6) Calculations

The amount of Nail sample removed is also measured by the difference in weight of the nail plate before and after drilling and collecting the core of power.

Drug penetration into the combined dorsal and intermediate layers of the center of the nail plate with the test carrier formulation and saline formulation is compared with both statistical analysis (Student's t-test) should show a greater penetration of drug into the ventral (inner) layer of the nail plate with the test carrier than saline control in case of antifungal formulation.

The above method is a basic technique to estimate or evaluate drug disposition across nail. Now we may embark upon certain overtures of Ungual Drug Delivery [45].

1. Topical application

The accumulation and activity of drugs in the nail on topical application depends upon the two most important parameters to be understood. These include:

1. The physicochemical properties of the drug need to be favorable for absorption through nail matrix.
2. Binding of the drug to keratin reduces the availability of the free drug.

The nail matrix favors hydrophilic drugs rather than lipophilic drugs and antifungal drugs have high binding affinity for keratin.

2. Chemical Penetration Enhancement

Keratolytic and thiolytic substances enhance permeability of nail matrix by chemical modification of keratin.

Topical monotherapy is less efficient in treating nail abnormalities such as onychomycosis due to poor trans-nail bioavailability of drugs.

3. Physical Penetration enhancement

Iontophoretic trans-nail delivery method increases the permeability of the drug to the nail membrane as shown with:

1. NanoPatch Nail Fungus

NanoPatch Fungus uses AC/DC electrochemistry and targeted drug delivery to actively push antifungal drugs right through the nail cuticle to the actual location of the fungus growth.

2. ChubTur™ cell

The cell is composed of donor compartment; nail adapter, receiver chamber and sampling outlet. The study, development and optimization of per unguis delivery systems in an environment close to those that would occur in vivo can be seen.

3. Mesosclissioning technology

Mesosclissioning technology creates a micro-conduit through the skin or nail within a specified depth range. Fully open pathways can be scized (cut) through the through the nail. These pathways can be used to deliver drugs across the skin such as micro conduits also permit access for drugs.

DRAWBACKS AND LIMITATIONS

Although nail lacquers, gels and other antifungal drugs in various dosage forms have entered the market. Such as Eco-Nail nail lacquer, Loceryl nail film, Umecta nail film, Tazorac 0.1% Gel, Zalain nail Patch, Penlac nail lacquer from various multinational companies like MacroChem, JSJ Pharmaceuticals, Labtec etc. Ungual drug delivery system faces major pharmaceutical setbacks in cases of:

1. Thickness

The nail plate is much thicker creating a much longer diffusional pathway for drug delivery.

2. Resistance to drug penetration

Stable disulphide bonds accentuate the hardness of the nail and restrict drug penetration.

3. Polarity Barrier

Unlike other barriers nail acts as a hydrophilic gel rather than lipophilic which is a convention for drug delivery systems across other body tissues having a bi-lipid membrane.

4. Physical and Chemical Differences

The chemical and physical differences between the nail plate and the *Stratum corneum* explain the long treatment times and lack of efficacy of topical formulations.

Hence any formulation or dosage form prepared for unguis drug delivery must understand physicochemical properties of the drug molecule (e.g. size, shape, charge log P etc), the formulation characteristics (e.g. vehicle, pH drug concentration), possible interactions between the drug and keratin and possible penetration enhancers [45].

CONCLUSIONS & DISCUSSIONS

The present paper hence gives us the basic understanding of unguis drug delivery system correlating at the complex nail disorders with the requirement of the dosage form.

Topical nail preparations like lacquers, enamel and varnish have aesthetic appeal but there usage as a medicament is understood as even basic nail varnish consists of solvents, film forming polymers, resins, plasticizers which give flexibility and durability to the film, which enable the film to adhere to nail plate and help it penetrate across the matrix.

The common disorders discussed such as onychomycosis, nail psoriasis, yellow nail syndrome, paronychia, etc. give us the functional requirements and knowledge of what kind of dosage form or drug delivery system unguinal drugs should be.

The recent modifiers and enhancers which physically, chemically and topically enhance the drug bioavailability are also looked upon in this paper.

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