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Enhanced Medicated Lacquer Formulation for Managing Psoriatic Nail Disease

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Abstract

Nail psoriasis often requires prolonged treatment, with frequent relapses being common. Effective management typically involves extended therapy, as oral anti-psoriatic medications can pose a risk of liver toxicity as a notable side effect. Alternative treatments include monthly corticosteroid injections into the nail folds. Topical therapies, such as medicated nail lacquers, offer the advantage of targeted drug delivery directly to the affected area, reducing systemic exposure and minimizing potential adverse effects. However, a significant challenge is achieving effective drug penetration through the dense keratin structure of the nail plate. This review examines recent advancements in medicated nail lacquer formulations, focusing on strategies to enhance drug delivery across the nail. Key factors discussed include the molecular size, hydrophilicity, lipophilicity, and overall formulation properties that influence efficacy. Commonly used medications in these formulations include clobetasol, tacalcitol, tazarotene, urea, and calcipotriene. By emphasizing the critical role of formulation, this review highlights the effectiveness of medicated nail lacquers in optimizing drug delivery for psoriatic nail disease.

Keywords: Nail psoriasis, Medicated nail lacquers, Transungual drug delivery, Factors responsible for the transportation, NAPSI.

Introduction

Psoriasis is a chronic inflammatory disease of the skin, nails, and joints[1]**.** 50% of skin psoriatic and 70% of psoriatic arthritis patients normally develop psoriasis in the nail apparatus[2,3] even though the first trigger for nail psoriasis remains unclear**.** The disease includes the nail matrix and nail bed, inducing aesthetic issues, and purposeful harm to patients[4]**.** The pathologic process of psoriasis involves tumour death factor-a (TNF-a) clarifies TNF or TDF, nerve fibre cells, and T-cells[5,6]. Fingernail psoriasis is an additional problem for several patients than toenail psoriatic disease. Additionally, psoriatic toenails are which can complicate treatment assessment**,** clinically, nail disease has several displays locking on the placement of the inflammatory method.

The impacts of nail psoriasis are often high. In the USA, the disease has an effect on between 7 and 4.5 million people, 1, 2 than in Canada; 1 million people comprise psoriasis[7,8]. Whereas nail psoriasis treatment is difficult and involves general therapies, topical and intralesional[9]**.**

Topical drug delivery system is advantageous over oral drug delivery that, it should have a smaller number of systemic side effects. In topical drug delivery drug concentration in the tissue is in higher concentration, which is generally required for topical infection of the

nails or skin. The several advancements in the transungual drug delivery that have been developed. By this route, anti-psoriatic drug therapy should be given for treating the nail Psoriasis[10]. The nail drug delivery is given in the form of nail lacquer which acts by forming a film on the upper surface of the nail. The nail lacquer formulations act as a film-forming system and these systems are given topically and transdermal formulations. This formulation contains drug and film former as a major constituent. The film-forming polymer thus acts as a matrix system for sustained or controlled release of the drug into the nail. The nail structure is hard, so for the drug delivery through the nail, several types of penetration enhancers are generally used e.g. physical, chemical, and mechanical methods to increase penetration of the drug via the hard keratin network of the nail[11].

Macroscopic anatomy of the nail unit:

The unit of the nail is made up of epithelial and connective tissue compartments. It forms a functional unit with the entire digital tip and contains the bone of the distal phalanx, the distal interphalangeal joint with its tendons and ligaments, 2 compartments of adipose tissue of the digital pulp, innumerable nerves and highly specialized sensory nerve organs, sufficient blood supply, and lymphatic vessels, The nail is a unique structure of the body and it consists of the nail plate, nail bed, nail matrix, nail folds and hyponychium[12].

Nail matrix:

It is a germinative epithelium responsible for the origination of the nail plate. The nail matrix is generally accountable for the nail plate substances. The proximal part generally resides in the nail fold, through the nail plate distal edge is clearly seen as a white lunula. The superficial portion is generally constituted by the proximal matrix and the under the surface of the nail plate is formed by the distal part of the matrix. In the lowest cell layer of the nail matrix, it contains melanocytes and gives pigments to the keratinocytes. Under normal circumstances in the nail plate of white individuals the pigments are not perceptible, but in people who have black pigment shows melanogenesis as pigmented bands[13,14].

Nail bed:

It generally comprises of an epidermal and underlying part of the dermis, which is opposing to the membranes of the distal phalanx. In the nail bed, there is an absence of body covering the fat layer, although microscopically dermis cells are perceptible. The epidermis of the nail bed, are not much thicker, and living keratinocytes to a dead ventral plate of a nail the transformation zone is instantaneous and occurring within the house of one horizontal cell layer[13,14].

Nail folds:

The nail fold is mainly divided into two types, proximal and lateral nail folds, and the first perform of a fold is to support and shield the nail from harmful agents. The proximal nail fold generally comprises cuticle, as it is a distal finish product of proximal nail fold and cuticle directly attaches in the nail plate and its main function is to protect the nail from irritants and environmental pathogens[15]. The nail folds are smooth tissue structures that defend the lateral and proximal edges of the nail plate. The proximal nail fold protects the nail matrix from trauma and ultraviolet rays[16].

Hyponychium:

Another part of the nail that is gift below the nail plate, in the joint of free edge and skin of fingertips. The main function of Hyponychium is the formation of sealer for the protection of a nail bed from external microorganisms[15]. The hyponychium is that the space distal to the nail bed and at a lower place the free finger of the nail plate[16].

Nail plate:

The basic structure of the nail plate is made up of three basic layers, the first one is the dorsal

layer, the second one is an intermediate layer and the last one is the ventral layer. The nail plate consists of a huge amount of calcium in the concentration of 0.1% by weight, which is substantial 10 times than hairs. The other elements which are exists in the nail plate are copper, manganese, zinc, and iron, in a small amount. The hardness of the nail is occurred because of the presence of sulphur as a protein, which is different from soft keratin relatively of the epidermis[17].

Clinical manifestations:

The simultaneous presence on both hands and any part of the nail might be affected by psoriasis. Yet if the nail matrix is disturbed, nail modification is even more severe. The site of the inflammatory response determines the severity of nail involvement. If the nail matrix is involved, indentation (pitting), leukonychia, red lunula spots, and onychodystrophy may occur. Extreme nail psoriasis can cause nail crumbing to occur[18]

Transungual Drug Delivery:

Transungual drug delivery is outlined as a system that's expounded to move of a drug across the fingernail or toe nail to realize targeted drug delivery to treat nail illness. Within the term transungual, Trans means "through" and unguis means "nails"[19]. Transungual drug delivery system is assumed to be quite effective, as a result, its localized action and higher adherence that provides less systemic side effects**.** Ungual therapy provides more additional advantages over the general drug delivery such that preparation is easily compared to the oral dosage form. Systemic adverse effects and drug interactions are absent. Less common native rash connected adverse effects like periungual erythema of the proximal nail fold bit by bit gradually disappear once a couple of minutes and frequently get small over time as a result of the body befits to the new medication. General absorption smaller amount in transungual and its supported topical formulation in older that is simply removed once required ungual therapy is appropriate for those that square measure unable to require general medication and supply improved adherence[20].

Table 1: Commercially available topical formulations for the treatment of nail psoriasis:

Drug	Dosage form	Brand name	Manufacturer
Clobetasol	Cream, ointment	Temovate®	GSK, philadelphia, USA
Tacalcito	0.05% cream	Curatoderm®	Almirall, Germany.
Tazarotene	0.1% gel or cream	Tazorac®	Allergen, Irvine, Califomia
Urea	40%	Umecta®	JSJ Pharmaceuticals, Charleston,south carolina.
calcipotriene	Cream	Dovonex®	Leo Pharma.Inc Dubin,Ireland.

Major Challenges:

There are some major challenges in the permeation or transportation of the drug through the nail which are as

follows-In the nail sulphide bonds are there, which generally makes the nail harder and restricted the penetration of medicated agents via nail to cure the diseases of the nail. So, for the delivery of the drugs, there are using some penetration enhancers (i.e. Physical, chemical and mechanical) which can easily penetrate through the nail barriers by breaking the sulphide bonds of the nails and delivers the drug into the required site. Designing the drug delivery, for the absorption of the drug via topical route it should be extremely important

to consider the physicochemical properties like- formulations characteristics (solvents, film formers, plasticizers, pH and concentration), drug molecule (size, log P, shape and charge), possible penetration, the possibility of drug and keratin content of nail[21].

Approaches for Transungual Drug Delivery:

Nail penetration may be attained by numerous ways like mechanical and physical methods as mentioned within the previous text.

Chemical Methods:

The chemical methods are more beneficial and suitable for lacquer preparation than physical and mechanical methods. A combination of 2-mercaptoethanol and N-acetyl-l-cysteine is delineated to improvise the delivery of tolnaftate, into the nails. The penetration of oxiconazole via N-acetyl-l-cysteine has additionally been documented[23]. Keratolytic agents like enzyme, urea, and 2-hydroxybenzoic acid were utilized in enhancing the penetration of few antifungals like ketoconazole, miconazole[24]. Furthermore, organic solvents like fermentation, isopropyl alcohol, humectants, and synthetic resin are in enhancing the penetration of drugs over the nail. Direct interaction of organic solvents gift in formulation with the nail plate just in case of transungual drug transport may lead to an increased barrier electrical phenomenon of the nail[25].

Nail lacquers:

To cure the nail psoriasis, it requires a high period of treatment and the recurrence is common. Oral period of treatment and the recurrence is common oral anti-psoriatic side effect cause liver toxicity while nail psoriasis therapy requires the monthly application of corticosteroids into the nail folds (skin around the nail plate). Topical treatment targets the medication to its place of action using nail lacquer as a delivery vehicle; therefore, opioid reaction and adverse effects resulting from acute exposure to narcotics can be prevented. The technology to manufacture, package, and apply nail lacquers has existed for a long time, most individuals are familiar with nail lacquers, and the procedure is straight forward and pain-free. After the lacquer is added to the nail plate, medicated nail lacquers for production, decoration, and used in cosmetics. This is one of the latest dosage forms especially for transungual delivery drugs when it is applied to the nail.

A major constituent of the medicated nail lacquers is the active ingredient, film-forming polymer, plasticizer, volatile organic solvent, pearlescent material, resins, and colorant, etc[25]. Due to the long contact time between the nail and the medicated nail lacquer, the optimum concentration gets into the target side. Drug distribution is based on matrix-controlled release system. The formation of the water-insoluble film maintains a high drug concentration than the normal nail lacquer[26]. Due to the high drug concentration, a concentration gradient takes place which helps in the diffusion of drugs across the nail. The drug store is replenished by applying a new layer of nail lacquer after taking off the previously applied nail lacquer or film either with organic solvents or mechanically. In the medicated nail lacquers, the dispersion of therapeutic agents in an apt lacquer base. After application, Fig.2 explains the drug release from medicated nail lacquer and film formed. The release of the drug across the nail unit area is determined by the Fick's law of diffusion[27] and the equation are bellowed.

$$J = -D\, dc/dx. \quad (1)$$

Where,

D=diffusion coefficient of drug in polymeric film.

dc/dx =difference in concentration across diffusion path length of dx.

The nail lacquer has additional pros such as prolonged residence time, aesthetic appeal, patent knowledge with the formulation, and decrease in the transbronchial loss of water. Transonychial water loss (TOWL) is the way water gets loss from the nail plate to the surrounding. TOWL can be prevented by applying the nail varnish[28] which leads to the hyperhydration of the nail plate. Due to the hydration and swelling, there is a formation of aqueous pore takes place which enhances the drug diffusion[29]. Most of the marketed Nail lacquers consists of water-insoluble based polymers as they supply high attach ability to nail plate.

Mechanism of film formation and Permeation:

The nail lacquer as a film-forming system is directly applied to the nail. These formulations generally penetrate through the nail by breaking the disulphide bond of the nail, then new pores will be formed and better the penetration of drugs via nail plate which is beneficial in treating the diseases of the nail[30].

Clinical Status of Psoriasis:

Transungual distribution area unit clinical trials started with the discovery that medication delivered locally could penetrate directly into the nails. Less nail permableness has observed the safe and efficient trans-ungual transport the safe and efficient trans-ungual transport of topical anti-psoriatic medication in psoriasis. Therapeutic potency can be gained in order to exert successful antipsoriatic activity which should bear permeation through the nail plate with quality. Varied clinical trials were had been conducted on anti-psoriatic and area units still in the current method to judge the potential of ant psoriatic in treating Psoriasis. Table 2 lists the clinical standing of medicine utilized in Psoriasis[31].

Table 2: Clinical studies conducted using nail lacquers as drug delivery vehicle

Formulation	Active. ingredient	Type of study	Dosage regimen	Observation	Remarks	1st Author and year
Hydrophilic NL	Horsetail extract and methyl sulfonyl methane		Applied once daily on the affected fingernails of the left hand for 24 consecutive weeks in 24 patients. The right hand was used as control	At the end of treatment, a 72% reduction in pitting, 66% reduction in leukonychia, 63% reduction in onycholysis at a reduction of 65% in NAPSI score were observed as compared to baseline. The value at baseline was 2.83 (0.99). No changes were observed in the untreated nails	The new water-soluble NL was observed to be effective in decreasing signs and symptoms of nail dystrophy in psoriatic patients	Cantoresi (2009)[31]

NL	Clobetasol (0.05, 1, and 8%)	A prospective, controlled and randomized pilot study	Group A treated with 0.05% clobetasol NL; Group B treated with 1% clobetasol NL, and Group C treated with 8% clobetasol NL twice a week for 16 weeks	Group C showed a statistically relevant clinical response in terms of NAPSI score	The 8% clobetasol NL was found to be effective and safe	Nakamura (2012)[32]
Hydro soluble NL	Equisetum arvense and methyl sulfonyl methane	Randomize double-blind, placebo controlled, parallel group trial	The test product or a placebo was applied once daily for 24 weeks to all fingernails in 43and 44 patients, respective	After24 weeks, 55% of patients treated with the HPCH NL vs. 31.7% of the placebo patients were cured	HPCH NL was reported to be a valid, effective, and safe option that can be used to decrease the signs of nail dystrophy in psoriatic patients	Cantoresi (2014)[33]
NL	Apremilast	Observational study	A 20-ll aliquot of NL formulation was applied on each nail twice a	NL formulation containing dexpanthenol and salicylic acid as penetration enhancer was able to improve the loading of apremilast in nail plate approximately two-fold more	The investigation illustrated that NL formulation was able to deliver a	Kushwaha (2017)[34]

			day for 15 days to 15 human subjects	compared to control (without enhancers)	sufficient amount of apremilast into and across the nail plate	

The formulation of nail lacquer consists of different types of antipsoriatic drug and their efficacy is tested clinically. The effectiveness of NLs formulation composed of eight percentages of clobetosol17-propionate was calculated. The nail lacquer formulation was tested on ten patients with nail bedand matrix once in a day for 504 hours two times in a week for 270 days. After the trials, there was a decrease in nail pain was seen and it depends upon the period of therapy. Lack of local adverse effects like atrophy were seen. Thus, nail lacquer formulation can be considered as a safe, effective, and cosmetically applicable to the patients of nail psoriasis[35].

In 2002, Nakamura et al. carried an experiment in order to find out the efficacy and safety of clobetasol nail lacquer on 15 patients who were all suffering from the nail psoriasis in different concentrations (0.05%, 1% and 8%). The patients were examined after 16 days by photographic records and NAPSI score. In conclusion, the author stated that the efficacy and safety of the 8% clobetasol were high and it is the concentration for the topical treatment of nail psoriasis[36].

Table 2 illustrates the various clinical studies carried out by different researchers to determine the efficacy of various drugs using NL as drug delivery systems In case of another clinical trial report on nail lacquer was applied to 87 patients once in a day for 6 months which are hydro soluble comprising hydroxypropyl chitosan, Equisetum arvense, and methyl sulphonyl methane. This trial results in the improvement in NAPSI score and very good level permissibility from 97% of patients**.** Even though there was excellent clinical documentation but the formulation of nail lacquer was a difficult one. The movement of drugs across the nail plate based on the drug characteristics, excipients used, product properties, and the drug permeation affected by the disease state. The factors influencing the movement of drugs across psoriatic nail are described in the following.

Factors responsible for transportation of the drug into and via nail plate:[37,38,39,40,41]

Molecular size of the drug: The molecular size of the drug is inversely proportional to the penetration of drugs into the nail plate. So, if the drug molecular size is enlarged, it is tougher to the molecules to diffuse via the keratin network of the nail, and then it results in diminish the permeability coefficient via the nail plate.

Hydrophilicity/ lipophilicity of diffusing molecule:

The permeation of lipophilic molecule over the nail by the means of lipid pathway. If the lipophilicity of the molecule is higher, then it leads to increase permeation across the nail. The permeation of aqueous molecule over the nails by swelling of the nail. The nail swells because water is an act by hydrating the nail and enlarging the keratins network, which finally leads to the formation of larger pores, which in turn easier the permeation of diffusing molecules.

Nature of vehicle:

The transport of drug via the nail plate nature of vehicle plays a major role. The use of aqueous vehicles mainly acts by moisturizing the nail which causes swelling of the nail plate. The swelling of the nail then causes an increase in distance between the keratin networks; it

then increases the permeation of large molecules across it. If in place of water use non polar solvents, leads to decreased hydration of the nail when the formulation is given via nail.

Formulation effects:

The formulation also has effects on the permeation of the drug via a nail. The pH of the formulation having to inflict an effect on the degree of ionization of weak acid and weak base which then reduces the permeation via the nail plate. Then it will lead to minimizing the solubility in the formulation and splitting of the formulation when it applies to the nail plate which then leads to minimizing the interaction of formulation with the keratin network of the nail.

Patent Reports on Nail Lacquer:

While a variety of analyses reported are often found in literature, numerous patents have additionally been reported specifying the business potential of nail lacquers for transungual drug delivery.

Table 3 Patents of formulations proposed for treatment of nail psoriasis

Patent number, year	Title of the patent	Descriptive comment	Reference
KR100610517B1, 2007	Nail polish for the treatment of psoriasis	Relates to formulation of a nail lacquer based on water insoluble film-forming polymer containing glucocorticoids (2– 15%)	[42]
ES2271373T3, 2007	Nail varnish containing tazarotene and its use in the treatment and/or prevention of psoriasis	Relates to the formation of a nail varnish-containing tazarotene, water-insoluble film-forming polymer and other components like co solvent and polar solvent	[42]
US20090175945A1, 2009	Systems, methods, and formulations for topically treating nail fungal infections and nail psoriasis	Relates to a system comprising an anti-psoriatic agent, at least 10% water by weight, and a first barrier film configured to form a sheath over said nail and said active agent formulation.	[43]
EP2349243B1, 2015	Urea-based film-forming solution for treating nail psoriasis	Relates to a film-forming solution comprising: 10–20% of urea, 5–15% of a film-forming polymer (Eudragit E100), 45– 65% of a polar solvent (ethyl alcohol) and 1–20% of a co solvent (propylene glycol)	[44]
US6352686,2002	Antipsoriatic nail polish	Relates to nail lacquer comprising one or more glucocorticoids, one or more physiologically tolerable solvent and film-forming agents containing quaternary ammonium groups for stable nail enamel	[45]

US4250164,1981	Method of treating psoriasis of the nail and composition	Relates to the nail lacquer for the effective management of nail acanthosis/psoriasis prepared by mixing 0.1% valisone lotion in Revlon clear nail lacquer in 50:50 mixture	[46]

Evaluation of nail lacquers[47]**:**

Evaluation of the dry time can be done by applying the nail lacquer on a glass plate and measuring the drying time with a stopwatch to find out the dried film by touching with the finger. The endpoint is no mark on touching the film by finger. The non-volatile is evaluated by weighing (1 0.2g) and homogeneous spreading the sample on a Petri dish and dried using hot air oven at 105±2°C for 60 mins, then reweighing. The non-volatile content can be determined using the weight difference. The blush test used to evaluate the water resistance or blistering of the nail lacquer. A sample (0.2ml) is poured and homogeneously spread over a glass plate, which forms a film on drying it at room temperature for one day. The glass plate was immersed as half part dipped and the other half part remains above the level in a beaker (250ml, 50% filled with water) for 240 mins. After, the plate was taken out, wiped using tissue paper, and kept for 240 mins at room temperature for drying. After this process, it was seen for blush/blisters. In vitro adhesion test is done with a glass plate by applying the nail lacquer film (1 9 2.5cm2) to the glass by using the brush In vitro adhesion measurement is done by applying a film on a glass with a brush. The film was dried at room temperature for a day and the film was tested using the pressure-sensitive adhesive cellophane tape by covering the film with this and applying the pressure with the thumb. Then it is removed aggressively. To determine the % of the film get the peel off, the adhered nail lacquer to the glass plate was calculated. Brookfield viscometer is used to determine the viscosity of nail lacquer. The in vivo efficacy and in vitro permeation of the nail lacquer was determined after the evaluation of physicochemical properties. Table 3 represents the different trails done by different researchers with various drugs using the nail lacquer formulation.

Advantages of nail lacquer[48,49]**:**

Medicated nail lacquer has several advantages than other conventional forms. The patient will never feel like he/she is affected with nail psoriasis because it masks the affected nail with coloured film. These formulations are not removed by wiping and rubbing. These formulations having prolonged contact due to the film formation on the applied surface so the controlled release of the drug for a longer period has been done and absence of systemic side effects. The drug-drug interactions are too low.

Disadvantages of nail lacquer[49]**:**

These formulations are having local side effects such as as-periungual erythema and proximal nail fold erythema. Other adverse effects include nail disorders such as as-shape change, irritation, and discoloration of the nails and ingrown toenail. The therapy takes longer time to cure diseases of the nail.

Future Prospective:

Nail Psoriasis has a great bang on the patient value of life as a result, high pain and aesthetic concerns. Topical formulations itself consists of the limitations. Effectively permeate and targeted to the nail bed and nail matrix, in this are needed to develop suitable formulation research for curing the nail psoriasis. Medicated nail NLs and particular permeation enhancer can be favorable and more effective formulation. For the nail psoriasis more evidence is needed to prove their efficacy. It is also used in combination with systemic agents

for more severe nail disorders to provide beneficial effects. Therefore, some medicated nail lacquer formulation research is ongoing. Newer effectively permeation enhancement and targeted to the nail bed and nail matrix approach under review using the serratiopeptidase, thioglycolic acid, and other sulfhydryl agents[49]. The analysis studies are being conducted to advanced and develop in-vivo and in-vitro models so the absorption, distribution, metabolism, and excretion of dosage form can be measured additional accurate and valid to judge the impact of association nail hydrogen ion concentration and alternative connected factors on the trans-ungual penetration[50]. An insight into the models for onycho pharmacokinetics is extensively deliberated in the literature that will facilitate full to seek out capable unharnessed technique which will withstand the barrier of the nail.

Conclusion:

The topical drug delivery system having advantages over the oral drug delivery system in topical drug delivery system targeting of drugs directly into the required site. In this review, we concluded that for the nail psoriasis, we generally used nail lacquer as topical drug delivery because the nail lacquer having a greater penetration rate than other topical formulations. Medicated nail lacquers generally act on a principle that it will form a film on the application surface from which the drug is released at a controlled rate for an extended period. So, we can say that nail lacquers are the best, cheap and it should have better patient compliance than other formulations or newer techniques that are employed for the enhancement of drug delivery over the nail plate.

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