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A REVIEW OF UV CURABLE GEL FOR NAIL DISEASES

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Abstract:

Nail diseases are common, cause significant distress and treatments are not much successful. The nail unit can be subjected to numerous disorders, some of which, for example , onychomycosis (fungal nail infection) and psoriasis , are often extremely painful, recalcitrant to treatment , and result in psychosocial and occupational consequences, reducing a person's quality of life. Current treatments include topical and oral antifungals. Oral therapy has the inherent disadvantages of systemic adverse effects , drug interactions and contraindications . Topical therapy , on the other hand, has a very low success rate. But ,in comparison with all these therapies ,UV curable gel formulations could act as a drug depot on the nail plate. The formulations typically contain three major components: a urethane methacrylate based monomer (at 75- 85% w/w) ,(meth)acrylate based monomer (at 15-25% w/w) and a polymerisation photo initiator (at 1- 3% w/w). Following application of the formulation on the nail plate surface , the nail is placed under a UVA lamp for approximately 2 minutes . The UVA lamp light initiates polymerisation and a glossy , cosmetically acceptable polymeric film is developed on the nail plate . The film has long residence on the nail plate and such a film could be used as an effective drug carrier to improve the topical therapy of nail diseases.

Keywords: *nail disease; topical therapy; UV curable gel; drug depot; UVA lamp.*

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INTRODUCTION:

Onychomycosis affects approximately 14-18% of the general population, up to 25% of the geriatric and diabetic populations and its occurrence is increasing day by day .Current treatments include topical and oral antifungals . Oral therapy is subjected to a failure rate of 20% as well as relapse of 25% . Topical therapy , on the other hand, has a very low success rate with medicines that are currently available[1].

Nail psoriasis affects approximately 1% of population and its treatment may include repeated injections of corticosteroids into the nail folds , and topical or systemic treatments depending on the symptoms .[2] But these have various adverse effects such as pain , systemic toxicity and drug interactions. Also topical management remains as a challenge due to low drug penetration through the nail plate .

UV curable gel formulations are currently used as nail cosmetics, where they are commonly known as UV gels[3]. These formulations could act as a drug depot on nail plate. Following application of the formulation on the nail plate surface , the nail is placed under a UVA lamp for approximately 2 minutes . The UVA lamp light initiates polymerisation and a glossy , cosmetically acceptable polymeric film is developed on the nail plate . The film has long residence on the nail plate and such a film could be used as an effective drug carrier to improve the topical therapy of nail diseases .The formulation would be applied and removed (when desired) by a health care professional treating the patient .

UV curing is a process in which ultraviolet light and visible light is employed to initiate a photochemical reaction that generates a cross-linked network of polymers [4] .UV curing is applicable to printing ,coating , decorating and assembling of a variety of products and materials . UV curing is a low temperature process , a high speed process and cure is by polymerisation rather than by evaporation technique.

UV gels have been widely used as cosmetics since 1982. Only a few cases of hypersensitivity and allergic reactions have been reported so far. Such adverse reactions are caused by the monomers (rather than the polymers) and occur after several months of overexposure .The cured film does not pose a hazard and therefore the adverse reactions can be avoided by applying the formulation to the nail plate only and avoiding its application to the skin surrounding the nail plate .This is done by leaving a formulation free margin at the nail folds . The use of UVA radiation to trigger polymerisation is not considered as a risk factor .The two hands of a person placed in a UV nail lamp for 10 minutes twice a month (as could happen for cosmetic use) is similar to that person spending an extra 2.7 minutes in sunlight every day for a month [5]. A person could use a UV nail lamp for 2.8 hours each and every day without any requirement for warning or protective measures. UVA radiation emitted by UVA nail lamps specifically designed for curing UV gel pose a low risk of skin carcinoma even when used weekly for over 250 years.

STRUCTURE OF HUMAN NAIL:

The human nail is the thin , translucent , horny sheath on the dorsal surface of the distal end of each terminal phalanx of fingers and toes . It consist of the nail plate , nail matrix , proximal and lateral nail folds , nail bed and hyponychium , which are collectively known as the nail unit.

Nail matrix:

The nail matrix is the tissue which the nail protects. It is the part of the nail bed which is beneath the nail and contains nerves, lymphs and blood vessels. The matrix is liable for producing cells that become the nail plate. The lunula is the visible part of the matrix, the whitish crescent shaped base of the visible nail.

Nail bed:

It is the skin beneath the nail plate. It is made up of two types of tissues; the deeper dermis, the living tissue which consist of capillaries and gland and the epidermis, the layer just beneath the nail plate, which moves towards the fingertip with the plate.

Hyponychium:

The hyponychium is the epithelium located beneath the nail plate and is at the junction between the free edge and the skin of the fingertip. It forms a seal that protects the nail bed.

Nail sinus:

The nail sinus is where the nail root is i.e., the base portion of the nail underneath the skin.

Nail plate:

It is the hard part of the nail , made of translucent keratin protein . It consists of 3 histological layers of keratinous tissue known as the dorsal , intermediate and ventral layers . The nail plate consists of both ‘hard’ hair type keratin and ‘soft’ epithelial type keratin .The hair type keratin is present only in intermediate layer and epithelial type keratin are found within the dorsal and ventral layers . Keratin is held together by globular, cysteine rich proteins whose disulphide links behaves like an adhesive.

Schematic diagram of nail

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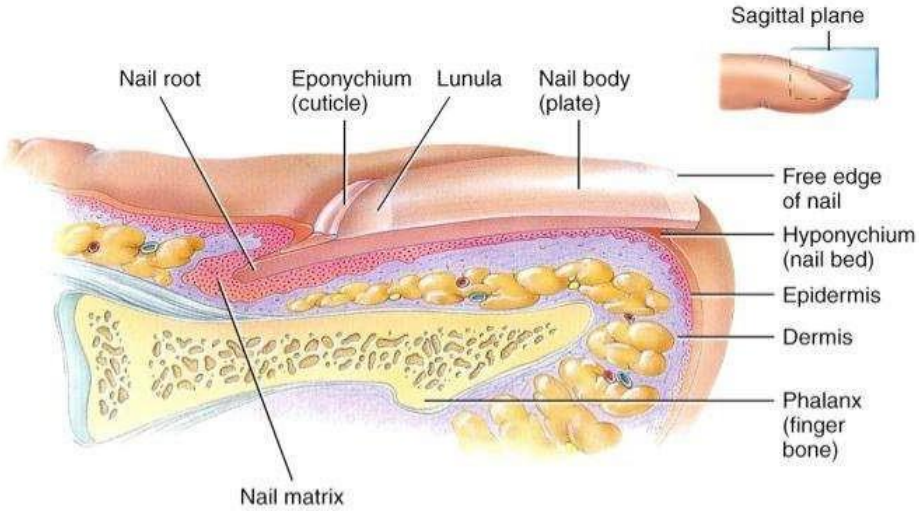


NAIL DISEASES

The majority of nail disorders arise from two nail diseases – Onychomycosis and nail psoriasis .

Onychomycosis

It is a fungal nail disease. It is found more frequently amongst the elderly , diabetic individuals with peripheral artery disease and sports active individuals . The dermatophytes Trichophyton rubrum and Trychophyton mentagrophytes , yeast such as Candida albicans , non dermatophytes such as Fusarium species have all being identified as the main causative agents for the disease . It mainly affect toenails compared to the fingernails .

Different categories are (A)-distal and local subungual onychomycosis (B) –Proximal subungual onychomycosis (C) –Superficial white onychomycosis (D) – Endonyx onychomycosis and (E) –Total dystrophic onychomycosis

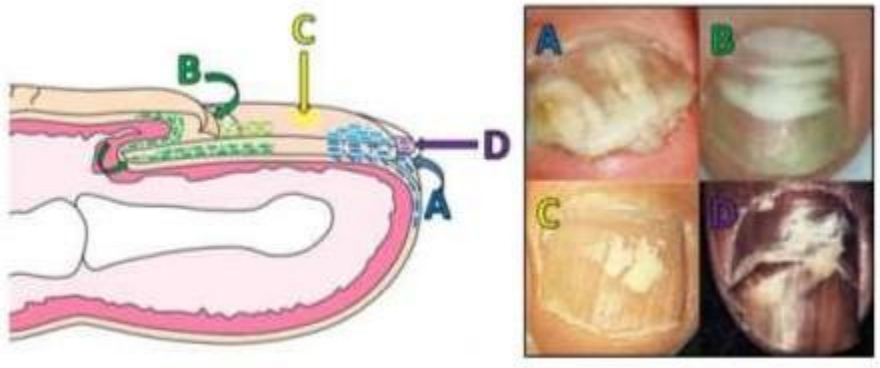


Fig: Schematic diagram of the nail unit cross section highlighting the sites of infection and hence forms of onychomycosis (left) and corresponding images of its clinical appearance (right) .

If left untreated, it acts like a fungal reservoir with the potential to spread to other nails , and to body sites such as groin , skin and scalp and to other people .A successful treatment is necessary for preventing the progression of disease to its total dystrophic form and to help restore nail's natural beauty.

Nail psoriasis

It is a chronic, immune mediated inflammatory disease of the skin which typically causes red , flaky , crusty patches covered with silvery scales . The main features are pitting , discolouration , onycholysis , subungual hyperkeratosis , nail plate dystrophy , splinter hemorrhages .

DIFFERENT THERAPIES FOR NAIL DISEASES:

Systemic therapies:

The agents used in systemic therapy enter the circulation following oral administration and absorption , and diffuse from the blood vessels into the nail plate via the nail bed .Widely used drugs for onychomycosis treatment are terbinafine and itraconazole . For nail psoriasis , the systemic therapies available include acitretin , methotrexate , cyclosporine and biological immunomodulators like adalimumab , etanercept , golimumab.

Intralesional therapy:

An intralesional corticosteroid injection (most commonly of triamcinolone acetonide) is taken into account owing to the anti-inflammatory and anti-proliferative effect of corticosteroid ,commonly administered through a 28 guage needle directly to target site . The therapy is more effective in treating ridging, nail thickening and subungual hyperkeratosis . The main disadvantage is pain ,however a local anaesthetic can be used to overcome this.

Radiation therapy:

Radiation therapy is not routinely employed in the treatment of psoriatic nails ,however a number of therapies have been investigated for their potential use . One kind of radiation therapy is photo chemotherapy with UVA in addition to the photosensitizer psoralen (PUVA) . PUVA has been found to be effective in subungual hyperkeratosis, onycholysis ,discolouration ,nail crumbling and proximal nail fold symptoms . But there is potential for side effects such as subungual haemorrhage, photo-onycholysis and local pigmentation .

Topical therapy:

Therapy with topical antifungals is limited only for mild cases of distal and lateral subungual onychomycosis
,for superficial white onychomycosis or when there is some contraindications in systemic therapy.

Topical therapy can be applied to the nail plate, nail fold and or to the nail bed depending up on the location of the psoriatic lesion . In order to fecilitate a successful therapeutic response, nails with onycholysis present are trimmed to the point where it get seperated from the nail bed, bulky nails are chemically avulsed, and patients may also be advised to cover the topical formulation with an occlusive dressing, such as non-porous tape or plastic gloves ,to improve drug movement to the nail unit .

TOPICAL DRUG DELIVERY:

Nail diseases are mostly treated with therapeutic agents which are administered systemically or topically . Systemic therapy is found to be more efficacious; however it is associated with a number of serious side effects,drug interactions ,contraindications ,high recurrence rates ,and is also costly. Topical therapies bypass the side effects , drug interactions and contraindications associated with systemic therapy and is therefore the ideal mode of therapy .

The efficacy of therapy with topical therapeutic agents are often limited by several factors ,one of which is poor patient compliance [6] because of the requirement of regular topical drug application until all the affected nail tissue has grown out ,which can take upto several months . The second important factor is the limited penetration of the therapeutic agent through the nail plates firmly bound layers of dead keratinous cells and compact dorsal structure .
Physical techniques can enhance ungual permeation by disrupting the dorsal nail plate layer prior to the application \ reapplication of drug loaded formulations, and simple techniques such as nail filing using an abrasive has shown success [7] .Other physical approaches to disrupt the dorsal nail plate surface include abrasion of the nail plate surface in an aggressive manner (i.e, by using electrical equipment and dental drills) , ablation of the nail plate using pulsed lasers ,microporation of the nail plate ,and application of low frequency ultrasound . While these approaches are shown to increase ungual drug penetration ,little has been done to examine how these techniques can be employed in practice.

The drug penetration into the nail plate can be enhanced using chemical agents which breaks the physical and chemical bonds that maintain the integrity of the nail keratin ,such as the disulphide ,peptide ,hydrogen and polar bonds .

Thiols – compounds containing a sulfhydryl group – are the most effective ungual penetration enhancers . Examples include N –acetylcysteine ,2 mercaptoethanol ,thioglycolic acid and N –(2-mercaptopropionyl)glycine . These compounds promote nail plate softening and swelling ,and increase nail plate porosity by irreversibly reducing and thus disrupting the disulphide bonds in keratin .[7] Sodium sulphite disrupts disulphide bonds in keratin by reduction. It act by increasing the hydration of the nail plate and also the thermodynamic activity of the drug .

Keratolytic agents ,such as urea and salicylic acid ,also promote nail softening and swelling but via keratin denaturation . When used alone these agents are not able to enhance ungual drug flux through the nail . However a combination of two keratolytic agents or a keratolytic agent and a thiol can enhance ungual drug flux by synergistic action. Hydrogen peroxide ,which is an oxidising agent ,will oxidise and cleave the disulphide bonds . When complexed with urea , it promotes nail plate softening and swelling [8] and similar to keratolytic agents , it augments the transungual permeation enhancing effects of thiols and is found to be ineffective when used alone ..Keratolytic enzymes which have the ability to hydrolyse nail keratins are expected to weaken the nail plate's barrier properties and thereby enhances the transungual permeation .

TOPICAL DRUG VEHICLES:

The drug permeation into an intact nail plate is encouraged by formulating the drug within a vehicle which enables drug partition out of the vehicle and into the nail plate . Even when factors that enhances the permeation are considered, such as disrupting the dorsal nail plate layer prior to the formulation application ,or using chemical enhancers, if the vehicle itself is insufficient ,the success rate following therapy will reflect this . There have been various topical nail formulations for onychomycosis and nail psoriasis including solutions ,lacquers
,gels ,ointments ,creams .

Nail solutions:

Nail solutions are highly concentrated solutions of a drug in a suitable solvent . When the nail solution is a concentrated aqueous or alcoholic antimicrobial solution in a volatile vehicle ,it is called as paint .[9] Following application of the nail solution on the nail surface ,the solvent will evaporate to leave a highly concentrated deposit of drug on the nail (not necessarily in the form of a film) ,which is anticipated to penetrate and diffuse through the nail plate .

Nail lacquers:

Nail lacquers contain a therapeutic agent dissolved in a suitable lacquer base . Following a nail lacquer's application on the nail plate surface , its volatile solvents gets evaporated leaving behind a highly concentrated deposit of drug in a polymeric film on the nail ,from which the drug is released and permeates through the nail plate . The polymeric film formed can reduce transonychial water loss (TOWL), and is supposed to hyper- hydrate the upper nail layers ,which can aid the drug permeation into and through the nail plate [10] . This hydration property is helpful in onychomycosis treatment ,as the hydration can also fecilitate germination of drug- susceptible fungal hyphae and limit the formation and persistence of drug-resistant fungal spores ,thus limiting the chances of reinfection . The polymeric film formed can inhibit the adhesion of fungal propagules on and underneath the nail plate ,which can prevent fungal infection or reinfection in its initial step itself , which is a useful property even when non-infectious nail diseases are treated.

The selection of film former used in the nail lacquer can affect several factors . The water insoluble films ,provide sustained drug release and are immune to washing ,however ,they require weekly removal either by mechanical means or by employing a suitable solvent ,which may affect the surrounding skin . Water soluble films ,adhere to the nail plate to greater extent and fecilitate a greater drug release ,however ,they can be easily washed aloof from the nail surface . In order to combine the advantageous occlusiveness and wash resistance of water insoluble films with the adhesion and drug release properties of water soluble films ,a bilayer nail lacquer composed of an underlying drug loaded hydrophilic layer and overlying hydrophobic layer was employed .Thus it becomes a complicated process .

Semisolids:

*Gels – Gels can hold considerable amount of water and thus have the potential to hydrate the nail plate upon application ,even more so than nail lacquers [11]. This in turn can enhance drug permeation because of

the formation of a less dense structural keratin matrix with large pores.

*Ointments – Ointments are used for topical treatment of various nail disorders. For example–Bifonazole (1%) and Urea (40%) ointment is used in onychomycosis treatment . However these formulations required the use of an occlusive dressing ,and the overall success following the therapy was still inadequate .

*Creams – They are emulsion based topical formulations and are typically water – in – oil (w/o) or oil – in – water (o/w) emulsions ,depending on the solubilities of the actives that are required to be incorporated . These are rarely used for nail diseases , because they can also be easily wiped off the surface of the nail plate during regular activities .

Hot – melt extruded films

Hot melt extrusion is the process of applying heat and pressure to melt an active compound embedded in a carrier formulation (consisting of polymeric materials)and forcing it through an orifice in a continuous process

.But the efficacy of such a topical therapy was never established .

THE NEED FOR A NEW NAIL MEDICINE:

There is an enormous range of topical drug vehicles available for nail diseases with the aim to deliver a therapeutic level of drug at the desired site .But these vehicles require repetitive applications ,which reduce patient compliance ,and are easily removed from the surface of the nail plate ,thus failing to maintain therapeutic drug levels .In spite of this, a nail medicine is needed which can overcome these limitations ,while being aesthetically acceptable in appearance.

UV CURABLE GELS AS POTENTIAL TOPICAL NAIL MEDICINES:

The concept of employing a nail product as a drug delivery vehicle was borrowed from the cosmetic industry. The cosmetic industry also uses artificial nail enhancements for decorative purposes or to cover unattractive nail deformities such as discolouration ,splitting and breaking .There are 3 main forms of artificial nail enhancements which include nail wraps ,liquid and powder and UV gels .[12]

UV gels are called as gel nails ,also been derived from the dental industry .UV gels are one component systems which generally contain a urethane methacrylate based monomer(75-85%), mono and multifunctional (meth)acrylate based monomers(15-25%) and a photoinitiator(1-4%)such as 1-hydroxycyclohexyl phenyl ketone or 2-hydroxy 2-methylpropiophenone .The gel cures under low intensity UVA light typically within the range of 435-325 nm ,and this can be provided by a UVA nail lamp ,which can hold one to five 6-9W bulbs depending on the design .lamp.[13]

Method of application:

*Prior to gel application ,inorder to ensure good adhesion ,the natural nail is cleaned ,lightly filed and dehydrated .

*A layer of gel is then applied on the nail plate surface and the nail is placed under a UVA lamp for about 1-3 minutes.

*The UVA light activates the photoinitiator in the gel to create free radicals which facilitate a polymerisation process to produce a polymeric film on the nail plate .

*Further gel layers are applied sequentially and cured as the UVA light does not efficiently penetrate more than afew millimetres into the UV gel .

*Following the curing process ,an occlusive polymer film is produced on the nail surface.

*This film is then wiped with isopropyl alcohol inorder to remove an unreacted monomer layer on its surface, which is caused by oxygen induced inhibition of polymerization.

*The resulting film is extremely durable and can be worn for upto 3 weeks without developing any visible effects .

*Removal of the UV gel requires acetone ,and nails are placed in a small bowl immersing them within the solvent ,and it takes about 45-60 minutes ,because the highly cross linked urethane methacrylate based polymers have an inherently greater solvent resistance.

Advantages:

*Of all the available artificial nail enhancements ,UV gels appear to be more favourable as they are much simpler and therefore will be a convenient and consistent system to work with .

*Their polymerisation process is controlled by an external source providing an unlimited application time & the complete cure time is relatively short(1-3 min).

*They display an inherently greater solvent resistance and produce a natural looking ,long lasting ,occlusive polymeric film on the nail plate surface .

*They are indeed a valuable tool in improving cosmesis and satisfaction among patients presenting with nail plate surface abnormalities .They address the present issues such as the need for frequent applications and failure to maintain therapeutic drug levels at the desired site .

COMPONENTS OF THE PHARMACEUTICAL UV CURABLE GEL FORMULATION:

The monomers:

The cosmetic UV gels had a mix of acrylate and methacrylate based monomers .(Meth)acrylates are α,β unsaturated ester monomers ,with the methacrylate esters differing in composition from their corresponding acrylate esters due to the presence of a methyl group substituted at the alpha carbon .This extra methyl group donates electrons to the double bond ,thereby stabilising it and also it will impose sterile hindrance .Both factors render methacrylates less reactive than their corresponding acrylates ,and this is reflected in their lower toxicity and lower sensitising capacity.[15]Due to this lower sensitising potential ,methacrylates are generally more favourable than their corresponding acrylates for nail enhancements .Methacrylate based monomers are safe to use when skin contact is avoided.

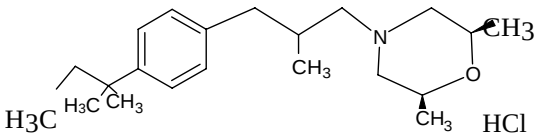
Diurethane Dimethacrylate (DUDMA) is chosen as the backbone of formulation ,similar to cosmetic UV gels ,because it is capable of producing a strong crosslinked polymer which imparts exceptional abrasion resistance and durability or sturdiness.The presence of further crosslinking momomers such as isopropylidene diphenyl bisoxyhydroxypropyl methacrylate ,PEG 4 dimethacrylate improve polymer toughness and solvent resistance ,but this would most probably compromise polymer flexibility and increase its brittleness .[16] Ethyl methacrylate(EMA) ,hydroxyethyl methacrylate(HEMA), hydroxyl propyl methacrylate(HPMA) and isobornyl methacrylate(IBOMA) are the alternative choices of monomers available .

The photoinitiator:

2-hydroxy-2-methyl propiophenone is often used as photoinitiator for formulation because it shows a high acrylate double bond conversion ,is capable of forming hard films ,and is available in a liquid form with good solvency properties .

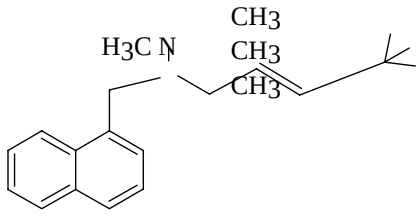
The antifungals and solvents:

Commonly used antifungal agents in formulations are amorolfine hydrochloride and terbinafine hydrochloride .



Amorolfine hydrochloride

Terbinafine hydrochloride



Terbinafine hydrochloride has high potency against onychomycosis- causing dermatophytes and is also sublimable at room temperature and at physiological temperatures(37 degree celcius) [17].The sublimable ability enable it to overcome air cavities in mycotic lesions and reach tissue layers on the other side of cavities ,thus contributing to therapeutic efficacy against onychomycosis. Amorolfine hydrochloride was earlier used in nail lacquer to treat onychomycosis .The drugs are insoluble in DUDMA and so solvents are used in UV curable gel formulation to attain a reasonable drug load .Ethanol and NMP are the solvents used because of their miscibility with the monomers and their solvency for the drug.

PREPARATION AND PROPERTIES OF GEL FORMULATION:

For experimental purposes , a total of four types of formulations were prepared (1)drug free and solvent free.(2)drug free containing solvent (3)drug and solvent containing (4)solvent free containing drug .Drug free formulations were prepared by mixing the excipients and leaving the mixture to stir overnight. Drug loaded formulations were prepared by first dissolving the drug within the chosen solvent ,and then adding the specified excipients to the drug solution and leaving the mixture to stir overnight.

Important properties of gel formulation are ,

***Drug loading:**

The drug loadings were determined based on the solubility of the antifungal drugs within the gel components

.(i.e, the monomers and solvents) .The actual drug load was determined by visualising the absence/ presence of drug crystals in the gel formulation at various drug concentrations .

The inclusion of ethanol (at 25%v/v) in an EMA containing gel allowed the loading of 3%w/v amorolfine HCl or 4%w/v terbinafine HCl .On the other hand, inclusion of NMP(at 25% v/v) allowed the inclusion of 1%w/v of amorolfine HCl or 1%w/v of terbinafine HCl .The lower drug load enabled by NMP is because of its lower solvency for the drugs. Inclusion of ethanol (at 25%v/v) in a HEMA containing gel formulation allowed higher drug loadings (4%w/v amorolfine HCl or 6%w/v terbinafine HCl) and it reflects HEMA's higher solvency for the drugs in comparison to other diluent monomers .

***Gel viscosity:**

The choice of solvent does not affect the final viscosity of the gel ,because ethanol and NMP have similar viscosity values (1.08 for ethanol ,1.67 for NMP)

When considering other nail technologies like nail enamels ,a viscosity with a range of 300- 400 mPas at 25 degree Celsius is desired for easy application .[18] This is because a lower viscosity material is too thin to remain on the application brush and thus become unable to deposit enough to cover the average nail ,while a higher viscosity material is thick and streaky when applied .

***Stability of antifungals in the gel formulation:**

The drug loaded UV curable gel formulations were stored under accelerated stability conditions and assessed for any changes in their appearance and drug concentration over time .Over a period of six months ,the drug loaded gel formulations showed no changes in colour , no visible signs of drug precipitation and no significant changes in drug concentration .The UV curable gel formulations were therefore considered to be stable .

Selection of UVA lamp:

The lamp used for curing was a 36 Watt cuccio professional UVA nail lamp which uses 4×9 W UV bulbs ,and is capable of emitting low intensity UVA light within the range of 320- 400 nm ,thus owing the chosen photoinitiator to absorb the wavelength of light (331nm) required for free radical production .For complete polymerisation ,a cure time of two minute was selected for curing the pharmaceutical UV curable gel formulations .The gel formulation will be exposed to UVA light and this exposure initiates polymerisation between DUDMA and other monomer (EMA ,IBOMA ,HEMA) ,where the original alkene bonds in the acrylate moieties of the monomers were converted into alkane ones .This was confirmed by FT – IR .

Fig: Photographic image of the UVA nail lamp used for curing the gel formulations

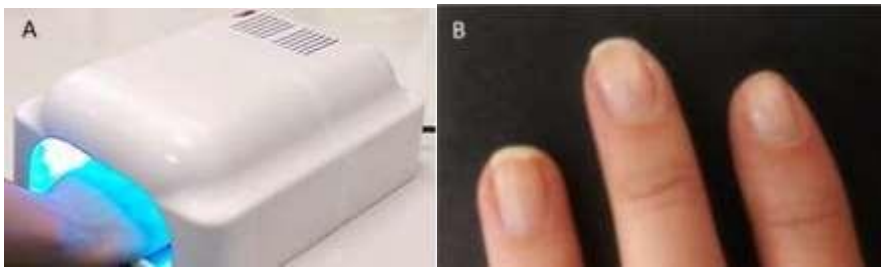


Fig:Steps to apply UV curable gel formulations .(A) Apply the UV gel on the nail surface and cure it under a UVA lamp for two minutes and (B) Wipe the nail surface with a nail wipe soaked with isopropyl alcohol to reveal the polymer film adhered to it .

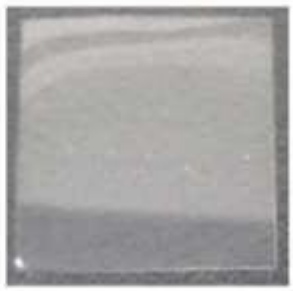


Fig :Photographic image of UV cured film produced from a DUDMA &EMA containing gel formulation.

UV CURED FILM CHARECTERISTICS:

UV gels can shrink between 12 -18% upon curing when applied on the human nail plate ,excessive shrinking can cause discomfort and trauma to the nail bed ,rendering the nail more susceptible to infection .This shrinkage phenomenon is therefore minimised in practise by applying multiple thin coatings of UV gels rather than single thick coating ,which incidentally also avoids the likelihood of increasing the maximum temperature of the UV gel curing process .For the pharmaceutical UV curable gels formulated ,the minimum amount of gel required to cover a given area while still capable of producing an adequate film was 13.3ηl/cm .sq .In the cosmetic industry,UV gel layers are sequentially applied and cured .It would be more convenient to use a pharmaceutical formulation as a single layer ,as this is not only simpler ,but also reduces application time and minimises the time a patient have to expose their hand under a UVA nail lamp .With this consideration ,the pharmaceutical UV gel was designed for application on nail plate as a single layer .This single cured layer produced a film which was visually smooth and transparent .

*__Morphology and thickness of UV cured films__ : UV cured films produced were both visually smooth and transparent for the films produced by all gels formulated containing EMA ,IBOMA ,or HEMA with or without solvent and with or without drug .The films were aesthetically applicable and thus visually suitable as a method for delivering drug .

The films formed from the drug free and solvent free gel blends with DUDMA to diluent monomer ratio of 85:15%v/v are about 210 micrometres thick .The drug free and solvent free HEMA formulation with a greater concentration of HEMA produced a slightly but statistically significant thinner film .The proportion of monomers ,rather than diluent monomer choice ,in the gel mixture predominantly responsible for the thickness of the resulting film .

*__Drug load in the UV cured film__ :The amount of drug incorporated in the gels formulated was the maximum that could be dissolved within the gel mixture .Upon UV curing ,the drug remained in the dissolved state with no crystals was observed by polarised light microscopy.

*__UV cured polymer film's adhesivity :__ Adhesion of a topical formulation to the nail plate surface is important in order to allow the drug to leave the formulation and penetrate the nail .The DUDMA backbone is primarily chargable for the resistance to separation displayed as it inherently provides excellent adhesion and abrasion resistance [19]. However as the DUDMA to diluent monomer ratio used (i.e,85:15%v/v or 25%v/v for HEMA) does not significantly alter the film's adhesion ,it appears that the diluent monomer ,also contribute to the copolymer's adhesive property .Presence of ethanol within the formulations caused no statistically significant change in film adhesion .

In contrast ,presence of NMP within the formulation significantly reduced film adhesivity .Because more NMP (than ethanol) remains in the film upon gel curing .The presence of a greater amount of solvent seems to cause a larger change in the properties of the NMP containing films ,which results in significant decrease in film adhesion to the substrate .

*__UV cured film's sensitivity to water__ :The water sensitivity scores of UV cured films produced from DUDMA and EMA gels (±solvent and ± drug) shows that the film produced by NMP containing formulations are extremely water sensitive .The films had detached from the substrate in about 5 hours. NMP is miscible in water and as it is present at a substantial level in the film ,contact with water causes the film to blister and subsequently detach from the substrate .Ethanol is also miscible with water ,but greater water sensitivity displayed by NMP containing films is because the large planar non – polar region of NMP intercalates with the polymer ,meanwhile more of the ethanol evaporates off during and after curing because of its lower boiling point .

*UV cured polymers reside on fingernails for extended time than lacquers ,due to the more durable nature of the DUDMA backbone in the gel formulations .By 14th day ,greater than 50% of the film produced from the drug loaded UV curable gel still remains on the finger nail plate .[20]

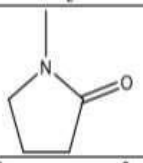
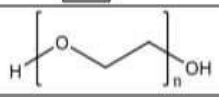
*The drug release profiles were similar for all the UV gels formulated .The release of drug was limited possibly by the films crosslinked and highly dense nature ,and the release of terbinafine from the films was almost half of amorolfine because of possible terbinafine – polymer binding .

*Permeation studies revealed that each formulations were capable of enabling drug permeation into and through the nail in vitro .The drug loaded DUDMA and HEMA gels containing ethanol displayed the greater ungual drug permeation profile because of their greater drug load.

OPTIMISING UV CURABLE GEL FORMULATIONS WITH THE USE OF PENETRATION ENHANCERS:

The gel's maximum drug load depends on the drug's solubility in ethanol and in the reactive diluent methacrylate based monomer .Thus the gels containing HEMA and ethanol dissolved the most amount of drug due to the greater drug solvency of HEMA .The film's drug release and ungual drug permeation was the best from the film with the highest drug – load ,and hence the DUDMA and HEMA gels containing ethanol (with a DUDMA to HEMA ratio of 85:15% w/v) and either 4% w/v amorolfine HCl or 6%w/v terbinafine HCl were the superior of the formulations developed .

However the percentage of drug within the formulation that permeated across the nail and remained within the nail was less than 2.7% and 3.6% respectively ,following the 30 day ungual drug permeation study using fingernail clippings as the nail model .Despite this ,the amount of amorolfine and terbinafine that had permeated across the fingernail clippings was sufficient enough to inhibit the growth of T. rubrum ,the most common pathogen that causes onychomycosis .Also the extent of drug permeation is expected to be significantly lower for toenails (which are predominantly infected)compared to fingernails .These formulations are therefore should be considered for optimisation to beat the poor permeability percentage and to guarantee treatment success . A chemical approach to boost ungual drug permeation was considered as it doesn't add to the formulation's application process when the chemical is incorporated into the UV gel ,and in turn will not compromise patient compliance .Commonly used penetration enhancers are 2 – mercaptoethanol (MPE) ,water ,NMP and polyethylene glycol 200 (PEG 200).

Penetration enhancer	Chemical structure	Molecular wt. (Daltons)
MPE		78.13
Water	H_2O	18.02
NMP		99.13
PEG 200		~200

MPE is a thiol compound which is capable of reducing the disulphide linkage in the keratin matrix of the nail as shown below ,

It is therefore capable of enhancing drug permeation across the nail by destroying the disulphide bonds of keratin .This mechanism renders thiols as the most effective of the ungual permeation enhancers and therefore considering it for optimising the pharmaceutical UV gel .Other potential thiol compounds ,such as N – acetylcysteine and thioglycolic acid were not considered ,as in a recent study which investigated nail lacquers containing MPE ,N – acetylcysteine or thioglycollic acid, MPE was found to enhance drug permeation to the greatest extent.[21] MPE enabled 8.5 ,1.5 and 3 times more terbinafine HCl to permeate through a nail model compared to the formulations with no penetration enhancer ,N – acetylcysteine and thioglycolic acid respectively .

Water ,NMP and PEG 200 can enhance ungual drug permeation without disrupting the bonds and thus maintaining the integrity of nail keratin .These enhancers instead promote nail swelling resulting in the formation of larger pores through which the drug can easily diffuse .Of these enhancers ,NMP and PEG 200 are found to enhance drug flux through a nail model when incorporated in a terbinafine loaded acrylic based transungual patch with enhancement ratios of 1.17 and 1.24 for NMP and PEG 200 respectively where, Enhancement ratio =flux with enhancer/flux without enhancer.

These enhancement ratios are higher than that achieved by MPE ,when incorporated in the transungual patch ,making NMP and PEG 200 also worth considering for optimising the pharmaceutical UV gel .

Ungual permeation studies revealed that MPE ,NMP and PEG 200 were capable of improving ungual permeation of antifungal drugs (amorolfine and terbinafine) when present in a UV curable gel vehicle .MPE was found to be the superior of the penetration enhancers ,not only due to the significant enhancement of ungual drug permeation ,but for being the least likely to affect the UV – cured film's residence on the nail .

CONSIDERATIONS FOR FUTURE WORK:

The considerations for future work include observing ways to further improve the pharmaceutical UV – curable gel formulation and thus guarantee treatment success . These are listed as ,

Physical approach to boost the ungual drug delivery of pharmaceutical UV curable gels

While the incorporation of a penetration enhancer (particularly MPE) in the pharmaceutical UV curable gel improved ungual drug permeation , it might be further improved by also using a physical means to enhance ungual permeation. The dorsal layer of the nail plate was identified as the main barrier to permeant transport through the nail plate and into the nail bed , and methods of disrupting this layer by physical means to improve ungual permeation were reviewed .One such technique which has shown success was nail filing using an abrasive which enhances permeation by decreasing the thickness of the dorsal layer. Additionally, it increases the surface roughness and hence surface area of the nail ,which in turn provides a greater opportunity for drug loaded films to adhere to the nail plate and thereby fecilitates drug permeation .

Coincidently ,prior to the application of commercially available cosmetic UV gels ,the nail is lightly filed with a low grit abrasive file to increase its surface area and to ensure good adhesion. Therefore, disrupting the dorsal layer of the nail plate with an abrasive file before the application of a drug loaded topical formulation to improve film adhesion and enhance ungual drug permeation further ,seems fitting for a pharmaceutical UV gel .Hence as a part of future work ,the influence of nail fitting on a UV – cured film adhesion and ungual drug permeation can be enhanced .

***3D printed pens as a delivery device for UV – curable gel formulations to improve formulation application procedure:**

While considering the application process of a UV curable gel formulation ,the procedure is not so clear cut.Not only there is a necessity for a UVA lamp to fecilitate the polymerisation of the gel formulation ,the film that subsequently forms contains an oxygen inhibition layer which is needed to be removed with a nail wipe soaked in alcohol .One way of addressing the problems highlighted is by investigating hand held 3D printing pens that emit UV (such as creopop) as a formulation delivery device , where the ink inside the pen is replaced with the pharmaceutical UV curable gel formulation on the nail plate via a creopop like device , would eliminate the need for a UVA nail lamp , prevent the formation of an oxygen inhibition layer and thus cut down total cure time , all of which could further help to overcome the issue of poor patient compliance .

CONCLUSION:

Nail plays an essential role in providing a protective barrier as well as in the appearance of a person .Along with face ,neck and hands ,the nails are one of the few areas of the body which receive consistent exposure .In addition ,nail may have an outsized psychological impact ,with the appearance of groomed and clean nails are considered as important for employability ,the conduct of business and social functions.The nail also protects the distal digits ,improves the fine tactile sensation and also assist in picking up and manipulating small objects .

Nail diseases ,especially the fungal nail diseases are quite common and affect the normal life of a large population .Treatment methodologies such as topical drug delivery had various side effects and toxic effects .UV curable gel can most probably be considered as an alternative vehicle for the delivery of topical nail medicines .Their use addresses current topical formulation issues like ,

1. The need for frequent applications and
2. Failure to keep up therapeutic drug levels at the desired site .

By residing on the nail longer compared to other nail formulations like nail lacquer .Anti – onychomycotic drugs can be incorporated within these gels ,in the

presence of an acceptable solvent .Ethanol containing formulations have favourable properties which include high stability and water resistance.

Also the drug loaded formulation will have an extended residence time on the nail ,allowing drug permeation into the nail over a long time .This is expected to improve the topical therapy of nail diseases .

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