## 2. Literature Review

### 2.1 Skin Fungal Infection

Skin fungal infections (SFIs) affect 25% of people worldwide. The majority of these infections only affects the epidermis, the skin's outermost layer, and is therefore superficial. Other SFIs are categorized as subcutaneous and deep, which have a considerable morbidity and mortality rate despite having a significantly lower prevalence (1). The most prevalent and frequent cutaneous and superficial fungal infections in people are called dermatomycoses (2). Humans frequently develop opportunistic fungal infections of the skin. Fungal infections have become more common recently, especially in immunocompromised people (3).

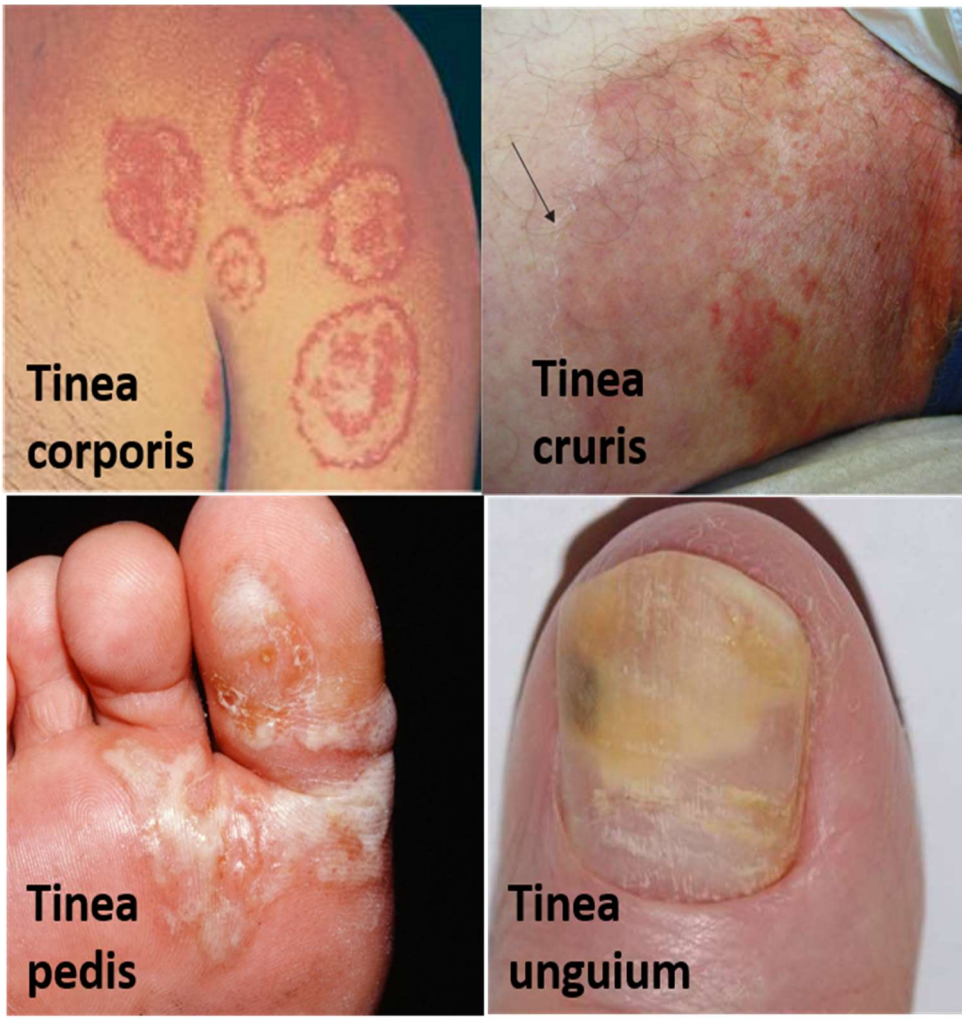


**Figure 2.1: Types of fungal infection (4)**

### 2.1.1 Etiology:

Dermatophytes that can infiltrate the stratum corneum and keratinized tissues, such as *Trichophyton, Microsporum*, and *Epidermophyton*, are the main source of skin fungal infections. Less frequently, nondermatophyte fungi (such Malassezia in tinea versicolor) produce skin fungal infections. Tinea infections, also known as dermatophytoses, are categorised based on the body place they affect. Dermatophytes are most frequently spread through direct human touch (anthropophilic organisms), although they can also be spread through contact with animals, the environment, the soil, or even spores (5). There are numerous fungi that can produce superficial mycoses, including *T rubrum, T mentagrophytes* var. interdigitale, and *M canis*. The most typical dermatophyte seen in developed nations and the urban centers of developing countries is *T. rubrum* (6).

### 2.1.2 Symptoms:

The symptoms of a fungal infection will depend on the type, but common symptoms include the following:

- Irritation
- Scaly skin
- Redness
- Itching
- Swelling
- Blisters (7)

### 2.1.3 Pathophyisiology:

To circumvent the host immune system and increase the severity of infections, fungal pathogens use a variety of strategies. Fungal infections can range in severity and include mucosal, systemic, cutaneous, subcutaneous, and superficial infections. By coming into direct touch with the damaged skin, dermatophytic fungus from the genera *Microsporum, Epidermophyton*, and *Trichophyton, Sporothrix*, and *Malassezia* spp. spread infection. To induce superficial mycoses in keratinized tissues, they secrete a variety of proteolytic enzymes. Inhaling spores or conidia that cause lung infections is the other main method of transmission (8). The majority of fungal pathogens are opportunistic invaders that favour immune compromised hosts, but the fact that

relative pathogenicity varies between fungal species (and even between different strains within a species) is proof that fungi have developed numerous, distinct molecular virulence factors (9).

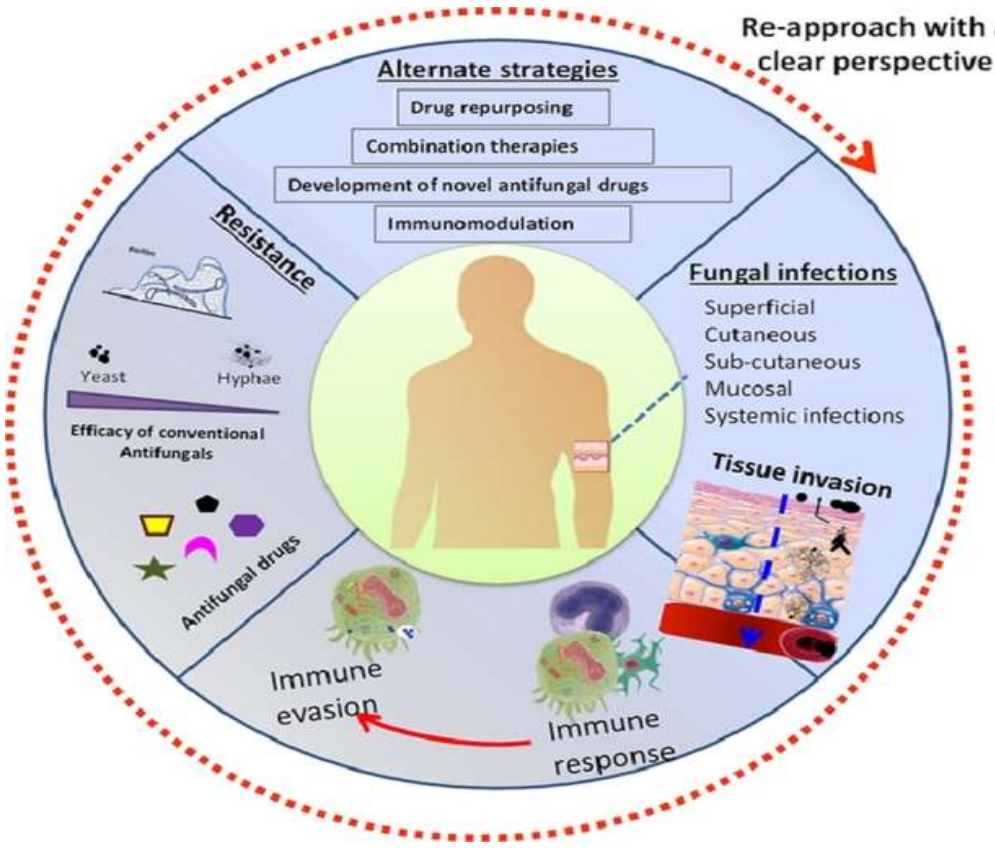


**Figure 2.2: Overview of skin fungal infection (8)**

### 2.1.4 Prevalence:

Dermatomycoses, or fungal infections of the skin, hair, and nails, are thought to affect about a billion people globally. The frequency and incidence of dermatomycoses vary based on socioeconomic and geographic factors (10). Globally, fungi-related pathogens cause at least 13 million illnesses and 1.5 million fatalities annually, mostly in people with weakened immune systems. These people are susceptible to infections that develop rapidly and cause considerable morbidity and mortality. Despite these worries, fungi are sometimes overlooked when it comes to public health issues, and funding for research into them is still far lower than that of diseases that cause similarly high rates of mortality (11). Various nations have various levels of prevalence. In tropical and subtropical nations like India, where temperatures and humidity are high for the majority of the year, it is more common (12).

## 2.2 Nail Fungal Infection:

Due to inadequate healthcare infrastructure, onychomycosis, a persistent fungal infection of the nails, is frequently underdiagnosed in underdeveloped nations like India. Around 5% of the world's population is affected, and it is still growing and enduring. Various employees in India have indicated that the incidences range from 0.5 to 5%. It affects toenails much more frequently than fingernails and makes up around 50% of all nail problems. Onychomycosis is thought to affect 5% of people in Western nations, and its frequency has been rising over the past few decades (13). It most frequently affects adults and can lead to foot infections. People who frequently use public swimming pools, gyms, or showers are more likely to develop fungal infections in their nails (14). Nail alterations are a significant medical worry for patients, so doctors and other healthcare professionals should pay attention to nail illnesses and give them the right attention and treatment.

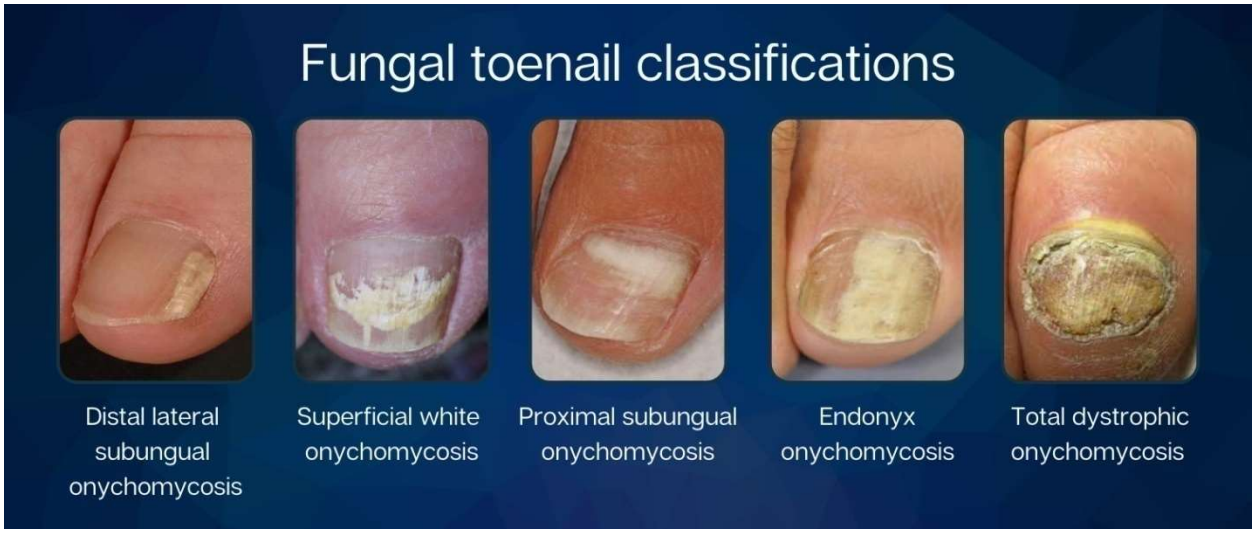


**Figure 2.3 Types of onychomycosis (15)**

### 2.2.1 Etiology

Tinea pedis, a dermatophytic infection of the feet, may be chronic or recurrent and can affect the interdigital web gaps or the sides of the feet. The most prevalent anthropophilic etiological agents are *Trichophyton rubrum*, followed by *Trichophyton interdigitale* and *Epidermophyton floccosum* (16).

### 2.2.2 Symptoms

Healthy-looking nails are a crucial component of one's overall body image, and patients may view any nail irregularities as serious cosmetic issues that have a negative impact on their self-

esteem. Discoloration, thickening, desquamation, and detachment from the nail bed are all symptoms of nail infections (tinea unguium or onychomycosis). There may be a number of symptoms, including brittle nails, hollow nails, bleeding around the nails, swelling and redness around the nails, discomfort around the nails, and the peeling of the fingernail from the skin (17). One of the most frequent causes of yellow nails is a fungus infection. As the infection worsens, the nail bed may peel back, and the nails may harden up before eventually collapsing. The lunula—the white half-moon at the front edge of the nail bed—disappears, an extravagant curve appears on the nail plate's lateral surface, and the nail turns yellow (18).

### 2.2.3 Pathophyisiology

The most prevalent fungi infections are mycoses, which mostly affect the skin and nails and are brought on by fungi called dermatophytes. The most frequent cause of dermatophytosis, followed by *Trichophyton interdigitale*, appears to be *Trichophyton rubrum*. The process through which fungal cells colonise host keratinized materials like nails, hair, and skin depends on mechanical and metabolic changes (19). A number of proteins, including lipases, phosphatases, and keratinolytic proteases, are produced by the fungus when they penetrate the host tissue to assure the establishment of infection. Short oligopeptides and free amino acids are absorbed by fungi by the proteolytic breakdown of keratinized structures (20). Additionally, the structure of rigid keratin, such as that found in hair and nails, must first relax in order for it to degrade. This process is facilitated by sulfite action, which breaks down disulfide bridges. A sulfite efflux pump, renowned for its role in loosening the keratin structure, secretes sulfite (21).

### 2.2.4 Prevalence

Onychomycosis affects roughly 10% of the population generally and has a point prevalence of 15%. More seldom than fungus colonisation, the nails can become infected by bacteria. Diabetics, dialysis patients, transplant recipients, and cancer patients are among the high-risk populations for nail abnormalities. Two-thirds of all psoriatic arthritis patients and roughly 40% of psoriasis patients without arthritis both have nail fungal infections (22). Depending on the location, mold-caused nail disease may be more common. In Saudi Arabia, India, and Thailand, there is a significant prevalence of *Candida* nail infections. Only in fingernails do *Candida* species pose a serious threat in temperate countries (23).

### 2.3 Treatment of skin and nail fungal infection

Conventionally, fungus infections of the skin and nails were treated either topically, orally, or by combining the two. Different topical treatments, including gels, creams, lotions, powders, and sprays, are used to treat fungal infections of the skin and nails. Topical preparations have a local effect, preventing systemic side effects (24). There is now a wide variety of antifungal medicines in use as both topical and oral formulations, with cure rates for the majority of dermatophyte infections affecting the skin ranging between 80 and 90%. For "localised" infections or those with limited dissemination, oral therapies are typically used, while topical treatments are used for more widespread infections for treating dermatophytosis that affects the skin. Due to the fact that many patients find it time-consuming and challenging to repeat treatments, compliance with topical treatment is sometimes a significant problem (25).

#### 2.3.1 Topical treatment:

Dermatophyte skin and nail infections have been treated with a wide range of topical treatments. With this strategy, serious negative consequences are rare, and allergic or irritating contact dermatitis is also infrequent. The effectiveness of imidazole preparations for topical use, such as Clotrimazole, Miconazole, Econazole, and Ketoconazole in treating ringworm infections with a low incidence of side effects is now well established. Other medications in this class, such as Tioconazole and Sulconazole, are also equally effective (26). Newer formulations like Isoconazole, Luliconazole, and Sertaconazole have joined these older topicals, however not all nations have approved them. The azole antifungals are often offered in 1% concentrations as cream, solution, or spray formulations. Although some medications, such bifonazole, are only allowed to be taken once day, most are used twice daily for 2-4 weeks. The effectiveness of the various azoles varies slightly from one another (27).

Topical 1% Terbinafine formulation is a successful alternative treatment. After only brief durations of use, such as seven days, Terbinafine cream administered locally in dermatophytosis causes remissions in various dermatophyte infections, such as interdigital tinea pedis. Terbinafine is also available as a topical film-forming solution that is applied once only for infections of the foot and sole. After applying the solution, it is given 3–4 minutes to dry. Naftifin and Butenafine are two other useful allylamines. In some nations, Cyclopirox is offered as a topical treatment for dermatophytosis. Older cream or powder medications like Tolnaftate or Zinc Undecenoate are available over-the-counter (28).

### 2.3.2 Oral Treatment:

Dermatophyte infections of the skin can be treated well with oral antifungals. For dermatophytosis, terbinafine is used orally once daily in a dosage of 250 mg. After two weeks, it causes tinea corporis, dry type tinea pedis, and tinea cruris to quickly and permanently remit. Some nations offer 125 mg tablets in a lower size for the treatment of youngsters. Itraconazole is efficacious in regimens of 100 mg for 2 weeks in tinea corporis and cruris, or 30 days in dry type tinea pedis, and is active against a wide variety of dermatophytes (29, 30). The currently recommended treatment includes 400 mg/day for two weeks for dry type tinea pedis and one week for tinea corporis. Sometimes, lengthier treatment times are required. Itraconazole now comes in a brand-new, better-absorbed version that is sold in select nations. For 2-4 weeks, fluconazole is administered as a daily treatment for skin infections caused by dermatophytes. For tinea corporis and tinea cruris, it can also be administered in a 150 mg/week regimen for 2–3 weeks, but for longer for dry-type tinea pedis (31, 32).

Fluconazole and Itraconazole are the most widely used oral therapy for candidosis, with most research concentrating on the mucosal infection or CMC. Itraconazole and Fluconazole are typically used at daily doses of 100–200 mg each. Fluconazole resistance is a recognised problem that has been documented in individuals with HIV/AIDS or CMC who are taking long-term medication. There may be both sensitive and resistant strains of Candia isolated in oral infection, demonstrating the variability of the population in an infection; it is unclear if this also holds true for cutaneous infections (33, 34). Patients at risk from medication resistance typically have persistent infections that require long-term suppressive therapy, are immunosuppressed, and typically have oral or intravaginal infections rather than cutaneous infections. It has been shown that some *C. albicans* species, as well as *C. krusei, C. dubliniensis, C. glabrata,* and *C. auris*, exhibit primary drug resistance to Fluconazole. However, patients with candidosis who are undergoing highly active antiretroviral (HAART) medication experience decreased candida resistance. Voriconazole and Posaconazole are two more azoles that are effective against *Candida* species. Both of these have been used for very unwell patients with severe oropharyngeal and oesophageal infections, but not for *Candida* skin infections (35, 36).

## 2.4 Luliconazole

Due to the incorporation of the imidazole moiety into the ketene dithioacetate structure, Luliconazole is an imidazole antifungal agent with a distinctive structure. The R-enantiomer of Lanoconazole, Luliconazole has stronger antifungal properties than the racemic combination Lanoconazole. An imidazole antifungal drug known as Luliconazole has been demonstrated to have significant efficacy against a number of fungi, including dermatophytes (37). In the USA, Luliconazole is being developed as a novel, broad-spectrum antifungal to treat dermatophytic skin and nail infections. One of the most effective antifungal drugs *in vitro* against filamentous fungi, such as dermatophytes, is Luliconazole. Market-available Luliconazole cream contains 1% w/w. There are numerous Luliconazole containing products that are available in market, including LUZU, Luzicon, Luliconaz, Lulisen, Lulivib, Lucinak, Lulifin, Lulix, Lofatin, Lu-gal, Lutoz, Lulicona, Lolyzole, Lunader, and Lulibet. Luzicute and Lilituf (1%w/v Luliconazole lotion). However, the 1%w/v cream LUZU® used in commercial topical Luliconazole formulations is linked to poorer skin permeability and reduced drug retention in the skin. With special molecular features that enable it to quickly reach fungicidal levels in the nail unit, Luliconazole has been prepared in a 10% solution that allows it to penetrate the nail plate. Due to these characteristics, Luliconazole is an effective drug for the treatment of onychomycosis (38). A novel azole antifungal compound called Luliconazole, which is regarded as a BCS class II drug, was found in Japan. Chemical name of Luliconazole is ((−)- (E)-[(4R)-4-(2,4-dichlorophenyl)-1,3dithiolan-2ylidene] (1H-imidazole-1-yl) acetonitrile possessing broad spectrum antifungal activity (39). $C_{14}H_9Cl_2N_3S_2$ is the chemical formula, and its molecular weight is 354.28. The chiral centre in Luliconazole, which is the R-enantiomer, is present. The dithiolane group's neighbouring double bond is in the E configuration (40).

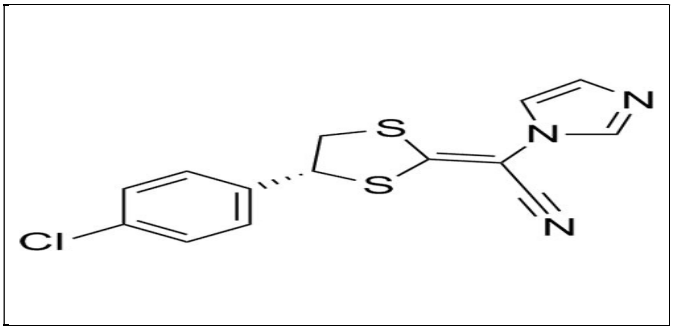


**Figure 2.4 Structure of Luliconazole (41)**

### 2.4.1 Mechanism of action of Luliconazole:

Due to the incorporation of the imidazole moiety into the ketene dithioacetate structure, Luliconazole is an imidazole antifungal agent with a distinctive structure. A crucial component of the fungal cell membrane is ergosterol (42). An antifungal that is in the azole class is Luliconazole. Luliconazole appears to prevent ergosterol formation by inhibiting the enzyme lanosterol demethylase, while the precise mechanism of action against dermatophytes is uncertain. As azoles inhibit the action of this enzyme, less ergosterol, a component of fungal cell membranes, is present, which causes a buildup of lanosterol (40).

**Table 2.1: Review of work done on Luliconazole**

| Sr. No. | Author | Formulation | Conclusion |
|---|---|---|---|
| 1 | Gauri Ramchandra Kapileshwari et al.(43) | Nanosponges | Data on drug release kinetics showed a prolonged release of up to 8 hours. The diffusion-controlled nature of the release pattern was discovered, and Higuchi's plot supported this finding. Improved penetration rate and skin retention duration were found in *in-vitro* permeation experiments. The new drug delivery system as a whole exhibited a higher penetration rate and longer retention time. The formulation was also discovered to be stable and non-irritating. |
| 2 | Manish Kumar et al. (44) | Nanocrystals loaded hydrogel | Nano-systems demonstrated a 5 fold increase in solubility overall, a 4 fold increase in the speed of dissolution, increased skin retention, and improved antifungal activity. Comparing LNC hydrogel (N-GEL) to coarse suspension, nanosuspension, and D-GEL, the amount of drugs retained from N-GEL in the various |

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| | | | skin layers after 8 hours was highest. It was shown that LNC laden hydrogel killed the fungus more effectively. |
| 3 | Manjot Kaur et al. (45) | Lipid nanocarriers based elastic lipogel and ethogel | The produced formulations showed no symptoms of instability during storage and had optimal pH, nanometric vesicle size, encapsulation effectiveness, zeta potential, and viscosity. Vesicle-based gel formulations were shown to be safe, non-irritating, and more successful in the topical treatment of fungal infections on albino rats through *in vivo* antifungal activity, with no drug reaching the systemic circulation. |
| 4 | Vivek Dave et al. (46) | Herbal ethosomal gel | The entire study makes it abundantly evident that the combination of Luliconazole and neem extract in an ethosomal formulation exhibits a synergistic impact, producing outstanding results in the treatment of a fungal illness. |
| 5 | Shinichi Watanabe et al.(47) | Luliconazole 5% nail solution | The results showed that topical Luliconazole 5% nail solution was clinically effective and proved to be well tolerated when applied once daily. |
| 6 | Ashish Kumar Garg et al (48) | Niosomal gel | The formulations did not exhibit storage instability and exhibited excellent nanometric vesicle sizes, encapsulation effectiveness, and Zeta potential. Niosomal gel's sustained-release profile, which was observed for up to 24 h, follows the Higuchi model. According to the findings, niosomal Luliconazole may increase Luliconazole's |

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|---|---|---|---|
| | | | effectiveness against *Candida albicans*. |
| 7 | Alhakamy, Nabil A., et al. (49) | Spanlastics | When compared to the Luliconazole treated groups, the entrapment of Luliconazole within the spanlastics carrier demonstrated considerable (p 0.0001) antifungal efficacy in the immunocompromised Candida-infected Swiss mice without causing any irritation. The microscopic examination revealed that the fungus colonies on the sick animals' skin had been almost entirely eliminated. As a result, Luliconazole spanlastics may be a potent formulation for *C. albicans* that has better topical administration. |
| 8 | Firdaus, Salma, et al. (50) | SLN gel | The improved 2 T-SLN gel was discovered to be stable at room temperature for 2 months without any visible non-uniformity/cracking/breaking and displays a skin-friendly profile without any major symptoms of erythema and oedema.. |
| 9 | Mahmood, Arisha, et al. (51) | Lyotropic liquid crystalline nanoparticles | Ex-vivo skin permeation tests showed that LUL-LCNP gel had a transdermal flux value (J) that was two times higher than that of commercial cream. In comparison to the commercial cream, LUL retention was 1.5 times higher in the stratum corneum and 2 times higher in the epidermis and other deeper layers. In comparison to commercial cream, the total quantity of medication that was absorbed (AUC0-) with the LCNP formulation was 4.7 folds higher in the |

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| | | | epidermis and 6.5 folds higher in the dermis. According to the study's results, LCNP can be a viable and efficient carrier system for the administration of antifungal medications with improved skin permeability. |
| 10 | Hemang Kansagra et.al. (52) | Microemulsion based gel | In comparison to the marketed formulation, the Luliconazole microemulsion-based gel showed improved skin retention and greater antifungal activity, which may be related to the unique properties of microemulsion. The Luliconazole microemulsion-based gel's short-term stability study results showed stable features. The Luliconazole microemulsion-based gel may thus be a more effective treatment for dermatophyte infection than traditional therapies in terms of reducing its symptoms and curing it. |

**2.5 Tavaborole:**

Anacor Pharmaceuticals Inc. is developing Tavaborole (AN-2690), a brand-new, low-molecular-weight oxaborole antifungal medication, for the topical treatment of onychomycosis of the toenail. For this indication, the medication has gained its first global approval in the US. The FDA authorised the first oxaborole antifungal medication in July 2014. It is sold under the brand name "Kerydin" (53). Tavaborole is a white to off-white powder with the chemical formula $C_7H_6BFO_2$, a molecular weight of 151.93, and the structural formula. It is easily soluble in ethanol and propylene glycol and only marginally soluble in water. The US Food and Drug Administration (FDA) has approved tavaborole topical solution 5% for the management of onychomycosis of the toenails. 5-Fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole is its chemical name (54).

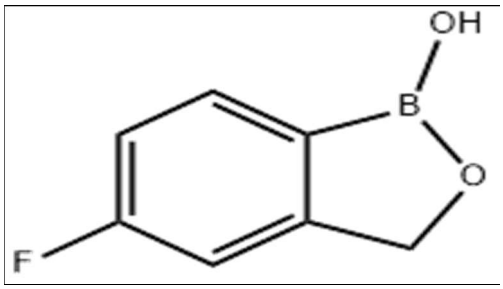


**Figure 2.5 Structure of Tavaborole (55)**

Tavaborole is derived from the borinic acid quinolone ester class of chemicals. Tavaborole is made with the addition of a 5-fluoro group and the replacement of a 1-hydroxy group, which improved hydrophilicity and antifungal action. This medication might penetrate the nail bed because it is water soluble. Tavaborole is effective against a variety of yeast, moulds, and dermatophytes, including *Trichophyton rubrum* and *Trichophyton mentagrophytes*, with a low minimum inhibitory concentration (MIC) in the g/ml range (56). The body substantially metabolises Tavaborole before it is eliminated through renal excretion. With low levels (below 25 ng/mL) identified in plasma when applied topically, Tavaborole has a little potential for systemic exposure and has a restricted potential for drug-drug interactions (57). In actuality, no systemic adverse effects or drug interactions related to the medication are noticed in practice. When utilizing Tavaborole, no safety alerts, adverse medication effects, or fatalities were noticed. The tolerability of treatment may be improved by the nail penetration of Tavaborole through nail paint on nails free of illness. Onychomycosis can be effectively and safely treated with Tavaborole, according to research (58). A panel of fungal strains, including the dermatophytes *T rubrum*, *T mentagrophytes*, *C albicans*, *Cryptococcus neoformans*, and *Aspergillus fumigates* were used to investigate the *in-vitro* activity of Tavaborole. Tavaborole (1 mg/mL) has shown inhibiton efficacy against all of the tested fungal species (59).

### 2.5.1 Mechanism of action:

Tavaborole is a highly selective inhibitor of fungal protein synthesis with a different mode of action from other antifungal medications. tRNAs, which recognise RNA triplets on the mRNA and contain a covalently bonded amino acid corresponding to that triplet in the genetic code, facilitate the translation of genetic information during the synthesis of fungal proteins. A class of enzymes known as aminoacyl-tRNA synthetases (AARS) are essential for maintaining and

translating the genetic code found in DNA as well as for the creation of proteins (60). Tavaborole targets cytoplasmic leucyl-tRNA synthetase (LeuRS), one of these enzymes with an editing or proofreading system that fixes enzymatic errors. On a different editing active site, proofreading takes place. Tavaborole binds to the editing site together with tRNA to bind to the fungal cytoplasmic LeuRS (61). The fungal development is inhibited as a result of the tRNA being stuck there and limiting further cellular protein synthesis. As opposed to other AARS inhibitors, tavaborole binds to the LeuRS editing domain. Compared to human LeuRS, tavaborole exhibits an affinity for fungal LeuRS that is more than 1000 times higher. Therefore, there is a very large margin of safety and relatively little human exposure (62).

**Table 2.2: Review of work done on Tavaborole**

| Sr. No. | Author | Formulation | Conclusion |
|---|---|---|---|
| 1 | Harak, Pravin D et al. (63) | Film forming solution | Results from the developed formulation for several characterisation tests were acceptable. The improved formulation demonstrated 97.2% drug release and 99.2% effective antifungal activity. Such a formulation may shorten the course of treatment, be more well-tolerated by patients, and represent a breakthrough in the management of skin infections. |
| 2 | Vikas Agrawal et. al. (64) | Microemulsion | The in-vitro nail clipping investigation showed that an improved microemulsion formulation resulted in increased tavaborole penetration. Additionally, it demonstrated enhanced antifungal efficacy against dermatophytes species as *Candida albicans*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes*. As a result, Tavaborole loaded microemulsion may be a candidate for topical onychomycosis treatment. |

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|---|---|---|---|
| 3 | Tracey Vlahovic DPM et.al. (65) | 5% topical solution (Nail Polish) | The nail bed was significantly penetrated by nail polish. This strategy can increase patient compliance because nail polish can hide an infected nail's appearance. |

## 2.6 Nanoemulsion in Topical drug delivery system

The goal of maximizing therapeutic benefit while reducing toxicity is achieved through an optimum drug delivery system. A surfactant molecule-based interfacial coating stabilizes the thermodynamically stable, isotropically transparent dispersion of two immiscible liquids, such as oil and water (66). Nanoemulsions have consistent, incredibly small droplet sizes between 20 and 200 nm. Nanoemulsions cannot be formulated directly; extra shear is required to separate bigger droplets into smaller ones. When compared to micro emulsion phases, there isn't a lot of information available regarding formulating and evaluating nano-emulsions. The earliest nanoemulsions, classified as oil-in-water (O/W), water-in-oil (W/O), and bi-continuous, were developed in the 1940s (67).

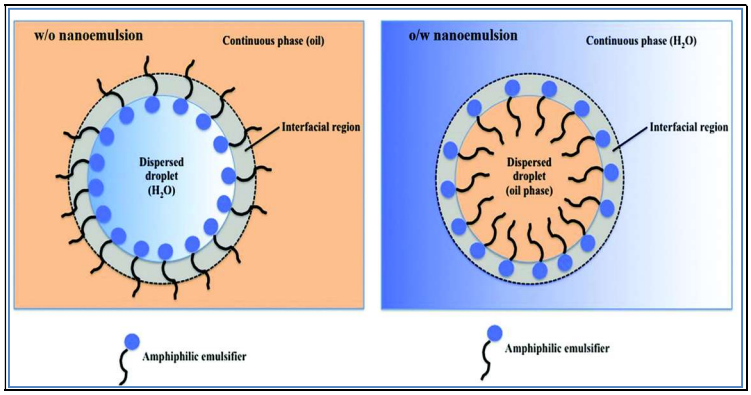


**Figure 2.6: Basic structure of w/o and o/w nanoemulsion (68)**

### 2.6.1 Formulation of Nanoemulsion

#### 2.6.1.1 Component of Nanoemulsion

**Oil:**

Due to its ability to solublize lipophilic drug molecules and enhance absorption via the body's lipid layer, oil is the second most significant transport medium after water. Because of its special

ability to penetrate cell walls, oil is particularly helpful for lipophilic active medication delivery. The swelling of the surfactant's tail group region is affected by the oil phase.(69) Short chain alkanes exhibit greater levels of penetration than long chain alkanes. The nanoemulsion is now created using a variety of new oils, including Captex 355, Captex 200, Captex 8000, Witepsol, Myritol 318, Isopropyl myristate, Capmul MCM C8, Acconon MC8 2, and many others (70).

**Surfactant**

Surfactant must be able to lower the interfacial tension as close to zero as possible in order to facilitate the dispersion of all components. When making a W/O nanoemulsion surfactants with HLB values of 3-6 are beneficial, whereas surfactants with higher HLB values of 8-18 are useful when formulating O/W nanoemulsions. Surfactants that have an HLB value of 20 or higher serve as cosurfactants to lower surfactant concentrations to acceptable levels and create microemulsions. There are several different types of surfactants, including cationic, anionic, cationic, and witter ionic surfactants (71). Ionic surfactants are vulnerable to stability concerns and generally are not preferred due to toxicity worries. However, non-ionic surfactants are more common than other types because they can be used to make safe medicinal dosage forms. The table below provides several non-ionic surfactant examples.

**Table 2.3: Examples of surfactant**

| Sr No. | Surfactant | Examples |
|---|---|---|
| 1 | Nonionic surfactant | Polyoxyl 40, Polysorbate80, d-α-tocopherolpolyethylene glycol1000succinateSolutolHS-15, Polysorbate20, Polyoxyl40 stearate, hydrogenated castor oil, Sorbitanmonooleate |
| 2 | Anionic surfactant | Carboxylate groups, Soaps, Sulfonates, Divalent ions |
| 3 | Cationic surfactant | Amines, quaternary ammonium compounds |

**Cosurfactant**

High quantities of single-chain surfactants are needed to lower the interfacial tension between oil and water to a point where a nanoemulsion can spontaneously form. Cosurfactant increases the fluidity of the interface because it contains fluidizing groups such unsaturated bonds, which subsequently destroy the liquid crystal or gel structure and change the HLB value in a way that results in the spontaneous creation of nanoemulsion (73).

**Aqueous Phase**

The aqueous phase's characteristics, such as pH, ionic concentration and electrolytes can affect the stability and droplet size of a nanoemulsion. For the examination of spontaneous nanoemulsification of nanoemulsion, aqueous phases such as plain water, simulated gastric fluid (pH 1.2), Ringer's solution, simulated intestinal fluid (pH 6.8) and phosphate buffered saline can be utilized (74). Based on the aqueous phase's aforementioned features, adding a medication with pH-dependent solubility to the system can significantly alter how nanoemulsions behave in phase. Ethyl oleate, polyethylene glycol 400, Tween 80, Span 80, ethanol, and deionized water were used to make the nanoemulsion. In this instance, deionized water served as the aqueous phase, Tween 80 and Span 80 served as surfactants, and ethanol served as a cosurfactant (75).

**2.6.2 Method of Preparation of Nanoemulsion**

**2.6.2.1 High Energy Approaches**

**High Pressure Homogenization:**

To prepare a nanoemulsion, a high pressure homogenizer is needed. This process formulates nanoemulsions with low particle sizes, between 10 and 100 nm. In order to generate dispersion, the oil and water mixture is forced through a small inlet orifice at extremely high pressure, often 500 to 5000 psi. This subjected the product to hydraulic shear and strong turbulence, resulting in extremely fine emulsion particles. The particles that result from this process have a liquid, lipophilic core that is isolated from the surrounding aqueous phase by a monomolecular phospholipid coating. For the purpose of developing the optimal formulation, the following process variables should be examined (76).

**Ultrasonication:**

It is the best method for formulating a nanoemulsion. The droplet size of a typical emulsion or microemulsion is lowered with the use of a sonication process. However, one drawback of this technology is that it can only be used to make tiny batches of nanoemulsions; it is not appropriate for big quantities. The ultrasonication method employs a probe sonicator to prepare nanoemulsions. It is possible to produce desired qualities by appropriately adjusting the level of oil, surfactants, and secondary surfactants (77).

**Micro fluidization:**

It is a trademarked mixing technique. This technique makes use of a micro fluidizer device. This apparatus uses a high-pressure positive displacement pump (500–20,000 psi) to push the product through the interaction chamber. Microchannels, which are tiny channels, make up this chamber. The product flows onto an impingement area, producing very small particles in the submicron range. In this instance, two solutions (the aqueous phase and the oily phase) are combined and treated in an inline homogenizer to produce a coarse emulsion. This rough emulsion enters a micro fluidizer where it undergoes additional processing to become a stable nanoemulsion. Although it is discovered to be more effective than Ultrasonography, this technology is less practical due to production expenses, equipment contamination, and aseptic processing (78).

**2.6.2.2 Low Energy Approaches:**

When low energy approaches arise from the emulsification process, nanoemulsions are formed as a result of phase transition. Usually, this is done by either changing the mixture or maintaining a steady composition and either maintaining a constant temperature or changing the temperature.

Temperature of the phase inversion: This approach produces a fine dispersion because phase transitions caused by the emulsification pathway generate chemical energy. An emulsion can create a phase transition by changing its composition while maintaining a constant temperature, or vice versa. A phase inversion can be of one of two types: (i) Transitional Inversion: This is brought on by shifting variables that have an impact on the system's HLB. Temperature and/or electrolyte content, for instance (ii) By adjusting the surfactant's HLB number while maintaining a steady temperature, catastrophic inversion can be produced (79).

Spontaneous Emulsification: The first stage in this procedure is to prepare a homogenous organic solution made up of hydrophilic and lipophilic surfactants dissolved in a water-miscible solvent. (ii) The o/w emulsion was created by injecting the organic phase into the aqueous phase while magnetic stirring was taking place. And with lower pressure, the water-miscible solvent is eliminated by evaporation (80).

**Table 2.4 Literature review of nanoemulsion for topical drug delivery system**

| Sr. No. | Author | API | Conclusion |
|---|---|---|---|
| 1 | Francisco et.al. (81) | Nystatin | The potential therapeutic index was increased because the nanoemulsion's pharmacokinetic release was shown to be quicker than that of the commercial ointment Mycostatin®. Nystatin was not absorbed into the systemic circulation, according to permeation studies, and the amount that was maintained in the skin was enough to produce an antifungal effect. The Nystatin-loaded nanoemulsion had a stronger antifungal impact than the Nystatin by itself. The Nystatin nanoemulsion treatment was found to be more therapeutically effective than traditional ones. |
| **2** | Hussain et.al. (82) | Amphotericin B | Histopathological analysis performed *in vivo* indicated that formulations for cutaneous infection are more effective and safe than oral distribution. In light of the aforementioned findings, it can be said that localised AmB distribution using NE gel is a cost-effective and secure method for treating a fungal infection**.** |
| **3** | Reddy et.al. (83) | Terbinafine hydrochloride | Gel-P and Gel-S were found to effectively treat *Trichophyton mentagrophytes* infection in Wistar rats after topical treatment, whereas Marketed cream took 14 days to do so *in vivo* antifungal trials. In order to address the permeability and efficacy issues, this study demonstrates that the nanoemulsion gels provide better permeation, followed by cure rates of poorly soluble TBH in animal models. As a result, these systems may be the preferable drug carriers for pharmaceuticals |

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| | | | intended for topical application. |
| **4** | Adel et.al. (84) | Clove oil - naftifine | By obtaining up to 2-, 3-, 5.75-, and 2.74-fold increases in the amounts of penetrated NF, steady-state flow, permeability, and diffusion coefficients, respectively, in comparison to a commercial product, the proposed nanoemulsion demonstrated good antifungal and anti-inflammatory effectiveness. Consequently, the developed nanoemulsions containing a mixture of Naftifine and clove oil could be seen as viable delivery systems for the treatment of tinea. |
| **5** | Campos et.al.(85) | Ketoconazole | When compared to KTZ cream, the *in-vitro* drug release profile showed that the NEs-CL-KTZ formulation could boost KTZ release by more than nine times. As a result, the NEs-CL-KTZ formulation examined in the current investigation has proven to be the most effective one for the treatment of *C. albicans* infections. |
| **6** | Malik et.al. (86) | Itraconazole | The MNE primarily affects the lipids and proteins of the skin, notably the stratum corneum, according to ATR-FTIR research, which leads to much increased permeation and retention of the medication. It was determined that the suggested MNE formulation can be used therapeutically to treat a variety of cutaneous fungal infections by delivering medication to the skin's target region. |
| **7** | Maha et. al. (87) | Miconazole nitrate | Nanoemulsion performed better in the evaluation than cream formulations. |
| **8** | José et.al. (88) | Clotrimazole | Developed According to the first order model, nanoemulsion delivered a prolonged release of the medication. The *in-vivo* tolerance research |

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| | | | validated the appropriateness for topical application, and antifungal efficacies were also better than commercial references, making CLT-NEs an excellent tool for clinical evaluation of topical candidiasis therapy. |
| **9** | Gorle et.al. (89) | Posaconazole | Posaconazole's solubility appears to have improved as a result of the release research, which may help it work more effectively to treat fungus-related disorders. |

**2.7 Nanostructured lipid carriers (NLCs) for Topical drug delivery system:**

Since a long time ago, topical medicine application has been used to accomplish a variety of goals on several layers (skin surface, epidermis, dermis, and hypodermis). However, there have been reports of a number of issues with standard topical treatments, including limited uptake because of the stratum corneum's barrier function and absorption into the bloodstream. Several techniques for delivering active pharmaceutical ingredients (APIs) over the skin are available in the scientific literature today (90). These comprise multilayer matrix assemblies, matrix diffusion-controlled devices, multiple polymer devices, and reservoir matrices. These include topical use of Solid Lipid Nanoparticles (SLN) and Nano Structured Lipid Carriers (NLC), which are innovative systems made of physiological lipid materials suited for topical and transdermal administration (91, 92). NLCs are made up of lipids that are biodegradable and have low toxicity. In addition to increasing the amount of medicine that is absorbed into the skin, the small size provides direct contact with the stratum corneum. Lipid nanoparticles' occlusive capabilities cause a skin hydration impact to be more pronounced. Lipid nanoparticles can also improve the chemical stability of substances that are vulnerable to light, oxidation, and hydrolysis (93). Healthy skin normally contains 20% water in the stratum corneum, which acts as a rather efficient barrier against the percutaneous absorption of exogenous chemicals. After using SLN or NLC, the skin becomes more hydrated, which results in less corneocyte packing and larger spaces between the corneocytes. This will make medication penetration and percutaneous absorption easier to the deeper skin layer (94).

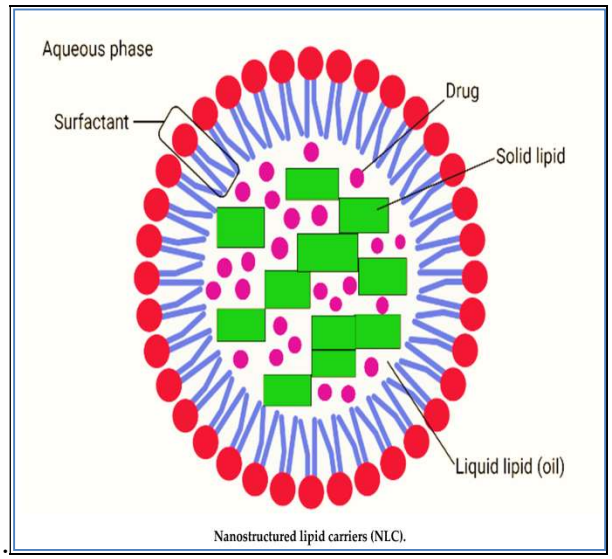


**Figure 2.7: Composition of NLCs (95)**

### 2.7.1 Formulation of NLCs

High pressure homogenization (HPH), which is separated into hot and cold procedures, is the most widely used process for producing NLC. This approach is particularly popular for manufacturing nanocarriers on a large scale and offers a number of benefits, including quick production times and simple scaling up. It also doesn't make use of organic solvents. In the hot approach, a hot surfactant solution is introduced while stirring quickly to a mixture of melted lipids that contains a specific medication and is heated around 5 to 10 degrees above melting point (96). The resultant emulsion is homogenised at high pressure (often at 500 or 800 bar) to produce a hot nanoemulsion, which is subsequently cooled to room temperature to form NLCs. Cold homogenization involves cooling down the melting lipid that contains the active ingredients (either with ice or liquid nitrogen). The obtained material is then broken up and ground. The produced microparticles are mixed in a surfactant solution that is cold before being homogenised at room temperature under high pressure. The hot HPH method's drawbacks include the usage of high temperatures, pressures, and surfactant concentrations. Burst release is a common way to categorise lipid compositions made using this technology. Some adjustments (such low temperature - cold homogenization, decreased surfactant content) are utilised to induce sustained release and to lessen the burst impact (97, 98). The microemulsion technique, solvent diffusion method, ultrasonication, and membrane contactor procedure are further approaches to NLC preparation. As an alternative to HPH, the solvent diffusion technique is frequently employed

since it is simple, does not call for specialised equipment, and provides prolonged drug release. The main limitations of this approach, however, are the usage of organic solvent and the absence of mass production (99). The solvent diffusion method involves dissolving lipids and medicines in an organic solvent (acetone, ethanol), which is then swiftly distributed into water while being mechanically stirred at 70°C. The organic solvent is eliminated during the evaporation procedure, which involves heating the pre-emulsion (100). After cooling the pre-emulsion to room temperature, the nanoparticles are successfully dispersed. The aqueous dispersions of NLCs are obtained during the preparation process. A preservative agent (such as phenoxy ethanol with ethyl hexyl glycerin, parabens, propylene glycol, or pentylene glycol) should be added to assure the stability of aqueous NLC dispersions. Water from the dispersion is removed using either the freeze-drying method or the spray-drying method to produce an NLC in solid form. An aqueous NLC dispersion or solid NLC is incorporated in premade topical treatments (such creams and gels) to prepare the final formulation for skin application. Another technique is to create a gel by mixing viscosity enhancers (such carbopol, chitosan, or derivatives of cellulose) with an aqueous dispersion of an NLC (101).

A medication may be incorporated in the NLC between fatty acid chains, lipid layers, or in lipid matrix flaws (amorphous structure). The "imperfect type," kind I, is distinguished by having a low proportion of liquid lipids in comparison to the solid phase. In the first step, a blend of liquid and solid lipids is used to create an o/w nanoemulsion. The nanoemulsion is then cooled to room temperature, where the crystallization process results in the formation of a highly disordered matrix (102). The crystal's triglyceride fatty acid chains are spaced apart in the defective matrix, which increases the drug's capacity. Type II is produced using a particular lipid mixture that results in an amorphous lipid matrix. When solid lipids are characterized by poor drug solubility, Type III, often known as a "multiple type," is particularly helpful since it has a large concentration of liquid lipids, which enhances drug solubility and increases drug loading (103).

**Table 2.5 Literature review of NLCs for topical drug delivery system**

| Sr. No. | Author | API | Conclusion |
|---|---|---|---|
| **1** | Sanap et.al.(104) | Miconazole nitrate | Rats' abdomen skin might discharge a greater amount of MN from commercial gel than from MN-NLC Gel. The research could be interpreted |

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| | | | as a successful development of MN-loaded NLC-bearing hydrogel to boost the encapsulation efficiency of colloidal lipid carriers with the benefit of improved performance in terms of stability and provides a sustaining MN topical effect as well as quicker relief from fungal infection. |
| **2** | Passos et.al. (105) | Itraconazole | All things considered, Itraconazole encapsulated in NLC is a workable method for improving cutaneous localization without sacrificing its effectiveness against fungus. |
| **3** | Bors et.al. (106) | Nystatin | The findings of this study showed that Nystatin may be successfully encapsulated in lipid nanocarriers based on emulgade, glyceryl monostearate, and olive oil to create antifungal formulations. |
| **4** | David et.al. (107) | Voriconazole | The potential of NLC as topical nail delivery systems for enhancing drug penetration into deeper hoof regions over unloaded drugs was demonstrated in this study, which was the first to propose the ungual application of NLC. Such findings might significantly affect how onychomycosis is treated. |
| **5** | Gujjar et.al. (108) | Econazole nitrate | Through the hot homogenization technique Due to the Glyceryl monostearate, Glyceryl monooleate, Poloxamer108 and 407, and Carbopol 934P, ECN-NLC gel has reduced particle size and improved stability, making it suitable for topical application. Econazole nitrate formulations have limitations and downsides (drug loading and skin irritation), which have |

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| | | | been overcome and alleviated by the newly created formulation. |
| **6** | Gardouh et.al. (109) | Clotrimazole | The findings suggest that NLC formulation may be a potential carrier for many anti-microbial and anti-fungal applications due to improved homing of Clotrimazole molecules and regulated drug release. |
| **7** | Gardouh et.al. (110) | Tolnaftate | Particles in the created formulation are in the nano-size range, according to the findings of the master sizer, TEM, and Zetasizer. This study has shown that NLCs are an effective delivery system for Tolnaftate. |
| **8** | Bianchin et.al. (111) | Fluconazole | Lipid core nanocapsules and nanostructured lipid carriers displayed nanotechnological properties, including a low polydispersity particle size distribution and a negative zeta potential. The findings of this study have implications for clinical therapy and may be utilised to treat fungal infections brought on by resistant isolates of Candida spp. |

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