1. Introduction

1.1. Fungal Infection

Infections caused by fungi, such as athlete's foot, ringworm, yeast infections, and infections of the finger and toe nails, can be very painful and last for a long time. Additionally, particularly in those with compromised immune systems, systemic and opportunistic fungal infections can result in more serious illnesses. The burden of fungal diseases in humans is caused by about 30 fungal species (1). More than 1.5 million people lose their lives to fungal infections, which afflict over a billion people worldwide (2). More than billion people are having skin, nail and hair fungal infection. In tropical nations like India, where fungal infections are more common, dermatophytosis is becoming more and more common (3). Many different kinds of fungal diseases exist that can harm the human body, cause recurrent infections, and even be lethal (4). Candida species infections in the mouth, skin, nails, vagina, and other areas are very concerning due to the formation of biofilms. Other major infectious agents that should also be taken into consideration include yeast, *Pseudomonas fluorescens, Aspergillus fumigates, Fusarium culmorum, Trichophyton rubrum*, and secondary infections of the *epidermophyton floccosum* (5). Human fungal infections can be fatal and detrimental to health, especially for those with weakened immune systems (6). A variety of epidemics involving the provision of healthcare have been caused by certain fungus spreading among patients in clinical settings, despite the fact that there have been very few reports of fungal outbreaks and limited human-to-human transmission in the past (7). Epidemiologic trends also show dramatic increase in the prevalence of resistant infections and the creation of emergence of multidrug-resistant fungus. In certain populations, the prevalence of candidemia has decreased as a result of the increased use of prophylactic antifungals, but this use has simultaneously increased the threat of rising resistance. 15 new risk factors have emerged as a result of improvements in medical practices and procedures, and the total number of susceptible hosts has also increased. For instance, the use of immunosuppressive drugs, chemotherapy, and antibiotics has dramatically increased, putting new and growing patient populations at risk (8). The global microbiome has changed significantly as a result of decades of widespread use of anti fungals and antibiotics in medicine and agriculture. This has caused a rise in drug-resistant fungal infections in people, animals, and plants (9).

1.1.1 Skin Fungal Infection

Fungi infection is a major contributor to skin diseases globally. Initially attacking the skin's surface, fungi later enter the deeper layer through desquamation. One of the fungi that cause the most superficial cutaneous infections is the Candida species (10). Nowadays, skin fungal infections are more common, and those with immune system-compromising illnesses like AIDS are more likely to have them. Patients frequently visit dermatological clinics due to skin fungal infections. Fungi are parasitic microorganisms that can infect several internal organs systemically and have an adverse effect on the skin and mucous membranes. According to reports, 20% to 25% of the human population has skin fungal infections (11). The most common infections caused by fungi include superficial mycoses of the skin, nails, and hair. They are spread by dermatophytes, non-dermatophyte molds, yeasts and yeast-like fungi. Fungal infections are prevalent in tropical and subtropical climates around the world. Their growth and proliferation are promoted by environmental factors such as high temperatures, high humidity, and poor hygiene. Even if it doesn't directly contribute to mortality, it is recognized to be associated with extreme morbidity, which might be physical or mental. This has an adverse effect on the affected people’s quality of life, which has a detrimental effect on their social, emotional, and professional standing. These infections are a major global concern as they spread across the world (12). Figure 1.1 shows the classification of fungal skin infections based on the depth of penetration of parasitic fungi into the skin.

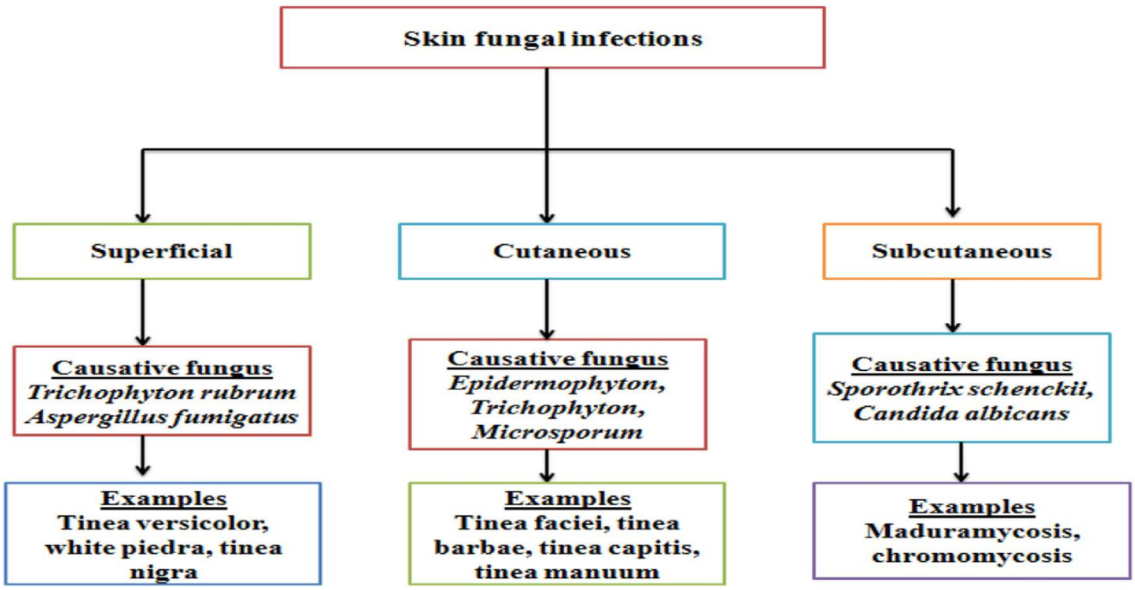

Figure 1.1: Classification of skin fungal infections depending upon the depth of penetration of parasitic fungus into the skin(6)

1.1.1.1 Prevalence

Dermatomycoses are fungal infections of the skin, hair, and nails that affect an estimated one billion people globally (13). Dermatomycoses vary in frequency and incidence depending on socioeconomic and regional factors. For instance, crowded housing, living near animals, and inadequate cleanliness all contribute to the higher occurrence of various fungal skin illnesses in lower socioeconomic areas. In addition, dermatophytes flourish in hot, humid environments, and dermatomycoses are more prevalent in tropical nations (14). Nearly a billion individuals are thought to have skin, nail, or hair fungal infections, as well as many tens of millions suffering from mucosal candidiasis and other serious fungal diseases that have a substantial impact on their life or are fatal (15). It has been determined that 20% to 25% of people worldwide have superficial fungal infections. The prevalence of fungi that cause surface fungal infections is changing today and is mostly influenced by climatic, ecological, and socioeconomic factors. Even while superficial fungal infections are not life-threatening conditions, they can still adversely affect a patient's quality of life (16).

1.1.1.2 Signs and Symptoms

Skin fungus infections can result in different types of skin rashes. The symptoms include red, scaly, and itchy skin, as well as fine scales that resemble dry skin and red, painful, pus-filled areas (17). Figure 1.2 shows the skin bearing fungal infection.

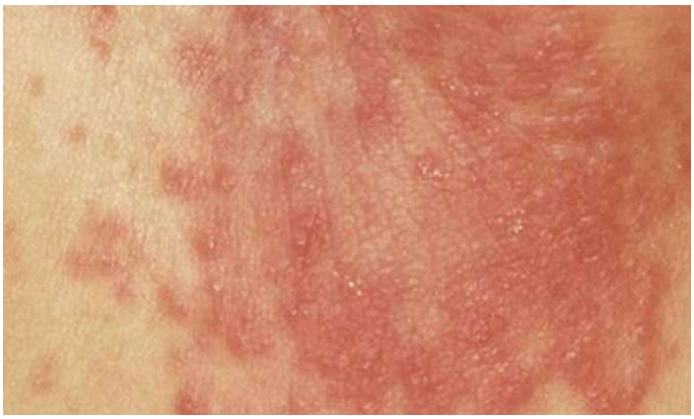

Figure 1.2: Skin fungal infection (11)

1.1.2 Nail Fungal Infections

Especially in people with impaired immune systems, nail fungal infections are notoriously difficult to treat and persistent, with potentially serious health consequences. Onychomycosis is a persistent nail fungal illness that is frequently misdiagnosed in underdeveloped nations because of inadequate medical infrastructure (18). 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. Different types of nail fungal are shown in figure 1.3.

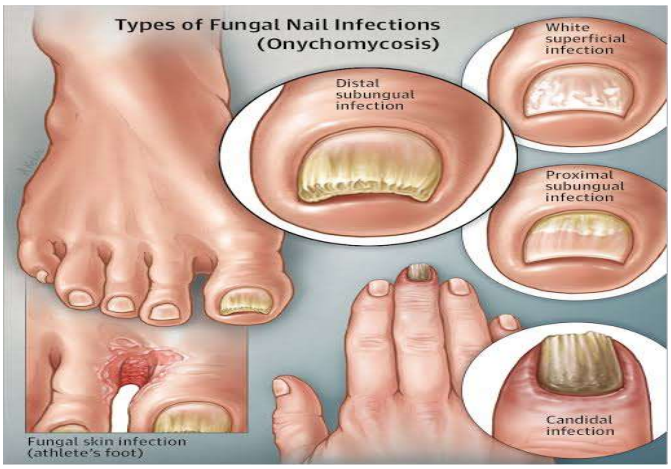

Figure 1.3: Types of Nail Fungal Infection (19)

1.1.2.1 Prevalence

Onychomycosis continues to spread and persist, affecting about 5% of the global population. The incidences in India have been reported to range from 0.5 to 5% by different workers (20). It impacts toenails far more frequently than fingernails and makes up around 50% of all nail

problems. In Western nations, the prevalence of onychomycosis has been calculated to be around 5%, and it has been rising over the past few decades (21). The below statistics show the global prevalence of dermatophyte toenail onychomycosis. General population-3.22%, children- 0.14%, elderly- 10.28%, Psoriasis patients- 10.22%, diabetics- 8.75%, HIV-positive patients- 10.40%, Dialysis patients-11.93%, transplant patients- 5.17% (22). Onychomycosis caused by dermatophytes is more common in dialysis patients and onychomycosis caused by yeast is more common in the elderly people. Onychomycosis not caused by fungi was more common in psoriasis patients. Due to weakened immune systems, reduced peripheral blood flow and alterations in the nail plate, some populations may have an increased prevalence of onychomycosis (23).

1.1.3 Pathophyisiology:

To circumvent the host immune system and increase the severity of infections, fungal pathogens use a variety of strategies. 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. (24,25) Fungal pathogens adapt to environmental stresses and drug pressure through various mechanisms, including stress response pathways, cell wall modulation, and the activation of drug efflux pumps, allowing them to survive and persist in challenging environments. (26)

1.2 Classification of drugs used for treatment of fungal infection (27)

1. Antibiotics: Amphotericin b, (amb), Griseofulvin ,Nystatin, Natamycin, Hamcyin
2. Antimetabolites: 5-fluorocytosine (5- FC)
3. Azoles:

   Imidazoles: Luliconazole, Clotrimazole, Miconazole, Oxiconazole, Econazole Ketoconazole,

   Trizoles: Itraconazole, Voriconazole, Fluconazole
4. Allyl amine : Terbinafine
5. Other topical agents:, , Tolnaftate, Benzoic acid, Quiniodochlor, Ciclopirox olamine, Sodium Thiosulfate, Tavaborole, Undecylenic acid

Oral antifungal medications are recommended in addition to topical antifungal medications for the treatment of nail and skin fungal infections. This is because of the poor penetration of medications into the skin and nails, which leaves insufficient concentrations to demonstrate the anti-fungal activity. Orally administered antifungal drugs, however, exhibit a wide range of adverse reactions because of their non-specific distribution throughout the body. Therefore, topical use of anti-fungal medications is preferred over oral treatment due to lower risk of problems and adverse effects related to systemic absorption (28). Additionally, topical treatments for nail and skin fungal infections present the antibiotic adjacent to the affected region, resulting in a more effective course of treatment. Topical treatments are particularly efficient for superficial, cutaneous, and subcutaneous skin infections as well as onychomycosis; however, because drugs cannot penetrate the skin and nails, their efficacy is diminished (29). Therefore, the goal of the current study was to create a better topical formulation of selected anti-fungal drugs.

1.3 Luliconazole

Japan has approved the imidazole antifungal cream 1% (Luliconazole; $C_{14}H_9Cl_2N_3S_2$) for the treatment of cutaneous mycosis since 2005. It has been demonstrated that Luliconazole is active against a number of fungi, including yeast, dermatophytes, and dermataceous fungus. It also exhibits considerable fungicidal activity against Trichophyton species. Luliconazole is also highly active against candida albicans (MIC range: 0.031-0.13 µg/ml), proving to be more potent than Terbinafine, Liranaftate, Butenafine, Amorolfine, and Bifonazole but less than Ketoconazole, Clotrimazole, Neticonazole, and Miconazole (30). Luliconazole has been shown to inhibit Candida albicans 14-demethylase much more effectively than Bifonazole or Lanconazole. After his 7 days of daily treatment with 10% Luliconazole *in vitro*, *T. Rubrum* infected nail model showed that therapeutic levels of Luliconazole reached the full thickness of the human nail plate. Luliconazole has a low affinity for keratin, so it is released from the keratinous nail plate and spreads throughout the nail bed. Unlike other azoles, keratin does not reduce its effectiveness (31). When administered as a topical preparation, Luliconazole has a very good tolerability profile and no systemic side effects have been reported. Luliconazole works on fungal cell membranes by blocking the synthesis of ergosterol (32). Marketed formulations of Luliconazole includes creams like LUZU, Luzicon,

Luliconaz, Lulisen, Lulivib, Lucinak, Lulifin, Lulix, Lofatin, Lu-gal, Lutoz, Lulicona, Lolyzole, Lunader and Lulibet which all contain Luliconazole 1%w/w. Other products are Luzicute and Lilituf (Luliconazole lotion 1%w/v). The skin penetration and drug retention times for marketed formulations are lower and shorter, respectively (33). Nanocrystal loaded hydrogel (33), Spanlastics (34), Herbal ethosomal gel (35) Nanosponge (36) Liposomal gel (37) Niosomal gel (38), SLN based gel (39) for skin infection, 5% solution (40) 1% cream (41) Nail Lacquer (42) of Luliconazole for nail fungal infection are reported for enhancement of permeation rate and antifungal activity.

1.4 Tavaborole

Tavaborole is a synthetic oxaborol antifungal agent. Through the boron atom in its structure, it attaches to the editing site to trap leucyl tRNA and stop it from being catalytically turned over, preventing the synthesis of new proteins in fungi. It is employed to treat mycosis on the skin and is effective against dermatophytes, fungus, moulds, and yeasts (43). According to research, Tavaborole is superior to other classes of antifungals such as imidazole, triazoles, polyne antimycotics, pyridine analogues in terms of its broad spectrum antifungal activity, low MIC for a variety of fungus species, high mycological cure rates, lower relapse rates and having low molecular weight resulting in higher skin penetration (44). Tavaborole microemulsion (45) and film forming solution (46) are reported to enhance the penetration and improved antifungal activity. Topical solution (5%) of Tavaborole is commercially available for treatment of fungal infection.

1.5 Topical Drug Delivery System

Common problem for topical delivery is the poor penetration ability of the drug and low retention time. Different approaches are used for enhancing the penetration and prolonging the retention of the drugs after topical application. Topical medication delivery via nanotechnology is a contemporary and fast developing technique. It uses a variety of nanocarriers, including liposomes, nanoemulsions, nanocrystals, polymeric nanoparticles, lipid nanocarriers, and dendrimers (47, 48). Lipid based drug delivery systems are preferable as nanocarriers for anti-fungal drugs due to the inherent antifungal activity of some of the lipids, which may give synergistic effect (49). There are number of essential oils such as lemongrass oil, Eucalyptus oil, Cinnamon bark oil, Fennel oil, Peppermint oil reported to possess antifungal activity (50). In the

present investigation, Nanoemulsion and Nanostructured lipid carriers have been selected as the lipid based nanocarriers for loading of the anti-fungal agents.

1.6 Nanoemulsion

Microemulsions and nanoemulsions (NEs) are colloidal nanocarriers with low viscosity and homogenous appearance that are kinetically stable. The pharmaceutical and cosmetic industries widely utilise them due to a number of advantages they offer, including as low preparation costs, high drug loading capacity, improved solubility of poorly water-soluble pharmaceuticals, decreased droplet size, and high drug penetration rate (51). Nanoemulsion (52-55) and microemulsion (56) are reported for enhancement of drug permeation through skin and nail. Mechanism of drug release from microemulsion in transangual route is shown in figure 1.4. Nanoemulsion require less concentration of surfactant and cosurfactant compared to microemulsion resulting in less toxicity, Thus nanoemulsion is selected as lipid nanocarrier. However, the most important feature of NEs is their capacity to improve skin penetration through a number of mechanisms, including a high solubilizing potential for hydrophilic and lipophilic drugs, a large surface area and good skin contact, and a direct permeation-enhancing effect through the stratum corneum (SC) as a result of their oil and surfactant composition (51). Release of drug from nanoemulsion through skin is shown in figure 1.5.

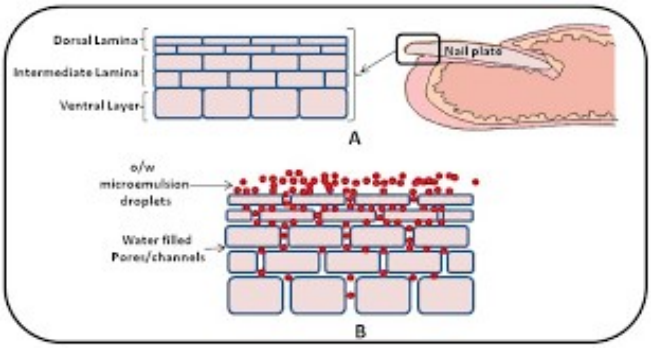

Figure 1.4: Drug permeation through transungual route from Microemulsion (56)

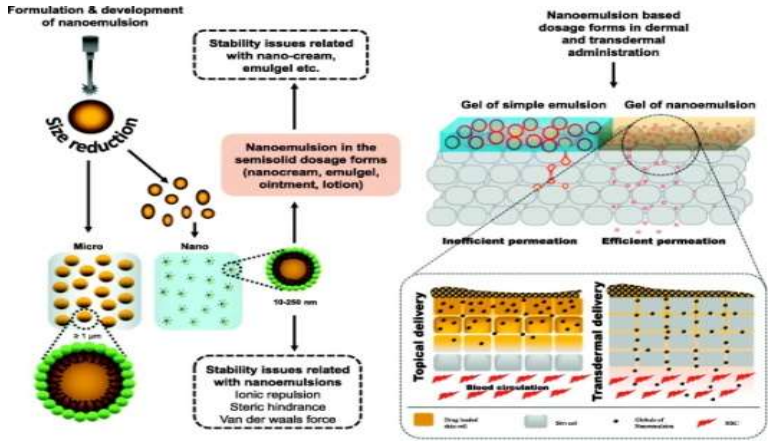

Figure 1.5: Drug permeation through skin from Nanoemulsion (57)

1.7 Nanostructured lipid carriers (NLCs)

Lipid nanocarriers like SLN and NLC, which are made of biodegradable, non-toxic, and non-irritating lipids, exhibit significant advantages over conventional drug forms. The small size (40–800 nm) of lipid nanocarriers ensures the adhesion of SCs to lipid membranes and increases the number of drug molecules reaching deeper layers of the skin (58). Solid lipid nanoparticles are composed of lipids that are solid at room temperature and have a surfactant coating that provides stability to the nanodispersion. SLNs improve skin permeability by increasing contact with the skin surface, forming an occlusive barrier that hydrates the skin and interacting with the lipids of the stratum corneum bilayer. The nanostructured lipid carriers are a colloidal system with a liquid lipid phase located on the surface of solid lipids and surfactant layer. Compared to SLNs, the spatial structure of lipids provides a large load on drugs and improves stability (59).

Drug delivery and targeting are now hot topics, with particular emphasis on the creation, characterization, and validation of drug-loaded NLCs' efficacy. Because most medications are lipophilic, their ability to dissolve in biocompatible liquid lipids is essential to the development of NLC (60). Therefore, less amount of drug will be required in dosage form. Voriconazole NLCs (61), Terbinafine NLCs (62) and Econazole NLCs (63) are reported for enhancing drug penetration in skin and diseased nail plate respectively. The mechanism of drug permeation through skin from NLCs is shown in figure 1.6.

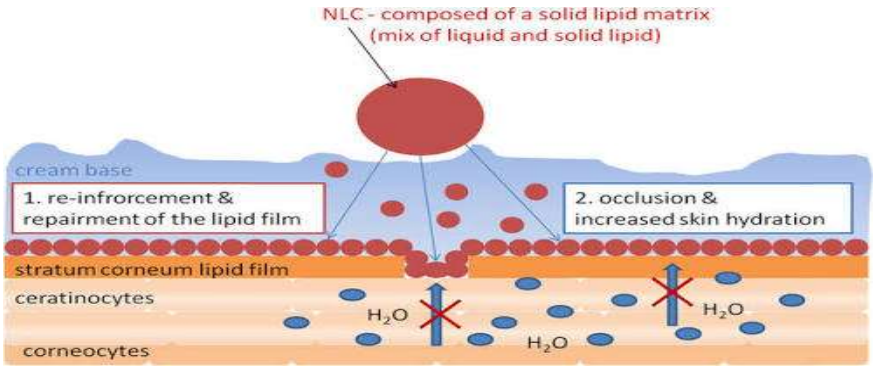

Figure 1.6: Drug permeation through skin from NLCs (64)

1.8 Hypothesis

It is hypothesized that the Luliconazole and Tavaborole loaded nano-lipid carriers i.e. nanoemulsion and NLC would lead to enhancement of topical permeation, retention time and extended release of respective drug.

1.9 Aim and Objectives

The following goals will be achieved by developing novel lipid-based topical formulations for the treatment of fungal infections of the skin and nails, incorporating them into gel, and testing their suitability for topical application through ex-vivo and in-vivo experiments:

- To enhance the skin permeation rate
- To enhance the skin retention time
- Sustained drug release for longer period
- Improvement in patience compliance
- Effective treatment or management of skin and nail fungal infections
- Enhancement in antifungal activity

1.10 Plan of work

- Literature review,
- Procurement of drugs and excipients
- Authentication of drug samples and drug-excipients compatibility study
- Analytical method development of drugs (UV/HPLC)
- Formulation development and Evaluation of Luliconazole and Tavaborole loaded Nanoemulsion
- Formulation development and Evaluation of Luliconazole and Tavaborole loaded NLCs

- *In-vitro* characterization of developed formulations
- Anti-fungal activity of the developed formulations
- Ex-vivo permeation studies and cell line studies
- *In-vivo* Pharmacokinetic and Pharmacodynamic study
- Stability studies

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