NOVEL CARRIERS IN TOPICAL ANTIFUNGAL THERAPY OF MICONAZOLE

Gajanan S. Sanap, Guru Prasad Mohanta, Ajay Kharche, Pankaj Khuspe and Bharat Vidhate

1Ideal College of Pharmacy and Research, Kalyan-421 306 Maharashtra, India.
2Department of Pharmacy, Annamalai University, Chidambaram-608 002 Tamil Nadu, India.

ABSTRACT
Fungal infections are amongst the most commonly encountered dermatological diseases in worldwide. The topical route is generally preferred due to the possible side effects of oral medication. Miconazole nitrate is an antifungal drug with a drawback of poor skin-penetration in the treatment of deep seated fungal skin infections. Currently, antifungal drugs are generally used as conventional cream and gel preparations in topical treatment. The efficiency of that treatment depends on the penetration of drugs through the target layers of the skin at the effective concentrations. A number of formulation strategies have been investigated for delivering antifungal compounds through targeted site of the skin. This review article focuses on the new alternative formulation approaches to improve skin penetration of antifungal drugs miconazole.

KEYWORDS: Miconazole nitrate; Antifungal; Nanocarriers; Topical delivery; Skin-penetration; formulation; fungal infections.

1. INTRODUCTION
Miconazole nitrate (MN) is a broad-spectrum antifungal agent of the imidazole group.[1] Azole-based antifungal agents can suppress antifungal characteristics by preventing the production of ergosterol through inhibiting cytochrome P450 responsible for 14-alpha-demethylation pathway.[2] Miconazole nitrate (MN) [(R,S)-1-(2-(2, 4-dichlorobenzyloxy)-2-(2, 4-dichlorophenyl) ethyl)-1 H-imidazole] (Figure.1). It acts by means of a combination of two mechanisms: ergosterol biosynthesis inhibition, which causes lysis of fungal cell membranes because of the changes in both membrane integrity and fluidity and direct
membrane damage of the fungal cells. The drug is active against dermatophytes and effective on pityriasis versicolor, tinea, otomycosis and vulvovaginal candidiasis, particularly Candida spp., Epidermophyton spp., Trichophyton spp., Micro-Sporum spp. and Pityrosporum orbiculare. The drug is primarily used as a topical treatment for cutaneous mycoses\textsuperscript{[3]}; poor dissolution and lack of absorption make it a poor candidate for oral administration. However, MN can be used as a systemic antifungal agent when amphotericin B or ketoconazole is either ineffective or contraindicated. Miconazole nitrate is poor skin-penetration capability presents a problem in the treatment of cutaneous diseases by topical application. The stratum corneum is the target organ of anti-mycotic treatment, and the improvement of local bioavailability leads to enhanced efficacy of the applied formulation. For effective treatment, the drug must be delivered in sufficient concentration to the site of infection.

Fig.1: Structure of Miconazole Nitrate (MN).

Topical agents that are conventionally used for the treatment of skin fungal infections are usually formulated as creams, lotions or gels. They either exhibit fungicidal or fungistatic actions depending on the agent being delivered. Since the side effects of fungal agents applied topically are less than their oral counterparts, they are the preferred agents.\textsuperscript{[4,5]} Another advantage of topical formulation is that it avoids drug-drug interactions, which are more common in case of oral administration.

Topical treatment of fungal infections has several superiorities including, targeting the site of infection, reduction of the risk of systemic side effects, enhancement of the efficacy of treatment and high patient compliance. The efficiency of the topical antifungal treatment depends on the penetration of drugs through the target tissue. Hence, the effective drug concentration levels should be achieved in the skin. In topical administration of antifungals, the drug substances should pass the stratum corneum, which is the outermost layer of the skin, to reach lower layers of the skin, particularly into viable epidermis. In this context, the formulation may play a major role for penetration of drugs into skin.\textsuperscript{[6]}
Various approaches have been used to enhance the access of such poorly skin-partitioned drug molecules. For example, the use of complexation with cyclodextrins has been reported to improve oral and topical delivery of MN.\[7,8\] Several reports have described the potential use of liposomes to topically deliver drugs into the deep layers of the skin. Development of alternative approaches for topical treatment of fungal infections of skin encompasses new carrier systems for approved and investigational compounds. Delivery of antifungal compounds into skin can be enhanced with the carriers including colloidal systems, vesicular carriers, and nanoparticles.

This review article focuses on recent study was carried out via descriptive and library analysis and was conducted through a stream of literature in the area of alternative formulation approaches for cutaneous administration miconazole.

2. Topical Delivery of Antifungals via Skin

Human skin is a well-organized membrane and, it has three main layers, which are called as epidermis, dermis and hypodermis. *Stratum corneum*, the outermost layer of epidermis is formed by dead and keratinized cells, and it is an excellent barrier to penetration of drugs through the skin.\[9\]

Drugs should penetrate into skin layers to ensure effective drug concentrations following topical administration. Types of the formulations as well as the physicochemical characteristics of drug molecules are effective parameters in topical delivery of drugs. In topical administration, the entering of drugs to systemic circulation is prevented or minimized. Thus, the systemic adverse effects of drugs are avoided.\[10\] Besides, topical preparations have better patient compliance due to their non-invasiveness and, they can be self-administered.\[11,12\]

Antifungal drugs should reach effective therapeutic levels in viable epidermis after dermal administration. The greatest challenge for dermal delivery is *stratum corneum*, and in order to improve its permeability, new formulation approaches have been investigated. Colloidal drug carriers such as microemulsions, vesicular carriers including liposomes, ethosomes and niosomes and, both lipidic and polymeric particulate carrier systems are among those new carriers to ensure dermal administration of antifungals by dermal targeting.\[13,14\]
3. The Conventional Dosage Forms in the Treatment of Fungal Diseases

Topical delivery is defined as the application of pharmaceutical dosage form to the skin for direct treatment of cutaneous disorder or the cutaneous manifestation of the general disease, with the intent of confining the pharmacological or other effect of the drug to the surface of the skin. Topical antifungal agents are conventionally compounded into various types of vehicles, such as ointments, creams, lotions, gels, or sprays. In addition, several agents used perorally or intravenously are also included because of the conducted studies aiming dermal/transdermal targeting of these antifungals.

4. Novel Carriers in Topical Antifungal Therapy of Miconazole

Present review focuses on various current alternative new formulation Approaches for Improving Treatment of Fungal Diseases in Skin of miconazole. Details of the experiments and results follow and summarize in Tables 1, 2 and 3.

4.1 Microemulsion-MN

Microemulsions, transparent, thermodinamically stable, and isotropic liquid dispersions, are promising colloidal carrier systems for topical and transdermal administration of drugs. The advantages of topical microemulsions include enhancing solubility of drugs, high thermodynamic stability, and ease of preparation and low costs.\(^{15}\) The oils and surfactants included in the composition of microemulsions act as enhancers for permeation of drugs across *stratum corneum*. These formulation components of microemulsions and the internal structure of phases enhance diffusion of the drug and, that can improve the partition of drug to *stratum corneum*.\(^{16}\)

They increase the cutaneous absorption of lipophilic and hydrophilic drugs and can act as a reservoir for poorly water soluble drugs.\(^{17-19}\) Miconazole sizes are frequently below 150 nm\(^{20,21}\) and are considered as a good choice for topically delivering antifungal drugs to treat local fungal infections.\(^{22}\)

The charged submicron emulsions are interesting candidates for skin drug delivery. Piemi and his colleagues (1999) incorporated MN in positively and negatively charged submicron emulsions using stearylamine or deoxycholic acid (DCA) respectively. Mean droplet size of the negatively and positively charged submicron emulsions were respectively 125 and 130 nm. Relationship between physicochemical characteristics of the vehicles particularly emulsioncharge and skin permeation was studied using liquid scintillation for radiolabeled
emulsions and HPLC for unlabeled emulsion vehicles. In various skin layers and receptor fluids, drug concentrations were lower for the radiolabeled emulsions than the regular emulsions. The positively charged submicron emulsions were more effective in terms of MN skin penetration than negatively charged emulsions. Diffusion kinetic studies using radioactivity technique demonstrated enhanced penetration rate of the MN negatively charged emulsion as compared to the positively charged emulsion. MN flux was fast and reached a maximum rate within 4 h with only negatively charged submicron emulsion (Table. 1). The results revealed that the surface-modified droplets pose a significant effect on the MN diffusion through skin.[23]

Peira et al. (2008) reported MN skin permeation and accumulation from positively charged MEs containing oil phase (1-decanol: 1-dodecanol 2:1 w/w), surfactant (Oramix NS 10 or a mixture of lecithin and Oramix NS 10), co-surfactant (PG and 1, 2-hexanediol) and aqueous phase (phosphate buffer 0.01 M at pH 5.8). Cationic charged-inducing agents (stearylamine (ST) (1% w/w), L-alanine benzyl ester (ALAB) (2% w/w) or cetyltrimethylammonium bromide (CTAB) (1.2% w/w)) were added to the various batches of drug-loaded MEs. Mean droplet size of the positively charged MEs ranged from 6.0 to 16.8 nm. After a single 24 h application, MN skin permeation was negligible for all MEs; accumulation from positively charged MEs was almost double compared to the negatively charged counterparts. Increased accumulation was ascribed to the relationship between positively ME systems and negatively charged skin sites; no significant difference was observed among a variety of cationic charged-inducing agents. Lower skin accumulation from ME containing lecithin indicated a phase transformation from ME to a liquid crystal system after reaching the skin (Table. 1). Therefore, the positively charged MEs were proposed as a promising formulation for skin drug delivery.[24]

Shahzadi et al. (2014) developed a novel ME system for MN topical application. Oleic acid as oil phase, tween 20 as surfactant and propylene glycol as co-surfactant were used for microemulsion preparation. Droplet size of the ME formulations was in the range of 37-91 nm. MN-microemulsions exhibited larger antifungal activity against Candida albicans than the reference sample; MN cream (2%). Considerable antifungal activity can be assigned to smaller globule size and larger surface area comparing with the normal emulsion present in the cream. In vitro drug release studies by Franz diffusion cell exhibited faster release rate for ME formulations than the marketed cream (Table 1).[25]
4.2 Solid Lipid Nanoparticles (SLNs) and Nano Structured Lipid Carriers (NLCs)

Solid lipid nanoparticles are carriers in which the drug is entrapped within a solid lipid core matrix. Examples of these lipids are triglycerides, diglycerides, monoglycerides, fatty acids, steroids, and waxes.\textsuperscript{26} Nanostructured lipid carriers are the second generation of lipid nanoparticles in which the matrix is composed of a mixture of solid and liquid lipids. Among the advantages of lipid nanoparticles are that the lipids utilized in their preparation are physiological lipids and that they can be prepared using organic solvent-free methods.\textsuperscript{27} Both solid lipid nanoparticles and nanostructured lipid carriers have been recommended as good carriers for the treatment of topical skin infections, especially for antifungal drugs.
which are known to be lipophilic, and hence, can be successfully entrapped within the lipidic core of solid lipid nanoparticles or nanostructured lipid carriers.\textsuperscript{[28]}

Bhalekar et al. (2009) developed MN-SLN dispersions (A-F) by hot homogenization method in which Compritol 888 ATO was used as lipid, tween 80, glycercylmonostearate as stabilizer surfactants and propylene glycol (PG) as enhancer of drug solubility in lipid. MN-SLN was an amorphous dispersion with high entrapment efficiency ranging from 80 to 100\% and average size of 244 to 766 nm. Chemical and physical stability of MN-SLN dispersion was examined for one month at 2–8°C. Particle sizes, entrapment efficiency of sample were 280±3.2 nm, 92±2.7\% and didn’t change for one month. Centrifugation of MCN-SLN at 3,000 rpm for 30 min indicated that the transition of the dispersed compritol 888 ATO in SLN dispersion from $\beta'$ to stable $\beta$ might occur extremely slowly. Lipid and surfactant contents displayed an essential role in particle size and drug entrapment efficiency. The influence of surfactant (Tween 80) concentration on the particle size was demonstrated by the particle sizes of the samples A, F, and C (261, 244, and 460 nm, respectively) with higher surfactant concentration and B, D, E (700-750 nm) with less surfactant concentration (1.25\%). Lower surfactant concentration led to the production of larger particle size. The entrapment efficiency of the samples was depended on the lipid content; samples A, B, and E with higher lipid content showed % EE of about 94\%, while samples C, D, and F revealed less % EE (almost 70\%). Higher MN was released by marketed gel (0.53 mg/cm$^2$) over SLN gel (0.29 mg/cm$^2$) through human cadaver skin. MN-SLN gel significantly created higher MN deposition in skin (57±0.6\%) as compared to marketed gel (30%±0.8) (Table 2). Therefore, MN-SLN formulations significantly increased the drug accumulative uptake in skin and markedly enhanced skin targeting effect compared with the marketed gel.\textsuperscript{[6]}
Table 2: Summary of the new Formulation Approaches of MN Using SLNs and NLCs.

<table>
<thead>
<tr>
<th>Research Question</th>
<th>Characterization Method</th>
<th>Study Type</th>
<th>Results</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLN-MN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A: 261±2.7 nm</td>
<td>- DSC</td>
<td></td>
<td>MN-SLN increase penetration of MN in skin over marketed gel</td>
<td>[6]</td>
</tr>
<tr>
<td>B: 720±3.4 nm</td>
<td>- X-ray</td>
<td></td>
<td>MN-SLN gel showed higher deposition than marketed gel</td>
<td></td>
</tr>
<tr>
<td>C: 460±4.8 nm</td>
<td>- FTIR</td>
<td>MN-SLN gel; 57±0.65%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D: 730±4.9 nm</td>
<td>- UV</td>
<td>MN marketed gel; 30%±0.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E: 766±3.7 nm</td>
<td>- Franz diffusion cell</td>
<td>High MN release from marketed gel of MN than SLN gel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F: 244±3.2 nm</td>
<td></td>
<td>MN-SLN gel; 0.289 mg/cm²</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MN marketed gel; 0.527 mg/cm²</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLN-MN : 206.4 ± 9.4 nm</td>
<td>- TEM</td>
<td>In vitro: Rat skin</td>
<td>Sustained drug release over 24 h by MN-SLN-hydrogel</td>
<td>[29]</td>
</tr>
<tr>
<td></td>
<td>- SEM</td>
<td>In vivo: Male albino rat</td>
<td>Negligible MN permeation after 24 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- HPLC</td>
<td></td>
<td>10 fold greater retention with MN-SLN-hydrogel as compared to MN suspension and MN hydrogel</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Franz diffusion cell</td>
<td></td>
<td>Less irritation by MN-SLN-hydrogel as compared to MN hydrogel and MN suspension after 24 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Tape stripping</td>
<td></td>
<td>more efficiency for SLN-bearing hydrogel in treatment of candidiasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NLC : 238.4±7.5 nm</td>
<td>- PCS</td>
<td>Ex-Vitro: Abdominal rat skin</td>
<td>Higher MN release from marketed gel than MN-NLC gel</td>
<td>[30]</td>
</tr>
<tr>
<td>MN-NLC1, MN-NLC2,</td>
<td>- SEM</td>
<td></td>
<td>Mean cumulative amount of MN (mg/cm²):</td>
<td></td>
</tr>
<tr>
<td>MN-NLC3, MN-NLC4:</td>
<td>- DSC</td>
<td></td>
<td>marketed gel; 0.687 MN-NLC gel; 0.260</td>
<td></td>
</tr>
<tr>
<td>206.3-233.9 nm</td>
<td>- UV</td>
<td></td>
<td>MN-NLC gel produced higher deposition of MN than marketed gel</td>
<td></td>
</tr>
<tr>
<td>ZPs: NLC: -19.6±0.9 mV</td>
<td>- Franz diffusion cell</td>
<td>Amount of MN Deposited skin (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MN-NLC1, MN-NLC2,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MN-NLC3, MN-NLC4:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(-13.2±0.4 mV) – (-13.9±0.1 mV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Drug release</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Jain et al. (2010) studied the effect of MN loading SLNs on the drug permeation profile. A variety of formulations and process variables were optimized to gain nano-sized particles with a maximum of drug entrapment efficiency. The stable SLN formulations with an average particle size of 206.3 ± 9.4 nm and a maximum drug entrapment percentage of 90.8 ± 5.2% incorporated into hydrogel. MN-SLN hydrogel exhibited better controlled drug release profile for a prolonged period. A negligible amount of MN was achieved from any of the applied formulations after 24 h in a rat skin permeation experiment. Tape stripping experiments showed 10-fold larger drug retention with MN-SLN hydrogel than the MN suspension and MN hydrogel. MN-SLN hydrogel exhibited less irritation as compared with miconazole hydrogel and suspension after 24 h of application. In vivo experiments on candida infected rats revealed more efficiency for MN-SLN hydrogel in the treatment of candidiasis.\[29\] Table 2).

Sanap and Mohanta (2013) investigated the systemic delivery of miconazole by SLN and NLC gels. Five SLNs and NLCs formulations were synthesized through hot high pressure homogenization technique. The prepared semi-solid systems indicated that mean particle size remained less than 250 nm and PI remained less than 0.50 after a three-month storage. MN-SLN1, -SLN2, -NLC1, -NLC2 showed 90% entrapment efficiency, while MN-SLN3, -SLN4, -NLC3 and -NLC4 indicated less entrapment efficiency. In the case of the marketed gel, an initial rapid release was observed with a lag time of 0.5 h, whereas MN-SLN gel exhibited a slow initial release with a lag time of 1 h. Ex vivo experiments showed MN controlled release via stratum corneum and dependency of release rate to the SLN lipid content. MN-loaded
SLN bearing hydrogel exhibited greater efficiency in the treatment of candidiasis. Sustained release was observed by MN-NLC, -SLN hydrogels. The results confirmed the potential of NLC and SLN as carriers for MN topical application with larger drug deposition into skin (Table 2).\(^{30,31}\)

### 4.3 Liposomes

Liposomes mainly composed of phospholipids have extensively suggested as vehicles for dermal drug delivery systems. Topically applied liposomes can transfer entrapped and non-entrapped hydrophilic drugs into skin.\(^{32-34}\) Liposomes are artificially-prepared spherical vesicles composed of a lamellar phase lipid bilayer identical to that of the natural cell membranes. They are often composed of phospholipid composition enriched in phosphatidylcholine and may also contain mixed lipid chains with surfactant properties such as egg phosphatidyl ethanolamine. They can be found as small unilamellar liposome vesicle (SUV), large unilamellar vesicle (LUV), giant unilamellar vesicles (GUV) and multi lamellar vesicle (MLV). Liposomes can transfer entrapped and non-entrapped hydrophilic drugs into skin. They have been suggested as a promising vehicle for drug enhancing skin penetration.\(^{35}\)

Relationship between MN antifungal activities with liposomal structures was studied by De Logu et al., (2000). Antifungal activity was decreased through MN entrapment in liposomal structures, due to the presence of sterols, especially ergosterol. To understand which liposome component interfered with the antifungal activity of MN, the effect of pure egg and soy L-α-phosphatidylcholine and cholesterol was examined on the activity against *Candida albicans* ATCC E10231. Association of the phospholipids with MN presented the antifungal activity similarly to the entrapped MN in SUV liposomes. Prevention of MN antifungal activity depended on the phospholipid concentration and independent of the phospholipid source. Cholesterol content of liposomes didn’t affect the antifungal activity of MN.\(^{36,37}\)

Elmoslemany et al. (2012) demonstrated enhanced retention and skin permeation of MN loaded propylene glycol (PG)-liposomes comparing with blank and MN-loaded conventional liposomes (not containing propylene glycol). Mean size values of the blank and MN loaded conventional liposomes were 1110.8 and 539.5 nm, respectively. Incorporation of PG resulted in reduction in vesicle size of both blank liposomes (867.9 nm) and drug loaded liposomes (351.0 nm) and narrower size range (lower corresponding PI values). Stability studies by considering the drug leakage out of the vesicles and changes in vesicle size were
carried out for conventional and PG (10%) liposome dispersions for both blank and MN loaded for 90 days at 4°C. Drug leakage was evident in both types of the liposomes with higher values recorded for conventional liposomes (percent drug remaining in vesicles at 90 days was 51.18% of initial values for conventional liposomes than 70.51% for PG liposomes). A variable reduction in vesicle size was observed for all systems over 90 days. Larger reduction in size was observed by conventional liposomes over the PG liposomes. Increased drug entrapment efficiency was reported for MN in PG liposomes than the conventional liposomes for 2 weeks of intervals via using the dialysis method. Release profiles showed extended MN release from all vesicles in contrast to the solution and suspension. MN skin permeation and retention were optimized with PG liposomes compared to both conventional liposomes and MN suspension. MN-loaded conventional and propylene glycol-liposomes showed higher antifungal activity against C. albicans, than empty liposomes (Table 3). Findings might provide more insightful into pharmaceutical aspects and the performance of PG phospholipid vesicles.38

Pandit et al. (2014) compared the topical performance of MN loaded ultra-flexible liposomes with conventional liposomes. A variety of liposomal formulations (UL-DC: ultra-flexible liposomes with sodium deoxycholate; UL-S80: ultra-flexible liposomes with Span 80; UL-S60: ultra-flexible liposomes with Span 60; UL-T80: ultra-flexible liposomes with Tween 80; LF: non-flexible liposomes) with the size range from 161 to 186 nm were formulated. The preparation of MN loaded ultra-flexible liposomes were done through conventional rotary evaporation sonication method. Ultra-flexible liposomes emerged as multi-lamellar vesicles which evenly spaced to the core as visualized by transmission electron microscopy. Span 80 showed the highest entrapment efficiency due to more lipophilic nature and allowed the incorporation of more drugs within the lipid bilayer. The percent of cumulative drug permeation for ultra-flexible liposomes was significantly high (72.4±3.2%) in 48 h in compared with the non-flexible liposomes and plain drug solution with the order of Span 80 > Span 60 > sodium deoxycholate> Tween 80.39 Transdermal flux was highest for Span 80 with the order of Span 80 > Span 60 > sodium deoxycholate> Tween 80. Higher rate of MN transfer across skin by ultra-flexible liposomal formulations suggested that the drug in liposolubilized state could have obtained an easy entry into tough barrier of subcutaneous. MN-ultra-flexible liposomal formulations exhibited larger antifungal activity compared with the traditional liposomes and plain drug solution (Table. 3). Thus, the ultra-flexible liposomes
optimized and localized MN action across the skin, fixed a better option to involve with deep seated skin problems.\[^{39}\]

### 4.3. Ethosomes

Ethosomes, novel lipid carriers are composed of phospholipids and high content of ethanol and water. Ethanol causes fluidization of ethosomal lipids and intercellular lipid of \textit{stratum corneum} and facilitate drug penetration through skin. They have received wide attention in topical dermal delivery.\[^{40}\]

Singh et al. (2010) compared the skin permeation of MN-ethosome and liposome with the plain ointment using skin model. Liposomes were prepared from soya lecithin (50 mg/ml) and cholesterol in the ratio of 7/3 by rotary evaporation method. The hydrophilic ointment was prepared through dissolving aqueous phase to the oil phase at the same temperature. \textit{In vitro} skin permeation study showed higher permeation with ethosomal ointment compared with the liposomal and plain ointment. Ethosomes flux was 3.6-folds higher than the liposomal formulation, and 1.2- folds higher than the plain ointment (Table. 3). The enhanced actives delivery using ethosomes over liposomes can be attributed to stronger interaction of ethosomes with skin lipids which facilitated drug absorption by skin.\[^{41}\]

<table>
<thead>
<tr>
<th>Research Question</th>
<th>Characterization Method</th>
<th>Study Type</th>
<th>Results</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional Liposome (1110.8 nm)</td>
<td>- TEM</td>
<td>Human skin</td>
<td>prolonged MCZ release from all vesicles in contrast to solution and suspension</td>
<td></td>
</tr>
<tr>
<td>Liposome-MCZ: 539.5 nm</td>
<td>- Franz Diffusion Cell</td>
<td></td>
<td>- Increased entrapment efficiency by PG liposomes in comparison to Conventional Liposome</td>
<td></td>
</tr>
<tr>
<td>Liposome-PG (10%): 867.9 nm</td>
<td>- HPLC</td>
<td></td>
<td>% EE: Conventional Liposome; 80.76 PG(10%)-liposomes; 95.59</td>
<td>[38]</td>
</tr>
<tr>
<td>Liposome-PG(10%)-MCZ: 351.0 nm</td>
<td>- UV</td>
<td></td>
<td>- Enhanced permeation, retention PG liposomes compared to both conventional liposomes and MCZ suspension.</td>
<td></td>
</tr>
<tr>
<td>- Drug release</td>
<td></td>
<td></td>
<td>% MCZ permeated through skin: PG (10%) liposomes; 1.85 conventional liposomes; 1.28 MCZ suspension; 1.34</td>
<td></td>
</tr>
<tr>
<td>- Entrapment efficiency</td>
<td></td>
<td></td>
<td>- MCZ-conventional and PG liposomes</td>
<td></td>
</tr>
</tbody>
</table>
5. CONCLUSIONS

As time progresses, the need to develop new drug formulations increases. Conventional delivery systems, including creams, ointments, and gels are traditionally being used for the treatment of skin fungal infections, even if they are deep seated. Various nano-formulations have been applied to optimize the topical delivery of MN. Present paper surveyed the efficiency of the prepared topical applied MN-loaded novel carriers. Carrier systems have the ability to overcome the immediate drug release caused by these conventional formulations, hence they avoid the possibility of induction of allergic reactions. Moreover, they are especially customized to enhance the penetration of the antifungal agents, leading to more effective treatment of skin fungal infections, especially the deeper ones. These carrier systems are expected to slowly replace the conventional systems as more commercial preparations become available.
REFERENCES


