Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Issue 6, 2014

Review Article

PERCUTANEOUS DRUG DELIVERY SYSTEMS FOR IMPROVING ANTIFUNGAL THERAPY EFFECTIVENESS: A REVIEW

MAXIMILIANO GLUJOY, CLAUDIA SALERNO, CARLOS BREGNI, ADRIANA M. CARLUCCI*

[1]Department of Pharmaceutical Technology, Faculty of Pharmacy and Biochemistry, University of Buenos Aires, Junín 956 - [1113] Buenos Aires, Argentina.
Email: adrianac@ffyb.uba.ar, amcarlucci@gmail.com

Received: 03 Jun 2013 Revised and Accepted: 15 Feb 2014

ABSTRACT

This article reviewed the current knowledge on percutaneous antifungal drug delivery systems in relation to their use to treat skin infections, not only the ones related with fungi but also with *Leishmania* parasites that grow in skin layers. Azoles are the most commonly used antifungals in clinical treatment of superficial fungal infections, but their physicochemical properties limit their bioavailability; consequently most of the azole-loaded delivery systems reported lately searched for the improvement of drug efficacy. Formulation design and optimization are key steps for increasing the therapeutic efficacy. The present work summarized the different drug delivery systems that have attracted most interest lately and also the most relevant achievements of pharmaceutical technology are described. Among the vesicular systems, liposomes and niosomes have shown relative therapeutic success; on the other hand, Transferosomes® and ethosomes seemed more promising. Solid lipid nanoparticles have shown interesting delivery parameters; microemulsions, which are extensively studied carriers, have demonstrated an enhanced percutaneous absorption of therapeutic agents and a significant improvement in antifungal effect. From the point of view of the Pharmaceutical Technology, dissolution properties by increasing chemical potential, stabilization of the drug delivery system and high concentration of drugs targeted to the infection sites were the most relevant aspects searched; ease of fabrication and cost were also considered.

Keywords: Percutaneous administration, Antifungal drug delivery, Superficial mycoses, Cutaneous leishmaniasis.

INTRODUCTION

It is well-known that to elicit a pharmacologic response following topical administration, drugs must enter and diffuse across the skin. The rate and extent of transport will depend on the interplay between the drug molecular properties and the characteristics of the biologic tissue. The drug may also interact with specific proteins or other membrane components. These interactions can prolong residence time and therapeutic effect; for example, azoles have affinity for keratin just like dermatophytes which are their therapeutic target. Drug properties that increase permeability across a given membrane may render the molecule less effective at another biologic tissue; the stratum corneum (SC) is a lipid barrier, in consequence, formulation design and optimization are key steps in increasing the therapeutic efficacy of topical antifungal therapy. [**1**]

The protective function of human skin imposes physicochemical limitations to the type of permeant that can go through this barrier. A drug to be passively delivered via the skin needs to have adequate lipophilicity and also a molecular weight <500 Da. Limited commercially available drugs fulfill these requirements for percutaneous delivery. Various strategies have emerged over recent years to optimize delivery which can be categorized into passive and active methods. The passive approach entails the optimization of formulation or drug vehicle to increase skin permeability. However, passive methods do not greatly improve the permeation of drugs with molecular weights >500 Da. On the other hand, active methods normally involve physical or mechanical strategies of enhancing delivery and have been shown to be generally superior. [**2**] Although therapeutically relevant doses could recently be delivered through skin with the use of iontophoresis and microneedles, these treatments need to be further explored to develop alternative therapies which will overcome the compliance and absorption issues associated with currently used treatments. [**3**]

Efficient topical drug administration for the treatment of fungal infections would deliver the therapeutic agent to the target compartment and reduce the risk of systemic side effects. Innovative delivery systems do not only allow this goal, but enhance the efficacy of drugs. However, the physicochemical properties of the commonly used azole antifungals make their formulation a considerable challenge. In general, azole antifungals tend to be highly lipophilic and they can readily partition into the lipid-rich intracellular space in the SC; the challenge is to develop a simple stable formulation that facilitates drug release into the skin. [**4, 5**] Both, new azole derivatives with a favorable risk-benefit ratio, and new formulations of older azoles were lately under development in various companies. Drug delivery technology scenario has become highly competitive and rapidly evolving. More and more development in delivery systems is being integrated to optimize the efficiency and cost of the therapy. Controlling the release rate of active agents to a predetermined site in human body has been one of the biggest challenges faced by drug industry. [**6, 7**]

Consequently, most of the azole-loaded delivery system reported lately searched for the improvement of drug efficacy. Some of these delivery systems are discussed in the following sections. Manipulation of drug formulations for improvement of the antifungal pharmacokinetic, targeted delivery, sustained release, and prolonged retention of high drug concentration at the infection site were some of the strategies. [**8**]

This article reviews the current market and knowledge on percutaneous antifungal drug delivery system in relation to the treatment of skin infections, not only the ones related with fungi but also with *Leishmania* parasites that grow in skin layers. The different drug delivery systems that have been published during the last five years were reviewed. The penetration rate of the loaded drug across the skin, mechanisms of skin permeation and dermal tolerability of these vehicles are described. A state of art of microemulsions (MEs) used as delivery systems for antifungal drugs is also extensively discussed.

Pharmacotherapeutical agents in the treatment of superficial mycoses

Currently used antifungal preparations: General concepts

The main categories of broad-spectrum agents are the allylamines and azoles, which have been tried and proven effective over more than two decades of usage with good safety. Although no new therapeutic groups have appeared, extensive development of innovative delivery systems for the topical route have enhanced

therapeutic results and increased patient compliance. Nonetheless, some vehicles such as foams, lacquers, and gels maintain their market share because no new topical formulations offer significant advantage. [**9**]

Azole antifungal agents are the most commonly used antifungals in clinical treatment of both superficial and systemic fungal infections. They are classified in two groups: imidazoles [miconazole (MCZ), ketoconazole (KTZ), clotrimazole (CLZ), econazole (ECZ)] and triazoles [fluconazole (FLZ), itraconazole (ITZ), voriconazole, and posaconazole]. [**10**] Azoles inhibit ergosterol synthesis by blocking 14α-demethylation of lanosterol, which leads to impaired membrane stability and growth inhibition. They are effective against dermatophytes, *Malassezia spp*, and *Candida spp*. Azoles hydrophobicity limits their bioavailability and antifungal effects. As a result of their limited bioavailability imidazoles are considered as safe as topical therapy for fungal skin infections during pregnancy. [**11**]

Millikan has recently published a review in which he pointed out that in USA [United States of America] several of these agents are now generic. CLZ has been OTC [over-the-counter] medication for many years; it has been long marketed as Lotrimin®. It is to notice that a trademark is not always related to an active compound, for instance, Lotrimin AF cream, lotion, and solution contain CLZ 1%, Lotrimin AF spray contains MCZ 2%, and the cream Lotrimin Ultra has butenafine 1%. In USA, MCZ has the largest number of preparations, such as Micatin® and Mon**i**stat®. [**9**]

In South America exists a similar situation with a high number of trademarks that are not always representative of the same loaded drug; these products have gained a main spot in the market. For example, Empecid® (Bayer, Argentina) is the most popular CLZ-OTC nowadays; it is available as cream, vaginal cream, vaginal softgel capsules, spray, foot powder and lotion. In contrast, there's another presentation called Empecid 'pie'® which includes bifonazole in its formulation. Furthermore, Lamisil® (Novartis Argentina S.A.) is the most popular Terbinafine (TB)-OTC trademark; it is available in solution and cream. Sinamida® (E.J.Gezzi, Argentina) is one of ECZ - OTC, which has several available dosage forms, however, Sinamida'pies'® contains undecilenic acid, Sinamida® cream contains ECZ or TB, and Sinamida® shampoo contains KTZ. In conclusion, it is not possible to associate a trademark with only one active compound, but it is usual instead, to see that the same trademark containing different active compounds [**12**].

There are few landmark studies to distinguish one imidazole as being superior to another when treating superficial infections. In all, the market offers a wide variety of products with no difference in treatment effectiveness among them. The development of novel delivery systems aims to improve administration and cure rate. In addition, the present market does not offer efficient treatments to every kind of infection. Onychomycosis is a fungal infection of nails caused by dermatophytes, yeasts or non-dermatophitic molds. It represents about 30% of mycotic cutaneous infections and is generally treated with orally administered TB, FLZ or ITZ for long periods of time. In some extensive or deep skin infections systemic therapy can be mandatory as well [**9**,**13-15**].

Leishmanicidal activity

Azole efficacy against *Leishmania* was first reported by Berman in 1981. Ergosterol is a membrane component in fungi and *Leishmania* parasites, which accounts for many antifungal drugs to have leishmanicidal activity as well. Azoles have been shown to be active against a wide range of *Leishmania* promastigotes and amastigotes. *Leishmania* species differ in their sensitivity to azoles as *L. donovani, L. braziliensis* and *L. amazonensis* promastigotes are more sensitive than *L. aethiopica, L. major, L. tropica* and *L. mexicana*. Both KTZ and FLZ have undergone evaluation in India and despite reports of their usefulness, their anti-leishmanial activity was not enough to induce clinical cure by themselves [**16**]. Beach et al. tested the effect of KTZ, ITZ and FLZ in strains of 6 species and 10 subspecies of *Leishmania* promastigotes in vitro; they were all proven to be effective inhibitors of *Leishmania* promastigotes growth and ITZ had the greatest growth and sterol biosynthesis inhibition. [17].

Physico-chemical and pharmacokinetic properties of antifungal drugs

The physicochemical and pharmacokinetic properties of these drugs plus their inherent antifungal potency determine their efficacy, so they are important issues to consider in pre-development stage. FLZ is more polar than other azoles, slightly soluble in water (5 mg/mL at 37ºC), metabolically stable and exhibits low protein binding. It presents excellent efficacy in vivo but a low activity in vitro. In contrast, other azoles are more lipophilic, metabolically vulnerable compounds, with high protein binding and negligible solubility in water. Although FLZ is less active than KTZ in vitro, its distribution throughout the body and the high levels of free drug reached in blood contribute to its efficacy. Even for KTZ the levels of free drug in blood may help efficacy. KTZ is a broad spectrum antifungal agent but it has two characteristics that make it difficult to use: it is poor water-soluble drug and it undergoes chemical degradation, such as oxidation and hydrolysis. KTZ molecular weight [MW] is 531.4 Da and its pKa values are 6.51 and 2.94 (dibasic), whereas MW of FLZ is 306.3 Da and has a pKa value of 3.7 (weak base). For very lipophilic agents like ITZ, drug blood levels are very low, and organ levels may correlate better with efficacy, however, tissue binding will be high and total drug levels in an organ may be misleading indicator of efficacy. [**18**-**20**] ITZ presents a MW of 705.6 Da and a pKa value of 3.7 (weak base). CLZ and MCZ have MW of 344.8 Da and 479.1 Da, and pKa values of 6.12 and 6.65, respectively. They are both very lipophilic drugs and are commonly used as topical antifungal agents. [**21-24**]

Allylamines [TB] and benzylamines (Butenafine) are recognized as the most innovative groups, which block the activity of squalene epoxidase and thus inhibit the cyclization to lanosterol. They are effective against dermatophytes, *Malassezia*, and *Candida* and are indicated for general superficial mycoses. These antifungals are characterized by very low minimum inhibitory concentration against dermatophytes, but these drugs are less effective against yeasts and molds. [**9**] TB (pKa 7.10; MW 291.4 Da) is poorly soluble in water; only when prepared as a solid dispersion showed improved solubility and dissolution. [**25, 26**] TB was demonstrated to be ineffective against *Leishmania amazonensis*-infected mice and *Leishmania chagasi*-infected hamsters. Generally, allylamines are not considered for Lesihmaniasis treatment. [**27, 28**]

Opportunistic oral infections caused by *Candida albicans* and non-albicans *Candida* species are particularly common in immune-compromised patients. Nystatin, which belongs to the polyene group of antimycotic drugs, is frequently used as topical agent in the treatment of oropharyngeal candidiasis. Nystatin works by binding to the sterols in cell membrane, resulting in leakage and permeability issues. It is only effective against *Candida*. It is available in cream, ointment, and powder forms. Nystatin is minimally absorbed and is effective for vaginal therapy. Therefore, it is the treatment of choice during pregnancy. [**9, 11**, **29**]

Drug delivery systems under current development

Vesicles

Liposomes and niosomes have received increasing attention over the last decades as means of transdermal drug delivery. They act as drug carriers to deliver entrapped drug molecules across the skin, as well as penetration enhancers because of their composition. In addition, these vesicles serve as a depot for the sustained release of active compounds in the case of topical formulations, as well as rate limiting membrane barrier for the modulation of systemic absorption in the case of transdermal formulations. Vesicle formulations can be classified into two categories: rigid vesicles - liposomes and niosomes- and elastic or ultra-deformable vesicles- transferosomes and ethosomes-. The rigid ones are generally not suitable for transdermal delivery as they get trapped in the superior layers of stratum corneum (SC), providing an essentially epidermal delivery. Elastic vesicles minimize the defective transdermal permeation of a number of drugs with high and low molecular weight, and they are one of the major advancements in vesicle research. [**30, 31**] A wide variety of lipids and surfactants can be used to prepare vesicles, which are commonly composed of

phospholipids (liposomes, ethosomes, transferosomes, transethosomes) or non-ionic surfactants (niosomes, spanlastics). Vesicle composition and preparation method influence their physicochemical properties (size, charge, lamellarity, thermodynamic state, deformability) and therefore their efficacy as drug delivery systems. Many novel formulations have utilized them topically to enhance either permeability or drug targeting to a specific layer of the skin. The main problem with these formulations is that a minimal change in the formulation could transform it from a local targeting preparation to a systemic one. [**32-35**]

On the view of all the systems shown in Table 1 it can be said that there is not a significant increase in skin permeation shown by these systems, even though an increase in activity is observed and modified release mechanisms are in most cases possible. Entrapment efficiency is also an issue to be considered.

Ethosomes have also been studied for topical applications. They are elastic phospholipid-based nanovesicles containing high percentages of ethanol (20–45%); they have demonstrated to be effective at enhancing dermal and transdermal delivery of both lipophilic and hydrophilic drugs. Ethanol is known as an efficient permeation enhancer. It can interact with the polar head group region of the lipid molecules, resulting in the reduction of the melting point of the SC lipid, thereby increasing lipid fluidity, and cell membrane permeability. The high flexibility of vesicular membranes from the added ethanol permits the elastic vesicles to squeeze themselves through pores, much smaller than their diameters. Thus, ethosomal systems are much more efficient in delivering substances to the skin in terms of quantity and depth than conventional liposomes. Research has also indicated that ethosomes possess good storage stability because of the presence of ethanol, which provides a net negative surface charge, thus avoiding aggregation of vesicles due to electrostatic repulsion. Microscopic examinations suggest ethosomes to be multilamellar spherical vesicles with a smooth surface. [34, 44, 45]

Table 1: Overview of Liposomal and Niosomal systems loaded with antifungal agents

Dosage Forms	Composition and preparation method	Results	References
FLZ-loaded liposomes/niosomes into carbopol gel	Lipid/nonionic surfactant-based dry-film hydration method	Size around 300 nm Maximum therapeutic efficacy Poor entrapment efficiency (< 30%). Increased drug accumulation - Sustained release of drug	Gupta et al. 2010 [**36**]
Ciclopirox olamine liposome system	Phospholipon® 90H/ Dicetyl phosphate /Cholesterol Ethanol injection method	Size 200 -1000 nm Entrapment efficiency lower than 50 % Higher cutaneous deposition of the drug	Shaikh KS, Pawar AP. 2010 [**37**]
KTZ in niosomes	Dicetyl phosphate/ Cholesterol Thin film hydration method	Entrapment efficiency with Span 60 > Span 40 Slow and more sustained release from span 60 than Span 40	Rajnish A, Ajay S. 2010 [**38**]
Niosomes of TB hydrochloride (TB-HCl)	Tween® 20, 40, 60, and 80/ Cholesterol Thin film hydration method	Increase in zone of inhibition due to the controlled release Tween 40 nisomes possess maximum zone of inhibition values followed by sustained release	Sathali AAH, Rajalakshmi G. 2010 [**39**]
Liposomes/niosomes containing CLZ	Lipid hydration method	Total penetration through vaginal mucosa increased by 1.5-fold Accumulation of CLZ into mucosa was increased by 3.1 in liposomes and 2.3-fold in niosomes.	Ning M. et al. 2005 [**40**]
KTZ niosomes	Tween® 40, 80/ Cholesterol Ether injection technique	Reduction of the therapeutic dose	Ning M. et al. 2005 [**41**]
Ciclopirox Olamine mucoadhesive liposomes	Phospholipon® 90H/ Diacetyl phosphate Hot injection method	Stable liposomes at vaginal pH Sustained release Pseudoplastic Gel	Karimunnisa S, Atmaram P. 2012 [**42**]
Miconazole nitrate (MCZ-N) liposomes	Lipoid S 100 [PC] (phosphatidyl choline %95.8) Propylene Glycol (PG) Hot injection method	Controlled delivery Improved vesicle stability Enhanced skin deposition	Elmoslemany RM. et al. 2012 [**43**]

Transferosomes® have been introduced the last decade and they are commercially available at the moment for a number of active compounds. They are a special type of liposome, consisting of phosphatidylcholine and an edge activator. They can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss of transported drug. These vesicles are several orders of magnitude more elastic than the standard liposomes and overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipids of the SC. Transferosomes for potential transdermal application, contain a mixture of lipids and biocompatible membrane softeners. This optimal mixture leads to flexibility of the elastic liposomal membranes and to the possibility of penetration through channels of the skin, which are opened by the carriers. [**30, 35, 46-48**]

The systems mentioned in Table 2 exhibited better entrapment efficiency than liposomes and niosomes. Additionally, they have accomplished very high skin permeation rates and antifungal activity. However, these systems are generally expensive.

Solid lipid nanoparticles [SLN] and Nanoestructured lipid carriers [NLC]

SLN are particulate lipid matrices in the form of lipid pellets that can be produced with well tolerated lipids and surfactants. Large scale production is possible using high pressure homogenization and through the preparation of microemulsions [**52**]. However, SLNs have some limitations: a limited number of drugs are soluble in the appropriate lipids, and these lipids may also crystallize into more stable structures causing the expulsion of the drug out of the particles. In addition, the concentrations of lipid particles in the aqueous dispersions usually reach a maximum of only 30%. NLCs were created to overcome these limitations; these particles consist of a mixture of solid and liquid lipids that provide an irregular structure. This structure contains holes were drugs are carried and thus they are less likely to be expelled out. Even though NLCs seem superior, SLN are still considered as useful carriers due to their ease of preparation [**53-56**].

In systems shown Table 3, high entrapment efficiency can be observed. Increased activity and permeation rate are also commonly found results.

Table 2: Overview of Ethosomal and Transferosomal systems loaded with antifungal agents

Drug and Dosage Forms	Composition and preparation method	Results	References
Econazole nitrate [ECZ-N] ethosomes	Cold Method	Size 200 nm, 81% entrapment efficiency Controlled release for 12 h across rat skin Drug diffused two-fold higher than from liposomal and hydroethanolic gels. Drug permeation as far as the last layer of epidermis (stratum basale)	Verma P, Pathak K. 2012 [**34**]
FLZ ethosomes	Soya phosphatidyl choline (SPC) PG Hot method	Ethosomes more fluid than liposomes Drug diffused nearly twice higher than from liposomes. Enhanced antifungal activity compared to liposomes	Bhalaria MK. et al. 2009 [**44**]
TB Transferosomes spray	TDT 067 (not declared composition) Lipid film hydration technique	MIC_{50} values 8-fold and 60-fold lower than those of naked TB and TB spray, respectively	Ghannoum M. et al. 2011 [**46**]
Griseofulvin deformable vesicles	Span® 85 Phospholipon® 90G Thin-film hidration method	Higher drug permeation and skin retention than conventional liposomes Complete clinical and mycological cure in treated animals. Non-sensitizing, safe and stable.	Aggarwal N, Goindi S. 2012 [**49**]
FLZ elastic vesicles [spanlastics]	Span	Smaller than niosomes Higher permeation than niosomes Safe and stable.	Kaur IP. et al. 2012 [**50**]
TB ethosomes and transferosomes	PC (%98) Sodium deoxycholate Ethanol-PG (binary ethosomes) Hot method	Permeation and skin deposition up to 1.56 and 9.88 times higher than liposomes, respectively. Binary ethosomes permeation depth greater than ethosomes and transferosomes.	Zhang JP. et al. 2012 [**47**]
Voriconazole transethosomes	Lipoid® S100 Tween® 80 and sodium taurocholate Film hydration method	Irregular spherical shape (Higher fluidity) Higher skin permeation than ethosomes and deformable liposomes. Enhanced skin deposition.	Song CK. et al. 2012 [**51**]
CLZ ethosomes	Cavamax W7 (β- cyclodextrin) PEG 400 Injection method	Higher in vitro % cumulative drug permeation in 8 h and steady state flux than marketed formulation. Uniform and deeper penetration. Better antifungal activity against *Candida albicans* and *Aspergillus niger*.	Akhtar N, Pathak K. 2012 [**45**]
KTZ transferosome	Lipid film hydration technique Eucalyptus oil (permeation enhancer)	Better in vitro release and permeation than formulations containing different permeation enhancers.	Reshmy Rajan and Deepa T. Vasudevan. 2012 [**48**]

Amphiphilic gels

They consist solely of nonionic surfactants where one surfactant causes the gelation of another. A range of drugs can be solubilized in this type of gels, with the possibility of delivering them into and through the skin as the surfactants act as penetration enhancers. Prasadet et al. stated that the surfactant nature of the gels would increase permeation of the active agents into and/or through the skin. The gels could be used as topical/transdermal carriers without causing significant irritation to the skin. Lalit et al. prepared different amphiphilc gel formulations using extensively known surfactants (Tween® 80 and Tween® 20) and observed a stable, safe and efficient delivery system for FLZ with an interesting cumulative percentage drug releases (more than 90 %) [61, 62]

Polymeric micelles

Aqueous micelle solutions of CLZ, ECZ-N and FLZ in polymeric micelles prepared with novel amphiphilic methoxy-poly[ethylene glycol]-hexyl substituted polylactide block copolymers were developed by Bachnav et al. ECZ-N was incorporated with an efficiency of 98.3%. ECZ delivery was compared to that from Pevaryl® cream, a liposomal formulation for topical application with ECZ 1% w/w. A significant penetration enhancement was observed in human skin; the amounts of ECZ-N deposited showed a 7.5-fold improvement in delivery [**5**].

Emulgels

Gellified emulsions or emulgels, have emerged as interesting topical drug delivery systems as they have dual release control system (emulsion and gel). Also the stability of the emulsion is increased when it is incorporated in gel. CLZ was formulated into emulgels using two grades of modified co-polymers of acrylic acid, namely Pemulen® TR1 and TR2. A selected formula containing jojoba oil showed excellent stability as well as high rate of CLZ release. However, the antifungal evaluation of this formula revealed an increase of only 1.2-folds compared to commercially available formulation. Deveda et al. developed a gellified emulsion for controlled delivery of ITZ, the emulsion was formulated and then incorporated in a Carbopol® gel. The results revealed that the optimized emulsion showed a 95.08% release in 48 h and a stable release rate for about 3 h. In the efficacy assays, the optimized emulsion showed a 46.6% inhibition, whereas the marketed preparation showed only a 32.3% inhibition. Furthermore, skin irritation tests show no edema or erythema [**63, 64**].

Microsponges

Microsponges for the controlled release of topical agents typically consist of macroporous beads of a diameter of 10-25 µm. When applied to the skin, they release the active ingredient gradually and also in response to stimuli such as rubbing, temperature, pH, etc. The advantages of this kind of technology involve appropriate entrapment of ingredients, improved stability, and enhanced formulation flexibility. This technology is being used currently in cosmetics, OTC skin care products, sunscreens and prescription products. Numerous studies have confirmed that microsponge systems are non-irritating, non-mutagenic, non-allergenic, and non-toxic. Microsponges containing KTZ with six different proportions of Eudragit RS 100 as polymer were successfully obtained using quasi-emulsion solvent diffusion method. These formulations were prepared as gel in 0.35 %w/w Carbopol®. They showed appropriate drug release profile, viscosity, spreadability and antifungal activity. [7, 65, 66]

Foams

The application of pharmaceutical foams in topical therapy can be traced back three decades. However, foam formulations have been gaining popularity with over 100 patents published globally just in the last 10 years. The use of foam technology to deliver topical active agents includes antifungals. Although foams present distinct application advantages and improved patient compliance, the real

reason for the rapid growth of topical foam technology is that foams are elegant, aesthetic and cosmetically appealing vehicles that provide an alternative and promising formulation strategy in the highly competitive dermatological market. Presently, there is a lack of sufficient clinical evidence to demonstrate any superiority of foams over other traditional topical vehicles such as creams and ointments for drug delivery. [**67**] The successful introduction of hydroalcoholic foams allowed the development of a new generation of foam products. Such foams, designated as emollient foams consist of oil-in-water or water-in-oil emulsions. They can carry a broad variety of topical drugs, including water-soluble, oil-soluble and suspended active agents. They have several functional advantages as vehicles of topical drugs including: improved usability, safety, controllable drug delivery, skin barrier build-up, hydration and enhanced clinical efficacy [**68**].

Table 3: Overview of SLN and NLC systems loaded with antifungal agents.

Drug and Dosage Forms	Composition and preparation method	Results	References
KTZ SLN hydrogels	Compritol® ATO 888, Precirol® ATO, almond oil Hot homogenization technique	Rheological characteristics suitable for topical applications Entrapment efficiency higher than 90%	Paolicelli, P. et al. 2011 [**18**]
MCZ-N SLN	Solvent injection method	10-fold greater skin retention than MCZ-N suspension and hydrogel. Sustained effect	Jain S. et al. 2010 [**57**]
MCZ-N SLN	Compritol® 888 ATO, Tween® 80 and glyceryl monostearate Hot homogenization method	Entrapment efficiency 80% -100% Increased accumulative uptake in skin Enhanced skin targeting effect	Bhalekar MR. et al. 2009 [**58**]
ECZ-N SLN	Isopropyl fatty esters (C 13-C23) and Precirol® ATO High shear homogenization method	Entrapment efficiency of about 100% Correlation between permeation effect and chain length of the fatty esters: maximum flux of drug for 17 and 19 C	Sanna V. et al. 2009 [**59**]
TB SLN	Compritol® and Precirol® Tween® and Cremophor® PG Microemulsion technique	TB penetrated the SC similar to Lamisil®Once (marketed formulation that releases a full dose in 24 h) TB penetrated the dermis higher than Lamisil® Once at 12 h	Ying Chen-Chen et al. 2012 [**60**]
CLZ SLN and NLC	Hot high pressure homogenization technique	Stable for 3 months of storage at 4- 20- 40ºC. Entrapment efficiency higher than 50%. Modified release over a period of 10 h	Souto EB. et al. 2004 [**53**]
KTZ SLN and NLC	Compritol® 888 ATO, Alpha-tocopherol (liquid lipid for NLC), Poloxamer® 188, sodium deoxycholate	Chemical degradation of KTZ in SLN under light exposure. Light-protected drug in NLC.	Souto EB, Müller RH. 2005 [**54**]
CLZ in SLN and NLC	Dynasan® 116, Miglyol® 812, Tyloxapol® Hot high-pressure homogenization	Spherical Size 400 nm Chemichal stability after 2 years	Souto EB, Müller RH. 2006 [**55**]
CLZ and KTZ in SLN and NLC	Polyacrylate hydrogels (mucoadhesive)	95% of CLZ and 30% of KTZ recovered from SLN and NLC after 2 years of shelf-storage [higher than reference emulsions] Pseudoplastic behaviour with thixotropy	Souto EB, Müller RH. 2006 [**56**]

Microemulsions

Recently, much attention has been paid to the application of microemulsions [MEs] as drug delivery systems. Part of this interest appears as a consequence of their ease of preparation and long-term stability. These properties as well as their ability for incorporating drugs of different lipophilicity are some of the reasons why MEs have been thoroughly considered for pharmaceutical purpose. They can be formulated not only to enhance the solubility of slightly soluble compounds but also to increase the dissolution rate of the drug [**69**].

MEs are isotropic, thermodynamically stable, transparent or translucent systems composed of oil, water, and surfactant, frequently in combination with a co-surfactant. Droplet size usually ranges 20–200 nm. Since their discovery, they have attained increasing significance both in basic research and in industry. Due to their distinct advantages such as enhanced drug solubility, thermodynamic stability, optical clarity, easy preparation, and low cost, uses and applications of MEs have been numerous. Azeem explored MEs as transdermal drug delivery vehicles with emphasis on components selection for enhanced drug permeation and skin tolerability of these systems. MEs have demonstrated to be an appropriate delivery system for topical and transdermal delivery as they also show excellent biocompatibility. Several plausible mechanisms have been proposed about the role of MEs in transdermal delivery of a drug: 1) a large amount of drug can be incorporated in the formulation due to the high solubilizing capacity that might increase thermodynamic activity towards the skin. The permeation rate of the drug from ME may be increased, as the affinity of a drug to the internal phase in ME can be easily modified to favor partitioning into SC by using different internal phase or changing its portion in the ME; 2) the surfactant and co-surfactant in the MEs may reduce the diffusional barrier of the SC by acting as penetration enhancers; and 3) the percutaneous absorption of drug will also increase due to hydration effect of the SC if the water content in ME is high enough [**33, 70-78**]. Table 4 summarizes MEs containing antifungal agents. Positive results involving ease of fabrication with low costs, increase in permeation rate and activity, safety, targeting possibilities and modified release rates have made MEs the most referred system in the present review and a very promising dosage form for future investigation.

Materials used in percutaneous antifungal drug delivery systems

Excipients used in ME and other lipid-based systems

Nowadays, topical administration tends to include 'generally regarded as safe' [GRAS] excipients, to enhance skin tolerability and reduce adverse effects, without disregarding the formulation and preparation.

As vesicular systems and MEs have been the most studied delivery systems for antifungal drugs, a brief summary of the currently preferred excipients for them is presented in the following paragraphs.

Table 4: Overview of ME systems containing antifungal agents.

Drug / type of ME	Composition	Results	References
MCZ-N Positively charged MEs	Charge-inducing agent stearylamine, L-alanine benzyl ester or cetyltrimethylammonium bromide.	Interaction between positive ME systems and negatively charged skin sites	Peira E. et al. 2008 [**70**]
	Jojoba oil, Cutina®, glyceryl stearate, glyceryl monostearate, Brij® 96, Capmul ®	Optimized drug targeting without increase in systemic absorption	
FLZ ME gel	Brij® 96,Capmul®, Jojoba oil	Highest values of release and permeation from ME compared with Cutina® lipogels FLZ antifungal activity showed the widest zone of inhibition	El Laithy HM, El-Shaboury KM. 2002 [**71**]
FLZ	Isopropyl palmitate, Aerosol OT and Sorbitan® Monooleate	Significant increase in antifungal activity as compared to marketed formulation	Jadhav KR. et al. 2010 [**72**]
FLZ ME-based organogel	Ethyl oleate, Lecithin	Formula with lecithin 300 mM showed higher drug release and better relative consistency. Safe for topical purposes Increased antifungal activity	Jadhav KR, Kadam VJ, Pisal SS. 2009 [**73**]
FLZ	Lauryl alcohol (LA), Labrasol® and ethanol Tween® 80	Enhanced percutaneous absorption with increasing LA and water contents and with decreasing Labrasol®/EtOH ratio in the formulation	Patel MR. et al. 2009 [**74**]
FLZ	Isopropyl myristate, Tween® 80 and propylene glycol 400	Permeability 2.5 fold higher than the marketed formulation	Shah RR. Et al. 2009 [**75**]
FLZ ME-based hydrogel	Diethyleneglycol monoethyl ether (Transcutol P®;TCL) Propylene glycol Cremophor® RH40	The whole contained dose delivered and enhanced skin penetration. ME with TCL better antifungal activity than the one containing PG	Salerno C, Carlucci A, Bregni C. 2010 [**76**]
KTZ	LA, Labrasol®, ethanol	Percutaneous absorption of KTZ from MEs was enhanced with increasing LA and water contents, and with decreasing Lab/EtOH ratio	Patel MR. Et al. 2008 [**77**]
CLZ	Lemon oil, Tween® 80, n-butanol, isopropyl myristate	Higher skin retention than marketed cream Higher in vitro activity against *C.albicans* than conventional cream Clinical evaluation proved efficacy and tolerability	Hashem FM. et al. 2011 [**78**]
CLZ ME-based gel	Cremophor® EL, Capryol® 90, Benzyl alcohol	Higher *in vitro* bioadhesion and antifungal activity than marketed product CLZ undergoes acidic pH-catalyzed degradation	Bachhav YG. et al. 2011 [**5**]
ITZ ME-based gel	Polymeric gels of Lutrol® F127, Xanthan gum	Controlled release Nonirritant and no erythema or edema Higher antifungal activity with Lutrol F127 ME gel	Chudasama A. et al 2011 [**22**]
TB-HCl	Oleic acid, Caprylo caproyl macrogol-8-glyceride (Labrasol® S), Transcutol P®	Higher anti-fungal activity against *Candida albicans* and *Aspergillus flavus* than the marketed product	Baboota S. et al. 2007 [**79**]
TB-HCl	Tween® 80, ajowan oil and peppermint oil	No physical changes when exposed to freeze-thaw cycles for 72 h *In vitro* drug concentration above MIC	Mehta K, Bhatt DC. 2011 [**69**]
TB-HCL ME-based gel	Oleic acid, Labrasol®, Transcutol®P	Better penetration and retention in the human cadaver skin than commercial cream. Three times higher permeated ammount after 12 h and better activity against *Candida albicans* and *Trichophyton rubrum* than the commercial cream.	Barot BS. et al. 2012 [**80**]
Voriconazole	Sodium deoxycholate or oleic acid Brij®97 Jojoba oil	4 h prolonged release, transdermal delivery 12 months storage stability at 25 °C. Better antifungal activity against *C. albicans* than supersaturated solution Pseudoplastic flow with thixotropy	El-Hadidy GN. et al. 2012 [**81**]

Oil phase

-Natural oils: lemon oil [**78**], ajowan oil and peppermint oil [**69** ex **68**], eucaliptus oil [**48**], jojoba oil [**71**]. Additionally, a number of plant oils have been reported to have antifungal, antiparasitic and antidermatophytic properties. A recent review updated information on plant essential oils with these properties. [**82**]

-Semisynthetic oils are more stable than their natural counterparts, thus, they have mostly replaced them: Ethyl oleate [**73**], Isopropyl myristate [**76,78**], Isopropyl palmitate [**72,73**], Isopropyl fatty esters C13-C23 [**59**], glyceryl monoestearate, [**58**] mono-diglycerides-Capmul® [**71**]. Also, semisynthetic medium-chain derivatives are amphiphilic compounds with surfactant properties.

Surfactants

Tween® [39, 41,58,58,69,78]

Brij® [71, 81]

Because of their effects over the SC and other dermis layers, and consequent adverse effects, it is recommended to diminish surfactant concentration as much as possible. However, the following surfactants are characterized for possessing good skin tolerance, extremely low toxicity, biodegradability, and large emulsifying capacity.

Phospholipids: Lecithin [70,73,83]. Fluid-state derivatives are of interest, gel-state derivatives are not able to permeate the SC efficiently [**84**]

Alkyl polyglycosides and alkyl esters [83]

Polymeric surfactants: Poloxamers [Lutrol®] [33]

Sugar surfactants: Sucrose esters [33]

Labrasol forms MEs with several non-alcohol cosurfactants [75,79]

Plurol Isostearique provides extensive regions of ME formation [85]

Cremophor® RH40 [56,76]

Cosurfactants

PG [43,56]

Ethanol [33,37,44,45,47,51,74]

Alcohols (C3 – C8) [78,86]

-Transcutol [76, 79]

They provide the interfacial film with sufficient flexibility to take up different curvatures required to form ME over a wide range of composition. Cosurfactant concentrations need to be optimized according to the loaded drug because they can reduce the partition coefficient of the drug between the skin and the vehicle. [87,88]

Thickeners

Carbopol® is the most used polymer for increasing viscosity, Carbopol® 974 [**42**], Carbopol® 934 NF [**34,77**], Carbopol®940 [**72,78**], Carbopol®ETD 2020 [**5**]. However chitosan-based formulations are gaining importance; topical gel formulations of TB-HCl were prepared using different types of chitosan with different MW. The antifungal activity of TB-HCl significantly increased when the drug was introduced into chitosan gels as compared with a marketed product. Higher drug release and the highest zone of inhibition were obtained from gels prepared with chitosan of the lowest MW [89].

Enhancers

One of the strategies to promote cutaneous drug penetration is through the use of absorption enhancers. They can provoke variations of flow through the skin due to modifications within cellular membrane structures, which alter the diffusion coefficient, the aqueous cutaneous content and/or they can lower interface oil-water tensions. Some examples of use are shown in Table 5. Although the list of substances that promote absorption is growing, in most cases, there is a direct correlation between the effects of absorption enhancers and their skin toxicity [**90**].

Table 5: Overview of absorption enhancers for antifungal agents

Drug	Enhancer	Results	References
TB	Pentane-1,5-diol and propane-1,2-diol	Increased percutaneous permeation The most efficient absorption enhancer was pentane-1,5-diol (5%)	Evenbratt H, Faergemann J. 2009 [**91**]
TB	Different molecular weight polyethylene glycols (PEGs)	Moderate enhancement in permeation and drug load with low-MW PEGs compared with control formulation Greater amount of TB being permeated during iontophoresis and loaded into the nail plate	Nair AB. et al. 2010 [**92**]
Griseofulvin	PG N-methyl-2-pyrrolidone	Increasing solubility and partitioning Increased flux compared with formulation containing PG alone Acceptable in vitro antifungal activity No skin sensitization	Shishu, Aggarwal, N. 2006 [**93**]
FLZ	PG Transcutol®P (TCL)	Greater drug retention into the skin with TCL. Lower *in vitro* antifungal activity of FLZ when PG is included.	Salerno C, et al. 2011 [**76**, **94**]
Griseofulvin	Ethanol D-α-tocopheryl Polyethylene glycol 1000 succinate (TPGS)	Enhanced drug permeation and retention in the skin Effective against *Microsporum gypseum* and *Microsporum canis*. Non-sensitizing, histopathologically safe, stable at 4°C, 25°C, and 40°C.	Aggarwal N. et al. 2012 [**95**]
TB	Urea hydrogen peroxide (0.5%), ethanol	Increased permeation Decrased in ATP to levels equivalent to control levels (uninfected).	Tarynor MJ. et al. 2012 [**96**]

CONCLUSIONS

Although vesicular systems assure targeted delivery, liposomes or niosomes do not achieve the desired requirement for appropriate percutaneous penetration in most cases. A new vesicular derivative, Transferosomes®, has demonstrated increased drug transdermal penetration, becoming a promising dosage form for antifungal drugs, as well as Ethosomes which exhibited enhanced antifungal activity compared to conventional liposome formulation. SLNs containing antifungal drugs showed high drug entrapment efficiency, sustained drug topical effect, and quicker relief from fungal infection. MEs showed enhanced percutaneous absorption and significant improvement in antifungal effects. Other delivery systems such as amphiphilic gels, polymeric micelles, emulgel and microsponges have also been studied for antifungal delivery.

A number of works showed antifungals therapeutic effectiveness for Leishmaniasis, however application of innovative dosage forms for improving the therapeutic efficiency in this pathology is still poor. *In vivo* prediction of antifungals efficacy from *in vitro* tests is a complicated task because of the pharmacokinetic characteristics of these drugs, therefore, the study of dosage forms that can be easily transferred to clinical evaluation should be a priority.

Finally, safety and cost of therapy along with the potentiality for technology transference of the different innovative delivery systems would drive the tendency for future research in the area.

ACKNOWLEDGEMENT

Support for this work was provided by the National Agency of Scientific and Technological Promotion (ANPCyT); Ministry of Science, Technology and Productive Innovation, Argentina.

CONFLICT OF INTERESTS

Declared None

REFERENCES

1. Ghosh TK, Abraham W, Jasti BR. Transdermal and topical drug delivery systems. Theory and Practice of contemporary pharmaceutics.1st Ed. Florida USA:BR Jasti, TK Ghosh Editors. CRC Press;2004:423-55.
2. Brown MB, Martin GP, Jones SA, Akomeah FK. Dermal and Transdermal Drug Delivery Systems:Current and Future Prospects. Drug Deliv 2006;13 Suppl 3:175-87.
3. Yang Y, Kalluri H, Banga AK. Effects of Chemical and Physical Enhancement Techniques on Transdermal Delivery of Cyanocobalamin (Vitamin B12) In Vitro. Pharmaceutics 2011;Suppl 3:474-(4)84.
4. Jain S, Jain S., Khare P, Gulbake A, Bansal D, Jain S.K. Design and development of solid lipid nanoparticles for topical delivery of an anti-fungal agent. Drug Deliv 2010;17 Suppl 6:443-51.
5. Bachhav YG, Mondon K, Kalia YN, Gurny R, Möller M. Novel micelle formulations to increase cutaneous bioavailability of azole antifungals. J Cont Rel 2011;153:126–32.

6. Degreef H, Heeres J, Borgers M. Antifungal azoles for skin disorders. Expert Opin Ther Pat 2006;16 (9):1235-53.
7. Shaha V, Jain H, Krishna J, Patel P. Microsponge drug delivery:A review. Int J Res Pharm Sci 2010;1 (2):212-8.
8. Yang W, Wiederhold NP, Williams RO. Drug delivery strategies for improved azole antifungal action. Expert Opin Drug Deliv 2008;11:1199-216.
9. Millikan LE. Current concepts in systemic and topical therapy for superficial mycoses. Clin Dermatol 2010;28:212–6.
10. Chapman SW, Sullivan DC, Cleary JD. In Search of the Holy Grail of Antifungal Therapy. Trans Am Clin Climatol Assoc 2008;119:197–216.
11. King CT, Rogers PD, Cleary JD, Chapman SW. Antifungal therapy during pregnancy. Clin Infect Dis 1998;27 (5):1151-60.
12. Formulario Terapéutico Nacional 11° Edición, 2011. http://www.comra.org.ar/formulario_terapeutico.pdf. Accessed 01/06/2012.
13. Elewski B, Tavakkol A. Safety and tolerability of oral antifungal agents in the treatment of fungal nail disease:a proven reality. Ther Clin Risk Manag 2005;1 (4):299-306.
14. Kaur R, Kashyap B, Bhalla P. Onychomycosis--epidemiology, diagnosis and management. Indian J Med Microbiol 2008;26 (2):108-16.
15. Niewerth M, Korting HC. The use of systemic antimycotics in dermatotherapy. Eur J Dermatol. 2000;10 (2):155-60.
16. Sundar S, Chatterjee M. Visceral leishmaniasis-current therapeutic modalities. Indian J Med Res 2006;123:345-52.
17. Beach DH, Goad LJ, Holz GG. Effects of antimycotic azoles on growth and sterol biosynthesis of Leishmania promastigotes. Mol Biochem Parasitol 1988;31 (2):149-62.
18. Paolicelli, P, Corrente F, Serricchio D, Cerreto F, Cesa S, Tita B, Vitali F.The system SLN-Dextran hydrogel:An application for the topical delivery of ketoconazole. J Chem Pharm Res 2011;3 (4):410-21.
19. Gregorí Valdés BS. Estructura y actividad de los antifúngicos. Rev Cubana Farm 2005;39 (2).
20. Mannisto T, Mantyla R, Nykanen S, Lamminsivu U, Ottoila P. Impairing Effect of Food on Ketoconazole Absorption. Antimicrob Agents Chemother 1982;730-733.
21. Jaruratanasirikul S, Sriwiriyajan S. Effect of omeprazole on the pharmacokinetics of itraconazole. Eur J Clin Pharmacol 1998;54:159-161.
22. Chudasama A, Patel V, Nivsarkar M, Vasu K, Shishoo C.Investigation of microemulsion system for transdermal delivery of itraconazole. J Adv Pharm Tech Res 2011;2 (1):30-8.
23. OSPAR 2005 commission update. Administrator of the Oslo and Paris Conventions for the protection of the marine environment of the North-East Atlantic. http://www.ospar.org/documents /dbase/publications/p00199_bd%20on%20clotrimazole.pdf. Accessed 01/06/2012.
24. Beggs WH. Influence of alkaline pH on the direct lethal action of miconazole against Candida albicans. Mycopathologia 1992;120:11-13.
25. Florea M, Arama CC, Monciu CM. Determination of terbinafine hydrochloride by ion-pair reversed phase liquid chromatography. Farmacia 2009;57:82-8.
26. Kumar N, Jain AK, Singh C, Kumar R. Development, characterization and solubility study of solid dispersion of terbinafine hydrochloride by solvent evaporation method. Asian J Pharm 2008;2 (3):154-8.
27. Sampaio RN, Takano GH, Malacarne AC, Pereira TR, de Magalhães AV. In vivo Terbinafine inefficacy on cutaneous leishmaniasis caused by Leishmania amazonensis in C57BL/6 mice. Rev Soc Bras Med Trop 2003;36 (4):531-3.
28. Simões-Mattos L, Teixeira MJ, Costa DC, Prata JR, Bevilaqua CM, Sidrim JJ, Rocha MF. Evaluation of terbinafine treatment in Leishmania chagasi-infected hamsters (Mesocricetus auratus). Vet Parasitol 2002;28:207-16.
29. Ellepola AN, Panagoda GJ, Samaranayake LP. Adhesion of oral Candida species to human buccal epithelial cells following brief exposure to nystatin. Oral Microbiol Immunol 1999;14 (6):358-63.
30. Rajan R, Jose S, Biju Mukund VP, Vasudevan DT. Transferosomes-A vesicular transdermal delivery system for enhanced drug permeation. J Adv Pharm Technol Res. 2011;2 (3):138–43.
31. Rakesh R, Anoop KR. Ethosomes for transdermal and topical drug delivery. Review article. Int J Pharm Pharm Sci. 2012;4 (3):17-24.
32. Sinico C, Fadda A.M.Vesicular carriers for dermal drug delivery. Expert Opin Drug Deliv 2009;6 (8):813-25.
33. Azeem A, Khan ZI, Aqil M, Ahmad FJ, Khar RK, Talegaonkar S. Microemulsions as a surrogate carrier for dermal drug delivery. Drug Dev Ind Pharm 2009;35:525-47.
34. Verma P, Pathak K. Nanosized ethanolic vesicles loaded with econazole nitrate for the treatment of deep fungal infections through topical gel formulation. Nanomedicine 2012;8 (4):489 – 96.
35. Nounou MM, El-Khordagui LK, Khalafallah NA, Khalil SA.Liposomal formulation for dermal and transdermal drug delivery:Past, present and future. Recent Pat Drug Deliv Formul 2008;2 (1):9-18.
36. Gupta M, Goyal AK, Paliwal SR, Paliwal R, Mishra N, Vaidya B et al. Development and characterization of effective topical liposomal system for localized treatment of cutaneous candidiasis. J Lipos Res 2010;20 (4):341-50.
37. Shaikh KS, Pawar AP.Liposomal delivery enhances cutaneous availability of ciclopirox olamine. Lat Am J Pharm 2010;29 (5):763-70.
38. Rajnish A, Ajay S. Release studies of ketoconazole niosome formulation. Journal of Global Pharma Technology 2010;2 (1):125-7.
39. Sathali AAH, Rajalakshmi G. Evaluation of Transdermal Targeted Niosomal Drug Delivery of Terbinafine Hydrochloride. Int J Pharm Tech Res 2010;2 (3):2081-9.
40. Ning M, Gu Z, Pan H, Yu H, Xiao K. Preparation and in vitro evaluation of liposomal/niosomal delivery systems for antifungal drug clotrimazole. Indian J Exp Biol 2005;43 (2):150-7.
41. Ning M, Guo Y, Pan H, Chen X, Gu Z. Preparation, in Vitro and in Vivo Evaluation of Liposomal/Niosomal Gel Delivery Systems for Clotrimazole. Drug Dev Ind Pharm 2005;31:375-83.
42. Karimunnisa S, Atmaram P. Mucoadhesive nanoliposomal formulation for vaginal delivery of an antifungal. Drug Dev Ind Pharm 2012 Aug 7.
43. Elmoslemany RM, Abdallah OY, El-Khordagui LK, Khalafallah NM. Propylene glycol liposomes as a topical delivery system for miconazole nitrate:comparison with conventional liposomes. AAPS PharmSciTech 2012;13(2):723-31.
44. Bhalaria MK, Naik S, Misra A.N.Ethosomes:A novel delivery system for antifungal drugs in the treatment of topical fungal diseases. Indian J Exp Biol 2009;47 (5):368-75.
45. Akhtar N, Pathak K. Cavamax W7 composite ethosomal gel of clotrimazole for improved topical delivery:development and comparison with ethosomal gel. AAPS PharmSciTech 2012;13(1):344-55.
46. Ghannoum M, Isham N, Herbert J, Henry W, Yurdakul S. Activity of TDT 067 (Terbinafine in Transfersome®) against Agents of Onychomycosis, as Determined by Minimum Inhibitory and Fungicidal Concentrations. J Clin Microbiol 2011;49 (5):1716-20.
47. Zhang JP, Wei YH, Zhou Y, Li YQ, Wu XA. Ethosomes, binary ethosomes and transfersomes of terbinafine hydrochloride:a comparative study. Arch Pharm Res 2012;35(1):109-17.
48. Reshmy Rajan and Deepa T. Vasudevan. Effect of permeation enhancers on the penetration mechanism of transferosomal gel of ketoconazole. J Adv Pharm Technol Res 2012 Apr-Jun;3(2):112–16.
49. Aggarwal N, Goindi S. Preparation and evaluation of antifungal efficacy of griseofulvin loaded deformable membrane vesicles in optimized guinea pig model of Microsporum canis-Dermatophytosis. Int J Pharm 2012 Nov 1;437 (1-2):277-87.
50. Kaur IP, Rana C, Singh M, Bhushan S, Singh H, Kakkar S. Development and evaluation of novel surfactant-based elastic vesicular system for ocular delivery of fluconazole. J Ocul Pharmacol Ther 2012;28(5):484-96.

51. Song CK, Balakrishnan P, Shim CK, Chung SJ, Chong S, Kim DD. A novel vesicular carrier, transethosome, for enhanced skin delivery of voriconazole:characterization and in vitro/in vivo evaluation. Colloids Surf B Biointerfaces 2012;92:299-304.
52. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles for controlled drug delivery-a review of the state of the art. Eur J Pharm Biopharm 2000;50:161-77.
53. Souto EB, Wissing SA, Barbosa CM, Müller RH. Development of a controlled release formulation based on SLN and NLC for topical clotrimazole delivery. Int J Pharm 2004;278(1):71-7.
54. Souto EB, Müller RH. SLN and NLC for topical delivery of ketoconazole. J Microencapsul 2005;22(5):501-10.
55. Souto EB, Müller RH. Investigation of the factors influencing the incorporation of clotrimazole in SLN and NLC prepared by hot high-pressure homogenization. J Microencapsul 2006;23(4):377-88.
56. Souto EB, Müller RH. The use of SLN and NLC as topical particulate carriers for imidazole antifungal agents. Pharmazie 2006;61(5):431-7.
57. Jain S, Jain S, Khare P, Gulbake A, Bansal D, Jain S.K. Design and development of solid lipid nanoparticles for topical delivery of an anti-fungal agent. Drug Deliv 2010;17 (6):443-51.
58. Bhalekar MR, Pokharkar V, Madgulkar A, Patil N, Patil N. Preparation and evaluation of miconazole nitrate-loaded solid lipid nanoparticles for topical delivery. AAPS PharmSciTech 2009;10 (1):289-96.
59. Sanna V, Mariani A, Caria G, Sechi M. Synthesis and evaluation of different fatty acid esters formulated into Precirol® ATO-based lipid nanoparticles as vehicles for topical delivery. Chem Pharmaceut Bull 2009;57 (7):680-4.
60. Ying-Chen Chen, Der-Zen Liu, Jun-Jen Liu, Tsung-Wei Chang, Hsiu-O Ho, Ming-Thau Sheu. Development of terbinafine solid lipid nanoparticles as a topical delivery system. Int J Nanomedicine 2012:7 4409–4418
61. Prasad V, Kumar N, Mishra PR. Amphiphilic Gels as a Potential Carrier for Topical Drug Delivery. Drug Deliv 2007;14:75–85.
62. Lalit SK, Panwar AS, Darwhekar G, Jain D.K.Formulation and evaluation of fluconazole amphiphilogel. Der Pharmacia Lettre 2011;3 (5):125-31.
63. Deveda P, Jain A, Vyas N, Khambete H, Jain S.Gellified emulsion for sustain delivery of itraconazole for topical fungal diseases. Int J Pharm Sci 2010;2 (1):104-12.
64. Shahin M, Hady SA, Hammad M, Mortada N.Optimized formulation for topical administration of clotrimazole using Pemulen polymeric emulsifier. Drug Dev Ind Pharm 2011;37 (5):559-68.
65. Patel SB, Patel HJ, Seth AK.Microsponge drug delivery system:An overview. Journal of Global Pharma Technology 2010;2 (8):1-9.
66. Saboji JK, Manvi F V, Gadad A P, Patel Formulation and evaluation of ketoconazole microsponge by quassi emulsion BD. solvent diffusion. J Cell and Tissue Research 2011;11 (1):2691-6.
67. Zhao Y, Jones SA, Brown MB. Dynamic foams in topical drug delivery. J Pharm Pharmacol 2010;62 (6):678-84.
68. Tamarkin D, Friedman D, Shemer A. Emollient foam in topical drug delivery. Expert Opin Drug Deliv 2006;3 (6):799-807.
69. Mehta K, Bhatt DC. Preparation, optimization and in vitro microbiological efficacy of antifungal microemulsion. Int J Pharm Sci Res 2011;2 (9):2424-9.
70. Peira E, Carlotti ME, Trotta C, Cavalli R, Trotta M.Positively charged microemulsions for topical application. Int J Pharm 2008;346 (1-2):119-23.
71. El Laithy HM, El-Shaboury KM.The development of Cutina lipogels and gel microemulsion for topical administration of fluconazole. AAPS PharmSciTech 2002;3 (4):E35.
72. Jadhav KR, Shetye SL, Kadam VJ.Design and evaluation of microemulsion based drug delivery system. Int J Adv Pharm Sci 2010;1 (2):156-66.
73. Jadhav KR, Kadam VJ, Pisal SS.Formulation and evaluation of lecithin organogel for topical delivery of fluconazole. Current Drug Deliv 2009;6 (2):174-83.
74. Patel MR, Patel RB, Parikh JR, Solanki AB, Patel BG. Effect of Formulation Components on the In Vitro Permeation of Microemulsion Drug Delivery System of Fluconazole. AAPS PharmSciTech 2009;10, (3):917-23.
75. Shah RR, Magdum CS, Wadkar KA, Naikwade NS. Fluconazole Topical Microemulsion:Preparation and Evaluation. Res J Pharm Tech 2009;2 (2):353-7.
76. Salerno C, Carlucci A, Bregni C. Study of in vitro drug release and percutaneous absorption of fluconazole from topical dosage forms. AAPS PharmaSciTech 2010;11 (2);986-93.
77. Patel MR, Patel RB, Parikh JR, Solanki AB, Patel BG. Investigating effect of microemulsion components:In vitro permeation of ketoconazole. Pharm Dev Technol 2011 Jun;16(3):250-8
78. Hashem FM, Shaker DS, Ghorab MK, Nasr M, Ismail A.Formulation, characterization, and clinical evaluation of microemulsion containing clotrimazole for topical delivery. AAPS PharmSciTech 2011;12 (3):879-86.
79. Baboota S, Al-Azaki A, Kohli K, Ali J, Dixit N, Shakeel F. Development and evaluation of a microemulsion formulation for transdermal delivery of terbinafine. J Pharm Sci Technol 2007;61 (4):276-85.
80. Barot BS, Parejiya PB, Patel HK, Gohel MC, Shelat PK. Microemulsion-based gel of terbinafine for the treatment of onychomycosis:optimization of formulation using D-optimal design. AAPS PharmSciTech 2012;13(1):184-92.
81. El-Hadidy GN, Ibrahim HK, Mohamed MI, El-Milligi MF.Microemulsions as vehicles for topical administration of voriconazole:formulation and in vitro evaluation. Drug Dev Ind Pharm 2012;38(1):64-72.
82. Nuzhat Tabassum & Vidayasagar GM. Antifungal investigations on plant essential oils. A review. Int J Pharm Pharm Sci. 2013 (5) suppl 2:19-28
83. Savic S, Lukic M, Jaksic I, Reichl S, Tamburic S, Müller-Goymann C. An alkyl polyglucoside-mixed emulsifier as stabilizer of emulsion systems:the influence of colloidal structure on emulsions skin hydration potential. J Colloid Interface Sci 2011;358 (1):182-91.
84. Kirjavainen M, Mönkkönen J, Saukkosaari M, Valjakka-Koskela R, Kiesvaara J, Urtti A. Phospholipids affect stratum corneum lipid bilayer fluidity and drug partitioning into the bilayers. J Control Release 1999;58 (2):207-14.
85. Kreilgaard M, Pedersen EJ, Jaroszewski JW. NMR characterisation and transdermal drug delivery potential of microemulsion systems. J Control Release 2000;69 (3):421-33.
86. Tenjarla S. Microemulsions:an overview and pharmaceutical applications. Crit Rev Ther Drug Carrier Syst 1999;16 (5):461-521.
87. Ghosh PK, Murthy RS. Microemulsions:a potential drug delivery system. Curr Drug Deliv 2006;2:167-80.
88. Turi JS, Danielson D, Woltersom JW. Effects of polyoxypropylene 15 stearyl ether and propylene glycol on percutaneous penetration rate of diflorasone diacetate. J Pharm Sci 1979;68 (3):275-80.
89. Özcan I, Abaci Ö, Uztan AH, Aksu B, Boyacioğlu H, Güneri T, Özer Ö.Enhanced topical delivery of terbinafine hydrochloride with chitosan hydrogels. AAPS PharmSciTech 2009;10 (3):1024-31.
90. Carpentieri-Rodrigues LN, Zanluchi J M, Grebogi IH. Percutaneous absorption enhancers:mechanisms and potential. Braz Arch Biol Technol 2007;50 (6):949.61.
91. Evenbratt H, Faergemann J.Effect of pentane-1, 5-diol and propane-1,2-diol on percutaneous absorption of terbinafine. Acta Derm-Venereol 2009;89 (2):126-9.
92. Nair AB, Chakraborty B, Murthy SN. Effect of polyethylene glycols on the trans-ungual delivery of terbinafine. Curr Drug Deliv 2010;7 (5):407-14.
93. Shishu;, Aggarwal, N.Preparation of hydrogels of griseofulvin for dermal application. Int J Pharm 2006;326 (1-2):20-4.
94. Salerno C, Carlucci AM, Chiappetta D, Bregni C. Inhibition of fluconazole in vitro in antifungal activity in formulation containing propylene glycol. Lat Am J Pharm 2011;30 (7) 1406-13.
95. Aggarwal N, Goindi S, Mehta SD. Preparation and evaluation of dermal delivery system of griseofulvin containing vitamin E-TPGS as penetration enhancer. AAPS PharmSciTech 2012;13(1): 67-74.
96. Traynor MJ, Turner RB, Evans CR, Khengar RH, Jones SA, Brown MB. Effect of a novel penetration enhancer on the ungual permeation of two antifungal agents. J Pharm Pharmacol 2010;62(6):730-7002E.