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Review Article

Current Alternative New Formulation Approaches for Improving Treatment of Fungal Diseases in Skin

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ABSTRACT:-

Fungal infections of the skin are one of the often faced with dermatological diseases in worldwide. Topical therapy is an attractive choice for the treatment of the cutaneous infections due to its advantageous such as targeting of drugs to the site of infection and reduction of the risk of systemic side effects. 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. However, stratum corneum, the outermost layer of the skin, is an effective barrier for penetration of drugs into deeper layers of the skin. The physicochemical characteristics of drug molecules and the types of the formulations are effective factors in topical drug delivery. Therefore, 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.

KEYWORDS: Antifungals; Colloidal Carriers; Vesicular Carriers; Particulate Carriers; Skin Delivery.

INTRODUCTION:-

The incidence of superficial fungal infections of skin, hair and nails has been increased in worldwide. It has been estimated that about 40 million people have suffered from fungal infections in developing and under developed nations. The progression of fungal infections can be rapid and serious due to compromising with immune function [1, 2]. Dermatophytes are one of the most frequent causes of tinea and onchomycosis. Candidal infections are also among the most widespread superficial cutaneous fungal infections.[3] Even, candida can invade deeper tissues as well as the blood which leads to life threating systemic candidiasis, when the immune system is weakened [4].

Topical and transdermal products are important classes of drug delivery systems and their use in therapy is more useful. Topical products to treat superficial infections from long time, for transdermal products skin is used as alternative route for systemic and in regional therapies.[5]

Topical drug delivery is one of the most suitable routes for administration of drugs that undergo first-pass metabolism. It is generally effective against fungal infections.[6] Topical administration of drugs to the skin by applying ointments, creams, gels directly to an external body surface by spreading and rubbing. The drug must enter and diffuse across the skin.[7-8] The rate and extent of transport will depend on the drug molecular properties and the characteristic of the biologic tissue.

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. Different type of topical effective antifungal compounds has been used in the treatment of a variety of dermatological skin infections. The main classes of topical antifungals are polyenes, azoles, and allylamine/benzylamines. Cicloprox is an antifungal agent also used topically. Currently, these antifungal drugs are commercially available in conventional dosage forms such as creams, gels, lotions and sprays.

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 [9]. 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 the classification of topical antifungals used in treatment of various superficial fungal infections of skin. Recent studies which deal with the optimization of alternative formulation approaches for cutaneous administration of antifungals have also been summarized.

Drug delivery across the skin

The skin is one of the most extensive organs of the human body covering an area of about 2 m2 in average

human adult. It is well-organized membrane; it has main three layers, which are epidermis, dermis, and hypodermis. Stratum corneum is the outermost layer of the skin and it is formed by dead and keratinized cells. Stratum corneum is a principle barrier to the permeation of topical drugs through skin. [10]

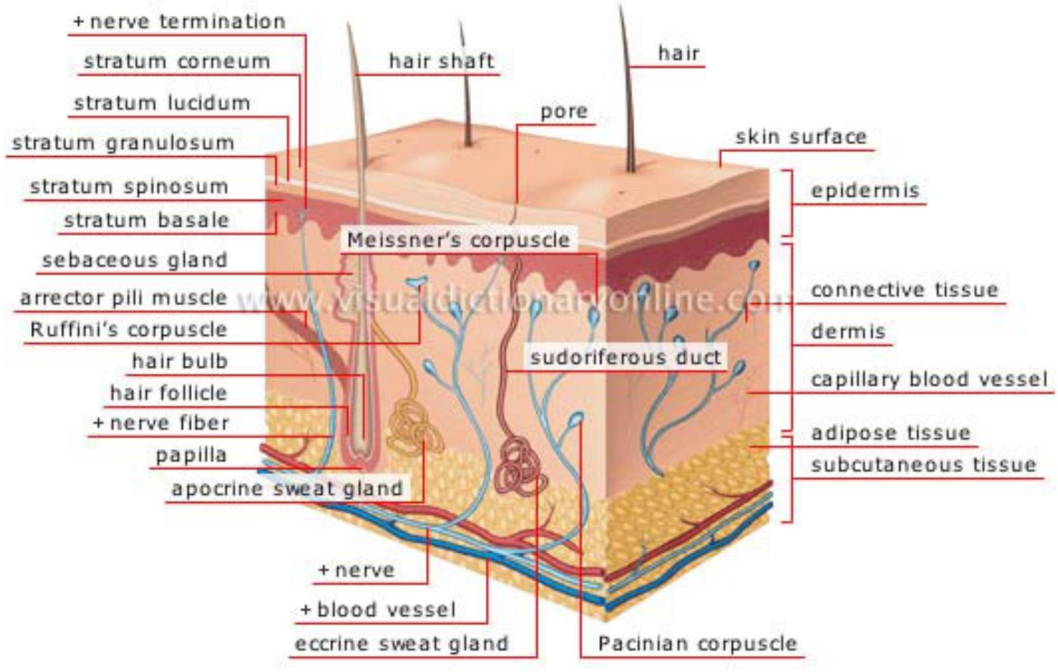

Figure 1: Structure of skin

Drug should penetrate into skin layers to ensure effective drug concentrations following topical administration. Types of formulation and physiochemical properties of drug molecule are effective parameters in topical delivery of drugs. [11] The drug to be passively delivered through the skin needs to have adequate lipophilicity and also a molecular weight <500 Da. Limited drugs fulfill these requirements for the percutaneous delivery. Topical route of administration having the principle goal behind delivery of such drugs through the skin is to achieve better systemic absorption or for local treatment. [12] Intravenous route may avoid gastrointestinal side effects but it is invasive and some patients are complaint that's why topical preparation have better patient compliance and they can be self administered.

Antifungal drugs should reach to effective therapeutic levels in viable epidermis after administration to skin. The topical delivery of drugs is most challenging because of stratum corneum and in order to improve permeability of drugs. A new advance formulation approaches have been investigated. Nanoparticulate carrier such as solid-lipid nanoparticles, nanostructured lipid carriers, vesicular carriers like liposomes, ethosomes, niosomes and transferosomes, colloidal particulate carriers like microemulsions, micelles, nanoemulsions are new carriers to ensure topical administration of antifungals by skin targeting. [13, 14]

PHYSIOCHEMICAL AND PHARMACOKINETIC PROPERTIES OF ANTIFUNGAL DRUGS

The physiochemical and pharmacokinetic properties of antifungal drugs and their inherent antifungal property determine their efficacy, so they are important issue for predevelopment stage. Fluconazole is more polar than other azoles, slightly soluble in water (8 mg/ml). It is metabolically stable and low protein binding. Fluconazole is less active than ketoconazole in-vitro, its distribution throughout the body and high levels of free drug reached in blood contribute to its efficacy. Ketoconazole is poor water soluble and it undergoes degradation such as oxidation and hydrolysis. Fluconazole having molecular weight 306.3 Da and pKa value of 3.7 (weak base) whereas the molecular weight of ketoconazole is 531.4 Da and its pKa value are 6.51 and 2.94 it is a dibasic. [18]

Candida albicans and non-albicans candida species are also causes oral infections in immune-compromised patients. Nystatin, which is belongs to the polyene antifungal class of antimycotic drugs, it is used in the oropharyngeal cadidiasis. Nystatin binds to the sterols in cell membrane results in leakage and permeability issue. It is available in creams, powder and ointment forms. It is effective only against candida. [19, 20]

The Conventional Dosage Forms, Classification and Mechanisms of Action Topical Antifungal Drugs

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.

Table 1.A list of approved and investigational topical antifungal compounds

Antifungal compound	Molecular weight(g/ml)	logP	Aqeous solubility(mg/ml)	PKa	Dosage form
Fluconazole	306.27	0.4	Slightly soluble(1-10)	2.03	Tablet,oral suspension,gel
Sertaconazole	437.77	6.2	Insoluble(‹0.1)	6.54	Cream, solution
clotrimazole	344.83	6.1	Insoluble(‹0.1)	6.7	Cream,solution,lotion
ketoconazole	531.43	4	Very slightly(0.1-1)	6.51&294	Cream,gel,foam, shampoo.
nystatin	926.095	0.5	Insoluble(‹0.1)	12.65	Cream,powder, ointment

CLASSIFICATION OF ANTIFUNGAL DRUGS [21]:

1. Antibiotics:-
A. Polyenes:- AmphotericinB, Nystatin, Hamycin, Natamycin
B. Heterocyclic benzofuran:- Griseofulvin

2. Antimetabolite:- Flucytosine

3. Azoles:-

A. Imidazoles: - Clotrimazole, Econazole,Miconazole,Oxiconazole,Ketaconazole

B.Triazoles:- Fluconazole, Itraconazole,Voriconazole

4. Allylamine:- Terbinafine

5. Other topical agents:-
Tolnaftate, Undecylenic acid, Benzoic acid, Quiniodochlor, olamine , Butenafine, Sodium thiosulfate.

Azole antifungals work through a common mechanism of action; they selectively inhibit the synthesis of fungal cell ergosterol and they alter the permeability of cell membrane by binding with the phospholipids in the fungal cell membrane. The azole antifungal agents in clini- cal use contain either two or three nitrogens in the azole ring and are thereby classified as imidazoles (e.g., ketoconazole and miconazole, clotrimazole) or triazoles (e.g., itraconazole and fluconazole), respectively [3, 18].

Allylamines work through inhibition of squalene epoxidase, which is an essential enzyme in the ergosterol biosynthesis pathway of fungal cell membrane formation. Alterations in fungal cellular membranes result in increased cellular permability and growth inhibition. Benzylamines block the epoxidation of squalene [3, 19].

The polyene antifungal agents exert their antifungal activity by binding irreversibly to fungal cell membrane ergosterol. Thus, the polyenes are fungicidal and have the broadest spectrum of antifungal activity of any of the clinically available agents. Nystatin is a polyene deriva- tive and is limited to topical use only. Clinically, nystatin has demonstrated broad antifungal activity in treating mucocutaneous fungal infections. The most common adverse effect reported with nystatin is allergic contact dermatitis [3, 19, 20].

Ciclopirox is a synthetic hydroxypyridone derivative that carries antifungal, antibacterial, and anti-inflammatory properties. Ciclopirox inhibits essential enzymes interfering with mitochondrial electron transport processes and energy production. It is active against many fungi including dermatophytes and yeast [3].

DRUG DELIVERY SYSTEM UNDER CURRENT DEVELOPMENT FOR IMPROVING TREATMENT OF FUNGAL DISEASES IN SKIN

Gelling Systems-polymeric Carriers

1. **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 %) [22, 23]

2. **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 [24].

3. **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 [25, 26].

4. 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. [27, 28, 29]

5. 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. [30] 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 [31].

Nanoparticulate Carriers

The nanoparticulate carrier systems as solid lipid nano- particles (SLNs) and nanostructured lipid carriers (NLCs) have gained interest for the topical treatment of skin as-sociated fungal infection as they facilitate the skin penetration of loaded drugs [32].

SLN are water-in-oil emulsions containing solids as oil phase, and these systems are prepared from solid lipids or from blends of the lipids. NLCs are defined as new generation of lipid particles, which have been developed to overcome certain limitations of SLNs. NLCs contain mixtures of different solid lipids blended with liquid oils. The most important advantage of these carriers is to have low risk of toxicity. Small size of lipid particles ensures close contact with stratum corneum, and may enhance dermal penetration of drug [33]. These carriers offer controlled release profiles for many compounds [32]. In recent years SLN and NLC carries have been evaluated as carrier for antifungal compounds.

Recently, fluconazole loaded SLNs and NLCs were prepared and characterized for different parameters. The data obtained from in vitro and in vivo experiments revealed that significantly higher amount of drug accumulation was observed in skin with the application of NLCs formulation. The antifungal efficacy study has been performed on experimentally induced cutaneous Candidiasis in immunosuppressed albino rats, the findings confirmed the maximum therapeutic efficacy of NLCs. It was con- cluded that NLCs provided a good skin targeting effect and might be a promising carrier for topical delivery of fluconazole offering the sustained release and maintain the localized effect, resulting in an effective treatment of a life-threatening cutaneous

fungal infection [32]. In another study, topical NLC delivery system of econazole nitrate for the treatment of deep seated fungal infection has been developed to improve drug permeability [34].

SLNs formulations of terbinafine have been formulated to overcome the problems of long treatment durations and frequent administration. In vitro penetration levels of terbinafine of the designed formulations and a commercial product, in the stratum corneum, viable epidermis, and dermis were measured. It was observed that the amount of terbinafine penetrated the skin layers have been enhanced by increasing the percentage of the lipid phase of the formulation. The authors also concluded that the application of terbinafine with SLNs formulations could resolve the practical problem of the longer administration period [35].

Sanna et al. showed that SLN formulations have promoted a rapid penetration of econazol nitrate across stratum corneum after 1 h and have improved the penetration of the drug into deeper skin layers after 3 h of application compared to reference gel [36]. Passerini et al. have also compared econazole nitrate loaded SLNs to solid lipid microparticles having identical formulation components. The results indicated that econazole delivery kinetics in porcine skin was not size dependent [37].

It was observed that SLN dispersions of miconazole nitrate significantly have increased the accumulative uptake of miconazole nitrate in skin over the commercial gel preparation and SLN dispersions also showed a significantly enhanced skin targeting effect [38].Mukherjee and co-workers designed and evaluated itraconazole loaded solid lipid nanoparticles SLNs to improve the therapeutic efficacy and reduction of the antifungal agent. The in vitro drug release profile from SLNs have prolonged up to 12 hours [39].

Clotrimazole-loaded SLNs and NLCs have led to modified drug release over a period of 10 hours [45]. In another study, it was also shown that both SLN and NLC formulations loaded with clotrimazole had a sustained/ prolonged drug release [40].

Table 2: 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 [41]
MCZ-N SLN	Solvent injection method	10-fold greater skin retention than MCZ-N suspension and hydrogel. Sustained effect	Jain S. et al. 2010 [42]
MCZ-N SLN	Compritol® 888 ATO, Tween and glyceryl monostearate ®Hot homogenization method	Entrapment efficiency 80% -100% Increased accumulative uptake in skin Enhanced skin targeting effect	Bhalekar MR. et al. 2009 [43]
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 [44]
TB SLN	Compritol® and Precirol® Tween® and Cremophor® PG	TB penetrated the SC similar to Lamisil®Once(marketed formulation that releases a full dose in 24 h)	Ying Chen-Chen et al. 2012 [45]

	Microemulsion technique	TB penetrated the dermis higher than Lamisil ®Once at 12h	
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 [46]
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 [47]
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 [48]
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 [49]

Colloidal Carriers

1. Microemulsions

Microemulsions are isotropic, thermodynamically stable,transparent or translucent systems composed of oil, water and surfactant, frequently in combination with a cosurfactant for topical and transdermal administration of drugs. Droplet size ranges from 0.1-1.0 μm. Advantages of microemulsion are enhanced drug solubility, thermodynamic stability, optical clarity, easy preparation,low cost. Due to their physicochemical properties,microemulsion often advantages over traditional topical and transdermal drug delivery systems. Microemulsions can be applied as liquid membrane carriers to transport lipophilic substance through an aqueous medium or to carry hydrophilic substances across lipoidal medium. Microemulsions are appropriate delivery system for topical and transdermal as they show excellent biocompatibility.The oils and surfactants included in the composition of microemulsions act as enhancers for permeation of drugs across stratum corneum. [50]

The optimization and characterization of topical microemulsion formulations of antifungal drugs have been widely studied in the literature. Microemulsion systems of voriconazole showed better antifungal activity against Candida albicans than that of its supersaturated solution.

Voriconazole permeation through pig skin has been prolonged up to 4 h with application of Jojoba oil-based microemulsion formulation. [51] Microemulsion systems for topical delivery of

clotrimazole were developed by using either lemon oil or iso-propylmyristate as the oil phase and Tween 80 and nbutanol as surfactant and co-surfactant, respectively. Gel forms of microemulsions were prepared using Carbopol 934 as the hydrogel matrix. The microemulsion gel system comprising of isopropyl myristate, Tween 80, n- butanol and water was determined as a successful topical delivery system of clotrimazole for treatment of cutaneous fungal infections. [52]

Table 3: 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 cetyltrimethyl ammonium bromide. Jojoba oil, Cutina®, glyceryl stearate, glyceryl monostearate, Brij® 96, Capmul	Interaction between positive ME systems and negatively charged skin sites Optimized drug targeting without increase in systemic absorption	Peira E. et al. 2008 [53]
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 [54]
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 [55]
FLZ	Isopropyl palmitate, Aerosol OT and Sorbitan®Monooleate	Significant increase in antifungal activity as compared to marketed formulation	Jadhav KR. et al. 2010 [56]
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 [57]
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 [58]
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 [59]
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 [60]
TB-HC	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 [61]
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 [62]
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 [63]
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 [64]

2. Nanoemulsion

Nanoemulsion is a heterogeneous system and it consist of two immisible phase, one phase is oil phase other is aqueous phase, while the droplet is of sub micron size range of 5-200 nm. Now-a-days nanoemulsion are used for topical preparation and administered by transdermal route. The major difference between emulsion and nanoemulsion [5] are: nanoemulsions are thermodynamically and kinetically stable while emulsions are

unstable. Nanoemulsions are formulated using oil such as glyceryltricaorylatecaprate, surfactants/ cosurfactants and aqueous phase. Surfactants such as tween 80, PEG (>4000), poloxamer, Brij-35 etc are used. Several types of oils-natural semi-synthetic and synthetic are used in the formultion of nanoemulsions. The capacity of nanoemulsions to dissolve large quantities of low soluble drugs along with their mutual compatibility and ability to protect the drugs from hydrolysis and enzymatic degradation make them ideal drug delivery vectors. A nystatin nanoemulsion for topical application was developed to avoid undesirable side effects as systemic absorption and toxicity. Ex-vivo human skin permeation studies showed that the retained amount of drug was sufficient to ensure an antifungal effect and nystatin was not absorbed into systemic circulation. [65,66]

3. Micelles

Micelles are nanosized colloidal carries with a hydrophobic core and hydrophilic shell. They are used as pharmaceutical carriers for water insoluble drugs also attractive drug carriers providing increased bioavailability.The specificity and efficacy of micelle-based drug delivery can be improved through the use of pH-, thermo-, ultrasound-, or light-sensitive block copolymers and the attachment of targeting ligands to the micelles. [67]

Vesicular Carriers

Colloidal vesicular carriers such as liposomes or niosomes have been extensively applied in drug delivery systems. Topical drug administration has been initiated since long time to accomplish several functions on different skin levels (skin surface, epidermis, dermis and hypodermis). But, several limitations have been associated with the conventional topical preparations e.g. low percutaneous penetration because of the barrier function of the stratum corneum, the outermost layer of the skin and absorption to the systemic circulation. The scientific reports now –adays offer several systems that can be able to deliver drugs through the skin. Topical drug delivery means the application of drug to skin for localized effect and in transdermal drug delivery system (TDDS) skin is used as a potential route for the delivery of systemic action of drugs.[68, 69]

1. **Liposomes and Niosomes**

They have 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. The classification of vesicle formulations can be categorized in to two classes: rigid vesicles-liposomes and niosomes and elastic or ultradeformable vesicles-transferosomes and ethosomes. The rigid vesicles are not suitable for the transdermal drug delivery.

A many types 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). Many types of 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. [68, 69]

Table 4: 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 [70]
Ciclopirox olamine liposome system	Phospholipon® 90H/ Dicetyl phosphate /Cholesterol Ethanol injection method	Size 200 -1000 nmEntrapment efficiency lower than 50 % Higher cutaneous deposition of the drug	Shaikh KS, Pawar AP. 2010 [71]
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 [72]
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 [73]
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 [74]
KTZ niosomes	Tween® 40, 80/ Cholesterol Ether injection technique	Reduction of the therapeutic dose	Ning M. et al. 2005 [75]
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 [76]
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 [77]

2. Ethosomes

Ethosomes contain phospholipids like classical liposomes; however, they also contain high levels of alcohol. The components can reach deeper layers of the skin or enter into systemic circulation. They are elastic phospholipid based nanovesicles contains high amount of ethanol for enhancing dermal and transdermal delivery of both hydrophilic and lipophilic drugs. Ethanol disrupts intercellular lipid structure of stratum corneum by phospholipid in their content. Ethanolic nanovesicles of econazole nitrate have been optimized and compared with liposomal and hydroethanolic gels. Ethosomal gel of econazole nitrate has been found potential to serve as a topical delivery system, having controlled drug release, providing better antifungal activity and good storage stability. [68, 78]

3. Transfersomes

Transfersomes are called as highly deformable, or elastic liposomes. They are composed of phospholipids and a surfactant which gives flexibility to the liposome structure. These vesicles are several orders of magnitude more elasic than the standard liposomes and overcome the skin

penetration difficulty by squeezing themselves along the intercellular sealing of lipids of the stratum corneum. Transfersomes have been used for topical and transdermal carriers for drugs and have also been shown to be effective carriers for genetic material and vaccines. Transfersomes have been evaluated as carrier for topical antifungal administration. [68, 79]

Table 5: 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 [80]
FLZ ethosomes	Soya phosphatidyl choline (SPC) PG Hot method	Ethosomes more fluid than liposomes Drug diffused nearly twice higher than from liposomes.	Bhalaria MK. et al. 2009 [81]
TB Transferosomes spray	TDT 067 (not declared composition)Lipid film hydration technique	Enhanced antifungal activity compared to liposomes MIC_{50} values 8-fold and 60-fold lower than those of naked TB and TB spray, respectively	Ghannoum M. et al. 2011 [82]
Griseofulvin deformable vesicles	Span®85Phospholipon ®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 [83]
FLZ elastic vesicles [spanlastics]	Span	Smaller than niosomes Higher permeation than niosomes Safe and stable.	Kaur IP. et al. 2012 [84]
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 [85]
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 [86]
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 [87]
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 [88]

Toxicities of Antifungal Agents

Although the safety and tolerability of systemic antifungal therapy has improved considerably, a growing proportion of heavily immunocompromised patients are receiving systemic antifungal agents for progressively longer treatment courses. Familiar dose-limiting toxicities associated with systemic antifungal agents (i.e.,

infusion-related toxicities and nephrotoxicity with amphotericin B, hepatotoxicity with triazole antifungal agents) and also longer-terms risks, including recurrent drug interactions, organ dysfunction, and cutaneous reactions and malignancies should be considered before administering systemic antifungal therapy [89-91]. Recent reports have linked phototoxic reaction to the subsequent development of squamous cell carcinoma and melanoma [92, 93]. Although rash is reported with all antifungal classes in 5% to 15% of patients, voriconazole treatment in ambulatory patients has been associated with unique retinoid-like phototoxic reactions that present with cheilitis, erythema, and occasional blistering [94].

CONCLUSION

Topical treatment of the skin infection has been mainly used due to its eminence over oral treatment to avoid systemic adverse effects, target the site of infection for application of drug formulation and to increase the patient compliance. The vesicular, colloidal and nanoparticulate

carriers systems are used for the topical antifungal treatment. A vesicular carrier such as transferosomes and ethosomes has demonstrated as they increased drug transdermal penetration. Formulation of topical product plays a main role for penetration of the drug through skin.

Lipophilicity of drug molecules is also effective parameter in physiochemical property. Some antifungal drugs are more lipophilic compounds which affect the penetration of drugs through stratum corneum. Various formulations have emerged, to optimize new drug delivery carriers for

antifungal treatment.

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