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A comprehensive review on topical vesicular drug delivery systems for antifungal therapy

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ABSTRACT

The prevalence of fungal infections of skin has increased rapidly, affecting approximately 40 million people across the globe. A wide variety of antifungal drugs has been utilized in the effective management of numerous dermatological infections. Fungal infections are often treated by topical or systemic anti-fungal therapy. Topical fungal therapy is usually preferred because of their targeted therapy, fewer side effects, enhanced efficacy of treatment, and improved patient compliance. Conventional delivery systems have restricted drug delivery across the skin resulting in insufficient therapeutic index and may exert local as well as systemic side effects. Thus, to facilitate the delivery of antifungal drugs and improve the treatment aspects, various novel delivery carriers have been developed. Advanced topical carriers because of their distinct structural and functional features, overcome biopharmaceutical challenges associated with conventional drug delivery systems like poor retention and low bioavailability. This review summarizes recent advances in novel strategies employed in topical carriers to improve the therapeutic performance of anti-fungal drugs.

INTRODUCTION

Fungal infection is one of the major burdens of skin disease worldwide. Fungal infections lead to significant rates of mortality and morbidity. Most of the fungal infection is due to opportunistic pathogens such as *Aspergillus*, *Candida* and *Cryptococcus* spp. In other words, immunocompromised patients are more vulnerable to fungal infections as compared to healthy individuals, in which their immune system may be suppressed by drugs or weakened due to their medical conditions [1]. Drugs effective against fungal infections are available, but the challenges encountered are the evolution of drug resistance and high incidence of side effects, particularly toxicity caused by the antifungal agents. On the other hand, topical delivery of anti-fungal drugs can cause adverse skin reactions like allergic reaction and itching. Further, conventional formulation needs high dose and repeated administration, associated with an increased risk of both local and systemic toxicity [2]. For this reason, novel drug delivery systems, especially vesicular delivery systems have been exploited with an objective to reduce local side effects and increase their therapeutic efficacy [3]. In this review a brief introduction about different types of fungal infection, its symptoms and causes have been discussed. A brief discussion about conventional and vesicular delivery systems for antifungal drugs has also been reviewed.

2 Fungal infections

The body, no matter how intensive is the efforts to clean it, will always have bacteria and fungi. Many of these microorganisms don't have the ability to cause any harm because the body itself has its own defense mechanism against them. But there are some of them, which begin as relatively ineffectual, gain the ability to cause infections. One group of such organisms is called the dermatophytes. Approximately 90% of fungal skin infections are caused by dermatophytes-types of fungi that cause skin, nail and hair infections. The body's immune system normally takes care of skin fungus and infection never sets in. But when some parts of the body stay moist and warm, the skin fungus on such area multiple exponentially, resulting in an infection [4]. Fungal skin infections are infections on the skin caused by a fungus. Fungi are ubiquitous organisms that are capable of colonizing almost any environment, including all human beings. They grow in irregular

masses and can be broadly divided into two basic forms: molds and yeasts. Diseases caused by fungi are called mycoses. These diseases can be superficial, deep or opportunistic. The prevalence of superficial mycoses now affect more than 20-25% of the world's population, making them one of the most frequent forms of infections. The distribution of the dermatomycoses, their aetiological agents and the predominating anatomical infection patterns vary with geographical location and a wide range of environmental and cultural factors [5]. Dermatophytes thrive at surface temperatures of 25-28 ^{o}C and infection of human skin is supported by warm and humid conditions. Due to their keratinophilic and keratinolytic nature they are able to use cutaneous keratin as a nutrient producing the infection in this way. For these reasons, superficial fungal infections are common in tropical countries. The frequency of dermatomycoses is greater in communities with low socioeconomic status: crowded living conditions provide multiple opportunities for skinto-skin contact. Superficial mycoses occur on hair, skin or mucus membrane and usually produce mild and superficial disease [6]**.** Superficial skin infections show a low tendency to self limitation, and absence of, or poor medical care that further increases the epidemic spread of skin mycoses. The immune-compromised patient has an inherent vulnerability to fungal infection because of impaired immune function. Superficial dermatophytes grow in ring like, erythematous patch with a raised border. The clinical appearance and the causative species of superficial infections vary with geographic region, socioeconomic conditions and habits. The fungal skin infections can be broadly categorized as following.

2.1 Superficial mycoses

These are caused by fungi that grow only on the surface of the skin or hair. An example of a fungal infection is Tinea versicolor, a fungus infection that commonly affects the skin of young people, especially the chest, back, and upper arms and legs. Tinea versicolor is caused by a fungus that lives in the skin of some adults. It doesn't usually affect the face [7]. This fungus produces spots that are either lighter than the skin or a reddish-brown. This fungus exists in two forms, one of them causing visible spots. Factors that can cause the fungus to become more visible include high humidity, as well as immune or hormone abnormalities.

2.2 Cutaneous mycoses

Also known as dermatomycoses, extend deeper into the epidermis, and also include invasive hair and nail diseases. These diseases are restricted to the keratinized layers of the skin, hair, and nails. Unlike the superficial mycoses, host immune responses may be evoked, resulting in pathologic changes expressed in the deeper layers of the skin. The organisms that cause these diseases are called dermatophytes. The resulting diseases are often called ringworm (even though there is no worm involved) or tinea. Cutaneous mycoses are caused by *Microsporum*, *Trichophyton*, and *Epidermophyton* fungi, which together comprise 41 species. One common disease is the athlete's foot which most commonly affects men and children before puberty [8]. It is divided in three categories: chronic interdigital athlete's foot, chronic scaly athlete's foot, and acute vesicular athlete's foot.

2.3 Subcutaneous mycoses

It involves the dermis, subcutaneous tissues, muscle, and fascia. These infections are chronic and can be initiated by piercing trauma to the skin, which allows the fungi to enter. These infections are difficult to treat and may require surgical interventions such as debridement.

2.4 Systemic

Systemic or deep mycoses are able to infect internal organs and become widely disseminated throughout the body. This type is often fatal. *Due to primary pathogens* originate primarily in the lungs and may spread to other organ systems. Organisms that cause systemic mycoses are inherently virulent. Generally, primary pathogens that cause systemic mycoses are dimorphic. *Systemic mycoses due to opportunistic pathogens* are infections of patients with immune deficiencies who would otherwise not be infected. Examples of immunocompromised conditions include AIDS, alteration of normal flora by antibiotics, immunosuppressive therapy, and metastatic cancer. Examples of opportunistic mycoses include *Candidiasis*, *Cryptococcosis* and *Aspergillosis*. Systemic mycoses can be better treated with oral antifungal agents while topical therapy is the choice of treatment for other cases of fungal skin infections. Fungal skin infections are also divided into groups, depending on the type of organism is involved. The full name depends on where the infection is found on body [9]**.**

3. Immunological events involved in fungal infection

Natural host resistance mechanisms contribute significantly in protecting against the opportunistic fungi. The first of the defensive innate mechanisms is the physical barriers that separate the organism from the environment: i.e. Skin. The skin surface is relatively inhospitable to fungal growth because of exposure to UV light, low moisture conditions, and competition from the normal bacterial flora of this site. Furthermore, the stratum corneum is continually renewed through keratinisation of the epidermal cells also present a form of defence against organisms infecting this site. Lipids of adult hair contain saturated fatty acids that are fungistatic against *Microsporum audouini,* formerly a common cause of hair and scalp infections**.** Inspite of all the barriers the skin is invaded by the fungus because of innumerable factors. In particular, various types of sphingosines have recently been found to be active against certain dermatophytes and *Candida Albicans* [9]**.** The skin also produces antimicrobial peptides that are active against fungi. They inactivate microbes, including fungi, through multiple direct effects on their membranes. Furthermore, they likely play a key role in activating and mediating the innate as well as adaptive immune response in infection and inflammation [9,10]**.** The infections with dermatophytes are generally confined to the keratinized stratum corneum and the cutaneous appendages like the hair and nail. This phenomenon has been related to the presence in the dermis of unsaturated transferring, which may prevent growth of the organisms in the deeper layers of the skin by competition for iron [11]**.** Once the fungi have passed the physical barriers, they are met with a series of innate mechanisms of defence, including cellular membranes, cellular receptors and several humoral factors. In the tissues, phagocytes, consisting of neutrophils, mononuclear leukocytes (monocytes and macrophages) and dendritic cells, have an essential role, and natural killer cells, T-cells are involved in the host defence. Chemokines regulate an array of biological activities in addition to chemotaxis, such as hematopoiesis, angiogenesis, cytokine induction, antigen presentation and Th cell differentiation [12]**.** After the organism is exposed to a dermatophyte, a sequence of events occurs in the skin such as presentation of the antigen, recruitment of cells and resolution of the process.

4. Symptoms of fungal skin infections

The symptoms and appearance of a fungal skin infection

depend on the type of fungus causing it and the part of body affected. Fungal skin infections can cause rashes with a variety of different appearances. Some are red, scaly and itchy; whereas others can produce appear similar to dry skin. The fungus may infect just one area or several areas of the body. Fungal infections of scalp or beard can lead to hair loss. Fungal rashes can sometimes be confused with other skin conditions, such as psoriasis and eczema.

5. Causes of fungal skin infections

The risks of getting fungal skin infections are more if the person:

- have recently taken a course of antibiotics
- are taking steroids
- have diabetes
- are overweight
- have had fungal skin infections in the past
- have a weakened immune system caused, for example, by cancer or HIV/AIDS

Moist skin encourages fungal skin infections. This means there are more chances of fungal infections if don't dry skin properly after sweating or bathing, or if wear tight clothes that don't allow sweat to evaporate. Damage to the surface of skin, such as a cut or graze, can also encourage fungi to grow. Fungal infections inside body can cause more serious health problems than those on skin. These infections only affect people whose immune systems aren't working properly - either as a result of an illness such as HIV/AIDS, or because taking medicines that suppress immune system.

6. Topical therapy

Topical therapy is considered to be the most promising as compared to other routes because of many potential advantages. To develop an ideal dosage form, one must take into account the flux of the drug across skin, the retention of the dosage form on the skin's surface, the reservoir capacity of the dosage form and patients acceptability of the formulation [13]**.** The stratum corneum is a barrier for transfer of drugs to the dermal and epidermal sites**.** So, the purpose of topical and dermatological dosage forms is to conveniently deliver drug molecules across localized area of skin. In treating skin disease, the primary purpose of applying drugs to the skin is to induce local effects at a very close site of application, so that cutaneous absorption is desirable but percutaneous is not. Sustained release becomes important to supply the skin with a drug over a prolonged period of time [14]. The benefits of topical therapy are represented in figure 1.

7. Conventional formulation for treatment of fungal skin infections

The fungal skin infections are surface infections that need to use antifungal treatments that are applied directly to the skin in the infected area (topical treatments). The treatments are available in the form of antifungal creams, lotions and medicated powders. The various antifungal drugs being used for the treatment of topical fungal skin infections for e.g. Clotrimazole (CANDID 1% cream, gel, lotion, SURFAZ, CLOTRIN, CLODERM 1% lotion, cream), Nystatine (Loprox cream), Miconazole (DAKTARIN 2% gel, ZOLE 2% ointment), Ketoconazole (NIZRAL 2% CREAM, FUNGINOC 2% CREAM, KETOVATE 2% cream), Econazole (ECOSTATIN cream), Terbinafine (TERBIDERM 1% cream), Tolnaflate (TINADERM, TINAVATE 1% lotion, TOLNADERM 1% cream), Ciclopirox olamine (BATRAFEN 1% cream, 1% topical solution, OLAMIN 1% cream), Butenafine (BUTOP, FINTOP 1% cream), Amphotericin B (3% FUNGIZONE cream). But some problems are associated with these conventional topical antifungal formulations such as limited efficacy, have high potential for skin irritation, high doses of drug required for treatment and have limited local activity.

To overcome the problem associated with conventional formulations some selective delivery system has to be prepared that enhances penetration of bioactive moiety into the skin, localizes the drug at the site of action and reduces the

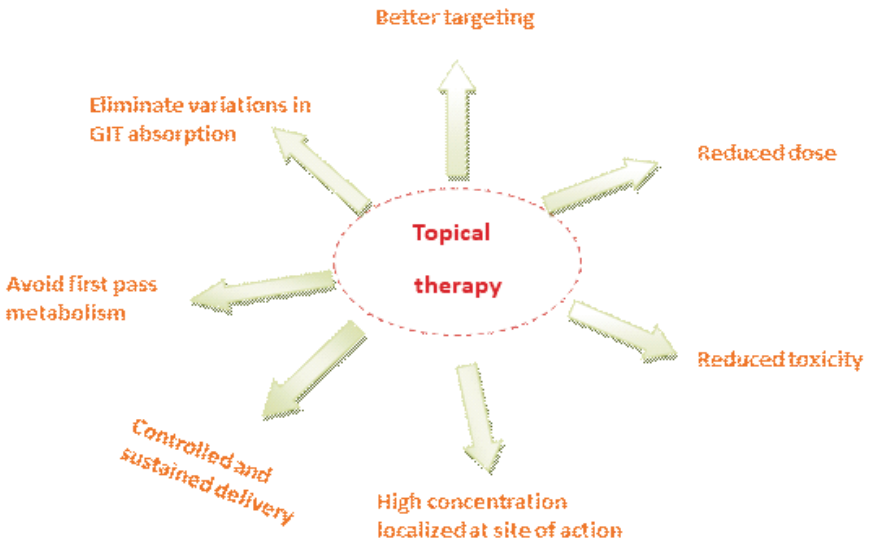

Fig. 1 : Benefits of topical drug therapy

percutaneous absorption; a number of approaches have been explored for the efficient delivery of bioactive molecules. Various vesicular systems (liposomes, ethosomes and transfersomes) are being exploited by various scientist used because now a day's vesicular approach is gaining insight due to the following reasons [15].

- Biodegradable, biocompatible and nontoxic carrier with better potential to deliver drug molecules into the skin.
- Prolonged and pronounced drug action
- Effective at low doses
- Non-allergic and non-immunogenic

8. Vesicular carrier systems

8.1 Liposomes

In the past decade, topical delivery of drugs by liposomal formulations has evoked considerable interest. Since that time, liposomes have been used in a broad range of pharmaceutical applications. Liposomes have been studied extensively for topical delivery of various bioactive agents. Liposomes are concentric bilayered vesicles in which an aqueous volume is entirely enclosed by a lipid bilayer. There are a number of components present in liposomes, with phospholipid and cholesterol being the main ingredients. Cholesterol added to improve bilayers characteristics of liposomes, for increasing microviscosity of the bilayers, reducing permeability of the membrane to water soluble molecules, stabilizing the membrane and increasing rigidity of the vesicles. Due to their biphasic character, liposomes can act as carriers for both lipophilic and hydrophilic drugs. Lipophilic drugs are generally entrapped almost completely in the lipid bilayers of liposomes while hydrophilic drugs are located inner aqueous core of liposomes [16]. Depending upon their solubility and partitioning characteristics, the drug molecules are located differently in liposomal environment and exhibit different entrapment and release properties. Liposomes can be prepared by a variety of methods. In general, on the basis of size and lamellarity (number of bilayers present within a liposome), liposomes are classified into three categories: multilamellar vesicles (MLVs), large unilamellar vesicles (LUVs), and small unilamellar vesicles (SUVs). Liposomes can also be classified in terms of composition and mechanism of interacellular delivery into five types as: (i) conventional liposomes (ii) pH sensitive liposomes (iii) cationic liposomes (iv) immunoliposomes and (v) long circulating liposomes. Liposomes have been widely used as safe vehicles for topical drug delivery systems due to their ability to entrap drugs and deliver them to the skin, thus enhancing their therapeutic effectiveness [17].

8.2 Ethosomes

These are the second generation of elastic vesicles consisting mainly of nonionic surfactant. Ethosomes are lipid vesicular carrier system embodying ethanol in relatively high concentration and are very efficient in deliverying drugs into and across the skin. Touitou et al have discovered and investigated this lipid vesicular system and named them ethosomes [18]. The ethosomes are vesicular carrier comprise of hydroalcoholic or hydro/alcoholic/glycolic phospholipids in which the concentration of alcohols or their combinations relatively high. Ethosomes also contain phospholipid with various chemical structures like Phosphatidylcholine (PC), hydrogenated PC, Phosphatidicacid (PA), Phosphatidylserine (PS), Phosphatidyle-

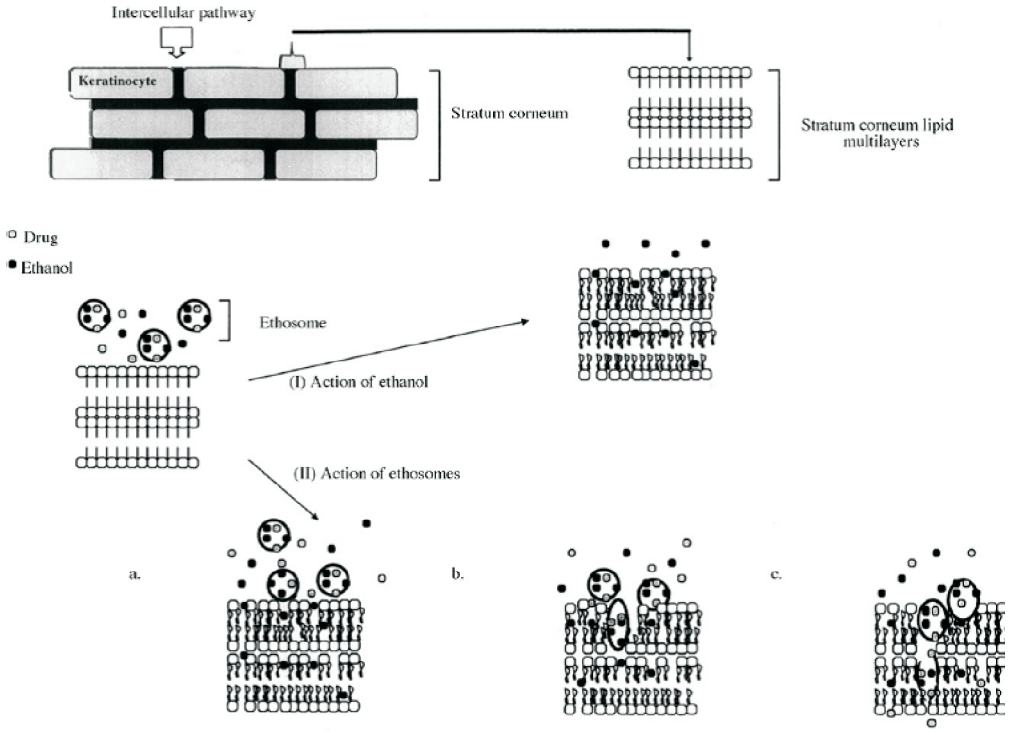

Fig. 2 : Hypothetical model suggested by (21), describing enhancement of penetration of drugs through stratum corneum lipids by ethosomes

thanolamine (PE), Phosphatidylglycerol (PPG), Phosphatidylinositol (PI) [19]. The basic difference between liposomes and ethosomes lies in their composition. Several researchers evidenced that ethosomal formulations were able to enhance permeation through the stratum corneum barrier, improve drug skin accumulation, and assure sustained drug release [18]. Recently, "ethosomes" revealed to be more efficient than classic liposomes at delivering drugs through the skin in terms of quantity and depth. Ethanol is an efficient permeation enhancer and it is present in quite high concentration (20-50%) in ethosomes. The high concentration of ethanol (20-50%) in ethosomal formulation could disturb the skin lipid bilayer organization. Therefore, when integrated into a vesicle membrane, it gives an ability to the vesicles to penetrate the stratum corneum. Due to high ethanol concentration the ethosomal lipid membrane was packed less tightly than conventional vesicles but have equivalent stability [20]. This gives a softer and malleable structure and also gives more freedom and stability to its membrane, which could squeeze through small openings created in the disturbed SC lipid. Therefore, when integrated into a vesicle membrane, it gives an ability to the vesicles to penetrate the stratum corneum. Figure 2 illustrates a hypothetical model, suggested by [21], of how ethosomes may enhance penetration of drugs through stratum corneum lipids. The stratum corneum lipid multilayers, at physiological temperature, are densely packed and highly conformationally ordered. Ethanol interacts with lipid molecules in the polar head group region, resulting in a reduction in the Tm of the stratum corneum lipids, increasing their fluidity. The intercalation of ethanol into the polar head group environment can result in an increase in the membrane permeability. In addition to the effects of ethanol on stratum corneum structure, the ethosomes itself may interact with the stratum corneum barrier. Ethanol may also provide the vesicles with soft flexible characteristics which allow them to more easily penetrate into deeper layers of the skin. In summary, the effect of ethanol on stratum corneum lipids and on vesicle fluidity as well as a dynamic interaction between ethosomes and the stratum corneum may contribute to the very effective delivery properties.

8.3 Transfersomes (deformable liposomes)

Deformable liposomes (Transfersomes) are the first generation of elastic vesicles introduced by Cevc and Blume in 1992. They consist of phospholipids and an edge activator [22]. An edge activator is a single chain surfactant, having a high radius of curvature that destabilizes lipid bilayers of the vesicles and increases deformability of the bilayers [14]**.** The phospholipid and edge activator contents have been optimized to attain the desired deformable nature of the elastic liposomes, to increase elasticity and penetrability. Elastic liposomes possessed the property that allowed them to successfully deliver drugs in the deeper layers of skin [23]**.** Although the exact mechanism for this has not been conclusively established, but their deformable character is suggested to be the main contributing factor**.** Sodium cholate, sodium deoxycholate**,** Span 60, Span 65, Span 80, Tween 20, Tween 60, Tween 80 and Dipotassium glycyrrhizinate were employed as edge activators. The transfersomal system is much more efficient at delivering a low and high molecular weight drugs to the skin in terms of quantity and depth e.g. analgesic, anesthetic, corticosteroids, sex hormone, anticancer, insulin, gap junction protein, and albumin. They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes. They have high entrapment efficiency, in case of lipophilic drug near to 90%. They protect the encapsulated drug from metabolic degradation. They act as depot, releasing their contents slowly and gradually. They can be used for both systemic as well as topical delivery of drug. Easy to scale up, as procedure is simple, do not involve lengthy procedure and unnecessary use or pharmaceutically unacceptable additives. Preparation of deformable liposomes involves methods similar to those used in preparation of traditional liposomes. Most commonly, the film hydration method is used. In several studies have shown that deformable vesicles were more effective than the conventional rigid vesicles in the enhancement of drug transport across animal and human skin [24]. The effectiveness of transfersomes was successfully demonstrated using model drugs, such as Lidocaine, Corticosteroids, Diclofenac and high molecular weight compounds, such as insulin. Transfersomes resemble lipid vesicles, liposomes, in morphology but,

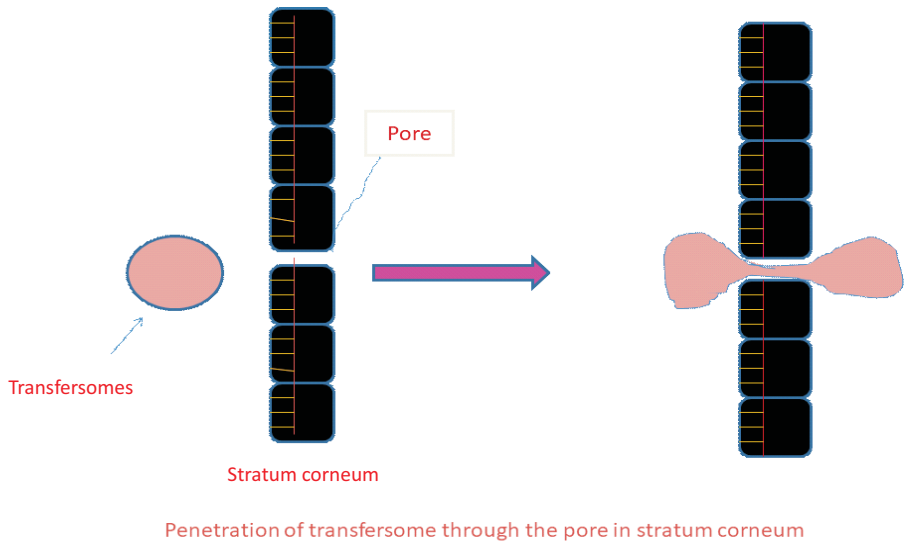

Fig. 3 : Penetration of transfersomes through the pore in stratum corneum

functionally, transfersomes are sufficiently deformable to penetrate pores much smaller than their own size [25]. Transfersomes are locally and controllably destabilized, but generally stable, mixed lipid vesicles. They are (quasi) metastable, which makes the vesicle membrane ultraflexible, and thus, the vesicles are highly deformable. The effects of incorporation of different edge activators on physicochemical properties (including vesicle size, entrapment efficiency, among others) of deformable liposomes were extensively investigated in several studies [26]. The interaction between edge activators and liposomes was also investigated. Transfersomes can deform and squeeze through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss [14,15]. The driving force for skin penetration of deformable vesicles is the osmotic gradient across the skin. Such a gradient is created by the difference in the total water concentration between the skin surface and the skin interior. Topically applied transfersomes dehydrate on the skin surface by evaporation and thus an osmotic pressure difference is originated between the highly hydrated regions inside the skin and the dehydrated skin surface, which makes transfersomes enter the stratum corneum into the deeper skin strata to avoid dehydration (Figure 3). Skin distribution from transfersomes was described as dose-dependent. The fate of aggregates that have crossed the skin barrier depends on the dose applied per unit area.

CONCLUSION

Fungal infections remain a continuous and growing threat to human health. Inappropriate and irrational use of antifungal chemotherapeutics resulted in the development of multidrug resistance fungal pathogens, unwanted toxicity, and low therapeutic efficacy. Vesicular system may enhance the efficacy of entrapped drug to deliver it at the targeted site and thus may enhance the therapeutic efficacy of antifungal drugs along with limiting the side effects of conventional drug delivery systems. Thus vesicular systems could be utilized for better treatment and management of various topical fungal diseases.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this article.

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