

**LIPOSOMES IN DERMATOLOGICAL DISEASES**M. Kamra*¹, A. Diwan²

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Liposomes are vesicles comprising of spherical phospholipids making them useful for topical applications of drugs. Liposome research has been expanded considerably and nowadays, it is possible to construct a wide range of liposomes varying in size, phospholipids composition and surface characteristics. In dermatological diseases, the topical application of liposomes has proven to be of high therapeutic value. Liposomes can be used as carriers for hydrophilic as well as lipophilic therapeutic agents because of their amphipathic character. They may improve stabilization of instable drugs by encapsulating them. They have the potential to target drugs into the pilosebaceous structures and hence have an advantage for treatment of hair follicle-associated disorders. Liposomal encapsulated drugs are found useful in the treatment of acne, atopic dermatitis, psoriasis, vitiligo, superficial vein thrombosis and hair removal etc

INTRODUCTION

It is the skin which is directly accessible for topical application of drugs. Optimum topical delivery of drugs into the skin requires penetration of the vehicle through the stratum corneum, liberation of the drug from the vehicle, absorption of the drug through the different layers of the skin. Safety aspects of topical drug delivery include the reduction of the risk of local and systemic side-effects by using appropriate drug concentrations, optimal vehicles and valid treatment [1]. Liposomes were described in 1965 by Bangham *et al.*, while studying the spontaneous aggregation of phospholipids into vesicles [2]. These vesicles were called liposomes. These were initially used as a model for membrane system studies [3]. Since 1970, liposomes have received considerable attention as a system for delivering drugs to the target tissue [3]. In spite of promising prospects, the systemic application of liposomal drugs has been limited but the topical application of liposomal preparations has attracted increasing attention in dermatology [4]. Liposomes are microscopic vesicles formed from phospholipids as biological membranes. A large group of biological membrane lipids that spontaneously form bi-layers

in water are the phospholipids. The ability of phospholipids to form a bi-layer structure is because of their amphipathic character resulting from the presence of a polar or hydrophilic (water-attracting) head-group region and a non-polar, lipophilic (water-repellent) tail. Therefore, liposomes contain a lipophilic compartment within the bi-layer membranes and hydrophilic compartments between the membranes. Under the right conditions, water-soluble substances can be stored into the water phase and lipophilic substances into the lipid phase [5]. Liposomes may be small, unilamellar vesicles (SUVs 25–50 nm in diameter), large, unilamellar vesicles (LUVs 50–500 nm in diameter) or large multilamellar vesicles (LMVs 500–10 000 nm in diameter). SUVs are less suitable for drug delivery because they lack stability and their volume is too small for entrapping drugs. The penetration of liposomes through the stratum corneum decreases with increasing diameters. Therefore, the preferred structures for drug delivery are LUVs that are 50–500 nm in diameter. LUVs made from lipid mixtures containing unsaturated phosphatidyl ethanolamine can fuse and mix with the skin lipids to loosen their structure providing a penetration enhancing effect [6]

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The skin acts as a two-way barrier, controlling the inward and outward passage of water and electrolytes. This barrier is situated in the stratum corneum and consists of the cornified material of the terminal differentiated keratinocytes, proteins and intercellular lipids. The main function of the cornified envelope is to form the outermost barrier layer of the skin, which prevents water loss and keeps out allergens and infectious agents [7]. Thus, the stratum corneum contains hydrophilic and lipophilic compartments, which act as a buffer to retard both water loss and absorption of water [8]. These lipid-rich structures might also influence the desquamation process in the stratum corneum [9]

MECHANISM OF PENETRATION OF LIPOSOMES

There are 3 mechanisms of penetration of liposomes into skin:

- Via lateral diffusion of liposomes in the stratum corneum. The molecular structure of liposomes is similar to that of endogenous skin lipids. Lipid exchange occurs via molecular diffusion from one membrane to the other. The rate of phospholipid exchange depends upon the relative sizes of the hydrophobic portions of the molecule [10]
- Via a *trans*-epidermal osmotic gradient and hydration force through which liposomes are sucked into the epidermis. An effective penetration of liposomes into the skin requires a dry skin surface [11]
- Via the pilosebaceous units [12]

The similarity of lipid composition of liposomes and membranes enables the liposomes to penetrate into the epidermal barrier to a greater extent as compared with other application forms [13]. This may result in an increase of drug absorption into the epidermis and decrease of drug clearance from the epidermis, promoting longer sustained release of drugs in the epidermis and lower absorption of drugs into the blood. Liposomes fuse with the outer cell membrane and deliver their contents to the cytoplasm via endocytosis [14] (Fig 1). Liposome research has expanded considerably over the last 30 years, and nowadays, it is possible to construct a wide range of liposomes varying in size, phospholipids composition and surface characteristics to suit the specific application for which they are intended. [16]. Liposomal formulations should have high entrapment efficiencies, narrow size distributions, long-term stabilities and ideal release properties. There are numerous lab-scale and a few large-scale techniques for liposome preparation giving rise to vesicles of different sizes and consisting of one or more bi-layers. Conventional and

novel preparation techniques have been introduced, each with its own advantages and possible limitations.

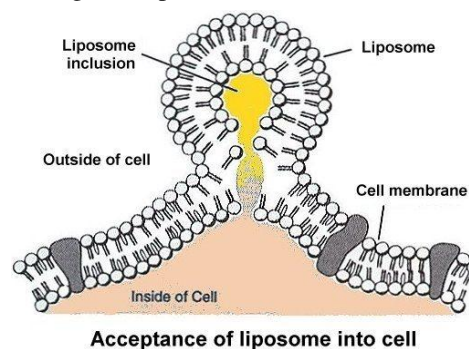


Figure 1 Liposomes fuse with the outer cell membrane and deliver their contents to cytoplasm of cells via endocytosis [15]

ADVANTAGES OF LIPOSOMAL PREPARATIONS IN DERMATOLOGY

- 1) The similarity of lipid composition of liposomes and membranes in the epidermis enables the liposomes to penetrate into the epidermal barrier to a higher extent as compared with other application forms and so do the compounds encapsulated into the liposomes. This may result in an increased drug absorption into the epidermis and a decreased clearance of drug from the epidermis resulting in a much longer sustained drug release and reduction of drug absorption into the blood. This is why liposomes may act as drug transporters as well as drug targeters. This may lead to increased effectiveness, reduction in side effects and a higher compliance of patients to treatment [3]
- 2) Liposomes have also the potential to target drugs into the pilosebaceous structures and hence they can be employed for treatment of hair follicle- and sebaceous gland-associated disorders [12]
- 3) Liposomes may serve as penetration enhancers facilitating the transport of compounds through the epidermis. The use of conventional penetration enhancers (e.g. dimethyl sulphoxide or propylene glycol) leads on the one hand, to an improved transport rate through the epidermal barrier but, on the other hand, to more unwanted side-effects because of an increased systemic drug level [17]
- 4) In addition, irritant- and allergic reactions to penetration enhancers have been reported leading to the conclusion that addition of penetration enhancers does not always mean an advantage in topical drug administration [18]
- 5) Side effects from liposomes are not to be expected because liposomes are similar to epidermal lipids, biodegradable and non-toxic [18]

6) Liposomes can be used as carriers for hydrophilic as well as lipophilic drugs because of their amphipathic character. Compounds like methotrexate and cyclosporin which cannot penetrate the epidermis may be usable for topical application when encapsulated in penetrating liposomes [19]

7) Liposomes may also improve stabilization of instable drugs by encapsulating them [20]

8) 'Empty' liposomes (without encapsulated drugs) hydrate the skin simply by contributing lipids to the stratum corneum. Additionally, the water content of liposomes promotes further hydration of the skin. In contrast with the 'wet-wrap' method, application of liposomal spray is a fast, easy procedure without any need of training. Liposomes help to reduce skin irritation to drugs (e.g. tretinoin) by hydration of the epidermis [20, 21]

INDICATIONS FOR LIPOSOMES IN DERMATOLOGICAL DISEASES ACNE

Acne is one of the most common disorders of the skin and has a considerable impact on the quality of life of adolescents. Standard treatment today consists of peeling the skin, eliminating the acnes and reducing inflammation by using topical benzoyl peroxide (BPO), tretinoin, adapalene and antibiotics. If this approach is not efficacious, systemic antibiotics and antiandrogens are the next step. However, the efficacy of antibiotic treatment is progressively reduced by increasing resistance of bacteria to antibiotics, and side-effects may also limit their use. In case of failure of treatment the final remedy is oral isotretinoin, which is very effective, even in recalcitrant acne, but its use is limited by moderate to serious side-effects. It was found that the efficacy and safety profiles of certain antiacne drugs may be improved by encapsulating them into liposomes [22]



Figure 2: Acne on face [23]

Liposome-encapsulated 1% clindamycin-solution was found to be superior than 1% clindamycin-solution in the treatment of

acne and no side-effects were reported [24]. Similarly, the efficacy and the local tolerability of liposomal tretinoin 0.01% was compared with commercial gel preparation with either 0.025% or 0.05% in 20 patients. The efficacy of liposomal tretinoin appeared to be equipotent to the reference gels, but liposomal tretinoin was superior with respect to skin irritancy.[25]. A comparative double-blind study in 30 patients demonstrated a 1.5-fold enhancement of drug efficacy and a marked decrease in all side-effects associated with tretinoin therapy for liposomal tretinoin gel compared with conventional tretinoin gels after 3 months of treatment [26]. BPO is an effective topical agent in the treatment of acne and acts by inhibition of the propionibacterium acnes in the pilosebaceous units. A comparative double-blind study of liposomal BPO vs. conventional BPO in 30 patients demonstrated a significant improvement in the therapeutic response (about 2-fold) after 3 months of treatment with liposomal BPO as compared with a conventional BPO gel, with marked reduction in adverse symptoms and bleaching of clothing [27]. In another study, a significantly higher antibacterial effect of a BPO liposome formula was observed as compared with commercial BPO formulations [28]

ATOPIC DERMATITIS



Figure 3: Atopic dermatitis of a child [29]

In atopic dermatitis patients disturbance of the outermost barrier layer of the skin is observed due to mutation in the filaggrin gene.[30]. This affects water permeability, leading to increased *trans*-epidermal water loss [31].Increased lamellar body secretion was demonstrated with coincidental clinical improvement after wet-wrap dressing treatment of atopic eczema [32]. Similar effects on the restoration of the skin barrier were described after application of liposomes on the skin. Due to the similarity between the structure of the liposomes and the lipid layers of the stratum corneum, the liposomes bind to the keratin layer of the stratum corneum and form a thin occlusive film, which reduces *trans*-epidermal water loss giving the patient immediate relief from the

discomfort associated with dry skin[.33]. Additionally, the water content of liposomes promotes further hydration of the skin. The wet-wrap treatment is very time-consuming, needs training and is not well tolerated by every patient. Application of liposomal spray is a fast, easy to use and requires no training. Moreover, a double-blind study showed that the patient's acceptance for liposomes containing preparations was significantly higher than that for commercially available moisturizing preparations [34]. Topically applied corticosteroid therapy is the first choice of treatment for atopic dermatitis and irritant and allergic contact dermatitis in addition to restoration of the damaged skin barrier and recognizing and elimination of a causative agent. Higher and sustained concentrations of a liposomal corticosteroid in the skin promise higher efficacy, less side-effects from absorption of corticosteroids into the blood and lower frequency of application.[35].

PSORIASIS

Psoriasis is a long-lasting autoimmune which is characterized by patches of abnormal skin. These skin patches are typically red, itchy, and scaly. They may vary in severity from small and localized to complete body coverage. Injury to the skin can trigger psoriatic skin changes at that spot.



Figure 4: Psoriasis on the back [36]

Recent breakthroughs in the treatment of psoriasis have led to improved understanding of the pathogenesis of this disease[37]. Although major advances in the development and the use of targeted biologicals for controlling psoriasis have been made, the need to develop safe, cost-effective and disease-effective cures remains [38]. Vitamin D₃ analogues such as calcipotriol, calcitriol and tacalcitol can be used in psoriasis. Calcitriol was tested at concentrations of 5, 15 and 20 µg/g in liposomes and in petrolatum in a mouse tail test. It was considered that by using a liposomal preparation, the vitamin D₃ concentration can be reduced as compared with commercial preparations without affecting therapeutic effect and also reducing local side-effects such as skin irritation and systemic side effects [39]. Similarly

Dithranol which is used in plaque type psoriasis, is considered inconvenient and troublesome because of side-effects such as skin irritation, burning sensation, staining and necrotizing effect on normal as well as the diseased skin. The entrapment of dithranol in liposomal vesicles promotes its bioavailability in the epidermis, which makes it possible to reduce the dose and in turn, the dose-dependent side effects [40]. In a double-blind study, the superiority of 0.5% dithranol encapsulated in a liposomal gel as compared with a conventional cream containing 1.15% dithranol, 1.15% salicylic acid and 5.3% coal tar was reported [41]. Cyclosporine A (CyA), a potent immunosuppressive drug can be used in psoriasis. But systemic administration causes serious side-effects, such as nephrotoxicity. Topical administration is hindered because of its physicochemical properties and the barrier property of stratum corneum. However liposomal vesicles containing 10% and 20% ethanol showed statistically enhanced deposition of CyA into the stratum corneum causing topical delivery of CyA using liposomes for the treatment of skin diseases like psoriasis [42]. Similarly systemic methotrexate can be used for controlling recalcitrant psoriasis, but may cause hepatotoxic effects. Topical application of methotrexate is limited being the drug is hydro-soluble limited for passive diffusion. However, in a liposomal preparation, 50% of the administered dose was found in the skin indicating that liposomes may be valuable in the topical application of methotrexate in the treatment of psoriasis[43]. It was confirmed that psoriasis can be treated by topical application of liposomal-entrapped methotrexate-paraffin wax in a small clinical trial. After 2 weeks of treatment, all plaques treated with liposomal methotrexate showed total clearance whereas those receiving free methotrexate didn't improve [43].

VITILIGO

Vitiligo is an acquired de-pigmentation disorder affecting about 1% of the population. It may have an important negative impact on the quality of life, particularly of those with pigmented skin. The inactive melanocytes in the outer root sheath of the hair follicles are not affected. Phosphatidylcholine liposomes are able to target molecules like khellin into the hair follicles After khellin is activated by ultraviolet A (UVA) and UVB, the inactive melanocytes proliferate and mature to an active state as they migrate into the epidermis[44]. The results of systemic khellin in combination with UVA are comparable with the rates reported from psoralenphotochemotherapy

(PUVA)[45] The major advantage of khellin is that it does not induce photo-toxic skin erythema and does not induce detectable DNA mutations in contrast to PUVA, but side-effects such as liver dysfunction have been reported. Topical photochemotherapy of vitiligo with khellin has also been reported to be efficacious.[46] The efficacy and the safety of topical treatment with 0.005% khellin encapsulated in l-phenylalanine stabilized phosphatidylcholine liposomes in combination with UVA/UVB light (KPLUV) therapy was demonstrated in 74 patients with vitiligo in a retrospective open trial [47]

SKIN CANCER

Skin cancer is the most common cancer in white people[48]. Basal cell carcinoma and squamous cell carcinoma are the most frequently occurring skin cancers[49]. Exposure to solar UV radiation is the main factor leading to the formation of skin cancers.[50]. Wavelengths especially in the UVB (280–320 nm) range damage DNA in the cells of human skin [51].The bacteriophage T4 produces a DNA repair enzyme (T4 endonuclease V), which is able to substitute the UV-damaged enzyme complex in humans to initiate excision repair[52]. It has been shown thatT4N5 containing liposomes protect the skin from UV-induced carcinogenesis by promoting the DNA repair and by inhibiting immunosuppression [53]. Photodynamic therapy (PDT) is widely used to treat actinic keratoses and superficial basal cell carcinoma. While changing the 5-ALA vehicle from a moisturizing cream to liposome encapsulation, the 5-ALA concentration can be lowered. Moreover a higher skin retention and a lower skin permeation of 5-ALA was demonstrated as compared with 5-ALA in aqueous solution[54]. The results of these studies indicated that 5-ALA in liposomes may be adequate for the 5-ALA PDT treatment of skin cancer because the liposomes deliver 5-ALA to the target skin layers (viable epidermis and dermis) [54]. Liposomes provide the opportunity for a more precise targeting of drugs into diseased cells and may contribute to optimize the quality of fluorescence diagnosis. This property of liposomes as a targeting method is not available in other topical applications [55]

THROMBOPHLEBITIS

Thrombophlebitis is vein inflammation related to thrombus (blood clot). Its symptoms include pain, skin redness, oedema and inflammation.



Figure 5: Thrombophlebitis on leg [56]

Superficial vein thrombosis is generally considered to be relatively harmless. However, deep venous thrombosis and pulmonary embolism following superficial vein thrombosis have been reported[57] Therefore, the importance of treatment with low molecular weight heparin (LMWH) in addition to compression therapy has increased, mainly because of the antithrombotic actions of heparin[58]. Topical liposomal heparin spray-gel appeared to be equally efficacious in reduction of pain, erythema and thrombus size as compared with subcutaneous injections of LMWH.[58]. Subcutaneous injections and applications of topical LMWH in ointment, cream & gels are painful (rubbing into skin at thrombophlebitis site) in contrast with liposomal heparin spray gel [59]

HAIR REMOVAL

Unwanted facial and body hair can represent a severe cosmetic disturbance with social and psychological implications often strong enough to motivate patients, especially women, to seek dermatologic treatment. The goal of laser hair removal is to damage stem cells in the bulge of the follicle or to replace the hair follicle at the level of the dermis with connective tissue through thermal injury. The primary mechanism of laser hair removal is selective photothermolysis whereby follicular melanin is the target chromophore for destruction by light energy. Laser hair removal of white, blond and grey hair is often unsuccessful due to the lack of melanin in the hair follicle. Melanin-encapsulated liposomes have demonstrated to deliver melanin selectively to the hair follicle and the hair shaft. (Hoffman 1998) Melanin-encapsulated liposomes (Lipoxome®) are used for staining hair follicles of people with blond, white or grey hair [60]. Pretreatment with Lipoxome® spray improved also the results of long pulsed Nd:Yag laser treatment for pigmented underarm hair. At 6 months after three laser treatment sessions, the percentage of hair reduction was 73% with the combined therapy and 43% with laser treatment alone [61]

TOPICAL ANAESTHESIA FOR SUPERFICIAL SURGERY

It was found that there is no need for occlusion after application of tetracaine 5% or lidocaine 4% in liposomal cream. Adequate anaesthesia is obtained after 30 min, vasoconstriction does not occur and there is no association with methemoglobinemia [62]

SKIN REJUVENATION

It was observed that Photo dynamic therapy (PDT)with 5 ALA (20%) rejuvenated the skin in the irradiated area, which resulted reduction of wrinkles, scars and large skin pores.[63,64]but the side-effects were very high.such as pain, oedema, erythema etc..Comparable clinical results were obtained by 1 to 2-h application of 5-ALA 0.5% liposomal solution with less side effects [65]. Tretinoin can be used to treat acne, for skin rejuvenation, to treat sun-damaged skin and to prevent epithelial (pre)malignancies because of its ability to regulate sebum production, collagen synthesis and epithelial cell growth and differentiation.[66,67].It has been demonstrated that the effect is promoted by incorporation of tretinoin in liposomes as compared with tretinoin in a conventional cream [68]

CONCLUSION

Topical applications of liposomes is rational, based on clinical data and pharmacological point of view because of their advantages over other application forms.The similarity of lipidcomposition of liposomes and membranes in the epidermis enables the liposomes to penetrate into the epidermal barrier to a higher extent which may result in an increased drug absorption into the epidermis leading to increased effectiveness and reduction of side effects.

Moreover liposomes have the potential to target drugs into the pilosebaceous structures so can be used for treatment of hair follicle and sebaceous gland disorders. Liposomes may also serve as penetration enhancers facilitating the transport of compounds through epidermis. This made liposomes effective in various dermatological diseases such as atopic dermatitis, psoriasis, acne and vitiligo etc.

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