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REVIEW

Liposomal systems as drug delivery vehicles for dermal and transdermal applications

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Abstract Enhancement strategies are necessary to improve the dermal/transdermal bioavailability of drugs applied to the skin due to its amazing barrier, the stratum corneum. Strategies to overcome this barrier, thus improving drug release to the skin include the use of penetration enhancers, specific delivery systems, supersaturated solutions and physical methods (iontophoresis, electroporation and ultrasound). Delivery of active agents to the skin by liposomal carriers has improved topical therapy in the field of dermatology. The interest in these carriers is based on their potential to enclose various types of biological materials and to deliver them to diverse cell types. Particularly, in recent years liposomes have been shown to be a promising drug-delivery system to the skin. Their use may produce several-fold higher drug concentrations in the epidermis and dermis and lower systemic concentrations when compared to conventional dosage forms. On the other hand, special characteristic vesicles like ethosomes, transfersomes and niosomes may be potential transdermal delivery systems for ionic molecules and polypeptides.

Keywords Liposomes · Topical · Transdermal · Delivery systems

Introduction

Past decades have witnessed increased interest in the exploration of new techniques to enhance drug absorption through the skin. Dermal delivery of drugs by liposomal formulations is a recent candidate receiving considerable attention [142, 178]. Successful percutaneous delivery relies strongly on adequate reduction of the barrier properties of the stratum corneum (SC), considered the main skin barrier. Application of high-voltage [178] and laser-light pulse sources are attempts to lower the permeability of this barrier by vaporization in a controlled and precise way, thus creating permeable "windows", which allow percutaneous transfer to be carried out [90]. Iontophoresis may act as a facilitator of ionizable drug delivery across the skin by an applied electrical potential [92, 126]. Electroporation uses short duration high voltage pulses to induce transient increases in skin permeability via the creation of "pores" through the SC lipids [127]. Sonophoresis [14, 104, 126] which uses ultrasound frequencies from KHz to MHz are capable of increasing the permeability of the skin. All these attempts are capable to increase the permeability of the skin.

Chemical permeability enhancers involve solvents like dimethylsulfoxide [30, 43], lecithin [10], cyclodextrin [4, 15, 129], glycerol [91], azone [43, 59, 170], highly concentrated surfactant solutions [42] or supersaturated solutions [61]. They increase permeability of the skin to topically applied agents by raising the fluidity of lipids in the stratum corneum layer. High formulation concentrations of solvents like propylene glycol, 1,3 butylene glicol, dipropylene glycol and ethanol, may remove lipids from the *stratum corneum* (SC) reducing its barrier function [125].

Liposomes have been used in dermatology in combination with classical penetration enhancers, and are expected to act as excipients or as a local drug depot [101]. In addition, their ability to change drug disposition in the body is a possible advantage in the use as drug carrier systems. They are microscopic vesicles that contain amphipathic phospholipids

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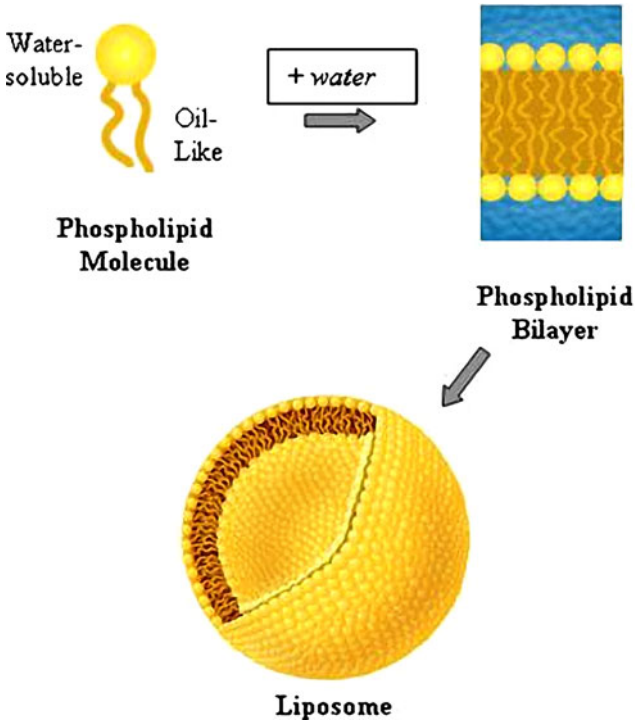

Fig. 1 Representation of liposomal structure built from phospholipid molecules [Encapsula NanoSciences, Technical Summary—an Introduction to Lipid Nanoparticles] http://www.encapsula.com/company.html. Acessed 01/may/2011

arranged in one or more concentric bilayers enclosing an equal number of aqueous compartments. In this form, as a spherical shell they resemble biological membranes (Fig. 1). The thermodynamically stable, lamellar structures form spontaneously when a lipid is brought into contact with an aqueous phase. Drug molecules can either be encapsulated in the aqueous space (hydrophilic compounds) or intercalated into the lipid bilayer (lipophilic compounds) depending upon their physicochemical characteristics.

Many types of liposomal products may be formulated depending on the lipid composition, methods of preparation and the nature of the encapsulated agents. A single bilayer enclosing an aqueous compartment is referred as unilamellar lipid vesicle; according to size, these are known as small unilamellar vesicles (SUV) or large unilamellar vesicles (LUV). If more bilayers are present they are referred as multilamellar vesicles or MLV [162]. Basically, liposomes are prepared from a single lipid or a mixture plus water, and steroids (cholesterol). When added, electrolytes provide isotonicity and enhance the lipid bilayer formation [173]. The ability of phospholipids to form bilayers is due to their amphipathic nature, the presence of a hydrophilic or polar region in the head (attracts water) and a non-polar region or lipophilic tail (repels water). Thus, a lipophilic behavior is shown within the bilayers and a hydrophilic environment between the membranes [28].

Various amphipathic molecules, natural or synthetic, have been used to form liposomes. Natural phospholipids, such as lecithin, the major component of most biological membranes are commonly encountered in liposome preparations. Cholesterol improves bilayer characteristics because it raises the fluidity of the membrane, reduces the permeability to water soluble molecules and improves stability of the bilayer in the presence of biological fluids such as blood/plasma [173]. Size and morphology can be controlled by the method of preparation. Liposome properties also vary depending on the lipids used in its composition (cationic, anionic and neutral lipidic species). Size is an important factor, both for circulation times in blood and disposition in vivo. The ability to control diameter and size distribution of liposomes is of critical importance in therapeutic applications besides the physical integrity and stability of the particles, per se. It is known that the penetration of liposomes through stratum corneum decreases as the diameter increases [28].

Initially, liposomes were attractive as model systems for biological membranes, because of similarities in lipid composition and structure [98]. Their usefulness as drug carriers was discovered by Sessa and Weissman [140], who reported the encapsulation of lysozime in multilamellar vesicles (MLV). Due to their entrapping ability, biodegradable and non-toxic nature, liposomes have several potential applications. They can be safely administered without serious side effects and are thus, useful as drug delivery vehicles.

Liposomes have been investigated extensively as a drug carrier system by various routes of administration and are accepted as potential carriers for a variety of drugs that include low molecular weight compounds, therapeutic proteins and diagnostic agents. One of the basic goals of chemical therapeutics is to deliver the drug efficiently and specifically to the diseased site. Some drugs may be delivered in the free form, whereas others require a carrier in order to reach and enter their final destination because of: (a) rapid clearance from the area of introduction or circulation or (b) obstruction by biological barriers, which cannot be permeated [107]. By altering the biodistribution of entrapped substances and protecting the enclosed materials from inactivation by host defense mechanism, liposomes can be used as vehicles for specific delivery of therapeutic drugs to target organs [107]. Moreover, liposome-encapsulated drugs exhibit better stability, penetration and efficacy at lower dosage.

The toxicity of antimicrobial [123, 143], antiviral [144] and chemotherapeutic agents [58] may be reduced by liposomes. As immunological adjuvants [97] they also showed the ability to modulate or potentiate the immunogenicity of antigenic substances. Accordingly, many drugs and antigens have been incorporated into liposomes and recently they have been demonstrated to be efficient vehicles for

Table 1 Liposomes for systemic administration approved for clinical use

Product	Drug	Lipid formulation	Marketed by	Indication	References
Doxil™, Caelyx™	Doxorubicin	PEGDSPE:HSPC: Cholesterol	Alza Corporation (formerly Sequus)	Kaposi sarcoma in AIDS; Recurrent Ovarian cancer; Metastatic Breast Cancer	[23, 72, 130]
Myocet™	Doxorubicin	DSPE:HSPC: Cholesterol	Alza Corporation (formerly Sequus)	Advanced (Metastatic Breast Cancer)	[130]
Daunoxome™	Daunorubincin citrate	DSPC:Cholesterol	Gilead Sciences (formerly NeXstar)	Kaposi sarcoma in AIDS	[72, 130]
Ambisome™	Amphotericin B	HSPC:DSPG: Cholesterol	Gilead Sciences (formerly NeXstar)	Serous fungal infections; Cryptococcal meningitis in patients HIV	[23, 72]
Amphotec™	Amphotericin B	Cholesteryl sulfate	Alza Corporation (formerly Sequus)	Serious fungal infections	[72]
Abelect™	Amphotericin B	DMPC:DMPG	Élan Corporation (formerly, The Liposome Company)	Serious fungal infections	[72]

gene therapy [23, 64, 72, 73, 79, 179]. Investigations reported in 2010 describe the development of several injectable liposome-based formulations licensed for human use [99, 130]. Table 1 shows examples of liposome preparations currently approved for clinical use.

Liposomes as drug carriers into/through the skin

Liposomes have a great potential as drug delivery systems, not only intravenously, but also as carriers of drugs to be effectively delivered on and through the skin [77, 111]. Their topical use for transdermal delivery depends on characteristics as size, surface, charge and chemical composition [22, 28, 35, 43, 106].

Dermal or transdermal drug delivery routes of liposome-entrapped drugs have some advantages when compared to systemic application. They are: (a) Similar to biological membranes, liposomes are able to store water-soluble or amphiphilic and lipophilic substances in their interior or membranes, respectively. [165]; (b) Most conventional vehicles are inefficient deliverers of the active ingredients into the skin because they fail to penetrate the horny layer. Interacting with the similar skin lipids, liposome bilayers may easily improve local drug concentrations [120, 137]; (c) Liposomes may serve as a local depots (reservoir effect) for the sustained release of dermatological active compounds including antibiotics, corticosteroids and retinoic acid due to the penetration capacity of individual phospholipid molecules into the lipid layers of the stratum corneum (SC) and epidermis [53]; (d) Liposomes can decrease systemic absorption and minimize collateral symptoms due to a reservoir effect [45, 78]; (e) Phospholipid-containing liposomal formulations may act as penetration enhancers and facilitate dermal delivery. By interacting with the SC they destabilizes the lipid matrix by fusing or mixing and increase the drug flux through the skin [80, 81]; (f) Liposomes may act as rate-limiting membrane barriers for the modulation of systemic absorption, i.e. they constitute a controlled transdermal delivery system [136].

Cosmetic properties of liposomes, such as moisturizing and restorative actions were initially the reason for use in dermatology [94]. Their usefulness as enclosing and delivering systems of different biological materials to epidermal cells or even deeper cell layers was later investigated.

Drug-containing liposomes when applied to the skin begin to merge with the cellular membranes and the payload of active materials is released into the cells. Therefore, it is not only a direct delivery system into the intended cells, but also one active for a long period of time [137]. Drugs may also be released at target sites in skin appendages, increasing systemic absorption [45].

It has been shown that vesicular preparations produce better results in the treatment of acne vulgaris in relation to conventional ones, by releasing drugs on targets in skin appendages [44]. In vitro permeation and in vivo deposition studies using hamster flank and ear models showed that liquid state liposomes were successful in delivering finasteride to pilosebaceous units [146].

The role of vesicles as topical delivery systems may vary with type and composition. In the field of vesicular transport systems, studies were reported using classic liposomes [12, 22, 28, 45] as well as novel systems specially designed as alternatives to improve drug delivery into skin [1, 5, 6, 8, 9, 35, 45, 47, 48]. The vesicles act as carriers by providing a deposit of topical compounds in the skin, thus improving release and the transdermal drug delivery. A variety of lipids and surfactants can be used to prepare vesicles, which are generally composed of phospholipids (liposomes) or non-ionic surface compounds (niosomes). Vesicle composition and methods of preparation in addition to physicochemical properties (size, charge, thermodynamic state, and

deformation) can influence their effectiveness as drug delivery systems [142].

Liposomes as dermal delivery systems

Miscelaneous dermatological applications

Topical liposomal preparations containing encapsulated compounds have recently attained commercial viability. The first one, a topical antifungal preparation contained 1% econazole in a liposomal gel form and was marketed in Switzerland in 1988 as Pevaryl Lipogel® by Cilag AG [108]. A formulation of melanin-encapsulating liposomes in spray form (Lipoxome®) delivers melanin selectively to the hair follicle and the hair shaft to stain hair follicles of people with bold, white or grey hair [31].

The treatment of many dermatological diseases by topical application is expected to be more efficient if a significant concentration of the drug is retained in the living epidermis and dermis. This means that the topical drug must reach the site of action and stay there in an effective concentration for a prolonged time. There are drugs, which are known to have severe side effects when administered by conventional topical administration. Glycolic acid, used in cosmetic products as an exfoliative agent and moisturizer has an irritant effect when applied on the skin. Loading glycolic acid [119] on to liposomes showed the advantage and feasibility of this topical controlled delivery system by reducing its side effects. Retinoids, drugs useful in the treatment of skin pathologies like acne and psoriasis and in the treatment of many tumors, were recently shown to have reduced side effects when applied by vesicular systems as liposomes [154]. Decreased skin burning and increased drug stability after exposition to light was demonstrated by the use of this delivery system.

The results have shown that all liposomal systems deliver increased amounts of drugs to the site of action as compared to conventional solutions, suspensions, or gel dosage forms. Examples of drugs carried are, progesterone [100], betamethasona dipropionate for treatment of atopic eczema [137] and dexamethasone in rats [145]. Enhanced drug delivery into skin has also been reported for disorders such as psoriasis, mycosis, idiopathic hirsutism and cutaneous infections [83]. In these systems, liposomal delivery results in the formation of a large drug reservoir on the skin, which is useful in local treatments. The findings suggest a reduction of drug dosage and skin irritation when a liposomal system is used. Several other liposome-based drugs were used for controlled and localized delivery by the topical route (Table 2).

Liposomes may also be used to deliver therapeutic doses of a wide variety of peptides (Ciclosporyn A) to skin tissues by topical application [109], as well as recover the barrier function of the stratum corneum (SC) in injuries like wounds and burns [96, 128]. Other authors [29, 63] have studied topical application of liposomes with composition similar to SC on the epidermal barrier of hairless mice. They reported higher recovery rates of the skin barrier when compared to a mechanical mixture of lipids.

Skin cancer treatment

Topical application of liposomal systems is another promising field in the treatment of skin cancer, the most common in humans. Yarosh et al. [171, 172] have treated xeroderma pigmentosum or skin cancer in patients with a liposomal system containing DNA repair enzymes. A bacteriophage T4-produced DNA repair enzyme (T4 endonuclease V) is able to substitute the UV-damaged enzyme complex in humans and initiate excision repair. In cell cultures, the defect in DNA repair has been corrected by the intracellular delivery of bacterial DNA incision repair enzyme, T4 endonuclease V. Treatment of the DNA-repair-deficiency in patients with skin diseases was carried out with T4N5 liposome lotion. Increased removal of DNA damage was shown in the first few hours after the treatment [171].

In another study, daily applications of T4N5 liposome lotion to sun-damaged skin in 30 xeroderma pigmentosum patients (with a history of skin cancer or actinic keratosis) during 12 months, significantly lowered the rate of production of new actinic keratoses and basal cell carcinomas [172].

The incidence of non-melanoma skin cancers as basal cell (BCC) and squamous cell carcinomas (SCC) is increasing in recent years [93, 149]. A new effective and selective non-invasive treatment, Photodynamic Therapy (PDT) has been developed for therapy of several kinds of cancers. In PDT, administration of tumor-localized photosensitizers is followed by photoirradiation (non-ionizing laser light), which initiates mechanisms of cellular destruction in the neoplastic area [28, 32, 33]. The photodynamic treatment can be considered to be selective per se, as toxicity to the tumor tissue is induced by local activation of the photosensitizer, while normal tissues not exposed to light are preserved [117].

A prodrug, 5 aminolevulinic acid (5-ALA) is mainly used in the PDT treatment of BCC and SCC by systemic or topical application to skin tumors. The 5-ALA application leads to endogenous porphyrin accumulation, particularly Protoporphyrin IX (PpIX), a known photosensitizer. However, 5-ALA is a hydrophilic drug that poorly crosses biological barriers such as stratum corneum (SC) in the skin and may cause recidivism in some kinds of neoplasms. Hence, improving the uptake of 5-ALA would be expected to increase the efficiency of PDT [32, 51, 117]. Solubilization the prodrug into bilayers such as liposomes, which act

Table 2 Vesicular systems for dermal deliveries in vitro and in clinical studies

Drug	Vesicular system	Indication	References
Fluconazol	Lipossomes	Antifungal	[2]
Econazol	Liposomes	Antifungal	[108, 135]
Melanin	Liposomes	Hair removal associate to laser therapy	[31]*
Lidocaine	Liposomes Transfersomes	Local anaesthesia	[38]*, [53]*, [147]* [124]*
Benzocaine	Liposomes	Local anaesthesia	[106]
Tetracaine	Liposomes	Local anaesthesia	[52]*, [53]*
Betamethasona Dipropionate	Liposomes	Topic eczema/psoriasis	[84]*
Tretnoin	Liposomes	Acne treatment	[115]*
Dithranol	Lipossomes	Psoriais treatment	[1, 132]*
T4N5	Liposomes	DNA repair enzymes	[171, 172]*
Glycolic acid	Liposomes	Exfoliant and moisturizing	[119]
Retinoids	Liposomes	Acne, psoriase	[154]
Methotrexate	Transfersomes	Antineoplasic for psoriasis treatment	[155]
Bupivacaine	Liposomes	Local anaesthesia	[70]
Cafeine	Liposomes	Hyperproliferative desease	[150]
Triancinolone acetonide	Liposomes	Topical corticosteroid	[69]
Diclofenac diethylamine	Liposomes	Antinflammatory	[87]
Oestradiol	Liposomes	Sex hormone	[40]
Retinoic acid	Liposomes	Acne and psoriasis	[56, 105]
Clindamicin phosphate	liposomes	Antibiotic for acne treatment	[3, 28]
Enoxacin	Liposomes and Niosomes	Antibiotic	[49]
Alpha-interferon and Ciclosporyn A	Liposomes	Peptidic drugs (imunossupression and psoriais)	[109]
Buflomedil hydrochloride	Liposomes	Recovering barrier function	[128]
No drugs, only lipids from natural sources in liposome composition	Liposomes	Recovering barrier function	[29, 63]
5 animolevulinic acid and its derivatives	Liposomes	PDT of skin cancers	[32, 33, 62, 120]

(*) References related to clinical trials

as skin drug localizers could improve tumor selectivity and photodynamic efficiency. Improved biodistribuition and consequently the local concentration of the drug would optimize topical therapy of skin cancers. Previous studies of 5-ALA encapsulation in liposomes by quenching fluorescence techniques have demonstrated 5-ALA incorporation in micellar and liposomal systems [121].

A preparation of liposomes having a lipid composition similar to mammalian SC (SCLLs) and loaded with the prodrug 5-ALA was proposed by Pierre et al [120] in order to optimize topical 5 ALA-PDT. The amount of 5-ALA loaded SCLL liposomes permeated through skin after 36 h was approximately 7.3 times lower as compared to an aqueous solution and the skin retention was increased 4.5 times. Considering that high interaction of drug and skin and low systemic toxicity is desired in topical formulations, SCLLs showed adequate characteristics as a 5-ALA vehicle.

Liposomes containing 5-ALA were formulated in different average diameters and positive surface charges. The results showed that the efficacy of PDT against murine thymic limphoma cells increased with the decrease in the average diameter of liposomes; 5-ALA-containing liposomes with diameters smaller than 63.5 nm enhanced PDT efficacy in comparison with 5-ALA alone. On the other hand, no differences were found with liposomes with different surface charges [86]. In another investigation [62] 5-ALA was entrapped in liposomes made of dimiristoyl-PC or glycerol dilaurate. In both formulations, PpIX expression increased in dorsal rat skin and pilosebaceous units, compared with free 5-ALA. However, decreased PpIX expression took place in hair bulbs after ionthophoretic delivery.

Hydrophobic 5-ALA derivatives were also investigated for use in PDT of skin cancers [11, 32, 33, 122]. These prodrugs are expected to have better diffusing properties because of enhanced lipophilicity and are converted into the parent 5-ALA after breakdown by esterases of the skin. Similarly to other drug molecules, such as anticancer and antiviral steroids and diagnostic agents with different

solubility, more lipophilic 5-ALA ester derivatives originate optimal liposomal formulations. Lipophilic derivatives interact with the lipid domain of the liposome bilayer, offering as main advantages the enhancement of drug incorporation as well as improvement of chemical and physical stability in the liposomal system [60].

Liposomes as transdermal delivery systems

Liposomes have been frequently used in attempts to enhance percutaneous absorption of several compounds like diclofenac [110], betahistidine [112], tetracaine [54] and triancinolone [46, 176]. No detailed explanations are available about the mechanism by which such large entities as liposomes can cross the skin layers more efficiently than smaller molecules. It has been proposed that a follicular pathway contributes to the liposomal delivery of drugs into the deeper skin strata. Liposomes delivery through skin is very dependent on size. Schramlova et al. [138] reported that liposomes up to 600 nm in diameter penetrate through skin rather easily, whereas liposomes with 1,000 nm and more remain interiorized in the stratum corneum. Although the stratum corneum is widely recognized as the main barrier to percutaneous absorption, it is also considered as the main route for penetration. However, recent reports have suggested that, besides the transepidermal route, hair follicles and sebaceous glands may significantly contribute to transdermal delivery.

The real meaning of the follicular route was not previously well accepted because the openings of hair follicles occupy only about 0.1% of the total surface area of the skin. However, hair follicles provide a large space for easy transport of vesicles into the skin, besides being an invagination of the epidermis extending deep into the dermis. This could provide a larger area for potential absorption and may influence the transdermal absorption of drugs [89].

Studies considering liposomes as carriers for targeted drug delivery into pilosebaceous structures have indicated that liposomal encapsulation could benefit the treatment of hair follicle-associated disorders such as acne and alopecia. In addition, the system may be a mediator in accelerated systemic delivery via transport through this pathway [89]. In other studies, liposomes were developed as hair-follicle-selective systems for large and small molecules, including genes, opening the field of gene and/or molecular therapy to restore hair growth or prevent hair loss in androgenic alopecia [168].

Special vesicular systems for transdermal delivery

It is generally agreed that classic liposomes have little or no value as carriers for transdermal drug delivery. Deep skin penetration is prevented and the vesicles remain confined to the upper layer of the SC. Especially designed carrier vesicles able to allow transdermal delivery are recent approaches in modulating delivery through the skin. Several procedures produce liposomes able to deliver molecules into the deeper layers and across the skin, showing better stability, high drug entrapment efficiency or delivery modulation into/through the skin [152]. Table 3 summarizes some examples of special vesicular systems for transdermal delivery.

Ethosomes® are soft phospholipids vesicles that have been found to be very efficient for enhanced delivery of molecules with different physico-chemical characteristics to/through the skin. Changes in ethosome formulation may restrict drug delivery to the skin only or allow full dermal penetration [151]. Ethosomes composed of phospholipids, water and ethanol are known as efficient permeation enhancers [152] by fluidization of the lipid domain of the stratum corneum [5]. An improvement in melatonin transdermal delivery, which usually shows low skin permeation, was obtained using an ethosomal system [35]. The system dramatically enhanced the in vitro skin permeation of *minoxidil* and *testosterone* compared with the ethanolic and hydroethanolic solution or phospholipid ethanolic micellar solution [152]. The deep penetration of a probe into the skin and the efficient delivery of its contents to the cytoplasm were enhanced by ethosomes as compared to a hydroethanolic solution or classic liposomes [153].

A proposed mechanism for the drug enhanced delivery by ethosomes invokes a so called “ethanol effect”. Ethanol is present in relatively high concentrations in this system and it may provide vesicles with soft flexible characteristics, which disturb the organization of the SC lipid bilayer and enhance its fluidity. This would be followed by the transdermal absorption, an “ethosome effect” that includes interlipid penetration and permeation to the disturbed SC, fusion with skin lipids and drug release at different regions along the penetration pathway [153].

Dayan and Touitou [27] compared in vitro skin permeation of an anti-M1 muscarinic activity drug (THP-HCl) in an ethosomal carrier versus classic liposomes. The results showed that the flux of THP through nude mouse skin from ethosomes was much higher than from liposomes, phosphate buffer or a hydroethanolic solution. The quantity of drug remaining in the skin at the end of the 18-h experiment was greater in the ethosomal system than in liposomes or a control hydroethanolic solution. Furthermore, ethosomes have shown a higher entrapment capacity and a great ability to deliver a fluorescent probe to the deeper layers of the skin.

Transfersomes®, are carrier systems constituted by ultradeformable liposomes having an edge activity in the lipid bilayer structure that promotes elasticity and deformability [8] facilitating a rapid penetration through the

Table 3 Some examples of special vesicular systems intended for transdermal delivery

Drug	Vesicular system	Indication	References
Tetracaine	Liposomes	Anaesthetic	[54]
Triancinolone acetonide	Transfersomes, Ethosomes, Niosomes and Liposomes	Topical corticosteroids	[46] [176]
Cyclosporin-A	Liposomes	Immunossupressant drug	[168]
α-interferon		Viral diseases	
Monoclonal antibodies		Restore hair grow	
Plasmid DNA for the human interleukin-1 receptor antagonist (IL-1ra) protein		Genetic therapy	
Minoxidil Testosterone	Ethosomes	Hair loss Testosterone deficiency in man	[152]
Trihexyphenidyl HCl (THP)	Ethosomes	Antimuscarinic (adjunctive treatment of all forms of Parkinsonian syndrome) and for dystonia therapy	[27]
Gap junction proteins (GJP)	Transfersomes	Transcutaneous immunisation	[115]
Insulin	Transfersomes	Diabetis	[17]
Hydrocortisone and dexamethasone	Transfersomes	Corticosteroids	[20] [74]
Ketoprofene	Transfersomes	Antinflammatory	[21]
Bleomycin	Transfersomes	Anti-tumour drug for treatment of non-melanoma skin cancer	[66]
Diclofenac sodium	Transfersomes	Antinflammatory	[18, 47]
Oestradiol	Transfersome	Sexual hormone	[39, 41]
Hydrocortisone Nicotine	Proliposomes	Corticosteroid Aid smoking cessation	[24]
Levonorgestrel	Niossomes	Contraception	[163]
Lidocaine hydrochloride	Niossomes	Anaesthetic	[160]
Cyclosporin-A and α-interferon	Niossomes	Immunossupressant drug and Viral diseases	[109]
Estradiol	Niossomes	Sexual hormone for hormonal insufficiencies	[161]
Enoxacin	Niossomes	Antibacterial agent	[49]
Nimesulide	Niossomes	Antinflamatory drugs	[141]
Daunorubicin Hydrochloride	Niossomes	Anticancer drug	[6]
DNA encoding Hepatitis B surface antigen (HBsAg)	Niosomes	Vaccine for genetic immunization against hepatitis B	[164]
Ibuprofen	Proniossomes	Antinflammatory	[71]
Estradiol	Proniossomes	Hormonal insufficiency	[50]
Hepatitis B surface antigen (HBsAg)-	Transfersomes	Transcutaneous immunization against Hepatitis B	[102]
Tetanus toxoid antigen	Vesosomes	Transcutaneous immunization	[103]

intercellular lipids of the SC [7]. These properties are the basis for the mechanism proposed for transfersomes to explain the efficiency of these transdermal carriers. [18]. The hydration energy of polar head groups in highly deformable vesicles is an important factor for penetration. An osmotic gradient generated by differences in the concentration of water between the skin surface and its inside, has been proposed as the major force that drives the penetration of transfersomes [17].

These specific liposomes were developed to penetrate the skin deep enough to reach the systemic circulation [46]. The skin surface must be intact and the application is non-occlusive [18, 68, 155]. *Transferosomes*® have been shown to be versatile for local and systemic delivery of large macromolecules such as various steroids, proteins [8, 116], insulin [17, 19], corticosteroids [20, 74], ketoprofene [21], anticancer drugs [66, 155], and hydrophilic macromolecules [17] in the transport of genetic material and also as potential for vaccine development [126].

In general, *Transfersomes*® are prepared from a mixture of ethanolic phosphatidylcholine from soya bean (SPC) with appropriate amounts of sodium cholate and the required drug [7]. They were also tested as carriers for spontaneous transport of macromolecules in immunologically active form through the skin. Gap junction proteins (GJP) incorporated into transfersomes were applied on the intact skin surface and compared to subcutaneous injections of GJP in transfersomes and other forms as mixed lipid

micelles or classical liposomes. *Transfersomes*® containing GJP were able to increase specific antibody production compared to other delivery systems tested. Mixed micelles and liposomes showed no significant biological response after epicutaneous administration [116].

Transfersomes® containing insulin were applied epicutaneously onto the intact surface of rat and human skin in vivo (non-occlusive) and shown that the drug was carried across tissue with an efficacy of ≥50%. Blood sugar concentration was kept constant for at least 10 h, suggesting that this formulation could be hypoglycemically active when applied on the intact skin [17, 19].

Diclofenac association with ultradeformable *Transfersomes*® carriers had a longer effect and reached concentrations 10 times higher in the tissues under the skin in comparison with drug delivered from a commercial hydrogel. The system was able to penetrate deep in the soft tissue, which is not obtained when the drug was used in a gel. The sustained release of diclofenac from the carrier deposited into the subcutaneous tissue could lower the dose range [18]. In recent observations transfersomes mixed with *Tween 80*®, for maximum deformability of the vesicle membrane, were used for enhanced transepidermal delivery of diclofenac sodium non-occlusively applied to skin. The system showed an increase in transepidermal flux and a well-controlled drug delivery, proving to be a good drug carrier and permeation enhancer [47].

El Maghraby [39] has compared the in vitro skin permeation of oestradiol from diverse formulations: classic and deformable liposomes and an aqueous solution. A higher drug flux through the skin was reached by using deformable vesicles as compared to classic liposomes. In another study [41], the in vitro transdermal delivery of oestradiol from ultradeformable liposomes was compared to saturated aqueous solution containing or not *Span 20*® or *Tween 80*®. The maximum flux of oestradiol through the skin was given by the ultradeformable liposomal system [71]. Other reports show that the lipid bilayer is more elastic in the presence of surfactants [42] concluding that these flexible liposomes are more efficient as transdermal delivery systems [44].

Production of *Proliposomes*® is another way to improve liposomal formulations in relation to stability. They are free flowing particles composed of drugs, phospholipids and a water-soluble porous powder working as a support (sorbitol or another polysaccharide) that increases the surface of dry lipid. The liposomal dispersion is immediately formed after hydration, but the sterilized preparation may be stored in a dried state. By controlling the size of the porous powder component, a relatively narrow range of reconstituted liposome sizes is obtained. Because of these properties, it is concluded that proliposomes appear to be a potential alternative for the design and fabrication of liposomal dosage forms [71]. The method is suitable for preparations in which the material to be entrapped is incorporated into a lipid membrane and contributes to solve problems encountered in the storage of liposomes. Large quantities of proliposomes can be prepared and stored in a dry state before use and resuspended when required to give batches of reproducible vesicles over a long period of time. Proliposomes have been prepared for administration by several routes, like oral [65, 88], injectable [133, 165] and nasal [76].

Chung [24] studying the release of nicotine powder from proliposomes across rat skin found that the initially retarded drug flux became constant afterwards and considered the preparation suitable as a sustained transdermal dosage form.

Industrial manufacturing of another kind of liposome called *Niosomes*® represents an attractive strategy. They have structure and properties similar to that of liposomes, are formed by *synthetic non-ionic surfactants*, show improved *chemical stability* and relatively low cost of materials [163].

Niosomes® may be formed from a diverse array of amphiphiles bearing sugar, polyoxyethylene, polyglycerol, crown ether and aminoacid hydrophilic head groups. The non-ionic surfactant vesicles appear to be similar to liposomes in terms of physical properties, are prepared in the same way and under a variety of conditions, forming unilamellar or multilamellar structures [175]. Niosomes have application in topical and systemic products and have also been used to encapsulate lidocaine [160], peptide drugs [109], estradiol [161], enoxacin [49], anti-inflammatory drugs [141], anticancer substances, anti-infective agents [6] and also non-invasive vaccines [164]. Several studies explored the transdermal delivery by niosomes. [67, 95, 139].

The enhanced delivery of niosome encapsulated drugs through stratum corneum has been observed by Junginger [75]. The small vesicles were found in both the upper layer of stratum corneum and in deeper skin but showed diverse behavior. In the former layer the *Niosomes*® membrane reorganized into individual components, but on arriving at the deeper layers, *Niosomes*® were reformed. The higher flexibility of these bilayers is said to be responsible for the improved transdermal penetration [16, 161].

The mixing of *Niosomes*® with skin lipids in the intercellular layers could be a mechanism contributing to the enhancement of drug permeation through the skin. One of the possible reasons for the mixing could be a structure modification of stratum corneum. It has been reported that the intercellular lipid barrier in SC could be dramatically changed to a looser and more permeable one by treatment with *Niosomes*® [25, 112]. Accordingly, the vesicles can act as permeation enhancers, predominantly in the intercel-

lular lipids of stratum corneum, by increasing the fluidity and weakness of the SC [157]. Thus, *Niosomes*® enhance skin permeation of drugs by disrupting the membrane properties of SC and directly fusing into the upper layer of skin [113].

Although *Niosomes*® were shown to have good chemical stability during storage, there may be problems in the physical stability of dispersions. Like liposomes, aqueous dispersions of niosomes may have a limited shelf life due to aggregation, fusion, leaking or hydrolysis of entrapped drugs. The disadvantage may be overcome by using *Proniosomes*, the delivery system produced in a dry form, which produces aqueous niosome dispersion similar to those produced by conventional methods when hydrated immediately before use. [131].

The sterilized material stored in a dry state is dispersed/dissolved to form an isotonic multilamellar niosomal suspension by addition of water as needed [71]. It provides additional convenience in transportation, distribution, storage and dosing. The non- ionic surfactant components used in these systems are Spans (sorbitan esters) or Tween (polyoxythylene sorbitan esters), cholesterol and phospholipids.

Proniosome formulations containing ibuprofen [71] and estradiol [50] have been investigated. In these studies proniosomes derived from *Niosome*® suspensions appear to be as good as or better than conventional niosome preparations in terms of morphology, particle size and drug release performance, suggesting that they may be appropriate preparations to use as a hydrophobic drug carrier. Proniosomes can also act as penetration enhancers, which is useful for increasing the permeation of many drugs [80, 174]. The surfactants in these preparations may interact with the solute affecting its permeability through skin [148]. The direct transfer of drug from vesicles to the skin or the penetration enhancer effect by non-ionic surfactants may be contributions to the understanding of the mechanism of drug permeation from proniosomal formulations [50].

Another kind of carrier is defined as *Pharmacosomes*®, a colloidal dispersion of drugs covalently linked to phospholipids. They are useful mainly for the entrapment of polar drug molecules in order to avoid the usual problems associated to low drug entrapment, leakage and poor stability in conventional liposomes. This approach was initially used to produce pharmacosomes of pindolol, a β-receptor blocking agent [156] but it was not tested in topical or transdermal applications. However, it could turn out to be an interesting way to deliver small and hydrophilic drugs in these instances.

Vesicles called *Vesosomes*® are vesicles inside another vesicle and are useful in topical immunization. They were developed recently as a promising system for transcutaneous immunization [102, 103].

Interactions between liposomes and skin

To further understand the pharmacological potential of liposomes, it is important to investigate their interaction with epidermis. Observations in this field suggest that only a compromised epidermal barrier enables intact liposomes to penetrate the skin, like in skin cancers and psoriasis vulgaris, where the permeability barrier is defected [57, 85].

Several mechanisms were proposed to explain the liposome-skin interaction. Composition and structure of the vesicles [80], size [138, 139] as well as charge [114] fluidity [82, 118] and vehicle [55] affect liposome ability to transfer or deposit drugs in SC [134, 158] or in the deeper skin strata [12, 13]. The SC of humans, mice and pigs has been shown to be devoid of phospholipids. The lipid composition is rather nonpolar in nature and consists primarily of ceramides (40%), cholesterol (25%), fatty acids (25%) and cholesteril sulfate (10%) [169]. These lipids are termed "skin lipids" and are arranged in bilayer sheet structures that fill the intercelullar space in the SC. The primary pathway for the transport of water and other drugs is believed to reside mainly in these bilayer structures. It is hypothesized that liposomes can cross the stratum corneum and act as micro reservoirs from which drugs may be slowly released. But the mechanism by which liposomes are able to increase the concentration of bioactive compounds both in epidermis and in the deeper layers of the skin is still under investigation. Several authors have proposed that liposome action in the transfer of drug through the skin is probably due the composition of the vesicle bilayer, similar to that of skin lipid, leading to a fusion of vesicles in the intercellular skin space [36]. Du Plessis [34] suggested that phospholipids in liposome bilayers could mix with the intercellular lipids of the stratum corneum (SC) originating an intracutaneous depot of active compound. Another explanation for the mechanism by which liposomal entrapment improves drug transfer into the skin would be the association between SC bilayers and liposomes, which after dehydration bind strongly to the surface of the skin. The surface liposomal—lipid bilayers containing drug would provide a reservoir allowing sustained release of the drug, especially lipophilic ones across the SC into the dermis and blood vasculature [167].

Egbaria and Weiner [37] reported that drug transfer is only efficient when the vehicle lipidic structure is in a bilayer configuration. The authors prepared liposomes using lipid components similar to those found in the SC (skin lipid-based liposomes) and demonstrated the superior efficiency of these when compared to phospholipid-based liposomal systems. In vitro and in vivo studies have shown that it occurs because of the greater molecular mixing of liposomal bilayers with those of the SC bilayers. Thus, to improve liposome penetration into the skin, the chemical

similarity of vesicle and lipidic composition of stratum corneum should be the approach of choice [26, 121].

Different methods such as differential scanning calorimetry [177], freeze-fracture electron microscopy [159] and confocal laser scanning microscopy [82] have been used to investigate the mechanism of stratum corneum-liposome interaction but it is still not entirely clear. According to these studies, lipid penetration into skin is greatly dependent on liposome composition and it is generally accepted that liposomes cannot penetrate intact, healthy skin. However, interaction between dispersed molecules and skin lipids may occur in normal skin. Indeed, Betz [12] studying the interaction proposed that penetration of phospholipids from a liposomal formulation is achieved in deeper layers of dermis probably by a follicular pathway. In contrast Foldvari [53] claimed that intact liposomes may penetrate into the skin (deposition in the dermis) although the structure and size of the vesicles demonstrated in the dermis differed markedly from those originally applied.

Entrapped drug penetration can be enhanced during the interaction between liposomal and epidermal lipids but depending on the physicochemical properties of liposomes, changes in skin intercellular lipid structures may be limited to the interface or extended to deeper parts of the stratum corneum.

Challenges and limitations of liposomal systems

The number of liposomal systems available in the market is far behind the euphoric expectations raised in the 1980s due to the relatively high cost of the products and problems related to physical stability. Often products need to be lyophilized requiring tedious reconstitution prior to administration. Optimal liposomal formulations should have high entrapment efficiencies, narrow size distributions, long-term stabilities and ideal release properties. Consequently, production methods require the potential use of a wide range of molecules as ingredients (e.g. lipids/phospholipids) to promote liposome stability. In addition, liposomes should be free of toxic solvents and detergents. Industrial production of liposomes began only in mid-1980 due to delays in solving technological problems and quality control of production processes on a large scale as the supply of high quality raw material (lipids and phospholipids), reproducibility of the process in the large-scale production, validation tests in the quality control of the final product, long term physico-chemical stability of liposomal preparations and production of sterile liposomal products. However, many problems need to be overcome before they can be commercialized. The direct mixing and homogenization are the most used preparation methods for scale-up of liposomes what produces vesicles in micro size, being difficult to reach nano size range if required. Another disadvantage is the high cost of ingredients such as phospholipids has hindered the emergence of products for industrial and clinical uses. Alternatives for resolving such costs to expand the use of these delivery systems along with changes in procedures for scale-up to industrial production are still challenges. There are numerous lab-scale and a few large-scale techniques for liposome preparation giving rise to vesicles of different sizes and special characteristics. However, sensitive substances may be exposed to mechanical stresses, extreme pHs values, harmful chemicals as detergents and volatile organic solvents during the preparation. Conventional and novel preparation techniques have been introduced, each with their own advantages and possible limitations. Nevertheless, the development of research in this area will provide in the future the appearance of new products and patents related to liposomes for dermal and transdermal delivery.

Conclusions

In conclusion, liposomes constitute a selective drug delivery system into/through the skin, which in a lot of cases has superior performance and pharmaceutical characteristics compared to other dosage forms. Novel liposomal systems, like *Ethosomes®*, *Niosomes®*, *Transfersomes®*, *Proliposomes®*, *Proniosomes®, Pharmacosomes® and Vesosomes®* are rational strategies to consolidate the vesicle systems for topical/transdermal use, but depend on the solving of effectiveness, safety and manufacturing problems.

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