EXPERT OPINION

Liposomes in cosmeceutics

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Introduction: Cosmeceuticals are cosmetic products with biologically active ingredients purporting to have medical or drug-like benefits. Some cosmeceuticals can act effectively when reaching their target sites in the deeper layers of the skin. However, the barrier nature of skin causes significant difficulties for compounds to be delivered through. Therefore, scientists are investigating various strategies to overcome these barrier properties. Liposomes have been claimed to improve the topical delivery of compounds.

Areas covered: This paper offers a brief overview of current approaches in the research and development of liposomal formulations to improve the performance of cosmeceuticals, from recent literature. This review deals with the potential of liposomes as a skin delivery system for cosmeceuticals, with a focus on the clinical application of liposomes.

Expert opinion: Liposomes are well-known vesicular cosmetic delivery systems. The topical application of liposomes offers a wide range of advantages including increased moisturization, restoring action, biodegradability, biocompatibility and extended and slow dermal release. Their similar structure to biological membranes allows penetration into the epidermal barrier, compared with other delivery systems. The incorporation of cosmeceuticals using suitable delivery systems is important in the management of cosmetic disorders.

Keywords: cosmeceuticals, dermatology, drug carrier, liposomes, topical delivery

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1. Introduction

Targeted drug delivery implies selective and effective localization of pharmacologically active ingredient at preselected target in therapeutic concentration, while restricting its access to nontarget areas, thus maximizing the effectiveness of the drug [1]. Skin is the largest, easily accessible organ for local and systemic drug administration. But the skin behaves as a passive barrier to the penetrant molecule. Cosmeceuticals refers to the combination of cosmetics and pharmaceuticals. Cosmeceuticals are cosmetic products with biologically active ingredients purporting to have medical or drug-like benefits. Some cosmeceuticals can act effectively when reaching their target sites in deeper layers of the skin [2]. The main barrier is located in the outermost layer of the skin, the stratum corneum, which contains flattened dead epidermal cells (corneocytes) embedded in hydrophobic lipid domains [3]. The stratum corneum provides the greatest resistance to penetration, and it is the rate-limiting step in percutaneous absorption [4]. The corneocytes of stratum corneum are entirely surrounded by crystalline lamellar lipid regions. The cell boundary, the cornified envelope, is a very densely cross-linked protein structure, which reduces absorption of drugs into the cells. For these reasons, most of the active substances applied onto the skin are diffusing along the lipid lamellae in the intercellular regions [5]. For successful dermal or transdermal delivery, a reversible overcoming of skin barrier is required. Therefore, many strategies have been assessed to overcome the barrier function of the stratum corneum and to improve drug transport into the skin [6,7]. The carrier is one of the most important entities required for successful targeted drug delivery. Consequently, as a vehicle for active substances and targeting to skin layers, lipidic carriers such as liposomal systems

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Article highlights.

- Cosmeceuticals are cosmetic products with biologically active ingredients purporting to have medical or drug-like benefits.
- Due to the similar lipids with epidermis, liposomes can also improve dermal drug delivery while reducing systemic absorption.
- Liposomes help to fix active ingredients to the outermost skin layers as desired for cosmetic products.
- Empty liposomes show occlusive properties and can retain and increase the skin humidity and consequently restore the barrier functions of the skin.
- Liposomal vesicles improve availability of the drug at the site that will also reduce the dose and, in turn, the dose-dependent side effects such as irritation and staining.

This box summarizes key points contained in the article.

are gaining more interest. Lipid-based drug delivery is becoming more popular because lipid materials are easily characterized, contain a high range of well-defined/tolerated surfactant molecules and can be developed for several administration routes. These systems are particularly suitable for topical delivery because many suitable compounds are soluble in these materials, they do not irritate the skin and they have extremely low acute and chronic toxicities [8]. Additionally, lipid particles can be used as penetration enhancers of encapsulated drugs through the skin because of their excellent occlusive and hydration properties.

2. Liposomes

The word 'liposome' is derived from the Greek: 'lipo' referring to their fatty constitution and 'soma' referring to their structure. A liposome is a spherical vesicle with a membrane composed of a phospholipid and cholesterol bilayer. Liposomes are simple, microscopic vesicles in which an aqueous volume is entirely enclosed by a membrane composed of lipid molecule [9]. Kind of structure makes it possible to incorporate lipophilic drug into lipid bilayers as well as hydrophilic drug into the aqueous compartment [10]. To target the active ingredients, the lipid bilayer can merge with the cell membrane, thus delivering the liposome contents [9]. Due to the similar lipids with epidermis, liposomes can also improve dermal drug delivery while reducing systemic absorption [11]. This includes the ability of lipid vesicles, depending on lipid composition, to alter cell membrane fluidity and to fuse with cells. In early studies, liposomes containing stratum corneum lipids have been tested in order to enable better skin penetration [12]. Usually, liposomes are classified into three categories on the basis of their size and lamellarity (number of bilayers): i) small unilamellar vesicles (SUVs) or oligolamellar (OLVs), ii) large unilamellar vesicles (LUVs) and iii) multilamellar vesicles (MLVs) [13]. Liposomes are one of the most investigated drug carrier systems due to their unique properties. The first work using liposomes as a drug delivery system for the local treatment of skin diseases was performed by Mezei and Gulasekharam (1980) [14]. and appeared in the cosmetic market in 1986 [15]. The suggestion was based on drug disposition data of the triamcinolone acetonide-loaded phospholipid liposomes formulated as lotions or gels. Encapsulation of triamcinolone acetonide into liposomes resulted around five times increase in drug skin deposition. The work of Mezei suggested that dermatological application of liposomal formulations compared with conventional ones led to increased drug skin deposition and decreased its systemic biodisposition [16]. Further studies were aimed to induce a local rather than a systemic effect [17]. Different penetration pathways into and through the stratum corneum are known: the transepidermal pathway, which means mainly intercellular penetration, and the transappendageal routes via sweat glands and hair follicles [18]. Lipid composition, size and surface charge of liposomes, and drug solubility affect stability and pharmacokinetic profiles of liposomes and drug release pattern [10]. Liposome formulations of many different drugs show a significant increase in therapeutic activity compared with nonliposomal formulation. Therefore, recently, a great deal of interest in the use of liposomes in skin gels or skin creams has been generated in the field of dermatology and cosmetics. Liposomes help to fix active ingredients to the outermost skin layers as desired for cosmetic products [19].

2.1 Advantages of topical liposomes

The major advantages of topical liposomes in dermatology are i) to reduce serious side effects and incompatibilities that may arise from its drug localizing characteristics and thus avoiding systemic absorption; ii) to increase drug accumulation at the skin due to the mimic epidermis composition, which enables liposome substantivity with biological membranes; iii) nontoxic and biodegradable characteristics of liposomes; iv) easy to scale up for manufacturing [20]; v) to encapsulate both water- and lipid-soluble active components [19]; vi) washing out may be delayed, which provides water-resistant character [21]; vii) to moisturize and restore action of the constitutive skin lipids membranes; viii) to localize drug depots in the skin, resulting in sustained release of dramatically active compounds, so improving the therapeutic index of the drug at target site while reducing the toxicity profile to its minimum [9]. Besides its unique beneficials, liposomes show some disadvantages such as low stability, low encapsulation efficiency, high cost of manufacturing, degradation by hydrolysis or oxidation, sedimentation, aggregation or fusion of liposomes during storage [10,22].

3. Indications for liposomes as drug carriers in cosmeceutics

3.1 Acne

Acne vulgaris (commonly called acne) is a skin disease that is most common during adolescence, afflicting more than 85% of teenagers [23]. Acne is an inflammation of sebaceous glands

and associates with the immune response to various Gram-positive bacteria including chiefly *Propionibacterium acnes* (*P. acnes*) and *Staphylococcus epidermidis* that colonizes sebum-rich follicles [24]. Clindamycin hydrochloride liposomes were prepared using either soya lecithin and cholesterol or hostaphate and cholesterol. Clinical treatment of acne vulgaris with a lotion of liposomal drug shows better efficacy than nonliposome lotion (especially of the treatment of pustules where clinical improvement was 77% of initial number). Application of a conventional lotion solution, a nonliposomal emulsion lotion and a liposomal emulsion lotion resulted in decreases of 42.9, 48.3 and 62.8%, respectively, in the total number of lesions after a 4-week treatment. The result supports the possibility of developing products utilizing the liposomal dosage form that are superior to the existing dosage forms for topical therapy [25]. Benzoyl Peroxide is a useful agent for treatment of acne, which acts by inhibition of the *P. acnes* in the pilosebaceous units. But its disadvantages such as bleaching of dyed clothing and local irritation with burning and erythema may limit patient compliance. A comparative double-blind study in 30 patients after 3 months showed a significant improvement in the therapeutic response (about two times) of treatment with liposomal benzoyl peroxide as compared with a conventional benzoyl peroxide gel, with obvious reduction in unfavorable symptoms and bleaching of clothing [26]. Liposomes were shown as an interesting carrier for tretinoin in skin disease. Liposomal tretinoin dermal delivery was found to be affected by several factors including vesicle composition, morphology and size of liposomes. In particular, it has been shown that negatively charged liposomes showed strongly improved newborn pig skin hydration and tretinoin retention in the skin [27]. In a comparative clinical evaluation of liposomal gel of benzoyl peroxide and tretinoin for acne, it was concluded that the liposomal tretinoin gel was shown to have better response in the treatment of comedones, whereas the liposomal benzoyl peroxide gel of this investigation showed a predominant response in the treatment of papules and pustules. Hence, concomitant therapy with liposomal tretinoin and liposomal benzoyl peroxide gel is expected to give more effective treatment of acne [26]. Cationic liposomes consisting of double-chained cationic surfactant, phosphatidylcholine, were found to increase delivery of retinoic acid about twofold suggesting the potential of the use of the cationic liposomes for the intradermal delivery of lipophilic drugs such as retinoic acid [28]. *In vitro* permeability experiments with [3 H]-trans retinoic acid show that its encapsulation into stratum corneum lipid liposomes not only prolongs drug release but also promotes drug retention by the viable skin in order to reduce systemic absorption and the side effects associated with topical application of the drug to skin [29]. Lauric acid was shown a suitable antimicrobial activity against *P. acnes*. However, a setback of using lauric acid as a potential treatment for inflammatory acne is its poor water solubility. Lauric acid was incorporated into a liposome formulation to aid its delivery to *P. acnes*. It was demonstrated that the antimicrobial activity of lauric acid was not only well maintained in its liposomal derivatives but also enhanced at low lauric acid concentration. Further study found that the lauric acid-loaded liposomes could fuse with the membranes of P. acnes and release the carried lauric acid directly into the bacterial membranes, thereby killing the bacteria effectively. Since lauric acid is a natural compound that is the main acid in coconut oil and also resides in human breast milk and liposomes have been successfully and widely applied as a drug delivery vehicle in the clinic, the developed lauric acid-loaded liposomes proposed as a great potential of becoming an innate, safe and effective therapeutic medication for acne vulgaris and other *P. acnes*-associated diseases [11]. Salicylic acid, a commonly used medicine in the treatment of acne, shows some degree of irritation. Salicylic acid was released at a controlled rate over an extended period of time from liposomal formulation. This pattern of release makes an opportunity to prepare less irritant dosage form of salicylic acid with lower frequency of application [30].

3.2 Occlusive effect

Hydration effect is of great interest for the dermatologists, since the hydration of the skin is considered to be a marker of its state of health, in the same way that skin dryness is a sign of malfunction. The penetration of active compounds into human skin depends strongly on skin hydration, which can be influenced by occlusive compounds [31]. The water content of the skin is 10 – 20% [32]. Deficiency of essential fatty acids, cholesterol and ceramides leads to enhanced transdermal water transport in addition to dryness of the skin (i.e., xerosis) [33]. The application of occlusives prevents water evaporation from the skin to the atmosphere and thus water is retained within the skin [34]. Moisturizing products constitute one of the largest and most important skin care product category. The function of moisturizers is to maintain the stratum corneum hydrated. Dehydrated skin loses elasticity and becomes rigid and brittle, which causes the skin to become rough and flaky [35]. Since many topical preparations have an undesirable esthetic appearance (e.g., petrolatum), the need for novel occlusives is rising [32]. Empty liposomes show occlusive properties and can retain and increase the skin humidity and consequently restore the barrier functions of the skin [19]. The liposome formulations showed higher hydration effects on human skin compared with reference product due to the potential occlusive effect of the phospholipid film deposited on the skin surface. With decreasing phospholipid content in the liposome formulation, a decrease in the hydration effect and its influence on the skin barrier function was observed. In order to increase the skin water content significantly, egg phospholipids are suggested to be used for the preparation of the topical formulation rather than other investigated phospholipids [17]. Glycolic acid is used in many cosmetic products as exfoliant and moisturizers [36] but it has a substantial potential for skin irritation

as far as burning. Glycolic acid-loaded liposomes represented a good delivery system to modulate release rate, which provide the best condition to control its adverse effects [37]. Liposomes fabricated with stratum corneum lipids and in particular ceramides have been applied in the treatment of atopic dry skin in order to restore the barrier function and to provide a drug delivery system at the same time [38]. The composition and properties of liposomes are the key factors in their interaction with and possible penetration into the skin. Liposomes also provide valuable raw material for the regeneration of skin by replenishing lipid molecules and moisture. Lipids are well hydrated and, even in the absence of active ingredients, humidify the skin. Often this is enough to improve skin elasticity and barrier function, which are the main causes of aging of the skin. Therefore, liposomes and liposome formulations have been implied for skin moisturization, due to the potential occlusive effect of the phospholipid film deposited on the skin surface [17].

3.3 Hyperpigmentation and melasma

Facial and neck pigmentations are custom and considerable cosmetic problems that are common in middle-aged women, related to endogenous (hormones) and exogenous factors (cosmetics, perfumes, sun exposure), and often represent paramount causes of emotional distress [39]. 4-*n*-Butylresorcinol is a derivative of resorcinol, which inhibits melanin production as well as the activity of both tyrosinase and tyrosinase-related protein-1. A randomized, double-blind, vehicle-controlled and split-face comparison study investigates the hypopigmenting efficacy of 4-*n*-butylresorcinol at lower concentrations. Liposomal 4-*n*-butylresorcinol 0.1% cream or vehicle was applied to each side of the face twice daily for 8 weeks of 23 patients with a clinical diagnosis of melasma. The melanin index of the 4-*n*-butylresorcinol-treated side showed a significant decrease when compared with the vehicle-treated side proved by mexameter measurements. No adverse reactions such as skin irritation were observed throughout the study. Liposomal 4-*n*-butylresorcinol 0.1% cream was well tolerated and demonstrated significant higher efficacy than vehicle alone in more than 60% of the patients for the treatment of melasma [40]. The whitening effect for hydrogel-containing liposomal linoleic acid was far greater than for free linoleic acid in ethanol or hydrogel-containing linoleic acid evaluated in the ultraviolet (UV) radiation-stimulated hyperpigmented dorsal skin of brownish guinea pigs and UV-stimulated hyperpigmented human upper arm skin. Liposomes might enhance the incorporation of linoleic acid into melanocytes [41]. It was also shown that the permeation rate of linoleic acid in the liposomal formulation was found to be lower than that in the conventional formulation without liposomes, suggesting the increased retention time of linoleic acid in the skin by the liposomal formulation [42]. The percutaneous permeation experiments of linoleic acid-loaded ethosomes (ethanolic liposomal) and transfersomes (deformable liposome) through human stratum corneum-epidermidis membranes were studied and showed that both carriers are accumulated in the skin membrane model as a function of their lipid compositions. The results showed that both vesicular carriers could be a potential system for the topical treatment of hyperpigmentation disorders. On the other hand, the permeation of ethosomes through the skin can be the result of the effect of ethanol both on the stratum corneum lipids and the vesicle fluidity, thus contributing to their superior clinical use to transfersomes [43].

3.4 Vitiligo

Vitiligo is an acquired idiopathic, dermatological disorder characterized by well-circumscribed milky white macules in which melanocytes in the skin are damaged. It may have an important negative impaction on the quality of life, even leading to attempted suicide in some cases [44]. De Leeuw *et al.* assessed the effect of a surgical technique, epidermal blister graft transplantation following the application of liposomal khellin, a psoralen-like compound but with substantially lower side effect, on patients' satisfaction. Its penetration into the hair follicles is enhanced by encapsulating it into liposomes. Subsequent activation of the khellin with UV light stimulates the melanocytes in the hair follicles. Seventy-five percent of the patients were satisfied with the cosmetic result [45].

3.5 Alopecia

The pilosebaceous unit containing hair follicle, hair shaft and sebaceous gland has a unique biochemistry, metabolism and immunology. Targeted drug delivery may enhance current therapeutic approaches to treat diseases of follicular origin. In a growing number of topical studies, liposomes have been shown to target drug delivery to the pilosebaceous unit [46,47]. Androgenic alopecia (male pattern hair loss) is the most common cause of hair loss in men and described by the progressive hair thinning in genetically susceptible men. Hair follicles were shown to be of great importance concerning the penetration and reservoir behavior of topically applied liposomes. In a study, the fluorescent dye-loaded liposomes mainly differed in their sphere diameter, lipid composition and surface charges are compared in their deep penetration into hair follicles with nonliposomal formulation. The penetration depth of the dyes was measured by laser scanning microscopy in histological sections. The liposomes showed a higher penetration depth compared with the standard formulation. Amphoteric and cationic liposomes reached an average relative penetration depth of approximately 70% of the full hair follicle length [48]. Minoxidil is the most widely used drug for the treatment of androgenic alopecia but its mechanism of action on hair follicles remains unknown [49]. Minoxidil-loaded liposome and niosome vesicles were prepared and their percutaneous absorption was examined *in vitro* using vertical diffusion Franz cells and human skin. The results compared with dissolved minoxidil in propylene glycol–water–ethanol solution as a control. Penetration of liposomal minoxidil in epidermal and dermal layers was

greater than niosomal formulations and the control solution. These differences might be attributed to the smaller size and the greater potential targeting to skin and skin appendages of liposomal carriers, which enhanced globally the skin drug delivery. This work suggests that liposomes have great potential for drug cutaneous targeting and could be used as a feasible therapeutic approach to skin diseases such as hair loss [50]. Jain *et al.* compared different types of liposomal formulation of minoxidil on drug deposition in the pilosebaceous units. A quantitative estimation of pilosebaceous delivery revealed that the concentration of minoxidil in each pilosebaceous unit decreased in the following order: neutral liposomal formulation > positively charged liposomal formulation > negatively charged liposomal formulation > nonliposomal formulation. The results showed that the neutral liposomes can deliver the drug molecules into pilosebaceous units more effectively than the other formulations [51]. Testosterone is converted to dihydrotestosterone by the enzyme 5α-reductase in hair follicles, which is suspected to be responsible for androgenetic alopecia. Finasteride inhibits this enzyme and its systemic side effects will be decreased if it acts locally in the hair follicles [52]. Both *in vitro* permeation and *in vivo* deposition studies demonstrated the potentials of liquid-state liposomes and niosomes for successful delivery of finasteride to the pilosebaceous units for efficient treatment of androgenetic alopecia [53]. Skin penetration and retention of freshly prepared finasteride-containing anionic, cationic and nonionic liposome suspension was evaluated on the hairless mouse skin using Keshary-Chien diffusion cell. Hydroalcoholic formulation of finasteride was also used as a control. The hair growth was assessed using depilated male C57BL/6N mice. Skin penetration and retention studies and hair growth study showed that topical application of finasteride using anionic liposome formulation appears to be useful option for the treatment of androgenetic alopecia to avoid systemic side effects of the drug [54]. Alopecia areata is a chronic cutaneous disease with a suspected autoimmune origin. Cyclosporine A-loaded liposomal formulation was applied to the Dundee experimental bald rat (DEBR) model and the results showed its promising potential as a topical treatment for alopecia areata in humans [55]. Despite the positive findings on follicular delivery of liposomes, negative reports with liposomes have also been reported [56]. For example, in an *in vitro* human facial skin study [57], it was determined that use of an ethanolic gel was as efficient as a liposomal or a mixed micellar gel in delivering isotretinoin to the sebaceous glands.

3.6 UV protection

UV radiation is responsible for a wide variety of different acute and chronic effects on the skin. Erythema is the acute responses of human skin to UV radiation. Long-term exposure of the skin to UV causes photoaging and photocarcinogenesis, which is considered to be induced by induction of immune suppression and mutations [58]. Epidemiological investigations demonstrate that more than 90% of epidermal squamous cell carcinomas and more than 50% of basal cell carcinomas show UV-induced mutations [59]. Recent focus on the harmful effects of UV radiation on the skin has resulted in an increased interest in photoprotectants such as sunscreens [60]. Lipidic delivery systems such as liposomes show UV-blocking effects dependent on lipid composition and the particle size. The smaller the particle size, the higher the sunscreen activity. The tested pigments ($BaSO_4$, $SrCO_3$ and TiO_2) incorporated into the lipid matrix of carnauba wax/decyloleate showed higher Skin Protection Factor (SPF) values during *in vitro* examinations [8]. The influence of vehicles (conventional o/w emulsion and multilamellar and small unilamellar liposomes) on the penetration of octyl methoxycinnamate, as a UV absorber, to the stratum corneum was studied by the stripping method on the midvolar forearms of six volunteers at a dose of 2 mg/cm^2. The result of this study indicates that multilamellar liposome could be better vehicle for octyl methoxycinnamate as a sunscreen since it has a slightly better SPF compared with a conventional formulation and more remains in the stratum corneum, reducing its penetration to the deeper layers [61].

3.7 Antioxidants

Skin aging is a complex process involving various genetic, environmental and hormonal mechanisms. Free radicals play a key role regarding both intrinsic and extrinsic aging. During the chronologic aging process, cell metabolism is responsible in the production of free radicals, while, in the extrinsic aging process, they are emerged by exogenous factors, such as UV exposure, cigarette smoking and alcohol consumption [62]. Antioxidants reduce free-radical damage by their scavenging, thus preventing destruction at the cellular level [63]. The main difficulty for topical delivery of antioxidant is its stability in the formulations and efficient penetration into the skin. Liposomes have been suggested as a suitable carrier for these purposes [64]. Sodium ascorbyl phosphate (SAP) is one of the most effective free radical scavengers and has a potential for decelerating the damaging effects of skin aging [62]. SAP-loaded liposomes as skin photoprotective were fabricated and it was concluded that liposomes facilitate SAP penetration through the stratum corneum in comparison with aqueous formulation of SAP as a control [66]. Dispersed ascorbyl palmitate (AsP)-loaded liposomes into poloxamer hydrogel matrix (lipogel) showed good skin permeation characteristics compared with control hydrogel containing Transcutol®, which is known as a drug solubilizer. Furthermore, the cathodal electric assistance increased skin permeation of liposomal AsP by electric repulsion probably via the appendageal routes. The lipogels were found to be a promising delivery system of AsP and combination of negatively charged lipogel and cathodal electric assistance was able to further enhance the skin penetration of AsP [67]. It was revealed that ethosome of melatonin, an endogenous antioxidant, provided an enhanced transdermal flux, low lag time, high entrapment efficiency

Table 1. Cosmeceutical application of liposomes.

Applications	Active ingredients	Vesicular system	Type of animal	Ref.
Acne	Clindamycin	Liposome	Human	[25]
	Benzoyl peroxide	Liposome	Human	[26]
	Tretinoin	Anionic liposome	Newborn pig skin	[27]
	Benzoyl peroxide + tretinoin	Liposome	Human	[26]
	Retinoic acid	Cationic liposome	Guinea pig	[28]
	Retinoic acid	Liposome	Rat	[29]
	Lauric acid	Liposome	*In vitro* study	[11]
	Salicylic acid	Liposome	*In vitro* release study	[30]
Occlusive effect	Empty liposomes	Liposome	human	[17]
	Glycolic acid	Chitosan-modified liposome	*In vitro* release study	[37]
Melasma	4-*n*-butylresorcinol	Liposome	Human	[40]
	Linoleic acid	Liposome	Human and guinea pigs	[41]
	Linoleic acid	Liposome	*In vitro* study on skin model	[42]
	Linoleic acid	Ethosome and transfersome	Human	[43]
Vitiligo	Khellin	Liposome	Human	[45]
Alopecia	Minoxidil	Liposome and noisome	Human	[50]
	Minoxidil	Anionic, cationic and nonionic liposomes	Rat	[52]
	Finasteride	Liposome and niosome	Guinea pig	[53]
	Finasteride	Anionic, cationic and nonionic liposomes	Mice	[54]
Alopecia areata	Cyclosporine A	Liposome	Rat	[55]
UV protection	Octyl methoxycinnamate	Multilamellar and small unilamellar liposomes	Human	[61]
Antioxidants	Sodium ascorbyl phosphate	Liposome	Pig	[66]
	Ascorbyl palmitate	Liposome	Rat	[67]
	Melatonin	Ethosome	Human and rabbit	[68]
	Aloe vera leaf gel extract	Liposome	Human neonatal skin fibroblasts	[69]
	Epigallocatechin-3-gallate	Liposome	Mice	[71]
	Ursolic acid	Liposome	Human	[72,73]
	Resveratrol	Liposome	HEK 293 cells	[74]
	Coenzyme Q10	Liposome	Rat	[77]
	Gamma-oryzanol	Liposome	Human foreskin fibroblast cells	[81]
	Vitamin E	Liposome	Rat	[82]
Psoriasis	Methotrexate	Liposome	Human and mice	[86]
	Methotrexate	Ethosome and liposome	Human	[83]
	Methotrexate	Deformable and normal liposomes	Pig	[87]
	Dithranol	Liposome and niosome	Mice	[88]
	Dithranol + salicylic acid + coal tar	Liposome	Human	[89]
	Tacrolimus	Liposome	Murine	[90]
Hirsutism	Cyproterone acetate	Liposome	Porcine	[93]
	Cyproterone acetate	Liposome	Guinea pig	[94]
	Tamoxifen	Liposome	Mice	[95]
Atopic dermatitis	Betamethasone dipropionate	Liposome	Human	[97]
	Dipotassium glycyrrhizinate	Deformable liposome	Pig	[98]
	Vitamin B_{12}	Liposome	Murine	[99]
Wound treatment	Povidone-iodine	Liposome	Human	[102]
	Povidone-iodine	Liposome	Human	[103]
Cellulite	Caffeine	Liposome	Human and rabbit	[106]

and low skin irritancy potential. It was concluded that this approach offers a suitable tactic for transdermal delivery of melatonin [68]. Liposomes including aloe vera leaf gel extract (AGE) were significantly enhanced by cell proliferation and collagen synthesis, compared with the case of AGE alone by investigation of the upgraded effects of liposomal AGE on proliferation and type I collagen synthesis in human fibroblasts, and on proliferation in human keratinocytes. Therefore, these findings indicated that the skin care properties and bioavailability of AGE are highly improved by liposome encapsulation. Liposomal AGE should have a great potential as an effective skin care formulation, especially for anti-aging

and/or regeneration of skin [69]. Green tea (*Camellia sinensis*) have gained great interest due to their potent antioxidant activities [70] and have been shown as chemopreventive and anticarcinogenic agents [71], which are attributed to its green tea polyphenols (GTPs). GTPs have been revealed to have substantial preventive effects against phototoxicity in murine models as well as in humans [70]. Most of the polyphenols present in green tea are flavanols, commonly known as catechins. Transdermal delivery of catechins was enhanced by liposomes incorporating anionic surfactants and ethanol. Epigallocatechin-3-gallate showed the highest encapsulation rate and *in vivo* skin deposition level in liposomes. The stabi-lity and *in vitro* transepidermal water loss test indicated the safety of the practical use of liposomes developed in this study [71]. Topical liposomal ursolic acid, a triterpenoid that is well known for antioxidant, anti-inflammatory, elastase inhibition, wound healing and promotion of collagen and ceramide production in final concentration of ursolic acid < 0.002% caused in increased skin ceramides in small-base forearm testing (n = 3; 11 days of treatment). The increased ceramides were suggested to indicate improved skin barrier [72]. In a double-blind, placebo-controlled, left-right randomized forearm clinical study of 20 subjects, treatment with topical liposomal triterpenoid (specific content not indicated) was done for 1 month and improvements in skin extensibility and firmness (instrumentally determined) were reported [73]. Caddeo *et al.* showed that liposomes enhanced the efficacy of resveratrol, a polyphenol with strong antioxidant and free-radical scavenging properties, in the prevention and treatment of human skin disorders caused by the excessive exposure to UV radiation compared with free resveratrol. Interestingly, liposomes prevented the cytotoxicity of resveratrol at high concentrations (> 10 M), even at 100 M, avoiding its immediate and massive intracellular distribution [74]. Coenzyme Q10 (CoQ10), an electron carrier in cellular respiration, shows potential antioxidant properties by clearing free radicals and protecting cells from oxidative stress [75]. CoQ10 is a potential preventive medication against skin photo-aging induced by UV-A [76]. Encapsulation of CoQ10 in liposomes composed of soybean phosphatidylcholine and vitamin E enhanced its accumulation at least -twofold in rat skin, compared with an unencapsulated suspension. Prolonging the treatment time and increasing the content of CoQ10 in the formulation both raised the amount of CoQ10 in rat skin. This study demonstrates that liposomal CoQ10 is a promising candidate for the topical application of CoQ10 [77]. Gamma-oryzanol, a main constituent in rice bran oil, has been reported to exhibit many properties such as reduction in serum cholesterol levels, inhibition of the platelet aggregation, possession in anti-inflammatory effect, improvement of the stability of food and stimulation of blood circulation under the skin [78,79]. It has also been proposed as a natural antioxidant to improve the stability of foods [80]. Oryzanol-loaded liposomes were fabricated with different compositions and compared in the points of encapsulation efficiency and antioxidant activity with each other and pure oryzanol, respectively. It was concluded that prepared liposomes are suitable for gamma-oryzanol incorporation without loss of antioxidant activity and in some formulations with enhanced antioxidant activity in normal human foreskin fibroblast cells [81]. Prepared liposomal dispersion of vitamin E showed sevenfold increase in drug deposition compared with control (plain drug dispersion). Improved drug deposition from liposomal preparations demonstrates its potential for dermal delivery. Variables such as amount of phospholipid, amount of stabilizer and lipid: drug ratio have a profound effect on the vesicle size and drug deposition in the rat skin. Increased drug deposition in rat skin as compared with control drug dispersion, control gel and marketed cream suggests that liposomal formulation promotes drug deposition in the rat skin thus has potential for dermal delivery [82].

3.8 Psoriasis

Psoriasis is an inflammatory condition of the skin and generally emerges between the ages of 20 – 40. Psoriasis, a T-lymphocyte-mediated autoimmune disease of the dermis and epidermis, is characterized by leukocyte infiltration into the skin and localized deregulated skin growth, which leads to the development of scaling erythematous plaques [83]. Although rarely life-threatening, it causes an unpleasant appearance that makes the patients to miss their confidence and suffer from itching, painful and disfiguring skin lesions. Fortunately, it is fully reversible with appropriate therapy. Coal tar, anthralin, methotrexate, corticosteroids, vitamin D_3 analogs, retinoids and tacrolimus are used topically for psoriasis treatment [84]. Methotrexate is an antifolate class of anti-neoplastic agent and is used for the treatment of psoriasis. The systemic use of this drug causes numerous side effects, the most important being the hepatic toxicity. Topical delivery of methotrexate would be beneficial to reduce its side effects [85]. Liposomal methotrexate in 2% carbomer 947 NF gel (0.25% methotrexate) formulations were applied once-a-day followed by 80 joules from 650-nm diode laser three times weekly for 12 weeks. The percutaneous absorption was carried out on albino mice skin and finally *in vivo* studies were done on human volunteers. The results compared with free methotrexate hydrogel. The treatment protocol was beneficial for relieving psoriasis and did not exert systemic toxicity compared with control nonliposomal methotrexate hydrogel [86]. Methotrexate-loaded ethosomal carriers enhanced transdermal flux and decreased lag time across human cadaver skin. Skin permeation profile of the developed formulation further evaluated by confocal laser scanning microscopy concluded improved permeation of rhodamine red-loaded formulations to the deeper layers of the skin (170 μm). The enhanced skin accumulation of methotrexate via ethosomal formulation causes interesting chances for targeted delivery of methotrexate to the epidermal and dermal sites for well-controlled and novel topical application of methotrexate in the treatment of

psoriasis [83]. In another study, deformable liposomes prepared using dipotassium glycyrrhizinate, a safe surfactant widely used in cosmetics, improved *in vitro* skin delivery of methotrexate compared with either aqueous solution or normal liposomes, which proposed to be a suitable candidate for the treatment of psoriasis [87]. It was claimed that deformable liposomes can target the drug efficiently to the deep skin layers due to its self-regulating deformability. The comparison of methotrexate skin accumulation of ethosomal [83] and transfersomal [87] methotrexate delivery systems show 31 and 51% drug deposition in the dorsal skin of 5- to 6-week old nude albino rat (Sprague Dawley strain) and full-thickness pig ear skin, respectively. Dithranol, one of the key medicines in the topical treatment of psoriasis, has irritating, burning, staining and necrotizing effects on the normal as well as the diseased skin. Entrapment of dithranol in liposomal and niosomal systems could be achieved after optimizing the various process and formulation variables. These systems showed size stability and improved drug permeation properties. The *in vitro* permeation study indicates that dithranol in exquisite amphiphilic atmosphere of closed lamellar system has an enhanced access to deeper skin layers. The *in vitro* study using laca mice abdominal skin shows six and two times more percutaneous permeation of dithranol in liposomal and niosomal vesicular systems, respectively, compared with the cream base [88]. In other study, 0.5% dithranol lipogel (dispersed liposomes in aqueous gel) was compared with a conventional cream containing 1.15% dithranol, 1.15% salicylic acid and 5.3% coal tar on 20 patients with bilaterally symmetrical stable plaque psoriasis for 6 weeks. Patients were assessed for disease severity, perilesional erythema and skin staining, pruritus and any other adverse effects at baseline, 2, 4 and 6 weeks. Both lipogel and the cream significantly reduced the total severity score compared with the liposomal base (without drug) at 4 and 6 weeks. There was no significant difference in the clinical response of dithranol cream and lipogel. Markedly low incidence and severity of perilesional erythema ($p < 0.001$) and skin staining ($p < 0.05$) was seen with the lipogel in comparison with the cream. It was concluded that 0.5% liposomal dithranol gel is as effective as 1.15% dithranol cream in the treatment of stable plaque psoriasis and produces almost negligible local adverse effects. It seems that due to low skin staining and its easy washability, dithranol lipogels has the potential to be much more acceptable to patients and physicians than currently available formulations [89]. The results obtained in both studies revealed that the entrapment of dithranol into liposomal vesicles improved availability of the drug at the site that will also reduce the dose and, in turn, the dose-dependent side effects such as irritation and staining. Tacrolimus is a useful and well-tolerated immunosuppressive drug used to prevent allograft rejection. It is also applied topically in the cases of psoriasis, vitiligo and severe atopic dermatitis [84]. Radiolabeled liposomal tacrolimus tested in the murine models of immune-mediated skin disease showed significant efficacy against psoriasis without the need for occlusive dressings and achieved nine times higher the tacrolimus concentration at a target site than did systemic administration and less toxic than free tacrolimus. This will be more important to patients who require higher concentrations of tacrolimus to treat large areas of skin [90].

3.9 Hirsutism

Hirsutism, a condition of excessive growth of body hair in females, particularly on visible areas such as the face and chest, is often a source of psychological distress. Cyproterone acetate is a steroidal anti-androgen used in acne and hirsutism [91], but its oral application needs a high dose that consequently shows systemic side effects such as loss of libido, lassitude breast tenderness and nausea [92]. Valenta and Janisch investigated permeation of cyproterone acetate liposomal formulations and Derma Membrane Structure (DMS) creams through the porcine skin. DMS creams are a new development in the field of topical preparations and compositions with hydrogenated soybean phosphatidylcholine by DMS technology. DMS stands for basic gels containing hydrogenated soybean phosphatidylcholine, sebum-compatible medium chain triglycerides, shea butter and squalane. The result demonstrated that addition of a phospholipid concentrate could be increased 2.6-times permeated cyproterone acetate of the DMS creams compared with the control DMS. Also decreasing the particle size of the liposomes by extruding procedures assessed twofold increase in cyproterone acetate permeation compared with the unextruded liposomes. It is possible to control the permeation rate of cyproterone acetate by various formulation components [93]. In another study Mohammadi-Samani *et al.* demonstrated that percutaneous absorption of cyproterone acetate from liposomal formulation has better penetration potential than conventional cyproterone acetate formulation (simple gel) [94]. Bhatia *et al.* provided a distinct lead toward the possible potential of tamoxifen liposomal gel in the treatment of hirsutism. The hair growth-retarding effect of tamoxifen observed in this study clearly demonstrated estrogen receptor agonistic effect of tamoxifen on the arrest of hair growth in mice [95].

3.10 Atopic dermatitis

Atopic dermatitis is an inflammatory, chronically relapsing, non-contagious and pruritic skin disorder [96]. The skin of a patient with atopic dermatitis reacts abnormally and easily to irritants, food and environmental allergens and becomes red, flaky and very itchy. It also becomes vulnerable to surface infections caused by bacteria. The effect of a liposomal preparation of betamethasone dipropionate (0.039%, BDP) has been compared with that of a commercial propylene glycol gel containing 0.064% BDP in a double-blind, randomized, paired trial lasting 14 days in 10 patients with atopic eczema and 10 patients with psoriasis vulgaris. In eczema, the liposomal formulation tended to reduce erythema and

scaling more than the conventional gel, the difference in the latter parameter being significant on day 7. There was greater improvement of psoriasis on the side treated with the reference gel. Hence, liposome encapsulation of BDP may increase the anti-inflammatory action but not the antiproliferative effect. Since inhibition of mitotic activity is linked to the atrophogenicity of topical corticosteroids, the results suggest that liposome encapsulation may improve the benefit–risk ratio in eczema [97]. Dipotassium glycyrrhizinate is a compound obtained from liquorice root, which has been apparently effective in treating acute and chronic dermatitis. Because of its chemical stability, good solubility and emulsifying properties, it is widely used in cosmetics and its continuous application is almost without side effects. Non-occlusive application of dipotassium glycyrrhizinate deformable liposomes significantly improved the *in vitro* skin delivery of dipotassium glycyrrhizinate compared with aqueous solution. The fact that the efficacy of the topical preparation containing dipotassium glycyrrhizinate was observed in an eczema-dermatitis group, a major pediatric dermal disease, suggests the therapeutic significance of this anti-inflammatory agent; it was supposed that the use of liposomes containing dipotassium glycyrrhizinate creates new opportunity for the well-controlled and modern topical medication [98]. Vitamin B_{12} has been shown to be effective for atopic dermatitis but it has low skin permeability. In a study, Jung *et al.* prepared a liposomal hydrogel of adenosylcobalamin, a vitamin B_{12} derivative, and investigated possible beneficial effects on atopic dermatitis using an NC/Nga murine atopic dermatitis model. Liposomes had enhanced skin permeability of adenosylcobalamin about 17-fold compared with adenosylcobalamin gel. The results demonstrate that liposomal gel of adenosylcobalamin has protective effects against atopic dermatitis symptoms and suggest that it might be of benefit in the treatment of human inflammatory skin diseases [99].

3.11 Wound treatment

The repair of injured tissue occurs in an overlapping sequence of events, which involves the inflammation, proliferation and migration of different cell types [100]. Povidone-iodine is an antimicrobial drug against gram-negative and gram-positive bacteria, protozoa, viruses, fungi and some spores that consist of a water-soluble complex of elemental iodine and polyvinylpyrrolidone, which has been used commonly as a topical antiseptic in wound care [101]. A monocentric, randomized, open, Phase II pilot study of new polyvinyl pyrrolidone-iodine liposome hydrogel formulation (betasom hydrogel) in patients receiving meshed skin grafts after burns or reconstructive procedures was carried out in 36 patients and the results were compared with wound dressed with chlorhexidine gauze in 15 patients. Daily assessment of wounds with photoplanimetry (rate of epithelialization) and impedance measurement (moisture of surface and wound healing quality) showed that rate of epithelialization was improved with betasom hydrogel compared with chlorhexidine gauze on day 11 (96.3 vs 75.9%) and significantly on day 13 (100 vs 82.3%). Impedance measurements showed an earlier return to normal values (day 9) in betasom-hydrogel-treated wounds as opposed to chlorhexidine treatment (day 11). Clinical assessment indicated better antiseptic efficacy and wound-healing quality ($p = 0.004$) of betasom hydrogel. Graft loss occurred at a significantly lower rate in betasom treatment ($n = 1$; 5%) than in chlorhexidine treatment ($n = 5$; 35.7%). Initial clinical results demonstrate earlier epithelialization and better healing in wounds treated with polyvinyl pyrrolidone-iodine liposome hydrogel compared with a conventional antiseptic chlorhexidine gauze according to a supply of higher moisture to the wound surface, release of polyvinyl pyrrolidone iodine at a low rate and target the substance more exactly by interaction with the cell surface [102]. Another study investigated liposomal hydrogel with 3% povidone-iodine and concluded that it is able to reduce inflammatory events responsible for the impairment of the wound healing process in patients with burns and chronic wounds and in smokers [103].

3.12 Cellulite

Cellulite is a cosmetically undesirable problem for most post-adolescent women. It occurs commonly on the lower limbs, pelvic region (gluteal-femoral regions) with its 'orange peel' or 'cottage cheese' appearance. Although not a pathologic condition, it remains an issue of cosmetic concern to numerous persons [104]. Caffeine is widely used in cosmetics due to its thinness effect. Caffeine also can apply topically to stimulate lipolysis in epidermal fat cells and in treatment of hyperproliferative skin diseases. The cosmetic formulation has to be optimized in a way that caffeine can be able to reach the active site in the adipocytes located in the hypodermis. For this purpose, liposomal and niosomal formulations of caffeine have been fabricated and characterized [105,106].

4. Expert opinion

It feels that by increasing the sales in the world for cosmeceutical products, there is a great necessity for more laborious studies on developing new formulations of cosmeceuticals. With the current lack of efficiency of these products on skin disorders, it is extremely difficult for both clinicians and consumers to trust these products. Liposomal carriers make a new horizon in dermatology. Liposomes are suggested to be good vehicles for delivery of therapeutics into skin because of associated hydrophobic lipid construction. It should be emphasized that, in general, liposomes not only play an important role as a drug delivery vehicle for skin tissue targeting, but also have a potential role in the transdermal application of cosmetics. In addition to the ability for drug delivery into skin layers, the liposomes are known to enhance skin hydration in dry skin conditions due to the similarity between liposome components and cutaneous lipids, thus making liposomes a novel application in cosmeceuticals and

pharmaceuticals. Clinical results indicate that liposomes will play the key role in the future of cosmeceutics. **Table 1** summarizes application of liposomes in the management of dermatological disorders as our literature review implied. Liposomes seem to be more beneficial for delivery of irritant, unstable and polar ingredients, which make them to be safer, more stable and easier to accumulate in skin, respectively. These advantages cause the concentration of cosmeceutical products formulators on liposomes, which consequently led to emerging the new classes of liposomes. The development of ethosomes and transfersomes recently became a key step toward an effective topical transdermal formulation. Although intensive research should take place to refine these systems, that could provide better efficiency and minimal side effects. Study on liposomes has developed substantially over the last 30 years and, nowadays, a wide range of liposomes varying in size, composition and surface characteristics were fabricated and introduced for required purposes. A number of extensive review articles have been published in this area [107,108]. But the number of commercialized liposomal systems is far behind the expectations due to the relatively high cost of the products and problems related to physical stability. The methods for scale-up of liposomes, which produces vesicles in micro size, being difficult to reach nano size range if required for industrial production. In spite of these limitations, the development of research in this area will provide in the future the appearance of new products and patents related to liposomes for cosmeceuticals. One of the main aims of research should be focusing on overcoming to problems against commercialization of liposomes. Exploring how to change or modify fabrication methods from laboratory to industry scale is important issue. Determining and fixing these problems is the challenge and mission for future development of new liposomal cosmeceuticals. Most of the studies cited in this review focused on *in vivo* applications of liposomes and clinical data, which have verified the enhancing efficiency of liposomes on topical drug delivery. Confirmation of liposomal use in clinical and *in vivo* systems may extend their applicability. Based on our presented information in this review, our conclusion is that liposomal formulations have been rightly highlighted in the topical dermatological treatments. This will guide the future studies to target other indications and show the benefits of liposomal cosmeceuticals in dermatology.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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