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REVIEW

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Research-based findings on scope of liposome-based cosmeceuticals: an updated review

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Abstract

Background: Cosmeceuticals are cosmetic products with biologically active components that have drug-like benefits. Cosmeceuticals are currently rapidly growing segments encompassing the personal care industry and numerous topical cosmetics-based therapies for treating different skin conditions. The barrier nature of skin causes limitations to topical treatment. The effectiveness of this cosmeceutical product has been enhanced a few folds by using nanotechnological modifications.

Main body: PubMed electronic searches for the literature were performed using combinations of the following terms: "cosmeceutical," "liposome-based cosmeceuticals," "acne and liposome," "photo-aging and liposome," "hyperpigmentation and liposome," "wrinkles and liposome," "fungal infections and liposome," and "hair damage and liposome" from the earliest publication date available to January 5, 2022. Among the various nanotechnological approaches, liposomes offer numerous advantages such as topical cosmeceutical products, starting from improved moisturization, biodegradability, biocompatibility, enhanced permeation and retention, improved bioavailability of the active ingredients, increased esthetic appeal of cosmeceutical products, slow and extended dermal release. This review outlines various liposome-based cosmeceutical products that has been investigated to treat skin disorders such as photoaging, wrinkles, hyperpigmentation, hair damage and fungal infections.

Conclusion: Liposome-based cosmeceuticals provide a better opportunity to deliver therapeutic moiety for various skin conditions and offer potential promise for future clinical applications.

Keywords: Nanotechnology, Liposomes, Cosmeceuticals, Skin disorder, Enhanced permeation, Improved bioavailability

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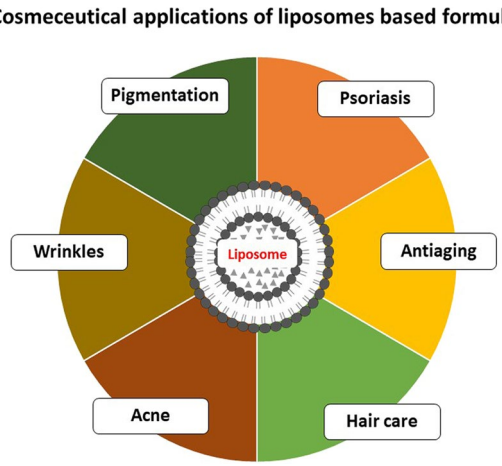
Graphical Abstract



Background

The field of nanotechnology has now been accepted widely for research and development of wide variety of formulations across the globe. Nanotechnology is defined as the field for suitable fabrication of a matter into submicron size particles using widely available polymers or lipids. This field was mainly adopted to achieve targeted delivery of therapeutic cargos for precise localization of therapeutics to the diseased site while restricting the non-specific biodistribution of the cargo [1]. A cosmetic is "any articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance" as per Federal Food, Drug, and Cosmetic Act, sec. 201(i) [2]. Several skin disorders like acne, pigmentation, photoaging, wrinkles, hair damage, fungal infections and psoriasis are currently treated with cosmetic products containing many drugs [3]. Thus, the products having both cosmetic and therapeutic value are better termed as cosmeceuticals. However, the infiltrating capability of the cosmeceutical products is required to reach the underlying skin tissues through the skin, the critical barrier concern for effective penetration [1]. So, it is a prime necessity to find out some strategy toward selective penetration of the therapeutic cargo from the cosmeceuticals through the skin and it has been reported in the literature that some carrier based on nanotechnology is playing active role in this case.

Gradual implementation of nanotechnology helps in designing different cosmeceuticals incorporated with colloidal carriers like liposomes, polymeric nanoparticles, solid lipid nanoparticles, etc. to improve its therapeutic efficacy [3, 4]. The size of these colloidal carriers helps to enhance the penetration of the incorporated molecules through the paracellular space of the skin into the underlying skin tissues [5, 6]. The use of liposomes over polymeric nanoparticles is more approachable due to unique features of liposome over polymeric nanoparticles. Moreover, liposomes are free from residual organic solvent [6, 7], simply fabricated from economical physiological lipids [8, 9]. In this regard, liposomes are reported to be a carrier of choice due to their biocompatibility, biodegradability, ability to release drug in sustained manner in reduced dose, improved therapeutic performance and improved patient compliance [10]. Further, the physiological composition of liposomes is similar to skin. Hence, the majority of drugs can pass through the lipid lamellae of the skin in the intercellular regions from liposomes-based cosmeceutical products. Furthermore, the liposomes can encapsulate both hydrophobic and hydrophilic drugs in it due to its distinct structure [9, 11]. Thus, liposomes are gaining more interest in the development of cosmeceuticals for topical applications in the management of different skin disorders mentioned earlier.

Main text

Methods

PubMed electronic searches for the literature were performed using combinations of the following terms: "cosmeceutical," "liposome-based cosmeceutical," "acne and liposome," "photo-aging and liposome," "hyperpigmentation and liposome," "wrinkles and liposome," "treatment fungal infections with liposome," and "hair damage and liposome" from the earliest publication date available to

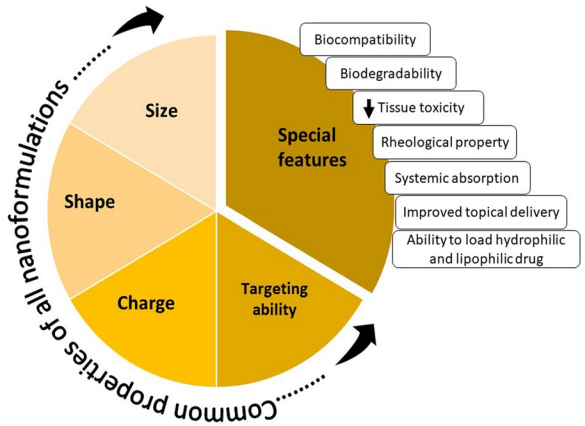


Fig. 1 Critical features of liposome-based cosmeceutical formulations

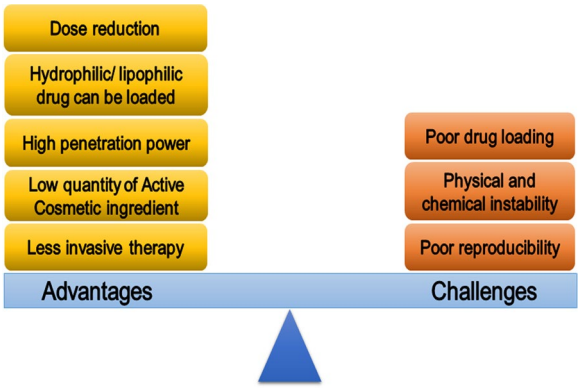


Fig. 2 Advantages and challenges of liposome-based cosmeceutical formulation

January 5, 2022. Only ongoing clinical trials involving liposomes for treatment of acne and psoriasis which are not commercially available for use were included.

Liposomes in cosmeceuticals

The word "liposome" is originated from the Greek words "lipo" (referring to their fatty constitution) and "soma" (referring to their structure). Liposomes are sphere-shaped vesicles at the macroscopic level, composed of one or more phospholipid bilayers and are stabilized by cholesterol where an aqueous volume is wholly fenced with a lipidic membrane. This structural resemblance of bilayer of liposome to the cell membrane helps to better interact with the skin during its topical application [12, 13]. Moreover, these colloidal vesicles have the capability to capture a hydrophilic or lipophilic drug, the hydrophilic drug is entrapped into the aqueous volume, and the hydrophobic drug is entrapped in the bilayers of phospholipid, enabling liposomes as a suitable carrier system for a number of drugs irrespective of their solubility. Further, the biocompatibility, biodegradability and the absence of potential tissue toxicity in comparison with the other colloidal carriers made liposomes an emerging drug delivery carrier system in cosmeceuticals applications. Figure 1 presents the characteristic features of liposomes.

The liposome-encapsulated cosmeceuticals are generally formulated as creams or gels. When applied onto the intact skin, the liposomal vesicle, due to its mimicking structure with the skin epidermis layer, is merged with the cell membranes and deliver the active pharmaceutical ingredients by trans-appendageal permeation through the skin [13–16]. Further, the number of stability-related problems is reduced for various drugs effective in different skin diseases when they are in entrapped or encapsulated state into the liposomal vesicles. Additionally, the skin hypersensitivity reaction is also reduced when formulated these pharmaceuticals into liposomes [14, 17–19].

In spite of having enormous advantages, there are some challenges that researchers may face while formulating liposomes for skin care cosmetics (Fig. 2) [20, 21]. This review focuses on the utilization of liposomes as carrier systems that might be an emerging way for the treatment and management of various skin disorders. We are quite confident that this concise and updated review may enrich the knowledge of readers from academia, research institutes as well as cosmeceutical sectors with the topic.

Recent uses of liposomes in cosmeceutical field

The liposomal formulations have enormous potential in treating various types of dermatological disorders (Fig. 3). Table 1 summarizes various liposomal formulations for cosmeceutical applications under research with their brief description.

Liposomes in the antiaging formulation

Skin aging refers to the innumerable progressions of wear and tear that continuously affect the structural and functional changes of human skin with time or age [60]. Natural skin aging is a slow and irreversible process, but premature aging also happens due to excessive exposure to different environmental factors such as long-term exposure to sun ray, infrared radiation, ultraviolet (UV) light (particularly UVA or UVB) and a pollutant in the atmosphere. Among the various environmental factors, UV irradiation is most important to cause skin aging. Excessive and long-term UV exposure of sunlight leads to the formation of reactive oxygen species (ROS) and nitric oxide that increases oxidative damages to DNA, such as the breakdown of DNA strand, oxidation of purine or

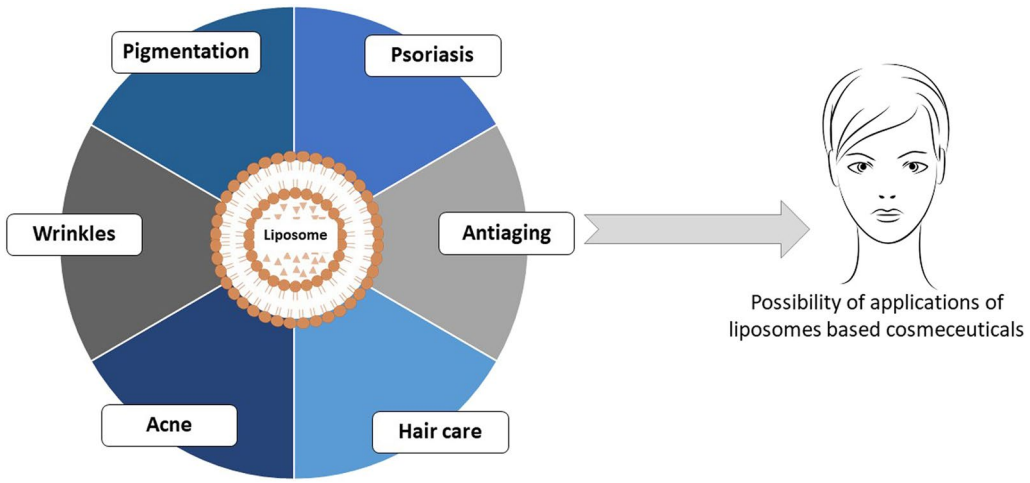


Fig. 3 Cosmeceutical applications of liposome-based nanoformulations

pyrimidine, lipid peroxidation, damage of epidermal cells by destroying cellular components, leading to the development of lines and creases onto the skin surface, leading to skin age. Additionally, ROS generation promotes skin cells to overexpress matrix metalloproteinases that destroy the tissues in the skin. The connective tissues in the skin are also get damaged; hence, the skin loses its pliability and normal appearance due to UV light exposure [49, 61].

Several therapeutic molecules, including retinoids (retinol and retinoic acid), vitamin C (ascorbic acid), hydroxy acids, vitamins B_3, vitamins D_3, vitamins E, coenzyme Q10 (CoQ10), etc. are used to prevent skin damage from the harmful effect of UV radiation. Still, the stability, toxicity and systemic exposure of the therapeutic molecule during topical application may be a great concern about the use of the molecules topically.

According to Bi et al., vitamin D3 is an effective drug which protects skin from photoaging but is also suffering from some drawbacks like it is sensitive to air, high-temperature and light and gets rapidly degraded in water/ethanol during the development of conventional topical preparations. Hence, they developed a new system based on liposomes encapsulated with vitamin D3 and demonstrated that the above problems were reduced, and the stability of the drug was also improved [49]. Figure 4 shows the histology of skin tissue section of male and female photoaging rat model and rats treated with liposomal vitamin D3 formulation [49].

Naturally occurring herbal compounds, such as *Curcuma longa* (Zingiberaceae), is reported to be a good candidate for aging prevention due to its antioxidant and other essential activities by forestalling UV ray-induced generation of oxygen free radical and lipid peroxidation [51] during UV exposure. A study reported the use of *Curcuma longa* extract for use in UV-induced damaging of skin by incorporating it in the different prototype of vesicular systems like ethosomes, transferrosomes and liposomes to improve skin hydration and sebum content into the underlying skin layers to combat the damaging effect of solar rays and prevent photoaging. The study concluded that *Curcuma longa* extract-loaded nanovesicular systems, particularly liposomes, can be an excellent way to maintain good skin health and protect skin from the damaging effect of UV rays toward aging [51].

Although curcumin (CU) is a drug of choice for aging of skin, but CU creams/gels available in the market have no significant in antiaging potential. It has been reported that CU is suffering from poor topical bioavailability due to its improper cutaneous absorption, and thus only traces of topically applied CU reach up to the dermis. Gupta and group demonstrated improved topical bioavailability of CU from the gel containing liposomes/niosomes loaded with CU [50]. They have prepared phosphatidylcholine complex with CU and converted it to phyto-vesicles. Further, they have also developed liposomes and niosomes of CU. These three formulations were incorporated into carbopol for topical application to compare their efficacy in terms of topical bioavailability against pure CU. Antiaging potentials of different formulations were compared in UV-induced oxidative stress in mice. The report revealed that all three preparations were very effective in enhancing the antioxidant and antiaging activity of CU over pure CU and concluded that phytovesicles had superior antiaging potential [50].

Glabridin, a flavonoid from natural source, was reported to be an effective candidate for treating individuals suffering from UVB-induced photoaging. Glabridin

Table 1 Cosmeceutical applications of liposome and description with the therapeutic molecule

Sl. No	Broad application area	Description	Reference
1	Acne	Liposomal gel loaded with benzoyl peroxide and adapalene	[22]
		Adapalene-encapsulated liposomes	[23]
		Tretinoin-loaded liposomal	[24, 25]
		Grape seed extract and resveratrol-loaded liposome effective on chloasma, skin aging, acne vulgaris, facial redness and wound	[26]
		Azelaic acid liposomal gel	[27]
		Liposomal methylene blue gel	[28]
		Liposomal gold nanoparticle entrapping curcumin (CU) mediated by iontophoresis	[29]
		Conventional and Labrasol® containing liposomes loaded with Tretinoin	[30]
		Topical liposomal gel containing benzoyl peroxide and resveratrol	[31]
		A peel-off facial mask comprising of myoinositol and trehalose-loaded liposomes	[32]
		Liposomes containing tetracycline hcl and tretinoin	[33]
		CU liposomal gel formulations	[34]
2	Psoriasis	Methotrexate-entrapped deformable liposome	[35]
		Tretinoin-encapsulated liposomes, solid lipid nanoparticles, ethosomes and nanostructured lipidic carriers	[18]
		Calcipotriol-loaded PEGylated liposomes	[36]
		Calcipotriol-loaded liposome	[37]
		Cyclosporine cationic liposomes	[38]
3	Melasma and Hyperpigmentation	Cream containing liposome-loaded 4-n-butylresorcinol and resveratrol	[39]
		Liposome-encapsulated 4-n-butylresorcinol 0.1% cream	[40]
		Liposomal tranexamic acid	[41]
		Liposome-encapsulated aloe vera	[42]
		Topical liposomal tranexamic acid	[43]
		Topical liposomal hydroquinone	[44]
4	Hypopigmentation and vitiligo	Khellin liposomes	[45]
		Ultradeformable liposome-encapsulated psoralen and resveratrol	[46]
		Baicalin and berberine ultradeformable vesicles	[47]
5	Antiaging	Rosmarinic acid-loaded ethosomes and liposomes and inhibition of collagenase and elastase enzyme	[48]
		Liposomal vitamin D3	[49]
		Liposomes and niosomes of CU incorporated carbopol gel for topical application for antiaging, antioxidant and antiwrinkle effect	[50]
		The alcoholic *C. longa* extract-loaded liposomes, ethosomes and transfersomes	[51]
		Liposomes loaded with avobenzone and arbutin as sunscreen and skin whitening	[52]
		Glabridin liposome for UVB-induced photoaging	[19]
6	Hair disorder	Liposome loaded with equol, dihomo-γ-linolenic acid and propionyl-L-carnitine	[53]
		Liposomal hydrogel containing Minoxidil and Tretinoin	[54]
7	Fungal Infection	Terbinafine HCl liposome-loaded nail lacquer	[55]
		Croconazole encapsulated in liposome and microemulsion-based gel	[56]
		Terbinafine hydrochloride-loaded liposome film formulation	[57]
		Miconazole nitrate-loaded ultraflexible liposomes	[58]
		Ultradeformable liposome-encapsulated amphotericin B	[59]

is an excellent skin-whitening compound having good antiaging potential but its poor epidermal penetration after topical application limits its success. Hence, this group of researchers thought to deliver the drug by incorporating it into liposomes. They fabricated glabridin incorporated liposomes by film dispersion method to improve the bioavailability and characterized differently [19]. The fabricated liposomes were demonstrated to be very effective in ameliorating UV-induced erythemal formation onto the skin surface and also preventing leathery

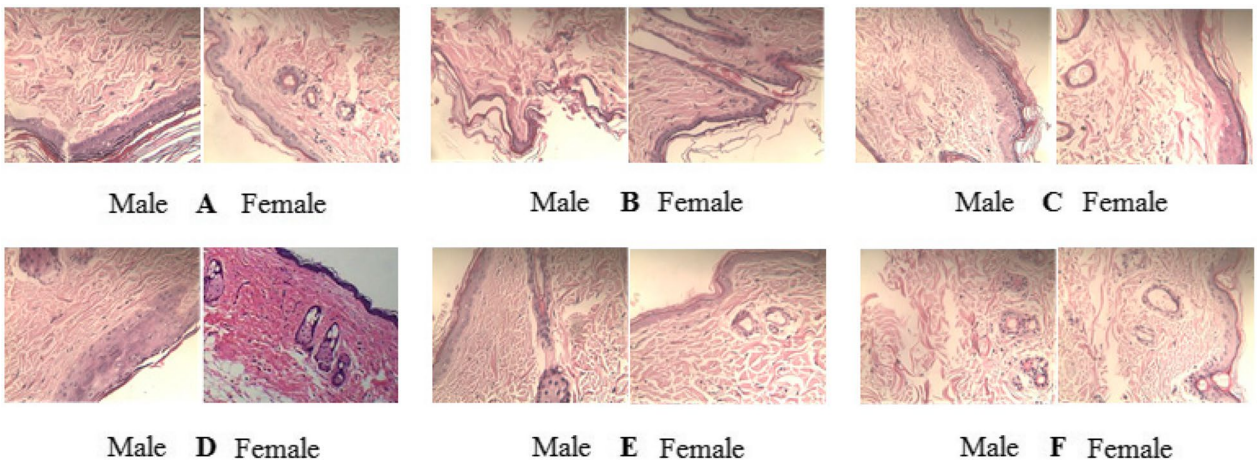


Fig. 4 Histology of skin tissue section. **A** Control, normal skin, **B** photoaging model, **C** treatment with vitamin D3 solution, **D** treatment with vitamin D3 liposomes, **E** treatment with aloe gel as positive control, **F** treatment with PBS. H&E 200x [49]

skin due to downregulation of inflammatory cytokines expression, including tumor necrosis factor α (TNF-α), interleukin (IL)-6 and IL-10. Thus, from this study it can be concluded that liposomal formulation of glabridin or similar drugs could be a very excellent strategy for topical application to prevent UVB-induced aging.

Rosmarinic acid (RA) is reported to have a profound antioxidant effect than other natural antioxidants like vitamin E and its analogue (trolox). RA acts as a free radical scavenger and is effective as antiaging by preventing the formation of lipid peroxidation of the underlying skin layers caused by UV irradiation. Ethosomes and liposomes were prepared to deliver RA as reported by Yücel Aşık & group. Their work demonstrated that RA incorporated ethosomes and liposomes for transdermal application could be an excellent way to prepare antiaging cosmeceuticals for much better effectiveness [48].

Liposomes in hair care

Alopecia is a common condition affecting both men and women in which predominant hair loss occurs. The hair loss may occur due to genetic, inflammatory, environmental, hormonal or a combination of these factors affecting the growth of hair follicles and life cycle of hair. Among the different types of alopecia, androgenetic alopecia is very common that occurs as a result of diminished blood circulation into the hair follicles of the scalp. It also occurs due to a higher level of dihydrotestosterone, a toxicant to the hair follicles. Conventional topical preparations are used to promote hair growth for the management of alopecia. However, due to their limited performance, intolerability and poor compliance due to different adverse effects limit their use [53, 62].

A work by Brotzu et al. reported the application of liposomal formulation for the management of alopecia. Their work demonstrated that the activity of different compounds such as dihomo-γ-linolenic acid (DGLA), S-equol and propionyl-l-carnitine could be improved when applied after loading into liposomes than the conventional topical preparation against alopecia [53]. Two marketed lotions named TRINOV Lozione Anticaduta Uomo and TRINOV Lozione Anticaduta Donna containing the above agents were used to treat early baldness, alopecia and hair thinning.

DGLA, a precursor molecule of prostaglandin PGE1, functions by increasing microcirculation of the scalp, and S-equol prevents 5α-reductases, thus foiling the conversion of testosterone into toxic dihydrotestosterone. Propionyl-l-carnitine augmented lipid metabolism which in turn stimulated energy production. A group of researchers encapsulated these three agents into liposomes for transdermal application onto the scalp and compared the fabricated liposomes with conventional lotions in 30 men (TRINOV Lozione Anticaduta Uomo; mean age 46.6 ± 6.4 years) and 30 women (TRINOV Lozione Anticaduta Donna; mean age 49.5 ± 9.0 years) suffering from androgenic alopecia. They concluded that liposomes containing DGLA, S-equol and propionyl-l-carnitine are more effective for treating androgenis alopecia in both men and women [53].

Due to the antioxidant potential along with antiaging properties of CoQ10 on human hair, it can be used to treat individuals suffering from androgenic alopecia. But CoQ10 is a poor drug candidate when used in the actual development of formulation for alopecia due to its poor aqueous solubility. The high molecular weight of CoQ10 limits its topical application leading to poor therapeutic outcomes. A recent work has been reported the improved therapeutic activity of

CoQ10 by promoting skin penetration by developing various nanovesicular drug delivery systems, including liposomes for the management of androgenic alopecia. This study revealed better penetration of CoQ10 in liposomal form and concluded that nanovesicular carriers could open a new avenue in the treatment of scalp disorders [63].

Liposomes in wrinkles

Wrinkles are the by-products of the aging process. It is described as the formation of lines and creases onto the skin surface. With age, the skin cells divide more slowly, and the dermis layer begins to thin. The elastin network (the protein capable of resuming the skin shape after stretch or contracting) and collagen fibers (the major structural proteins in the skin) support the outer layer of the skin. With aging, the skin loses the ability to retain moisture and the oil-secreting glands become less efficient. Moreover, the skin loses its elasticity and depicts a slower healing ability.

A study was successfully conducted to show the safety and efficacy of photodynamic therapy along with a novel 0.5% liposome-encapsulated 5-aminolevulinic acid spray in reduction of periorbital and nasolabial wrinkles in photoaging. A baseline visit was conducted on 30 healthy adult participants (aged 35–65) with skin types I through III and type 2 photoaging. The depth of the wrinkles developed was assessed using the modified Fitzpatrick wrinkle scale after three treatments using liposome and an intense pulsed light system were administered once every three weeks. There were no negative effects during or after the therapy, and periorbital wrinkles appeared to improve more generally than nasolabial wrinkles [64].

Acetyl-hexapeptide-3, a synthetic neuropeptide, reduces lines and wrinkles by reducing the intensity of facial muscle contraction and relaxing facial tension. However, the large molecular size and hydrophilic property of this drug resulted in its poor permeation and diffusivity through the lipophilic stratum corneum. The multilamellar liposomes containing acetyl-hexapeptide-3 were developed by the thin film hydration technique. This liposome formulation showed improved skin permeation through the skin [65]. Thus, this study showed to be an excellent way to prepare antiwrinkle cosmeceuticals for better therapeutic effectiveness and could be used for formulating similar potent hydrophilic active pharmaceutical ingredients.

Liposomes in acne

Acne vulgaris is a chronic and widespread skin disease involving occlusion and inflammation of pilosebaceous units (hair follicles, sebaceous gland and arrector pili muscle) of human skin caused by *Propionibacterium acnes*. Acne can appear either as inflammatory or non-inflammatory lesions or a mixture of both. It mainly affects the face but can also be found in the back and chest. It is primarily produced by blockage of pores or opening onto the skin by dead skin cells, causing sebum (oil) to build up inside the pore. The inflammatory response generated during acne development is further aggravated by different immune cells of the body, leading to increasing the synthesis of pro-inflammatory cytokines like interleukin 1β (IL-1β) and TNF-α, leading to hyper-keratinization of follicles and promoting inflammation [34].

Different anti-inflammatory and/or antimicrobialdrugs are generally used to treat acne, such as benzoyl peroxide (BPO), retinoids (i.e., isotretinoin, adapalene, tazarotene), antibiotics like erythromycin and clindamycin, and azelaic acid by topical and systemic route. Galderma sells adapalene under the brand names Differin and Epiduo (Lausanne, Switzerland). Both a gel [34] and a lotion version of Differin are offered. The US Food and Drug Administration authorized Epiduo, a topical gel that contains both adapalene and BPO, in 2008. These formulations are linked to a number of adverse reactions, including skin erythema, dryness and itching, which significantly reduces patient compliance [66]. The other drugs, as mentioned earlier, are also curative in acne, but they are also suffering from serious side effects such as teratogenicity, myalgias and arthralgias (in the case of retinoids) [34]. A few numbers of drugs that are usually used to treat acne have been reported to be unsuitable and ineffective in all the stages of the acne life cycle. The retinoids do not have any antibacterial effect against the pathogenic bacteria of acne. In contrast, antibiotics do have an antibacterial effect but are reported to weaken the intestinal vital microflora and cause the formation of antibiotic resistance in *Propionibacterium acnes* [67]. Sometimes hormonal treatment may be done as a remedial treatment option to retinoids, but again, the hormonal treatment leads to suppression of vital hormones produced by adrenal glands. Henceforth, as previously mentioned, it is an emergent demand to develop safe and effective medicines for acne therapy based on innovative drug delivery strategies that can reduce side effects and improve patient compliance with effective drug administration. Literature findings revealed that nano-based formulations, particularly liposomes, are novel approach to solving the issues of traditional antiacne drugs, as discussed earlier [34, 68–70].

A work by a group of scientists reported the role of natural agents such as CU and lauric acid in acne. Cationic liposomes were fabricated from biocompatible lipids and

Table 2 Clinical status of liposomes used for cosmeceutical purposes

Disease condition	Drugs	Description	Route of administration	Clinical Status	Identifiers
Acne	Povidone iodine (Repigel)	Liposomal hydrogel containing 3% povidone iodine	Topical	Phase 2	NCT02126709
Facial acne vulgaris	Retinyl palmitate	Retinyl palmitate-loaded ethosomes	Topical	Phase 2	NCT04080869
Psoriasis vulgaris	Anthralin	Liposomal preparation of anthralin	Short contact topical application	Phase 4	NCT03348462

subsequently incorporated them in carbopol gels which were compared with azithromycin. According to reports, topical azithromycin has a strong antiacne potential. As a result, the fabricated liposomes of CU and lauric acid were compared with azithromycin liposomal gel as a reference comparator. The prepared liposomes were reported to concentrate into the dermis easily by interaction with the negatively charged stratum corneum having cytocompatibility by using different cell lines such as L929, HeLa and MDA-MB-231 [34].

Adapalene-encapsulated liposomes were fabricated, characterized and reported to acquire better penetration capability of adapalene from the liposomal formulation as revealed from in vitro skin permeation studies. Comparing the liposomal formulation of adapalene to two comparators (a drug solution and a simple gel formulation of adapalene), the confocal microscopy results revealed that it penetrated the hair follicles in pig ear skin more effectively. Additionally, adapalene liposomal encapsulation may lessen side effects and boost patient compliance. As a result, liposomes provide an appropriate and promising carrier for follicular targeting of adapalene for the treatment of acne [23].

Another work reported the delivery of BPO and adapalene by encapsulating both the drugs into liposomes. The researchers investigated the therapeutic efficacy and tolerability of BPO and adapalene-loaded modified liposomal gel for improved acne therapy. The work demonstrated that fabricated liposomes significantly enhanced dermal bioavailability with reduced skin irritation potential as compared to free drugs and papule density as compared to Epiduo, both by performing animal studies [22].

Cryptotanshinone-encapsulated liposome-like formulations, called cerasomes, were developed and its in vivo performance after the topical application in rat acne model was evaluated. The cerasomes were formulated following ethanol injection method and characterized. The in vitro permeation study showed that cerasome gel demonstrated a greater penetration rate and considerable accumulation in the dermis layer of isolated rat skin. In vivo pharmacokinetics studies showed a maximal drug concentration, a quick peak time and minimal clearance. The cerasome gel showed improved antiacne efficacy compared to regular gel containing cryptotanshinone that inhibited the expression of interleukin-1α and androgen receptors efficiently, which has significant potential for treating acne induced by inflammation and over secretion of androgen [71]. Therefore, the above studies could open a broad scope of liposomal formulations for treating acne. Table 2 summarizes the clinical status of the liposomal formulation used in the treatment of facial acne.

Liposomes in psoriasis

Psoriasis is a chronic auto-immune disease mediated by T-cell and characterized by hyperproliferation of keratinocyte cells. The outcome is that the skin's top layer has a shorter lifespan. Additionally, it alters the desquamation process, causing cytokines to leak from affected patients' lesions and scaling marks to show up on the skin. The condition leads to hyperproliferation and other inflammatory responses on the skin. Mostly, it occurs due to overexpression of chemokines and cytokines, the pro-inflammatory substances such as interleukin (IL)-6, IL-23, IL-17, IL-22 and TNF-α [38]. It can be classified based on the severity of the disease and broadly three types: mild, moderate and severe. In mild conditions, the skin becomes rashy, followed by scaly skin in moderate conditions and that finally leads to the formation of red spots, and at this severe stage, the skin becomes itchy [72]. The primary treatment method for psoriasis is still topical therapy. To treat psoriasis, drug molecules should be chosen that have an affinity for the skin's tissues as well as effects that target other inflammations. Most currently used medications cause systemic toxicity and dryness when used in larger doses. Researchers have investigated a variety of systematic methods for topical distribution, including spray, nanogels, hydrogels, micro/nanoemulsion, liposomes, nanocapsules and transdermal delivery [72].

Cyclosporine cationic liposomes made from N-(1-(2,3-dioleoyloxy) propyl)-N, N, N-trimethylammonium chloride and cholesterol demonstrated an effective treatment option for psoriasis. They have fabricated cyclosporine liposome containing gel and used in imiquimod-induced psoriatic plaque model.

The main psoriatic cytokines TNF-α, IL-17 and IL-22, which are responsible for the development of psoriasis, were reduced by the liposomal gel as were psoriasis symptoms [38].

In another work, the use of methotrexate (MTX) in psoriasis treatment was reported. MTX was delivered topically by entrapping it in different concentrations (0.05%, 0.1%, 0.25% and 0.5%) into deformable liposomes made of phosphatidylcholine and oleic acid. The work expressed promising results in terms of the effectiveness of the fabricated liposomes in imiquimod-induced psoriasis in a mouse model [35]. Moreover, the study showed that liposomal MTX (0.05 and 0.1%) reduced psoriatic tissue thickness score significantly than conventional MTX injection in a dose-dependent manner in psoriatic animals. Further, a study was performed to identify the different inflammatory factors responsible for psoriasis development. Various pathological investigations of skin tissues of mice during treatment with liposomes demonstrated better performance without any associated organ toxicity and without any effect on the blood cell counts from liposomal MTX [35]. Hence, the study concluded that MTX-loaded deformable liposomes might be a promising strategy for the development of future nanomedicines for human psoriasis.

The liposomal formulation of anthralin for short contact topical application in the treatment of psoriasis vulgaris is under phase IV clinical trial (NCT03348462).

Liposomes in pigmentation disorder

Pigmentation disorder of skin is characterized by changes in skin colour. The colour of the skin depends on pigment melanin. Changes in the melanin secretion from the melanocytes in the underlying skin tissue layers cause pigmentation disorder. The levels of oxidized and reduced hemoglobin, carotenoid content, vascular state, skin thickness, light refraction and absorption qualities, and skin absorption all contribute to changes in skin colour. Among all the parameters, melanin secretion activity had the biggest impact on changes in skin tone. The term "pigmentation" refers to colour changes in the skin, hair and eyes brought on by genetic variability, melanocyte levels and melanin-producing cell locations. When the human body makes too much melanin, the skin gets darker, and when it is too little, the skin gets lighter. So, the pigmentation disorder may be either hyperpigmentation or hypopigmentation. Moreover, different pigmentation disorders are mainly attributed due to the activity of tyrosinase, the key enzyme responsible for melanin production and also contributes to hypopigmentation such as vitiligo, albinism and hyperpigmentation like melasma, lentigo, etc. [73, 74].

Liposomes in hypopigmentation

Vitiligo is a skin disorder related to hypopigmentation. It is characterized by white spots onto the skin surface owing to the loss of melanin-producing cells, melanocytes. Oxidative stress is also known to be a promoting cause of vitiligo and acts as a triggering factor. The therapeutic methods that are most frequently used are UV phototherapy, calcineurin inhibitors and topical administration of corticosteroids. Phototherapy (UVB) and photochemotherapy (also known as PUVA therapy using psoralen with UVA) are two examples of possible applications for UV treatments. Resveratrol (RSV) and psoralen are the drugs of choice used in vitiligo.

Many topical preparations, including methoxsalen (solution and cream), trioxsalen (solution), corticosteroids (solution, gel, cream and ointment) and calcineurin inhibitors (ointment and cream), are available for the management of vitiligo. However, the existence of side effects and poor efficacy limit patient compliance. So, a number of novel drug delivery strategies have been reported in the literature for improving the topical application of many drugs effective in hyopigmentation. The novel carriers acts either by increasing drug penetration, thus promoting drug localization into the underlying epidermal layer of the skin, or by reducing side effects, hence improving patient compliance [75].

RSV, an antioxidant, can lessen oxidative stress-induced vitiligo. However, RSV is a poorly water-soluble drug that limits its topical application and also psoralen has poor permeability through the skin to reach a sufficient concentration to melanocytes of the underlying skin layers for effectiveness. In a work, Doppalapudi et al. showed that psoralen with RSV can be effective for vitiligo by using liposomal formulation of these drugs. They have reported using a combination of UVA with Psoralen promote melanin synthesis and tyrosinase activity in melanocytes. They reported the preparation of ultradeformable liposomes by using 3ß-[N-(N′, N′-dimethylaminoethane)-carbamoyl] cholesterol hydrochloride (DC-Chol), cholesterol and sodium deoxycholate co-loaded with psoralen and resveratrol for the purpose of evaluating the effectiveness of PUVA and antioxidant combination therapy for vitiligo. B16F10 cell line was used to assess the liposomal formulation's effectiveness. In vitro antioxidant studies that demonstrated potential resveratrol activity were used to determine the free radical scavenging capability of these carriers. [46].

Numerous natural polyphenolic compounds, such as baicalin and berberine due to their antioxidant, anti-inflammatory and proliferative effects, are used in the management of the de-pigmentation disorder of skin like vitiligo. However, poor water solubility and poor absorption after topical delivery by conventional cream or gels

limit its proper efficacy to achieve in vitiligo treatment [47]. A study demonstrated the fabrication of ultradeformable liposomes containing baicalin and berberine which can be a promising strategy to overcome the solubility problem of these drugs, with improved ability to permeate through the epidermis easily and in a more effective concentration. The developed liposomes were small in size (< 100 nm) with negatively charged. Further, they found that penetration of these vesicles containing polyphenols was more than the intact polyphenols in PBS or in 5% sorbitol in water solution onto newborn pig skin. Additionally, the capacity of baicalin and berberine vesicles to enhance melanogenesis and skin pigmentation was examined in melanocytes and revealed noteworthy antioxidant and photoprotective effects. These formulations also showed effectiveness against oxidative stress damage in cells. Hence, the liposome could stimulate melanin production and promote the activity of tyrosinase. Thus, they concluded that ultradeformable vesicles of baicalin or berberine, mostly in their grouping, could be a promising approach for dealing vitiligo management [47].

Liposomes in hyperpigmentation and melasma

Melasma, chloasma or pregnancy spots are synonymous. Melasma is nothing but a chronic acquired pigmentation disorder due to hepermelanogenesis of the skin. The melanin dysfunction occurs in the sun-exposed areas due to excess melanin production. Chloasma is more prevalent in women than men, and it is known as the mask of pregnancy. Although the exact reason is still unknown, some known triggering factors have been identified, such as the use of oral contraceptive, pregnancy and menopause. Clinically, symmetrical distribution of irregular brown macules with distinctive margins is observed. These are frequently discovered on the face after sun exposure. Melasma is a condition that affects Asian women primarily in their thirties or forties. Melasma has been linked to factors such as prolonged exposure to UV, activation of the female sex hormone and genetic predisposition [76, 77].

The fundamental reason must be the focus of treatment in the initial instance. Additionally, oligopeptides, silymarin, an extract of the plant Silybum marianum, hydroquinone, 4-n-butylresorcinol and orchid can be used as local therapies. Additionally effective are the chemical peeling agents like tretinoin, trichloracetic acid, glycolic acid, kojic acid, etc. [78, 79].

A pilot study by Taghavi and group demonstrated that hydroquinone (1, dihydroxybenzene), a tyrosinase inhibitor, can be successfully given in the form of liposomes to increase its therapeutic efficacy in the management of melasma. 4% hydroquinone was encapsulated into liposomes by fusion method and physiochemically characterized. They compared the therapeutic efficacy of the prepared hydroquinone liposomes with conventional hydroquinone. A randomized clinical trial of double-blinded nature was designed with twenty female patients suffering from melasma. They were instructed to apply liposomal hydroquinone and conventional hydroquinone, topically on both opposite sides of the face for three months, and comparative therapeutic efficacy was judged by measuring Melasma Area and Severity Index (MASI). The MASI data from this plot study expressed a significant therapeutic efficacy of liposomal hydroquinone on melasma [44].

Ghafarzadeh and Eatemadi prepared liposome-encapsulated aloe vera gel extract using soybean lecithin. The liposomes obtained were small unilamellar vesicles with a diameter smaller than 200 nm. The liposomal gel was applied to patients with melasma in the form of gel. In the double-blinded, randomized clinical trial, two groups of pregnant women with melasma were given liposome and compared with the control group of patients. Liposome-encapsulated aloe vera gel extract was superior to aloe vera gel in decreasing the severity of melasma with lightening melasma in pregnancy due to their ease in percolation and minimal side effects [42].

Another work reported that a cream containing liposome encapsulated with 4-n-butylresorcinol and RSV is more effective in the treatment of melasma. At week 0 (baseline), week 2 and week 4, melanin index (MI) of the melasma lesion (lesional MI) and preauricular area (non-lesional MI) of the skin was measured. The MI of lesional skin was remarkably reduced 2 weeks after the initiation of treatment (from 201.08 ± 25.76 at week 0 to 189.46 ± 21.26 at week 2. Similarly, at the end of 4 weeks, the lesional MI was further lessened to 182.83 ± 18.61 with the use of the liposomal cream (Fig. 5). However, MI of non-lesional skin had no visible change throughout the study period (129.02 ± 21.54, 127.83 ± 22.94 and 128.32 ± 22.38, at week 0, week 2 and week 4, respectively). The improvement in investigator's global assessment (IGA) score was observed (Fig. 5C) during the treatment up to 4 weeks than that of week 0 [39].

Liposomes in fungal infection of the skin

Fungal infections are a global threat that may superficially affect the skin, nails, hair and mucous membrane or invade systemic circulation, causing distress to the entire body. The effectiveness of topical antifungal therapy depends primarily on the penetration ability of drugs through the skin, mainly the dead stratum corneum, to reach lower layers of the skin (viable epidermis) [58, 80]. Fungal infections can also occur in the nails also known as onychomycosis, triggered by dermatophytes [81].

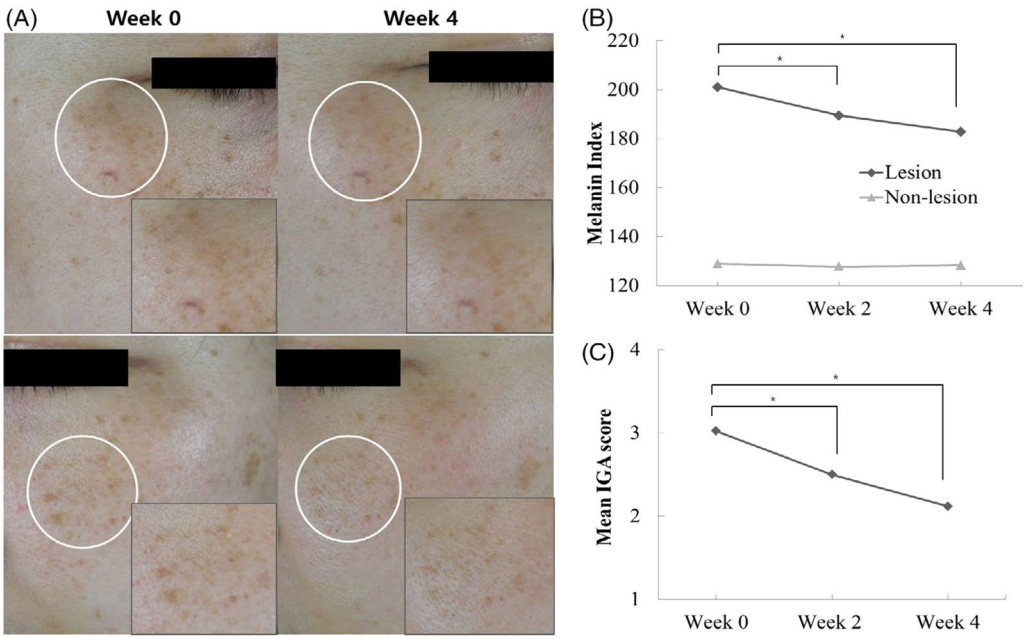


Fig. 5 **A** Photograph of a patient who showed a good response to the treatment with the 4-n-butylresorcinol and resveratrol (RSV) cream. **B** Lesional and non-lesional melanin index (MI) during the 4-week treatment with the 4-n-butylresorcinol and RSV cream. The lesional MI at weeks 2 and 4 were significantly decreased compared with the baseline. The non-lesional MI showed no significant change throughout the study (*$P < 0.05$). **C** Mean IGA score during the treatment. Reprinted under permission from John Wiley and Sons [39]

Croconazole, a synthetic imidazole antifungal agent, is effective in treating fungal infections caused by dermatophytes and yeasts, especially Candida albicans. Two different formulations of croconazole were formulated such as liposomal-based and microemulsion-based gel formulations for topical delivery, and compared with conventional gels prepared using different polymers (sodium carboxymethyl cellulose, Carbopol 971P, Poloxamer 407 and chitosan). Carbopol 971P was selected for incorporating liposomal and microemulsion of croconazole based on the drug release/skin permeation profile in the conventional gel. Both the experimental formulations exhibited greater effectiveness against several types of fungi. However, this study concludes the superiority of microemulsion-based products over liposome-based gel [56]. In another work, miconazole nitrate was loaded in ultraflexible liposomes and compared with conventional liposomes containing miconazole. The ultraflexible liposomes showed higher encapsulation efficiency and were more effective in transferring the drug to the skin in in vitro skin permeation studies [58].

Amphotericin B, a polyene antifungal drug, was encapsulated in elastic liposomes for effectively treat fungal infections such as Candidiasis and in dermatosis caused by Leishmania spp. In this study, they used two types of edge activators in the liposome formulation such as sodium cholate and Tween 80 to evaluate the deformation capacity. The liposomes prepared with Tween 80 showed a greater deformation capacity. This result can be attributed to the molecular structure of the surfactants and their subsequent incorporation into the lipid bilayer structure. Thus, the application of deformable liposomes to human skin in a non-occlusive way caused deep penetration of Amphotericin B up to viable epidermis [59].

In another study, the efficacy of the terbinafine hydrochloride-loaded liposome film formulation was compared with terbinafine-loaded liposome, ethosome, liposome poloxamer gel and ethosome chitosan gel formulations for the treatment of onychomycosis. The drug was accumulated in the nail plate within the therapeutic range for all film formulations composed of liposomes. Liposome containing film formulation showed improved antifungal activity on fungal nails [57].

Shah and co-workers were able to enhance ungual permeability of terbinafine HCl when delivered in liposome-loaded nail lacquer form to efficiently treat onychomycosis. They optimized the formulation by QbD Approach using a three-factor, three-level, Box–Behnken design. The superior transungual permeability flux of terbinafine HCl through liposome-loaded nail lacquer compared to nail lacquer containing a

permeation enhancer was observed. Thus, liposomal formulation could efficiently treat onychomycosis [55].

Conclusion

The demand for cosmeceutical products is increasing day by day, so the growth of the cosmeceutical industry is exponentially enhancing. Nanotechnology represents the modern technologies of the twenty-first century, offering exceptional opportunities for both research platforms and market place. The rapid spread and commercialization of nanotechnology in cosmeceuticals have given significant technical and economic aspirations. Particularly, liposomes gained enormous attention in the formulation of topical preparations due to their special features and ability of enhanced permeability and improved bioavailability. Thus, cosmeceutical products based on liposomes could be a boon for treating skin disorders.

Abbreviations

UV: Ultraviolet; ROS: Reactive oxygen species; CoQ10: Coenzyme Q10; CU: Curcumin; TNF-α: Tumor necrosis factor *α*; IL: Interleukin; RA: Rosmarinic acid; DGLA: Dihomo-*γ*-linolenic acid; BPO: Benzoyl peroxide; MTX: Methotrexate; RSV: Resveratrol; MASI: Melasma area and severity index; MI: Melanin index.

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Author contributions

Tapan Kumar Shaw was responsible for conceptualization, methodology, data curation, writing the original draft preparation and supervision; Paramita Paul was involved in methodology, data curation, literature review, editing, visualization, and writing, reviewing and editing; and Bappaditya Chatterjee participated in methodology, data curation, and writing and reviewing. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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