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Novel lipid based systems for improved topical delivery of antioxidants

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ABSTRACT: UV induced skin damage by reactive oxygen species is a rapid process which can be averted by application of antioxidants at the onset or during the development of oxidative stress. Antioxidant supplementation is an integral part of a multi-faceted approach in photoprotection. Lipid based carriers have been more and more explored in pharmaceutical technology, showing superior advantages for topical purposes over conventional colloidal carriers. Some of the lipid-based innovations are nanoemulsions which are transparent and have unique tactile and texture properties, nanoparticles which are used in skin-care products, and liposome formulations which contain small vesicles (range: 50–5000 nm) consisting of traditional cosmetic materials that protect light or oxygen-sensitive cosmetic ingredients. A review of the literature is presented in an attempt to emphasize several advantages of lipid based delivery systems for cosmetic and topical applications of antioxidants exemplified using suitable actives.

KEYWORDS: Antioxidants, lipid based carriers, liposomes, microemulsions, nanoemulsions, solid lipid nanoparticles, nanostructured lipid carriers.

INTRODUCTION

The phenomenon of aging is a course of diminished functionality and reserve capacity in all body organs, resulting in an increased likelihood of disease and death. Skin aging is a degenerative process wherein the results due to chronological/intrinsic aging are overlaid with effects produced by environmental factors (e.g., sun, heat, pollution and smoking). Among the extrinsic factors, solar ultraviolet (UV) irradiation is the most significant. Premature skin aging that occurs from excessive exposure to UV light is referred to as photoaging (1). With the decreased ozone layer and transplant immunosuppression there emerges an even greater demand for effective photoprotection (1).

Extensive research on the pathogenesis of photoaging has demonstrated that photodamage is mediated in a part by free radicals. Reactive oxygen species (ROS) are generated when human skin is exposed to UV light. ROS appear to mediate their deleterious effects on aging skin by damaging deoxyribonucleic acid (DNA), cell membranes, and proteins, including collagen. Exposure to ultraviolet B (UVB) also causes direct DNA damage, promoting carcinogenesis (2).

In the baby-boom generation, consumers are eager to reduce wrinkles and smooth out other skin defects. Thus, anti-aging products have acquired skyrocketing demand and brisk sales. As a consequence the global anti-aging market would be worth $115.5 billion by 2010 (3). This overview exemplifies the need for developing highly efficacious anti-aging formulations for the ever increasing global market demand.

Innovative strategies have emerged to protect skin, which help to overcome skin cancer and photoaging. The popular amongst them being sunscreens, which are functional in shielding the skin from UV radiation. However their protection is not ideal because of inadequate use, incomplete spectral protection, cost, safety, non-compliance and toxicity (1).

Recently research based focus is on usage of natural antioxidants (AO) for obliterating the free radicals mediated damaging effects of UV radiation (1). Therefore, formulations appropriately fortified by natural antioxidants could serve to be useful complements to sunscreens in halting the aging process induced by UV exposure (1, 4). Since mostly AO molecules are inherently unstable in nature, deeply coloured and are susceptible to photodegradation in presence of oxygen, it makes them difficult to formulate in an acceptable, stable aesthetic product for cosmetic use (5). Sometimes, chemical modifications may not help, for example, shortening the lipophilic chain of the coenzyme Q_{10} (CoQ_{10}) did not improve pro-oxidative properties of the derivatives. Further the use of conventional delivery systems (e.g. creams and lotions) in several cases showed a little or no improvement in AO properties/profile. These observations facilitate the doorway of novel delivery systems in the development of antioxidant formulations.

Lipid carriers form a protective barrier, make the skin water-resistant, reduce the transepidermal water loss and thus protect the skin against dehydration. By filling up microscopic indentations in the skin they lead to a noticeable smoothening of the skin which simultaneously also reduces minor wrinkles (6). It is also being proved that the unique properties of lipids viz their physiochemical diversity, biocompatibility, which reduces local irritancy, make them ideal carriers for topical usage (7). Besides these common features there are also some specific properties for these innovative systems.

Thus the aim of this paper was to review the scientific literature regarding newly developed lipid based delivery systems for topical antioxidant delivery.

INNOVATIVE LIPID BASED DELIVERY SYSTEMS

1. Emulsions: Following are the different emulsion delivery systems used in cosmetics.

a. **Microemulsions:** They are stable, transparent dispersions of oil and water stabilized by an interfacial film of surfactant molecules and having diameter <100 nm (7). Since microemulsions were discovered approximately six decades ago, their applications in cosmetics have increased because of their good appearance, thermodynamic stability, high solubilization power, and ease of preparation. Penetration of vitamin E and quercetin was enhanced when employed in a microemulsion. Quercetin encapsulated in microemulsion did not cause skin irritation and was effective against UVB induced damage. Microemulsion containing ascorbyl palmitate effectively prevents UVA induced lipid peroxidation (8-10). A study on development of a curcumin encapsulated in oil-in-water phospholipid based microemulsion showed that its degradation was prevented with increase in concentration in aqueous phase (11).

b. **Liquid crystals:** Liquid crystalline phase is the intermediary state between solid and liquid, representing a state of incomplete melting. Emulsions containing liquid crystals have been observed to release active at much slower rate than those without this stabilizing component. For example, timed release of vitamin A palmitate containing liquid crystals dispersed in water-based gel (8, 12).

c. **Multiple emulsions:** Multiple emulsions are a type of polydisperse systems, in which the dispersion phase contains another dispersion phase. They are of two types: w/o/w type and o/w/o type. These are excellent and exciting potential systems for slow or controlled release of actives. O/W/O multiple emulsions have potential applications because of more occlusivity on skin and acceptability. Moreover higher amounts of active substances can be retained in epidermis and dermis using these systems. Ascorbic acid and vitamin A formulated in o/w/o emulsion illustrated multiple emulsions to be effective carrier for stabilizing and improved release profile (5, 13).

d. **Nanoemulsions**: These systems are fine oil-in-water dispersions, having droplet diameter smaller than 100 nm with aesthetic properties i.e. low viscosity and transparency, making these systems suitable for their application in cosmetics. But, in comparison with microemulsions, they are in a metastable state and are very fragile systems by nature (14). The nanoemulsion of CoQ_{10} and vitamin E acetate was proven to be a promising cosmetic ingredient to prevent premature skin aging by protecting the mitochondrial DNA against UV-induced mutations (15). A study on antioxidant synergy formulation nanoemulsion (ASF) containing different tocopherol isomers indicated that preparations containing gamma, alpha, and delta tocopherol enhanced anti-inflammatory properties and increased bioavailability compared to their suspensions (16).

e. **Pickering emulsions:** These are lipid-based emulsions with internal nanostructures stabilized by solid particles such as silica, clays, calcium carbonate, titanium dioxide, latex and many others. The ultra-fine amphiphilic particles are defined as having particle sizes <200 nm. Pickering emulsions are new drug penetration vehicles with specific behaviour; they are well-suited either for targeting the stratum corneum or aimed at slow release of drug from stratum corneum used as a reservoir to the deeper layers of skin (17). The skin absorption of caffeine from silica stabilized pickering emulsion was three fold higher than emulsifier stabilized emulsion attributed to the higher adhesion potential of pickering emulsions (18).

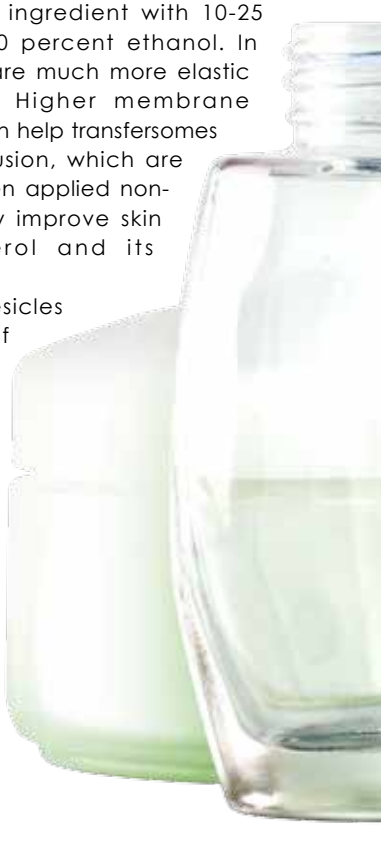
2. **Vesicular systems:** In several studies, the diffusion of a drug was facilitated or achieved certain selectivity into human and nonhuman skin by vesicle encapsulation (85 percent of the papers). Only a few papers claimed that the vesicles have no effect on the skin (5 percent) (17).

a. **Liposomes:** Liposomes are the most widely known vesicular cosmetic delivery systems. These vesicles contain from one to several concentric lipid bilayers with intercalated aqueous sections. Topically liposomes offer wide array of advantages including biodegradability, nontoxicity, moisturizing and restoring action, sustained dermal release and similarity to biological membranes enabling penetration into epidermal barrier compared to other delivery systems (5). Several drugs and cosmetics in this form are already commercially available and successfully used, with lesser incidence of side effects.

b. **Phytosomes:** Some studies have reported that phospholipids exhibit a marked affinity for some classes of flavonoids, a new series of compounds denominated as "phytosome" has been developed by complexation with polar botanical derivatives such as catechin, quercetin, escin and glycyrrhetinic acid. Phytosomes are complexes between a pure phospholipid and pure active principles from the chemical perspective. The soothing activity of silymarin has shown to be increased by six fold in silymarin phytosomes compared to free active principles, which is proposed to be due to higher affinity of complexes for skin phospholipids. The green tea (polyphenol), grape seed, *silybum marianum*, hawthorn extracts and olive polyphenols were successfully commercialized as phytosomes for antioxidant, free radical scavenger, uv protectant actions (19).

c. **Transferosomes**: In the 1990s, transfersomes, i.e., lipid vesicles containing large fractions of fatty acids, were introduced. Transfersomes are vesicles composed of phospholipids as their main ingredient with 10-25 percent surfactant and 3-10 percent ethanol. In consequence, their bilayers are much more elastic than those of liposomes. Higher membrane hydrophilicity and flexibility both help transfersomes to avoid aggregation and fusion, which are observed with liposomes. When applied non-occlusively, they significantly improve skin deposition of α-tocopherol and its photostability (5, 20).

d. **Ethosomes**: They are lipid vesicles containing high content of ethanol (20-50 percent) acting as drug penetration enhancer and fluidizer for membrane. It is proposed that the alcohol fluidises the ethosomal lipids and stratum corneum bilayer lipids thus allowing the soft, malleable ethosomes to penetrate. These carriers transport active substances more efficaciously through the stratum corneum into the



deeper layers of the skin than conventional liposomes (21). The *in vitro* release rate of azelaic acid was more rapid from ethosomal systems (plain and viscous formulations) than from liposomal systems (22).

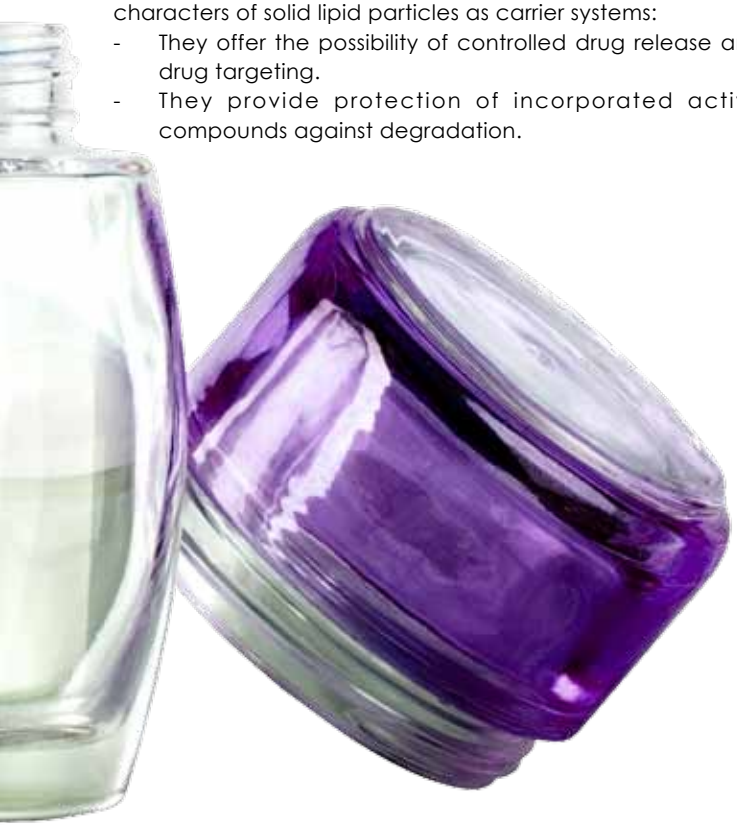
e. **Niosomes:** These are essentially non-ionic surfactant based multilamellar or unilamellar vesicles. The oil spreads uniformly over the surface of the skin; vesicles penetrate the stratum corneum in fractioned form while the continuous aqueous phase evaporates. Consequently a special sensation to touch, freshness, hydration and a feeling of protection because of the oily film is experienced. If the envelope is made of sphingolipids, vesicles are named sphingosomes (7). Manconi et al. concluded that unilamellar niosomes containing Brij® 30 conferred best protection of tretinoin against photodegradation. Gopinath et al. investigated the possibility of converting ascorbyl palmitate into bilayered vesicles with a view to exploit them as carriers for drug delivery. These vesicles were termed as Aspasomes and were found to possess much superior than that of ascorbic acid. Thus, they may find applications as drug delivery system in disorders implicated with reactive oxygen species (5).

f. **Nanotopes™**: Recent advancement in liposomes include monolayered Nanotopes ™ particles, which comprises of membrane having well defined ratio of a phospholipid (i.e., lecithin) and a co-surfactant. Nanotopes are formed at an optimum ratio of phospholipid to cosurfactant, which promotes intercalation of co-surfactant between the lecithin molecules to form a continuous array extending from the lipid-core into the aqueous phase. Baschong et al., showed that nanotopes containing vitamin E acetate exhibited smaller size, greater uniformity, increased skin penetration of active and higher occlusion effect compared to conventional liposomal system (23).

3. **Lipid particulate systems**

Biocompatible lipid micro- and nanoparticles have emerged as potential drug carrier systems as alternative materials to polymers in recent decades. Solid lipid particles combine several advantages and avoid the disadvantages of other colloidal carriers. The following are affirmative characters of solid lipid particles as carrier systems:

- They offer the possibility of controlled drug release and drug targeting.
- They provide protection of incorporated active compounds against degradation.



- Their solid matrix is composed of physiological and well-tolerated lipids.
- They allow for hydrophilic and/or hydrophobic drugs to be incorporated.
- They are stable and scale-up is easy.

The features which determine the loading capacity of drug in the lipid particles are drug solubility and miscibility in melted lipid, chemical and physical structure of lipid materials, and their polymorphic state. Their encapsulation efficiency can vary from 1 to 5 percent for hydrophilic compounds and up to 80 percent for lipophilic compounds (24).

a. **Lipid microparticles**

Microencapsulation is a process in which very thin coatings of inert natural or synthetic materials are deposited around micro-sized particles of solids or droplets of liquids. Commercial microparticles typically have a diameter between 1 and 1000 mm and contain 10 to 90 percent core. Microparticles with size >1 µm are retained in the skin surface or deposited on the surface of the hair follicles therefore preventing skin permeation of substances having a potential. Since microparticles are located on the skin surface forming a film, they can be used for protection against UV radiation in sunscreens. Lipid microspheres, often called lipospheres are fat-based encapsulation system for drug delivery. These are composed of a solid hydrophobic fat core (triglycerides) stabilized by a layer of phospholipids molecules embedded in their surface. The internal core contains the bioactive compound, dissolved or dispersed in the solid fat matrix. Lipid microparticles of cosmetic ingredients such as glycolic acid have shown decreased irritation potential (25) while incorporation of quercetin in lipid microparticles improved photo and chemical stability of the flavonoid (26).

b. **Lipid nanoparticles**

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLC) are novel colloidal delivery systems with many cosmetic and dermatological features; such as skin adhesive properties when applied to the skin resulting in occlusion, enhanced skin hydration, whitening effects, protection against degradation, absorption-increasing effects, active penetration enhancement, and controlled-release properties (7).

SLNs (Nanopearls®) are made of lipids solid at room temperature, the surface being covered by a surfactant shell which stabilizes the dispersion. NLC are mixtures of solid and fluid lipids, the fluid lipid phase is reported to be embedded into the solid lipid matrix or to be localised at the surface of solid platelets and the surfactant layer (27).

The stabilization of chemically labile actives against degradation (e.g., hydrolysis and oxidation) can be achieved using a solid matrix as in case of lipid nanoparticles. For instance, the stability of chemical labile hydrophobic antioxidants like retinol, CoQ_{10}, alpha-lipoic acid, beta-carotene and alpha-tocopherol could be enhanced when incorporated into lipid nanoparticles (7, 28, 29). Likewise iirritant drugs like tretinoin turns out to be less irritating if applied when encapsulated within SLN (30). In a clinical study on curcuminoids loaded SLN cream, these nanoparticles enhanced the anti-aging properties of curcuminoids when compared with conventional cream base with no signs of skin irritation (31). Alpha-lipoic acid encapsulated SLN and NLC formulations demonstrated antioxidant activity at similar level of 0.01 to 10 µM to pure alpha-lipoic acid with low cell cytotoxicity and good physical stability (29). Commercially available products,

NanoRepair Q_{10} ®cream and NanoRepair Q_{10} ®Serum (Germany) which were introduced to the cosmetic market in October 2005 epitomizes the success of lipid nanoparticles in tackling photoaging related crisis (32).

CONCLUSION

Incorporation of antioxidants or radical scavengers in suitable delivery systems is important in order to transport them as cosmetic ingredients against skin ageing, especially as curative/ therapeutic in addition to their prophylactic action. Novel lipid based delivery systems reviewed here possess the potential to develop as the "new generation smarter carrier systems" for topical delivery of antioxidants.

Carrier	Active ingredients	Effects observed	References
Emulsions			
Microemulsions	Quercitin and vitamin E	Incresed skin penetration and diminished skin irritation.	5
Microemulsions	Curcumin	Increased solubility; improved protection against degradation	11
Liquid crystals	Vitamin A palmitate	Sustained release	8,12
Multiple emulsions	Ascorbic acid and vitamin A	Stabilizing effect and improved release profile.	13
Nanoemulsion	CoQ_{10} and vitamin E acetate	Improved anti-aging effect	15
Pickering emulsions	Caffeine	Increased skin penetration	18
Vesicular systems			
Liposomes	(-)-Epigallocatechin-3-gallate and retinoic acid	Increased drug deposition	5
Phytosomes	Green tea (polyphenol), grape seed, *silybum marianum*, hawthorn extracts and olive polyphenols	Exhibit improved free radical scavenging and UV protectant action.	19
Transfersomes	alpha-tocopherol	Improved skin deposition and its photostability	5, 20
Ethosomes	Azelaic acid	*Increased in vitro* release rate compared to liposomes	22
Niosomes	Tretinoin	Protection against photodegradation	5
Nanotopes ™	Vitamin E acetate	Increased skin penetration of active and higher occlusion effect compared to conventional liposomal system.	23
Lipid particulate systems			
Lipid microparticles	Quercitin	Improved photo and chemical stability	
Lipid nanoparticles	Retinol, CoQ_{10}, alpha-lipoic acid, beta-carotene and alpha-tocopherol	Enhanced chemical stability	7,28, 29
SLN	Tretinoin	Diminished skin irritation	30
SLN	Curcuminoids	Enhanced the anti-aging effects with no signs of skin irritation.	31
SLN and NLC	alpha-lipoic acid	Exhibit low cell cytotoxicity and good physical stability	29

Table. 1. Novel lipid based systems explored for antioxidants.

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