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Review | Revisión

Nanocarriers for skin delivery of cosmetic antioxidants

[Nanovehículos para la liberación en piel de cosméticos antioxidantes]

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Abstract

The demand of natural skin care products is steadily growing since consumers perceive them as safe. Currently, cosmetic manufacturers are focusing their efforts on developing innovative natural products to address skin-aging signs, thus meeting consumers' needs of healthy appearance and well-being. To prevent or treat skin aging, topical supplementation with antioxidant is regarded as one of the most promising strategies. However, most antioxidants presently used in skin care formulations show unfavorable physicochemical properties such as excessive lipophilicity or hydrophilicity, chemical instability and poor skin penetration that actively limit their effectiveness after topical application. Therefore, nanocarriers such as liposomes, niosomes, microemulsions and nanoparticles have been widely investigated as delivery systems for antioxidants to improve their beneficial effects in the treatment of skin aging. In this article, the antioxidants most commonly used in anti-aging cosmetic products will be reviewed along with the nanocarriers designed to improve their safety and effectiveness.

Keywords: Anti-aging; antioxidant; cosmetic; nanocarrier; topical delivery system.

Resumen

La demanda de los productos naturales para el cuidado de piel es cada vez mayor ya que los consumidores los perciben como seguros. En la actualidad, los fabricantes de cosméticos centran sus esfuerzos en el desarrollo de productos naturales innovadores para abordar los signos de envejecimiento de la piel y, por tanto, satisfacer las necesidades de apariencia saludable y el bienestar de los consumidores. La suplementación con antioxidantes tópicos está considerada como una de las estrategias más prometedoras para prevenir o tratar el envejecimiento de la piel. Sin embargo, la mayoría de los antioxidantes que se utilizan actualmente en las formulaciones de cuidado de la piel muestran propiedades fisicoquímicas desfavorables como lipofilia o hidrofilia excesivas, inestabilidad química y escasa penetración de la piel, que limita su eficacia después de la aplicación tópica. Por lo tanto, nanovehículos tales como liposomas, niosomas, microemulsiones y nanopartículas han sido ampliamente investigados como sistemas de liberación para antioxidantes, para mejorar sus efectos beneficiosos en el tratamiento de envejecimiento de la piel. En este artículo serán revisados los antioxidantes más utilizados en productos cosméticos en la lucha contra el envejecimiento, junto con los nanovehículos diseñados para mejorar la seguridad y la eficacia.

Palabras Clave: Antienvejecimiento; antioxidante; cosmético; nanovehículo; sistema de liberación tópica.

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INTRODUCTION

Nowadays, consumers worldwide perceive their well-being and appearance as fundamental needs in their habitual lifestyle. Therefore, the demand for cosmetic products that effectively improve skin conditions is constantly growing. In particular, a lot of consumers' expectations are focused on anti-aging products.

Aging is a complex phenomenon in which "extrinsic" processes (photoaging), due to skin exposure to UV radiation, pollutants and cigarette smoke, are superimposed on "intrinsic" physiological processes (chronologic aging).

As reported by Kaur et al. (2007), there is consensus on the fundamental role of reactive oxygen species (ROS) and skin antioxidant capacity in skin aging. Exposure to ROS from different sources has led organisms to develop defense mechanisms (Benzie, 2000; Dröge, 2002) and in human skin, a network of enzymatic and non-enzymatic antioxidant systems is present to counteract oxidative injuries (Valko et al., 2007). This network, consisting of enzymes such as SOD, catalase, glutathione peroxidase and glutathione reductase and of lipophilic (e.g. vitamin E, ubiquinones, carotenoids) and hydrophilic (e.g. vitamin C, uric acid and glutathione) antioxidants, is responsible for the balance between pro-oxidants and antioxidants. When the production of ROS overwhelms the natural antioxidant defenses, the so-called "oxidative stress" occurs, involving damages of lipids, proteins and DNA.

Topical supplementation with antioxidants is regarded as a useful strategy that may improve skin antioxidant capacity to reduce ROS induced skin damages (Dreher and Maibach, 2001; Salavkar, 2011). Therefore, several pharmaceutical and cosmetic formulations have been specially designed to prevent or ameliorate the signs of aging connected to oxidative damage such as wrinkling, actinic lentigines and sagging, thus improving skin healthiness and appearance.

COSMETIC ANTIOXIDANTS

Most skin care formulations claiming anti-aging effects are based on exogenous antioxidants such as vitamins, polyphenols, and flavonoids that cannot be synthesized by our body (Fig. 1).

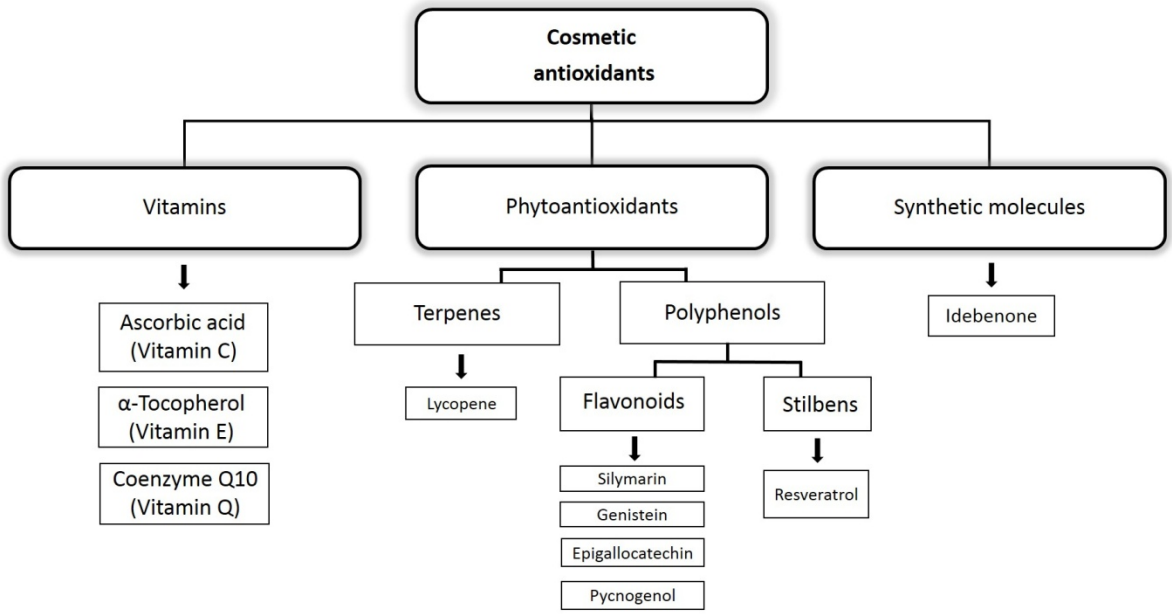

Figure 1. Scheme of some of the most commonly antioxidants used in skin care products.

Over the past decades, the popularity of cosmetic formulations from herbal origin to support the health and integrity of the skin and its appendages has been steadily growing because consumers perceive these agents as natural, healthy, nontoxic and full of beneficial effects.

Many cosmetic products based on botanical active ingredients possess potent antioxidant activity as plants produce plenty of antioxidant compounds to counteract the effect of UV radiation to which they are regularly exposed. Most of plant-derived active ingredients show other biologic properties such anti-inflammatory and anti-carcinogenic activity, apart from antioxidant capacity.

This article will review the most common or innovative antioxidants presently used in skin care products, highlighting their biological effects and their usefulness as anti-aging.

Endogenous antioxidant

Endogenous antioxidants are essentially enzymes such as superoxide dismutase, superoxide reductase, catalase, and glutathione peroxidase that catalytically remove oxidants, thus decreasing their content and preventing oxidative damage. Unfortunately, enzymes like superoxide dismutase and catalase are complicated to stabilize in cosmetic formulations because of their sensitivity to UV light, oxygen and heat. Another endogenous antioxidant is coenzyme Q10 (CoQ10), or ubiquinone, a very lipophilic compound present in all human cells as a component of the mitochondrial respiratory chain that play a key role in maintaining skin homeostasis. At skin level, CoQ10 content is 10-fold higher in the epidermis than in the dermis (Shindo et al., 1994; Hoppe et al., 1999). *In vitro* experiments on dermal fibroblast evidenced CoQ10 ability to suppress matrix metalloproteinases-1 (MMP-1) expression after exposure to UV-B radiation (Inui et al., 2008) while pretreatment with CoQ10 associated with vitamin E significantly inhibited the expression of collagenase, produced by the dermal fibroblasts in response to UVA (Scharffetter et al., 1991). MMP-1 and collagenase are responsible for collagen fibers degradation, playing a fundamental role in skin photo-aging. These findings, together with CoQ10 ability to increase the production of basement membrane components, such as laminin 332 and type IV and VII collagens, in keratinocytes and fibroblasts, respectively, suggest that CoQ10 could be useful as anti-aging (Muta-Takada et al., 2009). Although only few studies have been performed on the effects of CoQ10 after topical application in humans, CoQ10 is included in several anti-aging cosmetic products.

Exogenous antioxidant

Vitamin E

Vitamin E (tocopherol) is one of the better-known antioxidants used in skin care formulations. There are eight active isoforms of this lipophilic antioxidant, which is present in various foods, such as vegetables, seeds, and meat. α-Tocopherol is the most biologically active isoform (Traber and Sies, 1996), which in animals showed photo-protective effects after topical application being able to reduce the number of sunburn cells and UVB-induced damage, and inhibiting photocarcinogenesis (Gensler and Magdaleno, 1991; Trevithick et al. 1992). Further studies evidenced that oral administration of α-tocopherol did not increase its concentration in the skin (Werninghaus et al. 1994) while topical application of vitamin E homologues provided higher vitamin E concentrations in the skin of hairless mice (Thiele et al. 1997a; Weber et al., 1997).

Mayer et al. (1993) reported that topical application of vitamin E 5-8% cream to the face of volunteers resulted in improved signs of photo-aging when compared with placebo. Other researchers (Chung et al., 2002) evidenced that in vivo application to human skin under occlusion 24 h before UV irradiation of a vehicle containing vitamin E 5% inhibited the induction of human macrophage metalloelastase, a metalloproteinase involved in the degradation of elastin.

Many studies pointed out the ability of topically applied vitamin E and its derivatives to inhibit lipid peroxidation induced by UV irradiation (Jurkiewicz and Buettner, 1994; Lopez-Torres et al., 1998), and several researchers (Bissett et al., 1989;

Mayer et al., 1993; Jurkiewicz et al., 1995) have suggested the effectiveness of vitamin E as anti-aging.

Further investigations revealed that associating two or more antioxidants could increase their efficacy, thus providing better photoprotection as shown for the combination of vitamins E and C (Lin et al., 2003).

Vitamin C

Our body is not able to produce vitamin C (ascorbic acid). This essential water-soluble antioxidant can be obtained exclusively from dietary sources such as fruits and vegetables (lemons, oranges, green peppers, watermelon, papaya, grapefruit, strawberries, kiwi, mango, tomatoes) where it is normally present in its reduced form, ascorbic acid. Oxidation processes form dehydroascorbic acid that can revert to ascorbic acid. If oxidation leads to the irreversible opening of the lactone ring, d-ketogulonic acid is formed, from which ascorbic acid cannot be restored, thus making this vitamin ineffective. Therefore, products containing vitamin C should be kept in airtight, light-resistant containers to prevent exposure to air and UV radiation.

Different derivatives such as magnesium ascorbyl phosphate and ascorbyl-6-palmitate have been used to improve ascorbic acid stability in topical formulations. These derivatives are readily converted to ascorbic acid in cell and organ cultures (Nayama et al., 1999) or after ingestion, but they are not effective in improving vitamin C skin content after topical application (Pinnell, 2001).

Numerous biochemical pathways in the human body involve ascorbic acid, including the biosynthesis of collagen, a fundamental component of connective and epithelial tissue. Skin exposure to UV radiation and pollutants can reduce vitamin C content in the epidermis (Thiele et al., 1997b). Therefore, skin supplementation with vitamin C is supposed to be beneficial to restore the physiological functions of the cutaneous tissue.

Several studies evidenced the effectiveness of topical application of ascorbic acid or its derivatives in counteracting skin damages due to photo-aging (Darr et al., 1992). Reduction in UVA-induced lipid peroxidation and secretion of proinflammatory cytokines IL-1 and IL-6 has been reported in ascorbate treated cultured human keratinocytes (Tebbe et al., 1997). Humbert et al. (2003) observed a significant improvement of photo-aged skin after topical application of 5% vitamin C cream for six months in healthy female volunteers. Darr et al. (1996) reported that adding vitamin C to UVA or UVB sunscreens improved sun protection with respect to sunscreen alone.

Various studies outlined the synergic effect of vitamin C and E, pointing out that if free radicals oxidize vitamin E, vitamin C regenerates it (Halpner et al., 1998; Hamilton et al., 2000). Therefore, associations of these photo-protective agents, which act with different mechanisms, could be useful to improve skin photo-protection (Lin et al., 2003; Moison et al., 2002). Due its photo-protective effects and its ability to increase collagen production in human fibroblasts (Geesin et al., 1988), ascorbic acid and its derivatives are largely used in anti-aging products.

Green tea

Green tea is one of the most favorite beverages and the use of its extracts in cosmetic products is on the rise. Among the polyphenolic catechins contained in green extract obtained from the tea plant *Camellia sinensis*, epigallocatechin-3-gallate (EGCG) is the most abundant and the most biologically active. Several *in vitro* and *in vivo* studies in animals and humans evidenced the antioxidant, anti-inflammatory and anticarcinogenic properties of green tea extracts after oral or topical administration (Wang et al., 1991; Katiyar et al., 1995; Gensler et al., 1996; Katiyar et al. 2001). Topical application of green tea extract and some of its components were able to reduce the deleterious effects of sunlight on human skin (Elmets et al., 2001) and to prevent UVA-induced skin damage including wrinkling and sagging in hairless mice (Vayalil et al., 2003). In addition, green tea and EGCG have been reported to be effective free-radical scavengers (Wei et al., 1999; Kim et al., 2001). The overall data support the hypothesis that green tea extracts might be beneficial in preventing photoaging as well. However, as with most of the antioxidants, little clinical data are available on cosmetic products containing green tea extracts.

Although the concentration of phenols in the various products on the market is not standardized, five-percent green tea extract or polyphenols in the 90% range are generally accepted as effective concentrations. As the polyphenols of green tea are sensitive to light and oxidation and the EGCG is a hydrophilic compound with poor ability to penetrate into human skin, cosmetic products containing these active compounds require careful formulation to be effective.

Genistein

The main components of soy are phospholipids, such as phosphatidylcholine and essential fatty acids while among the minor elements, the most active compounds include isoflavones, saponins, essential amino acids, and phytosterols. The most potent isoflavones are the phytoestrogens genistein and daidzein. Recent studies have shown that the lower risk of cardiovascular disease and breast cancer in Asian populations could be attributed to their high intake of isoflavones, related to their large uptake of soy (Glazier and Bowman, 2001). Genistein is a potent antioxidant that can scavenge peroxyl radicals and protects against lipid peroxidation both in vitro (Hwang et al., 2000), and in vivo (Wiseman et al., 2000). In addition, soy isoflavones have potent anti-carcinogenic effects (Bingham et al., 1998) and genistein has been reported to show a strong inhibition activity on tyrosine kinases, which are involved in phosphorylation of proteins necessary for regulation of cell division (Barnes and Peterson, 1995). Topical treatment with estrogens resulted in collagen synthesis and skin thickness increase, which may be particularly useful for postmenopausal women showing thinner dermis with decreased collagen content (Weil et al., 2001). In particular, in vitro studies on skin fibroblasts evidenced genistein collagen-stimulating effects, related to its ability to increase collagen gene expression (Greenwel et al., 1995). Genistein photoprotective effects have been attributed to its ability to inhibit UV-induced oxidative DNA damage (Wei et al., 1996) and to effectively protect human skin against UVB-induced skin photodamage (Wei, 1998; Wei et al., 2003). Due to its different beneficial effects, genistein is included in various skin care formulations claiming anti-aging effects.

Lycopene

Lycopene is a terpene with eight isoprene units, which is responsible for the red color of fruits and vegetables such as tomato, watermelon, pink grapefruit, guava, apricots, papaya and rosehip, representing more than 80% of total tomato carotenoids (Story et al., 2010). Lycopene possesses antioxidant properties superior to those of β-carotene and other common carotenoids, due to its extreme reactivity (Stahl and Sies, 1996). Its many conjugated double bonds make lycopene an unstable molecule that is very susceptible to oxidation when exposed to air and light (Sharma and Le Maguer, 1996). In addition to antioxidant activity, lycopene shows anti-inflammatory, anticancer and anti-mutagenic effects (Giovannucci, 1999; Heber and Lu, 2002; van Breemen and Pajkovic, 2008). After topical application, lycopene can prevent oxidative damage more effectively than β-carotene (Ribaya-Mercado et al., 1995). However, being lycopene a very lipophilic molecule, its permeation into the deeper layers of the skin is unlikely, thus limiting its efficacy from conventional topical formulations. Due to its unfavorable physicochemical properties, at present, the use of lycopene as an active ingredient is not widespread in the cosmetic sector but different researches are in progress to design carriers to improve its skin delivery.

Silymarin

Silymarin is extracted from the fruit, seeds and leaves of the milk thistle plant, *Silybum marianum*, which is one of the oldest and better-known plants of ancient times for the treatment of liver and gallbladder disorders. Silymarin is a mixture of three natural polyphenolic flavonoids: silybin (silibinin), silydianin, and silychristine. The main component silibinin is considered the most biologically active, due to its potent antioxidant activity and its ability to modulate differently molecular changes caused by skin exposure to xenobiotics and UV radiations. Scavenging free radicals, preventing lipid peroxidation and decreasing the production of pyrimidine

dimers are some of silybin most known effects (Svobodová et al., 2003). In vivo studies in hairless mice, topically treated with silybin prior to UV irradiation, have shown photo-protective effects with a significant decrease in the number of skin carcinomas (Dhanalakshmi et al., 2004).

Hung et al. (2010), studying skin permeation of silymarin components reported that being silibinin the most lipophilic, it showed the highest skin deposition. Recently, topical application of silymarin cream for the treatment of melasma patients proved to be safe and effective, providing significant pigment improvement and lesion size reduction (Altaei, 2012). Topical creams containing silymarin are becoming increasingly popular due the ability of this extract to prevent a wide range of skin disorders, and SkinCeuticals Inc. have launched the first-skin care product based on silymarin.

CoffeeBerry®

Stiefel Laboratories launched a cosmetic product based on a new potent antioxidant extracted from the fruit of the coffee plant *Coffea arabica* in 2007, whose proprietary name is CoffeeBerry®. This extract contains polyphenols including chlorogenic acid, condensed proanthocyanidins, quinic acid, and ferulic acid (Farris, 2007). The oxygen radical absorbance capacity assay (ORAC) showed that the antioxidant activity of Coffeeberry® was stronger than that of other well-known antioxidants such as green tea extract, pomegranate extract, vitamin C and E (Farris, 2007).

In vitro assays on human cultured fibroblasts treated with different concentrations of Coffeeberry® evidenced its ability to increase collagen content by up-regulating gene expression for connective tissue growth factor and down-regulating metalloproteinases' expression (Chen et al., 2008). Clinical trials performed on patients with actinic damage evidenced a statistically significant improvement in fine lines, wrinkles, pigmentation, and overall appearance after a 6-week period of treatment with a skin care system consisting of 0.1% CoffeeBerry® cleanser and 1% day and night creams. In addition, no significant side effects have been reported, supporting the safety of these products. Investigations are currently ongoing to assess the use of the CoffeeBerry skin care system associated with retinoids and intense pulsed-light treatments (Farris, 2007). However, the antioxidant effects of skin care formulations based on CoffeeBerry® need additional studies to support their effectiveness and safety.

Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene), a polyphenolic phytoalexin found in grapes, nuts, fruits (colored berries), and many red wines (Siemann and Creasy, 1992), exists in two isoforms and the trans isomer is more stable and biologically active (Orallo, 2006). Resveratrol is a potent antioxidant with strong anti-inflammatory and antiproliferative properties (Amri et al., 2012). Recent studies reported that this compound was able to inhibit UV-induced lipid peroxidation being 95% efficient, compared with ~65% for vitamin E and ~37% for vitamin C (Miura et al., 2000). After topical application of resveratrol in hairless mice prior to UV-B radiation, inhibition of cellular proliferation was observed (Afaq et al., 2003). *In vitro* studies on cell cultures of keratinocytes exposed to UVA evidenced resveratrol ability to reduce ROS levels (Adhami et al., 2003). In addition, resveratrol acts on cellular signaling pathways, including pro-inflammatory mediators and regulators of cell survival and apoptosis (Kundu and Surh, 2008).

Because of its antioxidant and anti-inflammatory activities, resveratrol appears to offer anti-aging skin benefits, and different commercial skin care formulations contain this active ingredient. In quantities contained in skin care products, resveratrol seems to be safe.

Grape seed

Grape seed is obtained from *Vitis vinifera,* and its principal components are proanthocyanidins, fatty acids, and vitamin E, C, and D. Proanthocyanidins, belonging to the flavonoid family, are potent antioxidants due to radical scavenging, quenching, and enzyme-inhibiting actions (Ariga, 2004).

The antioxidant activity of proanthocyanidins was reported to be much stronger than vitamin C or vitamin E in aqueous systems (Bagchi et al., 2000).

Animal studies evidenced the preventive actions of proanthocyanidins on diseases such as atherosclerosis, gastric ulcer, large bowel cancer, cataracts and diabetes (Mittal et al., 2003).

In human epidermal keratinocytes, grape seed proanthocyanidins reduced UV-B photo-damage by inhibiting depletion of natural antioxidant defenses (Mantena and Katiyar, 2006).

Due to its skin moisturizing and antioxidant properties, grape seed oil is largely used as an active ingredient in cosmetic products. This oil contains fatty acids such as linoleic, oleic, palmitic, stearic, alpha-linolenic, palmitoleic acids and vitamins E, C, D. These fatty acids help repair damaged skin, wrinkles around the eyes, stretch marks and, therefore, grape seed oil has been included in cosmetic products claiming anti-aging effects.

Pomegranate

One of the most interesting active ingredients "re-discovered" in the last decade is pomegranate extract, obtained from different parts of the fruit *Punica granatum*, such as juice, seed, and peel. Because of its many beneficial effects, pomegranate extracts have been used in various cultures as a traditional medicine for centuries.

Pomegranate fruit contains a wide range of polyphenols including ellagic acid, flavonoids, anthocyanidins, tannins, and vitamin C. In particular, the phenolic components have potent antioxidant activity (Gil et al., 2000). *In vivo* studies evidenced that catalase, peroxidase, and superoxide dismutase activity increased after topical application of pomegranate peel extract (Chidambara et al., 2000). *In vitro* studies in normal human epidermal keratinocytes showed pomegranate extract ability to prevent photodamage induced by UV-A and UV-B radiations (Afaq et al., 2005; Syed et al., 2006).

In addition, pomegranate extract contains conjugated fatty acids that have anti-inflammatory activity because of their ability to inhibit the synthesis of prostaglandins from arachidonic acid (Schubert et al., 1999). Among these conjugated fatty acids, conjugated linoleic acid (CLA) has a particular importance, as it is one of the strongest cancer preventive natural compounds (Belury, 2002). Pomegranate seed oil contains other important bioactive compounds such as the steroidal estrogen estrone, and 17-alpha-estradiol, the last being the mildest and safest steroidal estrogen and a potent antioxidant (Sharaf and Nigm, 1964).

With its anti-inflammatory, anti-aging and soothing effects, pomegranate extracts are favorite ingredients for a number of cosmetic products.

Pycnogenol

Pycnogenol, derived from the French maritime pine, *Pinus pinaster,* is a water-soluble extract that contains flavonoids of the proanthocyanidin family, dimers and oligomers of these proanthocyanidins, along with some organic acids such as cinnamic, gallic, fumaric, caffeic, vanillic, ferulic. Pycnogenol acts as free-radical scavengers and antioxidant. It is more potent than vitamin E and C and has a synergic effect with these vitamins (Fitzpatrick et al., 1998). Oral administration of this active compound has been proven beneficial in the prevention of cardiovascular diseases while it is helpful in preventing skin oxidative damage after topical application. *In vivo* studies on mice evidenced immunosuppression and a reduction of the inflammatory sunburn reaction after topical application of pycnogenol (Sime and Reeve, 2004). Pycnogenol was able to provide photoprotection also in humans after oral administration (Saliou et al., 2001). As anti-aging, pycnogenol efficacy could be also attributed to its ability to inhibit proteolytic enzymes such as collagenase and elastase, thus slowing early wrinkles that occur because of collagen and elastin degradation, which affects skin elasticity (Vertuani et al., 2001). In addition, no adverse effect has been observed after oral or topical administration of pycnogenol. At present, only few anti-aging products contain pycnogenol as an active ingredient but their number is expected to increase due to pycnogenol favorable properties.

Idebenone

Unlike all the natural active compounds described in the previous paragraphs, idebenone is a synthetic molecule with a shorter acyl side

chain with respect to its natural analogue, CoQ10. *In vitro* studies evidenced that the idebenone can act as an antioxidant by inhibiting lipid peroxidation and protecting cell membranes and mitochondria from oxidative stress (Suno and Nagaoka, 1984; Suno and Nagaoka, 1985). McDaniel et al. (2005a) reported that the idebenone is a stronger antioxidant compared to vitamin E, CoQ10, kinetin, l-ascorbic acid, and alpha lipoic acid. Being less lipophilic than CoQ10, idebenone is expected to permeate the skin better than its parent compound. A clinical trial performed on female subjects with moderate photodamage showed that the topical application of skin care formulations containing idebenone was effective in reducing skin roughness/dryness and fine lines/wrinkles and improved the overall appearance of the skin (McDaniell et al., 2005b). However, the effects on wrinkles could be most likely attributed to increased skin hydration due to vehicle application rather than to idebenone antioxidant activity. Although idebenone is regarded as safe, cases of contact dermatitis have been reported after topical application of idebenone 0.5% creams (McAleer and Collins, 2008). At present, different idebenone based skin care formulations claiming anti-aging effects are available in the market.

NANOCARRIERS FOR COSMETIC ANTIOXIDANTS

Nanocarriers (NCs) are colloidal delivery systems having particles or droplets whose size is below 500 nm. At cutaneous level, NCs can be applied on the skin surface to achieve a local effect within the skin (dermal delivery) or a systemic effect (transdermal delivery).

In cosmetics, formulators' objective when using NCs is to optimize the delivery of the active ingredient(s) on or within the skin layers while limiting, as much as possible, percutaneous absorption processes and hence, systemic absorption (Arora et al., 2012).

NCs are especially advantageous as cosmetic delivery systems because they can improve perceived or measured performance of cosmetic products. In particular, NCs such as liposomes, niosomes, solid lipid nanoparticles, etc. could be useful to improve topical effectiveness of antioxidants as these carriers show many advantages compared to conventional topical formulations such as improved active compound stability and water solubility, increased bioavailability and targeting to specific skin layers.

As reported in the previous section, most antioxidants show unfavorable physicochemical properties that could limit their effectiveness after topical application. Some antioxidants are very lipophilic (e.g. CoQ10, lycopene, resveratrol) and being the outermost layer of the skin lipophilic, they could tend to accumulate in the stratum corneum while their penetration into the deeper layers, where they are supposed to exert their activity, could be weak. On the contrary, very hydrophilic antioxidants, like ascorbic acid, could not be able to penetrate into the lipophilic horny layer, thus resulting ineffective after topical application. Most antioxidants are unstable, and their sensitivity to UV radiation and to oxygen makes difficult to formulate acceptable, stable conventional compositions for cosmetic use. In addition, some antioxidants are colored, rendering the production of an acceptable aesthetic formulation very complex.

Loading cosmetic antioxidants into suitable NCs delivery systems could represent a successful strategy to increase the effectiveness of anti-aging products by improving the solubility, permeability, and stability of antioxidants.

In this article, the most promising nanocarriers of current interest to deliver cosmetic antioxidants will be reviewed.

Liposomes and niosomes

Liposomes consist principally of natural or synthetic phospholipids that spontaneously are aggregated in an aqueous medium to form spherical vesicles. Phospholipids are arranged in bilayer structures with the polar head groups located at the surface of the membranes, in contact with an aqueous medium, and the fatty acid chains forming the hydrophobic core of the membranes, shielded from the water.

Liposomes can entrap both hydrophilic and lipophilic active ingredients as polar molecules can be dissolved in the aqueous core, while

hydrophobic molecules can be encapsulated in the lipophilic domains of the bilayer structure (Schuber et al., 1998). Entrapment efficiency depends on different factors such as physicochemical properties of the active compound, phospholipids forming the bilayers and preparation methods.

Liposome size can range from 15 nm up to several μm and depending on the number of their bilayers; liposomes can be classified as small unilamellar vesicles (SUV, containing a single bilayer), large unilamellar vesicles (LUV, containing a single bilayer) or multilayer vesicles (MLV).

Many reasons account for liposome widespread use in the cosmetic industry: ease of preparation, safety, similarity of their structure with that of the skin, biodegradability, ability to improve skin penetration of active ingredients, feasibility of targeting the entrapped compounds to specific skin layers minimizing side effects due to systemic absorption, and skin moisturizing and restoring effects of their constitutive lipids. In addition, liposomes may form a reservoir of active compound in the skin and its appendages, thus providing a sustained release, which could be useful to prolong active compound effects.

The first liposomal cosmetic product was the anti-aging cream 'Capture', launched on the market by Dior in 1986. This formulation contains thymus extracts, collagen, elastin, and peptides and its beneficial effects on aged skin are attributed to its ability to increase the cellular activity and to enhance the strength and tone of the skin because of its content in connective tissue components. Later, several cosmetic active ingredients have been entrapped into liposomes to improve their topical delivery and, hence, their effectiveness. Some liposomal cosmetic formulations containing antioxidants to prevent or to ameliorate skin aging currently available in the market are reported in Table 1.

Foco et al. (2005), investigating the effect of sodium ascorbyl phosphate entrapment in liposomes on skin photoprotection, observed a significant increase of sodium ascorbyl phosphate skin penetration from liposomal vehicles. Ascorbyl palmitate was used to form vesicles (Aspasomes) in combination with cholesterol and a negatively charged lipid (dicetyl phosphate). *In vitro* assays evidenced a better antioxidant activity of Aspasomes compared to free ascorbic acid and skin permeation enhancing effects of ascorbyl palmitate (Gopinath et al., 2004).

Encapsulating CoQ10 into a liposomal formulation for topical application composed of soybean phosphatidylcholine and α-tocopherol, a significant increase of CoQ10 content in rat skin was observed compared to an unencapsulated suspension. This enhancement effect was dependent on the treatment time and the amount of CoQ10 in the vehicle (Lee and Tsai, 2010). Sacher et al. (2006) investigated the antioxidant activity of CoQ10 entrapped in flexible liposomes. These nanosized (80-250 nm) unilamellar vesicles are prepared of soybean phosphatidylcholine (>80%), having a high content of linoleic acid.

Clinical study have evidenced that flexible liposomes show cosmetic interesting properties such as wrinkle reduction and increase in skin smoothness. Likely it is due to their ability to provide the skin both with choline, a component of the natural moisturizing factor, and with essential polyunsaturated fatty acids, promoting the formation of ceramides. Entrapment of CoQ10 in flexible liposomes increased its intrinsic protection with respect to an ethanol CoQ10 solution and the anti-oxidative potential became immediately relevant.

Kanga et al. (2010) evaluated the effect of flexible liposomes on genistein skin permeation in haired and hairless skin. The authors concluded that skin permeation of active ingredients from flexible liposomes was affect by the presence of hair follicles as greater permeation rate and accumulation of genistein was obtained from the flexible liposomes in haired skin while conventional liposomes were more effective in hairless skin.

Phospholipids vesicles, structurally similar to liposomes but containing 10-25% percent surfactant and 3-10% ethanol or 20-50% ethanol and water, are defined transfersomes and ethosomes, respectively. These nanocarriers were designed as an improvement of liposomes to enhance the delivery of the entrapped active ingredients. Transfersomes are ultradeformable vesicles

initially developed as transdermal drug delivery systems (Cevc, 1996). These nanocarriers, along with flexible liposomes, could be useful to incorporate cosmetic antioxidants as they can protect these sensitive active ingredients from light and chemical degradation while improving their topical effectiveness.

Recently liposomes loading resveratrol were prepared from saturated phosphatidylcholine and cholesterol or its positively charged derivative (Bonechi et al., 2012). Liposome properties such as mean size and presence of oligolamellar structures depended on the loading of resveratrol that interacted with the bilayers and was more deeply inserted in cationic liposomes than in zwitterionic liposomes. Resveratrol loaded liposomes were reported to be safe, but their effects on skin permeation were not investigated. In another study, resveratrol was loaded into different nanocarriers (liposomes, polymeric lipid-core nanocapsules and nanospheres and solid lipid nanoparticles) and its photostability and skin permeation profiles were assessed in comparison with an ethanol solution of this active compound (Detoni et al., 2012). All the nanocarriers tested protected resveratrol from photoisomerization and improved its penetration into the skin.

Table 1. Anti-aging skin care products containing antioxidants loaded into nanocarriers.

Active ingredients/Nanocarrier	**Trade name**	**Manufacturer**	**Use**
Ascorbyl palmitate, tocopherol , retinol/ liposomes	Rovisome ACE Plus	Rovi Cosmetics International GmbH	Anti-aging, wrinkle reduction
Vitamin E/Nanotopes	Tinoderm E	Ciba Specialty Chemicals	Anti-inflammatory, anti-aging
Coenzyme Q10, Niacinamide/Liposomes	Ageless Facelift cream	I-Wen Naturals	Anti-aging, anti-oxidative, wrinkle reduction
Sea buckthorn pulp oil, vitamin E/Nanoemulsion	Nano Vit nc/oA	Mibelle Biochemistry	Celle regeneration, protection against UVA
Coenzyme Q10, Vitamin E acetate/Nanoemulsion	Nano-Lipobelle H-EQ10 cream	Mibelle Biochemistry	Anti-aging, anti – inflammatory
Pro-Retinol A/Nanosomes	Revitalift	L'Oreal	Anti-wrinkle, anti-aging
Coenzyme Q10/Nanostructured lipid carriers	Cutanova Nano Repair Q10 Cream	Dr. Rimpler GmbH	Revitalising, anti-aging
Genstein/Liposome	Lipobelle Soyaglycone	Mibelle Biochemistry	Antioxidant
CoQ10, vitamin E and C/Nanoemulsion	Nano-Lipobelle DN CoQ10 oA	Mibelle Biochemistry	Anti-photoaging, and metabolic activation
Vitamins A, E, and C/Nanoemulsion	Nano-Lipobelle H-AECL	Mibelle Biochemistry	Anti-wrinkle, anti-aging
Vitamin E, panthenol/Nanocapsules	Lancôme Soleil Soft-Touch Anti-Wrinkle Sun Cream SPF 15	L'Oreal	Revitalising, anti-aging
Grape seed extract, vitamin E, green tea extract/ Fullerenes	Sircuit Addict Firming Antioxidant Serum	Sircuit Skin Cosmeceuticals Inc.	Revitalising, anti-aging
Vitamin C/ Nanocapsules	Collagen Stimulator Factor MAP®	Cosmetochem	Stimulation of collagen production

Park et al. (2014) proposed the use of chitosan coated liposomes to enhance *in vitro* skin permeation of resveratrol. The results of this study showed that chitosan coating increased liposome stability and enhanced resveratrol skin permeation. As chitosan is a natural positively charged polymer, the authors suggested that a better interaction between chitosan coated liposome and the negatively charged skin occurred.

Different catechins, including epigallocatechin-3-gallate were encapsulated into liposomes prepared using anionic surfactants such as deoxycholic acid and dicetyl phosphate in the presence of 15% ethanol (Fang et al., 2006). The results of this study pointed out an increase of catechin permeation up to seven-fold as compared to the control and epigallocatechin-3-gallate showed the highest encapsulation rate and in vivo skin deposition level in liposomes among all catechins tested.

To improve topical delivery of vitamin E acetate, Padamwar and Pokharkar (2006) encapsulated this antioxidant in liposomes having different phospholipids/cholesterol ratios. The authors observed that vesicle size and vitamin E acetate deposition after *in vitro* topical application on rat skin were dependent on the lipid concentration and lipid/drug ratio. The most promising liposomal dispersion showed seven-fold increase in skin deposition of vitamin E acetate compared to control (free vitamin E acetate). An *in vitro* study comparing vitamin E acetate skin penetration from liposomes (Rovisome®), microparticles (Roviparts®) and an O/W lamellar type cream evidenced that the liposomal formulation delivered a greater amount of vitamin E acetate into the horny layer compared to the other vehicles (Lampen et al., 2003). The authors attributed these results to liposomal formulation ability to increase reservoir capacity of the stratum corneum and to activate the upper epidermal cells.

In addition to liposomes, phospholipids, having strong bond affinity for some polyphenols, can form the so-called "phytosome" (Bombardelli et al., 1989). Unlike liposomes, which consist of an aggregate of hundreds of phospholipid molecules into a single vesicle, a phytosome is a complex where two molecules, one phospholipid, generally phosphatidylcholine, and one polyphenol, form hydrogen bonds between the polar head of the phospholipid and the polar groups of the polyphenol (Kidd, 2009).

At the beginning, phytosomes, whose sizes range from 50 nm to a few hundred μm, have been developed to improve the efficacy of polyphenols with poor bioavailability after oral administration. As phytosomes are better absorbed than liposomes, they can improve the bioavailability of their phytoconstituents and hence, their beneficial effects (Sowjanya et al., 2010).

The first commercial phytosome formulation contained the flavonolignan silybin and was denominated Siliphos® Phytosome™. Clinical studies evidenced that the phytosome formulation provided higher plasma and liver concentrations of silybin than the conventional, non-phytosome form after oral administration (Kidd and Head, 2005). Investigations on Sylimarin Phytosome anti-aging activity demonstrated increased silymarin effectiveness after topical application in phytosome formulations compared to the free active ingredient. This improvement has been attributed to a higher affinity of the complex for skin phospholipids and to a prolonged release of the active ingredient from phytosome formulations (Bombardelli et al., 1991).

Other antioxidants such as curcumin, green tea and grape seed extracts have been used to form phytosomes (Kidd, 2009) but to date their activities have not been investigated after topical application, although phytosome could be helpful to improve the effectiveness of polyphenol antioxidants in cosmetic formulations (Bombardelli et al., 1995).

Liposomes based on a natural marine lipid extract containing a high polyunsaturated fatty acid (PUFA) ratio have been defined Marinosomes®. Although these lipids are not present in the skin, cutaneous enzymes can metabolize them leading to metabolites with

anti-inflammatory and anti-proliferative activity (Ziboh et al., 2000), which could be beneficial in the treatment of several skin disorders. As preliminary studies showed that these carriers are well tolerated at skin and ocular level, they have been suggested as promising delivery systems for both cosmetic and pharmaceutical formulations (Moussaoui et al., 2002).

Colloidal carriers similar to liposomes but having a mono-layered membrane, consisting of a phospholipid (i.e. lecithin) and a co-surfactant, surrounding a lipid core, have been marketed as "Nanotopes"®. These nanocarriers show very small particles size (20 -40 nm) and better stability compared to liposomes. To obtain Nanotopes, a suitable ratio of phospholipid to co-surfactant is required, allowing the co-surfactant to intercalate between the lecithin molecules and to form a continuous layer from the lipid core to the external water phase. Comparative studies on vitamin E acetate loaded into Nanotope and in liposomes revealed the superior ability of Nanotopes in depositing this vitamin in the skin, thus increasing its effectiveness (Baschong et al., 2001).

Niosomes are similar to liposomes in that they are vesicular carriers in the nano-size range but their bilayers consist of non-ionic surfactants instead of phospholipids (Manosroi et al., 2008). The primary advantage of niosomes compared to liposomes is their greater stability as they are not easily hydrolyzed or oxidized during storage.

Generally, niosomes are obtained from non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class, and they are stabilized by adding cholesterol and a small amount of anionic surfactant as dicetyl phosphate. These nanocarriers are formed by self-association of non-ionic surfactants in an aqueous phase and, like liposomes, are able to load both hydrophilic and lipophilic compounds. Their structure can be modified providing sustained or controlled delivery of the incorporated active ingredients (Waddad et al., 2013).

Niosome production was first started from cosmetic industry as they were patented by L'Oréal in the 1970s and 80s, and the first product 'Niosome' was launched in 1987 by Lancôme. Later, due to their peculiar technological properties, potential applications of niosomes as drug delivery systems were widely investigated for different molecules including doxorubicin, insulin, oligonucleotide, α-interferon and many others, having various applications such as antioxidant, anticancer, antimicrobial, anti-inflammatory and so on (Ali et al., 2012; Moghassemi and Hadjizadeh, 2014).

Niosomes have been investigated as carriers in skin care products because of their advantages such as ability to increase active ingredient stability and skin penetration and to improve bioavailability of poorly absorbed ingredients. Topical efficacy of niosomes in aqueous dispersions was evaluated with respect to conventional formulations such as emulsions. These nanocarriers showed lower toxicity allowing a controlled skin delivery of the entrapped active ingredients that are useful properties for skin moisturizing and tanning products (Handjani et al., 1979).

Junyaprasert et al. (2012) reported that niosomes entrapping ellagic acid (EA), a polyphenol found in different fruits and plants, were able to increase EA delivery through human epidermis and dermis compared to an EA solution. *In vitro* skin permeation studies showed that penetration of EA from the niosomes, consisting of Span 60 and Tween 60 2:1, depended on their vesicle size, their EA content and the type of solubilizers used for their preparation.

Elastic and non-elastic niosomes of gallic acid (GA), an antioxidant present in some fruits and plants, were prepared and assessed for their entrapment efficiency and their ability to improve GA skin permeation. Non-elastic niosomes showed better entrapment efficiency while elastic niosomes provided increased GA permeation through the skin (Manosroi et al., 2011). The authors concluded that elastic niosomes could be useful carriers for skin anti-aging molecules.

Polymeric nanoparticles

Polymeric nanoparticles are colloidal systems whose size can range from 10–1 000 nm in diameter and include nanospheres and nanocapsules. These carriers show some advantages

compared to conventional formulations such as increased solubility and improved absorption of active ingredients, good stability, biodegradability and good tolerability.

While nanocapsules, having an oily core surrounded by a polymeric membrane, are reservoir type systems, nanospheres are matrix systems, where a polymeric structure retains or adsorbs the active components (Guterres et al., 2007). Incorporated active ingredients can be located in different domains of the particles, depending on their physicochemical properties, and the structure of the carrier as they can be dissolved in the matrix (nanosphere) or in the liquid phase (nanocapsules) or adsorbed at the nanoparticles surface.

These particles can be obtained from natural or artificial, biodegradable polymers and the most commonly used are poly-L-lactic acid (PLA) and copolymers with glycolic acid (PLGA) (Alexis et al., 2008; Ajazuddin, 2010).

In recent years, nanospheres use in skin care products designed to address the signs of skin aging has been steadily increasing as these nanocarriers are supposed to provide deeper skin penetration of the incorporated active compounds, thus improving their beneficial effects.

PLGA nanospheres encapsulating a vitamin C derivative (ascorbyl tetraisopalmitate), tocopherol acetate and retinyl palmitate were assessed for their effectiveness as anti-aging (Tsujimoto, 2006). The results of this study showed a marked reduction of wrinkle formation when these nanospheres were topically applied before UVA irradiation, likely because of their ability to penetrate the skin, allowing vitamin accumulation in the dermis.

Polymeric nanoparticles entrapping natural antioxidants have been widely investigated to evaluate their effectiveness after oral and parenteral administration (Bonifácio et al., 2014) but their potential as carriers for cosmetic antioxidants is still to be explored.

A recent review (Watkinson et al., 2013) addressed the safety issue of topical application of nanoparticles, one of the major concerns of pharmaceutical and cosmetic manufacturers. The authors used a theoretical approach to determine nanoparticles ability to penetrate healthy human skin, clearly demonstrating that intact nanoparticles could not permeate through the skin due to their large sizes, although they were able to increase skin permeation of entrapped active ingredients.

Solid lipid nanoparticles and nanostructured lipid carriers

About two decades ago, solid lipid nanoparticles (SLN) were developed to overcome the drawbacks of other colloidal carriers while maintaining their positive features. Some of the main advantages of SLN can be summarized as follows: ability to incorporate lipophilic and hydrophilic active compounds, improved stability and bioavailability of the entrapped molecules, controlled release and targeting, safety, low cost of production and easy scale-up. Due to their great versatility, these nanocarriers have been investigated for different routes of administration such as oral, parenteral and topical (Ekambaran et al., 2012; Doktorovova et al., 2014). In particular, topical administration of active compounds loaded into SLN could allow preventing their systemic absorption and hence, side effects. Furthermore, their small size ensures a close contact with the stratum corneum, facilitating drug skin penetration.

These nanocarriers are prepared from solid lipids and stabilized by different surfactants. As the core of these lipid particles is solid, during preparation and storage lipid crystallization may occur, leading to active compound leakage from the nanoparticles and low encapsulation efficiency. To improve drug loading, a second generation of lipid particles, called nanostructured lipid carriers (NLC), were developed by partially replacing the solid lipid with a liquid lipid. As these systems contain a mixture of fluid and solid lipids, the matrix of the lipid core is less organized compared to SLN, thus accommodating greater amounts of active compounds with minor problems of leakage. Therefore, these novel lipid carriers show improved efficiency of encapsulation and reduced expulsion of the active ingredients during encapsulation and storage.

The feasibility of using SLN and NLC in cosmetic formulations has been widely reviewed (Schäfer-Korting et al., 2007; Pardeike et al., 2009) and several studies investigated the usefulness of these carriers as skin delivery systems for antioxidant agents.

An *in vitro* study on keratinocytes cultures evaluated resveratrol intracellular delivery from SLN or solutions (Teskač and Kristl, 2010). Loading resveratrol into SLN increased its solubility, stability, and intracellular delivery while resveratrol in solution was slightly cytotoxic. A comparison between SLN and NLC containing resveratrol evidenced a greater ability of NLC to increase the antioxidant *in vitro* penetration into rat skin (Gokce et al., 2012a).

These authors (Gokce et al., 2012b) also compared the antioxidant activity of CoQ10 loaded into liposomes or SLNs in cell cultures of normal human dermal fibroblasts. Their results evidenced CoQ10 ability to enhance cell proliferation when entrapped in liposomes while CoQ10 loaded SLN did not show any protective effect against ROS accumulation. Therefore, in this study liposomes proved superior to SLNs in improving CoQ10 antioxidant activity.

CoQ10 loaded NLC were tested in comparison with CoQ10 loaded nanoemulsions to determine the amount of antioxidant permeated through excised human skin (Junyaprasert et al., 2009), revealing that nanoemulsions provided greater CoQ10 skin penetration after 24 hours of topical application. On the contrary, Li and Ge (2012) studying in vitro permeation through guinea pig skin of the synthetic CoQ10 analogue idebenone from NLC, nanoemulsions, and an oil solution, reported that the cumulative amount of idebenone permeated from NLC was about three-fold greater than that observed from nanoemulsions or oil solution.

Recently, Montenegro et al. (2012) investigated *in vitro* skin permeation of idebenone from different SLN, evidencing a skin targeting effect depending on nanocarrier composition and the amount of active ingredient loaded.

The conflicting results obtained from the evaluation of lipid nanocarrier ability to improve skin permeation of antioxidants points out the need of further studies to investigate the actual potential of these delivery systems to improve topical effectiveness of antioxidant agents.

Microemulsions and nanoemulsions

As reported in the literature (Azeem et al., 2009; Huang et al., 2010), microemulsions and nanoemulsions are two different terms to define the same type of formulations consisting of oil, water, surfactants and eventually co-surfactants that are thermodynamically stable and that appear to be transparent or translucent with a bluish coloration.

In 1959, Schulman, Stoeckenius, and Prince, visualizing the existence of small emulsion-like structures by electron microscopy, coined the term “microemulsions. This term is a misnomer as these systems have droplet size in the nanometric scale (generally in the range of 10–100 nm). Therefore, they could be better qualified as nanoemulsions, a definition that is being increasingly preferred (Azeem et al., 2009). However, recently, some authors used the term nanoemulsions to indicate precisely systems having droplet diameter smaller than 100 nm that are in a metastable state compared with microemulsions, and hence, they are very fragile systems (Sharma and Sharma, 2012).

Compared to macroemulsions, microemulsions show better stability as they do not have problems such as creaming, flocculation, coalescence and sedimentation, commonly associate to macroemulsions. Microemulsions advantages include an active ingredient targeting and increased penetration, biocompatibility, and low toxicity because of their non-ionic nature, ability to incorporate lipophilic and hydrophilic active ingredients, controlled release of the active ingredients (Moghassemi and Hadjizadeh, 2014). Therefore, these nanocarriers have been investigated as drug delivery systems for oral, parenteral, intranasal, intra-tracheal and topical use.

In cosmetic skin care products, microemulsions are widely used in moisturizing formulations because of their occlusion effects, pleasant appearance and ease of application. Due to these peculiar properties, cosmetic companies have

been exploring microemulsion potential as delivery vehicles for anti−aging products and several studies have been performed to assess antioxidant skin permeation from these carriers.

In an *in vitro* study on porcine skin, topical delivery of lycopene from microemulsions containing different oil phases was investigated (Lopes et al., 2010). These microemulsions increased lycopene skin penetration both in the stratum corneum and in the viable skin, and the antioxidant activity of skin was ten-fold higher than untreated skin. In addition, these micro-emulsions proved safe as demonstrated by cytotoxicity studies in cultured fibroblasts.

Oxyresveratrol *in vitro* permeation through snake skin was evaluated from an optimized microemulsion or a conventional ointment (Vaseline), evidencing a 93-fold increase when this antioxidant was incorporated into a microemulsion (Sasivimolphan et al., 2012).

Microemulsions have been extensively investigated as carriers for topical delivery of vitamin E and C. In an initial study (Martini et al., 1984), an interesting targeting effect was evidenced from o/w or w/o microemulsions of vitamin E as these formulations delivered the vitamin mainly to the epidermis, avoiding its systemic absorption and its accumulation in organs other than the skin.

A temperature-sensitive gel microemulsion has been studied to assess its ability to release vitamin E and C in comparison with an o/w microemulsion, and a conventional gel micro-emulsion obtained using carbomer as gelling agent (Branka et al. 2009a). At skin temperature, the release of the vitamins from this innovative gel microemulsion was faster than that observed from the conventional gel microemulsion and similar to that obtained from the corresponding non-thickened o/w microemulsion.

A study on vitamin E and C permeation through reconstructed human epidermis from conventional and gel-like o/w and w/o micro-emulsions revealed that these nanocarriers increased vitamin E and C absorption in the skin (Branka et al., 2009b). The enhancement effect was dependent on the phase of the system in which the vitamin was incorporated, as the vitamins in the outer phase showed a greater absorption than in the inner phase.

Rangarajan and Zatz (2003) compared vitamin E *in vitro* skin permeation from different vehicles, including a simple solution, gels, emulsions and microemulsions. The results of this study evidenced that the best vitamin E delivery among all the formulations tested was achieved from a microemulsion containing isopropyl myristate as the oil phase.

Jurkovic et al. (2003), investigating ascorbyl palmitate skin permeation from microemulsions, reported that the effectiveness of this antioxidant after topical application was dependent on both its concentration in the vehicle and the type of microemulsion.

One of the major drawbacks of microemulsions is the high amount of surfactants needed to obtain the desired technological properties. Diec et al. (2001) prepared micro-emulsions with low surfactant content using the phase inversion temperature method. This type of microemulsions has been used to incorporated idebenone, showing good technological and release features (Montenegro et al., 2006). Therefore, these novel carriers could provide a promising approach to improve topical effectiveness of antioxidants.

CONCLUSIONS

As oxidative stress is regarded as one of the main mechanisms involved in skin aging, natural and synthetic compounds with antioxidant activity could be useful for preventing and treating skin aging. However, most compounds with proven antioxidant activity do not show suitable properties to achieve adequate concentrations in the skin layers where they should exert their action.

A rationale design of skin delivery systems based on nanocarriers could help these compounds to be delivered in a more efficient manner and could represent an undeniable benefit for many antiaging skin care products.

CONFLICT OF INTERESTS

The author declares that no conflict of interest exists.

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