Industrial Crops & Products 123 (2018) 424–433

Contents lists available at ScienceDirect

Industrial Crops & Products

journal homepage: www.elsevier.com/locate/indcrop

New cosmetic formulations with broad photoprotective and antioxidative activities designed by amaranth and pumpkin seed oils nanocarriers

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ARTICLE INFO

Keywords:
Oily plant products
Nanostructured carriers
Photoprotective action
Antioxidant properties
UV-filters

ABSTRACT

Plant oils are widely recognized for their beneficial effects in the cosmetic industry, possessing many biological activities. These natural oils provide multiple advantages such as superior antioxidant, nutraceutical, anti-aging, anti-inflammatory, antimicrobial and emollient properties. This study aims to consider the great importance of the various fractions of plant oils in the development of innovative sunscreen formulations based on nanostructured lipid carriers (NLCs) which act as delivery systems for three antioxidant and anti-UV bioactives. Amaranth oil (AO) – *Amaranthus cruentus* and pumpkin seed oil (PSO) – *Cucurbita seed spp* were fitted in the lipid NLCs core, forming new delivery systems able to simultaneously entrap two UVA and UVB filters (diethylamino hydroxybenzoyl hexyl benzoate – DHHB, 2-ethylhexyl salicylate – EHS), and an antioxidant (hesperidin – HES). The dimensional investigation showed that the type of vegetable oil had no significant influence on NLC size, the main diameters being ranged between 110 and 125 nm. The evaluation of physical stability during 3 months has revealed extremely electronegative zeta potential values, *e.g.* between −44 and −54 mV, reflecting an excellent physical stability. A unique feature of the developed nano-delivery systems is that they provide a differentiated release of the three active principles, *e.g.* a sustained release of the natural antioxidant *versus* maintaining significant amounts of UVA and UVB filters in the formulation. The antioxidant properties, evaluated by two *in vitro* techniques, showed that NLCs exhibit a high percent of short-time life radical inhibition, respectively 93–98%. The most effective scavenging system of oxygen free radicals has proved to be the NLC prepared with AO that contains 82% Squalene, while a better ability to inhibit ABTS cation radicals was detected for NLC prepared with an amaranth fraction of 34% Squalene. The entrapment process had a great influence on the UV-absorptive properties, the SPF and UVA-PF values being remarkable, even the amount of UV filters was extremely reduced in comparison with that one existent in commercial creams; the hydrogels based on NLC-EHS-DHHB-HES assure an absorption of 99% UVB radiations (SPF = 46/50.5) and have an ability tocombat 83% of UVA radiation (UVA-PF ranging between 13.9 and 15.5). In conclusion, this study provides an innovative and non-invasive design of herbal cosmetic formulations with superior photoprotection and enhanced antioxidant properties that could reduce the occurrence of skin cancer and delay the process of photoaging.

1. Introduction

Natural herbs and seeds are intensively studied for their bioactive action in the cosmetic industry, providing superior antioxidant, anti-inflammatory and anti-aging properties (Korac and Khambholja, 2011). Recent studies are focused on the development of safe and advanced cosmetic products based on different medicinal plants able to avoid the epidermis damage after the sun exposure (Duque et al., 2017; Marques et al., 2017). The UV penetration on the skin surface initiates different peroxidation reactions (Huang et al., 2009), producing reactive oxygen species which can react with DNA, proteins, or fatty acids, causing oxidative damage and the impairment of antioxidant system (Saraf and Kaur, 2010; Barbinta-Patrascu et al., 2009). These oxidative reactions lead to dermatologic diseases (inflammations, irritations, dermatitis, cancer *etc.*). In order to prevent the skin from the presence of peroxide free radicals, the actual tendency in the cosmetic field is the use of natural products such as plant oils enriched in many bioactive compounds and nanochemistry for the development of safe and advanced cosmetic formulations with broad photoprotective spectrum and appropriate antioxidant activity.

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https://doi.org/10.1016/j.indcrop.2018.06.083
Received 22 December 2017; Received in revised form 24 June 2018; Accepted 27 June 2018

Generally, the commercial creams do not present simultaneously these two properties (Scalia et al., 2013), despite the large number of active substances they contain (*e.g.* over 3 types of sunscreens in high concentrations, usually between 5 and 10%). Furthermore, the association of the two categories of active principles (anti-UV and antioxidant agents) and the natural oils in the same delivery system represents an innovative research in the cosmetic field. Because the increase of the bioactive action represents a mandatory condition to design new cosmetic formulations, the use of plant oils and natural antioxidants becomes really valuable. Therefore, the performance of various fractions of plant oils (obtained according to appropriate methodologies of processing herbs and seeds) it was studied, due to their rich content in bioactive compounds such as fatty unsaturated acids, tocopherols, related phenols *etc.* (Huang et al., 2009). Owing to their bioactive composition, the vegetable oils provide the skin revitalisation, protection against free oxygen radicals, producing healing, softening, rejuvenating, and sunscreen effects (Rastogi et al., 2012).

Two types of vegetable oils widely recognized for their health properties, *Amaranth oil AO*) – *Amaranthus cruentus* and *pumpkin seed oil* (*PSO*) – *Cucurbita seed spp* with high content of squalene (an important antioxidant and antimicrobial agent) have been selected for the NLCs production (Huang et al., 2009). Both plant seed oils, PSO and AO, are recognized as bioactive natural products, having a chemical composition abundant in ω-fatty acids, especially linoleic and oleic acids (Korac and Khambholja, 2011), phytosterols and tocopherols (Gutierrez, 2016). The superior content in ω-6 and 9 fatty acids led to a beneficial rejuvenating effect on the skin (Petras and Paulius, 2013), an emollient and regenerative skin action (wound healing effect) and an increased hydration effect (Korac and Khambholja, 2011).

Hong et al. underlined the strengthening of the immune system and the improvement of the skin tone by use of natural fractions of PSO (Hong et al., 2009). An intensive anti-inflammatory effect of PSO (Aburjai and Natsheh, 2003; Gutierrez, 2016) is sustained by significant contents of polyhydrocarbonated acids (oleic, palmitic, *etc.*), existent in amaranth and pumpkin oils (Gamel et al., 2007; Venskutonis and Kraujalis, 2013). The squalene from AO significantly reduces the free radical oxidative damage to the skin. Furthermore, it was reported that the phytosterols in amaranth oil fractions induce a cholesterol-lowering function (Venskutonis and Kraujalis, 2013), completed by anti-inflammatory and antimicrobial effects (Marcone et al., 2004).

Most of the commercial cosmetic products manifest protection only for UVB radiation which has a negative contribution regarding the skin integrity, favouring the irritations and dermatitis (Goettsch et al., 1998). UVB radiation is responsible for the direct destruction of cellular DNA as well as the appearance of skin cancer. UVA radiation is also an imminent danger for skin; it penetrates deep into the dermis, produces pigmentation and photo-aging of the skin, showing an indirect effect on cellular DNA by generating reactive oxygen species (ROS) (Krumova and Cosa, 2016). By integrating the UVA (diethylamino hydroxybenzoyl hexyl benzoate – DHHB) and UVB (2-ethylhexyl salicylate – EHS) organic filters (Fig. 1) together with an antioxidant agent into the nanostructured carriers-based formulations, this study is devoted to the development of plant cosmetic formulations with a strong protection against both types of UVA and UVB radiations, with unique antioxidant and release properties. The cosmetic formulations developed in this study could reduce the occurrence of skin cancer and delay the process of photoaging; they are effective and safe by virtue of the minimum amount of organic sunscreens, antioxidant content and vegetable oil that presents health benefits itself.

In comparison with inorganic sunscreens such as ZnO or TiO_2 that could be toxic over some concentrations, the organic sunscreens have the main advantage to absorb the UV-rays, their chemical composition providing superior properties, such as emollient effect and water-resistant action (Serpone et al., 2017). Despite the benefits of these sunscreens, they also exhibit some shortcomings in terms of too high concentrations and the possibility of entering the blood circulation

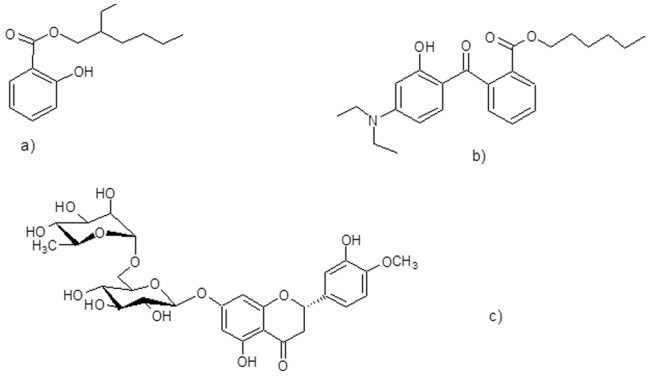

Fig. 1. Structure of UV-filters and natural antioxidant. (a) *Ethylhexyl salicylate (EHS)*; (b) *Diethylamino hydroxybenzoyl hexyl benzoate (DHHB)*; (c) *Hesperidin (HES)*.

(Hung et al., 2012). Various synthetic organic agents are used as photoprotectives, but the European legislation limits their concentration in the commercial products in order to avoid potential toxic effects and to remove the interferation in certain selected pathways of multistage process of carcinogenesis (Akhalayaa et al., 2014; Díaz-Cruz, et al., 2008). For this reason, many studies have been focused on encapsulation of anti-UV agents into appropriate delivery systems such as nanostructured lipid carriers (NLCs) (Niculae et al., 2014a,b; Badea et al., 2017). NLCs represent intelligent encapsulation systems that assure a high drug loading capacity and improved controlled release properties of different active compounds (Ott et al., 2015). NLCs are submicron particles composed by a solid lipid matrix (consisting of a mixture of solid and liquid lipids, spatially incompatible, surrounded by a mixture of surfactants) is stabilized by an outer shell of surfactants (Tamjidi et al., 2013). Several organic filters encapsulated into lipid nanocarriers include 2-ethylhexyl-2-cyano-3,3-diphenylacrylate, Octocrylen (Niculae et al., 2013), diethylamino hydroxylbenzoyl hexyl benzoate (Badea et al., 2015a), bis-ethylhexyloxyphenol methoxyphenyl triazine, Bemotrizinol (Niculae et al., 2014a,b), ethylhexyl salicylate (Badea et al., 2015b). The use of natural antioxidants in association with essential oil fractions is an efficient solution to improve the (Badea et al., 2015b) final cream properties, increasing the ability to inhibit the long-life time radicals. The reactive oxygen species produced after the sun exposure are neutralized by organic agents with an intensified antioxidant activity (Lacatusu et al., 2009a). In order to enhance the antioxidant character of the cosmetic formulations, the use of hesperidin (HES) offers multiple advantages such as anti-inflammatory and anti-allergenic effects on the skin, suppressing the cell proliferation in the case of different carcinoma diagnosis (Parhiz et al., 2015; Guardia et al., 2001). Due to its flavonoid structure, hesperidin is also being studied for its UV protecting action, and is considered a strong chemoprotective therapeutic agent that prevents the skin damages (Pisoschi and Pop, 2015).

The NLCs co-loaded with DHHB, EHS and HES were analysed in terms of their particle size, physical stability and thermal behaviour. Ability and performance of NLCs based on *amaranth oil* and *pumpkin seed oil* have been demonstrated initially by determining the encapsulation efficiency of the 3 active principles. The *in-vitro* release profiles from the NLCs-based carbopol hydrogels were achieved by using the Franz diffusion cells. The *in vitro* antioxidant activity was studied according to the chemiluminescence technique and ABTS method, while the anti-UV performances of the cosmetic formulations based on NLC-DHHB-EHS-HES were assessed by the *in vitro* evaluation of sun protection factor (SPF) and the Erythemal UVA protection factor (EUVA–PF).