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Review

Improvement of skin whitening agents efficiency through encapsulation: Current state of knowledge

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ABSTRACT

Hyperpigmentation is one of the most common skin disorder that affects both men and women of all ethnic groups, caused by several factors, such as UV exposure and skin inflammation. Topical whitening agents were found to be the best and the least aggressive therapy for treating hyperpigmentation compared to instrumental approaches. However, topical treatment faces several obstacles due to the low stability of the whitening agents. Therefore, the encapsulation of these agents was found to be crucial as it enhances their physicochemical stability and increases their concentration at the targeted site via an improved skin permeation, penetration or distribution. In this article, we review the literature aimed to enhance the stability and the targeting of skin whitening agents through their encapsulation in various nano and micro-particulate systems.

Contents

Abbreviations: AP, ascorbyl palmitate; AR, arbutin; AsA, ascorbic acid; AzA, azelaic acid; CD, cyclodextrin; CDC, cetyl dimethicone copolyol; Chol, cholesterol; COE, coevaporation; DCP, dicetylphosphate; dA, deoxyarbutin; DG, decyl polyglucose; DLS, *dynamic light scattering*; *DM-β-CD*, dimethyl-ß-cyclodextrin; DSC, differential scanning calorimetry; EE, encapsulation efficiency; ETOH, ethanol; FD, freeze-drying; FTIR, Fourier transform infrared spectroscopy; GLYC, glycerin; HP-β-CD, hydroxypropyl-ß-CD; IPB, isotonic Palitzsch buffer; IPM, isopropyl myristate; IPP, isopropylpalmitate; ISIS, isostearyl isostearate; KA, kojic acid; LA, linoleic acid; LUV, large unilamellar vesicles; ME, microemulsion; MLV, multilamellar vesicle; NE, nanoemulsion; NLC, nanostructured lipid carriers; NMR, nuclear magnetic resonance; NS, nanosponge; O-OL, octyloctanoate; PC, phosphatidylcholine; PDI, polydispersity index; PE, polyethylene; PG, propylene glycol; P90, phospholipon®90; P90G, phospholipon®90G; P90H, phospholipon®90H; RSV, resveratrol; SA, stearylamine; SC, sodium cholate; SEM, scanning electron microscopy; Sdi-ME, stearyl dimethicone; SLN, solid lipid nanoparticles; STPP, sodium tripolyphosphate; SUV, small unilamellar vesicles; TEM, transmission electron microscopy; TRA, tretinoin; UVs, unilamellar Vesicles; Vit C, vitamin C; Vit E, vitamin E.

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1. Introduction

An excess of melanin level in the skin leads to an aesthetically undesirable skin disorder, hyperpigmentation, resulting in a wide search for effective treatments. Nevertheless, the aggressiveness of physical treatments, such as cryotherapy, chemical peels and lasers (Kopera and Hohenleutner, 1995; Taylor and Anderson, 1994; Wattanakrai et al., 2010) have shed the lights on the importance of topical treatments in which natural skin whitening agents have been considered. Moreover, a multi-therapy approach is needed in most cases of hyperpigmentation. However, the poor chemical stability of the majority of whitening agents and the need to enhance their skin bioavailability have been the major concern of several studies focusing on carrier systems as potential protectors. This review highlights the studies aiming to incorporate effectively natural skin whitening agents into lipid vesicles, cyclodextrins, emulsions, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC) and chitosan nanoparticles. The search for an optimal formulation and the benefits offered by each system are discussed in terms of physico-chemical characteristics and stability of the delivery system, in addition to the active agent permeation, drug release and skin accumulation.

The review includes a general introduction of skin whitening agents, their mechanisms of action and their chemical stabilities. The delivery systems are presented in various sections where the properties of the systems encapsulating the whitening agents are detailed. Recapitulative and conclusive tables are presented at the end of each section.

2. Skin whitening agents

Skin whitening agents from both natural and synthetic sources have been identified. They include molecules from different chemical classes such as polyphenols (resveratrol (RSV)), isoflavonoids (glabridin), glycosides (arbutin (AR)), carboxylic acids (tretinoin (TRA) or (all-trans retinoic acid), fatty acids (linoleic acid (LA)), alpha hydroxy acids (kojic acid (KA) and azelaic acid (AzA)), in addition to antioxidants such as various forms of vitamin C (ascorbyl palmitate (AP) and ascorbic acid (AsA)) and vitamin E (Table 1).

Skin whiteners are developed and classified on the basis of their mechanism of interference with melanogenesis in addition to melanin transport and removal by skin turnover (Briganti et al., 2003; Kim et al., 2012) (Fig. 1). Their action may occur before melanin synthesis through the alteration of tyrosinase transcription and maturation, in addition to an increased tyrosinase ubiquitination and proteasomal degradation (Kim et al., 2012; Park et al., 2010). Whitening agents may also act during melanin synthesis causing the inhibition of tyrosinase, peroxidase and tyrosinase-related protein-1 (Kim et al., 2012; Park et al., 2010). They may also interfere after melanin synthesis by the inhibition of melanosome transfer from melanocytes to keratinocytes (Kim et al., 2012; Park et al., 2010). Antioxidants such as ascorbic acid and α-tocopherol have also shown a skin whitening effect by other mechanisms such as preventing the oxidative polymerization of melanin intermediates and tyrosinase inhibition (Kim et al., 2012; Park et al., 2010).

The active agents presented in this paper have an importance that exceeds their whitening effect as most of them possess additional biological activities such as antimicrobial (arbutin, linoleic acid, kojic acid) (Bentley, 2006; Das, 2006; Jahodar et al., 1985), anti-inflammatory (resveratrol, azelaic acid) (Jang et al., 1997; Mastrofrancesco et al., 2010), and radical scavenging effects (azelaic acid, resveratrol, glabridin) (Fukai et al., 2003; Jang et al., 1997; Passi et al., 1991), in addition to photoaging treatment (tretinoin) (Schmidt and Gans, 2011). They behave differently in presence of water. Their structures and log*P* values are presented in Table 1.

2.1. Arbutin

Arbutin is the glycosylated form of the hydrophilic anti-oxidant and tyrosinase inhibitor, hydroquinone (O'Donoghue, 2006). However, arbutin is less toxic than hydroquinone (Lei et al., 2002). Arbutin is widely used as a depigmentation agent by inhibiting tyrosinase activity, due to structural similarities to the