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Percutaneous absorption of benzophenone-3 loaded lipid nanoparticles and polymeric nanocapsules: A comparative study

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ABSTRACT

For the last years, the increase of the number of skin cancer cases led to a growing awareness of the need of skin protection against ultraviolet (UV) radiations. Chemical UV filters are widely used into sunscreen formulations as benzophenone-3 (BP-3), a usually used broad spectrum chemical UV filter that has been shown to exercise undesirable effects after topical application. Innovative sunscreen formulations are thus necessary to provide more safety to users. Lipid carriers seem to be a good alternative to formulate chemical UV filters reducing their skin penetration while maintaining good photo-protective abilities. The aim of this work was to compare percutaneous absorption and cutaneous bioavailability of BP-3 loaded into solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), nanostructured polymeric lipid carriers (NPLC) and nanocapsules (NC). Particle size, zeta potential and *in vitro* sun protection factor (SPF) of nanoparticle suspensions were also investigated. Results showed that polymeric lipid carriers, comprising NPLC and NC, significantly reduced BP-3 skin permeation while exhibiting the highest SPF. This study confirms the interesting potential of NPLC and NC to formulate chemical UV filters.

1. Introduction

Ultraviolet (UV) radiations have been correlated with the increasing incidence of skin carcinomas and melanomas (Armstrong and Kricker, 2001). Sunscreen use is a widespread practice protecting the skin against damages due to sun UV radiation over exposure. Sunscreen formulations contain physical and/or chemical UV filters able to scatter and/or to absorb UVB and UVA radiations respectively. Chemical UV filters are preferentially incorporated into sunscreen preparations since they are easily formulated and do not leave unpleasant white marks at skin surface as compared to physical UV filters (Anderson et al., 1997; Krause et al., 2012; Gilbert et al., 2013). To be efficient, UV filters must remain at the uppermost skin regions (Lu et al., 1999). Although the *stratum corneum* (SC) is considered to be an efficient barrier to exogenous agents, UV radiations can weaken this barrier function enhancing chemical skin penetration (Yamamoto et al., 2008). Some studies revealed that several chemical UV filters, like benzophenone-3 (BP-3), could permeate through the skin leading to undesirable effects (Krause et al., 2012; Gilbert et al., 2013). Indeed, physico-chemical properties of BP-3 (Table 1) make it a good candidate to penetrate SC which ensures skin barrier function. BP-3 has often been reported to be allergenic (Bryden et al., 2006), to act as an endocrine disruptor (Kim et al., 2014) and to be detected into blood plasma, human breast milk as well as urines which renders this molecule to be considered of high concern in relation to human risk (Kasichayanula et al., 2007; Schlumpf et al., 2008; Wong and Orton, 2011). Due to the favorable properties of BP-3 to penetrate the skin, the study of the effect of different formulation in infinite dose on the penetration properties of BP-3 could produce interesting data. Several studies focused on the interest of micro and nanocarriers to formulate chemical UV filters protecting them from photo-degradation and preventing their permeation across the skin (Jiménez et al., 2004; Mestres et al., 2010; Sanad et al., 2010; Lacatusu et al., 2011). Indeed, previous studies showed that BP-3 incorporation into solid lipid nanoparticles (SLN), in comparison with classical oil in water emulsion, reduced its percutaneous absorption by 50% (Wissing

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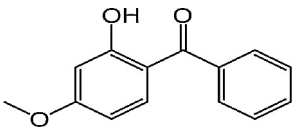
Table 1
Physico-chemical properties and toxicological reported data of benzophenone-3 (BP-3).

Physico-chemical properties		Toxicological reported data
IUPAC Name	2-hydroxy-4methoxybenzophenone	Photo-allergic contact dermatitis (Bryden et al., 2006; Palm and O'Donoghue, 2007)
Chemical structure		Skin penetration in humans (Treffel and Gabard, 1996; Walters and Roberts, 2002)
Molecular weight	228.24 g mol^{-1}	ROS production into cytoplasm of human keratinocytes (Hanson et al., 2006)
Log P	3.7	Distribution in plasma, urine and breast milk (Hany and Nagel, 1995; Hayden et al., 1997; Janjua al., 2008)
Water solubility at 20 °C	3.7 mg L^{-1}	Estrogenic activity (Bolt et al., 2001; Schlumpf et al., 2004; Morohoshi et al., 2005)
Melting point	62 °C –65 °C	Ecologic and environmental pollutant (Poiger et al., 2004; Balmer et al., 2005; Meinerling and Daniels, 2006)

and Mülle, 2001; Wissing and Müller, 2002a; Puglia et al., 2014). Polymeric lipid nanocapsules were also previously shown to decrease BP-3 skin permeation while enhancing their photo-protection abilities (Marcato et al., 2011). The many studies published confirm the interest of formulating innovative UV filter carriers to achieve high skin photoprotection while reducing undesirable effects linked to their penetration into the skin. Lipid nanoparticles and nanocapsules are colloidal carriers which are extensively under investigations as drug carrier systems for poorly water-soluble compounds (Müller et al., 2002a; Dash and Konkimalla, 2012; Steelandt et al., 2014). These lipid carriers permit (i) to protect chemical compounds from photo-degradation phenomena, (ii) bioavailability improvement and (iii) controlled release while allowing large scale production (Jee et al., 2006; Puglia et al., 2012; Frank et al., 2015). These colloidal carriers have been demonstrated to enhance the accumulation of UV filters at the uppermost skin layers, where they are designed to act, and to enhance their photo-protection abilities (Müller et al., 2002b; Marcato et al., 2011; Puglia et al., 2012). Lipid nanocarrier size facilitates their formulation in dermatological products and enables comfortable skin application (Müller et al., 2002b). SLN are based on melt-emulsified lipids which are solid at room temperature and made of physiologically well tolerated and biodegradable raw materials (Wissing and Müller, 2001; Alvarez-Roman et al., 2001). Nanostructured lipid carriers (NLC) are characterized by a solid lipid matrix in which a liquid lipid is added (Chen et al., 2014). NLC are the second generation of SLN permitting (i) a more efficient drug loading, (ii) a modulation ofthe drug delivery profile and (iii) a prolonged drug entrapment during storage (Das et al., 2012). Nanostructured polymeric lipid carriers (NPLC) and nanocapsules (NC) are characterized by a wall of hydrophobic polymer that surrounds their lipid core. The polymeric lipid wall of nanocapsules permits a sustain release of lipophilic compounds and protection of molecules encapsulated from photo-degradation phenomena (Dash and Konkimalla, 2012; Steelandt et al., 2014). The aim of this study was to compare the ability of SLN, NLC, NPLC and NC to entrap BP-3 minimalizing its penetration and permeation into living epidermis. All suspensions were characterized in terms of particle size, polydispersity index (PdI) and zeta potential. Moreover, *in vitro* sun protection factor (SPF) of the different suspensions was investigated. Cutaneous absorption data are discussed from granulometry analysis, encapsulating yield and SPF.

2. Materials and methods

2.1. Materials

BP-3, poly-ε-caprolactone (MW: 45 kDa), phosphate buffered saline (PBS) tablets and chicken egg white albumin were purchased from Sigma Aldrich (St. Louis, Missouri, USA). Suppocire® AIML (Semi-synthetic glyceride base comprising saturated C8-C18 triglyceride fatty acids and lecithin), Plurol® oleique CC497 (polyglyceryl-6 dioleate, HLB 3) and Labrafil M1944CS® (mixture of mono-, di-, and triglycerides and mono- and di-fatty esters of polyethylene glycol 300, HLB 9) were gifts from Gattefossé (St Priest, France). Oleic acid and

Table 2
Composition of BP-3 loaded SLN, NLC, NPLC and NC suspensions and BP-3 albumin aqueous solution (% w/w).

Concentrations (% w/w)					
Components	SLN	NLC	NPLC	NC	Albumin aqueous solution
Suppocire AIML®	10	10	10	–	–
Oleic acid	–	5	5	–	–
Labrafil M1944CS®	–	–	–	10	–
Plurol oleique CC497®	–	–	–	10	–
Poly-ε-caprolactone	–	–	0.5	0.5	–
Benzophenone-3	5	5	5	5	5
Montane 80®	6	4	4	–	–
Montanox 80®	–	–	–	0.08	–
Montanox 20®	4	6	6	–	–
Poloxamer 188®	–	–	–	24	–
Chicken egg white albumin	–	–	–	–	2
PBS solution	–	–	–	–	Qs 100%
Deionized water	Qs 100%	Qs 100%	Qs 100%	Qs 100%	–