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Note

Solid lipid microparticles containing the sunscreen agent, octyl-dimethylaminobenzoate: Effect of the vehicle

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Abstract

Solid lipid microparticles (SLMs) loaded with the sunscreen agent, octyl-dimethylaminobenzoate (ODAB), were prepared in order to achieve enhanced sunscreen photostability. The microparticles were produced by the melt dispersion technique using glyceryl behenate as lipidic material and poloxamer 188 as the emulsifier. The obtained SLMs showed proper features in terms of morphology, size distribution (1.67–15.81 μm) and ODAB loading (16.15 ± 0.11%, w/w). The sunscreen release from the SLMs was slower than its dissolution rate and the photodecomposition of ODAB was markedly decreased (>51.3%) by encapsulation into the lipid microparticles. The efficacy of the SLM carrier system was also evaluated after their introduction in model topical formulations (i.e., hydrogel and oil-in-water emulsion). Further in vitro release measurements, performed using Franz diffusion cells with polycarbonate membranes, indicated that the retention capacity of the microparticles was lost after their incorporation into the emulsion, whereas it was retained in the hydrogel. Moreover, the SLMs achieved a reduction of the sunscreen photodegradation in the hydrogel vehicle (the ODAB loss decreased from 87.4% to 59.1%), whereas no significant photoprotective effect was observed in the emulsion. Therefore, the efficacy of the ODAB-loaded SLMs was markedly affected by the vehicle.

Keywords: Solid lipid microparticles; Sunscreen agents; Octyl-dimethylaminobenzoate; Release; Photostability; Topical formulations

1. Introduction

Because of the increasing concern on the harmful effects (erythema, cutaneous photoaging, immune suppression and various forms of skin cancers) of sunlight UV radiation (290–400 nm), the use of topical sunscreening preparations has expanded [1]. The active constituents in these products, commonly referred to as UV filters or sunscreen agents, attenuate the transmission of the solar UV rays to the skin by absorbing, reflecting or scattering the radiation [1]. High photostability represents one of the most important requirements for the efficacy and safety of UV filters [2,3], since the light-induced decomposition of the sunscreen decreases the expected UV-protective power and can generate harmful photolytic products [2].

Octyl-dimethylaminobenzoate (ODAB) is a common sunscreen agent which is included in the list of authorized UV filters in Europe, in the USA and Australia [4]. However, several studies have demonstrated that ODAB undergoes marked decomposition under sunlight exposure [4,5]. Therefore, there is a need for new systems able to reduce the photoinstability of ODAB.

Solid lipid microparticles (SLMs) represent an alternative and appropriate carrier for sunscreen agents [6]. They possess a solid fat core based on naturally occurring lipids and hence they are biocompatible and biodegradable [7]. Moreover, SLMs exhibit sufficient entrapment capacity for lipophilic compounds, such as most of the UV filters, and their solid matrix protects loaded labile substances

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against decomposition [7,8]. Additional advantages include good affinity for the stratum corneum where the sunscreen is intended to act and proper size for reduced skin absorption [6,8].

The present study focuses on the preparation and characterization of SLMs loaded with ODAB. The influence of the microparticles on the UV filter photostability was examined before and after incorporation of the SLMs in model formulations (i.e., emulsions and gels) suitable for topical application. Moreover, the effect of the vehicle on the stabilization of the microparticle-entrapped sunscreen was also evaluated.

2. Materials and methods

2.1. Materials

Octyl-dimethylaminobenzoate (ODAB) was supplied by Merck (Darmstadt, Germany). Glyceryl behenate (Compritol® 888 ATO) was from Gattefossé (Cedex, France) and poloxamer 188 (Lutrol® F68) from BASF (Ludwigshafen, Germany). Polysorbate 80 was obtained from Uniqema (Everberger, Belgium). Caprylic-capric triacylglycerols (Miglyol 812) were provided by Beiersdof (Hamburg, Germany). The excipients for the hydrogel and cream preparations were from Sigma–Aldrich (Steinheim, Germany) and Henkel (Fino Mornasco, Italy), respectively. Polycarbonate membranes were obtained from Sartorius (Goettingen, Germany). Methanol, acetonitrile and water were high-performance liquid chromatography (HPLC) grade from Merck. All other reagents and solvents were of analytical grade (Sigma).

2.2. Methods

2.2.1. High-performance liquid chromatography

The HPLC system comprised an L-6000 pressure pump, an L-7350 column compartment, an L-7200 autosampler, an L-7400 UV detector and a D-7000 interface (Merck-Hitachi). The system was controlled by a computer using the acquisition software (HPLC System Manager) developed by Merck-Hitachi. Separations were performed at 30 °C on a Lichrospher 100 RP-18 column (5 μm, 125 × 4 mm; Merck). The mobile phase consisted of a mixture of methanol, acetonitrile and water (60:30:10, v/v). The flow-rate was 0.8 ml/min and the injected sample volume was 5 μl. The detector was set at 310 nm.

2.2.2. Solid lipid microparticle preparation

Unloaded SLMs were prepared by adding hot water (90 ml) containing various amounts (0.1 or 1%, w/w) of poloxamer 188 to melted glyceryl behenate (5 g) at 85 °C under stirring with an Ultra-Turrax T25 (IKA-Werk, Staufen, Germany). The obtained oil-in-water emulsion was rapidly cooled at room temperature without stirring and the formed SLMs were recovered by decantation and freeze-dried. The ODAB-loaded SLMs were obtained by dissolving the UV filter (1.0 g) in the melted lipid phase prior to emulsion formation.

2.2.3. Microparticle characterization

SLMs, morphological structure was examined by scanning electron microscopy (SEM; model DSM 962®, Carl Zeiss Inc., Germany). The particle size was determined by laser diffractometry using a Mastersizer 2000-Scirocco® instrument (Malvern Instruments, Malvern, UK).

The amount of ODAB entrapped in the SLMs was determined by dissolving the microparticles (30–40 mg) in ethanol under sonication (30 min). The obtained sample was diluted to volume (20 ml), filtered and assayed by HPLC. Data were determined from the average of at least three determinations.

2.2.4. In vitro release

The sunscreen dissolution and release were studied by adding ODAB (12 mg) alone or loaded in SLMs to an aqueous solution (16 ml) containing 3% (v/v) polysorbate 80 to ensure sink conditions. Forty millilitres of Miglyol 812 was placed on top of the aqueous solution [7] and the sample was maintained at 37 °C under stirring (50 rpm). At appropriate time intervals, 100-μl aliquots were taken out of the oil phase and diluted with 900 μl of ethanol. The samples were assayed for ODAB spectrophotometrically at 310 nm, using an Hitachi U-3000 spectrophotometer (Hitachi Europe, Krefeld, Germany). Each series of experiments was repeated at least three times.

2.2.5. Hydrogel and emulsion formulations

Hydrogels containing ODAB (0.2%, w/w; this concentration producing uniform dispersions in the gels) alone or entrapped in SLMs were prepared by dispersing, with constant stirring, Carbopol 980 (1.5%, w/w) in deionised water containing *p*-hydroxybenzoic acid methyl ester (0.2%). The dispersion was neutralized by the addition of trihydroxymethylaminomethane (1.5%). Plain ODAB (solubilized in ethanol) or the sunscreen-loaded microparticles (dispersed in water) were then added to the rest of the formula.

Oil-in-water (o/w) emulsions containing 1% (w/w) ODAB or an equivalent amount of sunscreen loaded in microparticles were prepared according to the common procedure used in compounding practice. The emulsion excipients were: sorbitan monostearate (2%), polyoxyethylene sorbitan monostearate (4.5%), butylated hydroxyanisole (0.02%), isopropyl isostearate (9.0%), cetearyl isononanoate (8.0%), cetearyl alcohol (7.0%), sodium benzoate (0.1%), glycerin (2.0%), dehydroacetic acid (0.1%), EDTA (0.1%) and water (66%). ODAB was dissolved in the oil phase, whereas the SLMs were dispersed in water and added in the cooling phase of the emulsion preparation at about 40 °C.

2.2.6. Diffusion cells

These studies were performed in Franz-type vertical glass diffusion cells (cross-sectional surface area, 1.7 cm^2)

which were thermo-regulated at 37 °C. Polycarbonate membranes with an average pore size of 0.8 μm were inserted between the donor and receptor compartment of the diffusion cells. The receptor medium (approx. 8 ml) consisted of HEPES buffer solution (pH 7.4) containing randomly methylated-β-cyclodextrin (50 mM) to ensure sink conditions (solubility of ODAB in the receptor fluid, 2.3 mg/ml). The fluid was stirred (100 rpm) with a magnetic bar throughout the experiment. Portions (350 mg) of the hydrogel or emulsion formulations were evenly spread on the membrane surface in the donor chamber. At appropriate time intervals, 1 ml-aliquots of the receptor phase were withdrawn and replaced by an equal volume of fresh fluid. Samples from the receptor phase were assayed for ODAB by HPLC. At least five replicates were used for each series of experiments.

2.2.7. Photodegradation studies

Photolysis experiments were performed on SLMs before and after their introduction into the emulsion or hydrogel formulations. The lipid microparticles (20 mg) were spread onto the bottom of a beaker, whereas the emulsion and hydrogel preparations were distributed, as uniform as possible layer, onto a Transpore™ tape (3M Health Care, Neuss, Germany) at a level of 2 mg/cm^2 [3]. The samples were irradiated for 1 h with a solar simulator (Suntest CPS+, Atlas, Linsengericht, Germany) equipped with a xenon lamp, an optical filter to cut-off wavelengths shorter than 290 nm and an IR-block filter to avoid thermal effects. The solar simulator emission was maintained at 700 W/m^2. The applied UV energy was equivalent to 20 minimal erythemal dose (MED) which is considered representative of daily solar emission [2]. After the exposure interval, the beaker containing the microparticles was removed, its content quantitatively transferred into a 20-ml calibrated flask with ethanol and sonicated for 15 min. The Transpore™ tape was cut into small pieces and extracted with methanol–ethanol (25:75, v/v), under sonication (15 min). The extraction was repeated with fresh solvent and the combined fractions were adjusted to volume (20 ml). The obtained samples were filtered (0.45 μm membrane filters) and analysed for ODAB by HPLC. The degree of photodegradation was evaluated by measuring the percentage of recovered sunscreen agent with respect to non-exposed samples. The results are the average of at least five experiments.

3. Results and discussion

3.1. Lipid microparticle preparation and characterization

Lipid microparticles loaded with ODAB were developed through a melt dispersion technique [9] using glyceryl behenate as lipidic material and poloxamer 188 as the emulsifier. Several process variables including the surfactant concentration (0.1 and 1%, w/w), the stirring rate (10,000–25,000 rpm) and time (1–5 min) were investigated in order to obtain SLMs with satisfactory sunscreen loading, morphological structure and particle size homogeneity.

Optimal microparticle features (Fig. 1) were obtained at poloxamer 188 concentration of 0.1 % (w/w) using a stirring rate of 24,000 rpm for 1 min. Table 1 reports the volume distribution (d_{10}, d_{50}, d_{90}) for the obtained SLMs. The amount of ODAB incorporated in the microparticles was found to be 16.15% ± 0.11 (w/w), which corresponded to an encapsulation efficiency of 84.1%.

To evaluate the retention capacity of the lipid particles, initial release studies were performed using a lipophilic medium (Miglyol 812). Sunscreen release rate from the microparticles was lower than the ODAB dissolution rate (Fig. 2), the release curve exhibiting a biphasic pattern. The first part was characterized by a rapid release suggesting that a fraction of the sunscreen is adsorbed at the microparticle surface. This initial portion of the profile was followed by a slower release rate (Fig. 2) which can be attributed to entrapment of the UV filter in the solid lipid matrix. Additional in vitro release experiments, using Franz-type diffusion cells, were performed on the SLMs after their introduction into hydrogels and o/w emulsions. The latter step is necessary in order to obtain preparations which can be administered to the skin. The foregoing vehicles were selected as model formulations since they comprise the majority of sun-care products [10] and thus reproduce the conditions prevalent under actual use by consumers. The influence of the vehicle on the release of ODAB from the microparticles and thereby on its diffusion through polycarbonate membranes was then evaluated. The sunscreen permeation profiles from the emulsion and hydrogel preparations are illustrated in Fig. 3. The release of ODAB was found to be higher from hydrogels than from emulsions (Fig. 3). This difference is due to the greater affinity of the UV filter towards the latter vehicle which results in decreased thermodynamic activity of the

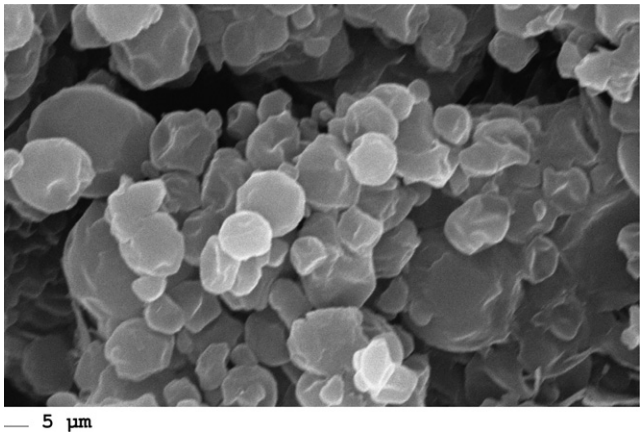

Fig. 1. Scanning electron microscopy (SEM) micrographs of SLMs loaded with ODAB.

Table 1
Particle size distribution (means ± SD, $n = 3$) of the SLMs expressed as d_{10}, d_{50}, d_{90} (particle size below which 10%, 50% and 90% of the sample lies)

Sample	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)
SLMs	1.67 ± 0.05	5.25 ± 0.17	15.81 ± 1.53

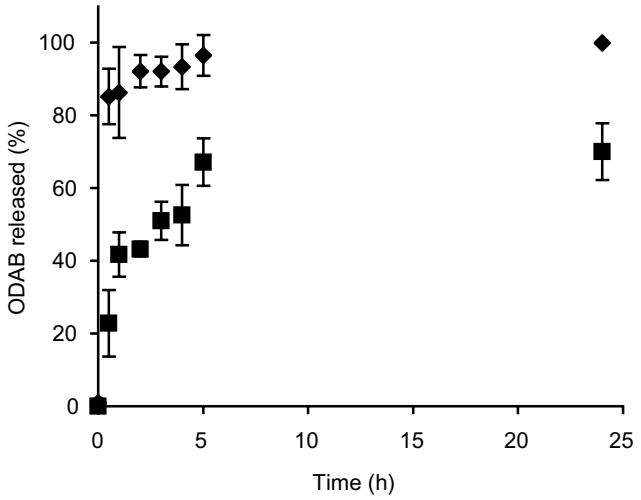

Fig. 2. ODAB dissolution (◆) and release from SLMs (■) into Miglyol 812. Values are means ± SD ($n = 3$).

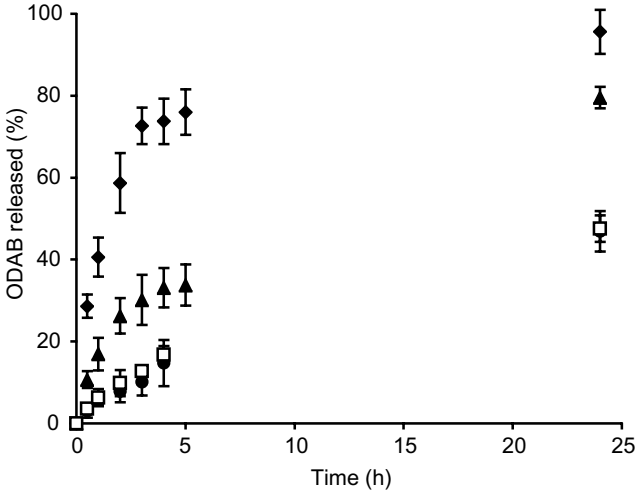

Fig. 3. Franz diffusion cells: release profiles of ODAB from o/w emulsion (●), hydrogel (◆), SLMs in o/w emulsion (□) and hydrogel (▲). Values are means ± SD ($n = 5$).

solute and hence reduced permeability. In contrast with the results of the release studies illustrated in Fig. 2, after introduction of the SLMs in the emulsion formulation, their release modulation capacity was lost (Fig. 3). In fact, no significant differences in sunscreen release behaviour were observed between the emulsions containing free or microencapsulated ODAB. This effect could be ascribed to ODAB expulsion from the lipid carrier due to partitioning of the lipophilic UV filter between the microparticles and the oil phase of the emulsion. Conversely, in the case of the hydrogel vehicles, the sunscreen release and hence its permeation rate across the polycarbonate membrane was reduced by the SLMs (Fig. 3), in accordance with the data obtained for the lipid particles alone (Fig. 2).

3.2. Photodegradation studies

In order to study the effect of the lipid particle matrix on the photochemical reactivity of ODAB, the photostability experiments were performed initially on solid samples including ODAB with empty microparticles and the sunscreen-loaded microparticles. The samples were exposed to the solar simulator and the extent of photodegradation was measured by HPLC. As shown in Fig. 4, the ODAB entrapment in the SLMs produced a marked reduction of the photo-induced decomposition of the UV filter as compared to non-encapsulated ODAB (the percentage sunscreen losses were 43.8 ± 6.4% for free ODAB in combination with empty microparticles and 20.0 ± 5.6% for SLMs). This effect is due to reflection and scattering of the UV radiation by the particle matrix [6–8].

In order to simulate conditions of real use of sun-care products, further photolysis experiments were performed on the formulations submitted to the foregoing Franz diffusion cell studies. The o/w emulsion and hydrogel preparations containing ODAB free or entrapped in the SLMs were applied onto Transpore™ tapes (a surgical tape able to simulate the texture of human skin) and irradiated with simulated sunlight. No statistically significant difference (unpaired t-test, $P > 0.1$) in the degree of sunscreen photodecomposition was observed between the emulsions containing plain ODAB or the microencapsulated sunscreen agent (Fig. 4). This indicates a loss of the photostabilization effect of the SLMs after their introduction in the emulsion vehicle, in accordance with the results from the membrane diffusion experiments (Fig. 3). This phenomenon could be traced to the release of ODAB from the lipid

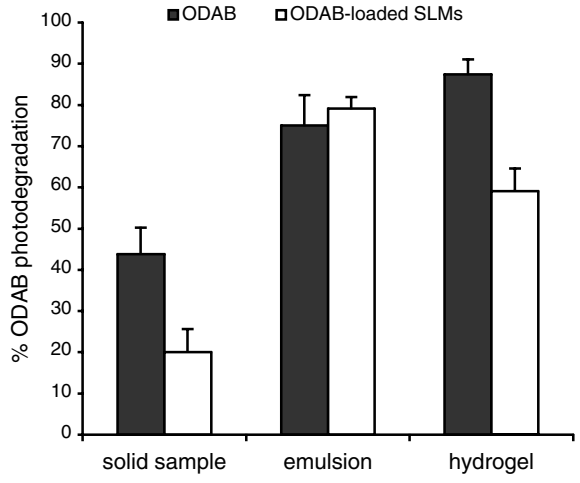

Fig. 4. ODAB photodegradation (%) in its formulations after 1 h irradiation with the solar simulator. Values are means ± SD of at least five experiments.

particles into the oil phase, which minimize the sunscreen fraction protected by the microparticle matrix.

At variance with the data obtained for the emulsions, the SLMs significantly decreased (unpaired *t*-test, $P < 0.001$) the irradiation-induced decomposition of ODAB in the hydrogel preparations (Fig. 4). The percentage sunscreen loss was $87.4 \pm 3.6\%$ for the formulation containing the non-encapsulated UV filter and $59.1 \pm 5.5\%$ for the hydrogel containing the microparticle-entrapped ODAB (Fig. 4). Hence, the photostabilization effects of the examined microparticle systems correlate with their release modulation capacity (Fig. 3). These results demonstrate that the reduction of the light-induced decomposition of the UV-filter achieved by the SLMs carrier was retained in the hydrogel vehicle. However, the observed improvement in sunscreen photochemical behaviour was not as marked as that measured for the lipid microparticles alone (Fig. 4).

4. Conclusions

The results reported in the present study indicate that entrapment of ODAB in lipid microparticles represents a suitable strategy to enhance the UV filter photostability. Moreover, the biocompatibility and sustained release properties of the SLMs carrier represent additional advantages for the preparation of sunscreen products. The obtained data also demonstrate that the effectiveness of the sunscreen-loaded microparticles can be markedly hampered by their incorporation in topical formulations, this aspect being often neglected. Consequently, in order to elicit the intended SLM effect, it is very important to examine the influence of the vehicle and to select the most suitable formulation.

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