Drug Development and Industrial Pharmacy, 35:192–198, 2009

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040802244300

informa
healthcare

Co-loading of a Photostabilizer with the Sunscreen Agent, Butyl Methoxydibenzoylmethane in Solid Lipid Microparticles

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The sunscreen agent, butyl methoxydibenzoylmethane (BMDBM), one of the most widely used UV-A filter, undergoes decomposition under sunlight exposure, which is a limiting factor on its overall performance. To reduce the sunscreen photodegradation, this study investigates the incorporation into solid lipid microparticles (SLMs) of BMDBM together with the photostabilizer, 4-methylbenzylidene camphor (MBC). The microparticles were produced by the melt dispersion technique using various lipid materials (tristearin, glyceryl behenate, and stearic acid) and hydrogenated phosphatidylcholine as the surfactant. The highest retention capacity for BMDBM and MBC was achieved with tristearin microparticles. These SLMs were characterized by scanning electron microscopy and powder X-ray diffraction analyses. The BMDBM and MBC loading was 10.4 and 10.1%, respectively. The efficacy of the SLMs was evaluated after their introduction in a conventional cream (oil-in-water emulsion). The light-induced decomposition of BMDBM was decreased by encapsulation into the SLMs (the extent of degradation was 33.8 ± 5.5% for unencapsulated BMDBM/MBC and 25.3 ± 4.2% for BMDBM-loaded microparticles in conjunction with free MBC). Moreover, the co-loading of the MBC stabilizer in the SLMs produced a further reduction of the photodegradation of the UV-A filter (the BMDBM loss was 16.9 ± 5.9%) compared with the microparticles containing BMDBM without MBC. Therefore, incorporation in lipid microparticles of BMDBM together with the MBC photostabilizer is more effective in enhancing the UV-A filter photostability than the SLMs loaded with BMDBM alone.

Keywords solid lipid microparticles; sunscreen agents; butyl methoxydibenzoylmethane; photostabilizer; release; photodegradation; topical formulations

INTRODUCTION

Increasing evidence of the detrimental effects on human skin (erythema, cutaneous photoaging, immune suppression, and various forms of skin cancers) of solar UV radiation (Matsumura & Ananthaswamy, 2004) has prompted the widespread use of topical sun protective products (Gasparro, Mitchnick, & Nash, 1998; Shaath & Shaath, 2005). The active ingredients incorporated in these preparations, referred to as sunscreen agents or UV filters, reduce the dose of UV light impinging on the skin by absorbing, reflecting or scattering the radiation (Gasparro et al., 1998). While the damaging effect of UV-B radiation (290–320 nm) has been recognized for decades (Gasparro et al., 1998), the role of UV-A wavelengths (320–400 nm) has been ignored for a long time (Fourtanier et al., 2006). However, in recent years the involvement of UV-A exposure in sunlight-induced skin pathologies has been unambiguously demonstrated (Agar et al., 2004; Fourtanier et al., 2006). Accordingly, the European legislation recommends that sunscreen products should be effective also against the UV-A radiation and the UV-B and UV-A protection should be related (EC Commission Recommendation, 2006). Thus, to achieve consistent UV-B and UV-A protection, the incorporation of UV-A filters in solar formulations has become increasingly important (Chatelain & Gabard, 2001; Fourtanier et al., 2006; Herzog, Hueglin, & Osterwalder, 2005).

Among the authorized UV-A absorbers, butyl methoxydibenzoylmethane (BMDBM) is the most widely used compound (Bonda, 2005). It is approved by the regulatory authorities of Europe, USA, Australia, and Japan (Steinberg, 2005). However, BMDBM undergoes photodegradation under sunlight illumination and therefore loses part of its protection capacity during usage (Bonda, 2005; Chatelain & Gabard, 2001; Tarras-Wahlberg et al., 1999). In addition, several studies have demonstrated that the light-induced decomposition of this UV-A filter generates free radicals that can cause biological damage to the skin (Scalia, Simeoni, Barbieri, & Sostero, 2002). The photolability of this sunscreen agent is thus a major problem and the reason for the need of new systems able to reduce the BMDBM photodegradation.

Several strategies have been developed to enhance the stability of BMDBM under solar radiation, including the addition of photostabilizing agents (substances acting as quenchers of the triplet state of BMDBM by an energy transfer mechanism), inclusion complexation with cyclodextrins, and encapsulation

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in polymeric or lipid microparticles (Anselmi et al., 2002; Bonda, 2005; Iannuccelli, Sala, Tursilli, Coppi, & Scalia, 2006; Scalia, Villani, Scatturin, Vandelli, & Forni, 1998).

Recently, increasing attention has been given to solid lipid microparticles (SLMs) as a promising carrier system for sunscreen agents (Iannuccelli et al., 2006; Tursilli, Piel, Delattre, & Scalia, 2007; Yener, Incegül, & Yener, 2003). They consist of a solid lipid core based on naturally occurring lipids and stabilized by a layer of surfactant molecules on the surface (Jaspart, Piel, Delattre, & Evrard, 2005). Consequently, their components are biocompatible and biodegradable, providing excellent in vivo tolerability (Jaspart et al., 2005; Müller, Radtke, & Wissing, 2002). Additional advantages of SLMs include high entrapment capacity for hydrophobic substances, such as most of the UV filters, good substantivity toward the stratum corneum, where sunscreens should act, and proper size for reduced percutaneous absorption (Toll et al., 2004; Yener et al., 2003). Moreover, their solid matrix improves the stability of loaded actives (Jee, Lim, Park, & Kim, 2006; Jenning, Schafer-Korting, & Ghola, 2000).

In previous studies (Iannuccelli et al., 2006; Scalia, Tursilli, Sala, & Iannucceli, 2006), we demonstrated that the incorporation of BMDBM in SLMs decreased the extent of photodegradation of the UV-A filter. To enhance the SLMs protective efficacy, we report here the co-loading of BMDBM with a known photostabilizing agent (4-methylbenzylidene camphor [MBC], a UV-B filter) in SLMs. The influence of the microencapsulation process on the light-induced degradation of BMDBM was determined after introduction of the SLMs in a model topical formulation (i.e., emulsion). For comparison purposes, lipid microparticles containing BMDBM alone were also prepared and examined.

MATERIALS AND METHODS

Materials

BMDBM and MBC were supplied by Merck (Darmstadt, Germany). Glyceryl behenate (a mixture of mono-, di-, and tri-esters of glycerol and behenic acid) was from Gattefossé (Saint-Priest Cedex, France). Tristearin and stearic acid were purchased from Fluka Chemie (Bucks, Switzerland). Hydrogenated soybean phosphatidylcholine was a gift by Cargill (Hamburg, Germany). The excipients for the cream preparations were from Sigma Aldrich (Steinheim, Germany) and Henkel (Fino Mornasco, Italy). Methanol, acetonitrile, and water were of high-performance liquid chromatography (HPLC) grade from Merck. All other reagents and solvents were of analytical grade (Sigma).

High-Performance Liquid Chromatography

The HPLC apparatus comprised a Model LabFlow 3000 pump (LabService Analytica, Bologna, Italy), a Model 7125 injection valve with a 20-µL sample loop (Rheodyne, Cotati, CA, USA), and a Model 975-UV variable wavelength UV-Vis detector (Jasco, Tokyo, Japan). BMDBM was detected at 360 nm and MBC at 290 nm, using the wavelength time-programming facilities. Data acquisition and processing were accomplished with a personal computer using Borwin software (JBMS Developpements, Le Fontanil, France). Sample injections were effected with a Model 701 syringe (10 µL; Hamilton, Bonaduz, Switzerland). Separations were performed according to the method of Scalia, Mezzena, and Iannuccelli (2007), using a 5-µm Zorbax SB-CN column (150 mm × 3.0 mm i.d.) fitted with a guard column (5-µm particles, 4 mm × 2 mm i.d.) and eluted isocratically, at a flow-rate of 0.5 mL/min, with methanol–acetonitrile–water (35:25:40, by volume), containing 0.5% (vol/vol) acetic acid. Peak identity was assigned by cochromatography with the authentic standards. Quantification was carried out by integration of the peak areas using the external standardization method.

Preparation of Lipid Microparticles

Unloaded lipid microparticles were prepared by adding hot (70–80°C) water (60 mL) containing 1% (wt/wt) of previously dispersed hydrogenated phosphatidylcholine, to the melted lipid phase (3.6 g) under high-shear mixing (13,500 rpm for 2 min) with an Ultra-Turrax T25 (IKA-Werk, Staufen, Germany) at 80°C. The resulting oil-in-water emulsion was rapidly cooled at room temperature under magnetic stirring and the formed microparticles were recovered by centrifugation ($4{,}100 \times g$ for 15 min), washed with water and freeze-dried. The SLMs loaded with BMDBM or with combined BMDBM and MBC were obtained by dissolving the UV filters (1.0 g) in the melted lipid phase prior to emulsion formation.

Microparticle Characterization

SLM morphological structure was examined by scanning electron microscopy (SEM; Cambridge Stereoscan 360, Cambridge Instruments, Bar Hill, UK). The particle size distribution was determined by computerized image analysis (Micrometrics™ camera 122CU and software Vision 1.0) of at least 100 particles using an optical microscope (Nikon Diaphot inverted microscope, Tokyo, Japan).

The powder X-ray diffraction patterns were recorded on a D5000 powder diffractometer (Siemens, Munich, Germany) using a voltage of 45 kV and a current of 25 mA for the generator, with Cu anode material. The wavelength of the graphite-monocromated radiation was 1.5406 Å. The diffractograms were recorded from 3° (2θ) to 35° (2θ) at an angular speed of 1° (2θ) per minute using 1°–1°–1°–0.15° slits.

The amount of BMDBM and MBC entrapped in the SLMs was determined by dissolving the microparticles (35–50 mg) in ethanol under sonication (15 min). The obtained sample was diluted to volume (20 mL), filtered, and assayed by HPLC. The encapsulation efficiency was calculated as the percentage ratio between the quantity of actives entrapped in the microparticles

and added to the melted lipid phase, during preparation. Data were determined from the average of at least three determinations.

In Vitro Release

The sunscreen dissolution and release from the SLMs were studied by adding previously sieved (100 μm) BMDBM (5 mg) and MBC (5 mg) or SLMs containing an equivalent amount of the sunscreens, to propylene glycol (50 mL) under mechanical stirring at 50 rpm and 37°C. The particle size of BMDBM and MBC ranged, respectively, from 43.1 to 242.0 μm and 15.3 to 48.1 μm, before the sieving process and 47.3–106.0 and 12.7–37.6 μm, after the sieving process. At appropriate time intervals, 1-mL aliquots of the release medium were withdrawn and replace with an equal volume of fresh medium. The samples were filtered (0.45 μm) and assayed for BMDBM and MBC by HPLC, after dilution (1:1) with methanol. Each series of experiments was repeated at least three times.

Photodegradation Studies

Photolysis experiments were performed in cream preparations (oil-in-water emulsions) containing 1% (wt/wt) of BMDBM and MBC in conjunction with unloaded SLMs or entrapped in microparticles. A cream containing microparticles loaded only with BMDBM was also examined. The emulsion excipients were: sorbitan monostearate (2.0%), polyoxyethylene sorbitan monostearate (4.5%), butylated hydroxyanisole (0.05%), octyl palmitate (5.0%), liquid petrolatum (5.0%), cetearyl alcohol (5.0%), sodium benzoate (0.1%), glycerin (2.0%), dehydroacetic acid (0.1%), EDTA (0.1%), and water (67.0%). The creams were prepared according to the common procedure used in compounding practice (Martin, 1993). Briefly, the oil- and aqueous-soluble components were separately heated to about 60°C and the aqueous phase was added to the oil phase while stirring with a mixer. BMDBM and MBC were dissolved in the oil phase, whereas blank or loaded microparticles (~9 g per 100 g of cream) were dispersed in water and added in the cooling phase of the emulsion preparation at about 40°C. Portions (35–45 mg) of the test creams were homogeneously distributed onto a Transpore™ tape (3M Health Care, Neuss, Germany) at a level of 2 mg/cm^2 (surface area, 20 cm^2). The samples were secured by gumming them to a support and then irradiated for 2 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 500 W/m^2. The applied UV energy was equivalent to 10 minimal erythemal dose (MED), which is considered representative of daily solar emission close to the equator (Tarras-Wahlberg et al., 1999). After the exposure interval, the Transpore™ tape was cut into small pieces and extracted with ethanol (5 mL) under sonication (5 min). The sonication was repeated twice with methanol (5 mL) followed by overnight extraction, under stirring, with fresh methanol (15 mL). The combined fractions were adjusted to a volume (50 mL) and the obtained sample was filtered (0.45-μm membrane filters) and analysed by HPLC. The degree of photodegradation was evaluated by measuring the percentage of recovered sunscreen agent with respect to nonexposed samples. The results were the average of at least six experiments.

In Vitro Sun Protection Factor Measurement

The in vitro determination of the cream sun protection factor (SPF) was carried out according to the Diffey and Robson (1989) technique, with minor modifications. The method is based on the measurement of the transmission spectrum of the UV radiation (290–400 nm) through a Transpore™ tape, before and after application (2 mg/cm^2) of the sunscreen preparation. The tape was placed into the spectrophotometer (Model V-530PC UV-VIS; Jasco, Tokyo, Japan) sample compartment, over the quartz input optics of the detector. The spectral data were processed with a personal computer and the SPF calculated according to Diffey and Robson (1989).

Statistical Analysis

Statistical analysis of data was performed using analysis of variance (ANOVA) and nonparametric multiple comparison test (Kruskal–Wallis test) and post test (Tukey test). p values $<.05$ were considered significant. All computations were carried using the GraphPad Instat software (GraphPad Software, San Diego, CA).

RESULTS AND DISCUSSION

Lipid Microparticle Preparation and Characterization

For the preparation of lipid microparticles loaded with the BMDBM/MBC mixture, a hot emulsion technique (Jaspart et al., 2005) was employed, utilizing different lipid materials (tristearin, stearic acid, glyceryl behenate) and hydrogenated phosphatidylcholine as emulsifier. The latter was selected because of its physiological compatibility. The highest microparticle yield (percentage ratio between the weight of microparticles and the weight of lipid, emulsifier and actives fed initially) was obtained at a lipid:emulsifier ratio of 6:1. To examine the influence of the lipid matrix on the entrapment capacity of the SLMs, in vitro release studies were performed using a medium (propylene glycol) in which BMDBM and MBC were sufficiently soluble (BMDBM solubility, 1.62 g/L; MBC solubility, 2.5 g/L) to ensure sink conditions, whereas the lipoparticles remained intact. Marked differences in sunscreen release behavior were observed among microparticles prepared with the different lipids (Figure 1). The sunscreen release rates from the systems based on glyceryl behenate and stearic acid were not significantly lower (Kruskal–Wallis test) than the

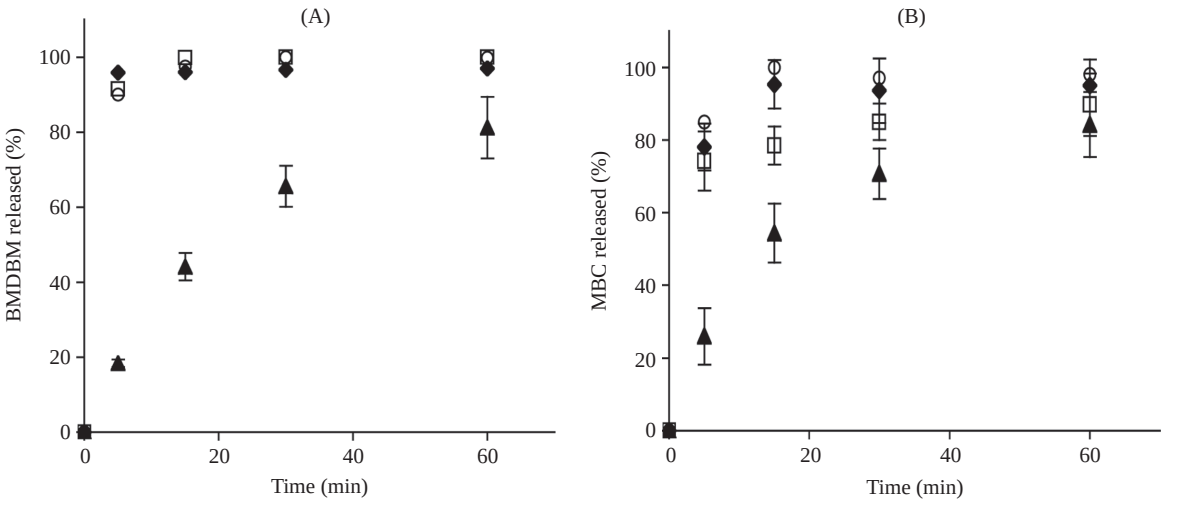

FIGURE 1. Dissolution (❍) and release of BMDBM (A) and MBC (B) from SLMs prepared with stearic acid (□), glyceryl behenate (✦), or tristearin (▲). Values are $M \pm SD$ ($n = 3$).

dissolution rates (Figure 1A and B), exhibiting burst-effect phenomena, that indicated adsorption of the actives at the microparticle surface. Conversely, SLMs prepared with tristearin gave rise to decreased release for both BMDBM (frame A of Figure 1) and MBC (frame B of Figure 1), thus suggesting the incorporation of the examined substances in this triglyceride matrix. These results indicate that the type of lipid excipient has a major influence on the microparticle sustained-release effect. This phenomenon is probably due to different affinity between the UV filters and the examined lipid materials (Jaspart et al., 2005). Moreover, variation of the production temperature, due to the different melting points of the examined lipids, represents another factor which could affect the performance of the obtained SLMs, because it has been shown that higher temperatures favor burst release phenomena (Müller et al., 2002).

Additional production variables including the stirring rate (9,500–17,500 rpm) and time (1–5 min) were evaluated to obtain particles with satisfactory morphological structure and size homogeneity. At higher stirring rates (17,500 rpm) and shorter time (1 min) the particles were smaller but irregular. In contrast, satisfactory results in terms of particle size, polydispersity, and surface smoothness were obtained at 13,500 rpm for 2 min.

SEM micrographs of the optimized microparticles, based on tristearin and hydrogenate phosphatidylcholine, revealed a spherical shape, although some irregular fragments were present (Figure 2). The particle size was between 19 and 40 μm (mean diameter, 29.9 ± 5.9 μm), the majority (58%) of the population being in the 30–40 μm range, which is suitable for the topical application of substances whose percutaneous absorption must be avoided, such as the sunscreen agents (Scalia et al., 2007). The microparticle loading capacity for BMDBM and MBC were 10.4 ± 0.9% (wt/wt) and 10.1 ± 0.3% (wt/wt), respectively. The encapsulation efficiency values were in the range 56.7–58.4%.

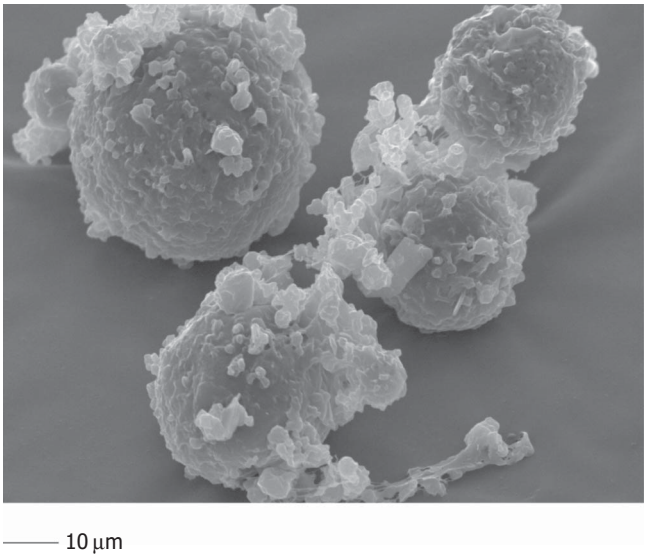

FIGURE 2. Scanning electron microscopy (SEM) micrographs of SLMs loaded with BMDBM and MBC.

Lipoparticles based on tristearin and phosphatidylcholine and containing only BMDBM were also prepared and characterized. No significant differences in particle morphology and dimensional distribution (mean diameter, 27.2 ± 8.4 μm) were observed compared with the system containing BMDBM together with MBC. Therefore, the physical properties of the SLMs were not affected by the co-loading of MBC with BMDBM. However, the encapsulation efficiency was higher (65.5%) for the lipoparticles prepared with BMDBM alone. This is probably due to reduced BMDBM dissolution in the

melted lipid phase when MBC is added during lipoparticle preparation.

Additional characterization of the optimized SLMs was carried out by powder X-ray diffractometry. As illustrated in Figure 3, the diffractogram of the physical mixture of the sunscreens with the microparticle excipients (Figure 3A) displayed the characteristic crystalline peaks of BMDBM (10.8°, 19.6°, 20.1°) and MBC (8.3°, 8.5°, 14.9°, 15.2°). In contrast, these peaks were not observed in the diffraction pattern of the lipid microparticles (Figure 3B). This suggests that the UV filters are in an amorphous state in the SLMs. The peaks at 5.7° and 19.3° present in the SLM pattern (Figure 3B) are due to tristearin. Moreover, compared to the physical mixture (Figure 3A), the lipid microparticle diffractogram (Figure 3B) exhibited an increase of the two signals at 22.9° and 23.9° and the absence of the tristearin peak at 21.5°. This finding can be ascribed to polymorphic modifications of tristearin (from stable β-form to unstable α- and β′-form) due to its crystallization in lipoparticles (Iannuccelli et al., 2006).

Photodegradation Studies

Previous investigations of the effect of SLMs on the photochemical behavior of BMDBM have been performed on microparticles loaded with the UV-A filter alone (Iannuccelli et al., 2006; Scalia et al., 2006). In contrast, in this study, lipoparticles incorporating BMDBM together with the photostabilizer MBC, were prepared and compared, in terms of light stability, with conventional SLMs containing the UV-A filter without photostabilizer. To examine the influence of the lipid particle matrix on the photodegradation of BMDBM, the photolysis experiments were performed in creams (oil-in-water emulsions) as topical vehicles. These systems were selected as a model formulation as they represent the majority of sunscreen preparations (Klein & Palefsky, 2005) and hence simulate conditions of real use of these products.

Lipoparticles prepared by loading BMDBM together with MBC were incorporated into the cream. Creams containing lipid microparticles loaded with BMDBM only in conjunction with free MBC or nonencapsulated BMDBM and MBC were also prepared. The emulsions were applied onto Transpore™ tapes (a surgical tape able to simulate the texture of human skin), irradiated with simulated sunlight and the degree of degradation was measured by HPLC (Figure 4).

In the formulation containing nonencapsulated BMDBM and MBC, the extent of the photoinduced decomposition of the UV-A filter was 33.8% (Table 1). This value is in agreement with the data reported in previous studies (Bonda, 2005; Gaspar & Maia Campos, 2006). The percentage loss of the UV-A filter decreased to 25.3% (see Table 1) in the cream containing the BMDBM-loaded microparticles with the nonencapsulated MBC. A further and statistically significant ($p < .05$) reduction of the sunscreen degradation to 16.9% was attained by the microencapsulation of BMDBM together with MBC (Table 1). These results indicated that the co-loading of the MBC stabilizer enhanced the photostability of BMDBM encapsulated into SLMs.

This phenomenon could be ascribed to a more effective interaction of the MBC photostabilizer with BMDBM in the

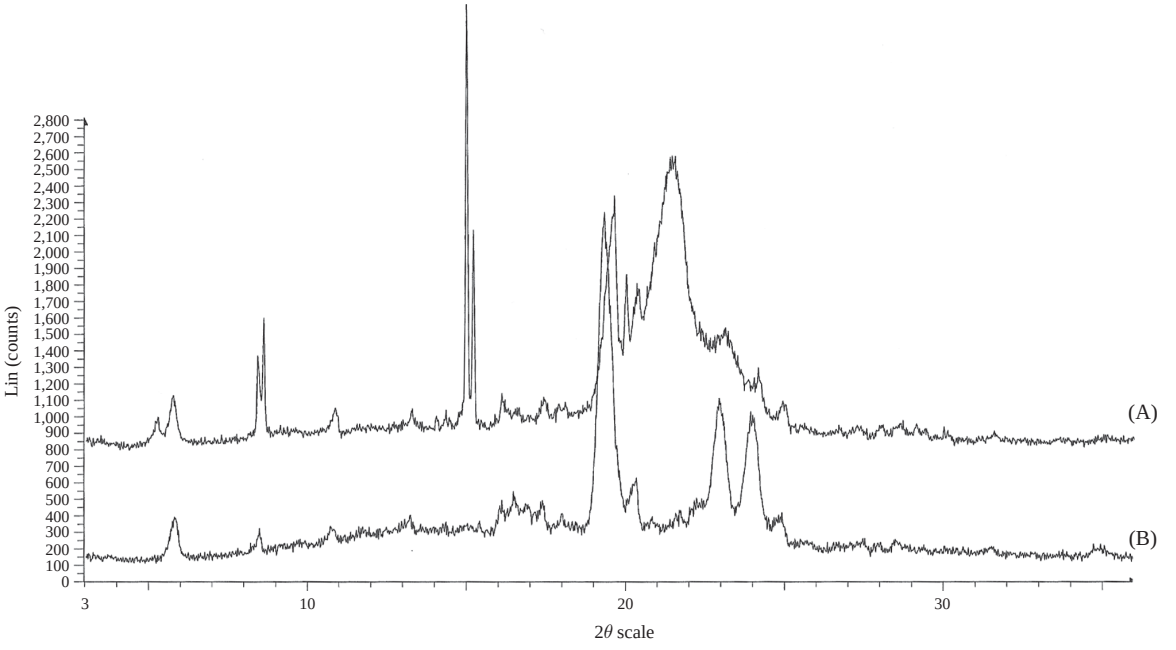

FIGURE 3. Powder X-ray diffraction patterns of BMDBM/MBC—lipoparticle excipients physical mixture (A) and lipoparticles loaded with BMDBM and MBC (B).

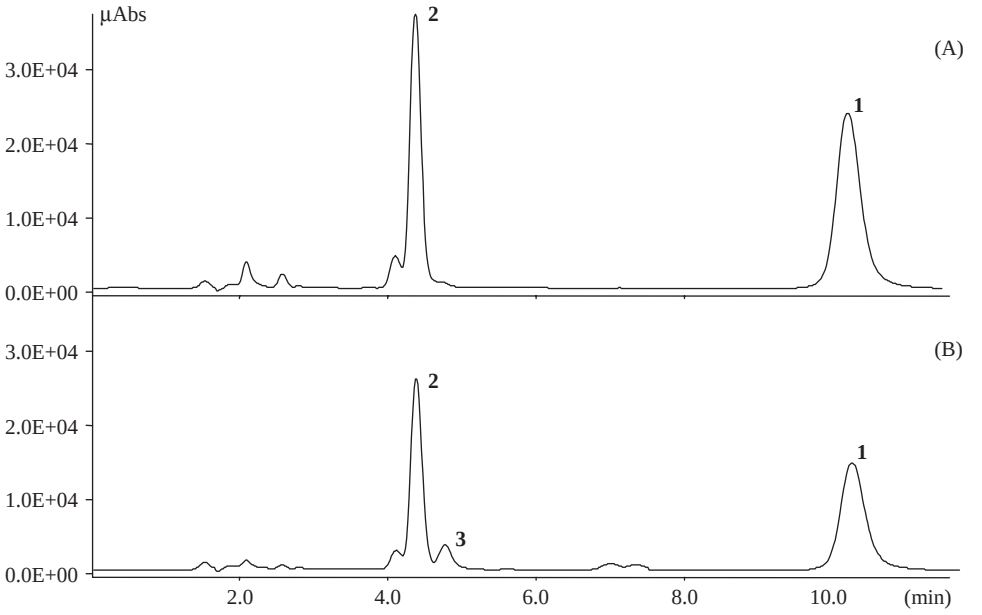

FIGURE 4. HPLC chromatograms of a cream sample containing nonencapsulated BMDBM and MBC, before (A) and after (B) 2-h irradiation with the solar simulator. Peaks: 1, BMDBM; 2, MBC; 3, *cis*-isomer of MBC (photoproduct of MBC raw material that consists of the *trans*-isomer).

TABLE 1
Comparative Photodegradation Data for Nonencapsulated and Microparticle-Entrapped BMDBM in Cream Preparations Containing MBC Free or Loaded in the Microparticles

Sample	BMDBM Loss[a] (%)	p[b]
Free BMDBM/MBC	33.8 ± 5.5	
BMDBM-loaded SLMs/free MBC	25.3 ± 4.2	<.05
BMDBM/MBC-loaded SLMs	16.9 ± 5.9	<.001

[a]Each value is the $M \pm SD$ of six determinations.
[b]p values (Tukey post test) versus free BMDBM/MBC.

lipid particle core, without interferences by the emulsion excipients. In addition, following irradiation, 23.9 ± 2.3% of MBC degraded in the cream containing the nonencapsulated photostabilizer, whereas only 14.9 ± 3.9% of MBC was lost in the preparation based on its microencapsulated form. Therefore, protection of the MBC stabilizer by the SLMs could also contribute to the higher effectiveness of the microparticles coloaded with BMDBM and MBC.

Because one of the most important criterion for the evaluation of a sunscreen product efficacy is the SPF, this parameter was determined in vitro in the examined formulations (Diffey & Robson, 1989). The SPF values measured for the creams containing the free or encapsulated sunscreen agents ranged from 3.8 to 4.3, the differences being not statistically significant ($p > .05$, ANOVA). This indicated that incorporation in the SLMs of the sunscreen agents has not altered their overall attenuation characteristics. Another parameter obtained from the in vitro SPF measurements is the UV-A/UV-B ratio, an indicator of the UV-A absorbing performance in relation to that in the UV-B (Steinberg, 2005). For all tested formulations, the UV-A/UV-B ratio was 0.8. The measured in vitro SPF and UV-A/UV-B ratio fulfilled the minimum requirements for sunscreen products, as indicated by the US, Australian, and Japan legislations (Steinberg, 2005).

CONCLUSIONS

From the results obtained in this study, it can be deduced that entrapment of the UV-A filter BMDBM in SLMs together with the MBC photostabilizer, enhanced the protective effect of the lipid particle matrix against light-induced degradation.

Although encapsulation of UV filters in lipoparticles has already been described (Iannuccelli et al., 2006; Tursilli et al., 2007; Yener et al., 2003), this is the first report on the co-loading of a sunscreen agent with a photostabilizer in SLMs.

Moreover, the encapsulation process should reduce unfavorable interactions of the UV-A filter with the skin, thereby reducing the potentially associated toxicological risks.

ACKNOWLEDGMENTS

The authors are grateful to MIUR (Ministero dell'Istruzione, dell'Università e della Ricerca, Rome, Italy) for financial support.

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