

상구조가 조절된 고분자 미립구에서 자외선 흡수제의 거동에 대한 연구

이 종 석 · 김 진 웅[†] · 김 준 오 · 한 상 훈 · 장 이 섭

태평양 기술 연구원 피부과학연구소

New Photochemistry of UV-Absorbing Chemicals in Phase-Controlled Polymer Microspheres

Jong-Suk Lee, Jin-Woong Kim[†], Junoh Kim, Sang-Hoon Han, and Ih-Seop Chang

Amore Pacific R&D Center, 314-1, Bora-ri, Giheung-eup, Yongin-si, Gyeonggi-do 449-729, Korea

요약 본 연구는 poly(methyl methacrylate) (PMMA) 마이크로 입자 내의 상 조절을 통하여 자외선 A 흡수제인 butyl methoxydibenzoylmethane (BMDM)을 효과적으로 안정화시킨 새로운 자외선 흡수 시스템에 관한 것으로, 마이크로 입자 내의 BMDM의 광학특성을 고분자와의 상 특성에 연관하여 해석함으로써 자외선 A 흡수제의 분자거동과 광 에너지 흡수 거동을 체계적으로 이해하고자 하였다. 본 연구에서는 고분자 마이크로 입자 내에서 BMDM의 상 특성을 제어하여, BMDM의 광 및 열 안정성을 유지하면서 자외선 A를 효과적으로 차단할 수 있었다. 본 연구를 통하여 고분자 마이크로 입자 내에 자외선 흡수제의 상 특성을 조절하는 것이 자외선 흡수제를 함유하는 화장품 제형 내에서 광화학 및 광 안정도를 결정하는 중요한 인자임을 알 수 있었다.

Abstract: In this study, a different UV (ultra-violet) ray absorption system is presented in which butyl methoxydibenzoylmethane (BMDM, a model UV-A absorbent, 320~400 nm) is stabilized in phase-controlled poly(methyl methacrylate) (PMMA) microspheres. The photochemistry of BMDM in the microspheres was investigated considering its phase characteristics therein. The analysis of a differential scanning calorimeter and X-ray diffractometer showed that the BMDM in the microspheres was present with a non-crystalline state. The phase control of BMDM in the polymer microsphere has an excellent ability to protect UV-A with maintaining its photo- and thermal stability. The results obtained in this study illustrate well that the phase control of the UV absorbents in the polymer microspheres is another key factor that determines its photochemistry and photostability in the final formulations.

Keywords: UV ray absorption, phase-controlled, non-crystalline, photostability, photochemistry

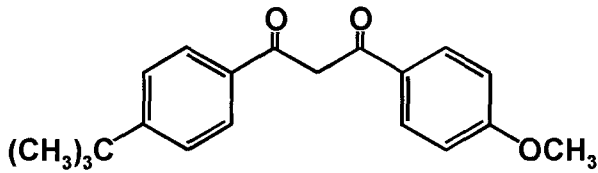
1. Introduction

Recently, there has been an intensive concern with the protection of ultra-violet (UV) light, since UV exposure induces serious damage to human skin[1,2]. UV light can be classified with UV-A (320~400 nm) and UV-B (290~320 nm), depending on its wavelength. Many studies have proved that UV-A is the reason for the sun light-induced skin damages, such as, cutaneous photoaging, immunosuppression, and photocarcinogenesis[3,4]. Therefore, there have been many tries to protect UV-A using appropriate UV-A absorbing chem-

icals in sunscreens. However, when exposed to UV light, UV-A absorbing chemicals are decomposed or rearranged easily, which happens because the excited energy cannot be transferred efficiently to other energies, such as light and/or heat. UV-induced decomposition of the chemicals not only reduces its UV-protecting performance but also promotes phototoxic or photoallergic contact dermatitis[5,6].

In this contribution, we introduce a different approach to stabilize an UV-A absorbent with maintaining its UV-absorbing performance in the formulations. We selected butyl methoxydibenzoylmethane (BMDM, refer to scheme 1) as a model UV-A absorbent. As far as we know, the BMDM is one of the most well known

[†] 주 저자 (e-mail: kjwoong@amorepacific.com)



Scheme 1. A chemical structure of butyl methoxydibenzoylmethane (BMDM).

chemicals that provide excellent protection against UV-A. In particular, the BMDM is characterized to have an excellent UV absorption in the UV-A wavelength region (320~400 nm). However, it has been reported that BMDM is also decomposed easily by UV radiation in solutions and in emulsion formulations[7-9]. Hence, in order to improve its stability, a number of methods have been proposed, including the chemical modification, the coacervation with polymer, and the complexation with cyclodextrins[10-14]. To the best of our knowledge, however, an acceptable result related to its stabilization has not been reported in the literature.

In this study, we emphasize the importance of phase control, especially, the crystallinity of BMDM molecules, to get an excellent photostability. The phase characteristics of BMDM are controlled considering its compatibility with polymer in the microsphere system. Finally, this paper describes the effect of the BMDM phase in the polymer microspheres on the photostability, thermal stability, and UV-A absorbing performance for the purpose of designing a new UV-A absorbing system.

2. Experimental Methods

2.1. Materials

Butyl methoxydibenzoylmethane (BMDM) was purchased from Roche Vitamins Inc. (Zurich, Swiss) and used without further purification. Poly(methyl methacrylate) (PMMA, $M_w = 3.5105 \text{ g mol}^{-1}$) and methylene chloride (MC) were all reagent grades and purchased from Aldrich (USA). Polyvinyl alcohol (PVA, $M_w = 8.8 \times 10^4 \sim 9.2 \times 10^4 \text{ g mol}^{-1}$, 87~89% degree of saponification) was kindly supplied from Kuraray (Japan).

2.2. Preparation of BMDM/PMMA Microspheres

BMDM/PMMA microspheres were produced by solvent evaporation technique[15,16]. Both BMDM and PMMA

Table 1. A Standard Recipe for BMDM/PMMA Microspheres

Ingredient	Composition (g)		
	BMDM-C10	BMDM-C30	BMDM-C50
PMMA	18	14	15
BMDM ^a	2	6	15
MC	70	70	70
PVA ^b	2	2	2
Water	198	198	198

^a Butyl methoxydibenzoylmethane

^b 1 wt% against total water weight

were dissolved in MC and then, BMDM/PMMA/MC solution prepared was poured into 1 wt% of PVA solution and emulsified with a MX-5 homogenizer (Nihonseiki Co., Japan). Then, MC in the emulsion droplets was eliminated completely by the evaporation at 40°C for 1 h. The microspheres produced were repeatedly washed by decantation in water and dried at ambient temperature. A typical recipe is summarized in Table 1.

2.3. Analytical Characterizations

The apparent image of microspheres was observed with an optical microscope (OM, Nikon) and a Scanning Electron Microscope (SEM, JSM-6300, JEOL). A differential scanning calorimeter (DSC, TA Instruments, DSC 910) was used to measure the thermal properties of the microspheres. DSC traces were recorded from 20 °C to 100°C with a heating rate of 5°C/min under a stream of a nitrogen flow. The crystallinity of BMDM was investigated by the measurement of X-ray diffractometer (XRD, Riguka Denki, model RAD-C) in the 2 ranges. Cu K radiation ($\lambda = 1.542$) was used in XRD measurements. To evaluate *in vitro* photostability of BMDM, UV-vis spectrophotometer (Shimadzu Co., UV 1601, Japan) measurements were carried out. First, BMDM and BMDM/PMMA microspheres were mixed evenly in capric/caprylic acid triglyceride oil, respectively. Then, UV-A was radiated with the intensity of $9.0 \times 10^{-3} \text{ W/cm}^2$ for 0.5 h at room temperature (UV-A Tech. Inc.). After the net concentration of BMDM was controlled with 10 ppm in the dimethyl sulfoxide solution, the UV absorption behaviors were compared.

2.4. Thermal Stability Measurements

To evaluate the stability of BMDM in the microspheres, HPLC (HP1100 series) measurements were carried out with the storage time. First, the BMDM/PMMA microspheres were formulated together with a simple oil-in-water (O/W) emulsion consisted of liquid paraffin (10 wt%), cetearyl alcohol (2 wt%, Croda Inc.), sorbitan monostearate (0.5 wt%, Uniqema America), polysorbate 60 (1.2 wt%, Uniqema America), and deionized water. The concentration of BMDM in the O/W emulsion was adjusted with 2 wt%. Then, the formulations prepared were sealed in a plastic tube and stored at 40°C. In the HPLC measurements, the chromatographic separation was achieved by the use of a Nova-Pak C18 column (3.9×150 mm, Waters). The flow rate of the carrier solvent composed of methanol/water (90/10, v/v) was 1 mL/min. The detection wavelength was set at 350 nm. The sample injection volume was 10 μL. The stability of BMDM was defined by the ratio of measured concentration to initial concentration, $[BMDM]_m/[BMDM]_0$.

2.5. Determination of *in-vitro* UV-A Protection Factor (UV-A PF)

The ability of BMDM/PMMA microsphere to protect UV-A rays was estimated in the O/W emulsions. The protection of UV-A rays was estimated measuring the UV-A protection factor (UV-A PF). First, 2 mgcm⁻² sample was placed onto a transpore tape (3 M Co.). After 15 min, UV-A PF was measured five times with a sun protection factor (SPF) 290 analyzer system (Optometrics USA Inc.). The UV-A PF was calculated using Eq. (1), as described by Ferrero *et al.*[17].

$$UV-A PF = \frac{\sum_{320}^{400} E_{\lambda} I_{\lambda} \Delta\lambda}{\sum_{320}^{400} E_{\lambda} I_{\lambda} T_{\lambda} \Delta\lambda}$$

where T is the sunscreen transmittance at wavelength; E the spectral irradiance of terrestrial sunlight at wavelength, expected for a clear sky at noon in mid-summer for a latitude of 40N; I the biological action spectrum for UV-A.

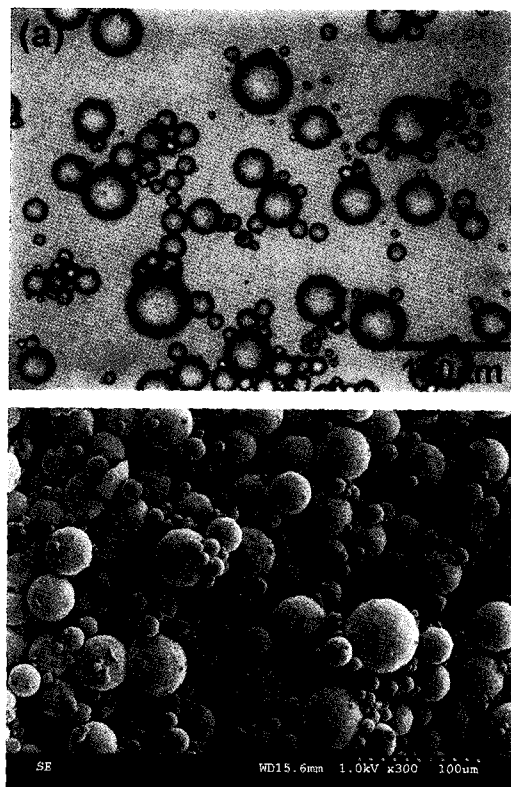


Figure 1. OM and SEM photographs of BMDM/PMMA microspheres. In this observation, the sample was BMDM-C50.

3. Results and Discussion

3.1. Formation of BMDM/PMMA Microspheres

In this study, BMDM/PMMA microspheres were produced by a conventional solvent evaporation method. Figure 1 shows OM and SEM photographs for the BMDM/PMMA (BMDM-C50) microspheres after complete elimination of MC. From the OM Image, it is evident that the BMDM was mixed homogeneously with PMMA. There was no phase separation between BMDM and PMMA, meaning the two phases are very compatible. After recovery of the microspheres, their surface was observed with SEM (Figure 1b). The surface of the BMDM/PMMA microspheres was smooth and spherical in shape. The average size of the microspheres was about 20 μm. The maximum loading amount of BMDM in the microspheres was 50 wt%. Within that concentration, there was no evidence of collapse of the microsphere walls as a result of evaporating and drying.

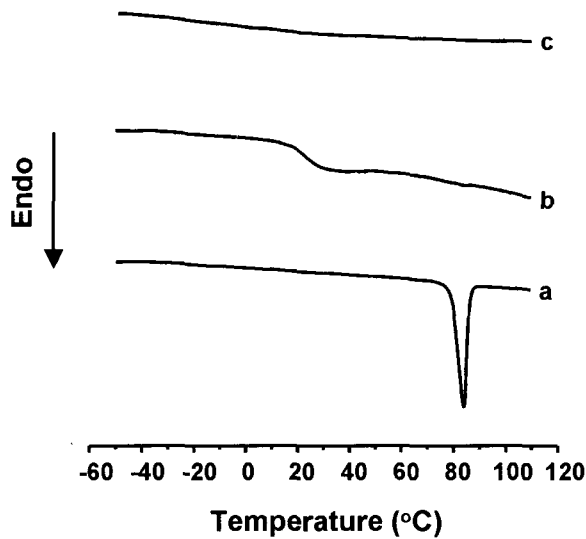


Figure 2. DSC thermograms of BMDM/PMMA microspheres. (a) BMDM, (b) BMDM/PMMA microspheres (BM-DM-C50), and (c) PMMA microspheres.

3.2. Phase Characteristics of BMDM/PMMA Microspheres

The phase characteristics of BMDM in the microspheres were observed with DSC and XRD measurements. Figure 2 shows the DSC thermograms of the BMDM/PMMA microspheres. The pure BMDM had a typical endothermic peak at 83.5°C, corresponding to its melting point (T_m). However, when the BMDM was incorporated into the PMMA microspheres, the thermal behavior was quite different from the pure BMDM. The BMDM in the PMMA microspheres displayed just a broad weak endothermic peak over the temperature range from 20°C to 50°C. From this result, it is assumed that the phase of BMDM in the PMMA microspheres changed from crystalline to non-crystalline. In order to confirm this unique phase behavior of the BMDM in the PMMA microspheres, in this study, the degree of crystallinity of BMDM was observed by XRD measurements and shown in Figure 3. In the dried state, the pure BMDM showed a bundle of typical crystal peaks. However, when the BMDM was incorporated into the PMMA microspheres, its crystal peaks could not be detected. The XRD pattern of the BMDM/PMMA microspheres was exactly consistent with that of PMMA. From the DSC and XRD data, it is verified that the BMDM was mixed homogeneously in the PMMA microspheres, forming a non-crystalline state

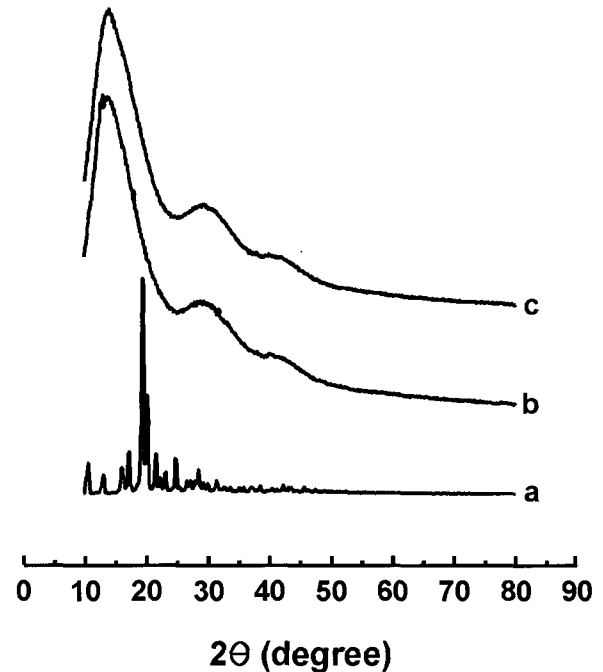


Figure 3. X-ray diffractograms of BMDM/PMMA microspheres. (a) BMDM, (b) BMDM/PMMA microspheres (BMDM-C50), and (c) PMMA microspheres.

owing to its good compatibility with PMMA.

3.3. Photo- and Thermal Stability

In this study, *in vitro* photostability of the BMDM was evaluated measuring the progress of photodegradation with UV-vis spectrophotometer. Figure 4 shows UV-vis spectra of BMDM after the UV irradiation for 0.5 h at room temperature. It can be found that the BMDM itself had a very low photostability. With only 0.5 h UV radiation, the maximum intensity of UV absorbance was lowered significantly with about 44%, compared with that of initial state. On the contrary, the BMDM located in the PMMA microspheres showed a high photostability. Even after 0.5 h UV irradiation, only 9% of BMDM was photodegraded, indicating that most of the BMDM molecules in the microspheres remained safely against strong UV rays. Furthermore, the thermal stability of BMDM was measured with the storage time at 40°C in the O/W emulsions and shown in Figure 5. One can easily found that the BMDM located in the PMMA microspheres showed an enhanced thermal stability. Irrelative to the loading concentration, the BMDM located in the PMMA

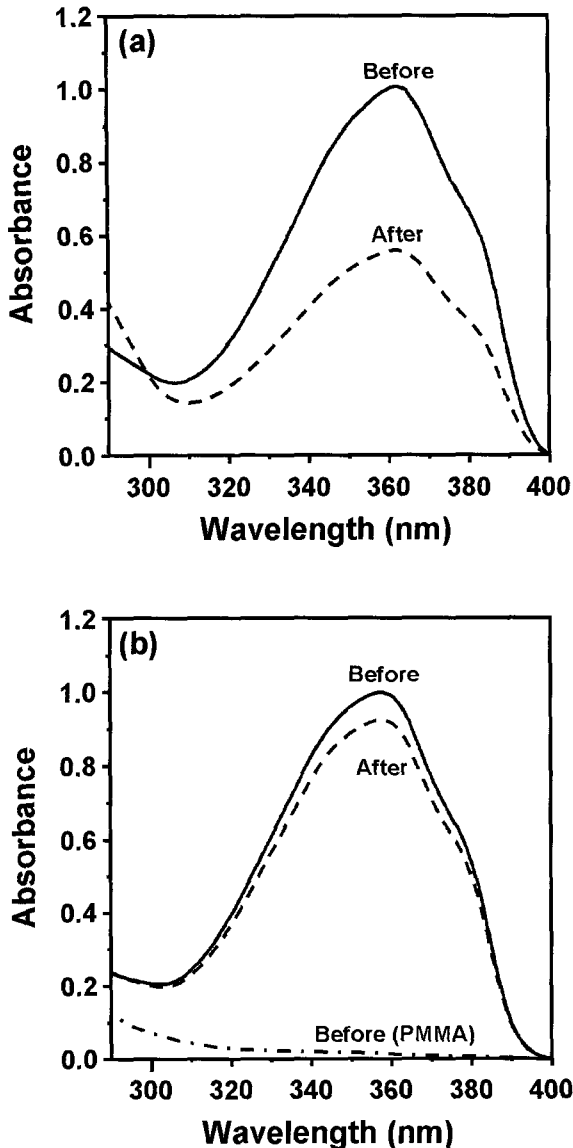


Figure 4. UV-vis. spectra of BMDM in solution. (a) BMDM and (b) BMDM/PMMA microspheres (BMDM-C50). The UV-vis spectra were obtained before and after UV-A radiation, respectively. For comparison, the UV-vis spectrum for 5 ppm of PMMA before the irradiation was shown in Figure 4(b).

microspheres was very stable at high temperature for a long time.

Generally, by absorption of UV radiation, UV-absorbing molecules are transferred to an excited state from which the energy may dissipate into molecular vibrations and further into heat via collisions with surrounding molecules[18-20]. Therefore, when an efficient

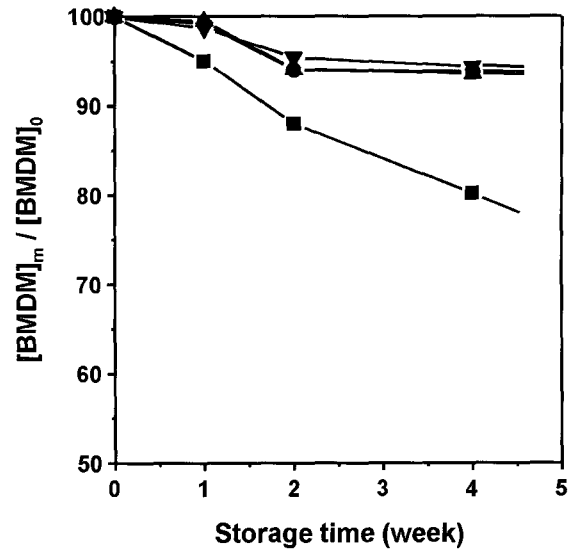


Figure 5. Thermal stability of BMDM/PMMA microspheres with the storage time. Pure BMDM (■), BMDM-C10 (●), BMDM-C30 (▲), and BMDM-C50 (▼). To accelerate the degradation speed of BMDM, the stability measurements were carried out at 40°C. The concentration of BMDM was fixed with 2 wt% in the O/W emulsions.

dissipation of the excited energy does not occur, the chemical bonds of the UV-absorbing molecules may be broken and new bonds may be formed, leading to an irreversible molecular change. The BMDM is one of the most instable UV-absorbing molecules[8,9]. In our study, however, the BMDM located in the PMMA microspheres displayed good stability against UV rays, meaning that the excited energy of BMDM molecules was dissipated efficiently without causing any molecular degradation. It is assumed that the formation of non-crystalline BMDM in the PMMA microspheres was closely related with the high photostability. In the non-crystalline state, the excited energy in a BMDM molecule may be transferred easily to other neighbor molecules. In our system, therefore, it is postulated that the excited BMDM molecules returned to their original state by dissipating eventually their excited energy as heat, which is evident from the fact that there was no serious molecular degradation at high temperature for a long time.

3.4. UV-A Protection Behaviors

Figure 6 shows the ability of BMDM/PMMA mi-

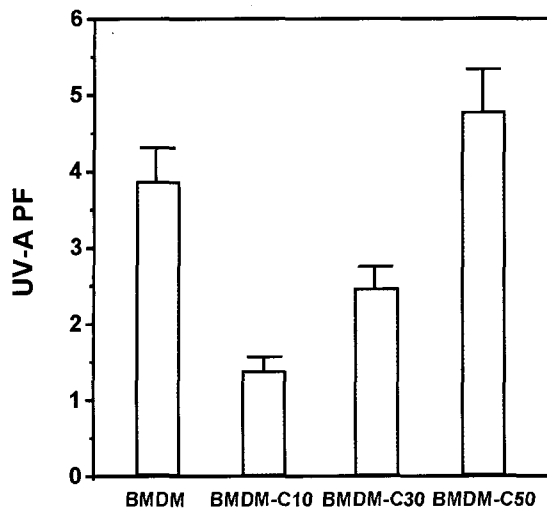


Figure 6. UV-A protection factors of BMDM/PMMA microspheres in a simple O/W emulsion formulation. The concentration of BMDM was fixed with 2 wt% in the O/W emulsions.

microspheres to protect UV-A in the O/W emulsions. The UV-A PF value increased with the increase of BMDM in the PMMA microspheres. At a low concentration of BMDM in the PMMA microspheres, below 30 wt%, the BMDM molecules didn't absorb effectively the UV rays, which is fundamentally attributable to the thick polymer phase. However, as the concentration of BMDM increased, the degree of UV-A protection increased dramatically. Especially, when the concentration of BMDM in the microspheres was 50% (BMDM-C50), the UV-A PF value was much higher than that of the BMDM at the same concentration in the O/W emulsions. With regard to this interesting result, the solubility of BMDM should be considered in the emulsion formulations. It has been reported that most of the UV-absorbing molecules including BMDM have low solubility to conventional oils [10,21]. Therefore, when the BMDM is solubilized directly in oil part and emulsified mechanically, its partial precipitation may take place to form small crystals (actually, in our study, the BMDM crystals could be detected in OM observations). However, in the case that the BMDM is confined with non-crystalline phase in the polymer microsphere, it can absorb effectively UV-A rays, not depending on its solubility to oils. Consequently, in our study, it is established that the efficacy of BMDM to absorb UV-

A rays could be maximized by controlling its phase characteristics in the polymer microspheres.

4. Conclusion

In this study, BMDM/PMMA microsphere was prepared using by a solvent evaporation technique. The phase characteristics of BMDM within PMMA microsphere were investigated with DSC and XRD measurements. Uniquely, it was found that the BMDM molecules were present with non-crystalline state in the PMMA microspheres. The BMDM located in the PMMA microspheres had an improved photo- and thermal stability as well as an excellent ability to protect UV rays, which seems to be attributed to the formation of non-crystalline phase in the microspheres. The importance of BMDM/PMMA microsphere system is found in the fact that it can be applied very usefully to develop highly stable sunscreens against UV rays and heat.

Acknowledgment

This work is supported in part from the National Research Laboratory (NRL) program (Project No. 2000-N-NL-01-C-270) by the Ministry of Science and Technology, South Korea.

References

1. National Institute of Health Consensus Statement Online, Sunlight, Ultraviolet Radiation, and the Skin 7, 1 (1989).
2. S. Site, D. Moyal, S. Richard, J. Rigal, J. L. Lvque, and A. Fourtanier, Mexoryl® SX: a broad absorption UVA filter protects human skin from the effects of repeated suberythemal doses of UVA, *J. Photochem. Photobiol. B: Biol.*, **44**, 69 (1998).
3. S. R. Pinnell, Early onset of action and efficacy of a combination of calcipotriene and betamethasone dipropionate in the treatment of psoriasis, *J. Am. Acad. Dermatol.*, **48**, 1 (2003).
4. M. S. Duthie, I. Kimber, and M. Norval, The effects of ultraviolet radiation on the human immune system, *Brit. J. Dermatol.*, **140**, 995 (1999).
5. M. M. Rieger, Photostability of cosmetic ingredients

- on the skin, *Cosmet. Toil.*, **112**, 65 (1997).
6. A. Schrader, J. Jakupovic, and W. Baltes, Photochemical studies on trans-3-methyl butyl 4-methoxy cinnamate, *J. Soc. Cosmet. Chem.*, **45**, 43 (1994).
 7. W. Schwack and T. Rudolph, Photochemistry of dibenzoyl methane UVA filters Part 1, *J. Photochem. Photobiol. B: Biol.*, **28**, 229 (1995).
 8. N. Tarras-Wahlberg, G. Stenhagen, O. Lark, A. M. Wenngerg, and O. Wennerstrm, Changes in ultra-violet absorption of sunscreens after ultraviolet irradiation, *J. Invest. Dermatol.*, **113**, 547 (1999).
 9. R. M. Sayre and J. C. Dowdy, Photostability testing of avobenzone, *Cosmet. Toil.*, **114**, 85 (1999).
 10. S. Scalia, S. Villani, A. Scatturin, M. A. Vandelli, and F. Forni, Complexation of the sunscreen agent, butyl-methoxydibenzoylmethane, with hydroxypropyl- β -cyclodextrin, *Int. J. Pharm.*, **175**, 205 (1998).
 11. P. Perugini, S. Simeoni, S. Scalia, I. Genta, T. Modena, B. Conti, and F. Pavanetto, Effect of nanoparticle encapsulation on the photostability of the sunscreen agent, 2-ethylhexyl-p-methoxycinnamate, *Int. J. Pharm.*, **246**, 37 (2002).
 12. D. Fairhurst and M. Mitchnick, Submicron encapsulations of organic sun screens, *Cosmet. Toil.*, **110**, 47 (1995).
 13. C. Anselmi, M. Centini, C. Rossi, A. Rastrelli, M. Andreassi, A. Buonocore, and C. L. Rosa, New microencapsulated sunscreens: technology and comparative evaluation, *Int. J. Pharm.*, **242**, 207 (2002).
 14. S. A. Wissing and R. H. Miller, A novel sunscreen system based on tocopherol acetate incorporated into solid lipid nanoparticles, *Int. J. Cosmet. Sci.*, **23**, 233 (2001).
 15. B. Simon, *Microencapsulation methods and industrial applications*, Marcel Dekker, Inc., New York, pp 1 (1996).
 16. B. Patrick and J. W. McGinity, Preparation of microspheres by the solvent evaporation technique, *Adv. Drug. Deliver. Rev.*, **28**, 25 (1997).
 17. L. Ferrero, M. Pissavini, S. Marguerie, and L. Zastrow, Sunscreen *in vitro* spectroscopy: application to UVA protection assessment and correlation with *in vivo* persistent pigment darkening, *Int. J. Cosmet. Sci.*, **24**, 63 (2002).
 18. E. Chatelain and B. Gabard, Early onset of action and efficacy of a combination of calcipotriene and betamethasone dipropionate in the treatment of psoriasis, *Photochem. Photobiol.*, **74**, 401 (2001).
 19. C. Bonda and D. C. Steinberg, A new photostabilizer for full spectrum sunscreens, *Cosmet. Toil.*, **115**, 37 (2000).
 20. C. J. Bouillon, Recent advances in sun protection, *Dermatol. Sci.*, **23**, S57 (2000).
 21. J. Hewitt and J. Woodruff, Formulating water-resistant TiO₂ sunscreens, *IFSCC Magazine*, **3**, 18 (2000).