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Inclusion Complexation of the Sunscreen Agent 2-Ethylhexyl-*p*-dimethylaminobenzoate with Hydroxypropyl-β-cyclodextrin: Effect on Photostability

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Abstract

The interaction between the UV filter, 2-ethylhexyl-*p*-dimethylaminobenzoate, and unmodified and modified α-, β- or γ-cyclodextrins was studied in water by phase-solubility analysis.

Of the cyclodextrins available, only hydroxypropyl-β-cyclodextrin caused a marked increase in the aqueous solubility of 2-ethylhexyl-*p*-dimethylaminobenzoate. The data from the solubility study indicated the formation of a 1 : 1 (sunscreen–cyclodextrin) complex. The inclusion of the sunscreen agent into the hydroxypropyl-β-cyclodextrin cavity was confirmed by thermal analysis and by nuclear magnetic resonance spectroscopy. Irradiation-induced degradation of 2-ethylhexyl-*p*-dimethylaminobenzoate was reduced by complexation with hydroxypropyl-β-cyclodextrin, this effect being more pronounced in solution (the extent of degradation was 25·5% for the complex compared with 54·6% for free 2-ethylhexyl-*p*-dimethylaminobenzoate) than in the emulsion vehicle (the extent of degradation was 25·1% for the complex compared with 33·4% for free 2-ethylhexyl-*p*-dimethylaminobenzoate).

Although photodegradation of the sunscreen agent is significantly reduced by formation of the inclusion complex it is important to design a suitable vehicle. Inclusion of 2-ethylhexyl-*p*-dimethylaminobenzoate-DMAB into the hydroxypropyl-β-cyclodextrin cavity limits interaction of the UV filter with the skin reducing the side-effects of the formulation.

Sunlight has both beneficial and adverse effects on the skin of man. The harmful effects are because of the UV component of solar radiation and can be divided into two general types, acute and chronic (National Institute of Health 1989). Acute effects include inflammatory responses (sunburn erythema) whereas chronic exposure to the sun's UV rays can cause certain forms of skin cancer, cutaneous photoageing and damage to the skin immunological system (National Institute of Health 1989; Pathak 1991; Ziegler et al 1994). Increasing knowledge about the risks of exposure to sunlight has resulted in the increasingly widespread use of topical sunscreen agents (National Institute of Health 1989; Dromgoole & Maibach 1990; Schrader et al 1994; Hayden et al 1997). Chemical sunscreens are compounds which absorb the energy of both the UV-B (290–320 nm) and UV-A (320–400 nm) radiation reaching the stratum corneum, thereby protecting it from the deleterious effects of sunlight UV wavelengths (National Institute of Health 1989; Siemer 1991; Jiang et al 1996; Hayden et al 1997; Rieger 1997).

The most important characteristic of an effective UV filter is high photostability (Deflandre & Lang 1988; Schwack & Rudolph 1995; Berset et al 1996; Rieger 1997)—the photochemical decomposition of the sunscreen agent under sunlight irradiation not only reduces the photoprotective power of the sunscreen during use, but can also lead to degradation products which might promote phototoxic or photoallergic contact dermatitis (Deflandre & Lang 1988; Dromgoole & Maibach 1990; De Leo et al 1992; Roscher et al 1994; Schrader et al 1994; Rieger 1997).

2-Ethylhexyl-*p*-dimethylaminobenzoate (EH-DMAB) is a commonly used UV-B filter in sunscreen preparations (Tomasella et al 1991;

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Roscher et al 1994; Jiang et al 1996); it is preferred to *p*-aminobenzoic acid because of its lower sensitization potential (Dromgoole & Maibach 1990). EH-DMAB is included in the list of authorized sunscreen agents both in Europe (EEC Directive 1976) and in the USA (US Food and Drug Administration 1993) and it is also approved by the Australian and Japanese regulatory authorities. Several authors have described the irradiation-induced decomposition of EH-DMAB, both in solution (Roscher et al 1994; Dunlap et al 1996) and in a model emulsion (Deflandre & Lang 1988). EH-DMAB has also been known to cause photocontact allergy, although the number of sensitization cases is lower than that reported for other derivatives of *p*-aminobenzoic acid (Dromgoole & Maibach 1990; Rieger 1997). Hence, to enhance the effectiveness and safety of this sunscreen agent, there is a need for new formulations with improved EH-DMAB photostability.

Cyclodextrins are cyclic oligosaccharides which can interact with appropriately sized organic molecules by forming non-covalent inclusion complexes (Duchêne 1987; Loftsson & Brewster 1996). This complexation can result in several physicochemical advantages for the guest molecule, such as increased aqueous solubility and dissolution rate (Rajewski & Stella 1996), usually with improvement of the stability of the included molecule to air and light (Uekama et al 1983; Duchêne 1987; Loftsson & Brewster 1996). In a previous paper (Scalia et al 1998) we reported a reduction of the photodegradation of the UV-A filter butylmethoxydibenzoylmethane by inclusion in hydroxypropyl-β-cyclodextrin. This study describes the preparation of the complex between EH-DMAB and hydroxypropyl-β-cyclodextrin. The complex was characterized by phase-solubility studies, nuclear magnetic resonance (NMR) spectroscopy and by thermal analysis. The effect of the cyclodextrin on the photochemical behaviour of EH-DMAB was also studied both in solution and in a model emulsion.

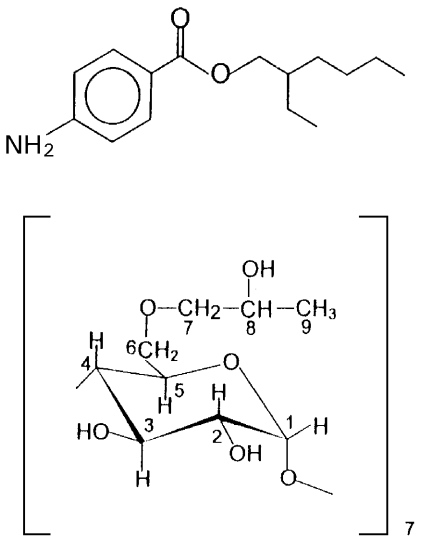

Figure 1. The chemical structures of EH-DMAB (upper) and hydroxypropyl-β-cyclodextrin.

Materials and Methods

Materials

EH-DMAB (Figure 1) was supplied by VanDyk (Belleville, USA). The cyclodextrins used in this study included α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin (average molar substitution 0·6), hydroxypropyl-α-cyclodextrin and hydroxypropyl-γ-cyclodextrin. These were purchased from Aldrich Chimica (Milan, Italy). Methanol and acetonitrile were high-performance liquid chromatography (HPLC)-grade from Baker (Phillipsburg, NJ). Water was purified by use of a Modupure Plus system (Continental Water Systems, San Antonio, TX). Other chemicals were of analytical-reagent grade (Sigma, Milan, Italy).

Solubility studies

Solubility measurements were conducted according to Higuchi & Connors (1965). Excess EH-DMAB was added to different concentrations of the cyclodextrins (0–60 mM for hydroxypropyl-β-cyclodextrin and 0–15 mM for the other cyclodextrins) in purified water (5 mL). The suspensions were stirred in 10-mL screw-capped vials at 25 ± 2°C and shielded from light. After equilibration (ca 3 days), the contents of each vial were filtered through 0·45-μm membrane filters (Millipore, Bedford, MA) and analysed by HPLC to determine the EH-DMAB concentration. All data are averages from at least five determinations (relative standard deviations were within 6·5%).

Physical mixture preparation

A finely-powdered physical mixture of EH-DMAB and hydroxypropyl-β-cyclodextrin with a guest/host molar ratio of 1 : 1 was prepared by simple dry mixing of exactly weighed amounts of the two components, adopting the geometric dilution method.

Preparation of the inclusion complex

The inclusion complex was prepared at an equimolar ratio of EH-DMAB to hydroxypropyl-β-

cyclodextrin, as reported below. EH-DMAB (69·3 mg, 0·25 mmol) was dissolved at room temperature in 95% ethanol (8·0 mL), to which purified water (3·0 mL) containing hydroxypropyl-β-cyclodextrin (344·6 mg, 0·25 mmol) was added. The solution obtained was stirred for 24 h at room temperature and shielded from light. The solvent was then evaporated under vacuum at 40°C by rotary evaporation. The solid complex was kept under vacuum in a desiccator for 3 days before analysis. The EH-DMAB content of the complex was determined by HPLC.

Thermal analysis

Differential thermal analysis (DTA) and thermal gravimetric analysis (TGA) were conducted on a Netzsch STA 409 simultaneous thermal analyser (Netzsch Italiana, Verona, Italy). The samples (2–10 mg) were heated in platinum pans (Netzsch) at a scanning rate of 10° min^{-1}.

NMR spectroscopy

^{1}H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, by means of a Bruker AC-200 spectrometer. Samples were dissolved in deuteromethanol at a concentration of ca 10^{-2} M. Chemical shifts (δ) for hydrogen and carbon resonances are reported in ppm relative to TMS. Typical parameters for ^{1}H spectra were 0·4 Hz/pt resolution, 16 scans, 18 s relaxation delay, 90° pulse, and for ^{13}C NMR ^{1}H-decoupled spectra were 0·7 Hz/pt resolution, 8192 scans, 5 s relaxation delay, 45° pulse.

High-performance liquid chromatography

HPLC was performed with a LabService Analytica (Bologna, Italy) LabFlow 3000 pump, a Rheodyne (Cotati, CA) 7125 injection valve with 5-μL sample loop, and a Jasco (Tokyo, Japan) 975-UV variable-wavelength UV-Vis detector operated at 310 nm. Data acquisition and processing were accomplished with a personal computer using Borwin software (JBMS Developements, Le Fontanil, France). Sample injection was effected with a Hamilton (Bonaduz, Switzerland) 80365 syringe. Compounds were separated on a 150 mm × 3·0 mm i.d., 5-μm particle, Hypersil (Runcorn, UK) BDS Phenyl column eluted with methanol–acetonitrile–water, 55 : 15 : 30 (v/v) containing 0·5% (v/v) acetic acid. The column temperature was maintained at 40°C by use of a Jones Chromatography (Hengoed, UK) 7990 space column heater. Chromatography was performed under isocratic conditions, at a flow-rate of 0·4 mL min^{-1}. The identity of EH-DMAB peak was assigned by co-chromatography with the authentic standard. Quantification was performed by integration of peak areas using external standardization.

Gas chromatography–mass spectrometry

Gas chromatography–mass spectrometry (GC–MS) was performed with a CE Instruments (Milan, Italy) GC 8060 chromatograph coupled with a TermoQuest Italia (Milan, Italy) MD 800 mass spectrometer operating in electron-impact mode (electron energy 70 eV) with transfer-line and ion-source temperatures maintained at 250°C. Compounds were separated on a 25 m × 0·25 mm i.d. fused silica SE-54 capillary column (CE Instruments) with helium as carrier gas (inlet pressure 70 kPa). The injector temperature was 250°C; the column temperature was maintained at 150°C for 1 min after injection then programmed at 5° min^{-1} to 250°C. Samples (1 μL) were introduced by use of split injection (split ratio 20 : 1). The GC–MS was controlled by Mass Lab 1.12 software (TermoQuest Italia).

Photodegradation

Photodegradation studies were conducted in solution (95% ethanol) and in a lotion (oil-in-water emulsion); both contained free or complexed EH-DMAB (0·15%, w/w). The lotion excipients were sorbitan monostearate, polyoxyethylene sorbitan monostearate, butylated hydroxyanisole, *p*-hydroxybenzoic acid ethyl ester, isopropyl isostearate (Henkel Fino Mornasco, Italy), cetearyl isononanoate (Henkel), cetearyl alcohol (Henkel), D-sorbitol, dehydroacetic acid, imidazolidinylurea, EDTA and water. To prepare the lotion the emulsifiers and the free EH-DMAB were first incorporated into the oil phase. The oil and aqueous phases were heated to approximately 60°C and the aqueous phase was slowly added to the oil phase while stirring with a Silverson mixer (Chesham, UK). Mild agitation was continued until the emulsion had cooled to room temperature. Butylated hydroxyanisole, imidazolidinylurea, hydroxypropyl-β-cyclodextrin and complexed EH-DMAB were added during the cooling phase of the production process at ca 40°C.

A portion of the test preparation (0·65 mL for the solution, 700–750 mg for the lotion) containing free or complexed EH-DMAB, was transferred into a quartz cuvette (path-length 2 mm) and exposed to the solar simulator—a 200 W xenon–mercury lamp (Hanovia 901-B1) fitted with focusing lens, to

centre the light on the sample, and with a WG 300 filter ($\lambda > 290$ nm). The samples were placed in front of the filter and air-cooled during irradiation. After the appropriate exposure time (4 h), the cuvette was removed and its contents transferred quantitatively into a 10-mL calibrated flask, diluted to volume with methanol, and filtered (0·45-μm membrane filter). A portion (5 μL) of the resulting solution was analysed by HPLC. The extent of degradation was measured by comparing the peak areas of EH-DMAB from the irradiated samples with those obtained by analysis of an equivalent amount of the non-exposed preparation. Statistical analysis of the results was performed by use of Student's *t*-test. A value of $P < 0{\cdot}05$ was taken as indicative of significance.

Measurement of in-vitro sun protection factor

In-vitro determination of the sun protection factor (SPF) of the lotion was performed according to Diffey & Robson (1989), with minor modifications. The method is based on the measurement of the transmission spectrum of UV radiation (290–400 nm) through Transpore 3M tape before and after application of the sunscreen preparation, by means of a Jasco V-530PC UV-Vis spectrophotometer. The product was applied to the tape surface at 2 mg cm^{-2} and spread uniformly. The Transpore tape was then placed into the spectrophotometer 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 & Robson (1989).

Results and Discussion

Characterization of the complex

The solubility curves of EH-DMAB in aqueous solutions of the different cyclodextrins examined in this study are shown in Figure 2A. The diagrams obtained were indicative of major variations in the interaction between EH-DMAB and unsubstituted and modified α-, γ- or β-cyclodextrins. This can be ascribed to the different cavity dimensions and to the aqueous solubility of the macrocycles. In particular, only hydroxypropyl-β-cyclodextrin caused a substantial increase in the aqueous solubility of the UV-B filter and consequently this cyclodextrin was selected for further experiments.

Over the entire concentration range used in this study (Figure 2B) the solubility of EH-DMAB increased linearly with increasing hydroxypropyl-β-cyclodextrin concentration (A_L-type curve). The solubility enhancement can be attributed to the formation of an inclusion complex with greater solubility than EH-DMAB alone. Moreover, the linear A_L-type relationship (Figure 2B) suggests the existence in solution of a complex with 1 : 1 stoichometry (Higuchi & Connors 1965).

The complex was characterized in the solid state by thermal analysis. Because EH-DMAB is a liquid, the influence of complexation with hydroxypropyl-β-cyclodextrin on the thermal behaviour of the sunscreen was studied by simultaneous DTA

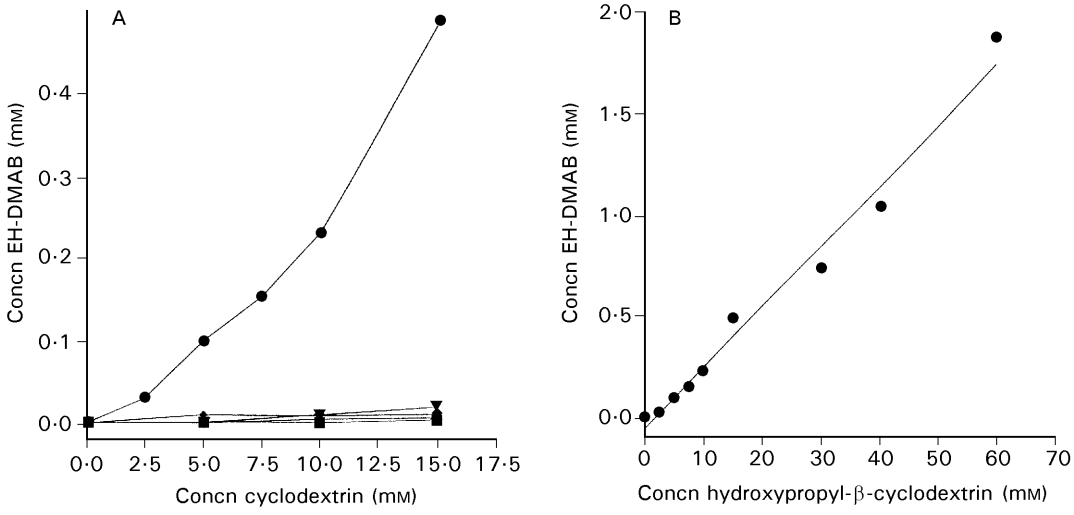

Figure 2. A. Phase-solubility diagrams in purified water at 25°C for EH-DMAB with different cyclodextrins (0–15 mM) (■ α-cyclodextrin, ▲ hydroxypropyl-α-cyclodextrin, ▼ hydroxypropyl-γ-cyclodextrin, ◆ β-cyclodextrin, ● hydroxypropyl-β-cyclodextrin) B. Phase-solubility diagram in purified water at 25°C for EH-DMAB in the presence of hydroxypropyl-β-cyclodextrin (0–60 mM).

and TGA. The DTA curves of hydroxypropyl-β-cyclodextrin, EH-DMAB and the EH-DMAB–hydroxypropyl-β-cyclodextrin complex are shown in Figure 3A. The corresponding TGA thermograms are illustrated in Figure 3B. The trace for hydroxypropyl-β-cyclodextrin shows only water loss characterized by a broad endothermic peak between ca 40° and 100°C (Figure 3A). The DTA profile for EH-DMAB contains an endothermic peak at ca 250°C corresponding to its boiling temperature, as confirmed by the weight loss as a result of evaporation (TGA curve, Figure 3B). Evidence of this transition was absent from the DTA thermogram of the complex (Figure 3A) but was present in that of the physical mixture (thermogram not shown). In addition, the TGA curve of the EH-DMAB–hydroxypropyl-β-cyclodextrin complex (Figure 3B) shows that interaction with hydroxypropyl-β-cyclodextrin leads to a dramatic reduction of the volatility of EH-DMAB; this can be ascribed to conversion of the liquid sunscreen into a solid form. Hence, the results of thermal analyses indicate the inclusion of EH-DMAB into the hydroxypropyl-β-cyclodextrin cavity.

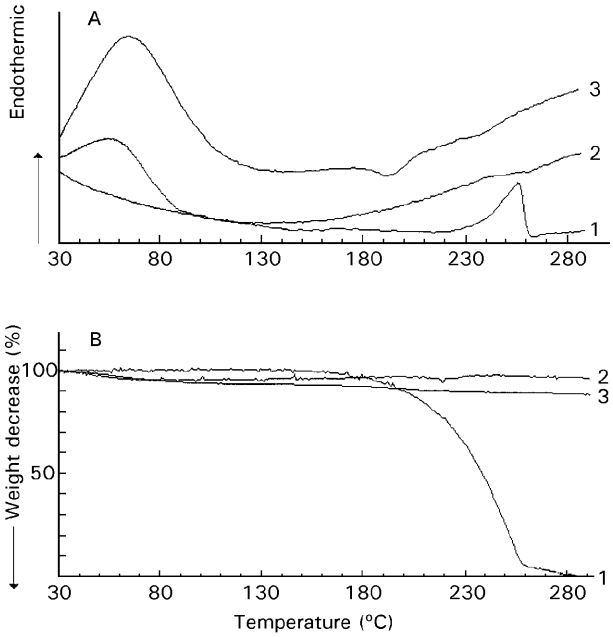

Figure 3. A. DTA and B. TGA thermograms for 1. EH-DMAB, 2. hydroxypropyl-β-cyclodextrin, 3. EH-DMAB-hydroxypropyl-β-cyclodextrin complex.

To obtain further evidence about the complexation of EH-DMAB with hydroxypropyl-β-cyclodextrin, interaction between the sunscreen and the cyclodextrin was studied in deuteromethanol solution by NMR. The ^{1}H NMR chemical shifts (Table 1) of selected protons of hydroxypropyl-β-cyclodextrin (see Figure 1) alone or as a complex with EH-DMAB demonstrate that the presence of the sunscreen molecule induces changes in the ^{1}H NMR chemical shift values for both the protons (H-3 and H-5) located inside the cyclodextrin cavity and the external protons. This implies interaction of the guest compound with the external surface of the macrocycle also. Among the signals detected, those corresponding to the inner H-3 (negative shift) and to the external H-4 (positive shift) protons were the most affected (Table 1). The major changes in hydroxypropyl-β-cyclodextrin ^{13}C NMR signals upon complexation are also listed in Table 1. The data obtained indicate that the ^{13}C chemical shifts are more sensitive to complexation than the ^{1}H shifts and that C-1 and C-4 have the highest $\Delta\delta$ (^{13}C) values. The large shifts for C-1 and C-4 can be attributed to conformational changes affecting the cyclodextrin glucosyl residues upon complexation (Mucci et al 1996). Table 2 reports

Table 1. ^{1}H NMR and ^{13}C NMR chemical shifts (δ, ppm) for hydroxypropyl-β-cyclodextrin in the absence and presence of EH-DMAB.

	^{1}H NMR chemical shift, δ, for proton no.:					
	1	2	3	4	5	
Hydroxypropyl-β-cyclodextrin	4·959	3·691	3·942	3·520	3·820	
Cyclodextrin–EH-DMAB complex	4·964	3·697	3·931	3·537	3·814	
$\Delta\delta$	+0·005	+0·006	−0·011	+0·017	−0·006	
	^{13}C NMR chemical shift, δ, for carbon atom no.:					
	1	2	3	4	5	9
Hydroxypropyl-β-cyclodextrin	102·284	74·335	83·456	73·955	62·137	19·767
Cyclodextrin–EH-DMAB complex	102·175	74·288	83·257	73·895	62·076	19·709
$\Delta\delta$	−0·109	−0·047	−0·199	−0·060	−0·061	−0·058

$\Delta\delta = \delta_{complexed} - \delta_{free}$

some of the ^{1}H and ^{13}C chemical shifts of EH-DMAB (see Figure 1) in the free form and in the presence of hydroxypropyl-β-cyclodextrin. As observed for the cyclodextrin, the ^{13}C signals are more affected than those from ^{1}H. Interaction with hydroxypropyl-β-cyclodextrin produces shifts of the EH-DMAB proton signals, the largest variations being observed for the methyl protons on the nitrogen atom and the aromatic protons *ortho* to the dimethylamino group (Table 2). These data are indicative of a strong interaction of this part of the sunscreen molecule with the cyclodextrin, and are confirmed by the high $\Delta\delta$ (^{13}C) on C-4 (Table 2). Moreover, the high-field (negative) shifts of the ^{13}C NMR signals of the carbons located on the alkyl chain (Table 2) suggest the insertion of this portion of the sunscreen molecule into the cyclodextrin cavity (Vandelli et al 1995). Conversely, the low-field (positive) shifts of C-3, C-4 and the dimethylamino group carbons are consistent with their interaction with the external part of the wider rim of the cyclodextrin hollow cone (Vandelli et al 1995), in accordance with the hydroxypropyl-β-cyclodextrin ^{1}H NMR data (Table 1). Thus the NMR results are indicative of complexation of EH-DMAB with hydroxypropyl-β-cyclodextrin and imply that the sunscreen molecule penetrates into the cyclodextrin cavity from its aliphatic chain with the aromatic ring not completely enclosed.

Photostability studies

To study the effect of hydroxypropyl-β-cyclodextrin on the photochemical behaviour of the sunscreen agent, initial photolysis experiments were performed on solutions (95% ethanol) containing free or complexed EH-DMAB (0·15%, w/w) and exposed for 4 h to the xenon solar simulator (Deflandre & Lang 1988; Dunlap et al 1996). The extent of photodegradation of the UV filter was measured by HPLC (Figure 4). The major products originating from the photodecomposition of EH-DMAB were identified by GC–MS as 2-ethylhexyl-*p*-monomethylaminobenzoate and 2-ethylhexyl-*p*-aminobenzoate. In addition to these compounds, 2-ethylhexyl-*p*-dimethylamino-(*o*/*m*)-methylbenzoate was detected by Roscher et al (1994) after photolysis of EH-DMAB in cyclohexane, although these authors employed rather drastic irradiation conditions ($\lambda > 185$ nm and irradiation for 100 h) which do not simulate natural exposure to sunlight. In the solution containing EH-DMAB alone, the percentage loss of the sunscreen agent reached 54·6% (Table 3). A significant reduction of the extent of degradation to 25·5% (Table 3) was recorded for the solution containing EH-DMAB complexed with hydroxypropyl-β-cyclodextrin; this indicates that the photostability of the UV-B filter is markedly improved by complex formation. In addition, the drastic reduction in the amount of 2-ethylhexyl-*p*-aminobenzoate produced by the photolysis reaction (Figure 4) is an important advantage of complexation, because the unsubstituted amino group has been shown to be very important in the development of sensitization reactions to the *p*-aminobenzoic acid derivatives (Dromgoole & Maibach 1990). The physical mixture of EH-DMAB and hydroxypropyl-β-cyclodextrin did not, on the other hand, significantly affect the photochemical behaviour of the sunscreen in the tested solution. The data reported in Table 3 indicate that complexation does not com-

Table 2. ^{1}H NMR and ^{13}C NMR chemical shifts (δ, ppm) for EH-DMAB in the absence and presence of hydroxypropyl-β-cyclodextrin.

	^{1}H NMR chemical shift, δ, for proton no.:				
	2	3	5	1′	3′–5′
EH-DMAB	7·828	6·649	2·974	4·139	1·336
Cyclodextrin–EH-DMAB complex	7·808	6·697	3·026	4·152	1·356
$\Delta\delta$	−0·020	+0·048	+0·052	+0·013	+0·02

	^{13}C NMR chemical shift, δ, for carbon atom no.:										
	1	2	3	4	5	2′	4′	5′	6′	7′	8′
EH-DMAB	118·09	132·429	112·106	155·255	40·449	40·647	25·423	24·343	11·863	32·090	14·784
Cyclodextrin–EH-DMAB complex	117·999	132·410	112·174	155·399	40·513	40·588	25·302	24·309	11·720	31·967	14·725
$\Delta\delta$	−0·091	−0·019	+0·068	+0·144	+0·064	−0·059	−0·121	−0·034	−0·143	−0·123	−0·059

$\Delta\delta = \delta_{complexed} - \delta_{free}$.

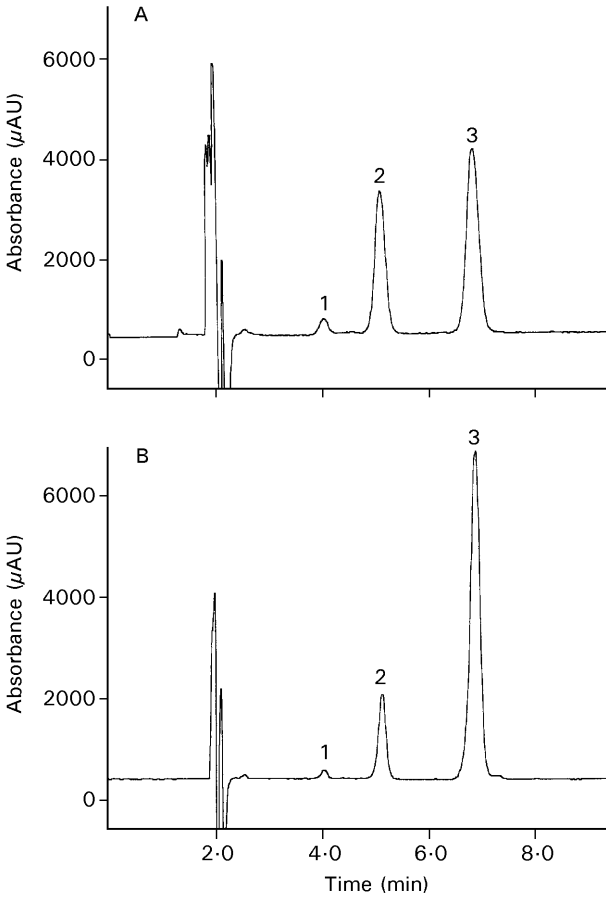

Figure 4. HPLC chromatograms of ethanolic solutions of A. free EH-DMAB and B. EH-DMAB–hydroxypropyl-β-cyclodextrin complex, after 4 h irradiation with the solar simulator. 1. 2-ethylhexyl-*p*-aminobenzoate; 2. 2-ethylhexyl-*p*-monomethylaminobenzoate; 3. EH-DMAB.

pletely prevent EH-DMAB photodecomposition reactions leading to the elimination of the methyl groups linked to the nitrogen atom. This can be traced to the geometry of the complex. In fact, the NMR studies reported above suggest that the aromatic ring bearing the dimethylamino substituent is protruding from the cyclodextrin cavity and thus is not efficiently shielded from the reactive environment.

Table 3. Comparative photodegradation data for free and complexed EH-DMAB, in solution or in a lotion, after 4 h irradiation with the solar simulator.

Sample	Sunscreen loss (%)	
	EH-DMAB	Complex
Solution	54·6 ± 5·5	25·5 ± 8·8*
Lotion	32·8 ± 6·8	28·5 ± 3·2
Lotion + 5% hydroxypropyl-β-cyclodextrin	33·4 ± 5·3	25·1 ± 1·8*

Each value is the mean ± s.d. of results from six determinations. * $P < 0.05$ compared with EH-DMAB alone.

Although investigation of photochemical stability in solution (Roscher et al 1994; Dunlap et al 1996) has the advantage of producing clear-cut results, to simulate more realistic conditions further studies were performed using a lotion (oil-in-water emulsion) as irradiation medium. This system was selected as a model formulation because it represents the most widely used type of sunscreen preparation (Siemer 1991). Free or complexed EH-DMAB was incorporated (0·15%, w/w) into the lotion and irradiated with simulated sunlight. At variance with the results obtained in solution, the difference in the extent of sunscreen photodegradation observed between the two formulations (Table 3) was not statistically significant, which is indicative of a reduction in the effect of complexation in the lotion vehicle. At this point it seemed reasonable to assume that the discrepancy between the data obtained from the solution and from the emulsion could be ascribed to the competitive displacement of the UV filter from the cyclodextrin cavity by the lotion excipients. To verify this hypothesis, 5% (w/w) hydroxypropyl-β-cyclodextrin was included in the formulation. Under these conditions a 25·1% decrease in the level of the UV filter was measured in the lotion containing the complexed EH-DMAB (Table 3); 33·4% of the sunscreen content was lost after irradiation of the preparation containing free EH-DMAB (Table 3). Although the observed improvement in sunscreen photostability was not as marked as that achieved in solution (Table 3), statistical analysis demonstrated that the difference between the lotions containing free EH-DMAB or the inclusion complex with a cyclodextrin excess is significant ($P < 0.05$). Moreover, the in-vitro determination of the sun protection factor (SPF) of the two formulations revealed that the cyclodextrin had no significant influence on the SPF (SPF values ranged from 3·1 to 3·2).

Conclusions

The complexation of EH-DMAB with hydroxypropyl-β-cyclodextrin was proved in the solid state by thermal analysis (DTA and TGA) and in solution by NMR spectroscopy. Although the results obtained demonstrate that photodegradation of the sunscreen agent is significantly reduced by formation of the inclusion complex, the effectiveness of complexation on UV filter photostability can be hampered by interference from the numerous components of the cosmetic preparations. Consequently, to elicit the desired effect of the cyclo-

dextrin it is very important to design a suitable vehicle. Moreover, the inclusion of EH-DMAB into the hydroxypropyl-β-cyclodextrin cavity limits the interaction of the UV filter with the skin and the formation of potentially toxic photoproducts, thus reducing irritation and allergic side-effects of the formulation.

Acknowledgements

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