Journal of Inclusion Phenomena and Macrocyclic Chemistry **48:** 117–123, 2004.

Cyclodextrin Complexes of UV Filters

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(Received: 14 March 2003; in final form: 14 October 2003)

Key words: cyclodextrin, inclusion complexation, photostabilisation, UV filters

Abstract

A UVA and a UVB filter (4-*tert*-butyl-4′-methoxydibenzoyl methane and 3-(4-methylbenzylidene) camphor) insoluble in water have been complexed with various cyclodextrins and β-cyclodextrin derivatives. The molar ratio of the included UV filter to cyclodextrin in the solid complexes have been calculated from thermal analysis data. Among the cyclodextrins studied randomly methylated β-cyclodextrin was found to be the best solubilizer of both UV filters. The photostability of a model sulfonamide drug in aqueous solution has been improved in the presence of a UVA filter solubilised by RAMEB.

Introduction

Cyclodextrins (CDs) are known to improve the solubility of poorly soluble compounds capable of entering their cavity [1]. The UV absorbers used in sunscreen cosmetics are usually poorly soluble in water, their aqueous solubility can be improved by inclusion complexation. The phase solubility method has been generally applied for the study of the interaction between the UV absorbers and various CDs [2–4]. The native CDs proved to improve the solubility less efficiently if at all than their derivatives. With βCD and eventually with γCD often B_s type isotherms having a plateau are obtained showing that the complexes precipitate from the solution [2, 5]. The solubility isotherms with the CD derivatives are usually of A type (continuous increase with increasing CD concentration). Linear (A_L type) isotherm was reported for 2-ethyl-hexyl methoxycinnamate (EMC) [2] and 2-ethyl-hexyl-p-dimethylaminobenzoate (EDB) [3] in hydroxypropyl βCD (HPBCD) solutions, while AP type isotherm (positively deviating from linear) for EMC in RAMEB [2] and 4-*tert*-butyl-4′-methoxydibenzoyl methane (BMD) [4] in HPBCD solutions. When solubilising two water-insoluble UV absorbers, 3-(4-methyl-benzylidene)-camphor (MBC) and 2-hydroxy-4-methoxybenzophenone (HMB) by βCD, random methylated βCD (RAMEB), γCD, and acetyl γCD (AcGCD) the substituted cyclodextrins were markedly more effective solubilisers than the unsubstituted ones as usual [6]. 2-hydroxy-4-methoxybenzophenone was successfully solubilised with a mixture of the water-soluble βCD polymer and HPBCD [7].

The data from the solubility study indicated the formation of a 1:1 stoichiometry for the EDB/HPBCD and EMC/HPBCD complexes in solution. A lower guest/host molar ratio was suggested by the AP isotherms (EMC/RAMEB and BMD/HPBCD).

The molar ratio in the solid complexes calculated by evolved gas analysis (thermal analysis coupled to flame ionisation detector of a gas chromatograph) showed that not all the guest molecules are included in the cavity, some of them are loosely coupled to the CD, only adsorbed on the surface of the CD or of the complex particles [2]. According to these calculations in the case of EMC the 1:1 molar ratio was achieved only for γCD, but not for α- and βCDs.

Molecular modelling studies of EMC/native CD complexes indicated that in solution no real inclusion takes place, second sphere complexes represent the lowest energy state [2]. Optimising the structure of the solid complexes only γCD was found to form real inclusion complexes.

Complexation with cyclodextrins can stabilize the UV-filter compounds against photolysis. BMD was found to be stabilised by βCD [5] and HPBCD [4], while the non-stabilising effect of βCD was found in another study [8]. The photodegradation of EDB was significantly reduced by formation of the inclusion complex with HPBCD [3]. Complexed with HPBCD the photochemical decomposition of both sunscreen agents was decreased even in lotions, in cosmetic emulsions also containing other ingredients, which are potential competitors in complex formation [3, 4].

The latest results of Scalia *et al.* showed that the free radicals generated by BMD when exposed to simulated sunlight are effectively scavenged by inclusion complexation of the sunscreen agent with HPBCD [9]. The effects related to photoallergy/phototoxicity may be reduced through inclusion of the photoproducts, too [8].

Cosmetic preparations containing UV filter/CD complexes, not irritating for the human skin have been patented

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[7, 10]. For instance, cosmetic and pharmaceutical formulations containing Vitamin A or its fatty acid esters were stabilized by a composition containing also a UV absorber (benzophenone)/CD inclusion compound [11, 12].

Photodegradation and the rate of decomposition of pharmaceuticals can often be reduced by complex formation, as is published in review articles, discussing the various stabilizing effects of cyclodextrins [13–15]. Light exposure may accelerate oxidative decomposition of D_3 vitamin, which can be considerable inhibited by inclusion of the vitamin with β-cyclodextrin [16, 17]. The light sensitivity of clofibrate [5] and guaiazulene [18] were reduced by inclusion in β- or γ-cyclodextrin. The decomposition half life of Vitamin B_1 and Furosemid were increased successfully by application of different derivatives of β-cyclodextrin [19].

UV absorbers and dyes often act as photostabilizing agents in pharmaceutical formulations [20, 21]. They can effectively protect the drug, however, only if they absorb the specific rays of wavelengths causing the degradation or isomerization of the drug. For instance, in case of tretinoin, which is very susceptible to degradation under daylight a UVB sunscreen could not retard the photodegradation, while a UVA sunscreen had very little effect. Incorporation of tretinoin in β-cyclodextrin or in some surfactants (Brij) did not have any effect either. Irradiation at selected wavelengths revealed that 420 nm was the most harmful wavelength for the degradation of tretinoin, so the addition of the yellow dyes, absorbing in the region of 420 nm, successfully protected the drug [22].

In the present work we have studied the solubilisation of two compounds: 4-*tert*-butyl-4′-methoxydibenzoyl methane, (BMD, a UVA filter) and 3-(4-methylbenzylidene) camphor, (MBC, a UVB filter) by parent CDs and CD derivatives. Solid complexes have been prepared by using various methods and investigated by thermal analysis. The stabilising effect of the RAMEB-solubilised UV filters on photosensitive sulfonamide type model drug was also studied.

Experimental

Materials

The UV filters: 4-tert-butyl-4'-methoxydibenzoyl methane, [BMD, Parsol 1789] and 3-(4-methylbenzylidene) camphor, [MBC, Parsol 5000] (Givaudan-Roure, Switzerland) were used (Figure 1).

The following cyclodextrins were involved in the study: α-cyclodextrin (ACD), Lot No. 850902 (Chinoin, Hungary), β-cyclodextrin (BCD), Lot No. 8709187/14 (Chinoin, Budapest), γ-cyclodextrin (GCD), Lot No. 1006 (Wacker Chemie, Munich), hydroxypropyl β-cyclodextrin (HPBCD), DS = 2.7 (Cyclolab, Budapest), maltosyl β-cyclodextrin (G2BCD), DS $\approx$ 1 Lot No. 93281 (Ensuiko Sugar Refining Co., Yokohama), random methyl β-cyclodextrin (RAMEB), DS = 1.8 Lot No. 12/2/92 (Wacker Chemie, Munich).

As a light-sensitive model drug a sulfonamide type compound (Chinoin, Hungary) was used (Figure 1).

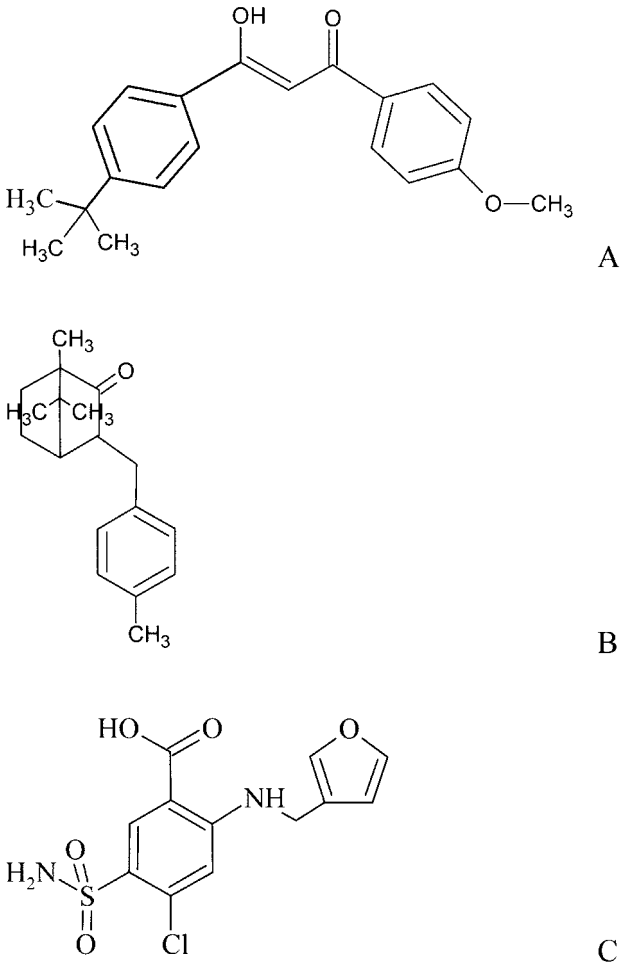

Figure 1. Chemical structure of UV filters BMD (A) MBC (B), and the light-sensitive sulfonamide (C).

Solubility studies

The phase-solubility studies were performed according to Higuchi and Connors 23]. Stock solutions of 20% (w/v) CD content (15% in case of α-cyclodextrin and 1.5% in case of β-cyclodextrin) were prepared. Excess amounts of UV filter were added to 5 mL of the properly diluted cyclodextrin solutions and stirred for 1 hour. The suspensions were filtered through a glass prefilter and the concentration of the dissolved UV filters was measured spectrophotometrically.

Preparation of solid complexes

Suspension method

In case of the parent CDs the proper amount of CD was suspended in water at room temperature and the UV filter was added under rigorous stirring. The stirring was continued for 5–24 h, then the suspension was freeze-dried and the product was washed with diethyl ether and dried on air, then analysed for the total and free active ingredient content.

In case of βCD derivatives the stirring was continued for 3 h, then the suspension was filtered and the clear solution freeze-dried.

Coprecipitation method

The proper amount of CD was dissolved in water and the UV filter was added under vigorous stirring at room temperature. The stirring was continued for 2 h and the suspension was centrifuged at 5000 *g* for 15 min. The supernatant was decanted, the precipitate was suspended in acetone and filtered through a G-3 glass filter. The product was obtained after drying at 60 °C.

Measurement of total active ingredient content

The material was dissolved in 1:1 ethanol-water and from the UV absorption curve the total active ingredient content was calculated based on a calibration curve.

Evolved Gas Analysis

Evolved Gas Analysis (EGA) was measured with a Du Pont 916 Thermal Evolution Analyser (TEA) apparatus, with a heating rate of 8 °C/min and nitrogen atmosphere (1.8 L/H). The quantitative evaluation was based on the comparison of the area under the peak of unbound guest to that of the pure ingredient.

Photostability test

The solution of the model drug (CYL-2020) was prepared by dissolving 0.3 mM CYL-2010 in 10 cm^3 methanol. To aliquots of this solution 75 mM RAMEB, 0.003 mM BMD and/or 0.004 mM MBC were added in 0.02 mM pH 3.17 phosphate buffer and the solutions were exposed to sunlight. Samples were withdrawn after 0, 1.5, 3, 4.5, 6, 24 and 48 h solar irradiation and analysed by HPLC.

HPLC method

Equipment: Waters ALC/GPC 201 (U6K injector, UV detector Waters Model 440) Column: NUCLEOSIL C_{18}-10 (4 mm × 250 mm) Eluent: methanol/pH 3.17 phosphate buffer 35/65, flow rate; 1 cm^3/min UV detection at 280 nm wavelength

Results and discussion

Phase solubility studies

Both UV filters involved in this study have very low aqueous solubility (1.5 and 2.8 μg/ml for BMD and MBC, respectively), which can be improved by adding cyclodextrins. The solubilising effect of parent CDs and βCD derivatives have been compared (Figures 2 and 3). The solubility isotherms were of B_s type in case of BMD/βCD, MBC/βCD and MBC/γCD systems suggesting precipitation of solid complex. Linear isotherms (A_L type), corresponding to formation of soluble 1:1 mole/mole inclusion complex, were obtained for both UV filters with the βCD derivatives except for BMD with RAMEB, which together with αCD gave A_P type isotherm. The latter type of isotherms suggests the formation of soluble complexes of different stoichiometry.

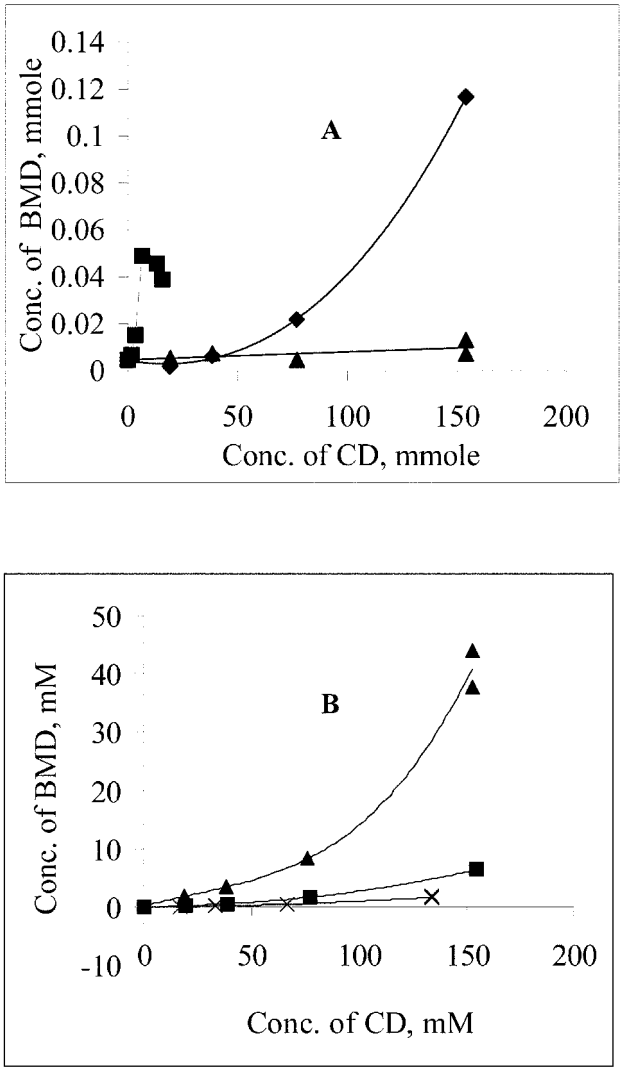

Figure 2. Phase solubility diagrams of BMD in aqueous solutions of various cyclodextrins A: αCD, ♦; βCD, ■; γCD, ▲; B: RAMEB, ♦; HPBCD, ■; G_2BCD, ×.

The slope of the isotherms depends on the stoichiometry and stability of the complex. Among the parent CDs β CD shows the steepest slope, it forms complexes of the highest stability. The inherent solubility remained practically unchanged in case of BMD/γCD system showing that the complex if it exists is not more soluble than BMD itself. RAMEB was found to be the best solubilising agent for both UV filters: at 150 mM RAMEB concentration 7800 and 6000 fold enhancement of solubility was obtained related to the aqueous solubility of the pure BMD and MBC, respectively.

The association constants have been calculated from the initial linear section of the isotherms according to Higuchi and Connors (Table 1) [16]. The value obtained for BMD/HPBCD (2.70×10^3) is in good agreement with that reported by Scalia *et al.* for the same system (2.23×10^3) [4]. About ten times higher value was obtained for BMD/RAMEB, while practically no complex formation was detected between BMD and γCD. RAMEB gave the

Table 1. Complex association constants (M^{-1})

	αCD	βCD	γCD	RAMEB	HPBCD	G_2BCD
BMD	1.65×10^2	1.44×10^3	6.20	2.48×10^4	2.70×10^3	2.72×10^3
MBC	1.09×10^2	1.80×10^3	1.07×10^3	6.64×10^4	1.24×10^4	5.48×10^4

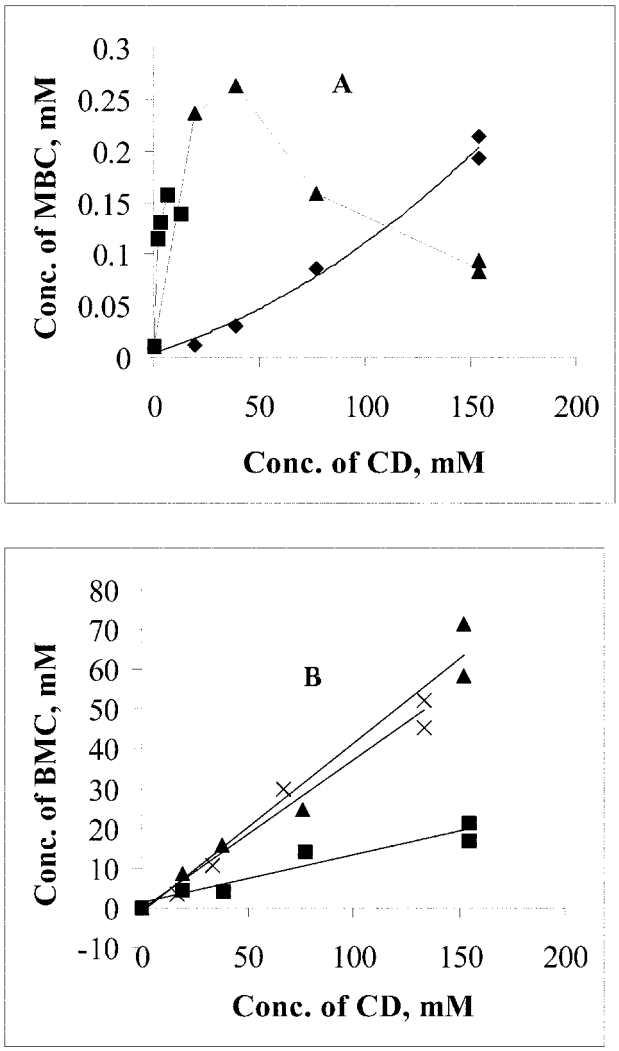

Figure 3. Phase solubility diagrams of MBC in aqueous solutions of various cyclodextrins A: αCD, ♦; βCD, ■; γCD, ▲; B: RAMEB, ♦; HPBCD, ■; G_2BCD, ×.

best result for MBC, too, lightly overcoming the effect of G_2BCD.

Solid products

The methods of preparation of the soluble and insoluble complexes in solid state were different. The parent CDs showing B_s type solubility curves form complexes of low solubility. These complexes can be prepared by coprecipitation. Applying the suspension method the suspension was freeze-dried without filtration and the excess of the guest compound was removed by washing.

The βCD derivatives of high-solubility and high-solubilising capacity required a modified technology: the suspensions were filtered before freeze-drying to separate the complex from the insoluble free guest.

The solid products were characterized by Evolved Gas Analysis (EGA) and compared with the pure ingredients. After the completion of EGA experiments of the pure cyclodextrins it was concluded, that no organic compound evolved from the cyclodextrins up to 250 °C (when their decomposition started) except in case of HPBCD, when small amount of other components (e.g., technological impurities) left upon heating as it has been summarized previously [24].

According to EGA profile of the pure BMD, the evaporation and thermal decomposition starts at about 140 °C and the process does not complete up to 250 °C (Figure 4, curve a). Comparing the EGA curve of the pure BMD to that of the BMD/γCD mechanical mixture, one can see that the evolution of organic compounds from its physical mixture starts at about 10 °C lower temperature. The peak maximum shifted toward the lower temperatures with 20 °C (T_{peak} = 223 °C). This finding can be explained by the fact that the evaporation/decomposition of BMD takes place from a larger surface in case of the physical mixture.

Comparing the EGA curves of the physical mixtures and the putative complexes, less amount of organic evolution was found in these three latter cases (Figure 4, curves c, d and e) and it started at higher temperatures. This can be attributed to the successful inclusion complex formation. On the other hand, the small peaks in the EGA profiles of BMD/γCD (Figure 4, curve c) and BMD/HPBCD (Figure 4, curve e) represent the evolution of a certain amount of uncomplexed guest from the samples. (According to our previous experiences, the EGA peak at 152 °C on the curve of the BMG/HPBCD complex corresponds to the evolution of a small amount of impurities in HPBCD, which may have technological origin.)

Figure 5 illustrates the EGA curves of MBC – cyclodextrin samples. The pure guest evaporates between 80 and 160 °C (Figure 5, curve a), while the evaporation of the adsorbed MBC from the surface of the γCD shifted with 20 °C towards the higher temperatures indicating the formation of some kind of weak interactions between the MBC and the cyclodextrin (Figure 5, curve b).

According to the EGA curve of MBC/βCD sample the evaporation of the guest takes place practically in the same temperature-interval (Figure 5, curve c), when the pure guest evaporated itself (Figure 5, curve a) showing that a large amount of adsorbed guest is present.

Table 2. Conditions of the preparation and characteristics of the UV filter/CD complexes

Code No.	Type of UV filter	Type of CD	Conditions of the preparations			Product			
			Method	Stirring time (h)	Initial molar ratio (mole/mole)	Active ingredient content (%)			Calculated molar ratio* (mole/mole)
						Total	Free	Bound	
1	BMD	βCD	Susp.	5	1:1	7.9	7.8	0.1	–
2		βCD	Susp.	16	1:1	9.9	0.8	9.1	0.4:1
3		βCD	Susp.	24	2:1	12.2	3.7	8.5	0.3:1
4		βCD	Coprec.	2	1:1	17.4	13.0	4.4	0.2:1
5		γCD	Susp.	24	2.5:1	13.8	6.8	7.0	0.3:1
6		γCD	Coprec.	2	1:1	17.4	4.2	13.2	0.8:1
7		RAMEB	Filtered susp.	3	0:4	5.8	0	5.8	0.3:1
8		HPBCD	Filtered susp.	3	0:4	0.8	0.8	<0.1	<0.1:1
9	MBC	βCD	Susp.	5	1:1	4.9	1.2	3.7	0.2:1
10		βCD	Susp.	16	1:1	12.4	0.5	11.9	0.6:1
11		βCD	Susp.	24	2:1	14.8	5.5	9.3	0.5:1
12		βCD	Coprec.	2	1:1	12.2	2.0	10.2	0.5:1
13		γCD	Susp.	24	2.5:1	17.8	4.6	13.2	0.8:1
14		γCD	Coprec.	2	1:1	12.8	0.7	12.1	0.7:1
15		RAMEB	Filtered susp.	3	0.5:1	7.4	0	7.4	0.4:1
16		G_2BCD	Filtered susp.	3	0.5:1	5.1	0	5.1	0.3:1

* Sound guest/CD.

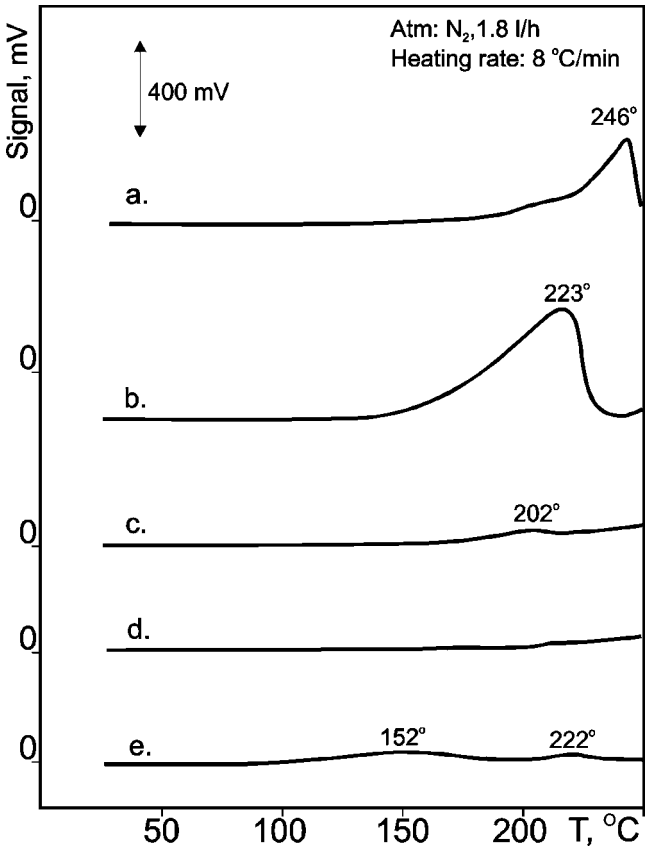

Figure 4. Evolved Gas Analysis of BMD (a), BMD/γCD physical mixture (b), inclusion complex of BMD/γCD (c) prepared by co-precipitation (Code No. 6), BMD/RAMEB (d), BMD/HPBCD (e) complexes prepared by lyophilisation (Code Nos. 7 and 8, respectively).

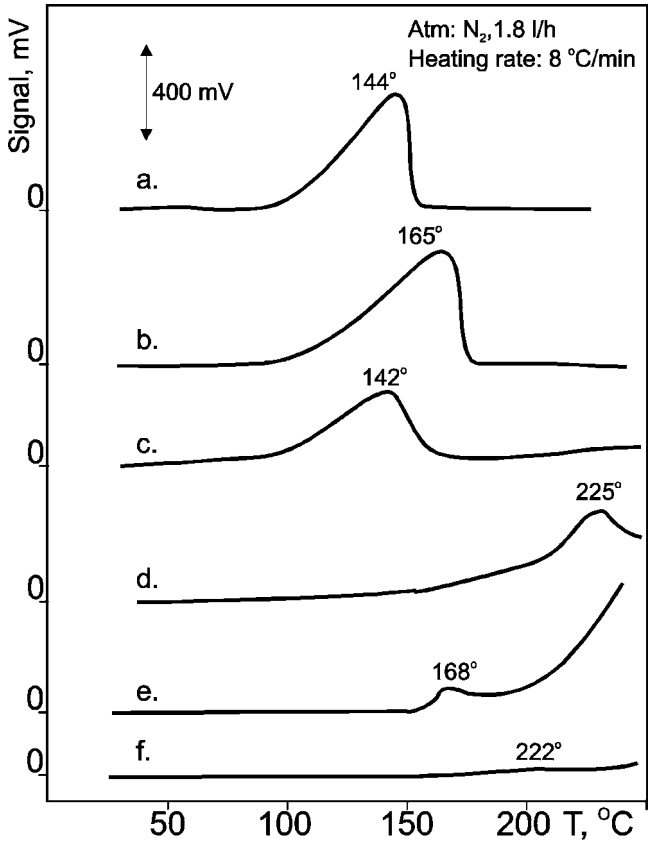

Figure 5. Evolves Gas Analysis of pure MBC (a) MBC/βCD physical mixture (b), MBC/βCD (c) and MBC/γCD (d) inclusion complex prepared by the suspension method (Code Nos. 10 and 13, respectively), MBC/RAMEB (e), MBC/HPBCD (f) complexes prepared by lyophilisation (Code Nos. 15 and 16, respectively).

In contrast, successful complexation has been established between MBC and γCD as is indicated by the shifted evaporation/decomposition in Figure 5, curve d.

When modified cyclodextrins (RAMEB and G2BCD) were used as hosts, the EGA profiles support the assumed complex formation (Figure 5, curves e and f). In both cases the evaporation/decomposition of the entrapped MBC started above 150 °C, practically at higher temperature compared to the one when the evaporation of pure UV filter finished (see Figure 5 curve a).

The EGA curves (Figures 4 and 5) show the non-included guest, which is probably only adsorbed on the CD or complex particles. The included guest appears only at above 300 °C, at a temperature where the host is decomposed. By integrating the peaks and related to that of the peak area of the pure guest, the amount of the non-included guest can be calculated. The stoichiometry of the complexes was obtained by subtracting the amount of adsorbed guest determined from the EGA measurement from that of the total guest content measured by UV photometry. The results summarized in Table 2 show that the products prepared with β- and γCD always contain adsorbed guest. The bound guest/CD ratio could not be improved by increasing the strirring time and the excess of the UV filters.

By γCD the 1:1 molar ratio of guest/CD was approached even with BMD which was not solubilised by γCD. With βCD, however, the 0.5:1 molar ratio could not practically be surpassed suggesting that 1:2 complexes are mostly formed.

The thermal analysis of the RAMEB and G_2BCD complexes points to real inclusion of the guests. No signs of adsorbed guest have been observed. The molar ratio of the bound guest/CD (Table 2) suggests that beside the 1:2 complexes those of higher stoichiometry may also be formed with RAMEB and G_2BCD. The total guest content was the lowest in case of BMD/HPBCD. The EGA curves show that practically all the guests are located outside of the cavity, the inclusion of BMD by HPBCD was unsuccessful. In this case the solubilisation may have been based upon other effects, e.g., on outer sphere complex formation.

The above results clearly indicate that the phase solubility studies might give misleading results: BMD seems not to interact with γCD in solution giving a very low apparent stability constant, but the EGA curves (in solid state) show a nearly 1:1 inclusion complex formation. On the other hand, HPBCD enhanced the solubility of this UV filter giving a rather high apparent stability constant in spite of the fact that according to the EGA curves inclusion complex in solid state does not exist.

Protection against UV light in solution

The drug used in the study is sensitive to the light. The photolysis experiments were carried out by irradiation of the sample solutions containing the model drug without and with additives. The degradation was followed by measuring the drug concentration with HPLC. Four decomposition products have been separated (Figure 6). The loss of the model compound was 73% within 6 h in the absence of additives. The presence of RAMEB had no significant effect

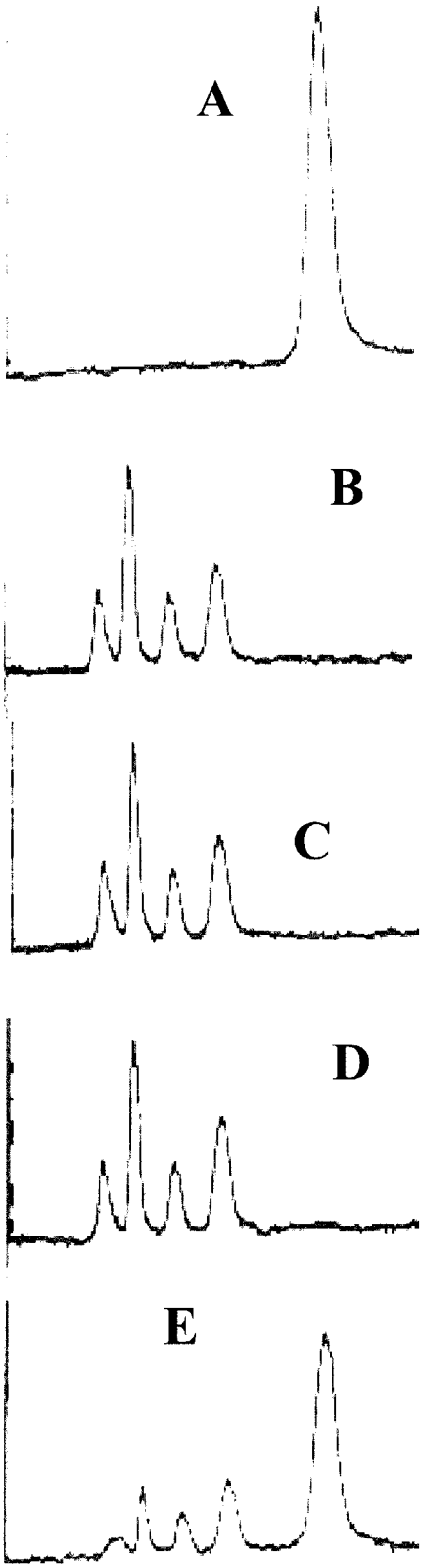

Figure 6. HPLC chromatograms of the model drug at the start (A) and after irradiation in the absence of any additives (B), in the presence of RAMEB (C); of MDC solubilised with RAMEB (D) and of BMD solubilised with RAMEB (E).

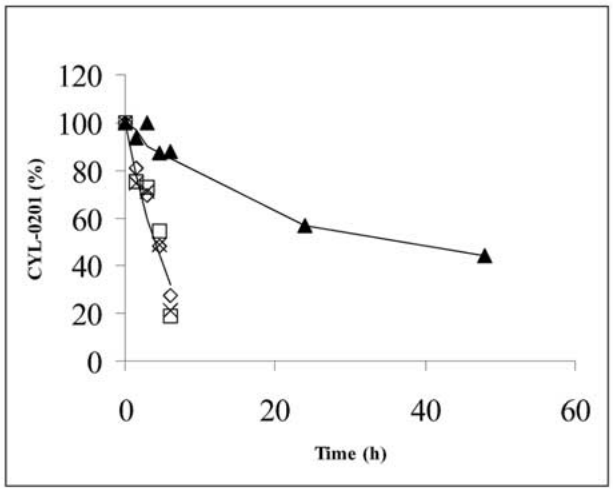

Figure 7. Photolytic decomposition of the model drug exposed to UV light in the absence of additives (◇), in the presence of RAMEB (□); of MDC solubilised with RAMEB (×) and of BMD solubilised with RAMEB (▲).

on the photodecomposition (Figure 7). UV filters solubilised by RAMEB were added. MBC was found to be ineffective, but in the presence of BMD the rate of decomposition was remarkably decreased and the half life of the drug enhanced from 4 h to 35 h. This indicates that the photostability of the system was improved by applying a UVA filter solubilised by inclusion complexation.

Acknowledgements

The work was supported by a grant from the Hungarian Research Fund (OTKA T 022003). The technical assistance of Zs. Nagy and Sz. Tóth is greatly acknowledged.

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