ATTACHMENT 1

Investigations on Photostability of UV-Absorbers for Cosmetic Sunscreens

Bernd Herzog and Katja Sommer

Ciba Specialty Chemicals Inc., Consumer Care,
Grenzach-Wyhlen, Germany

Introduction

The purpose of UV-filters used in cosmetic sunscreen formulations is to attenuate the UV-radiation of the sun. By absorption of UV-radiation organic UV-absorbers are transferred to an excited electronic state from which the energy may dissipate into molecular vibrations (internal conversion) and further into heat via collisions with surrounding molecules. The probability for internal conversion is strongly enhanced when the filter molecule in its excited electronic state can switch between isomeric structures such as by cis-trans-isomerisation or by intramolecular H-transfer [1, 2].

When an efficient dissipation of the excitation energy is not possible, chemical bonds of the UV-absorber may break and new bonds may be formed leading to irreversible changes of the chemical structure. A system where the chemical structure is irreversibly changed due to light exposure can be designated as photoinstable. However, this must not necessarily lead to the destruction of the UV-chromophor, and UV-attenuating properties may be maintained.

In this paper the photostabilities of different UV-filters (formulations containing one UV-filter or mixtures of two different UV-filters) are investigated via irradiation and subsequent analysis in terms of recovery of the absorber molecules using HPLC and in terms of sunscreen performance using in vitro SPF measurements, respectively.

UV-Absorbers and Formulations

The following UV-absorbers were used: the UVA-filter Butyl Methoxydibenzoylmethane (BMDBM), the UVB-absorbers Octyl Methoxycinnamate (OMC) and 4-Methylbenzylidene Camphor (MBC), the UV-broadband absorber Bis-Ethylhexyloxyphenol Methoxyphenyl

Triazine (BEMT), and the organic micronised UVA-filter Methylene Bis-Benzotriazolyl Tetramethylbutylphenol (MBBT).
All filter combinations studied were formulated using two different formulations, one of the w/o- and the other of the o/w-type. Except BEMT which was dispersed in the water phase all other UV-absorbers were dissolved in the oil phase. In the experiments with HPLC-analysis the w/o-formulation and in those with in vitro SPF analysis the o/w-formulation was used. In contrast to ref. [3] there was no indication of an influence of the formulation on the photostabilities of the UV-filters. Filter concentrations were chosen in a realistic range with respect to commercial sunscreen formulations (BMDBM: 2.4%, OMC: 3.4%, MBC: 2.4%, BEMT: 2.0%, MBBT: 5.0%, percentages as w/w).

Sample Preparation, Irradiation, and Sample Analysis

Irradiation was performed with an ATLAS Suntest CPS+ equipped with a COLIPA standard sun filter and operating at 765 W/m^2 corresponding to an UV-intensity of 5 MED/hour (assuming that 1 MED equals a dose of 250 J/m^2). The samples were exposed to doses of 0, 5, 10, 20, and 50 MED.
For the experiments with HPLC-analysis 5.6 µl of the respective formulation were equally distributed on a quartz-plate with a sand-blasted deepening of an area of 2.8 cm^2 (Hellma, Germany), resulting in an amount per area of 2 $\mu l/cm^2$ which has been also proposed in ref. [4]. With each formulation and irradiation condition eight plates were prepared, irradiated and analysed. After irradiation sunscreen films were rinsed off with dioxane and sampled into volumetric flasks (5 ml). The UV-filter content was measured via HPLC with UV-detection (column: Hewlett Packard Asahipak ODP-50 at 35°C, gradient: five minutes constant with 47% acetonitrile plus 53% water, during further 15 minutes the amount of acetonitrile was linearly increased to 100% and kept constant at this level for additional 15 minutes). Peak areas after irradiation were related to those without irradiation, setting the latter ones to 100%. With OMC and MBC both, the trans- and the cis-isomers were taken into account. Two vials were measured with each sample and the mean was taken. Afterwards the results of the eight parallel samples of each formulation and condition were averaged and confidence intervals with a significance level of 95% were calculated.
For the experiments with the in vitro SPF analysis quartz plates with a rough surface and an area of 40 cm^2 were employed (UQG Ltd., UK). With each formulation and irradiation condition four plates were prepared using an amount per area of 1 $\mu l/cm^2$. Two of these plates were irradiated, the other two plates were kept dark at the same temperature in

order to check for in vitro SPF changes occuring without radiation. Each sample was measured at nine different positions with a Labsphere UV-1000S Ultraviolet Transmittance Analyser. The 18 values obtained were averaged and normalised with respect to changes of the non-irradiated plates. Confidence intervals with 95% significance level were calculated.

Results and Discussion

In the first set of experiments formulations containing only one filter species were exposed to irradiation and analysed via HPLC. Figure 1 summarises the results in terms of the recovery of each individual filter in the range of doses between 0 and 50 MED. BMDBM is degraded to almost 100% after the full dose whereas the amounts of BEMT and MBBT under these conditions stay constant within the experimental error. The decreases of OMC and MBC range in between of these extreme cases. For both the cis- and the trans-isomers have been taken into account.

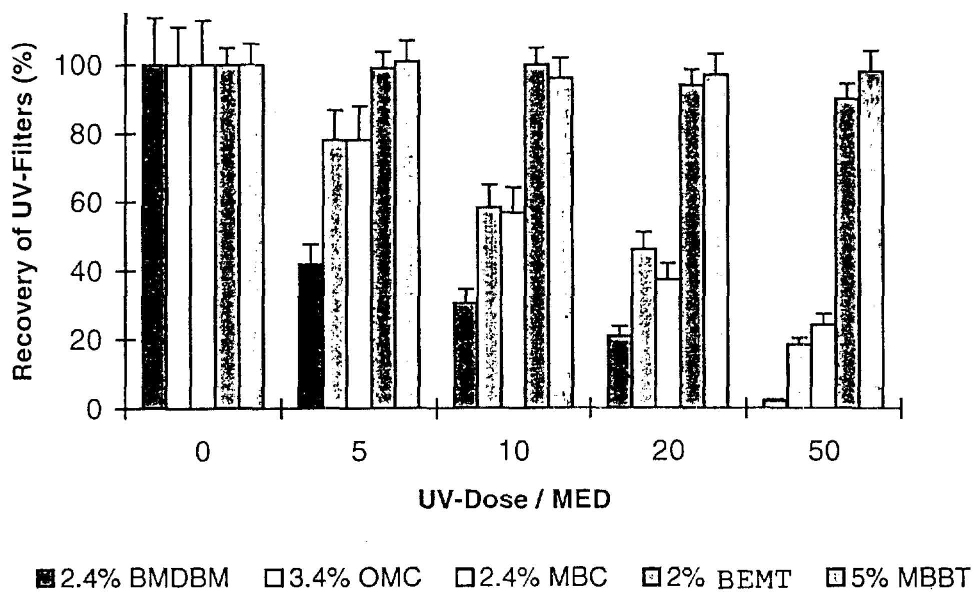

Fig. 1: Recovery of the individual filters after irradiation, expressed as percentage of the initial filter amount

The purpose of the following experiments was to study the influence of a second filter on the photostability of BMDBM and of OMC. Figure 2 shows the results for the case of BMDBM the amount of which was analysed after irradiation in the presence of OMC, MBBT, BEMT, and MBC, respectively. For comparison, the case with BMDBM as the only UV-filter is also shown.

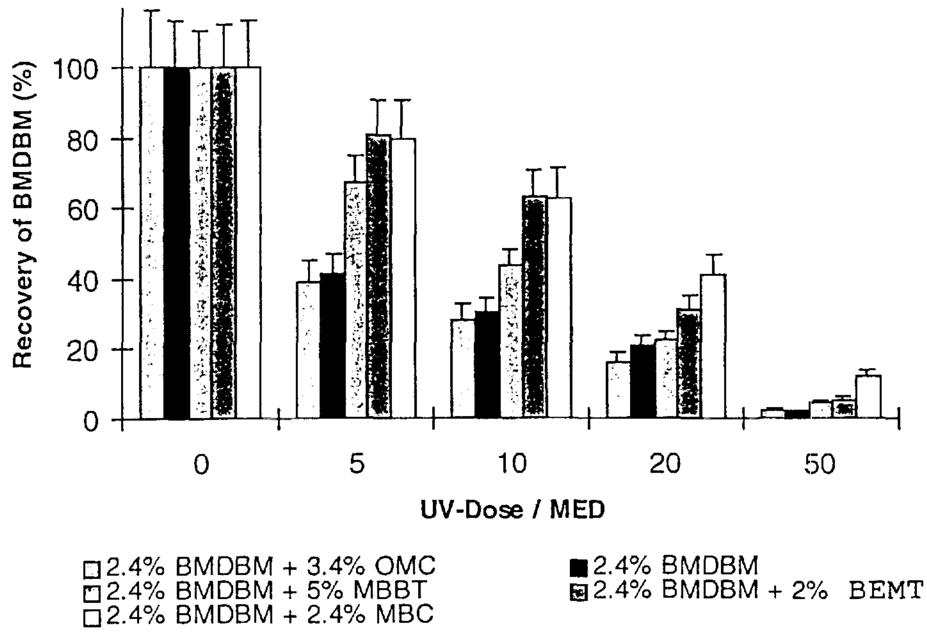

Fig. 2: Recovery of BMDBM without and in the presence of a further UV-absorber

The data show that in the presence of OMC there is almost no effect on BMDBM when compared to the case without additional UV-filter. However, MBBT, BEMT, and MBC show a stabilising effect on BMDBM which is strongest with MBC. When no other filter is present, the amount of BMDBM left after 20 MED is about 20% of the initial value. In the presence of MBC after 20 MED still 40% of the initial amount of BMDBM is existing.

In Figure 3 in vitro SPF measurements on formulations with the same filter combinations and concentrations are shown. Although the overall effect of the filter combination is probed with this method, similar features as in the BMDBM recovery data are observed. The results in Figure 3 indicate that there is an accelerated breakdown of the in vitro SPF when OMC is present (from 9.5 to 3.3). With MBC an obvious decrease occurs only at doses higher than 10 MED. In the case of MBBT there is a drop of the in vitro SPF of about 35% (from 9.5 to 5.9) during the first five MED but then it stays constant. With BEMT there is only a slight decrease of the SPF up to the dose of 50 MED, reflecting the photostability of this compound and its stabilising effect towards BMDBM.

Another quantity obtained from the in vitro SPF measurements is the UVA/UVB-ratio [5], an indicator of the UVA absorbing performance in relation to that in the UVB. The change of the UVA/UVB-ratio under irradiation of the same formulations is shown in Figure 4.

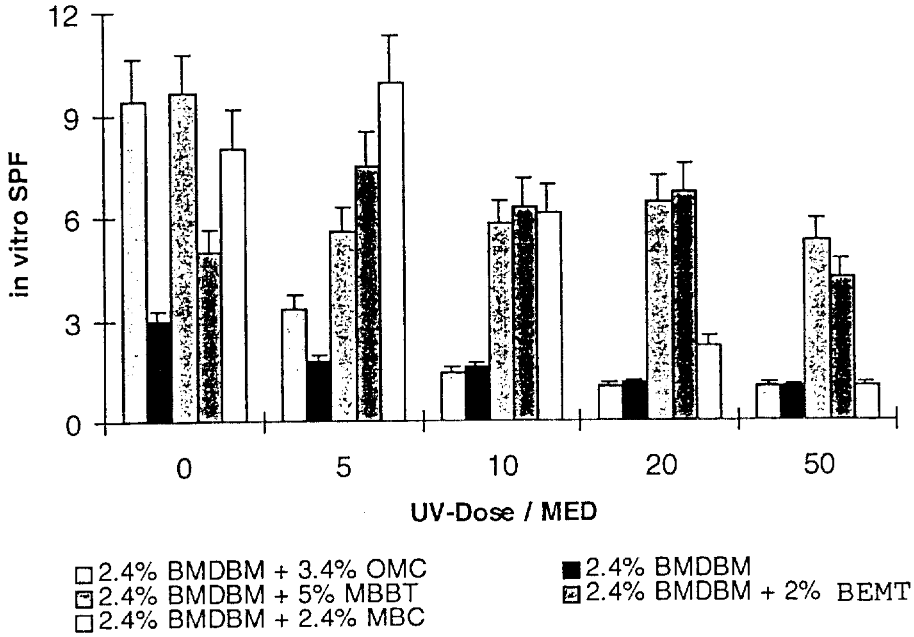

Fig. 3: in vitro SPF of formulations containing BMDBM without and in the presence of a further UV-absorber

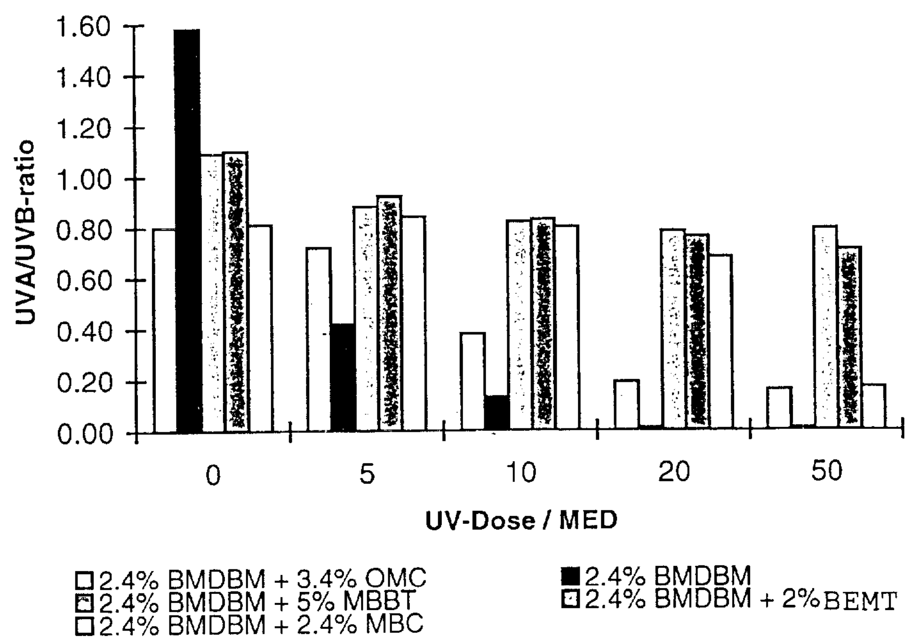

Fig. 4: UVA/UVB-ratio of formulations containing BMDBM without and in the presence of a further UV-absorber

The UVA/UVB-ratio of the mixture of BMDBM with OMC only slightly decreases during the first five MED indicating a parallel degradation of both compounds (the SPF drops dramatically during this period). At higher doses the UVA/UVB-ratio drops significantly indicating a faster decrease of BMDBM. With MBC this parameter stays at the same level up to 20 MED indicating a constant ratio of BMDBM and MBC over this period. In the presence of MBBT and BEMT there is a drop of about 20% during the first five MED of the UVA/UVB-ratio but then it remains constant up to 50 MED.
Figure 5 shows the results of experiments where the recovery of OMC was analysed after irradiation in the presence of BMDBM, MBBT, and BEMT, respectively. For comparison, the case with OMC as the only UV-filter is also shown.

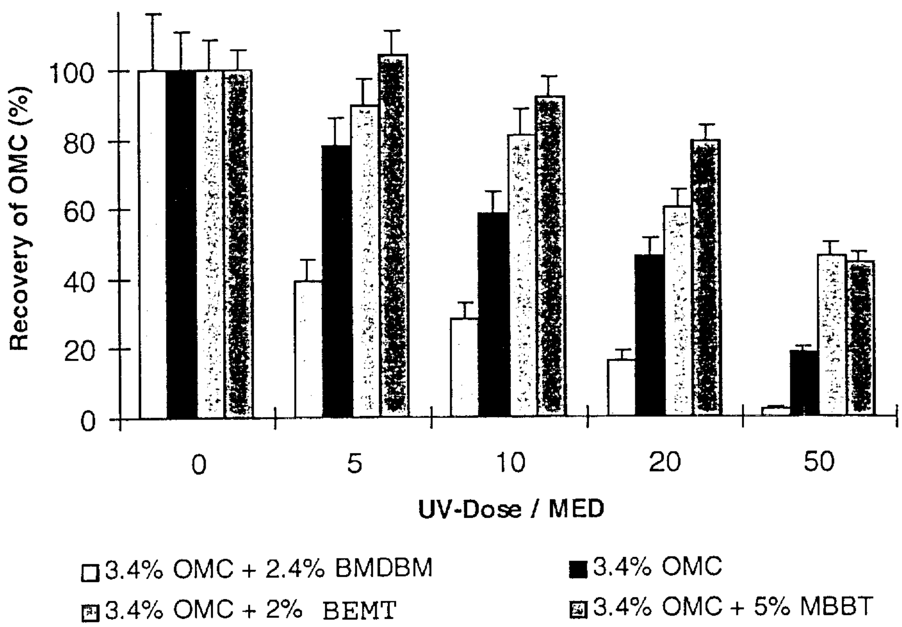

Fig. 5: Recovery of OMC without and in the presence of a further UV-absorber

A striking result in Figure 5 is that the degradation of OMC ist strongly enhanced by the presence of BMDBM. In that case already after 5 MED only 40% of the initially existing amount of OMC is left. When OMC is used as the only UV-absorber after five MED still 80% of the initial amount are remaining. This destabilisation of OMC in the presence of BMDBM is probably caused by a photochemical reaction of the two compounds, which occurs to be analogues to the photocyclodimerization of OMC itself [6, 7]. OMC is stabilised by BEMT and MBBT, an effect most significant at 10 MED and higher doses.

Figures 6 and 7 show in vitro SPF data and UVA/UVB-ratios with the same filter combinations and concentrations as discussed for the OMC recovery data, respectively.

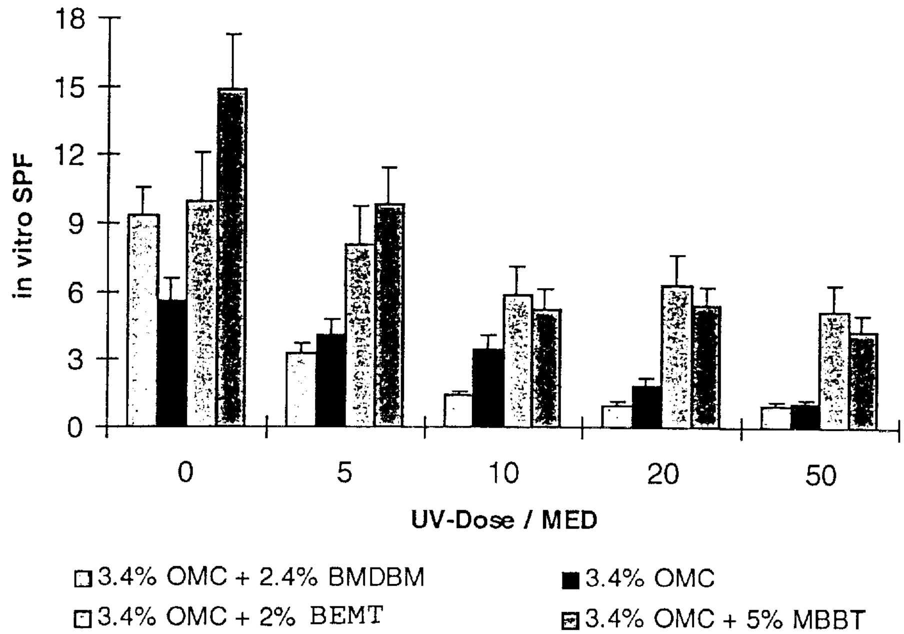

Fig. 6: in vitro SPF of formulations containing OMC without and in the presence of a further UV-absorber

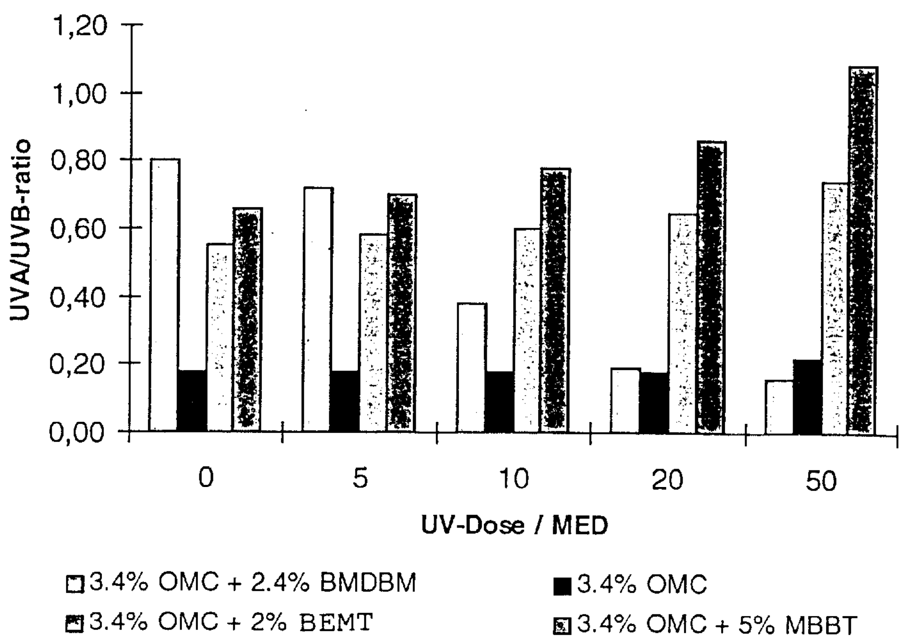

Fig. 7: UVA/UVB-ratio of formulations containing OMC without and in the presence of a further UV-absorber

Again, the trends obtained from the analysis of recoveries are also reflected in the in vitro SPF results. The decrease of the in vitro SPF of OMC is more pronounced in the presence of BMDBM compared to the situation when OMC is the only filter indicating the destabilising effect of BMDBM. On the other hand, with addition of BEMT or MBBT a stabilisation can be observed in terms of a slower decrease of the in vitro SPF. In the presence of these UV-filters the UVA/UVB-ratio increases with ascending UV-dose. BEMT and MBBT both are UV-filters with strong UVA-absorption and their photostabilities are close to 100% under the experimental conditions of this study (Figure 1). In combinations of these filters with OMC, UV-irradiation causes only a decrease of the OMC content leading therefore to a decrease of the UVB-relative to the UVA-performance noticeable in an increase of the UVA/UVB-ratio.

Conclusion

Irradiation doses up to 50 MED have been applied in this study which may appear rather high. However, depending on geographical location and exposure time this amount is realistic in the sense of a worst case scenario.

The photostabilities of the five UV-absorbers investigated show the following ranking: MBBT ≥ BEMT > MBC ≥ OMC > BMDBM. The extreme cases are represented by the most stable filter MBBT the recovery of which is 98% after 50 MED and the most instable filter BMDBM the recovery of which is 2% after 50 MED.

BMDBM is stabilised under irradiation by the presence of MBC, BEMT, or MBBT where MBC has the strongest effect followed by BEMT and MBBT, respectively.

The photodegradation of OMC is significantly accelerated by the presence of BMDBM. In contrast, MBBT and BEMT have a stabilising effect towards OMC under irradiation.

References

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