Designing Broad-Spectrum UV Absorbers

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UVA, UVB, UV filters, SPF, sunscreen simulator, photostability, solubility, efficacy, safety, registration, patent freedom

Abstract
Design considerations for broad-spectrum UV filters include photostability, solubility, efficacy, safety, registration, patent freedom, and PPD performance. These criteria are described and then applied in the case of bis-Ethyl-hexyloxyphenol methoxyphenyltriazine (BEMT), a new broad-spectrum sunscreen active.

Overexposure of human skin by UV light leads to sun-burn, an increased risk for skin cancers and also premature aging of the skin.[1] Although the role of UVA is not entirely known, it is now widely recognized that a certain UVA protection must be ensured in the development of sunscreens. More than 90% of ultraviolet energy received by the unprotected skin comes from the UVA range. Because there is no natural immediate warning sign similar to sunburn for UVB radiation, sunscreens with poor UVA protection may be transmitting vast amounts of UVA radiation onto the skin. This has even led to the assumption that sunscreens may contribute to rather than protect against skin cancer.[2]

The example in Table 1 illustrates the effect of three sunscreens with the same degree of sunburn protection of SPF 8, but different degrees of UVA protection. The examples were calculated by using the standard CIE solar spectrum[3] and a sunscreen simulator[a].[4,5]

The UVA dose received during sun exposure varies largely, without causing any short-term effects. A person of photo-skin type 2 (fair skin, easily burned and rarely tanned) can expect mild sunburn after a sun exposure of about 15 minutes without protection. During this period that person receives a UVA dose of 5.5 J/cm^2. With any SPF 8 sunscreen, the amount of time to get mild sunburn is, by definition, two hours for that person. The maximal UVA dose that could be received during that time would be eight times the UVA dose received with no protection after 15 minutes. Two hours with no protection would of course result in bad sunburn with painful blistering mainly due to the UVB radiation. With an SPF 8 sunscreen, this sunburn is avoided for exposures up to two hours, but the example of three different SPF 8 sunscreens shows that the UVA dose received can vary significantly up to six times in the case of a "pure" UVB sunscreen. To ensure that not only sunburn is prevented but also the UVA dose is not excessive, photostable broad-spectrum or UVA/broad-spectrum filters are required.

[a]*Sunscreen Stimulator is a product of Ciba Specialty Chemicals, Basel, Switzerland.*

Designing a New UV Filter

Any new UV filter must demonstrate efficient UV absorption, photostability,

Table 1. Comparison of three SPF 8 sunscreens with different degrees of UVA protection

Protection type	None	UVB only	UVB plus little UVA	Broad-Spectrum
Sunscreen actives	UVB: None UVA: None	UVB: 5.9% EHMC UVA: None	UVB: 4.0% EHMC UVA: 1.6% Benzo-phenone-3	UVB: 0.9%EHMC UVB/UVA: 1.8% BEMT, 1.8% MBBT
UVA-Parameters:				
UVA/UVB ratio	(1.0)	0.25	0.35	0.85
Critical wavelength λ_c	(290)	339 nm	351	384
Australian UVA-Standard fulfilled:	No	No	No	Yes
Effect of UVR				
Mild Sunburn after	15 minutes	2 hours	2 hours	2 hours
UVA dose J/cm^2	5.5	33	27	8.5

EHMC= ethylhexyl methoxycinnamate BEMT= Bis-ethylhexyloxyphenol methoxyphenyltriazine
MBBT= methylene bis-benzotriazolyl tetramethylbutyl phenol

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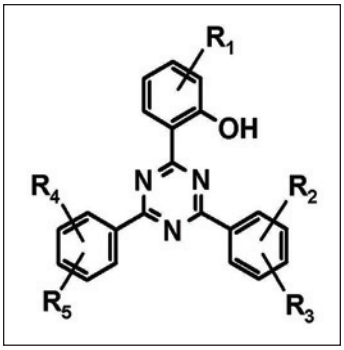

Figure 1. General structure of hydroxyphenyltriazines (HPTs)

and solubility. UV filters for personal care applications must also demonstrate their performance in vitro and in vivo, and they must meet four additional requirements: efficacy, safety, registration and patent freedom.

Photostability: UV absorbers are widely used to protect polymers (e.g. plastics, fibers, coatings) against photo-degradation. Numerous investigations have demonstrated that photostability is of key importance to the filters in order to provide long-term protection of polymer substrates (e.g. no degradation after several years of Florida outdoor testing).

In general, the photostability of a UV filter depends on how well the molecule is able to release the absorbed energy to the environment in the form of heat rather than radiation. Also in general, UV absorbers with an intramolecular hydrogen bond exhibit very efficient radiation-free energy transformation processes resulting in inherent photostability.

For polymer applications, the following UV stabilizer technologies have been developed over the years:

Methyl salicylates (1960) ➠

o-hydroxybenzophenones (1965-1970) ➠

2-(2-hydroxyaryl)-benzotriazoles (1975-1990) ➠

2-(2-hydroxyaryl)-1,3,5-triazines (since 1995)

Presently, hydroxyphenyltriazines (HPTs) represent the most advanced class of UV absorbers for the photoprotection of all kinds of polymer substrates.[6-8] Their general structure is shown in Figure 1.

Table 2. Typical international safety dossier of a new sunscreen[8]

Acute oral and dermal toxicity
Dermal, ocular irritation, skin sensitization
Photo-irritation, photo-sensitization
Subchronic oral and topical toxicity
Chronic toxicity
Fertility, early embryonic development
Embryofetal toxicity and peri-/post-natal toxicity
In vitro and in vivo percutaneous absorption
Topical and oral pharmacokinetic and metabolism
In vitro and in vivo genetic toxicity
Carcinogenicity
Photo-carcinogenicity
Safety and efficacy in man

Solubility: Without solubilizing substituents, HPTs are nearly insoluble in cosmetic oils. They exhibit the typical properties of pigments (e.g. high melting points). In order to increase solubility in oil phases, the structure of the UV filter has to be modified accordingly. An example in the case of BEMT is given later.

Efficacy: Besides efficient UV absorption, photostability and solubility as described above, there are other important parameters regarding efficacy to be considered. The UV absorber substance must be compatible with all other ingredients in a formulation; there should be no discoloration of skin and hair, no staining of textiles, and no odor. For the water-resistant claim the UV absorber should be insoluble in water. And last but not least the UV filter should be economical in its use.

Safety: Sunscreen actives should have no adverse effect on humans and the environment. Although direct comparison with a new pharmaceutical drug is not appropriate, the development of a new sunscreen active for global use is highly demanding. The toxicological studies required for a global registration are listed in Table 2.[9]

International registration: In order to exploit the full economic potential of a UV filter, UV absorber manufacturers are aiming for global registration. In Europe, South America, Asia and Africa, where sunscreens are labeled cosmetics, approval is possible within two years of filing. In Australia, Japan and the United States it takes longer.

Only recently in the U.S., a new procedure (TEA: Material Time and Material Extent Application) was introduced. After a minimum of five years foreign marketing experience in five countries, a new sunscreen active can be submitted for registration.[10] After the marketing experience, efficacy and safety data have to be submitted.

So far three UVB filters that are widely used outside the U.S. have received the status of "eligibile to enter the Sunscreen Monograph."[11] These three are: isoamyl p-methoxycinnamate (IMC) or Amiloxate (U.S. drug name); 4-methylbenzylidene camphor (MBC) or Enzacamene (U.S. drug name); and ethylhexyl triazone (EHT) or octyl triazone BEMT (U.S. drug name: Bemotrizinol). They will start the TEA process in 2005 when the five years of marketing experience will be available.

Patent freedom: Patent freedom means the free use of sunscreen actives by any sunscreen manufacturer, i.e. avoiding the infringement of any third-party patent rights.

Until about 10 years ago UV absorber manufacturers protected their inventions by simple substance patents that included the basic applications, e.g., "invention of a novel UV absorber for the incorporation in personal care formulations for the protection of skin and hair)."

In the mid 1990s important cosmetics manufacturers started to patent not only their specific technologies but also generic combinations of different ingredients. This strategy is aimed to keep competitors from using new technology that emerged on the market.[12] This limits the potential of the competitors, which is part of business. But it also is detrimental for the supplier who suddenly sees the potential of his new

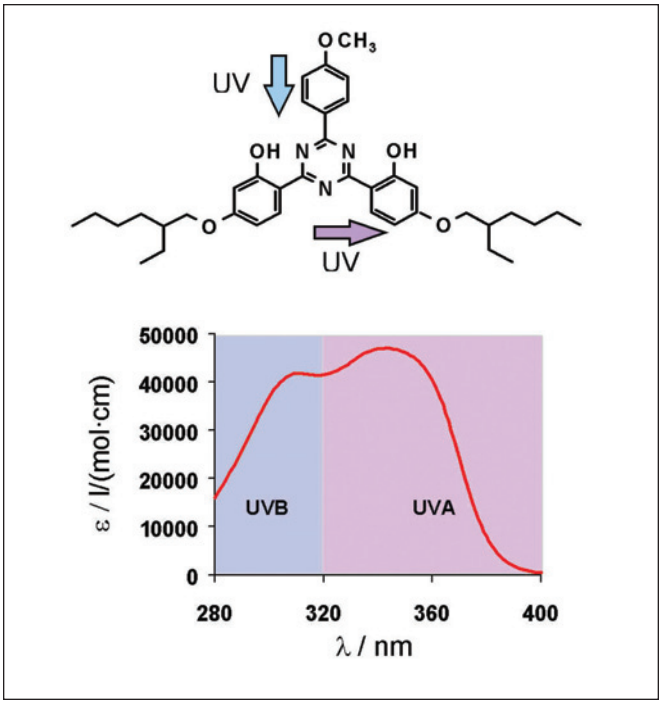

Figure 2. Molecular structure and UV-absorption spectrum of BEMT, measured in EtOH, E1,1 max = 820 (342 nm) (arrows indicate the polarization of the UVA and UVB transitions)

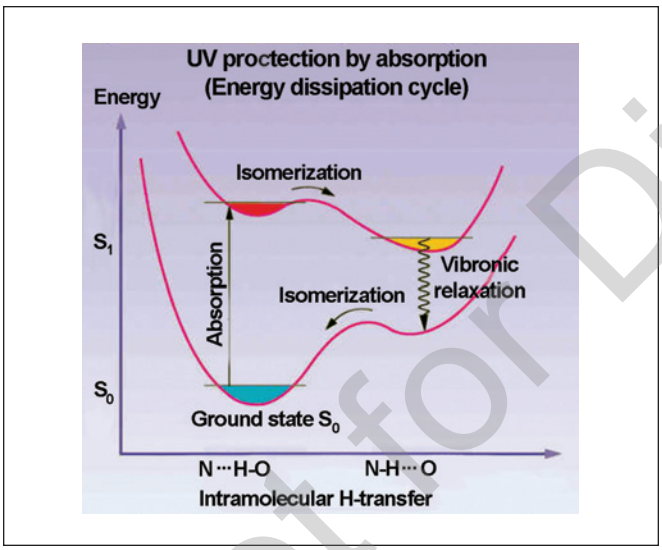

Figure 3. Model for the conversion of absorbed UV-energy to heat by extremely fast photo-tautomerism (approximately 10^{-12} seconds)

sunscreen active shrinking due to patent restrictions.

As a consequence the suppliers had to react and rethink the patenting strategy and the whole innovation process. As soon as the identity of a new ingredient becomes known, "all" measures have to be taken. These measures include publication of combinations of that novel ingredient with other sunscreen actives and other compounds such as emollients, emulsifiers or thickeners.

Gaining OTC Sunscreen Monograph Status via TEA

In January 2002, the FDA published the "foreign marketing rule", the so-called material Time and material Extent Application (TEA) process,[23] which opens all OTC drug monographs to foreign drugs or cosmetic ingredients under certain conditions. Here's how TEA works for a sunscreen ingredient.

1. The manufacturer submits evidence to the FDA showing that the ingredient has five years of continuous foreign marketing experience.
2. The FDA has approximately 120 days to determine eligibility and will issue a Federal Register Notice of eligibility. This concludes the first phase (TEA1) of the "two-step" TEA process.
3. FDA's Notice of Eligibility triggers the second phase of the TEA process (TEA2), which requires that data on efficacy and safety be submitted to demonstrate that the ingredient and formulation can be generally regarded as safe and effective (GRAS/E). For example, in the case of Ciba's bemotrizinol under TEA2, Ciba will provide FDA with the necessary toxicological and efficacy studies, including a 2-year dermal carcinogenicity study and an 18-month photocarcinogenicity study to support the GRAS/E status.
4. FDA reviews the submitted efficacy and safety data. If they meet the requirements for GRAS/E status, FDA will make a determination of approval for inclusion of the ingredient into the OTC Sunscreen Monograph.

BEMT – An Example of a New UVA Filter

HPT structure suggested the use of HPT chemistry to design an efficient broad-spectrum sunscreen active. As a consequence of their molecular structure, HPTs exhibit a UV spectrum with two distinctive absorptions. This is due to the presence of two electronic transitions with strong dipole moments, both of which are polarized perpendicular to each other. In order to obtain broadband absorbance, OH and OR substituents at the three phenyl groups were introduced and positioned (as shown in Figure 2), resulting in the formation of bis-Ethylhexylphenol methoxyphenyltriazine (BEMT), a new oil-soluble UV filter with true broad-spectrum performance. The two ortho-OH groups not only contribute to the broad-spectrum characteristics, but also enable efficient energy dissipation via intramolecular hydrogen bridges. Figure 3 illustrates the role of the intramolecular hydrogen bridge in the quantitative conversion of UV light to vibrational (heat) energy.[13]

In the United States, bemotrizinol is not yet approved as a sunscreen active ingredient by the United States Food and Drug Administration (FDA), however the ingredient will have five years of continuous marketing experience by March 2005 and can then seek approval via the TEA process (see sidebar).

Photostability: BEMT contains two intramolecular hydrogen bonds, which enable an excited state intramolecular

proton transfer (photo-tautomerism) after photoexcitation. This results in rapid radiationless conversion ensuring that the UV radiation, efficiently absorbed by the filter, is almost quantitatively transformed into harmless vibrational (heat) energy. The entire photo-tautomeric cycle only lasts about 10^{-12} seconds, leaving no time for undesirable side reactions (e.g. population of triplet states, formation of singlet oxygen or formation of radicals). This explains the excellent photostability of BEMT (>95% recovery of parent BEMT is observed analytically after UV irradiation of 50 minimal erythema doses, MED).[14]

Table 3. Solubilities of BEMT in cosmetic solvents

Caprylylpyrrolidone	20.0%
Ethylhexyl methoxycinnamate	17.0
C_{12}-C_{15} alkylbenzoate	13.0
Diethylhexylsuccinate	7.0
Isopropylmyristate	6.0
Hexyl laurate	6.0
Caprylic/capric triglyceride	5.0
Coco caprylate/caprate	5.0
Isopropylpalmitate	5.0
Sesame oil	3.0

Solubility: Solubility of BEMT in different cosmetic solvents is given in Table 3. The product form is a very fine yellow powder with a melting point of 80°C that is easily solubilized in most emollients.

In vitro/In vivo performance: The performance of BEMT as a cosmetic UV filter has been assessed in in vitro and in vivo studies.[15] For rating UVA performance, the Australian standard is increasingly used. UVA protection is recognized when a sunscreen preparation transmits between 320 nm and 360 nm (in an 8 µm cuvette) less than 10% of the incoming light (Figure 4).[16]

In a comparative test with other oil soluble filters it was shown that BEMT exhibits the highest efficacy to satisfy the Australian Standard - only 1.9% of this broad spectrum filter is required in formulation.

In vivo assessment of UVA protection: The UVA protection factors (UVA-PF) obtained from in vivo Persistent Pigment Darkening (PPD) studies increases steadily, as expected, with the concentration of the UVA broad spectrum filter BEMT (Figure 5). Already low BEMT concentrations of 1-2% are sufficient for a PA++ protection, rated after the Japanese standard.[17] In combinations of BEMT and ethylhexyl methoxycinnamate (EHMC), a synergy regarding the PFA performance has been observed.

Due to its spectral performance, BEMT is able to boost photoprotection (SPF) when combined with conventional UV filters such as EHMC.[18] No adverse effect (incompatibility) has been observed in combinations of BEMT with other soluble filters or pigments. Moreover it has been observed that BEMT stabilizes photolabile sunscreens such as butylmethoxydibenzoylmethane (BMBM) and EHMC (Figure 6).[19]

Safety: A safety testing program was conducted with BEMT. According to applicable OECD/EC test guidelines, BEMT was GLP-compliant. The toxicological test results indicate no adverse effects for human use.

BEMT toxicology data have been reviewed by the European Commission Scientific Committee on Cosmetic Products and Non-Food Products Intended For Consumers (SCCNFP) and found to support an approved safe use level of up to 10% BEMT as a UV filter in leave-on and rinse-off cosmetics.

BEMT has no acute aquatic toxicity up to its maximum solubility and also no toxicity to microorganisms. The substance is not readily biodegradable but has an expected elimination of greater than 70%. BEMT has no bioaccumulation. The resulting Environmental Risk Assessment according to the EC "Technical Guidance Document" has a PEC/PNEC ratio[b] of < 0.001 in the environmental compartments water, sludge, sediment and soil. These favorable results indicate no adverse effects to the environment.

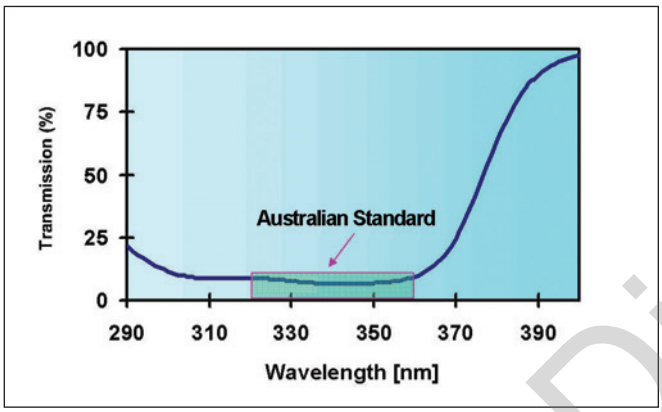

Figure 4. BEMT fulfilling the Australian UVA Standard

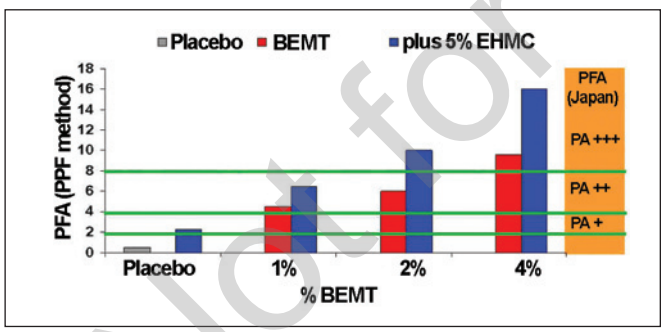

Figure 5. UVA protection with BEMT, alone and with EHMC (PPD method)

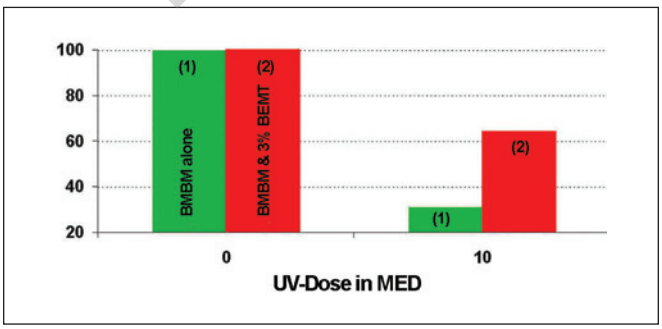

Figure 6. Stabilization of BMBM by BEMT

[b]*PEC = Predicted Environmental Concentration. PNEC = Predicted No Effect Concentration. PEC/PNEC ratios <1 indicate no immediate concern to the environment.*

Patent freedom: In an attempt to protect both the filter and combinations of the filter with other ingredients, patents[20] have been issued for both BEMT and combinations thereof with commonly used cosmetic UV filters. Regarding BEMT there exist several specific third-party patent rights. However, according to our view there are no serious patent restrictions.

Conclusions

From the new broad-spectrum UV absorbers we expect better UVA coverage when incorporated into a sunscreen or day cream. To illustrate and quantify the improvement, we carried out some calculations with different formulations using a new sunscreen simulator.[4,5]

Figure 7 shows the composition of three formulations with similar SPF (i.e. similar UVB protection) but different degrees of UVA protection.[21] The area below the sunscreen with the highest UVA transmission (320-400 nm) was Formula F-1 (with 3% benzophenone-3). We arbitrarily set that area as 100%. Formula F-3 (with BEMT) reduces this UVA exposure through the sunscreen already to below 60%. With formula F-5 (using BEMT and another new UVA/broad-spectrum filter such as methylenebisbenzotriazolyl tetramethyl-butylphenol or MBBT, U.S. drug name: Bisoctrizole[22]), the UVA exposure is reduced down to a quarter of the value achieved with the conventional formulation F-1. With modern broad-spectrum filters it is thus possible to achieve better UVA protection by using lower amounts of UV filter.

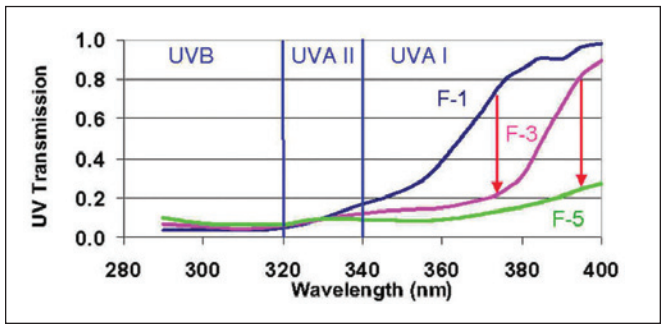

Figure 7. Improvement in UVA protection with new broad-spectrum filters

Formula	Composition	SPF(calc)	(relative %)
F-1	7% EHMC, 3% BP-3	14.0	100
F-3	5% EHMC, 3% BEMT	15.5	60
F-5	1% EHT, 3% MBBT, 3% BEMT	14.1	25

In spite of great differences, all these formulations could make "UVA" or "broadband" claims at the moment. What thus is needed is a standardized and harmonized method for the UVA assessment that discriminates between the vast differences in the degree of UVA protection.

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