Photostabilisation: for safe, pleasant sunscreens

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Abstract

During the photostabilisation process, the excited state energy of a light-absorbing species is removed by energy transfer and/or by an electron transfer quenching mechanism. By thus returning it to its ground state, photostabilisation stabilises the light-absorbing species, which prevents its photodegradation and the generation of reactive oxygen species (ROS). Hallstar has pioneered photostabilisation technology to promote effective sun protection and comprehensive photoageing prevention. Our photostabilisers for UV filters protect photolabile UV filters from decomposition and shield photosensitive UV filters from generating ROS. A paradigm shift from UV filter protection resulted in the development of our revolutionary anti-ageing technology, which is based on stopping photosensitisers in skin from generating any ROS when excited by light.

Sunlight, including ultraviolet radiation, provides the energy necessary to sustain life on Earth. The solar energy reaching the Earth's surface at sea level consists of non-ionising radiation spanning wavelengths of 290-3000 nm. This non-ionising radiation contains infrared radiation (~ 50%), visible light (~ 40%), and ultraviolet radiation (~ 10%).

Ultraviolet radiation (UVR) is the solar spectrum of wavelengths between 100 and 400 nm, and it is invisible to human eyes. UVR is categorised into UVA (320-400 nm), UVB (290-320 nm), and UVC (100-290 nm), with UVC rays being unable to reach the Earth's surface.

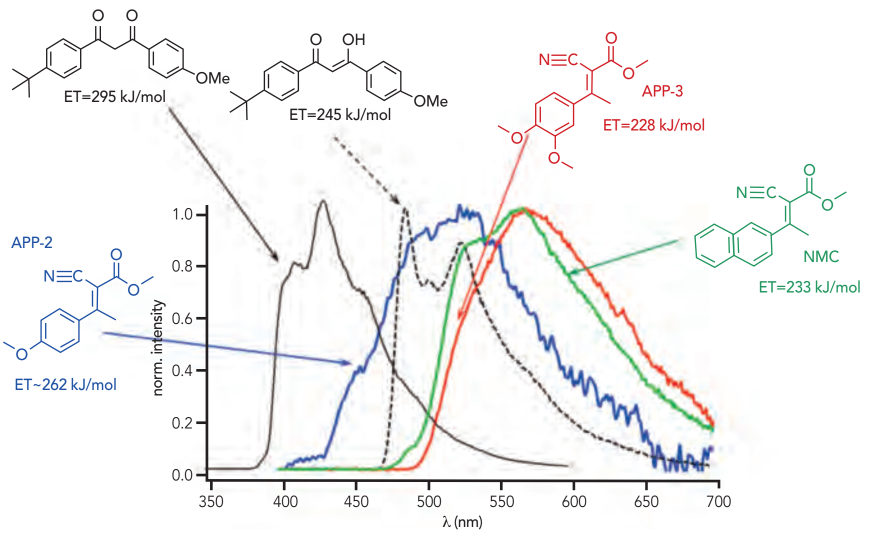
Terrestrial UVR levels change according to natural conditions such as the season, latitude, altitude, atmospheric effects, and the angle of the sun's rays through the atmosphere as defined by the solar zenith angle. Due to UVB's shorter wavelengths, these factors have a much more pronounced effect on daily terrestrial UVB levels than on UVA levels. For instance, cloud cover can reduce UVB radiation by 15%-30%, and air pollution can reduce UVB levels up to 20% by absorbing, scattering and reflecting UVB rays. In contrast, the atmosphere filters out little UVA, and its intensity remains relatively constant throughout the day. Consequently, the ratio of UVA intensity to UVB intensity can vary from 120:1 in the morning and evening to 5:1 at noon.

UVR can be both beneficial and harmful to the human body. Certain doses of UVR are required to produce vitamin D, which is critical to many basic human functions. Appropriate doses and types of UVR can also provide therapeutic improvements to some skin disorders. However, both long and short-term exposure to UVR can also cause a variety of detrimental biological effects such as sunburns, photoageing, and skin cancer in humans.

The thick outer layers of the epidermis offer a natural defence against UVR by absorbing or reflecting 90%-95% of incidental UVB. But UVA, with its longer wavelengths, can penetrate the skin more deeply than UVB and can more easily reach the proliferative basal layers of the epidermis and dermis. Between 19%-50% of UVA reaches the basal layer of the epidermis, whereas only 9%-14% of UVB does. The total amount of UVA energy reaching the basal layers of the epidermis is up to 100 times higher than the total amount of UVB energy. This is supported by findings that show that the epidermal basal layers of patients with certain skin cancers harbour more UVA than UVB mutations.

UVA can act on chromophores, the functional groups capable of absorbing the UVA energy, which then undergo photoreactions and cause direct damage at a cellular level. The epidermis contains several known UVR chromophores, such as certain proteins, DNA, trans-urocanic acid, and melanins and their precursors. UVA radiation can also indirectly cause photodamage by generating reactive oxygen species (ROS) and free radicals from photosensitisation.

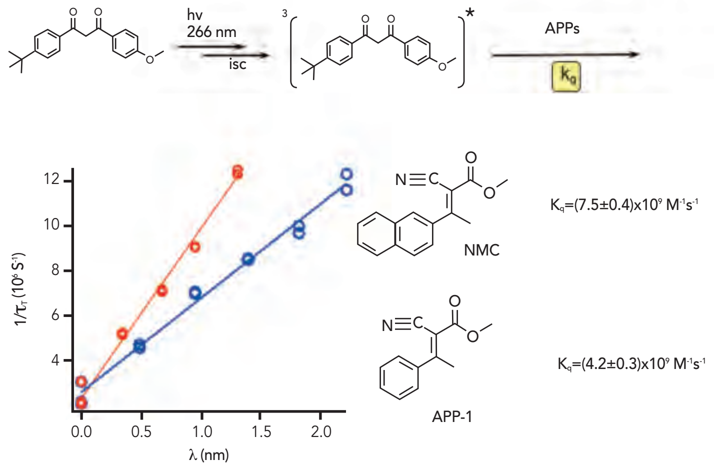
Photosensitisers are molecules that absorb light, become excited, and then



Phosphorescence spectra in ethanol glass at 77k. Metyl iodide was added to increase the phosphorescence yields for APP-2 (33% MeI), APP-3 (20% MeI) and NMC (20% MeI). App-1 did not show detectable phosphorescence. NMC should quench triplet states of the keto form, but not the enol form of avobenzone.

Figure 1: Triplet state energy levels as measured using phosphorescence spectra at 77K.

transfer that excited state energy to oxygen, initiating a series of chemical reactions that may generate ROS; the photosensitiser may be chemically changed in this process as well. Although both UVA and UVB rays can generate ROS, it is now widely recognised that photosensitisation causes many of the detrimental biological effects associated with UVA. In contrast, it is generally accepted that most of the damaging effects of UVB result from its direct interaction with chromophores in the skin such as DNA. Many ROS are normal byproducts of cellular metabolism; however, an imbalance in or elevation of ROS levels can cause significant damage to cells through oxidative stress. For example, singlet oxygen has a relatively long lifetime (10^{-6}s -close to 100 s) and reacts indiscriminately with a wide range of biological targets, including DNA, RNA, proteins and lipids. In addition, the hydroxyl radical is a highly reactive and indiscriminate oxidant that can cross cell membranes, further increasing the range of and potential for UVA-induced oxidative damage.



Laser flash photolysis of *Keto-Avobenzone* (266nm, 5ns pulse width) in deoxygenated acetonitrile solutions. To determine the quenching rate constant of triplet *Keto-Avobenzone*, decay traces of the triplet absorption of keto-Avobenzone in the absence and presence of varying concentrations of APP-1 or NMC were recorded. Keto-Avobenzone was generated by photolysis of enol-Avoenzone at 350nm.

Figure 2: Triplet state quenching rate constant measured using laser flash photolysis.

Unfortunately, visible light can damage human skin just as UVA does. There are plenty of chromophores in human skin that can absorb energy from sunlight in the visible range. Chromophores excited by visual light can serve as photosensitisers and generate ROS. However, protecting against ROS generated by visible light demands a paradigm shift, since traditional sunscreens protect skin from UV irradiation by blocking the energy with UV filters, and any filters that block visible light will have a distinct colour that consumers do not find aesthetically pleasing. To solve this seemingly impossible dilemma, Hallstar invented Micah™ technology.

Formulation 1 and 2: Sunscreen Formula using AvoBrite:

Phase	Tradename	INCI Name (INN/SAN) (Other Information)	% Wt
A	HallBrite EZ-FLO TDX	Butyloctyl Salicylate, Titannium Dioxide(nano), Triceteareth-4 Phosphate,Dimethicone Crosspolymer, Silica	6.00
	AvoBrite™	Acrylates copolymer	6.00
	HallBrite BHB	Butyloctyl Salicylate	6.00
	HallStar GMS SE/AS	Glyceryl Stearate, PEG-100 Stearate	2.00
	HallStar GMS PURE	Glyceryl Stearate	1.00
	HallStar TA-1618	Cetearyl Alcohol	1.00
	Olivem© 800	Ceteareth-6 Olivate	1.00
	Tween 60	Polysorbate 60	0.50
	SP-10 Kobo	Nylon 12	1.00
	GTCC	Caprylic/Capric Trigly Ceride	1.50
B	GalSORB Avobenzone	Butyl Methoxydibenzoylmethane [Avobenzone]	3.00
	EDTA-2Na	Disodium EDTA	0.05
	D.I-Water	Water	22.65
C	Olivem 1000	Cetearyl Olivate, Sorbitan Olivate	3.00
	Xanthan gum	Xanthan gum	0.3
	1,3-Butylene glycol	1,3-Butylene glycol	3.00
	1,2-Hexanediol	1,2-Hexanediol	1.00
D	Trienthanolamine	Trienthanolamine	3.00
	Water D.I.	Water D.I.	30.00
E	Parsol HS	Phenylbenzimidazole Sulfonic Acid	6.00
F	DC 345	Cyclopentasiloxane, Cyclohexasiloxane	2.00

Results

Principles of photostabilisation

When irradiated, active species capable of absorbing light energy normally convert to their singlet excited states before converting via intersystem crossing to their triplet excited states. Both the singlet excited states and the triplet excited states are capable of returning to the ground state via radiative or non-radiative relaxation pathways.

Depending on the structure of the light-absorbing species, these relaxation pathways are often not efficient enough in returning the excited state molecules to their ground states. When this happens, the excited state energy can be diverted to molecular oxygen, which will in turn become excited singlet oxygen, the leading source of reactive oxygen species (ROS).

Alternatively, these excited state molecules easily undergo chemical structure alterations, leading to photodegradation of the original molecules. Both ROS-generation and photodegradation can be significantly reduced or avoided when Hallstar photostabilisers (quenchers) are introduced in the system. Photostabilisers rapidly quench the excited states of the active species, bringing them to ground state unchanged. This also eliminates the possible transfer of excited energy to oxygen, stopping ROS generation. Rapid regeneration of ground state active species increases their efficacy in handling light irradiation.

Photostabilisers use two mechanisms to stabilise excited molecules. One mechanism involves the photostabiliser

Formulation 2: Sunscreen Formula without using AvoBrite:

Phase	Tradename	INCI Name (INN/SAN) (Other Information)	% Wt
A	HallBrite EZ-FLO TDX	Butyloctyl Salicylate, Titannium Dioxide(nano), Triceteareth-4 Phosphate, Dimethicone Crosspolymer, Silica	6.00
	NO	Control polymer	6.00
	HallBrite BHB	Butyloctyl Salicylate	6.00
	HallStar GMS SE/AS	Glyceryl Stearate, PEG-100 Stearate	2.00
	HallStar GMS PURE	Glyceryl Stearate	1.00
	HallStar TA-1618	Cetearyl Alcohol	1.00
	Olivem 800	Ceteareth-6 Olivate	1.00
	Tween 60	Polysorbate 60	0.50
	SP-10 Kobo	Nylon 12	1.00
	SP-10 Kobo	Nylon 12	1.50
B	GalSORB Avobenzone	Butyl Methoxydibenzoylmethane [Avobenzone]	3.00
	EDTA-2Na	Disodium EDTA	0.05
	D.I-Water	Water	22.65
C	Olivem 1000	Cetearyl Olivate, Sorbitan Olivate	3.00
	Xanthan gum	Xanthan gum	0.3
	1,3-Butylene glycol	1,3-Butylene glycol	3.00
	1,2-Hexanediol	1,2-Hexanediol	1.00
D	Trienthanolamine	Trienthanolamine	3.00
	Water D.I.	Water D.I.	30.00
E	Parsol HS	Phenylbenzimidazole Sulfonic Acid	6.00
F	DC 345	Cyclopentasiloxane, Cyclohexasiloxane	2.00

modifying the electronic environment of the UV filter molecules so that they can return to their ground states more effectively. Butyloctyl Salicylate, the prototypal Hallstar product HallBrite® BHB, works by this mechanism. The second mechanism involves the photostabiliser accepting the excited state energy from the UV filter molecule and then quickly releasing this energy via non-radiative decays. We will use our most recently developed photostabiliser product, Acrylates Copolymer (AvoBrite™), as an example to illustrate the design principles and effectiveness of this technology.

Protecting UV filters against photodecomposition: increase filter efficiency

Avobenzone (INCI: Butyl Methoxydibenzoylmethane (BMDBM)) is one of the most effective UVA filters and the only one accepted in the global market. Unfortunately, it is unstable when exposed to UVR. The photodegradation reaction of the BMDBM molecule has been thoroughly studied by Hallstar and others; these studies are widely available in the open literature, so we will not discuss the reaction further. As the desire for UVA protection grows, stabilising avobenzone provides a universal approach to improving UVA protection performance.

While designing our newest photostabilisers, Hallstar focused on the triplet excited states of avobenzone. First, we measured the triplet excited state energy levels of both the enol and keto structures of avobenzone. Next, we designed many possible quencher structures with the right energy levels, so they could accept the excited state energy from avobenzone. Several representative structures are included in Figure 1 with the triplet state energies of avobenzone.

We then used laser flash photolysis to accurately measure the quenching rate constant of avobenzone by the different quencher structures. Representative results and structures are shown in Figure 2. Acrylates Copolymer ingredient incorporates the most effective quencher structures from this study.

The effectiveness of Acrylates Copolymer was demonstrated in a sunscreen formulation (Figure 3). By making avobenzone more stable and efficient, Acrylates Copolymer provides formulations with much better sun protection performance.

Protecting UV filters against ROS generation: increase safety and effectiveness

Semiconducting metal oxides such as TiO_2

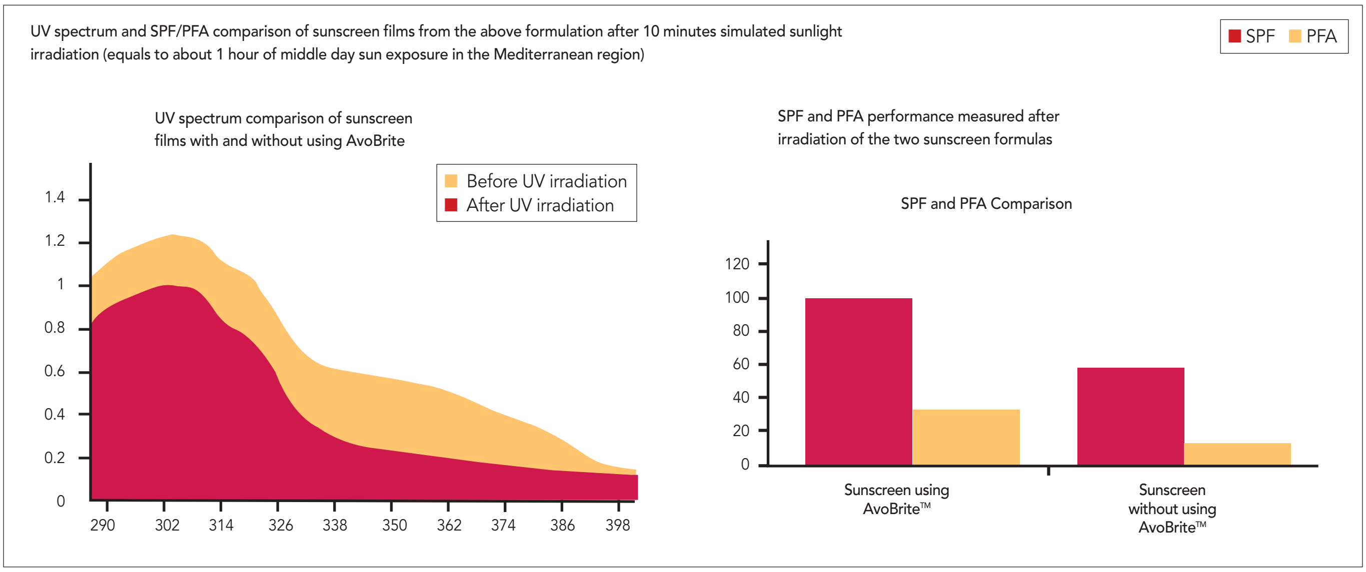


Figure 3: Sunscreen formulation with and without using AvoBrite and their performance comparison.

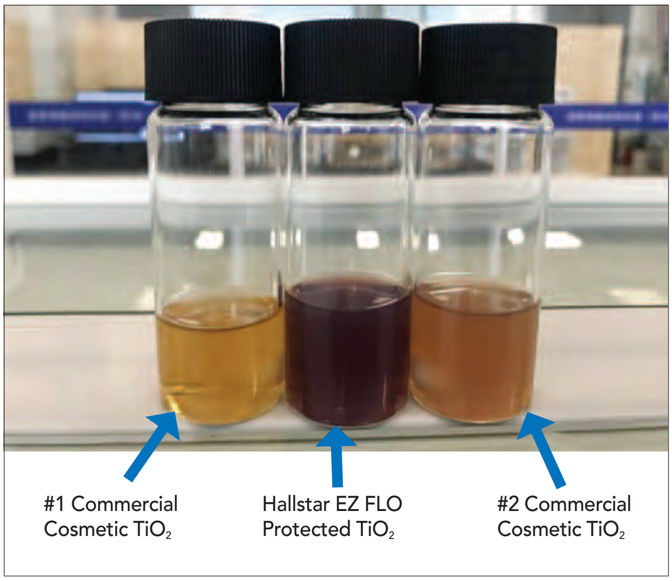


Figure 4: DPPH solutions of different TiO_2 samples after sun exposure.

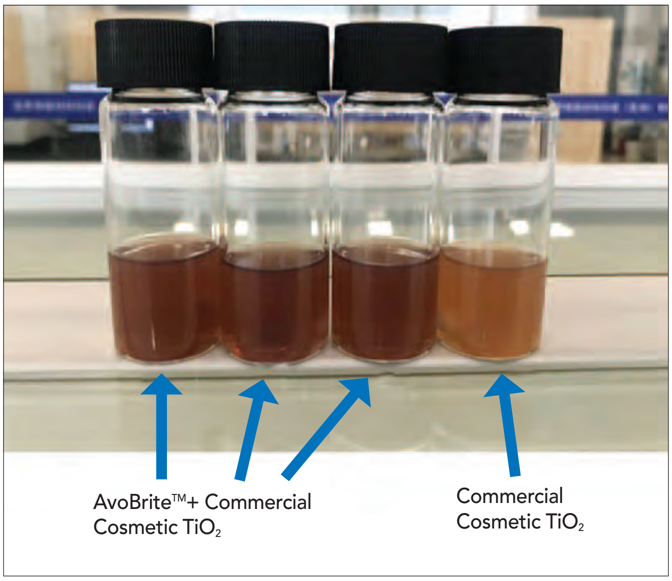


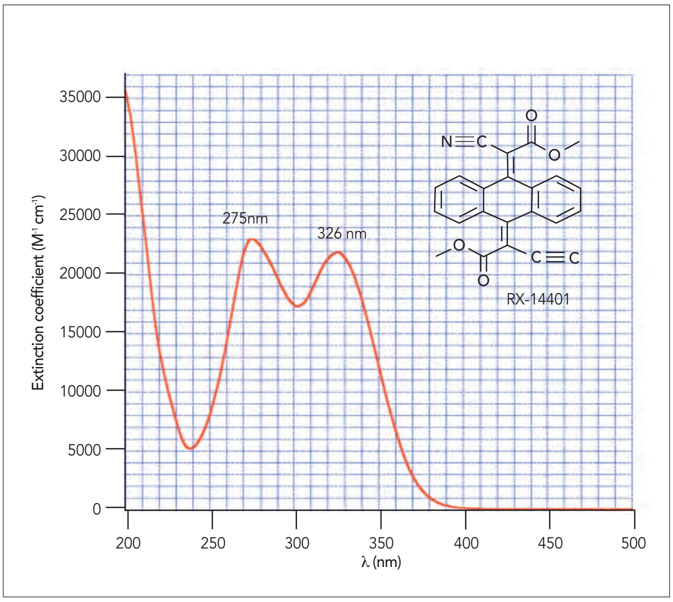
Figure 5: DPPH solutions of a commercial TiO_2 with and without AvoBrite protection after being exposed to the sun.

and ZnO absorb UV light because of electrons hopping between the valance band and the conduction band. When excited by UV light, these metal particles become photosensitisers; they transfer their energy to oxygen and generate ROS. Such ROS can then decompose large organic molecules. For example, TiO_2 particles exposed to sunlight or UVR have been used in self-cleaning sprays for glass surfaces and to disinfect contaminated water by killing germs. Therefore, TiO_2 particles used for personal care must be carefully treated to minimise their photosensitivity. We discovered that current commercial treatments for cosmetic grade metal oxides were not thorough enough to eliminate their photosensitivity. Hallstar photostabilisers, on the other hand, can provide further protection to these mineral filters, eliminating photo-generated ROS.

To test the efficacy of Hallstar photostabilisers, we used the DPPH assay to detect ROS. DPPH is the abbreviation for 2,2-diphenyl-1-picrylhydrazyl, a dark-coloured crystalline powder composed of stable free radicals. DPPH is commonly used to monitor chemical reactions involving radicals; most notably, it is a common antioxidant assay. This is because DPPH is both a radical and a trap ('scavenger') for other radicals. Due to its strong absorption band centred at about 520 nm, the DPPH radical has a deep violet colour in solution, and it becomes colourless or pale yellow after reacting with another radical or ROS. In other words, as more ROS are generated, more DPPH molecules are neutralised by the ROS, and the solution becomes more yellow than violet in colour. Therefore, the number of initial radicals generated can be counted from the change in the optical absorption at 520 nm.

Figure 5 displays DPPH solutions of three different TiO_2 samples after 10 minutes of natural sun exposure. Both commercial cosmetic TiO_2 samples were obtained from very reputable ingredient suppliers, and both generated enough free radicals derived from ROS that their DPPH solutions turned pale yellow. The Hallstar EZ-FLO TiO_2 samples were protected with Hallstar photostabilisers, and its DPPH solution remained deep violet, indicating no significant ROS/free radical generation. Hallstar photostabilisers effectively protected TiO_2, preventing it from generating ROS.

In a subsequent experiment, we added Acrylates Copolymer to one of the commercial cosmetic TiO_2 samples. After sun exposure, we observed that the solutions with Acrylates Copolymer were darker in colour, indicating that Acrylates Copolymer can effectively protect the



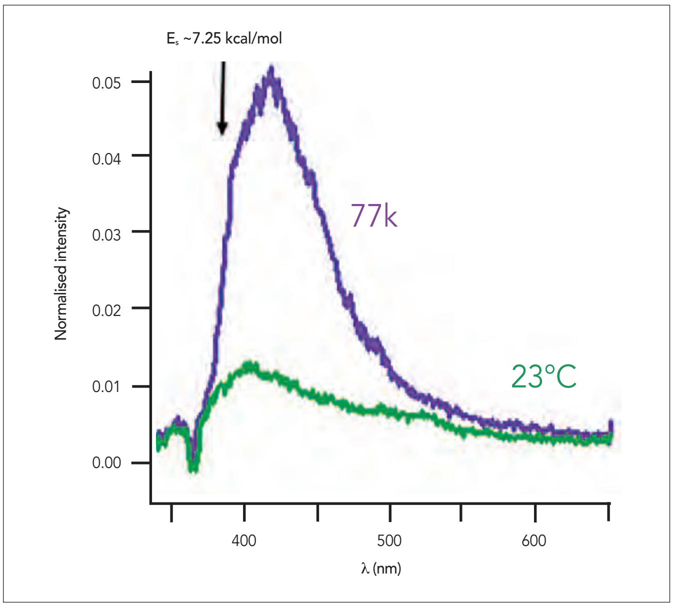


Figure 6: UV-visible absorption spectrum of a typical Micah compound, RX-14401

Figure 7: Luminescence spectrum of

RX-14401.

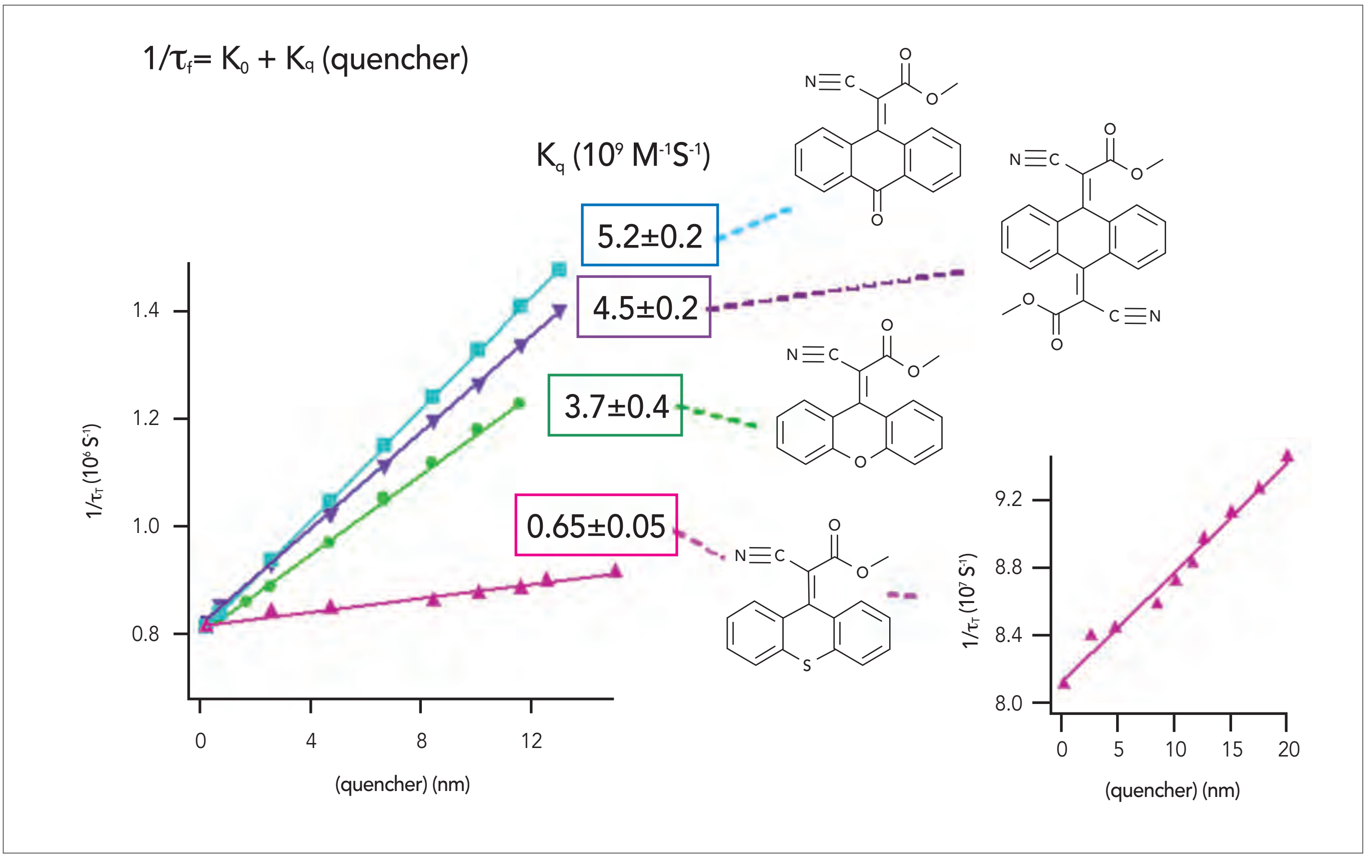


Figure 8: Determination of the bimolecular quenching rate constants kq of quenching of PPIX fluorescence (singlet states) by the Micah compounds using PPIX fluorescence decay traces at different Micah concentrations. Inverse fluorescence lifetime vs. quencher (stabiliser) concentration.

commercial TiO_2 product and prevent ROS generation. Based on this observation, we developed our series of Hallstar EZ–FLO mineral dispersions.

Protecting skin chromophores against ROS generation: the ultimate solution to photoageing— Micah technology

Current available technologies for combating solar energy-inflicted ageing processes can be classified into two families:

Blocking or shading: This family is exemplified by present-day sunscreen products, where absorbing compounds (filters) are applied onto skin to block some of the harmful energy. This essentially creates a shade to shield the skin from solar radiation. But this approach has two fundamental defects. First, the quality of the shading is highly dependent on the quality of the blocking layer established on the top of the skin, which can be influenced by many variables, making this technology far from foolproof. Second, shading from visible light is not cosmetically feasible. Any material that is capable of blocking energy in the visible spectrum will itself be coloured. To block all wavelengths of visible light, a product's colour would essentially have to be black.

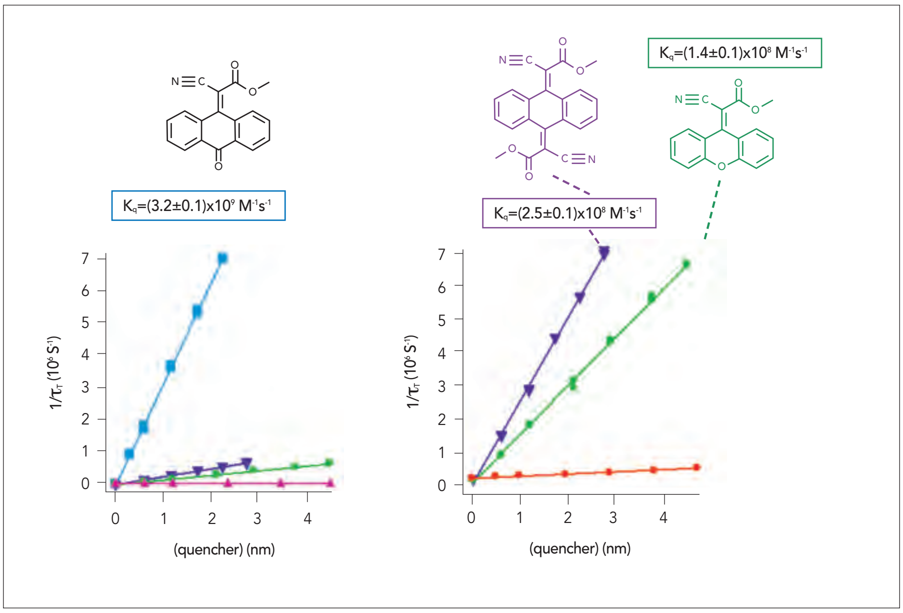


Figure 9: Determination of the bimolecular quenching rate constants kq of quenching of PPIX triplet states by Micah compounds using PPIX triplet absorption decay traces monitored at 440 nm and different Micah concentrations. Inverse triplet state lifetime vs. quencher concentration. PPIX triplet states in deoxygenated acetonitrile solutions were generated by pulsed laser excitation (532 nm).

Neutralising or fire-fighting: Antioxidants work by this mechanism. In this approach, the aftermath of solar energy assault is addressed. Antioxidants are employed to neutralise the harmful reactive species produced after skin is irradiated by the sun. To perform this neutralisation, antioxidants must be fairly reactive and sensitive, making their application challenging and their long-term performance unpredictable.

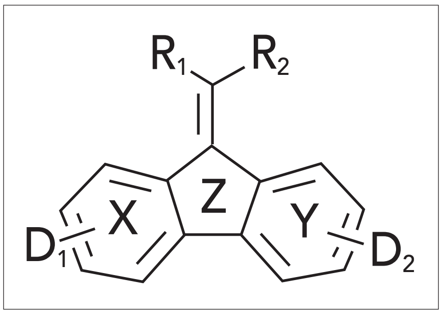
Hallstar's technology takes a completely different approach. Micah compounds were designed to quickly and effectively resolve energy-rich components in the skin immediately after solar irradiation; they return these components to their stable ground states and preventing all harmful consequences such as ROS generation. Micah compounds are extremely stable at both ground states and excited states. In addition, they can rapidly and efficiently return to ground states from energy-rich states via nonradiative decay pathways.

Micah compounds are a family of conjugated, fused polycyclic molecules containing a substituted ethylene double bond with Chemical Structure 1.

Micah compounds absorb in the UV region due to the extended conjugation in their structure. Because the substituted ethylene group is crowded, the molar extinction coefficient of Micah material is lower than those of most conventional UV filters. At a usage level of 1% and below, Micah compounds have a negligible contribution to the UV absorption of a formulation, and they do not absorb visible light. The UV absorption spectrum of the Micah compound with the strongest absorption, RX-14401, is shown in Figure 6.

Luminescence data in ethanol was recorded on RX-14401 (Fig 7). Based on this data, the singlet excited state energy of RX-14401 is about 72.5 kcal/mol.

Micah compounds, as exemplified by RX-14401, stop the generation of ROS by efficiently resolving the excited state energy of common solar energy absorbers (such as PPIX). This process is based on an electron transfer mechanism rather than the traditional energy transfer mechanism because the energy level of RX-14401 is higher than that of PPIX. Experiments below were carried out at irradiation wavelengths in the visible region where RX-14401 shows no absorption.



Chemical structure 1.

Micah compounds effectively quench the excited state energies of PPIX's singlet and triplet states. The reaction constant of several Micah compounds quenching the singlet states of PPIX is shown in Figure 8.

The reaction constant of several Micah compounds quenching the triplet states of PPIX is shown in Figure 9.

As a result, Micah compounds effectively stop the generation of singlet oxygen ($^1O_2$) derived from solar irradiation of the PPIX chromophore as shown in Figure 10.

Furthermore, we have conducted cell studies (*ex vivo* and *in vivo* skin studies) that validate Micah's efficacy in stopping skin photoageing. It was consistently found that Micah can eliminate the root causes of skin photoageing at relatively low (<0.5%) use levels.

Conclusion

Hallstar has pioneered photostabilisation technology for decades. We have thoroughly researched the chemistry and physics of this process. Because of this work, we have commercialised products aimed at protecting photolabile UV filters from decomposition and shielding photosensitive UV filters from generating ROS. Applying Hallstar photoprotection technology will allow formulators and brands to develop the most robust and broad-spectrum sun protection and anti-ageing products in the world. Micah, our revolutionary anti-ageing technology based on preventing skin photosensitisers from generating any ROS, has been shown to effectively eliminate the root cause of photoageing.

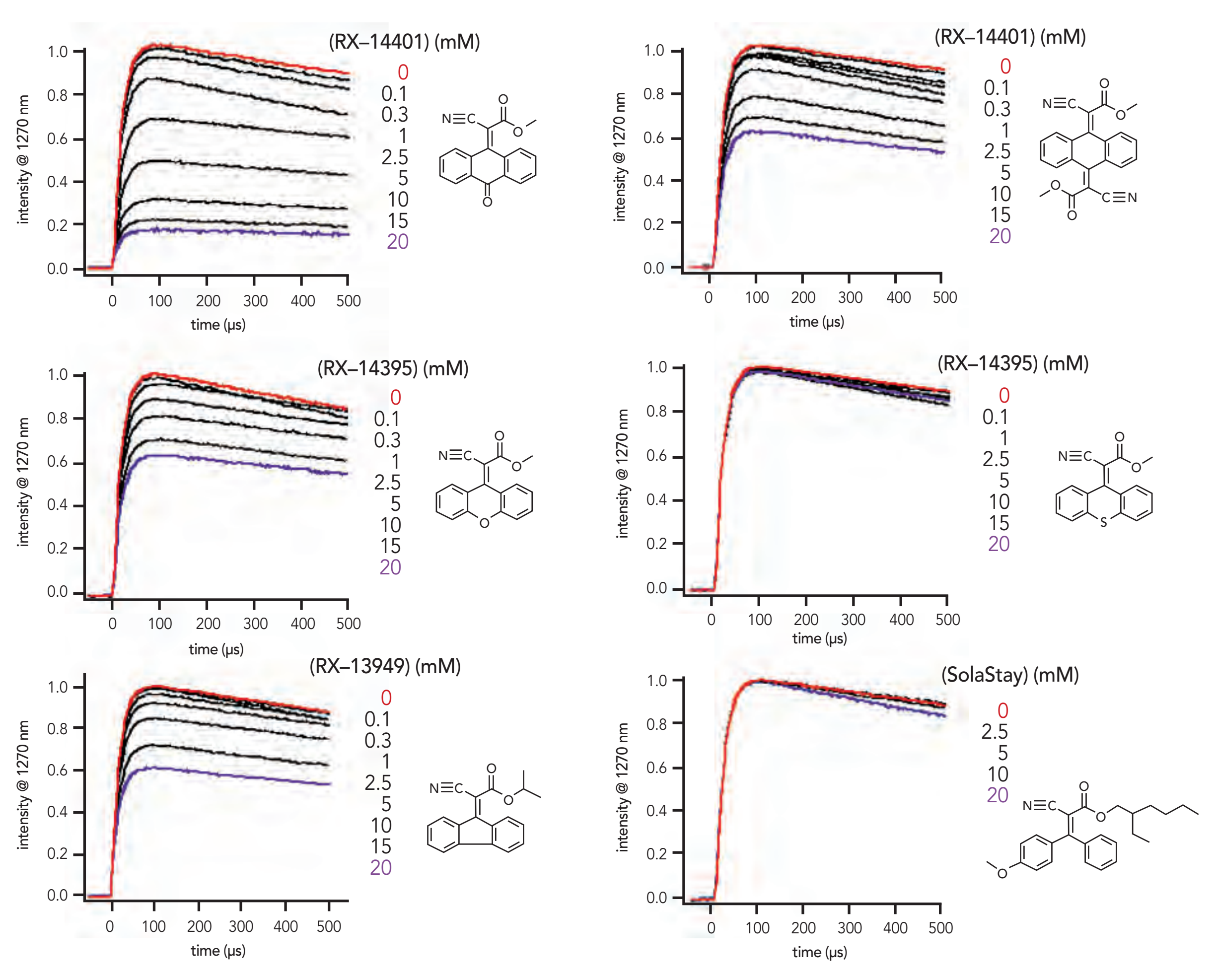


Figure 10: Singlet oxygen phosphorescence traces monitored at 1270 nm generated by pulsed laser excitation at 532 nm of MePPIX (17 μM) in air saturated CDCl3 solutions in the absence (red) and presence of variable amounts of Micah compounds