Hong Kong J. Dermatol. Venereol. (2007) **15**, 118-127

Review Article

Factors affecting the clinical efficacy of sunscreens

影響防曬產品功效之因素

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The efficacy of a sunscreen to protect the skin against the various detrimental effects of ultraviolet radiation (UV) depends on (1) its protection spectrum; (2) photostability of the product; and (3) how it is applied. Ideally, a sunscreen should provide adequate protection (depth) across the whole of the UV spectrum (breadth), including UVAI. Labelling of UVA protection is not universal and different definitions are used with the Persistent Pigment Darkening (PPD) method being the most popular. Photoinstability is a factor which may affect the efficacy of sunscreens especially in the UVA range. Newer UVA filters are now available which are photostable. Sunscreens should be applied at a thickness of 2 mg/cm^2 to achieve the stated protection. Unfortunately, sunscreens are often applied at much lesser amounts resulting in drastic reduction of the level of protection.

防曬產品能否達到保護皮膚免受日光帶來的種種傷害取決於：（1）防曬產品能否對紫外線光譜提供全面的覆蓋，（2）經日照後的穩定性，及（3）塗抹是否足夠。理想的防曬產品應能對紫外線全個光譜，包括對長波UVAI，都起足夠的阻隔性。現時防曬產品對紫外線A波的保護性未有劃一的測試及標籤方法；最常採用的是「持續性色素增深」的釐定方法。很多防曬產品經日照後都會出現不穩定的情況，尤其令對紫外線 A 波的保護性減低。不過近年來已有新的成份提供日照穩定的紫外線 A 波阻隔。使用防曬產品時塗抹的厚度應有每平方厘米 2 毫克，以達至標籤上的保護效果，不過大多數人都塗抹不足，令保護度驟降。

Keywords: Persistent pigment darkening, sunscreen, ultraviolet

關鍵詞：持續性色素增深，防曬產品，紫外線

Introduction

Sunscreens were first developed in the 1920's to enable people to stay longer in the sun without painful sunburns. With increasing knowledge of the detrimental effects of solar radiation, sunscreens now are also expected to protect against skin cancers, sun-sensitive dermatoses, photoaging and pigmentation. How successful sunscreens can achieve these objectives depends not only on the product itself but also on compliance. This review aims to discuss the factors affecting the effectiveness of sunscreens including issues of UVA (Table 1) protection and photostability.

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Table 1. Commonly used abbreviations in photoprotection

Abbreviation	Description
UVR	Ultraviolet radiation
UVB	Ultraviolet B (290-320 nm) (some authorities also use 280 nm as the lower cut-off)
UVA	Ultraviolet A (320-400 nm). UVA accounts for >95% of UVR reaching the earth's surface
UVAII	Short-wave ultraviolet A (320-340 nm)
UVAI	Long-wave ultraviolet A (340-400 nm)
MED	Minimal erythema dose or lowest dose that induces minimum perceptible erythema with definite borders

Importance of UVA protection

The harmful effects of solar radiation on the skin are primarily due to UVB and UVA. As erythema (=sunburn) is mediated mainly by UVB,[1] the early sunscreens were formulated for UVB protection. However, with increasing recognition of the skin damaging effects of UVA, including those by UVAI, it is important for sunscreens to protect against the whole UV spectrum.

Carcinogenicity potential of UVA

While UVB is the main cause for epidermal non-melanoma skin cancers, UVA may be a more important carcinogen for malignant melanoma.[2] The mechanisms with which UVB and UVA induce cancers may be different. Whereas UVB causes direct DNA damage in the epidermal layer, UVA, especially the longer UVAI, can indirectly damage DNA by the generation of reactive oxygen species (ROS).[3] Moreover, UVA has been shown to have a stronger immunosuppressive effect than UVB.[4] This compromises the skin's ability to repair damaged DNA and may also account in part for the observation that UVA is more potent than UVB at inducing delayed mutations.

Photoaging

Clinical signs of photoaged skin include wrinkling, roughness, dryness, laxity, telangiectasia, irregular pigmentation and a variety of benign, premalignant and malignant neoplasms. The histologic hallmark for photoaging is dermal elastosis with accumulation of abnormal elastin and reduction of normal collagen fibre.

Both UVB and UVA cause photoaging. However, UVA, with its longer wavelengths, penetrates deeper and causes more damage in the dermis than UVB.[5,6] In the dermis, UVR-generated ROS triggers inflammation and lead to proteolytic activation and abnormal extracellular matrix turnover that result in increased degradation of collagen and elastic fibres.[7] Even low doses of UVA, when repeated, cause considerable photoaging.[6,8]

Pigmentation

Darkening of skin due to UVR can be even (tanning) or irregular (hyperpigmented lesions). UVA is much more effective at inducing pigmentation than UVB. UVB-induced tanning is delayed and it only occurs after erythema has taken place. UVA-induced tanning involves three distinct phenomena: immediate pigment darkening (IPD), which is due to oxidation of pre-existing melanin and precursors, persistent pigment darkening (PPD), and delayed pigmentation. Delayed pigmentation by UVA involves formation of new melanin and only becomes evident after 2 to 3 days. It occurs after high dose erythemogenic UVA exposure or after repeated sub-erythemogenic UVA doses.[1,9]

Mechanisms of sunscreens: clinical implications

Sunscreens work by reflection, scattering or by absorbing and converting the solar energy into a

harmless form. Sunscreens are classified into organic and inorganic.

Organic (chemical) sunscreens

Organic filters absorb UVR and the energy is converted and dissipated through different ways. Molecular vibration, such as cis/trans insomerization or intermolecular H-transfer, is the preferred mode. In contrast, chemical reactions which lead to formation of new molecules may decrease the effectiveness of the sunscreen, and may even generate potential harmful photoproducts like ROS.[10-12] Whether these ROS cause damage depends on whether the UV filter can penetrate and reach the viable layers of the skin.[10]

Inorganic (physical) sunscreens

Titanium dioxide (TiO_2) and zinc oxide (ZnO) are the only inorganic filters. They work mainly by reflecting and scattering UVR. They provide broad spectrum coverage but thick coating is necessary for adequate protection and this is often cosmetically unacceptable due to the opaqueness. By decreasing particle size into micronized from (10-50 nm), as compared to 200-500 nm of non-micronized form, opaqueness is reduced due to less scattering of light. However, micronizing decreases the protection against longer UVA. Compared to microfine TiO_2, microfine ZnO offers better protection against UVAI (up to 380 nm).[13]

It is of interest to note that apart from reflecting and scattering, inorganic sunscreens can also absorb UVR. ROS are formed after TiO_2 is exposed to UVR.[11,12] So inorganic sunscreens may not be as inert as one would think.

Factors affecting the clinical efficacy of sunscreens

How well a sunscreen can protect the skin against the harmful effects of the sun depends on:

- The breadth and depth of UV protection by the sunscreen
- The stability of the sunscreen upon exposure to UVR
- User factor: how well the sunscreen is applied

Breadth and depth of UV protection

As both UVB and UVA have deleterious effects to the skin, sunscreen products should ideally provide sufficient protection (depth) across the whole spectrum of 290-400 nm (breadth). Although all sunscreen products offer good protection in the UVB range, their UVA protection can be very varied.[14,15] Sun Protection Factor (SPF) reflects only the UVB, and not the UVA protection level of a product.

UVB protection: sun protection factor

SPF was first designed to indicate the level of protection offered by a sunscreen against acute sunburn. SPF is defined as the ratio of the dose of UVR (290-400 nm) required to elicit minimal erythema (MED) on sunscreen-protected skin (applied at 2 mg/cm^2) to the MED of unprotected skin.[16]

$$\text{SPF} = \frac{\text{MED of sunscreen-protected skin}}{\text{MED of non-protected skin}}$$

As UVB is 1,000 times more erythemogenic than UVA, SPF reflects primarily the acute protection against UVB but gives little indication of a product's protection against UVA.

UVA protection

Currently, there is no single universally accepted method to measure and indicate UVA protection. It is not practical to use erythema as an endpoint as for SPF, as a very long exposure time will be required to deliver enough energy by solar simulators to evoke an erythema response in the UVA spectrum. Therefore, other endpoints are used to measure UVA protection.

Immediate pigment darkening (IPD)

IPD refers to the *in-vivo* response of bluish-grey discolouration that develops immediately following

exposure to UVA. It is due to the photooxidation of a melanin precursor.[17] The main limitation of this method is that the darkening fades so quickly that it is difficult to obtain a reliable reading.

Persistent pigment darkening (PPD)

PPD is at present the most widely used method to measure UVA protection. PPD refers to the brownish-grey skin discolouration that follows IPD and is stable between 2 and 24 hours after exposure. An additional advantage is that as PPD requires UVA doses of greater than 10 J/cm^2, which is much higher than that required for IPD, it means the stability of sunscreens is also challenged during PPD testing.[18]

The PPD method has been officially adopted by the Japan Cosmetic Industry Association (JCIA) for labelling UVA protection since 1996. PA (Protection Grade of UVA) + corresponds to a UVA protection factor between two and four, PA++ between four and eight, and PA+++ greater than eight.

The protection factor for UVA (PFA)

As with PPD, reading is done at 24 hours after irradiation. The end point is either erythema or darkening. The proposed advantage of this method over PPD is that subjects with type 1 skin can be included, as the IPD or PPD is difficult to invoke in this population.[19]

Critical wavelength (λc)

This is an *in vitro* method to measure the UV absorbance of a sunscreen on a wavelength-by-wavelength basis from 290 to 400 nm. The critical wavelength is defined as the wavelength below which 90% of sunscreen's UV absorbance occurs (Figure 1). This method gives some indication of the "breadth" of UV protection (Figure 2).

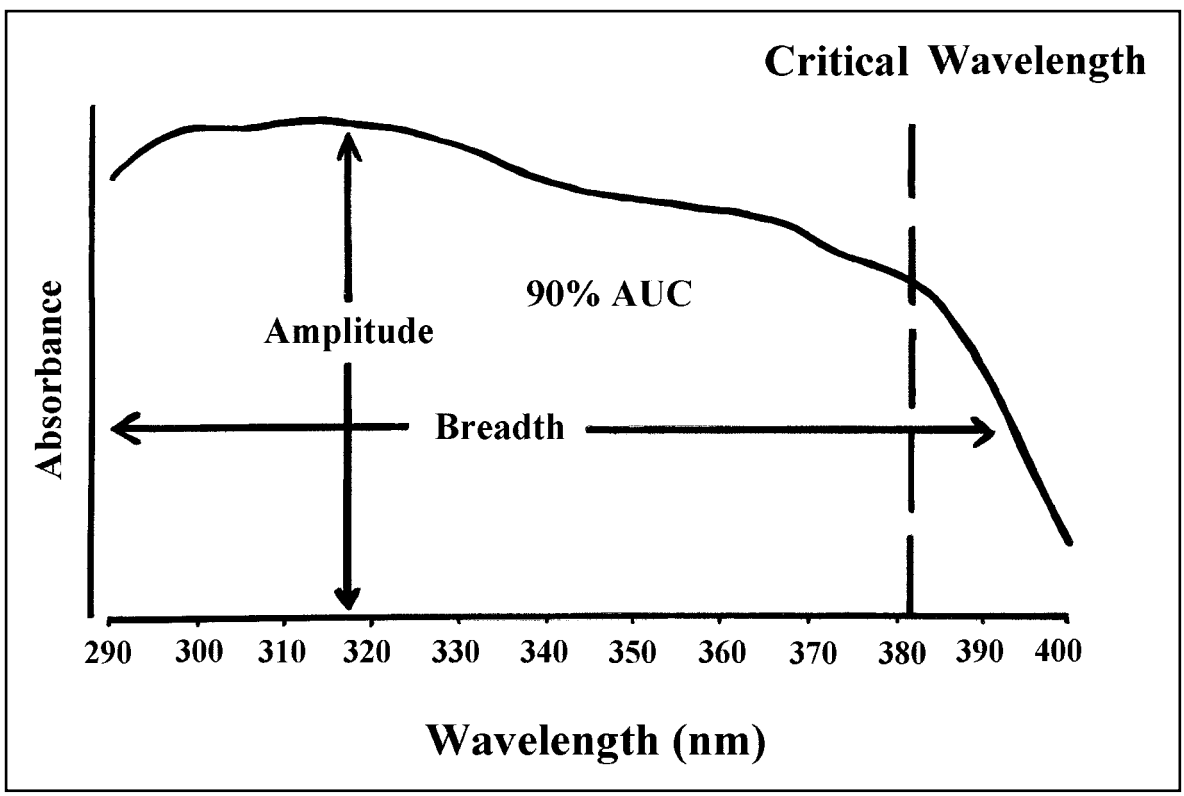

Figure 1. Critical wavelength is the wavelength below which 90% of the area under the whole absorption spectrum from 290 to 400 nm falls. The shape of the absorption spectrum is independent of application density.

The disadvantage of the critical wavelength is that it does not show the "depth" of protection. Two sunscreen products having similar critical wavelengths can also have very different absorbance curves (Figure 3). The critical wavelength of a sunscreen product is a result of the combination of UVB and UVA filters. If a sunscreen product contains only a single UVA filter, by increasing the concentration of the filter will not affect the critical wavelength of the product. However, the critical wavelength will decrease if a UVB filter is added into this product.[15,20]

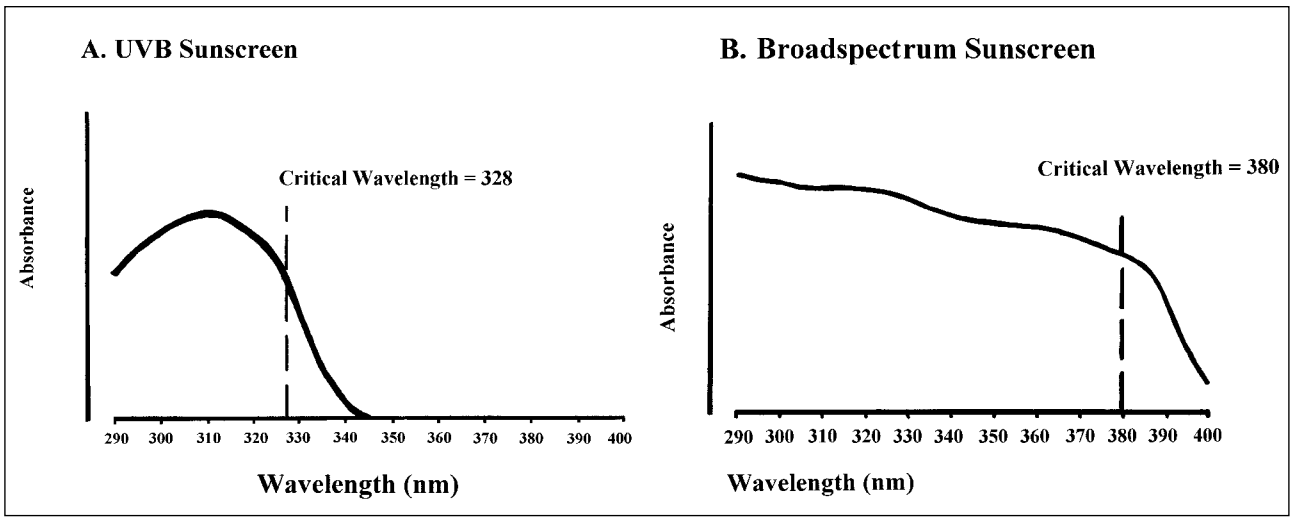

Figure 2. Absorption spectra and critical wavelengths for UVB (A) and broad-spectrum (B) sunscreen products. Shaded areas represent 90% of the area under the absorption curves from 290 to 400 nm.

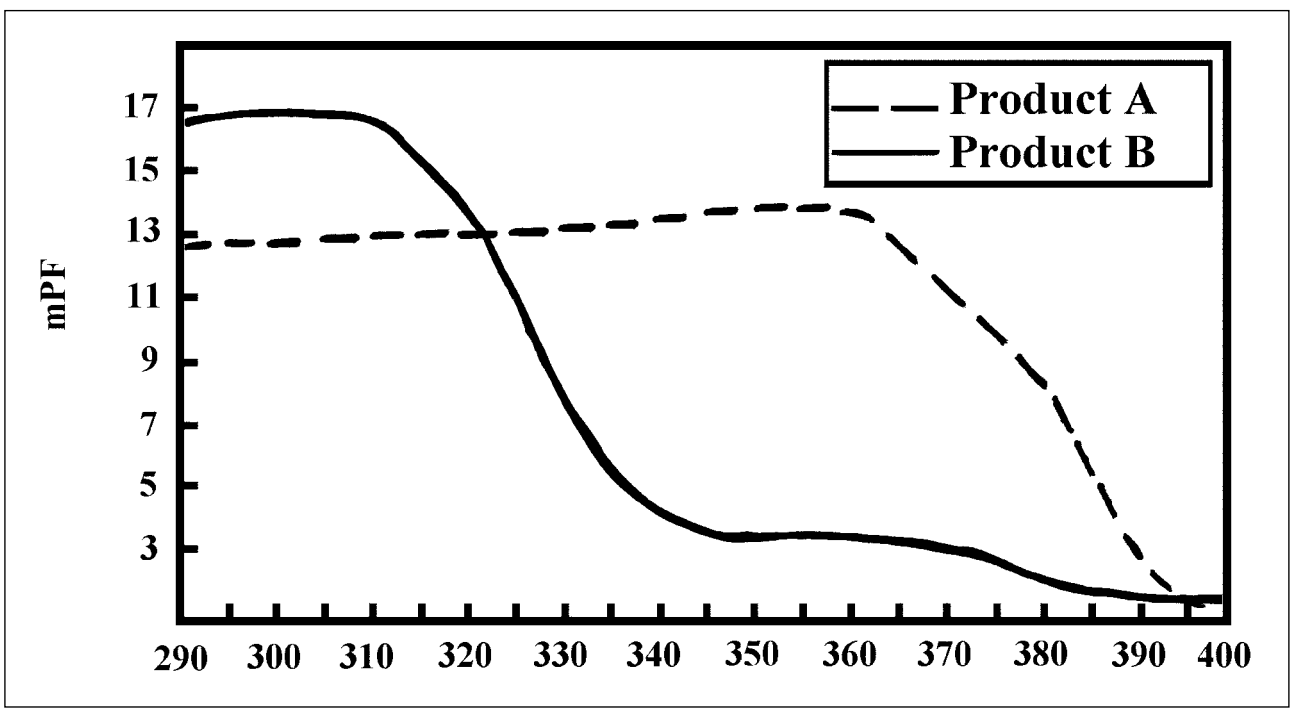

Figure 3. Absorption spectra of 2 sunscreens. The critical wavelengths of the 2 products are similar: 379 nm for product A and 372 nm for product B. However, it is clear that product A offers much better protection against UVA than product B.

The critical wavelengths and peak absorbance wavelengths of some common UV filters are shown in Table 2.

Immune protection factor (IPF)

Immune protection factor is increasingly looked into as a possible performance indicator for sunscreens. The methods now used are based on the fact that UVR suppresses the induction and elicitation arms of the contact hypersensitivity (CHS) and delayed-type hypersensitivity (DTH) responses. The methods are not yet standardised and are complicated and cumbersome.[21]

$$IPF = \frac{ID_{50} \text{ or MISD of sunscreen protected group}}{ID_{50} \text{ or MISD of non-protected group}}$$

MISD = minimal immunosuppressive dose
ID_{50} = 50% immunosuppressive dose

As UVA plays a more important role than UVB in solar induced immunosuppression, IPF may be a feasible indicator for UVA protection.[4,21]

UVA protection: legislative issues

UVA protection level labelling is not mandatory in most countries. The Food and Drug Administration (FDA) of the United States has not issued any concrete guidelines regarding UVA protection for sunscreens. Products are allowed to claim "broad spectrum protection" or "UVA radiation protection" as long as they (1) "contain sunscreen active ingredients with absorption spectra extending to 360 nm or above", and (2) "that demonstrate meaningful UVA radiation protection using appropriate testing procedures to be developed".[16]

The American Academy of Dermatology (AAD) recommends that for a sunscreen to qualify as

Table 2. Critical and peak absorption wavelengths of some common UV filters

UV filter	Other name(s)	Critical wavelength (nm)	Peak absorption wavelength (nm)
2- phenylbenzimidazole -5-sulfonic acid	Ensulizole	324	310
Octyl salicylate	Octisalate	327	307
Oxybenzone	Benzophenone-3	361	288, 325
Homosalate		328	306
Octyldimethyl PABA	Pandimate O	330	311
Ethylhexyl methoxycinnamate		337	285
Octyl methoxycinnamate	Octinoxate	339	311
Octocrylene		356	303
Butyl methoxy dibenzoyl methane	Avobenzone, Parsol® 1789, Neo Heliopan® 357, Uvinul®	383	360
Terephthalylidene dicamphor sulphonic acid	Mexoryl® SX		345
Drometrizole trisiloxane	Mexoryl® XL		303, 344
Bis-ethylhexyloxyphenol methoxyphenyl triazine	Tinosorb® S	370	343
Methylene bis-benzotriazolyl tetramethylbutylphenol	Tinosorb® M	386	361

"broad spectrum", other than providing good UVB protection (SPF >15), the critical wavelength should be >370 nm, and it should provide a minimum of 4-fold protection against UVA using in-vivo PPD or PFA method. AAD also recommends that an increase in SPF must be accompanied with a proportional increase in UVA protection.[22]

The stability of the sunscreen upon exposure to UVR

Photoinstability is a common problem with sunscreens. Many products lose their effectiveness in the UVA range by more than 50% upon sun exposure.[20,23-25] Ethylhexyl methoxycinnamate, oxybenzone (benzophenone-3), octyl methoxy-cinnamate and especially butyl methoxy dibenzoyl methane (avobenzone/Parsol® 1789) are all known to be photolabile.

It is worth noting that several organic UVA filters that are photostable are now available: terephthalylidene dicamphor sulphonic acid (Mexoryl® SX), drometrizole trisiloxane (Mexoryl® XL), bis-ethylhexyloxyphenol methoxyphenyl triazine (Tinosorb® S) and methylene bis-benzotriazolyl tetramethylbutylphenol (Tinosorb® M). The absorbance curves of these four filters are shown in Figures 4 and 5. These filters are developed in Europe and to date, only Mexoryl® SX has been approved by the U.S. FDA.

The combination of sunscreen filters affects the final photostability of a product. Octocrylene has a photostabilising effect on avobenzone, oxybenzone and octyl methoxycinnamate. Tinosorb® S stabilises avobenzone and ethylhexyl methoxycinnamate while Tinosorb® M stabilises octyl methoxycinnamate and avobenzone. Avobenzone is stabilised by octocrylene but not in the presence of ethylhexyl

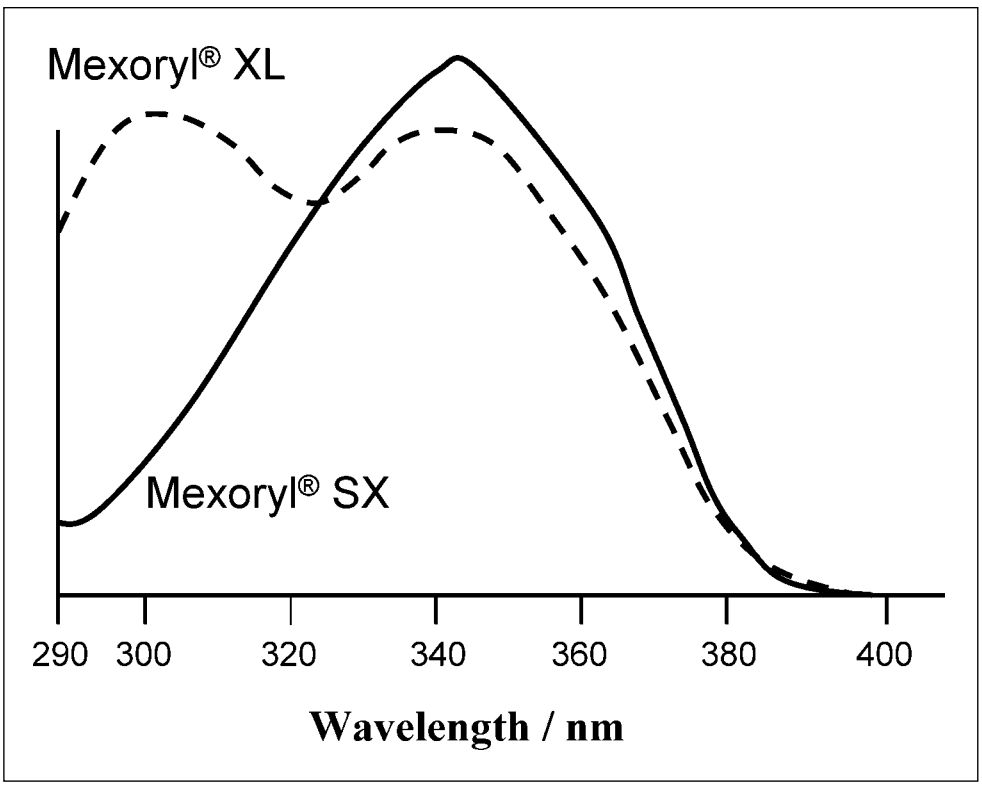

Figure 4. Absorption spectrum of terephthalylidene dicamphor sulphonic acid (Mexoryl® SX) (——) and drometrizole trisiloxane (Mexoryl® XL) (------).

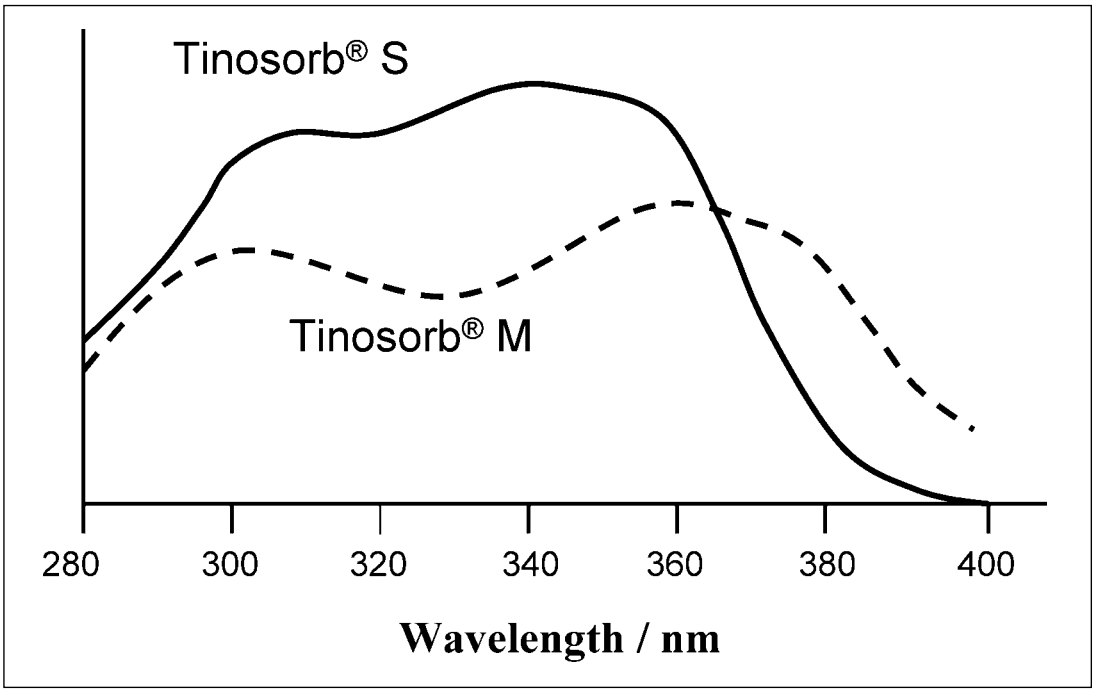

Figure 5. Absorption spectrum of bis-ethylhexyloxyphenol methoxyphenyl triazine (Tinosorb® S) (——) and methylene bis-benzotriazolyl tetramethylbutylphenol (Tinosorb® M) (-----).

methoxycinnamate. Avobenzone also destabilises ethylhexyl methoxycinnamate and octyl methoxycinnamate.[20,24-26] So before we have a reliable indicator for photostability, consideration should be given to the characteristics of the UV filters used and their combination when choosing sunscreens.

User factor: how well sunscreen is applied

Compliance is a major determinant for the efficacy of sunscreens. Inadequate application is probably the most important reason for sunscreen failure.

How much sunscreen should be used?

The recommended thickness to apply is 2 mg/cm^2, which is the thickness used for SPF and PPD testing. This will translate into using about 1.6 ml (around half-teaspoon) for the face and 35 ml for a single whole-body application.

Most people tend to apply less than the recommended amount, using 0.5 to 1 mg/cm^2. Applications are often uneven with missed areas. The SPF value of a sunscreen is exponentially related to the thickness applied. A sunscreen with a labelled value of SPF 16 may only give a protection at SPF 2 when applied at 0.5 mg/cm^2.[27]

It has been suggested that a SPF 30+ broad spectrum sunscreen should be used in tropical and subtropical areas as many sunscreens actually provide less protection than their labelled SPF, even at 2 mg/cm^2. Furthermore, a higher SPF sunscreen may partially compensate for the inadequate thickness of sunscreen applied.[28]

The act of rubbing in, as opposed to just applying to the surface of the skin, is found to reduce the final protection by sunscreens.[29]

When should sunscreen be reapplied?

Sunscreens should be reapplied after swimming,

vigorous sweating or rubbing of the skin. Labels on sunscreens usually recommend routine reapplication after 2 to 3 hours. However, it has been shown that increased protection can be obtained if sunscreens are reapplied soon after sun-exposure has begun. This may be due to the doubling of the resultant thickness of sunscreens or better coverage of the skin's uneven topography.[30]

Should sunscreens be used daily?
As it is now clear that even low dose UVR, including UVA, causes cumulative damage to the skin which can result in photoaging and carcinogenesis, daily protection of a broad spectrum sunscreen is recommended. Patients should understand that even on cloudy days when the sun does not "burn", there can still be substantial UVA reaching the earth's surface. UV index is weighted by the erythemal action spectrum and is biased towards UVB and does not represent the total UVR.

Topical antioxidants

Topical antioxidants are not classified as sunscreens but they are discussed here as they can mitigate the harmful effects of UVR. Systemic antioxidants may also play a useful role but will be outside the scope of the article.

Sunscreens are unlikely to block out UVA & UVB entirely, due to their less than complete spectral coverage especially for UVAI. Photostability issues and inadequate application further compromise the efficacy of sunscreens. ROS are generated in the skin by UVR, or even by sunscreens themselves. Although the skin possesses a natural antioxidant system, this may not be adequate in times of increased demand. Topical antioxidant therapy is a logical adjunct to sunscreens, especially as their reservoir effect inside the skin does not necessitate them to be physically on surface of the skin during sun exposure as with sunscreens.

Many topical antioxidants have been shown to be effective in neutralising the damaging effects of UVR. The best recognised ones are topical vitamin C and E. Other possible useful topical antioxidants include ferulic acid, coenzyme Q10 (ubiquinone), and green tea polyphenols.

Conclusion

Labelling of sunscreen products at present still has much to be desired especially concerning UVA protection and photostability. It is not sufficient for us just to tell our patients to "use sunscreens". They need to be counselled as to how to choose an effective, broad spectrum product and more importantly, how to use sunscreens properly to minimise photodamage.

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