

Chapter 14

An Overview of Physical (Particulate) Sunscreens

David Fairhurst

Abstract Skin is constantly assaulted by sun exposure and terrestrial solar ultraviolet radiation (UVR) is a major factor deleterious to our health. The most reliable approach to sun protection is to cover up the skin by using a thin film of a topical sunscreen formulation containing active chemical ingredients that absorb, scatter or reflect the incident UVR to reduce the direct penetration and effect of UV exposure. Physical (particulate) actives are very stable and benign. From a regulatory perspective, zinc oxide and titanium dioxide are the only ones universally allowed as sunscreen actives. The development of sunscreen formulations containing ZnO and TiO₂ requires knowledge of their optical properties as these dictate both the resulting aesthetics and the efficacy of the final sunscreen product and, thereby, acceptance by the user; these factors critically impact the economics of commercial sunscreen manufacturing and sales. The optical properties are uniquely related to the particle size (distribution) and particle morphology (e.g., surface area) of the two oxides. Precise measurement of these parameters is therefore a critical metric in formulating sunscreen products. X-ray disc centrifugation, acoustic attenuation spectroscopy and nuclear magnetic resonance relaxation are useful techniques that can be used to characterize fundamental properties of particulate suspensions at concentrations that are commercially relevant.

14.1 Introduction

For those not familiar with the topic under discussion in this chapter, it is perhaps instructive to first briefly review the issue of sun protection and the formulation of sunscreen products containing what are termed physical (particulate) sunscreen actives.

D. Fairhurst (✉)
Particle Sciences Inc, Bethlehem, PA18017, USA
e-mail: colloidman@atlanticbb.net

14.1.1 Ultraviolet Radiation and Sun Protection

Skin, the outermost defense against noxious stimuli, is constantly assaulted by environmental insults, most prominently sun exposure; sunlight is a part of our everyday life. However, while generally perceived as “good” and beneficial to our well-being, with the advent of our knowledge in cutaneous photobiology and photodermatology within the last 50 years, it has become evident that terrestrial solar ultraviolet radiation (UVR) has become a major factor deleterious to our health [3]. For convenience, the solar UV spectrum is arbitrarily divided into three bands; the UVA from 400 to 320 nm, the UVB from 320 to 290 nm and the UVC from 290 to 100 nm.

UVC

The UVC spectral band, is referred to as the germicidal band because it is erythemogenic, mutagenic and carcinogenic but is absent at the surface of the earth because it is absorbed and filtered by the stratospheric ozone layer. Hence, the heightened concern regarding depletion of this layer by chlorofluorocarbons, nitric oxides, halons, etc., since this will, inevitably, contribute to an increase in effects harmful to human life [70]. Although solar UVC does not currently constitute a risk to the general population, UVC is emitted from artificial sources [7] and can be hazardous in certain occupations such as arc welding.

UVB

UVB rays do pass through the ozone layer and are responsible for most of the effects induced by sun exposure such as sunburn (erythema), photoaging, skin cancer and immunosuppression [20]. UVB radiation values have increased, on average, more than 6 % annually since the early 1980’s [31]. Until fairly recently, the active ingredients used in the vast majority of commercial sunscreen products (see Sect. 14.1.2) absorbed primarily UVB radiation; they efficiently provided, thereby, high *sun protection factor* (SPF) products. Erythema (sunburn) is the most familiar manifestation of UVB exposure and the *minimal erythema dose* (MED) is used as a metric in the determination of the SPF number, as approved by the US Food and Drug Administration (FDA) [25].

The SPF is defined as the ratio of the time of exposure necessary to produce MED in sun-protected skin to that time for unprotected skin. However, the question of the appropriate *methodology* to determine the effectiveness of sunscreen products, as expressed by the SPF number, is of considerable international industry concern. European, American, Australian and Japanese sunscreen products compete in world markets but national marketing concerns, tradition and less than unanimous scientific opinion have hampered agreement on many aspects of significant testing details. Further, in the USA, sunscreen products are regulated as

drugs; in the EU they are considered to be cosmetics. Thus, there is a difference not only in the legal status of sunscreen products between the US and the EU but also in the number of chemical ingredients approved for use as sunscreen actives.

Although UVB-blocking sunscreens decrease the risk for development of non-melanoma skin cancer [59], paradoxically, since high-SPF sunscreen products prevent sunburn, their use allows for prolonged UVA exposure without a warning sign thus encouraging susceptible individuals to spend more time in the sun [27] leading to an increased risk of the development of melanoma skin cancer. Further, issues of photo- and nonphoto-induced toxicity and allergy/irritancy have been raised with some of the UVB sunscreen actives [66].

UVA

Unfortunately, until only fairly recently the UVA region was considered to be innocuous and of little concern to dermatologists. The importance of UVA radiation, which is much more abundant – at approximately 99 % of UVR – than UVB in natural light, is now apparent [13]. UVA radiation, although of lesser energy, penetrates the skin more efficiently and deeply than UVB [29] and we know now that, in contrast to UVB, UVA radiation constitutes a severe oxidative stress [69] that can lead to DNA mutations [8]. UVA is especially efficient for generating free radicals and many of the harmful effects produced by UVB radiation are induced by UVA radiation. Thus, it is clear that providing complete broad-spectrum protection (i.e., both UVB and UVA radiation) is paramount [16].

Sadly, the action spectra for UVA-induced phenomena (including photosensitivity dermatitis and melanoma) have yet to be specifically defined and so, currently, there is no consensus of an *in-vivo* assay to assess protection against UVA. A variety of methods has been described [43] and the FDA has recently made some proposals to address this very important issue [26].

14.1.2 Sunscreen Actives

The most reliable approach to sun protection *is to cover up the skin* by using a thin film of *topical sunscreen* formulations (with SPF values of 15 or higher) and they have become an essential armament in providing protection to human skin against acute and chronic adverse effects of UVR. Topical sunscreens contain *active chemical ingredients* that absorb, scatter or reflect the incident UVR; they reduce the direct penetration and effect of UV exposure. These actives are broadly classified as organic (chemical/soluble) or inorganic (physical/particulate).

Organic (Chemical/Soluble) Actives

This constitutes by far the largest category of commercially available sunscreen actives. These chemicals are generally aromatic compounds conjugated with a

carbonyl group and with typically an amine, or methoxyl, group substituted in the *ortho*- or *para*-position of the aromatic ring. They are (as mentioned earlier) primarily UVB-*absorbing* chemicals [55] and the vast majority are oil-soluble. Hence, the choice of the oily vehicle (solvent), when formulating a sunscreen product, is important; because of its polarity, it may modify the action of the sunscreens by shifting the absorption spectrum toward, or away from, the desired range [42, 58].

Since these actives absorb UVR, the absorbed radiation must be dissipated as either heat or light, or else be used in some chemical reaction. With the organic sunscreens this may result in the creation of reactive oxygen species (ROS) or photoproducts and this has led to questions regarding their photostability [6]. In most cases, the radiation simply is re-emitted at a longer wavelength. The skin, itself contains many compounds capable of such behavior; under radiation melanin, for example, produces free radicals [38]. Indeed, a key reason to use a sunscreen product is to “sacrifice” the extrinsic molecule (the sunscreen active) to spare the body’s own chromophores.

Currently, there are very few UVA-absorbing chemicals allowed for general use in cosmetics. Only one, avobenzone, has been approved for use in the USA. It absorbs in the longer UVA wavelengths (from 350 to 390 nm) but studies have shown that it rapidly degrades under solar radiation [12] and, moreover, as avobenzone degrades other sunscreen actives in the formula may also be destroyed [61]!

Because they have been solubilized in the carrier vehicle, the organic actives can be systemically absorbed into the skin. Long-term use and increased daily exposure to these chemicals will likely result in an increased incidence of adverse reactions such as allergenicity and toxicity [57].

Inorganic (Physical/Particulate) Actives

The incorporation of sunscreen actives into daily-wear products is beginning to push the existing organic (soluble) actives to their limit. Physical (particulate) actives offer additional flexibility in the formulation of broad-spectrum, high SPF products without the concerns associated with the organic actives.

Physical sunscreen agents comprise particles of a size that scatter, reflect and absorb solar radiation in the UV, visible and IR ranges. *Particulate* is generally accepted to describe any material that is insoluble in the chosen medium. Commonly recognized particulates include zinc oxide, titanium dioxide, talc, iron oxide, kaolin, bentonite, silica and mica. These physical sunscreens are very stable and benign [10, 30]. As insoluble particulates they lay on top of the skin and are not absorbed systemically; for example, application of a 40 % zinc oxide (ZnO) ointment has not been found to raise serum zinc level [14]. An important consequence of this is the lack of opportunity for direct contact with any meaningful cellular structures. For this reason, they are perceived as safer than the organic sunscreen actives. They are especially useful in UVR-sensitive patients and they do not cause photosensitization nor any photoallergic or contact dermatitis.

Ironically, particulates were amongst the first actives to be recognized; in an article in the first volume of the Journal of the Society of Cosmetic Chemists in 1947 [28] the author discloses the UV absorption spectrum for several metal oxides including ZnO and titanium dioxide (TiO₂). From a regulatory perspective, these latter two oxides are the only ones universally allowed as sunscreen actives and they account for almost all of the physical sunscreen actives used today because they are the two most effective materials in terms of UVR attenuation efficiency and are widely available; consequently, what is discussed in the section on characteristics is focused on them. The other particulates tend to be used as adjuncts to help increase the optical path length and so “boost” the SPF number, or as fillers, especially in colored products such as face powders and lipsticks.

14.2 Sunscreen Formulations

Although the cosmetic chemist has many types of delivery vehicle from which to choose – emulsions, oils, gels, sticks, mousses, aerosols and ointments – by far the most popular of all for sunscreens, the emulsion, offers almost unlimited versatility in meeting the primary market objectives of efficacy, aesthetics and cost parameters [62]. Although emulsions are the most popular delivery type, they are also the most difficult to stabilize, particularly at elevated temperatures [5].

There are two basic “varieties” of emulsions used to formulate sunscreen products: oil-in-water (O/W) and water-in-oil (W/O). The former are used for daily-wear products such as moisturizers, while the latter are virtually exclusively used for beach-wear products. The proper oil vehicle can enhance a sunscreen’s *substantivity* or ability to remain on the skin and be effective. Substantivity is of enormous importance because sunscreen products are used outdoors and many times in settings where abundant sweating and repeated immersion in water is common [35].

There are two basic “styles” of emulsions: lotions and creams. Lotions are more popular than creams owing to their easier spreadability on the skin and dispensability (from tubes, bottles, etc.). An emulsion is termed a cream or a lotion on the basis of its viscosity (resistance to flow). The exact point at which a lotion becomes a cream is quite arbitrary but lotions typically have viscosities below 50 Pa.s.

In order to produce a true broad-spectrum product, and especially one also having a high SPF value, a combination of two or more sunscreen actives with overlapping or complimentary attenuation spectra is necessary, no matter what variety or style of emulsion is used. Indeed, the design of a sunscreen formulation is quite complex and, in addition to the sunscreen actives, it typically can comprise 15 or more components (emollients, humectants, thickeners, etc.). Thus, it often requires several iterations to produce a stable, efficacious, safe, cost effective and elegant product.

14.3 Characteristics of Physical (Particulate) Sunscreens

The development of sunscreen products containing ZnO and TiO₂ requires knowledge of both their optical properties and their surface chemistry relative to the dispersion medium.

14.3.1 Optical Properties

Here, two separate aspects need to be considered:

1. The color strength (whiteness/opacity/hiding power) of the “film” applied to the skin. What is of concern here is light in the visible part of the spectrum (from about 400 to 720 nm). The particulate active should impart as little opacity as possible. Ideally, it should be transparent to the human eye.
2. The ability of this film to act as a sunscreen by attenuating (stopping) UV radiation (specifically from 300 to 400 nm) from reaching the skin.

The first is an aesthetic concern, the second is one of performance (e.g. SPF) but they are equally important for, without proper aesthetics (minimal whitening) no level of sunscreen performance is high enough because most persons will simply not use it. Both of these aspects are uniquely related to the particle size (distribution) and particle morphology (e.g., surface area) of the material.

14.3.2 Particle Size

Both ZnO and TiO₂ are commercially available in *pigmentary* and *microfine* grades. The pigmentary grades are used to provide opacity in, for example, paints and “whiteness” in paper. Microfine is also termed micronized, ultrafine or nanosize. By definition, micronized refers to a pigment that has been physically reduced to its given particle size by grinding or milling. Microfine is a term without a universally agreed meaning; it is used commercially to describe particles with claimed particle size (PS) anywhere from 20 nm to a few micrometers. This loose terminology has led to a great deal of confusion. It is the microfine grade that concerns us when using ZnO and TiO₂ as sunscreen actives. Figure 14.1 is a schematic illustrating the typical difference in particle size distribution (PSD) between *pigmentary* and *microfine* grades of TiO₂.

Light Absorption in the Visible Spectrum

The parameter that describes the scattering-absorption characteristic of a material is its *refractive index* (RI); though an oversimplification, this single number does

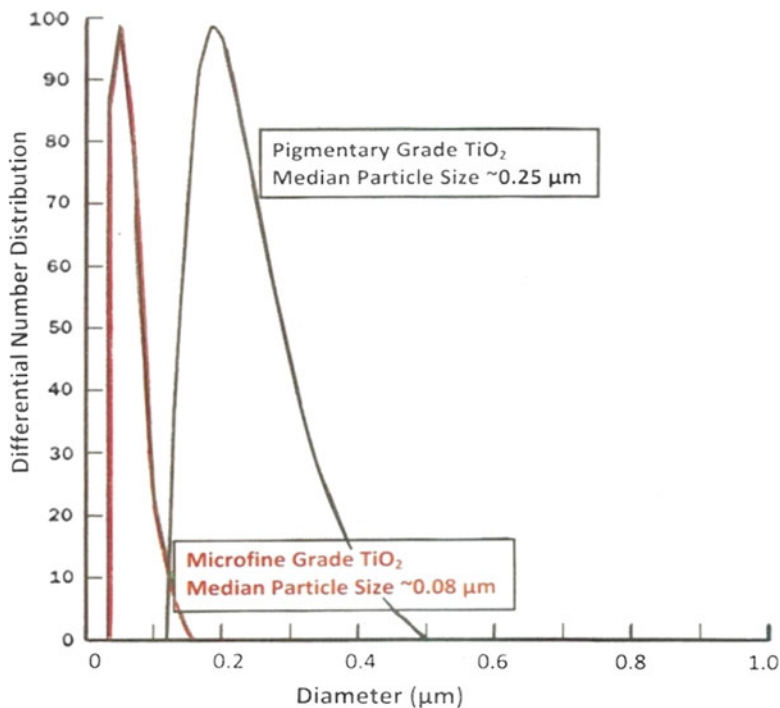


Fig. 14.1 Schematic of comparison of PSD for Microfine and Pigmentary grades of TiO₂

allow reasonable real-world predictions. Both ZnO and TiO₂ are white pigments. The actual “whiteness” of a suspension is a function of the ratio of the RI values for the material and its dispersion medium. The organic actives have RI values similar in magnitude (typically <1.5) to those of the oily vehicles in which they are solubilized. Although an emulsion will appear white in bulk, when it is spread as a layer onto skin and the water phase evaporates what is left is a thin film of the oil phase. Since the RI values are virtually matched, no matter what the concentration of organic active (and it can be as high as 30 % wt) the film will appear transparent. It is a much different situation for the physical particulates TiO₂ and ZnO; these materials have RI values of ca 2.4–2.8 and 2.01–2.03 respectively. The RI is an intrinsic property of a material and is, therefore, fixed. The particle size, however, can be chosen. As a rule of thumb, the scattering power of a material is highest when its PS is equal to about half the wavelength of the incident light. For monochromatic light this is straightforward. The problem is the visible spectrum which constitutes “white” light; it is not a single wavelength. Thus, there is no single optimum PS for a white pigment. Interestingly, the human eye has a peak response at about 560 nm (in the green portions of the spectrum).

The relation between particle size and scattering can be estimated using Lorenz-Mie theory [36] and is graphically illustrated in Fig. 14.2 for TiO₂ and ZnO using an integrated value for the wavelength of “white” light. The maxima in the two plots

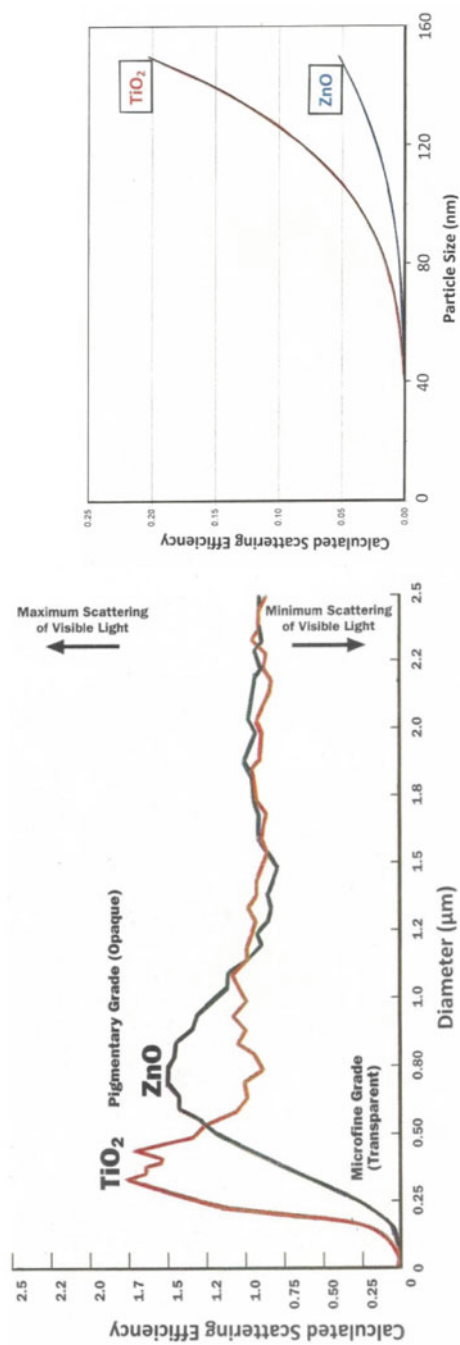


Fig. 14.2 Extinction efficiency against wavelength for aqueous suspensions of TiO₂ and ZnO; at right: graph expanded for small particle sizes

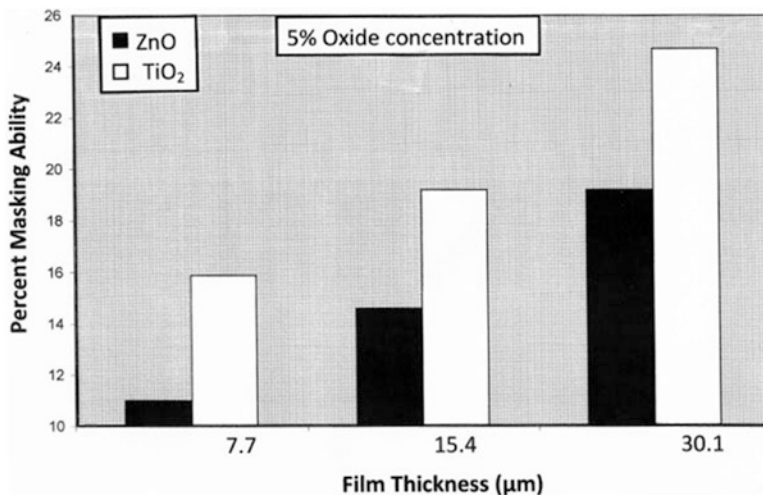


Fig. 14.3 Masking efficiency against film thickness for TiO₂ and ZnO

are the “sizes” where maximum scattering (i.e. highest opacity) will be obtained for the two materials. In other words, for the pigmentary grades the greatest hiding power occurs at something around mean sizes of 250 nm for TiO₂ and 750 nm for ZnO (see also Chaps. 2 and 12).

These theoretical calculations are based on oversimplified assumptions and it is not possible to derive a mathematical treatment in any rigorous form for the optical properties of an actual film such as that from a sunscreen emulsion, although attempts have been made for paint films [52]. What is clear is that for all PS sizes less than 500 nm, TiO₂ is a much more efficient light scatterer than ZnO and so will be more difficult to “hide” in a topical product. The cosmetic elegance of these sunscreen actives is limited by the degree of whiteness they impart. Figure 14.2, right, expands the plot below 200 nm from which it can be seen that a microfine grade of ZnO or TiO₂ with a PS less than about 150 and 100 nm respectively should be effectively transparent to the human eye.

Film Thickness

The thickness of a film and the number of particles in a unit volume of that film will both impact the degree of scattering. This is illustrated in Fig. 14.3 in which the relative masking ability of microfine ZnO and TiO₂ is compared at 5%wt concentration as a function of film thicknesses. Although both ZnO and TiO₂ have allowed use levels of up to 25 % [25], typical concentrations in commercial sunscreen products are from 2 % to 8 %. The procedure followed to obtain the data in Fig. 14.3 was adapted from an ASTM standard method for determining the hiding power of paints [4]. It can be seen that, at a given film thickness, TiO₂ has almost twice the

hiding power of ZnO. The practical implication of this in the formulation of a sunscreen product is that a much smaller TiO₂ particle size (PS) (typically ca 50–90 nm) is needed for “transparency”. Furthermore, maintenance of this size throughout formulation is critical. Should agglomeration occur the TiO₂ reverts to behaving as a pigimentary material thereby increasing interaction in the visible and, hence, appearing white. In this respect, ZnO is a much more forgiving pigment.

The amount of sunscreen product mandated by the US FDA in the determination of SPF *in-vivo* [25] is 2 mg/cm² and this would represent a film thickness of approximately 20 μm. It is most important that the sunscreen application be very uniform; large variations of SPF value are obtained with irregularly applied amounts of sunscreen. Hence, technicians in testing laboratories are carefully trained in this *in-vivo* technique. Studies suggest that, in “real-life” use, the average individual typically applies < 2 mg/cm² [60, 65]; this could result in less protection than the product label SPF value suggests.

Light Absorption in the UV Spectrum

Scattering and adsorption are not restricted to the visible spectrum. However, at shorter wavelengths the optical behavior of ZnO and TiO₂ becomes more complex. Not only the PS but also the crystal structure and the energy gap between valence and conduction bands have to be taken into consideration. For all crystals there is some characteristic wavelength that will excite an electron from the valence band to the conduction band. This is the process through which these metal oxides owe their semiconductor properties. Wavelengths that are shorter than this characteristic wavelength and that fall on the crystal will, therefore, be dissipated (i.e. absorbed by the crystal structure).

Being crystalline semiconductors, they have the ability to contain, internally, the production of ROS. As with the organic actives, most of the radiation can be re-emitted at a longer wavelength (e.g., heat). However, they may also produce oxygen free radicals at their crystal surface; this *photoreactivity* has been extensively studied [71]; generally TiO₂ is much more photoactive than ZnO [50]. Although it has been suggested that photoactive metal oxides may initiate deleterious events in the skin, to do so a particle would have to traverse the *stratum corneum*; TEM studies have concluded that there is no evidence that this occurs [18]. Furthermore, for a variety of reasons, manufacturers of ZnO and, especially, TiO₂ apply coatings (both inorganic and organic) [74] and these result in the reduction or even elimination of photoreactivity [37]. In the US, owing to regulatory concerns, virtually no uncoated ZnO or TiO₂ is used as a sunscreen active.

The ZnO crystal structure efficiently absorbs radiation over virtually the whole UV spectrum (380 nm and shorter); the attenuation efficiency varies very little with PS from about 80 to about 150 nm. In contrast TiO₂ is predominantly a very efficient *UVB absorber* but a *UVA scatterer*. For example, at 360 nm about 90 % of TiO₂'s attenuation is via scattering, whereas for ZnO about 90 % is by absorbance. Thus, when using ZnO and TiO₂ as sunscreen actives for human applications

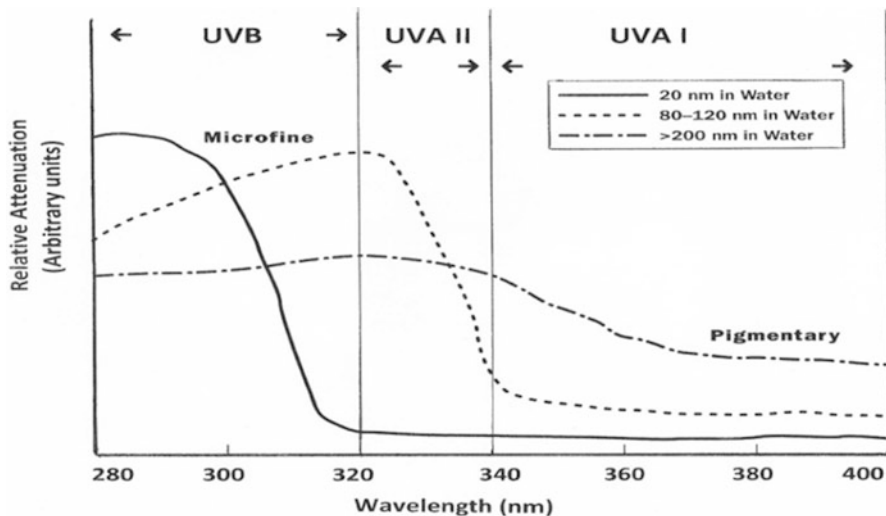


Fig. 14.4 Particle size dependence of UVR attenuation for TiO₂

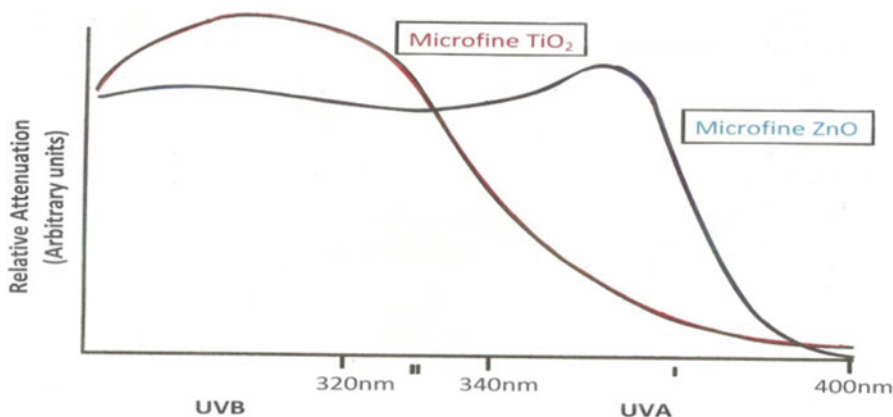


Fig. 14.5 Schematic of comparison of UVR attenuation for microfine TiO₂ and ZnO

this distinction has some important consequences. Figure 14.4 shows the efficacy of attenuation for TiO₂. Very small (ca 20 – 60 nm PS) TiO₂ particles that are non-whitening are very efficient in attenuating in the UVB but are very poor at attenuating UVA radiation; larger 80 – 100 nm TiO₂ particles have good UVA attenuation but lose their ability to attenuate UVB. Microfine TiO₂ and ZnO can, therefore, be considered complimentary in terms of their sun protective effects (Fig. 14.5); TiO₂ is primarily used for UVB protection and ZnO for UVA protection. Thus, they are often used in combination to obtain true broad-spectrum coverage.

14.4 Measurement of Particle Size

Although both uncoated ZnO and TiO₂ are hydrophilic and could be dispersed in the water phase of either an O/W or a W/O emulsion, more often than not these particulates are dispersed into the oil phase because this provides a continuous film on the skin after dry-down and also there are a wide variety of primary oil vehicles from which to choose – including mineral oils, fatty esters, triglycerides and silicone fluids [73] – depending upon the aesthetics required, such as skin feel. In this case, coated versions of the ZnO or TiO₂ are used in which the coating is chosen to match as closely as possible the vehicle – for example a dimethicone coated ZnO in a silicone fluid. It is critical that an optimized stable dispersion be prepared before the other components are added and the whole then emulsified. Indeed, “pre-dispersions” can be obtained from cosmetic ingredient suppliers eliminating this initial step in the formulation. In either case the particle size needs to be determined.

14.4.1 Techniques

Particle size analysis techniques are often applied inappropriately, primarily because of a lack of understanding of the underlying principles of size analysis and confusion arising from claims and counter-claims of the analytical ability of the various size determination techniques and the wide choice of commercially available instrumentation. Further, techniques will *weight* the raw data differently. An excellent comprehensive treatise on the whole subject of particle size measurement has recently appeared [48].

Most data, particularly in pharmaceutical applications, is useful when quoted as volume-weighted since drugs are delivered by volume or mass (proportional to volume for a fixed density). In sunscreen applications, it is number-weighted data that is preferred because it more closely correlates with coating and SPF efficiency.

14.4.2 Dynamic Light Scattering/Photon Correlation Spectroscopy

The size of these microfine pigments would seem to make them candidates for measurement by dynamic light scattering (also termed photon correlation spectroscopy). However, DLS is a technique in which the signal, from which the size distribution is calculated, is a sum over all the signals from all the particles during the entire measurement [72]. Thus, the results are an average over an ensemble of particles. In general the resolution is low since the particles are neither counted nor physically separated. Instead, over the duration of the entire measurement, particles of all sizes contribute to the final signals. Then the signals are mathematically

deconvoluted to produce size distribution information. As these signals are not simple linear functions of particle size, but often complicated functions of size, it is not surprising that information is lost. Also, DLS requires that the dispersion under investigation be extremely dilute; as mentioned earlier typical use concentrations of microfine pigments are from 2 % to 8 % wt. The viscosity of the oily vehicles can be >10X that of water. This slows diffusion increasing the length of time to obtain a useful autocorrelation function necessitating repeat measurement and lengthening the total time to obtain reliable data. A complication is that both ZnO and TiO₂ are dense materials ($\rho_p = 5.6$ and 4.2 respectively); even at the microfine size settling occurs and this impacts reproducibility.

Finally, in DLS measurement of very small particles the intensity of the light scattered is weighted by the 6th power of the diameter. Hence in relatively broad PSD as found in microfine pigments the data tends to be skewed towards the larger end of the PSD. Further, most data, particularly in pharmaceutical applications, is most useful when quoted as either volume- or number-weighted values. Although it is a simple matter to write equations for converting one type of weighting to another, the results calculated this way are often erroneous, especially in the case of intensity-weighting – in part because of the assumptions that need to be made. A fundamental tenet of particle size analysis is, if at all possible, to choose a technique whose fundamental weighting is closest to that which is needed, or used, in practice [2].

14.4.3 X-ray Disc Centrifugation

Given the above, the preferred method for PSD measurement of ZnO and TiO₂ pigments tends to be X-ray disc centrifugation [47]. In any particle sizing techniques based on an optical system to monitor the sample, the extinction efficiency of particles of different sizes must be taken into account [68]. Such corrections become unnecessary when the detection is based on X-rays rather than visible radiation. X-rays are absorbed in direct proportion to the total mass of particles present. X-ray detection is therefore ideal for metal oxides in general. By using both combining gravitational sedimentation with centrifugal sedimentation an extremely wide range of sizes can be analyzed. Importantly, for an instrument that weights by volume (such as an XDC device), even if a few of the larger particles are missed, the volume-weighted diameter is not much affected. The maximum particle concentration allowed is 2 % vol, thus the typical use concentrations of ZnO and TiO₂ can be measured directly, without dilution.

An example is shown in Fig. 14.6 that compares the PSD (measured using an XDC device) for two commercial samples of supposedly equivalent microfine ZnO supplied by different manufacturers; in this case, 5 % wt suspensions of the ZnO materials were prepared in isopropyl myristate (IPM), an ester commonly used in sunscreen formulations [73].

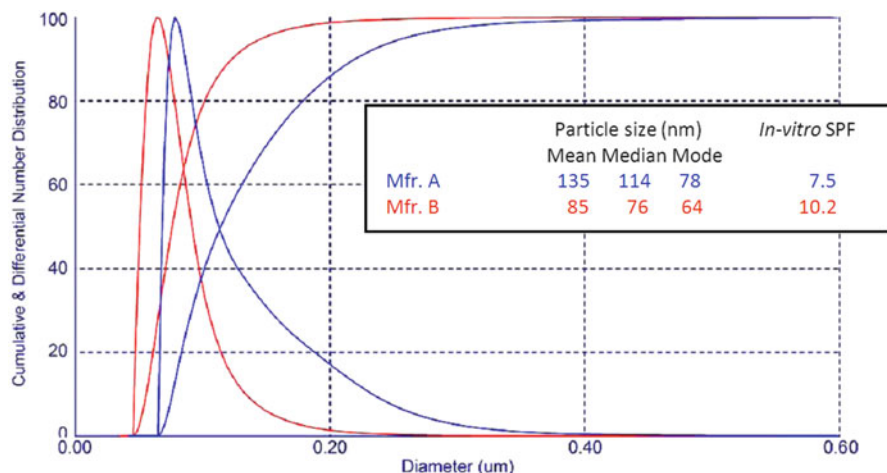


Fig. 14.6 Comparison of PSD for two microfine ZnO samples

The particle size data is displayed as number-weighted values. The resolution obtained is unlikely to be achieved with DLS. Although the modal values (the majority fraction comprising any PSD) for the two pigments are very similar (at 64 and 78 nm), the “tails” of each PSD (made up of massive single particles, aggregates and agglomerates) differ enormously and this critically affects the resultant SPF values that would be obtained. The SPF values shown in Fig. 14.6 were determined from *in-vitro* measurements [15] using the 5 % ZnO dispersion in IPM and the data shows that the ZnO from manufacturer B is clearly superior. While not allowed for labeling purposes, *in-vitro* SPF measurements are routinely used to screen formulations before submission for *in-vivo* measurements which are extremely expensive, using as they do human volunteers. Since the microfine ZnO tends to be the most expensive component in a sunscreen product, the economic impact of choice of this material can be considerable.

14.4.4 Acoustic Attenuation Spectroscopy

Ideally, it would be preferable to be able to measure the PSD of microfine ZnO and TiO₂ in an actual finished sunscreen product. Alas, cosmetic (sunscreen) emulsions are multi-component systems that contain, in addition to the microfine pigments, emulsified oil (or water) droplets and solid particles such as waxes and fillers that have particle sizes well into the micrometer range.

It has been long known that ultrasound based techniques open an opportunity to eliminate dilution [46]. However, instrumentation hardware was too complex and suffered from weaknesses in practical application of the technique to systems of high internal phase concentration. In addition, the theoretical basis of the

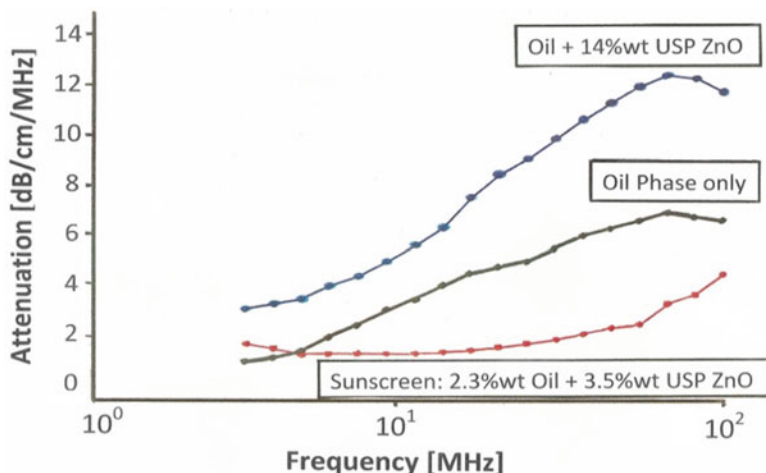


Fig. 14.7 Ultrasound attenuation spectra of an oil phase alone, with predispersed ZnO and diluted to the ultimate sunscreen

deconvolution of the raw data was not capable of dealing with particle-particle interaction – an essential feature of concentrated dispersions. Recently, these problems have been addressed [17] and initial results, from studies of a series of commercially formulated cosmetic (O/W and W/O) emulsions, suggest that acoustic attenuation can be used as a formulation aid to “fingerprint” emulsion composition [23].

Figure 14.7 compares the attenuation spectra of three different “components” that would typically be produced during the course of the formulation, or manufacture, of a sunscreen product. These were an “oil phase”, the same oil phase containing predispersed 14 % wt USP ZnO and the final sunscreen following addition of water and homogenization. The spectra are clearly different and track the compositional nature. There is an increase in attenuation of the oil phase upon addition of the particulate ZnO because, as a solid, it has a larger attenuation than any liquid. However, the final sunscreen has the smallest attenuation; it is considerably less than the oil phase even though it contains ZnO. This is primarily because a large concentration (ca 60 % wt) of water was added (to create the final emulsion) and water has the smallest attenuation (almost zero) of any liquid. In addition, the oil/ZnO attenuation is also significantly reduced because the concentration of that component is now only about 35 % wt; hence, the actual ZnO concentration in the sunscreen is only 3.5 % wt. Thus, the use of the attenuation spectrum as a measure of reproducibility and repeatability at any stage of formulation could lead to improvement in the consistency of the final product and, overall, result in a cost benefit.

The raw attenuation spectra for two examples of non-ionically stabilized O/W moisturizers are shown in Fig. 14.8. Primarily they differ in that one also contains 3.5 % wt of a microfine “hydrophobically coated” ZnO; they are clearly

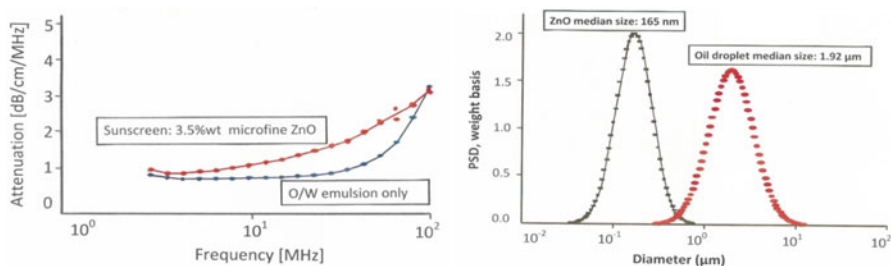


Fig. 14.8 Particle size distributions (*right*) and ultrasound attenuation spectra (*left*) of a ZnO sunscreen and its O/W emulsion basis

distinguishable from one another and it is also apparent that the shapes of the two spectra are dissimilar. Note also, the good reproducibility of the technique. While not straightforward, it is possible to obtain the PSD of both the oil droplets and the ZnO, dispersed therein from the two spectra. In contrast to light scattering methods, the raw data so obtained from AAS measurements is *volume-weighted* [17]. The PSD is calculated assuming a log-normal distribution (Fig. 14.8, *right*); the median values of 1.92 μm and 165 nm are typical for emulsion oil droplets and microfine ZnO particles respectively. Indeed, the ZnO size is in very good agreement with the mean volume-weighted PS value of 148 nm, measured for a predispersion of the ZnO in the oil phase prior to emulsification using an XDC.

14.5 Particle Shape

Particle shape is a factor of considerable importance in determining the overall properties (especially those of a physico-mechanical nature) of colloidal systems and this includes dispersions of microfine ZnO and TiO_2 . The activity of catalysts is a consequence not just of their surface-to-volume ratio but also the particle shape; different crystal facets result in different selectivity [1]. The difference in crystal shape is also a reason why uncoated TiO_2 is much more photoreactive than uncoated ZnO.

It has long been recognized that the shape of TiO_2 and ZnO pigment particles affects the way they pack in a paint film [40]. In sunscreens it is critical for optimum efficacy that the active particles be evenly distributed within the oil phase so that a uniform coating can be applied to the skin. TiO_2 has a compact tetragonal crystal lattice; that for ZnO is hexagonal. Because of their different symmetry they will pack differently; in uniform films, at equal concentrations, microfine TiO_2 is a much more efficient UVB absorber than ZnO.

While it is known that particle shape can be manipulated during the manufacturing formation [9] or altered during subsequent processing [49], for two important reasons there has been no impetus for formulators to use anything

other than standard production material. The first relates to cost. Contrary to what the consumer might think when looking at the price paid at a retail store for a 120 mL (4 oz) tube, or bottle, of sunscreen product, the actual total raw ingredient cost is quite low; typical figures (including manufacturing) for a W/O beach-wear product and an O/W daily-wear (moisturizer) product, both containing microfine ZnO, are about \$8.50/kg and about \$7.00/kg respectively. The profit margin on manufacturing is very small and manufacturers are reluctant to pay even a few cents more for an ingredient. The second relates to formulation. As mentioned earlier, it is critical that an optimized stable dispersion initially be prepared and then kept so throughout the whole formulation process. Even starting with a material of optimum morphology and a finely controlled PSD, poor formulation will always result in aggregates and agglomerates that result in inferior aesthetics and mediocre performance.

14.6 Particle Surface Area

It is clear that the particle size of particulate sunscreen actives is important, determining as we have seen the aesthetics and performance of sunscreen products formulated with them. It is also evident that as the size is reduced during the dispersion process the particle surface area will increase (as $1/D^2$, for spheres). However, what is less obvious is the exceptionally large surface area-to-volume ratio per given mass for the particles involved – an essential characteristic common to all colloidal dispersions and of critical import to microfine pigments and especially so with nanoparticulate systems; it becomes orders of magnitude larger than it is for particles of even only a few micrometers in size [21].

In practical terms, the total *wetted* surface area of a given suspension is a consequence of the concentration and size of particles. The latter derives from the specific dispersion process used, *viz* the choice/type and concentration of dispersion aids (i.e., wetting agent, de-agglomerating agent and stabilizing agent) and the type/duration of the mechanical dispersing treatment [22].

An approximate amount of surfactant or dispersant required for surface coverage can be estimated using the Sauter mean diameter (SMD; $D_{3,2}$) [48]. SMD is an average of the particle size traditionally used in applications where active surface area is important (e.g., in catalysis). NMR relaxation measurements can be used to study adsorption at interfaces [24] and so offers the possibility of determining optimum coverage directly and, moreover, using industrially relevant particle suspension concentrations.

The practical significance to product performance and the economics of manufacture of the use of excessive mechanical attrition during the formulation of wet suspensions that results in “fines” can be considerable [11]. This is especially so for crystalline materials such as ZnO and TiO₂ in which fracture can occur at defect crystal planes. Monitoring the presence of nanoparticles in suspensions that have a broad particle size distribution is a general problem for many current particle sizing instruments.

In addition, the increase that occurs in particle surface area can dramatically affect not just adsorption of surfactants/dispersants and other moieties onto the particle surface but also the interaction between particles and system properties such as suspension rheology, coating and adhesion. All of these performance factors impact sun products formulated to contain microfine ZnO and TiO₂.

14.6.1 Measurement of Particle Surface Area

BET Method

The most common method of particle surface area determination is BET nitrogen (N₂) gas adsorption [44]. This technique requires the material under test to be a dry powder. However, drying wet suspensions inevitably results in unintentional (and unwanted) aggregates and agglomerates. As a consequence, the subsequent surface area results will be skewed. Indeed, it has long been accepted that any procedure which requires a dry sample (such as BET or Knudsen flow of a gas at low pressure) may give an area which, for all its accuracy, has little relation to the effective area in suspension [34].

It should be obvious that the state of dispersion will critically affect the particle surface area and, to be useful, it is essential that a technique appropriate to the application be used. While it is possible to calculate surface area from measurements of the particle size this assumes spherical particles and a mono-disperse size distribution, a condition clearly not met by microfine pigment dispersions; any calculated surface area is, at best, only a crude approximation and it is well-recognized that particle shape, surface irregularities and porosity will inevitably lead to estimated values significantly less than the true value [2].

NMR Relaxation

It is clear that it is the *wetted* particle surface area of any suspension (and especially for colloidal dispersions and nanoparticulate systems) that is the vital metric in quantifying the performance of such materials and, ideally, measurement should be made directly on suspensions as formulated.

High resolution nuclear magnetic (NMR) spectroscopy is one of the most powerful analytical tools used to probe details of molecular structure and dynamics. The determination of wetted surface area from NMR relaxation measurements is well-established [45] and, with the advent of small powerful permanent magnets, a low field (13 MHz) NMR bench-top device is now available to measure the wetted particle surface area of suspensions [24, 56]. The technique is based on the fact that liquid in contact with, or “bound” to, the particle surface behaves differently than the bulk or “free” liquid. The NMR relaxation time of bound versus bulk liquid is markedly different: the relaxation time of the latter is much longer. There are no

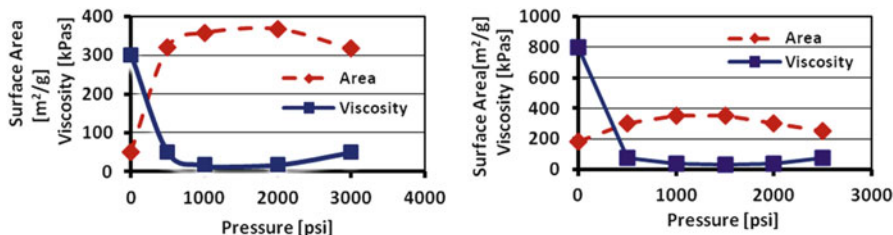


Fig. 14.9 Surface area and viscosity as a function of mill pressure; (*left*) without dispersant; (*right*) with 0.1 % dispersant

assumptions made about the particle size (distribution) or shape in the determination of the wetted surface area. Measurement of virtually any particle in any fluid is accessible and the technique does not require dilution of the sample.

Figure 14.9 (*left*) shows the effect of milling a pre-mix high solids (52 % wt) suspension of a microfine grade ZnO in C₁₂-C₁₅ alkyl benzoate (widely used as an emollient in cosmetic formulations for the skin such as sunscreens and facial moisturizers). No dispersing agent was used; the pre-mix was initially prepared using high shear (rotor/stator) mixing and then further processed using a cavitation device run at increasing processing pressures. The initial wetted surface area of pre-mix was determined to be 50 m²g⁻¹ and the optimum (milled) value was 365 m²g⁻¹; for this particular ZnO material, milling at pressures over 2,000 psi (1.4 · 10⁴ kPa = 140 bar) is, clearly, counter-productive.

Figure 14.9 (*right*) then demonstrates the effect of using a dispersing agent. The same ZnO was used; a dispersing agent – polyhydroxystearic acid (PHSA) – was added at a concentration of 0.1 % wt (determined empirically) and it was found possible in the pre-mix to significantly increase the ZnO solids loading (to 60 % wt) without any detrimental change in pre-mix viscosity. Importantly, with the use of only 0.1 % wt PHSA, the initial pre-mix wetted surface area increases 50 – 180 m²g⁻¹ and an optimum (milled) value of was 355 m²g⁻¹ at only 1,500 psi (10⁴ kPa = 100 bar).

In both experiments the dispersions were all measured at full concentration, without dilution. The correlation of milling with surface area measurement is quite clear and since each surface area measurement took less than five minutes this suggests that NMR relaxation could prove useful in monitoring a milling process, almost in real-time, to obtain optimum conditions thus saving time and money – clear economic advantage to manufacturer. The data further suggests that NMR relaxation could be used to optimize the amount of dispersant used.

Although the flow behavior of real commercial suspensions is complex – the systems are visco-elastic (VE) – it is directly related to the particle size distribution (PSD) of the dispersed phase [51]. Thus, milling should result in changes in viscosity and this is evident also from Fig. 14.9; milling dramatically decreases the dispersion viscosity. A lower viscosity means that the ZnO dispersions are easier to pour making them more “processable”, an advantage since these materials will subsequently be used in the preparation of emulsions.

14.7 Particle Surface Chemistry

Whatever the so-called primary PS of ZnO or TiO₂ particles, it is the state of dispersion of the final product that determines the “effective” PS and thus the optical properties. However, the preparation of wet suspensions having a defined dispersed state, with specific properties, is often difficult to achieve because complete knowledge of the dispersed system is usually lacking. It is probably fair to say that most industrial (cosmetic) methods of formulation have been developed and optimized empirically, or on the basis of working hypotheses that provide adequate guidance to the formulation chemist, but are insufficient as a basis for understanding how and why suspensions of particles in liquids behave as they do and, many times, not as the formulator wants.

And this is never more so true than in the formulation of particulate-based sunscreen products where a stable (non-agglomerating) reproducible PSD needs to be achieved. There is a natural tendency to treat all particulates as being alike. This makes no more sense than treating all the organic (soluble) sunscreens as being the same. All oxides have quite distinct surface chemistries [33]. For example, the point of zero charge (PZC) for pure, uncoated TiO₂ and ZnO are found at ca pH6 and ca pH9 respectively [39]. This means that in neutral water (pH7, 25 °C) TiO₂ will be mildly acidic and have a small negative charge whereas ZnO will be basic and positively charged. The actual PZC for a specific material is influenced by its source or preparation method, pretreatment and presence of trace impurities [53, 64]; and should be determined batch-to-batch and lot-to-lot; there is probably greater manufacture-to manufacture variation with the particulates than with the organic (soluble) sunscreen actives. Add to this the wide variety of surface treatments and the result is that sunscreen formulation is more of an art than a science. And it is this, more than anything else, which to-date has limited the wider adoption of particulate actives.

The subjects of surface chemistry and the dispersion of particulates, though important, are beyond the scope of this chapter. There are a variety of references to which the interested reader is directed [22, 41, 54, 67].

14.8 Regulatory Issues

Because of perceived concerns regarding the safety of so-called nanoparticles (NP), especially because of a less than well-informed public and organizations with their own agendas, regulatory bodies both in the USA [75] and the EU [19] have recently presented “guidelines” regarding the manufacture and the use, and the application, of “nanotechnology” as it relates to cosmetics. In 2007, an FDA Task Force issued a report in which nanotechnology was defined as “the ability to measure, see, manipulate and manufacture *things* usually between one and 100 nm”. In 2011,

the European Commission defined a “nanomaterial” as “anything made up of natural, or manufactured, particles that are *unbound or aggregated/agglomerated*. At least 50 % of particles *must have one or more dimensions* between 1 nm and 100 nm and/or have a *specific surface per unit volume* of greater than $60 \text{ m}^2\text{cm}^{-3}$ ”. Although presently just “guidelines”, this author has little doubt that the regulatory agencies will move to make them “regulations”.

The Hepatitis B virus (42 nm in diameter) is biologically active and penetrates the skin. Thus, as long as the minimum particle size of a pigment is not less than 42 nm it should be physically impossible for such an “inert” particle to be absorbed through the skin; however, the oily components of a sunscreen formulation may impact potential penetration. Penetration of NP can be aided by damage of the skin, e.g. by removing hairs. Although studies of TiO_2 and ZnO NP suggest that they are mainly localized in hair follicle openings and on the stratum corneum surface, there are indications for cytotoxicity (TiO_2) and genotoxicity (ZnO) [63]. The picture is less certain for particles whose primary size is <40 nm. A complicating factor is that NP are often agglomerated in formulation so that the “effective” PS is much larger. A recent overview of the pathology and toxicology of nanoparticulates concludes that significant data gaps exist on skin penetration and the toxicology of true NP [32].

Notwithstanding the fact that “fines” have been present for decades in commercially available pigments, that ZnO, for example, has been used a skin therapeutic agent for at least 300 years and that a search of available literature has not revealed a single adverse reaction, from this authors perspective these guidelines now impose an unnecessary need to measure, or evaluate, not just the particle size of particulate actives (and now as a **number**-weighted value and not on the traditional volume-weighted basis) but also the surface area of materials (and the guidelines do not specify whether it is to be determined on a sample of the dry powder or on a suspension...) and, potentially, an added requirement to determine particle characteristics such as the aspect ratio.

All this will certainly have an impact, as yet unknown, on the use of microfine grade pigments as sunscreen actives.

14.9 Definitions, Abbreviations and Symbols

BET equation	Linearized equation to extract the specific surface area from gas adsorption results at different gas pressures (see Sect. 3.6.3)
Emulsion	(Stable) dispersion of small liquid droplets in another, immiscible, liquid
Substantivity	Ability of a sunscreen to remain on the skin and be effective
BET	Brunauer-Emmett-Teller
DLS	Dynamic light scattering
ESD	Equivalent spherical diameter: the diameter of a sphere of equivalent volume of an irregular-shaped particle, measured according to a defined technique

(continued)

(continued)

EU	European Union
FDA	Food and Drug Administration (USA)
IPM	Isopropyl myristate
MED	Minimal erythema dose
NMR	Nuclear magnetic resonance
NP	Nanoparticle
O/W	Oil-in-water emulsion
emulsion	
PHSA	Polyhydroxystearic acid
PS	Particle size
PSD	Particle size distribution
PZC	Point of zero charge: the pH at which oxide particles dispersed in water have no effective surface charges
RI	Refractive index
ROS	Reactive oxygen species
SPF	Sun protection factor
TEM	Transmission electron microscopy
US(A)	United States of America
UVA	Ultraviolet radiation in 320 – 400 nm range
UVB	Ultraviolet radiation in 290 – 320 nm range
UVC	Ultraviolet radiation in 100 – 290 nm range
UVR	Ultraviolet radiation
VE	Visco-elastic
W/O	Water-in-oil emulsion
emulsion	
XDC	X-ray disc centrifuge
<i>D</i>	Particle size
% vol	Percentage by volume
% wt	Percentage by weight
ρ_P	Particle density

References

1. Ahmadi, T.S., et al.: *Science* **272**, 1924 (1996)
2. Allen, T.: *Particle Size Measurement*, 4th edn. Chapman and Hall, London (1990)
3. Armstrong, B.K., Kricger, A.: *Cancer Surveys – Skin Cancer*, pp. 133–153. Imperial Cancer Research, Oxford (1996)
4. ASTM D2805-11: Standard Test Method for Hiding Power of Paints by Reflectometry. ASTM, Philadelphia (2011)
5. Becher, P.: *Encyclopedia of Emulsion Technology*, 2nd edn. Marcel Dekker, New York (1985)
6. Beck, I., et al.: *Int. J. Cosmet. Sci.* **3**, 139–152 (1981)
7. Birmingham, D.J.: *Prog. Dermatol.* **3**, 1–8 (1968)
8. Black, H.S., et al.: *Photochem. Photobiol.* **40**, 29–47 (1997)
9. Buckley, H.E.: *Crystal Growth*. Wiley, New York (1951)
10. Butler, H.: *Poucher's Perfumes, Cosmetics and Soaps*, 10th edn. Kluwer Publisher, Dordrecht (2000)

11. Daniel, F.K.: Natl. Paint, Varn. Lacquer Assoc. Sci. Sect. Circ. No.744, (1950)
12. Deflandre, A., Lang, G.: *Int. J. Cosmet. Sci.* **10**, 53–62 (1988)
13. de Laat, J.M., de Gruijl, F.R.: *Cancer Surv.* **26**, 173–191 (1996)
14. Derry, J.M., McLean, W.M., Freeman, J.B.: *J. Parenter. Enteral Nutr.* **7**(2), 131–135 (1982)
15. Diffey, B.L., Robson, J.: *J. Soc. Cosmet. Chem.* **40**, 127–133 (1989)
16. Diffey, B.L.: *Int. J. Cosmet. Sci.* **16**, 47–52 (1994)
17. Dukhin, A.S., Goetz, P.J.: *Ultrasound for Characterizing Colloids*. Elsevier, Amsterdam (2002)
18. Dussert, A.S., Goori, E., Hemmerle, J.: *Int. J. Cosmet. Sci.* **19**, 119–129 (1997)
19. ec.europa.eu/nanotechnology/
20. Epstein, J.H.: In: Smith, K.C. (ed.) *The Science of Photobiology*, 2nd edn, pp. 155–192. CRC Press, Boca Raton (1989)
21. Everett, D.H.: *Basic Principles of Colloid Science*. RSC Publications, London (1988)
22. Fairhurst, D., Mitchnick, M.A.: In: Lowe, N.J., Shaath, N.A., Pathak, M.A. (eds.) *Sunscreens: Development, Evaluation and Regulatory Aspects*, 2nd edn. Marcel Dekker, New York (1997)
23. Fairhurst, D., Dukhin, A.S., Klein, K.: *ACS Symposium Series* 472, Chapter 16 249 (2004)
24. Fairhurst, D., Prescott, S.: *Spectrosc. Eur.* **23**(4), 13–16 (2011)
25. Federal Register: Sunscreen Drug Products for Over-the-Counter Human Use; Tentative Final Monographs: Proposed Rule, The Code of Federal Regulations, 21 CFR Part 352, pp. 28–33. FDA, Washington, DC (1998)
26. Federal Register: Final Rule: Testing and Labeling Requirements, 21 CFR 201.327, 17 June 2011
27. Garland, C.F., et al.: *AEP* **3**, 103–110 (1993)
28. Grady, L.D.: *J. Soc. Cosmet. Chem.* **1**(1), (1947)
29. Groves, G.A.: *Drug Cosmet. Ind.* **37**(2), 155 (1994)
30. Harry, R.G.: *The Principles and Practice of Modern Cosmetics*, vol. 2. Leonard Hill, London (1963)
31. Herman, J.R., et al.: *Geophys. Res. Letter* **23**, 2117 (1996)
32. Hubbs, A.F., et al.: *Toxicol. Pathol.* **39**(2), 301–324 (2011)
33. Hunter, R.J.: *Zeta Potential in Colloid Science*. Academic, London (1981)
34. James, R.O., Parkes, G.A.: In: Matijevic, E. (ed.) *Surface and Colloid Science*, vol. II. Wiley, New York (1980)
35. Kaidby, K.H.: In: Lowe, N.J., Shaath, N.A. (eds.) *Sunscreens: Development, Evaluation and Regulatory Aspects*. Marcel Dekker, New York (1990)
36. Kerker, M.: *The Scattering of Light and Other Electromagnetic Radiation*. Academic, New York (1969)
37. Kobayashi, M., Kalreis, W.: *Sun Products: Protection and Tanning*, pp. 142–146. Allured Publishing, Carol Stream (1998)
38. Kochevar, I.E.: In: Gilchrist, B.A. (ed.) *Photodamage*, pp. 201–220. Blackwell Science, Cambridge (1995)
39. Kosmulski, M.: *Surface Charging and Points of Zero Charge*. CRC Press, Boca Raton (2009)
40. Lambourne, R. (ed.): *Paint and Surface Coatings; Theory and Practice*. Ellis Horwood, Chichester (1987)
41. Laskowski, J.S., Ralston, J.D. (eds.): *Colloid Chemistry in Mineral Processing*. Elsevier, New York (1992)
42. Lowe, N.J., Weingarten, D., Wortzman, M.: *J. Dermatol. Surg. Oncol.* **17**, 744–746 (1991)
43. Lowe, N.J., Friedlander, J.: In: Lowe, N.J., Shaath, N.A., Pathak, M.A. (eds.) *Sunscreens: Development, Evaluation and Regulatory Aspects*, 2nd edn. Marcel Dekker, New York (1997)
44. Lowell, S., Shields, J.E.: *Powder Surface Area and Porosity*. Chapman Hall, London (1984)
45. Maciel, G.E.: In: Grant, D.M., Harris, R.K. (eds.) *Encyclopedia of Nuclear Magnetic Resonance*. Wiley, New York (1996)
46. Marlow, B.J., Fairhurst, D., Pendse, H.P.: *Langmuir* **4**, 611–626 (1983)
47. McFadyen, P.: In: Freer, R. (ed.) *Nanoceramics*. Institute of Materials, London (1993)

48. Merkus, H.G.: Particle Size Measurements; Fundamentals, Practice, Quality. Springer, Netherlands (2009).
49. Mitchnick, M.A.: Sun Products: Protection and Tanning. C&T Ingredient Resource Series. Allured Publishing, Carol Stream (1998)
50. Mitchnick, M.A., Fairhurst, D., Pinnell, S.R.: *J. Am. Acad. Dermatol.* **40**, 85–90 (1999)
51. Mollet, H., Grubenmann, A.: Formulation Technology. Wiley-VCH, Weinheim (2001)
52. Orchard, S.R.: *Oil Color Chem. Assoc.* **51**, 44 (1968)
53. Parfitt, G.D., Sing, K.S.W. (eds.): Characterization of Powder Surfaces. Academic, London (1976)
54. Parfitt, G.D. (ed.): Dispersion of Powders in Liquids. Applied Science, New York (1981)
55. Pathak, M.A., Fitzpatrick, T.B.: In: Fitzpatrick, T.B. (ed.) *Dermatology in General Medicine*, 4th edn, pp. 1689–1717. McGraw-Hill, New York (1993)
56. Race, S., Fairhurst, D., Brozel, M.: US Patent, 7,417,426, 26 Aug 2008
57. Reiger, M.M.: *Cosmet. Toil.* **108**(12), 43 (1993)
58. Riegelman, S., Penna, R.: *J. Soc. Cosmet. Chem.* **11**, 280–291 (1960)
59. Roberts, J.: In: Auerbach, P. (ed.) *Management of Wilderness and Environmental Emergencies*, 2nd edn. Mosby, St. Louis (1989)
60. Sayre, R.M.: *Arch. Dermatol.* **12**(2), 745–746 (1986)
61. Sayre, R.M., Dowdy, J.C.: *Photodermatol. Photoimmunol. Photoderm.* **38**, (1998)
62. Schlossman, M.L. (ed.): *The Chemistry and Manufacture of Cosmetics*, Vol. II, Formulating, 2nd edn. Allured Publishing, Carol Stream (2000)
63. Smijs, T.G.M., Bouwstra, J.A.: in *J. Biomed. Nanotechnology* **6**(5), 469–484 (2010)
64. Solomon, H., Hawthorne, G.: *Chemistry of Pigments and Fillers*. Wiley, New York (1983)
65. Stenberg, C., Larko, O.: *Arch. Dermatol.* **121**, 1400–1402 (1985)
66. Szczurko, C., et al.: *Photodermatol. Photoimmunol. Photomed.* **10**, 144–147 (1994)
67. Tadros, T.F.: *Solid–Liquid Dispersions*. Academic, New York (1987)
68. Tschamuter, W.W., Weiner, B.B., Fairhurst, D.: ACS Symposium Series 472, Chapter **14**, 184 (1991)
69. Tyrell, R.M.: *Photochem. Photobiol.* **63**, 380–386 (1996)
70. Urbach, F.: In: Urbach, F. (ed.) *Biological Responses to Ultraviolet Radiation*, pp. 1–6. Valdenmar Publishing, Overland Park (1992)
71. Wamer, W.G., Yin, J.J., Wei, R.R.: *Free Radic. Biol. Med.* **23**, 851–858 (1997)
72. Weiner, B.B.: In: Barth, H. (ed.) *Modern Methods of Particle Sizing*, pp. 93–116. Wiley-Interscience, New York (1984)
73. Wenniger, J.A., McEwen, G.N.: *Cosmetic Ingredient Handbook*, 2nd edn. CTFA, Washington, DC (1992)
74. Wiseman, T.J.: In: Parfitt, G.D., Sing, K.S.W. (eds.) *Characterization of Powder Surfaces*. Academic, London (1976)
75. www.fda.gov/nanotechnology/