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2.1 Introduction

Excessive exposure to ultraviolet (UV) radiation induces a wide range of adverse effects such as sunburn, photoaging, photoimmunosuppression, and photocarcinogenesis. Use of sunscreen is an important practice by the public to protect against excessive UV exposure and reduce UV damages. In general, inorganic-based sunscreen composed of mineral UV filters, such as titanium dioxide (TiO_2) and zinc oxide (ZnO), work by reflecting and scattering UV radiation. These agents are regarded as safe and effective. Compared to organic UV filters, such as avobenzone and oxybenzone, inorganic filters are less irritating on individuals with sensitive skin and chronic skin disorders. For these reasons, TiO_2 and ZnO have been widely recommended as the safest UV filters in sunscreen products. Despite these benefits, older sunscreens containing these ingredients were limited in popularity by their poor cosmetic appearance. Due to the broad particle size distribution and poor dispersive qualities of the TiO_2

and ZnO particles, these sunscreens left a white or opaque film, as well as grainy-residue on the skin. The diminished aesthetics of these sunscreens hindered wide acceptance by the public.

This problem was met with a solution in nanotechnology. Nanotechnology involves the design, production, and application of materials in the size range of 1–100 nm. As existing materials are reduced to this size, a new set of physical, chemical, mechanical, and electrical properties are revealed. Application of this technology has aided in the development and advancement of new tools in numerous fields. Today, nanomaterials are found in electronics, paints, foods, cosmetics, and coatings and are increasingly applied to the medical field in diagnosis and drug delivery. The advent of nanotechnology also brought about great concern for the potential risks and toxicity of these foreign materials. Concerns surrounding nanotechnology in cosmetics and sunscreens predominantly surround penetration into human skin and possible systemic exposure from topical application.

2.2 History of Nanosized TiO_2 and ZnO

The broad distribution of particle size in older-generation sunscreens caused excessive whitening of the skin, resulting in consumer reluctance to use products containing TiO_2 and ZnO . The solution arose from reducing their size to nanoparticles. The average size of these minerals was <100 nm,

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had superior UV protection, and had improved cosmetic appearance. By the 1980s, patents were filed and commercial sunscreens containing TiO_2 nanoparticles were introduced on a large scale by 1990. Nanosized ZnO was used in the later part of the decade [1]. Since that time, nanosized TiO_2 and ZnO ingredients have been approved and deemed safe for use by various consortiums and organizations including the US Food and Drug Administration (FDA). These materials now represent one of the largest applications of oxide nanoparticles with estimations that 70 % of titanium sunscreens and 30 % of zinc sunscreens are formulated with nanoingredients [2].

The current sunscreens on the market are more aesthetically acceptable and superior to older-generation sunscreens due to nanoparticle technology. In terms of cosmetic elegance, the smaller particle sizes minimize visible light scattering so the resulting topical application appears “transparent.” However, it is a misconception that the nano- TiO_2 and ZnO particles are truly transparent. In reality, they appear transparent at or below concentration thresholds due to increased light transmittance in the visible light range. Not only must particle size remain small, but also the particle size distribution must be narrow to avoid any whitening effect. Mineral particles of TiO_2 reflect and scatter UV light most efficiently at a size of 30–100 nm; whereas ZnO has an optimal size of 60–100 nm particles [3, 4]. Another benefit of

nanoingredients is the greater ease of the product to blend into the skin, due to the small particulate size. The reduction in particle size scatters and reflects UV more efficiently, improving human skin protection against UV-induced damage. For all of these reasons, nanometal oxides have been included into sunscreen products.

2.3 Three States of Nano TiO_2 and ZnO

Nanosized TiO_2 and ZnO can exist in three different states, encountered during the manufacturing process: primary nanoparticles (5–20 nm), aggregates (30–150 nm), and agglomerates (1–100 μm) (Fig. 2.1). The first stage in manufacturing nanoparticles is creation of the primary particles. The strong crystal attractions force primary particles to cluster together, forming chemically bound aggregates. These aggregates represent the smallest units that actually occur in a final sunscreen formulation because the forces required to break apart aggregates are far greater than those encountered during production of sunscreen formulations or application onto the skin. Aggregates may also form loosely bound agglomerates with sizes greater than 1 μm (1000 nm). This is the typical size of nano- TiO_2 and ZnO powder and results from the drying and heat treatment processes of manufacturing. The sunscreen’s vehicle formulation can also cause formation of large agglomerates

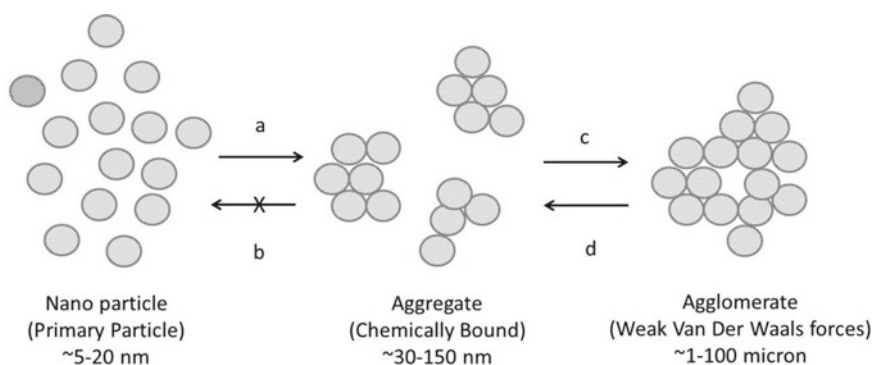


Fig. 2.1 Formation of aggregates and agglomerates from nanoparticle building blocks

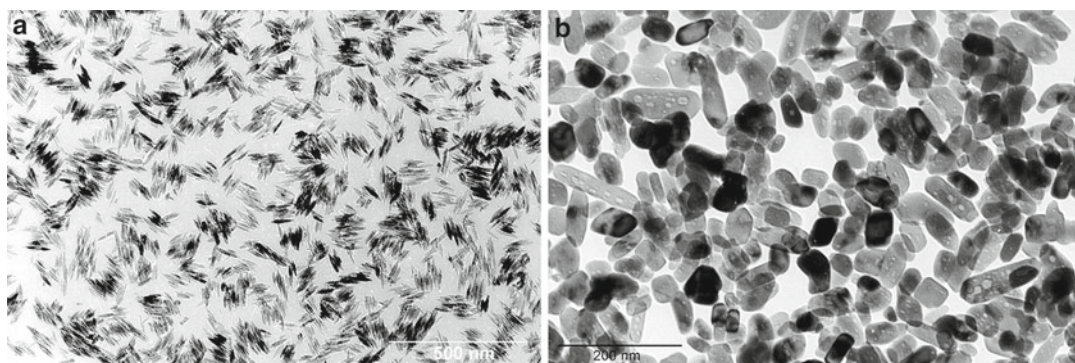


Fig. 2.2 (a) 15 nm TiO₂ and (b) 35 nm TiO₂ primary particles and aggregates measured by TEM

which do not provide effective UV attenuation. Special inert coating materials (commonly silica or dimethicone) can be applied to the surface of mineral particles to improve dispersion in sunscreen products and resist the formation of large particle agglomerations [5]. Nanoparticle-containing sunscreen emulsions can be visualized under transmission electron microscopy (TEM) (Fig. 2.2a, b). Typically, individual TiO₂ and ZnO nanoparticles cannot be detected, but present mainly in clusters (usually aggregates of 30–150 nm in size). On the market, sunscreen grade nanosized TiO₂ ranges from an ultra fine size of 30 nm to micro-sized aggregates. On the other hand, ZnO particles are used in the size range between 60 and 200 nm and the aggregate form is the smallest size that will occur in a sunscreen formulation.

2.4 UV Attenuation Based on Particle Size

Nanosized ultrafine inorganic sunscreens have the advantage of having both UV-reflecting and UV-absorbing properties. UV attenuation is the sum of scattering and absorption and depends on several factors including (1) dispersion of the inorganic particles (2) particle size and (3) refractive index [1]. With decreasing particle size, UV protection shifts towards protection to shorter UV wavelengths. In other words, smaller particles

attenuate shorter wavelengths of UV radiation. By TEM studies of UV attenuation and particle size, it is also known that nanoparticles reflect and absorb UV light most efficiently at the aggregate size (Fig. 2.3). At the average aggregate size of approximately 100 nm (red curve), TiO₂ particles offer effective UVA and UVB coverage. However, significant scattering is noted in the visible region. In comparison, TiO₂ particles with an average aggregate size of approximately 50 nm (green curve) have less visible light scattering and offer higher UVB and lower UVA protection. TiO₂ particles with an average aggregate size of 20 nm (blue curve) offer significantly lower protection from UVA and UVB radiation compared to 50- and 100-nm aggregates. The sunscreen with a smaller particle size will be a more transparent product; however, its UV efficacy will require additional UVA filters to achieve broad spectrum protection. Thereby, the best sunscreen would be one containing a mixture of TiO₂ nanoparticle aggregate sizes ranging between 50 and 120 nm [3]. ZnO has an optimal size between 60 and 100 nm particles. To achieve the optimal size and desired UV absorption profile, nanometal oxides are usually stabilized with dispersing agents to maintain stability and prevent the reformation of agglomerates. Therefore, sunscreen formulators must find an optimum particle size in order to achieve the desired UV absorption profile while delivering a pleasing aesthetic formula.

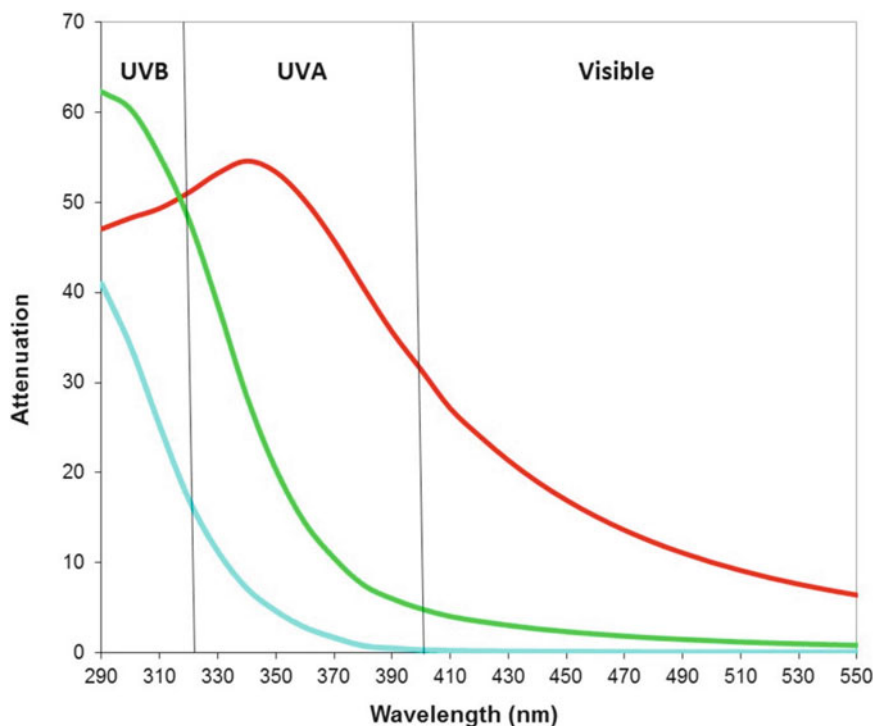


Fig. 2.3 UV attenuation vs. wavelength for spherical TiO_2 of varying particle size. Blue line, 20 nm; green line, 50 nm; and red line, 100 nm

2.5 Safety Concerns for Nano TiO_2 and ZnO

With the advent of TiO_2 and ZnO-based sunscreens, the safety concerns are centered around several issues: the endogenous toxicity of nanoparticles, the potential toxicity on the epidermis, and the percutaneous penetration of nanomaterials through skin. In their small size, nanoparticles are able to form protein complexes, evade immunologic defense mechanisms, and most importantly, induce free radical formation [6]. Because of the small size of nanoparticles and their increased surface reactivity, there is a greater potential to cause harm than larger particles. For example, the large surface interface can result in nanoparticles reacting with biologic proteins. When nanoparticles bind to proteins, they form complexes which can result in protein surface modifications and downstream signaling pathways and metabolic routes which are different

from the original protein. In addition, nanoparticles can evade the human defense system by escaping phagocytosis, either due to their small size or by carrying unrecognizable surface protein signals. Nanoingredients may also be intentionally engineered to avoid clearance in order to achieve therapeutic effects resulting in a prolonged half-life, ability to penetrate the blood brain barrier, and preference to collect in specific organs.

Besides the endogenous toxicities of nanoparticles, there is concern that TiO_2 and ZnO in topical sunscreens generate free radicals during exposure to UV radiation. When exposed to UV radiation, TiO_2 and ZnO generate electrons in the local media which in turn can induce the formation of peroxides, free radicals, and other reactive oxygen species (ROS). In turn, these ROS can cause damage to proteins, lipids, and DNA. This conglomeration of damage can alter the genetic code, as well as irreversibly injure cells and tissue.

The potential phototoxicity of TiO_2 nanoparticles was first demonstrated as DNA damage from hydroxyl radicals ($\cdot\text{OH}$) after exposure to UV irradiation [7–10]. In the presence of free radical quenchers such as dimethyl sulfoxide and mannitol, the DNA damage could be suppressed. The target damage included oxidative biomarkers such as 8-oxoguanosine [11], DNA strand breakage [7, 10], and structural chromosomal aberrations [12]. TiO_2 and ZnO in combination had similar genotoxic effects [10]. Further *in vitro* studies demonstrated that the DNA damage resulting from TiO_2 and ZnO agents are cytotoxic in the presence of cell cultures [11–13]. By using the technique of electron spin resonance spin trapping to catch these short-lived, volatile molecules, other ROS have been proposed to be generated in the process: hydrogen peroxide (H_2O_2) [14, 15], superoxide anion (O_2^-) [16], singlet oxygen ($^1\text{O}_2$) [16, 17], and carboxyl radical anion ($\cdot\text{CO}_2^-$) [18]. The size and crystal form of the metal oxide also affects toxicity: the anatase form of TiO_2 is more effective at generating $\cdot\text{OH}$ radicals than the rutile form [9]. These studies suggest that metal oxides are phototoxic by way of generating free radical species upon UV irradiation. In order to determine whether the phototoxicity was truly due to the presence of metal oxides alone, Dufour et al. [12] studied mammalian cells to examine the ability of ZnO to damage DNA in the presence of UV light when compared to its activity in the dark. The authors measured the effects of ZnO on Chinese hamster ovarian cells under three conditions: in the dark, pre-irradiation followed by ZnO treatment (PI) and simultaneous irradiation with ZnO treatment (SI). Interestingly, the nature, incidence, and severity of chromosomal aberrations (CA) in the PI and SI group were nearly identical. Therefore, the timing of exposure of the test agent and cells to UV radiation appeared to have had no effect on the frequency of CA induction. This is in contrast to true photoclastogenic agents, in which clastogenic potency would be significantly higher under simultaneous irradiation conditions. Therefore, the authors concluded that UV radiation mediated enhanced susceptibility of mammalian cells to ZnO , but ZnO itself was non-photoclastogenic.

There are several arguments that support the safety profile of nanoparticles. In the previous studies, the behavior of nanoparticles has only been elucidated *in vitro*, not in a true biological setting. In fact, the skin has in place an elaborate antioxidant mechanism, composed of enzymatic and nonenzymatic molecules, to quench ROS. Therefore, ROS generated by TiO_2 and ZnO during UV exposure can be neutralized by the body's natural defense mechanism. Besides endogenous protection, there are numerous synthetic techniques which have been developed to reduce these potential risks and decrease the reactivity of these nanoparticles. Pflucker et al. [19]; Livraghi S, et al. [20] tested a carbon coating on TiO_2 powder and demonstrated significant reductions in the formation of superoxide anion ($\cdot\text{O}_2^-$) and hydroxyl radicals ($\cdot\text{OH}$), even after UV exposure. Pan et al. [21] grafted an organic coating which could prevent nanoparticle adherence to the cell membranes of human dermal fibroblasts, and effectively reduce the cytotoxicity of ROS. Other techniques such as manganese doping and hydrophobic polymers have been proposed to prevent the contact of the TiO_2 surface with oxygen and water to inhibit the formation of radical species [22, 23]. The final argument in support of nanotechnology in sunscreens is the overall safety record of TiO_2 and ZnO . Both metal oxides have been used in mineral sunscreens and other topical products for years, with no studies demonstrating adverse effects of potentially harmful free radicals. TiO_2 can be found in toothpaste, lotion, skimmed milk, and cottage cheese, and ZnO is a major component in many baby powders, anti-dandruff shampoos as well as barrier creams.

Another component of the safety of nanoparticles is predicated on the dermal penetration of these materials and whether these small-sized minerals can penetrate the human skin. Are there new risks of cosmetic formulations containing nanosized particles when compared to traditional ingredients? The obvious concern is that the smaller particle size can enhance skin penetration, pass the skin barrier, and increase the risk for systemic toxicity and exposure. For most substances, the stratum corneum (SC) is the rate-limiting barrier against the percutaneous penetration

of topically applied substances. This non-viable outermost layer of the epidermis is approximately 15–20 μm thick in humans. Nanoparticles must pass the SC to reach the living skin in order to exert its toxicities. Most studies done under in vitro or in vivo conditions must be interpreted cautiously for several reasons. Animal skin samples have differing permeability for certain materials. In general, the order from most permeable to least permeable is rabbit, rodent, pig, and lastly, human skin. In addition, penetration of substrates may be favored if skin occlusion methods (which increases swelling of the corneocytes) were used in the studies. Finally, destruction methods such as tape stripping of the skin may artificially capture particles in the deep hair follicles or skin furrows to incorrectly conclude that a substance has penetrated the epidermis. In light of these study limitations, the consistent findings from these studies suggest that TiO_2 and ZnO nanoparticles remain on the surface of the SC and are unable to reach the living skin layers (Tables 2.1, 2.2, 2.3). Most studies have reported

that nanoparticles only penetrate into hair follicle openings and skin furrows, with negligible materials found below the SC. In 2000, the EU Scientific Committee on Cosmetics and Non-Food Products (SCCNFP) summarized a series of ten studies all investigating the percutaneous penetration of nanosized TiO_2 pigments [24]. Nanoparticles were detected using a myriad of imaging techniques including electron and light microscopy, X-ray fluorescence, particle-induced X-ray emission (PIXE), and electron emission spectrophotometry. All studies concluded that nanosized TiO_2 particles remain on the outer layers of the SC and do not penetrate into the living skin. Similarly, ZnO nanoparticles showed negligible penetration beyond the SC in animal and human skin studies. These skin penetration studies consistently summarize that neither nanoparticle can penetrate beyond the SC.

A number of factors may explain the poor penetration through the stratum corneum of intact and healthy human skin. From the field of transdermal drug delivery, it is known that the

Table 2.1 TiO_2 skin penetration studies (Adapted with permission from Newman et al. [6])

Study	Material	Particle size	Skin model/design	Results
Tan et al. [22]	TiO_2 (no coating specified)	Not specified	Human skin, in vitro	No significant penetration into skin
Lademann et al. [32]	TiO_2 (Al_2O_3 , stearic acid coated)	150–170 nm	Human skin biopsy	Penetration into upper layers of stratum corneum; ~1 % of particles in ostium of follicle
European Union SCCNFP Opinion [24]	TiO_2 (anatase and rutile forms, various coatings)	14–200 μm	Pig skin, in vitro Human skin, tape stripping, or biopsy	No penetration beyond the stratum corneum in any study
Pflucker et al. [19]	TiO_2 (SiO_2 , Al_2O_3 , $\text{Al}_2\text{O}_3 + \text{SiO}_2$ coated)	10–100 nm	Human skin biopsy	Penetration into upper layers of the stratum corneum
Schulz et al. [33]	TiO_2 ($\text{SiO}_2 \pm \text{Al}_2\text{O}_3$ coated)	10–100 nm	Human skin biopsy	Penetration into the upper layers of the stratum corneum
Gottbrath and Muller-Goymann [34]	TiO_2 -containing sunscreen (no coating specified)	Not specified	Human skin, tape stripping	Particles into upper layers of stratum corneum
Menzel et al. [13]	TiO_2 (various forms, no coating specified)	45–150 nm	Pig skin, in vitro	Particles in stratum corneum; minimal penetration into stratum granulosum
Popov et al. [3]	TiO_2 (rutile form)	100 nm	Human skin, tape stripping	No penetration beyond the stratum corneum
Mavon et al. [23]	TiO_2 (SiO_2 coated)	20 nm	Human skin, tape stripping and in vitro	Penetration in upper layers of stratum corneum

Table 2.2 ZnO skin penetration studies (Adapted with permission from Newman et al. [6])

Pirot et al, 1996 [35]	ZnO (no coating specified)	Not specified	Human skin, in vitro	0.36 % penetration in 72 h
European Union SCCNFP Opinion [36]	ZnO	Not specified	Pig skin, in vitro Human nonpsoriatic and psoriatic skin	No increase in plasma zinc levels; in vitro, penetration <1 % of dose; most ZnO recovered from stratum corneum
Cross et al. [4]	ZnO (siliconate coated)	15–30 nm	Human skin, in vitro	<3 % of applied Zn recovered in stratum corneum; penetration into upper layers of the stratum corneum
Zvyagin et al. [26]	ZnO (uncoated)	26–30 nm	Human skin, in vivo and in vitro	No penetration beyond stratum corneum, accumulation in skin folds and hair follicles

Table 2.3 Combination TiO₂ and ZnO skin penetration studies (Adapted with permission from Newman et al. [6])

Lansdown and Taylor [37]	TiO ₂ , ZnO (no coating specified)	<2–20 μm	Rabbit skin, in vivo	Penetration into stratum corneum and outer hair follicle
Dussert et al. [38]	TiO ₂ , ZnO (no coating)	TiO ₂ : 50–100 nm ZnO: 20–200 nm	Human skin, in vitro	Penetration into upper layers of stratum
Gontier et al. [39]	TiO ₂ , ZnO (Al ₂ O ₃)	Not specified	Human, pig, mouse skin, in vitro	TiO ₂ found in intercellular space between corneocytes of upper layers of stratum corneum
Gamer et al. [40]	TiO ₂ (SiO ₂ , dimethicone coated) ZnO (uncoated)	TiO ₂ : 30–60 nm ZnO: <160 nm	Pig skin, in vitro	Penetration into upper layers of stratum corneum; 0.8–1.4 % of applied dose recovered
Filipe et al. [41]	TiO ₂ (SiO ₂ ± Al ₂ O ₃ -coated ZnO	TiO ₂ : 20 nm ZnO: 20–60 nm	Human skin (intact, compromised, and psoriatic), tape stripping	No penetration beyond stratum corneum

upper limit of molecular size of a drug capable of skin penetration is 500 Da (2.5 nm) [10, 25]. Common dermatological drugs such as corticosteroids and antifungals all fall below this size and can penetrate the stratum corneum. As mentioned, nanosized TiO₂ and ZnO exist as aggregates and agglomerates in sunscreen products, their final size often exceeding 100 nm, 40 times larger than the upper limit. Besides molecular size, the drug substance must meet the criteria for polarity, concentration, and melting temperature. Nanoparticles are also considered insoluble

substances, lacking a diffusion driving force to promote penetration into the skin. Besides the physiochemical properties of nanoparticles, the local skin environment may be preventative of skin penetration. The stratum corneum is constantly turning over and this constant shedding process prevents long-term accumulation and penetration of nanoparticles into the viable components of the skin tissue. Finally, there is a potential penetration pathway of nanomaterials through the follicles, first proposed by Lademann et al. [26]. Hair follicles, with its tight network

of capillaries, are an important target for transdermal drug delivery and potential nanoparticle uptake. TiO_2 nanoparticles were found collecting in the “follicular sink” (the hair follicle openings and superficial portion of the follicles) at concentrations two orders of magnitude smaller than the upper part of the stratum corneum. However, it was later determined that the penetration process depends on a certain phase of the hair growth cycle; nanoparticles are only found when hair growth and sebum production are active. Therefore, despite the discovery of nanomaterials in the follicular orifices, the potential for them entering the living skin tissue is negligible, mainly because growing hair shafts push these materials to the surface of the skin [27, 28].

It is hypothesized that the percutaneous absorption of topically applied substances will be altered if the skin barrier is compromised or disrupted. In general, it is unknown what degree of compromised skin integrity will significantly increase skin penetration of small-sized particles. In hyperkeratotic skin conditions such as psoriasis vulgaris, a thicker epidermis actually enhances the skin's barrier function, which reduces penetration of topical drugs. Similarly, it has been found that there is identical or lower percutaneous absorption on intact compared to inflamed skin (from UVB-induced sunburn) following application of a [14C]methylprednisolone aceponate-containing lotion. The percutaneous absorption increased after skin tape stripping (removal of the stratum corneum) [29]. Skin conditions which disrupt the skin barrier such as eczema have increased penetration of topically applied substances [30]. In a recent study of four sunscreen formulations containing nanosized TiO_2 and ZnO (primary particle size 10–50 and 140 nm, respectively), UVB irradiation slightly enhanced the SC penetration of both types of nanoparticles in pig skin (TiO_2 deeper than ZnO). However, there was no evidence of systemic absorption [31]. Though a large amount of studies has rendered nanoparticle safety in cosmetic products in normal skin, their safety should be further assessed taking into account abnormal skin conditions and the possible impact of mechanical effects on skin penetration.

2.6 Conclusion

Sunscreen will continue to be an important component of photoprotection. The advancement in nanotechnology has allowed nanosized TiO_2 and ZnO ingredients to be amply incorporated into more effective and cosmetically acceptable sunscreen products. In developing modern inorganic sunscreens based on nanoparticles, formulators need to understand the UV-visible properties of TiO_2 and ZnO nanomaterials in relation to their particle size. A systemic and methodical approach is required to maintain the optimal size of these nanoparticles in the final sunscreen formulation. The safety debate is ongoing, despite overall consistent findings from laboratory studies demonstrating no penetration of nanoparticles into the living layers of the skin. Despite their inert behavior, nanoparticles could still pose a risk on compromised, sun damaged skin or from inhalation (such as from spray sunscreens). Such questions remain to be answered.

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