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(54) **VISIBLY TRANSPARENT UV
PHOTOPROTECTIVE COMPOSITIONS**

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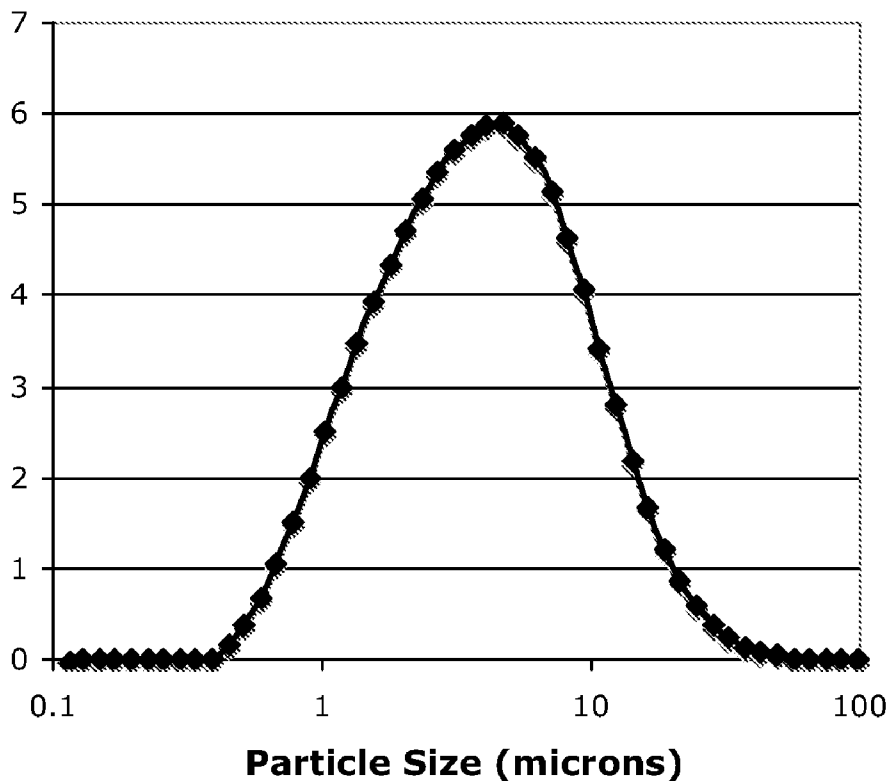
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030725, filed on Jan. 12, 2009.

(57) **ABSTRACT**

A broad-spectrum UV photoprotective composition is described. The composition is characterized in that the composition comprises mesoporous zinc oxide aggregates having an average aggregate size of at least 0.8 microns dispersed in a carrier and the composition is visibly transparent. Sufficient zinc oxide is included in the composition to achieve an SPF greater than 15, greater than 25, greater than 30, or greater than 50.



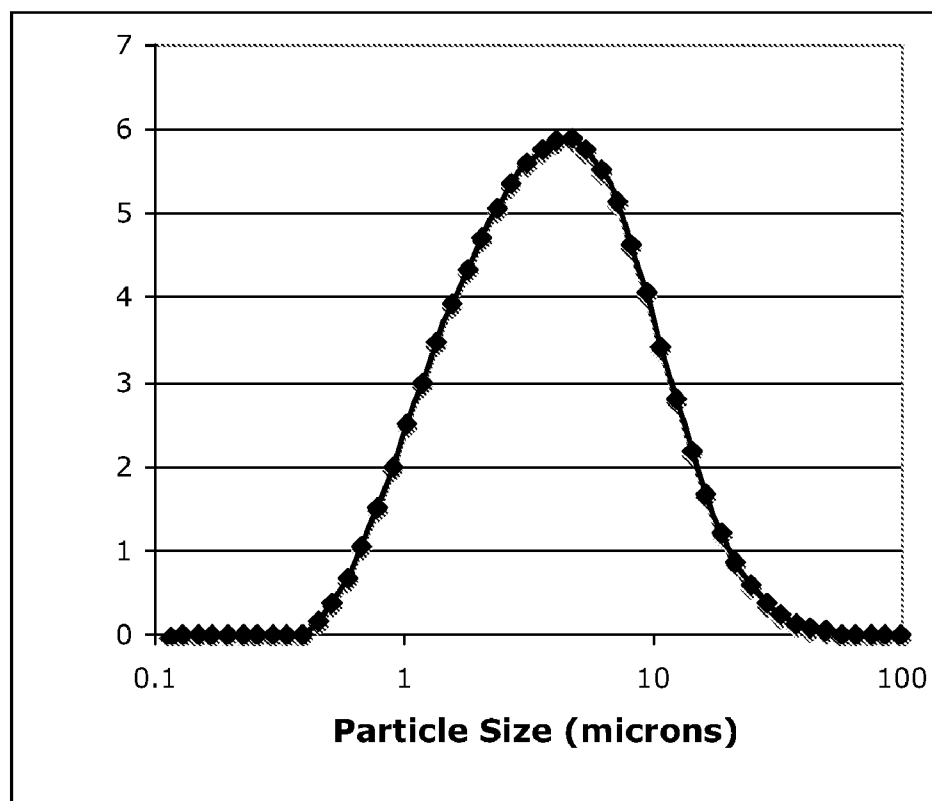


Figure 1

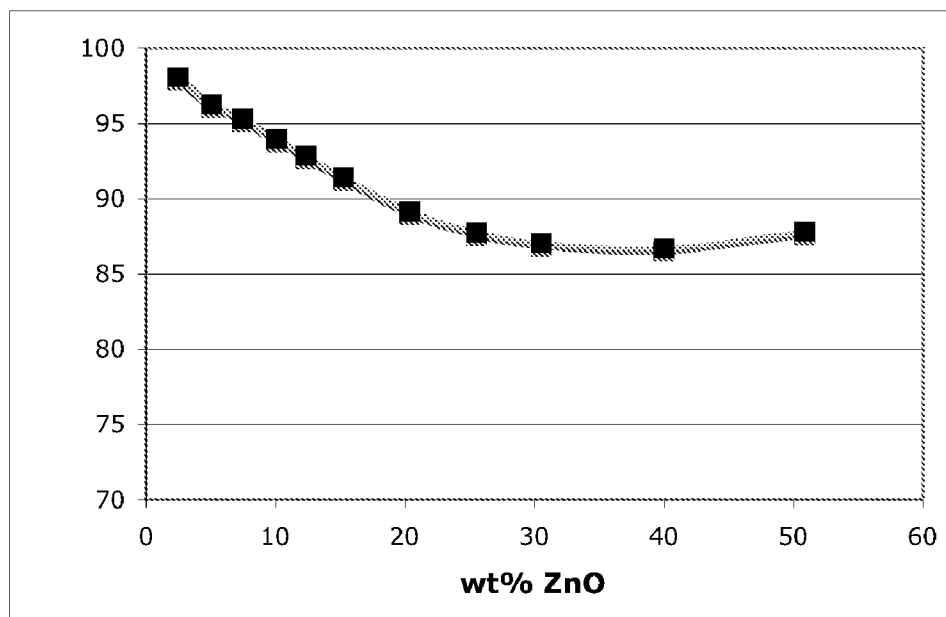


Figure 2

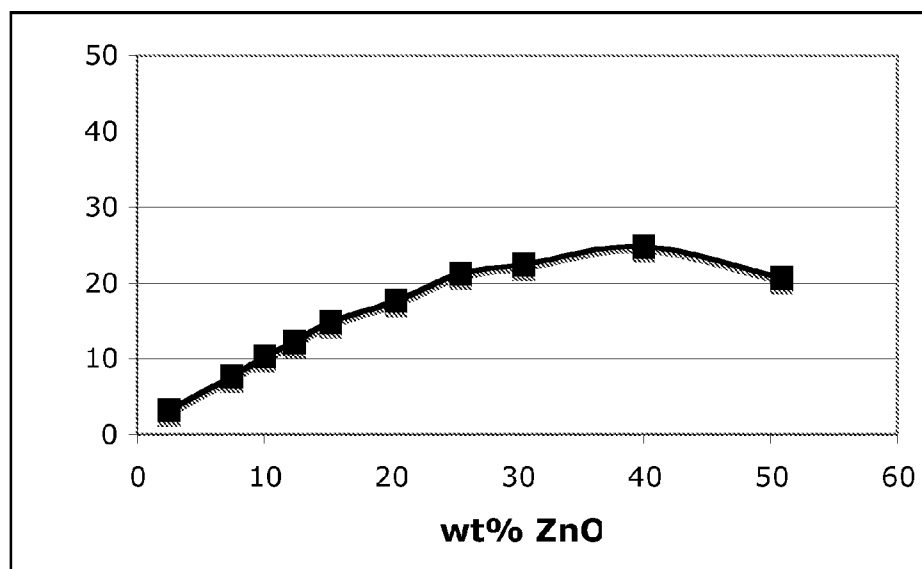


Figure 3

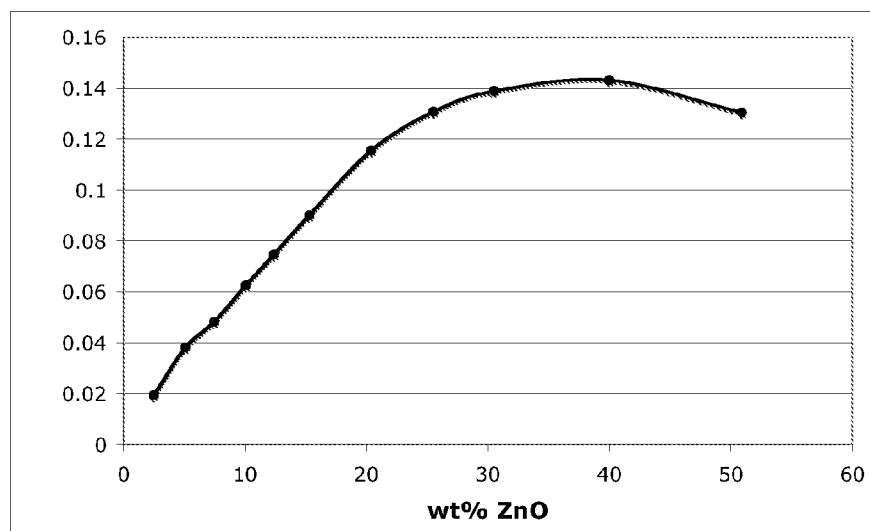


Figure 4

VISIBLY TRANSPARENT UV PHOTOPROTECTIVE COMPOSITIONS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of PCT/US2009/30725, filed Jan. 12, 2009, and entitled “Visibly Transparent UV Photoprotective Compositions”, which claims priority from U.S. Provisional Patent Application Ser. No. 61/006,398, filed Jan. 11, 2008, and titled “Visibly Transparent UV Photoprotective Compositions”. The entire contents of these applications are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

[0002] The present invention is directed to the use of mesoporous zinc oxide aggregates in visibly-transparent compositions that provide broad-spectrum photoprotection when applied to a substrate.

BACKGROUND TO THE INVENTION

[0003] The adverse health consequences associated with exposure to ultraviolet (UV) radiation (i.e., light having wavelengths between 290 nm and 400 nm) are widely-reported in the scientific literature. Short-term sequelae include erythema and sunburn; longer term effects include premature aging of the skin (manifested as lines, wrinkles and lentigines), premalignant solar keratoses, and skin cancer. More particularly, UVB radiation (290-320 nm) is associated with burns and erythema, while UVA radiation (320-400 nm) is reported to contribute to premature skin ageing and photosensitivity to certain chemicals.

[0004] UVA protection has been measured and communicated to consumers in a number of ways. In Europe, the European Cosmetic Toiletry and Fragrance Association (COLIPA) has developed a labelling scheme whereby photoprotective products having a UVA protection factor of at least $\frac{1}{3}$ that of the sun protection factor (SPF) may print “UVA” in a circle on the product container or label. In the United Kingdom, companies frequently label their products using the Boots Star system based on the ratio of UVA to UVB. In Japan, the Japan Cosmetic Industry Association has issued a three-tiered system: Protection Factor (PFA) of 2 to less than 4 is “PA+”; PFA of 4 to less than 8 is “PA++”; and PFA of 8 or more is “PA+++”. In the US, the Food and Drug Administration (FDA) issued proposed amendments of the Final Monograph on Sunscreen Products for Over-the-Counter Human Use. The proposed regulation creates a rating system based on a scale of one to four stars that is designed to help consumers identify the level of UVA protection offered by a product.

[0005] It is well-known in the art that zinc oxide blocks UV radiation from 290 nm up to about 375 nm. In addition, zinc oxide has long been utilized in cosmetic and sunscreen formulations for its antimicrobial and non-sensitizing properties. Despite these beneficial properties, use of zinc oxide has been limited primarily due to undesirable white residue deposited on the substrate to which a ZnO-containing product was applied. To the extent that ZnO was incorporated in cosmetic and sunscreen formulations, formulators minimized levels and/or users applied the product sparingly or at levels lower than indicated to reduce or minimize whitening. In so doing, however, the photoprotective efficacy of the product

was lessened, making it necessary to incorporate chemical UV absorbers to meet SPF requirements. Similarly, whitening was and is undesirable in transparent coatings and transparent plastic films.

[0006] Whitening on a substrate (e.g., skin) after application of a photoprotective product containing ZnO is attributable to diffuse reflection, the scattering of light in the backward direction (i.e., away from the substrate and toward the viewer). In contrast, light scattered in the forward direction (through the substrate) contributes to the transmittance of light. This is known in the art as diffuse transmittance. Total transmittance of incident light through a ZnO-containing photoprotective product is thus comprised of the diffuse light transmittance as well as light that is transmitted without scattering, known in the art as “specular” transmittance. The diffuse component of total transmitted light gives rise to a “soft focus effect”, a highly desirable property of cosmetic products that, among other things, helps to reduce the appearance of fine lines and wrinkles.

[0007] Prior art approaches to the problem of surface whitening caused by ZnO-containing photoprotective products have concentrated largely on reducing the average size of the zinc oxide particles to below at least 0.2 μm . This particle size reduction increases transparency and reduces whiteness (by decreasing the scattering of visible light).

[0008] U.S. Pat. No. 5,587,148 teaches a substantially visibly transparent topical sunblock formulation comprising a dispersion of micronized particles of zinc oxide having an average particle diameter of less than about 0.2 μm . U.S. Pat. No. 5,032,390 teaches sunblock compositions comprising from 1% to 25% by weight of particulate zinc oxide having an average particle size of from 0.07 μm to 0.3 μm . The disclosed compositions are further taught to include from 1% to 25% of particulate titanium dioxide having an average particle size of from 0.03 μm to 0.07 μm . International Patent Publication WO 2006/010214 discloses a UV photoprotective composition comprising zinc oxide nanoparticles in the size range of 0.015 μm to 0.5 μm in combination with a plant-derived oil.

[0009] Reduction of ZnO particle size to nanoscale (e.g., particularly less than about 0.2 μm) is not, however, without consequences. The greater available surface area of nanosized particles increases the amount of flocculation and, in turn, agglomeration. Photoprotective products containing nanosized particles therefore may be unstable, exhibiting particle settling and, in the case of emulsions, phase separation. This instability can lead to higher scattering of light and increased whiteness than would otherwise be expected based on particle size alone, as well as a reduced level of photoprotection.

[0010] Nanoporous alumina and polymer films are known to exhibit decreased refractive index and high transparency with low reflection losses. U.S. Pat. No. 7,075,229 teaches a light-emitting device incorporating a transparent nanoporous alumina film.

[0011] US Patent Publication No. 2006/0188432 teaches a method of producing porous titanium oxide powder with improved transparency. International Patent Publication WO 03/080515 and German Patent DE10212680 teach the synthesis of nanoscale, pyrogenically produced zinc oxide, in the form of aggregates of anisotropic primary particles, the primary particles having an average diameter of 50-300 nm.

[0012] The high surface area of nanosize ZnO particles has been associated with a high level of photocatalytic activity, resulting in degradation of polymeric ingredients typically

contained in cosmetics, plastics, and paints. Moreover, in photoprotective personal care products, high photocatalytic activity can produce free radicals which have been reported to result in deleterious health effects. See, e.g., L. Jing et al. "The Surface Properties and Photocatalytic Activities of ZnO Ultrafine Particles", *Applied Surface Science*, Vol. 180, pp. 308-314 (July 2001).

[0013] Recently, concerns have been raised regarding potential negative health consequences of transdermal absorption of nanoparticles, including submicron sunblocking agents. In the case of topical photoprotective products, according to authorities, such as the Australian Therapeutic Goods Administration, the weight of current evidence is that nanoparticles in sunscreens remain on the surface of the skin and in the stratum corneum. Nonetheless, negative perceptions have and will continue to affect consumer acceptance of these products.

[0014] In the United States, the FDA has approved the use of two agents as safe and effective for use in topical products to attenuate the effects of UVA-zinc oxide (which, as discussed above, acts as a physical block) and avobenzone which absorbs UVA via a chemical reaction. While the combination of avobenzone and zinc oxide in UV photoprotective compositions is known in the art—see, e.g., U.S. Pat. No. 5,827,508 (teaching a sunscreen composition comprising from 0.1% to about 10% of avobenzone and from about 0.1% to about 20% of a surface-treated zinc oxide)—this combination is not presently permitted under regulations now in effect in the US. The avobenzone/ZnO combination would be permitted if the amendments to the FDA monograph as proposed in late August 2007 are implemented in a final regulation.

[0015] It is well-known in the art, however, that avobenzone is not photostable particularly when used in combination with other UV absorbers. Attempts to photostabilize avobenzone, with physical as well as chemical agents, are described in U.S. Pat. Nos. 5,576,354; 5,587,150; 5,849,273; 5,985,251; 6,033,649; 6,071,501; 6,444,195; 7,235,587 and 7,244,416. For example, U.S. Pat. No. 7,244,416 teaches a method of photostabilizing avobenzone in topical photoprotective formulations containing zinc oxide at a concentration of from about 6% to 25% by adding ensulizole.

[0016] The scientific literature has reported transdermal penetration and systemic absorption of organic sunscreen filters and their breakdown products. This, in turn, has raised health concerns. There have also been reported concerns about transdermal penetration of nano-sized pigments. Irrespective of whether and the extent to which these concerns are substantiated, there has been and remains an as yet unmet need for topical UV photoprotective compositions that minimize or, preferably, do not contain organic sunscreen filters and/or nano-sized physical sunscreen blocking agents.

[0017] There has been and remains a need for photoprotective formulations comprising zinc oxide that provide substantial visible transparency or decreased whitening, which (because of sizing) does not raise concerns about transdermal penetration. These needs are met by compositions of the present invention.

SUMMARY OF THE INVENTION

[0018] According to a first aspect of the present invention there is provided a broad-spectrum UV photoprotective composition characterized in that the composition comprises mesoporous zinc oxide aggregates having an average aggregate size of at least 0.8 microns dispersed in a carrier and the

composition is visibly transparent. In one form, the zinc oxide aggregates may have an average aggregate size of at least one of; greater than 1.0 microns, greater than 2.0 microns or greater than 3.0 microns.

[0019] In one form, the mesoporous zinc oxide aggregates are present in an amount effective to provide an SPF of at least one of; greater than 15, greater than 25, greater than 30, or greater than 50.

[0020] The level of visible transparency depends in part on the weight percentage of zinc oxide included in the composition. In one form of the present invention, the composition may have a total absorbance through a path length of 20 microns at 550 nm not greater than 0.15 when the composition includes zinc oxide aggregates at a concentration of at least 40 or 50% by weight of the total composition. In another form, the composition may have a total absorbance through a path length of 20 microns at 550 nm not greater than 0.14 when the composition includes zinc oxide aggregates at a concentration of 30% by weight of the total composition. In yet another form, the composition may have a total absorbance through a path length of 20 microns at 550 nm not greater than 0.12 when the composition includes zinc oxide aggregates at a concentration of at least 20% by weight of the total composition. In yet another form, the composition may have a total absorbance through a path length of 20 microns at 550 nm not greater than 0.06 when the composition includes zinc oxide aggregates at a concentration of at least 10% by weight of the total composition.

[0021] In one form, the zinc oxide aggregates may have an average aggregate size of at least 3.0 microns and the composition has a total absorbance at 550 nm through a path length of 20 microns not greater than 0.20.

[0022] In one form, the zinc oxide aggregates may have an average aggregate size of at least 2.0 microns and the composition has a total absorbance at 550 nm through a path length of 20 microns not greater than 0.16.

[0023] Alternatively or additionally, the composition may further comprise a dibenzoylmethane derivative. Alternatively or additionally, the composition may include less than 5% or less than 3% of an organic sunscreen filter. In one form, the visibly-transparent, broad-spectrum UV photoprotective composition is photostable and the organic sunscreen filter is avobenzone.

[0024] Alternatively or additionally, the zinc oxide aggregates may have an average aggregate size of at least one of; greater than 1.0 microns, greater than 2.0 microns or greater than 3.0 microns and the composition has a soft focus factor at 550 nm greater than 40.

[0025] Alternatively or additionally, the zinc oxide aggregates may have an average aggregate size of at least one of; greater than 1.0 microns, greater than 2.0 microns or greater than 3.0 microns and the composition has a CIE Whiteness index less than 25. Alternatively or additionally, the zinc oxide aggregates have an average aggregate size of at least one of; greater than 1.0 microns, greater than 2.0 microns or greater than 3.0 microns and the composition has a CIE L*lightness less than 30.

[0026] Alternatively or additionally, the composition may include one or more non-mesoporous zinc oxide aggregate (MZO) photoprotective agents, wherein the one or more non-mesoporous zinc oxide aggregate (MZO) photoprotective agent(s) are present in a concentration that increases the SPF of the composition by not more than 2 units of SPF.

[0027] According to a second aspect of the present invention there is provided a method of providing protection from ultraviolet radiation to mammalian skin or hair comprising contacting the skin or hair with a composition according to the first aspect of the present invention.

[0028] According to a third aspect of the present invention there is provided a method of treating a human dermatologic condition selected from the group consisting of acne, psoriasis, eczema, ichthyosis, pruritus, dryness and dermatitis by applying a therapeutically-effective amount of a visibly-transparent topical preparation comprising the composition according to the first aspect of the present invention.

[0029] According to a fourth aspect of the present invention, there is provided a visibly-transparent, broad-spectrum UV photoprotective composition having substantially as herein described with reference to the examples and accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] In order to facilitate a more detailed understanding of the nature of the invention, embodiments will now be described in detail, by way of example only, with reference to the accompanying drawings, in which:

[0031] FIG. 1 illustrates graphically the aggregate size distribution of formulation D as measured using laser light scattering for Example 1;

[0032] FIG. 2 illustrates graphically the effect of ZnO concentration on total visible transmittance;

[0033] FIG. 3 illustrates graphically the effect of ZnO concentration on the CIE whiteness index; and,

[0034] FIG. 4 illustrates graphically the effect of ZnO concentration on total absorbance.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0035] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Unless otherwise indicated, as used in the present application, numerical percentages refer to the percentage by weight of a specified ingredient relative to the total weight of the composition.

[0036] The term “microns”, “micrometers” and the symbols “μ” and “μm” are used interchangeably throughout this specification to refer to a unit of measurement that is one millionth of a meter in length.

[0037] As used in the present application, the term “MZOAs” refer to zinc oxide particles comprising a plurality of primary zinc oxide crystallites bonded together at shared interfaces. Embodiments of the MZOAs of the present invention have an average crystallite size of from about 10 nm to about 20 nm.

[0038] MZOAs contained within the UV photoprotective compositions of the present invention are “mesoporous” by which is meant that the bonded primary zinc oxide crystallites form aggregates having pores ranging from about 2 nm to about 100 nm.

[0039] MZOAs used in the present invention may be prepared by known processes, including the mechanochemical process (MCP), the French and American methods, and precipitation methods. U.S. Pat. Nos. 6,203,768 and 6,503,475 describe the manufacture of ultrafine and aggregate particles such as ZnO using MCP. In the French method, zinc metal is

heated to a high temperature, vaporized and then condensed in an oxidizing atmosphere to form porous aggregates of interconnected crystallites. In the American method, zinc oxide aggregates are obtained by calcining zinc oxide ores with carbon and then oxidizing the zinc metal. In precipitation processes, a soluble zinc salt such as zinc sulphate is crystallized into zinc oxide aggregates through the addition of a base. The precipitated aggregates are then washed, and sintered. The structural features of the MZOAs suitable for use in compositions of the present invention may be tailored using any of the aforementioned methods by techniques known to those of skill in the art. Preferred MZOAs suitable for use in compositions of the present invention are available from Antaria Limited (Bentley, Australia).

[0040] The MZOAs in compositions of the present invention may have total meso porosities of from 50% to about 75% of the MZOA volume. The closed porosity may be measured using helium gas pycnometry (Micromeritics AccuPyc 1330). The open porosity may be measured using gas adsorption techniques (Micromeritics Tristar) according to the Barrett-Joyner-Helenda method (described in *Techniques de l'Ingenieur [Techniques of the Engineer]* and entitled “Texture des solides poreux ou divises” [Texture of porous or divided solids], p. 3645-1 to 3645-13). In particularly preferred embodiments of the present invention, MZOAs have a distribution of mesopores with an average pore size of about 35 nm.

[0041] MZOAs are incorporated into the UV photoprotective compositions of the present invention as dispersions. The carriers in which the MZOAs may be dispersed include dermatocosmetic carriers known to those of skill in the art. Suitable carriers include, but are not limited to, esters such as C₁₂₋₁₅ alkyl benzoate, capric caprylic triglyceride, isopropyl palmitate, octyl stearate, dicaprylyl carbonate, natural oils such as macadamia oil, olive oil, jojoba oil, silicones such as cyclomethicone, dimethicone and methyl trimethicone.

[0042] The term “aggregate size” as used hereinbelow refers to the overall size of discrete unattached aggregates that are individually dispersed in a liquid, semi-solid or solid media. The average aggregate size is defined mathematically according to the following equation:

$$\langle d_v \rangle = \sum f_i \cdot d_i$$

[0043] Wherein

[0044] $\langle d_v \rangle$ is the volume weighted average aggregate size;

[0045] d_i is the aggregate diameter; and

[0046] f_i is the volume fraction of aggregates with a diameter value of d_i .

[0047] The size of MZOAs is expressed in terms of a distribution of aggregates as measured using microscopy, light scattering and other techniques known to those of skill in the art. A preferred method of measuring the size distribution of MZOAs is based on light scattering. For purposes of the present application, sizing of MZOAs is measured using static laser light-scattering.

[0048] Compositions within the scope of the present invention provide broad-spectrum UV photoprotection. As used in the present invention, by the term “broad-spectrum UV photoprotective composition” is a composition that blocks, absorbs or otherwise attenuates electromagnetic radiation having a wavelength of from 290 nm to 400 nm.

[0049] A composition is “visibly transparent” if that composition is able to be applied to a substrate and light is able to

pass through the composition with little or no distortion so that the substrate can be clearly seen through the composition using the eye. The transparency is measured using methods known to those skilled in the art. In this specification, measurements of total absorbance are used to demonstrate the level of transparency achieved using various embodiments of the compositions being claimed.

[0050] As used herein, by the term “organic sunscreen filter” is meant an organic compound that absorbs ultraviolet radiation. Non-limiting examples of organic sunscreen filters include: p-Aminobenzoic acid (PABA), preferably up to 15%; Avobenzone, preferably up to 3%; Cinoxate, preferably up to 3%; Dioxybenzone, preferably up to 3%; Homosalate, preferably up to 15%; Menthyl anthranilate, preferably up to 5%; Octocrylene, preferably up to 10%; Octyl methoxycinnamate (Octinoxate), preferably up to 7.5%; Octyl salicylate, preferably up to 5%; Oxybenzone, preferably up to 6%; Padimate O, preferably up to 8%; Phenylbenzimidazole sulfonic acid (Ensulizole), preferably up to 4%; Sulisobenzene, preferably up to 10%; Trolamine, preferably salicylate up to 12%; 4-Methylbenzylidene camphor (USAN Enzacamene); Methylene Bis-Benzotriazolyl Tetramethylbutylphenol (USAN Bisotrizole) marketed under the tradename Tinosorb® M; Bis-Ethylhexyloxy-phenol Methoxyphenyl Triazine (USAN Bemotrizinol) marketed under the tradename Tinosorb® S; Terephthalylidene Dicamphor Sulfonic Acid (USAN Ecamsule) marketed under the tradename Mexoryl® SX; Drometrizole Trisiloxane marketed under the tradename Mexoryl® XL; Disodium Phenyl Dibenzenimidazole Tetrasulfonate marketed under the tradename Neo Heliopan® AP; Diethylamino Hydroxybenzoyl Hexyl Benzoate marketed under the tradename Uvinul® A Plus; Octyl Triazone marketed under the tradename Uvinul® T 150; Diethylhexyl Butamido Triazone marketed under the tradename Uvasorb® HEB; Polysilicone-15 marketed under the tradename Parsol® SLX.

[0051] The term “non-MZOA photoprotective agent” refers to an organic sunscreen filter as defined above, as well as non-porous metal oxide pigment particles, coated or uncoated, that block ultraviolet radiation.

[0052] When light hits skin exhibiting signs of aging (e.g., fine lines and wrinkles) the amount of light reflected back to the observer is less than that from smooth skin and, as a result, the eye will perceive the wrinkled skin regions as darker and thus more noticeable. If the skin is covered with a thin layer of embodiments of a visibly transparent photoprotective composition comprising MZOAs of the present invention diffuse transmittance of light through the layer reduces the perceived appearance of fine lines and wrinkles by diffusing the light emanating from the skin.

[0053] As used in the present application, the term “soft focus effect” refers to a cosmetic reduction in the appearance of surface fine lines and wrinkles on the skin by allowing light that is highly diffused, but while remaining highly transparent, to show natural skin tones, and is expressed by the following formula:

$$SFE = \frac{\text{total transmittance}(\%) \text{ at } 550 \text{ nm}}{\text{transmittance}(\%) \text{ at } 550 \text{ nm}} \times \frac{1}{100}$$

[0054] The SFE of visibly-transparent, UV photoprotective compositions according to the present invention is greater than about 20, more preferably greater than about 30, still more preferably greater than about 40.

[0055] Visibly-transparent, broad-spectrum UV photoprotective compositions according to the present invention may be applied directly to a substrate (e.g., as a cream, lotion, gel,

foam, mousse or spray) or in the form of a wipe, towelette or non-woven fabric. These compositions may be formulated as anhydrous compositions (e.g., gels or sprays) as well as two- or three-phase emulsion, including water-in-oil, oil-in-water, water-in-silicone, silicone-in-water, water-in-oil-in-water, water-in-silicone-in-water. Where the composition is an emulsion, it comprises one or more surfactants at a concentration of from about 0.01% to about 20%, preferably from about 0.1% to about 15%, and more preferably from about 0.5% to about 10% by weight of the total composition. The surfactant(s) are selected from the group consisting of amphoterics (e.g., propionates, alkylidimethyl betaines, alkylamido betaines, sulfobetaines and imidazolines), anionics (fatty alcohol sulphates, alpha olefin sulfonates, sulfosuccinates, phosphate esters, carboxylates and sarcosinates), cationics (alkyl quaternaries, allylamido quaternaries, imidazoline quaternaries), and/or non-ionics (alkanolamides, ethoxylated amides, esters, alkoxyated alcohols, alkoxyated triglycerides, alkylpolyglucosides, amine oxides, sorbitan esters and ethoxylates) as well as silicone surfactants (e.g., dimethicone copolyols, alkylidimethicone copolyols, silicone quaternary compounds, silicone phosphate esters and silicone esters) as well as glycerol and sorbitan esters as further described in O'Lenick Jr., *Surfactants: Strategic Personal Care Ingredients* (Allured Publishing (2005) and McCutcheon's *Detergents and Emulsifiers* (1986), the disclosures of which are each incorporated by reference.

[0056] Compositions according to the present invention may optionally contain one or more film-forming agents including, but not limited to, cross-linked silicone polymers and non-silicone polymers comprised of polymerized ethylenically unsaturated monomers, alone or in combination with one or more organic moieties. The cross-linked silicone polymer may be either an elastomer or resin.

[0057] Compositions according to the present invention may also optionally contain one or more agents that increase the water resistance of the composition.

[0058] One aspect of the present invention is directed to methods of providing broad-spectrum protection to mammalian skin and/or hair from photodamage caused by exposure to ultraviolet radiation by application of embodiments of the visibly-transparent topical compositions of the present invention. The Cosmetic, Toiletries & Fragrance Association International Cosmetic Ingredient Dictionary and Handbook (11th Edition, 2006) (“CTFA Dictionary”) describes a wide variety of non-limiting cosmetic and pharmaceutical ingredients commonly used in the skin care industry. Embodiments of a visibly-transparent topical broad-spectrum compositions according to the present invention may comprise one or more plasticizers, structuring agents, viscosity modifiers, thickeners and/or gellants as further described in U.S. Pat. Nos. 6,492,326 and 6,277,892 and US Patent Publication Nos. 2004/0180020 and 2005/0142095. Additionally, embodiments of a visibly-transparent topical broad-spectrum composition according to the present invention may comprise one or more skin or hair active ingredients including, but not limited to, antioxidants, free-radical quenchers, external analgesics, anti-inflammatory agents, humectants, moisturizers, skin soothing and/or healing agents, vitamins and derivatives thereof, as well as ingredients useful in reducing the appearance of fine lines, wrinkles, and hyperpigmentation as described in the '326 and '892 Patents as well as the '020 and '095 Application Publications.

[0059] Embodiments of the present invention may be directed to the treatment of acne, psoriasis, eczema, ichthyosis, pruritus, dryness and dermatitis by applying a therapeutically-effective amount of a visibly-transparent topical preparation. Such preparations may further comprise dermatopharmaceutic agents known to those of skill in the art to be therapeutically-effective in treating the dermatologic condition of interest. Suitable dermatopharmaceutic agents are described, for example, in Kerdel, et al., *Dermatologic Therapeutics* (2005), and in Hardman et al., *Goodman & Gilman's: The Pharmacological Basis of Therapeutics* (10th Edition, 2001), the disclosures of which are incorporated herein by reference.

[0060] Embodiments of the present invention are directed to a photostable visibly-transparent, broad-spectrum UV photoprotective composition comprising avobenzone. For purposes of the present invention, "a photostable product" is a product that has the desired efficacy (e.g., SPF, persistent pigment darkening) after UV irradiation (e.g., at a specified number of MEDs). See, COLIPA Method for the In Vitro Determination of UVA Protection provided by Sunscreen Products (2007), the disclosure of which is incorporated herein by reference. For example, photostability can be determined by measuring absorbance on a Labsphere UV-1000S Ultraviolet Transmittance Analyzer (software version 1.27) before and after irradiation with a Solar Light Company model 16S solar simulator (equipped with a WG 320 filter to transmit radiation greater than 290 nm) in 5 MED increments up to 35 MED. Output is monitored by a PMA 2105 UV-B DCS Detector (biologically weighted) and controlled by a PMA 2100 Automatic Dose Controller (Solar Light Co.). After a composition has been exposed to 35 MED of irradiation, the absorbance of each composition is measured between 290 nm and 400 nm (the U_b range).

[0061] MZOAs of the present invention are of a sufficiently large size that they do not penetrate the epidermal barrier. Accordingly, a second aspect of the present invention is directed to UV photoprotective compositions that provide a desired SPF and UVA Protection while minimizing or, preferably, eliminating organic sunscreen filters and/or nano-sized physical sunscreen blocking agents.

[0062] The following formulation examples are further illustrative of embodiments of the present invention. The components and specific ingredients are presented as being typical, and various modifications can be derived in view of the foregoing disclosure within the scope of the invention. All percentages, ratios and proportions herein are by weight, unless otherwise specified. All temperatures are in degrees Celsius unless otherwise specified.

Example 1

Aggregate Sizes

[0063] Five formulations (designated A-E) were prepared by dispersing MZOAs into suitable carriers by grinding in a bead mill following standard procedures. The MZOA concentration was 50 wt %. The carriers used were caprylic/capric triglyceride (CCTG) for formulation A and B, and C12-15 alkyl benzoate (AB) for formulations C-E. With formulations A-B and C-E the effect of milling condition (intensity) on the average aggregate size was investigated.

[0064] Table 1 shows the volume-weighted average aggregate size of each of the samples. In all formulations, the average aggregate size of the MZOA dispersion was larger

than 1 μ m. Increasing milling intensity caused a decrease in the average aggregate size consistent with accepted milling theory.

Formulation	Carrier Liquid	Milling Intensity	Volume weighted average size
A	CCTG	HIGH	1.7 μ m
B	CCTG	MEDIUM	3.2 μ m
C	AB	HIGH	2.0 μ m
D	AB	MEDIUM	4.7 μ m
E	AB	LOW	6.9 μ m

[0065] The aggregate size distribution of formulation D as measured using laser light scattering is presented in FIG. 1.

Example 2

Optical Properties

[0066] The optical properties of formulations B and C of Example 1—specifically, total absorbance, soft-focus, CIE whiteness index and CIE L*Lightness—are listed in Table 2, described in greater detail below. The concentration of MZOAs in each formulation was 50%.

[0067] Each of formulations B and C was placed in a quartz cell of 20 microns in optical path length. Optical transmittance measurements were carried out using a Carey 300 bio UV-Vis spectrophotometer equipped with an integrating sphere.

[0068] The total Absorbance, A, was calculated from the total transmittance by the formula

$$A = -\ln [T(\%)/100]$$

[0069] Where T is equal to the total transmittance to visible light at a wavelength of 550 nm expressed as a percentage, through an optical pathlength of 20 microns.

[0070] The soft-focus factor was calculated from the total and diffuse transmittance values.

[0071] The CIE whiteness index and L*Lightness value of the formulations were calculated from reflectance values according to the Australian standard ASTM-E313. The CIE whiteness index indicates how close the color is to total whiteness in the scale from 0-100 with the higher the value, the whiter the product. A low CIE whiteness index is an indication of high transparency.

[0072] It will be appreciated by a person skilled in the art that the CIE whiteness index does not necessarily correlate with transparency because it is affected by color. For example, if the color is black, the CIE whiteness index is zero and transparency is poor. CIE L*Lightness provides an indication of the human eye's perception of brightness as opposed to darkness on a scale of 0 to 100 and is independent of color. Thus, CIE L*Lightness is a good indicator of whiteness for transparent materials.

[0073] For comparison purposes, Table 2 also includes data for several prior art formulations comprising 40-60 wt % of the following types of zinc oxide single crystallite particles dispersed in CCTG:

- Silicone-coated ZnO nanoparticles having an average particle diameter of ~30 nm prepared using the method described in U.S. Pat. No. 6,503,475;
- stearic-acid coated ZnO nanoparticles having an average particle size of ~30 nm prepared using the method described in U.S. Pat. No. 6,503,475;

c) silica-coated ZnO nanoparticles having an average particle size of 82 nm prepared using the method described in U.S. Pat. No. 5,587,148.

[0074] Compositions of the present invention comprising MZOAs have significantly higher transparencies and lower diffuse reflectances than the comparative prior art formulations. This results in lower absorbance (0.16) and lower whiteness (less than 25), and lightness (less than 27) values. Formulations B and C also exhibited significantly higher soft focus factors in comparison to the prior art formulations.

ing concentration as predicted by linear Beer-Lambert law behaviour. At higher zinc oxide concentrations, the absorption leveled out with increasing zinc oxide concentration, reaching a maximum value. This behaviour is associated with a change in nature of light scattering from discrete scattering events to continuum scattering at high zinc oxide concentrations due with the mesoporous structure of the aggregates. The change in the light scattering mechanism is responsible for the high transparency and low whiteness exhibited by the dispersions.

TABLE 2

	Formulation B	Formulation C	Silicone- coated ZnO nanoparticles	Stearic acid coated ZnO nanoparticles	Silica coated ZnO nanoparticles
Average particle size	3.2 m	2.0 m	30 nm	30 nm	82 nm
Total Absorbance at 550 nm	0.20	0.16	0.2	0.35	0.68
Soft-focus factor at 550 nm	42.6	22.7	8.6	12.2	18.0
CIE Whiteness index	22.2	19.5	34	53	60
CIE L*	29.9	26.3	30	40	54
Lightness					

Example 3

Optical Properties—Non Linear Beer Lambert Law
Behaviour

[0075] Formulations consisting of dispersions containing concentrations of 2.5% to 50 wt % MZOAs in Caprylic Capric Triglyceride were prepared using a laboratory bead mill. Optical transmittance measurements were carried out using a Carey 300 bio UV-Vis spectrophotometer equipped with an integrating sphere. The samples were placed in a quartz cell having optical path length of 0.02 mm.

[0076] FIG. 2 shows the effect of zinc oxide concentration on the visible light transmittance. The transmittance measurements were taken at a wavelength of 550 nm (middle of visible spectrum) and the path length (cell thickness) is 20 microns. The results show that the transmittance initially decreased and then leveled out for zinc oxide concentrations greater than 25 wt %.

[0077] A similar levelling out was also observed in measurements of the CIE whiteness index as shown in FIG. 3.

[0078] An analysis of the transparency measurements using the Beer Lambert law was carried out.

[0079] The total Absorbance, A, may be expressed as

$$A = -\ln [T(\%)/100]$$

[0080] Where T is equal to the total transmittance to visible light at a wavelength of 550 nm expressed as a percentage.

[0081] For linear Beer-Lambert law behaviour to be exhibited, the total Absorbance should increase linearly with the concentration of zinc oxide.

[0082] Values of the total Absorbance, are plotted as a function of zinc oxide concentration in FIG. 4. At low concentrations the Absorbance increased linearly with increas-

Example 4

Sunscreen Formulation 1

[0083] The following sunscreen formulation was prepared based on Formulation D described above in Example 1 using C₁₂₋₁₅ alkyl benzoate as the carrier:

	% w/w
Phase A	
Water	44.29
Magnesium sulphate	0.60
Aloe Vera 200x	0.01
Versene Na	0.10
Sodium PCA	0.50
Phase B	
Isolan PDI	3.00
Isopropyl Myristate	1.00
Octyl Palmitate	0.50
Abil Wax 9840	2.00
Hydrogenated Castor Oil	0.50
White Bees Wax	0.50
Vitamin E Acetate	1.00
Vitamin A Palmitate	1.00
Panalene L14E	0.50
Permethyl 99A	4.000
Zinc Oxide (MZO)	20.00
C12-15 Alkyl benzoate	18.40
Isostearic acid	1.600
Microcare MTG	0.500

[0084] Phases A and B are separately prepared by mixing the chemicals together and heating to about 80° C. At 80° C.,

Phase A is slowly added to Phase B, and mixed for 15 minutes with a mixer or until uniform. The mixture is then cooled to 40° C. and preservative (MTG) is added. The mixture is further cooled to 30° C. and then milled until uniform. The in-vivo SPF of this formulation was 27.

[0085] In order to characterize the optical properties of the formulation, the formulation was de-emulsified and dried in the dark and applied onto a quartz cell with 20 micron of optical path length. The optical properties of the sunscreen formulation are summarized below:

Particle concentration as demulsified dry film	36 wt %
Soft-focus factor	31
CIE Whiteness index	34
CIE Lightness	41

Example 5

Sunscreen Formulation II

[0086] The following sunscreen formulation comprising a dispersion of 20% MZOAs according to the present invention was prepared using the raw materials listed below.

Raw Materials	Wt %
Water	35.95
Propylene glycol	3
Sodium chloride	2
Keltrol F	0.15
50% ZnO (MZO) in	40
Crodamol AB	
Crodamol AB	10.9
Parsol 1789	2
Ariacel P135	3
Monomuls 90-0 18	1
Performalene 400	1
Phenonip	1

[0087] Measurements of in vivo SPF were carried out following Australian/New Zealand Standard, AS/NZS 2604:1993. The measured in vivo SPF was 31.2. Measurements of the in vitro UVAPF were carried out following COLIPA guidelines. The Colipa in vitro UVAPFDx was 12.98.

Example 6

Sunscreen Formulation III

[0088] The following sunscreen formulation comprising a dispersion of 20% MZOAs according to the present invention was prepared.

Raw Materials	Wt %
ZinClear-IM in LexFeel 7 (55%(MZO))	36.5%
LexFeel 7	20.5%
Abil EM90	3%

-continued

Raw Materials	Wt %
Water	38%
Solterra boost	2%

[0089] The SPF was measured to be 53.2 using in vitro testing

Example 7

Photostabilisation of Avobenzone

[0090] The following sunscreen formulation comprising a dispersion of 15% MZOAs according to the present invention and 2% avobenzone (Parsol 1789) was prepared in the following carrier.

Raw Materials	Wt %
Water	39.95
Propylene glycol	3
Sodium chloride	2
Keltrol F	0.15
50% ZnO (MZO) in	30
Crodamol AB	
Crodamol AB	20.4
Parsol 1789	2
Polyethylene	1.5
Ariacel P135	3
Monomuls 90-0 18	1
Performalene 400	1
Phenonip	1

[0091] Measurements of in vitro SPF and UVA were carried out under the following conditions following Australian/New Zealand Standard, AS/NZS 2604:1993. On the basis of these measurements, photostability was determined according to the AS/NZS 2604:1993 standard.

[0092] Test results are given in the Tables below. The combination of 15% MZO and 2% Avobenzone exhibited a pre-irradiation UVA/UVB ratio of 0.94, critical wavelength of 378 and a five star Boots rating. The formulation was shown to be photostable.

Prior to Photodegradation

[0093]

SPF	UVA Ratio	Star Rating	Category	Critical Wavelength
10.72	0.94	*****	Ultra	378

Post Degradation (Using Med 5.5)

[0094]

SPF	UVA Ratio	Star Rating	Category	Critical Wavelength	Quantitative Photostability	Qualitative Photostability
9.68	0.87	*****	Ultra	375	Yes	Yes

[0095] It will be apparent to persons skilled in the relevant art that numerous variations and modifications can be made without departing from the basic inventive concepts. All such modifications and variations are considered to be within the scope of the present invention, the nature of which is to be determined from the foregoing description and the appended claims. In the statement of invention and description of the invention, except where the context requires otherwise due to express language or necessary implication, the word “comprise” or variations such as “comprises” or “comprising” is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

1. A broad-spectrum UV photoprotective composition characterized in that the composition comprises mesoporous zinc oxide aggregates having an average aggregate size of at least 0.8 micron dispersed in a carrier and the composition is visibly transparent.

2. The composition according to claim 1 wherein the zinc oxide aggregates have an average aggregate size of at least one of greater than 1.0 micron, greater than 2.0 microns and greater than 3.0 microns.

3. The composition according to claim 1 wherein the mesoporous zinc oxide aggregates are present in an amount effective to provide an SPF of at least one of greater than 15, greater than 25, greater than 30, and greater than 50.

4. The composition of claim 1 having a total absorbance through a path length of 20 microns at 550 nm not greater than 0.15 when the composition includes zinc oxide aggregates at a concentration of at least 40% or 50% by weight of the total composition.

5. The composition of claim 1 having a total absorbance through a path length of 20 microns at 550 nm not greater than 0.14 when the composition includes zinc oxide aggregates at a concentration of 30% by weight of the total composition.

6. The composition of claim 1 having a total absorbance through a path length of 20 microns at 550 nm not greater than 0.12 when the composition includes zinc oxide aggregates at a concentration of at least 20% by weight of the total composition.

7. The composition of claim 1 having a total absorbance through a path length of 20 microns at 550 nm not greater than 0.06 when the composition includes zinc oxide aggregates at a concentration of at least 10% by weight of the total composition.

8. The composition of claim 1 wherein the zinc oxide aggregates have an average aggregate size of at least 3.0 microns and the composition has a total absorbance at 550 nm through a path length of 20 microns not greater than 0.20.

9. The composition of claim 1 wherein the zinc oxide aggregates have an average aggregate size of at least 2.0 microns and the composition has a total absorbance at 550 nm through a path length of 20 microns not greater than 0.16.

10. The composition of claim 1 further comprising a dibenzoylmethane derivative.

11. The composition of claim 1 including less than 5% or less than 3% of an organic sunscreen filter.

12. A photostable visibly-transparent, broad-spectrum UV photoprotective composition according to claim 11 wherein the organic sunscreen filter is avobenzone.

13. The composition of claim 1 wherein the zinc oxide aggregates have an average aggregate size of at least one of greater than 1.0 micron, greater than 2.0 microns and greater than 3.0 microns and the composition has a soft focus factor at 550 nm greater than 40.

14. The composition of claim 1 wherein the zinc oxide aggregates have an average aggregate size of at least one of greater than 1.0 micron, greater than 2.0 microns and greater than 3.0 microns and the composition has a CIE Whiteness index less than 25.

15. The composition claim 1 wherein the zinc oxide aggregates have an average aggregate size of at least one of greater than 1.0 micron, greater than 2.0 microns or greater than 3.0 microns and the composition has a CIE L*lightness less than 30.

16. The composition of claim 1 including one or more non-mesoporous zinc oxide aggregate photoprotective agents, wherein the one or more non-mesoporous zinc oxide aggregate photoprotective agent(s) are present in a concentration that increases the SPF of the composition by not more than 2 units of SPF.

17. A method of providing protection from ultraviolet radiation to mammalian skin or hair comprising contacting the skin or hair with a composition according to claim 1.

18. A method of treating a human dermatologic condition selected from the group consisting of acne, psoriasis, eczema, ichthyosis, pruritus, dryness and dermatitis by applying a therapeutically-effective amount of a visibly-transparent topical preparation comprising the composition according to claim 1.

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