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ORIGINAL ARTICLE

Particle size determination of sunscreens formulated with various forms of titanium dioxide

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Abstract

Background: There has been some apprehension expressed in the scientific literature that nanometer-sized titanium dioxide (TiO_2) and other nanoparticles, if able to penetrate the skin, may cause cytotoxicity. In light of a lack of data regarding dermal penetration of titanium dioxide from sunscreen formulations, the Food and Drug Administration Center for Drug Evaluation and Research initiated a study in collaboration with the National Center for Toxicology Research using minipigs to determine whether nanoscale TiO_2 in sunscreen products can penetrate intact skin. Four sunscreen products were manufactured. *Method*: The particle size distribution of three TiO_2 raw materials, a sunscreen blank (no TiO_2) and three sunscreen formulations containing uncoated nanometer-sized TiO_2, coated nanometer-sized TiO_2 or sub-micron TiO_2 were analyzed using scanning electron microscopy (SEM), laser scanning confocal microscopy (LSCM), and X-ray diffraction (XRD) to determine whether the formulation process caused a change in the size distributions (e.g., agglomeration or deagglomeration) of the TiO_2. *Results*: SEM and XRD of the formulated sunscreens containing nanometer TiO_2 show the TiO_2 particles to have the same size as that observed for the raw materials. This suggests that the formulation process did not affect the size or shape of the TiO_2 particles. *Conclusion*: Because of the resolution limit of optical microscopy, nanoparticles could not be accurately sized using LSCM, which allows for detection but not sizing of the particles. LSCM allows observation of dispersion profiles throughout the sample; therefore, LSCM can be used to verify that results observed from SEM experiments are not solely surface effects.

Key words: *Laser scanning confocal microscopy; nanoparticle; scanning electron microscopy; titanium dioxide*

Introduction

Nanotechnology has been touted as the next industrial revolution[1–3] and the use of nanotechnology in cosmetics, foods, medical products, and other areas is rapidly expanding[4–10]. The US Food and Drug Administration (FDA) Nanotechnology Task Force has not adopted formal, fixed definitions of 'nanotechnology' or 'nanoscale material' for regulatory purposes at this time[11]. Even though the FDA has not established its own formal definition, the agency participated in the development of the National Nanotechnology Initiative (NNI) definition of nanotechnology[12]. NNI defines nanotechnology as involving all of the following: '(1) Research and technology development at the atomic, molecular or macromolecular levels, in the length scale of approximately 1–100 nm range. (2) Creating and using structures, devices and systems that have novel properties and functions because of their small and/or intermediate size. (3) Ability to control or manipulate on the atomic scale'[13].

For some materials, certain chemical and/or physical properties change with reduction in size to the nanometer size range[5,7,8,14–16]. One product area where this difference is advantageous is in sunscreens that contain titanium dioxide (TiO_2). As a consequence of this, various skin-care products such as sunscreens, cosmetics, lotions, and creams are being formulated with nanosize TiO_2[6]. The use of TiO_2 as a sunscreen component is approved by the USFDA[17], but the regulations do not specify particle size[10,18]. A concern has

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been expressed in the literature that nanometer-sized TiO_2 (and other nanoparticles), if able to penetrate the skin, may cause cytotoxicity[4,15,16,19–23]. In light of the lack of data on the impact of dermal penetration of titanium dioxide in sunscreen formulations, the FDA Center for Drug Evaluation and Research initiated a study in collaboration with the National Center for Toxicology Research using minipigs to determine whether nano-scale TiO_2 in sunscreen products can penetrate intact skin. Four sunscreen products were manufactured, varying only in the content and characteristics of the TiO_2: (1) no TiO_2, hereafter called 'blank sunscreen'; (2) micrometer-sized uncoated TiO_2 ('submicron TiO_2 sunscreen'); (3) nanometer-sized coated TiO_2 ('coated nano TiO_2 sunscreen'); and (4) nanometer-sized uncoated TiO_2 ('uncoated nano TiO_2 sunscreen').

Both particle size and dispersion are critical performance factors for sunscreen products[24,25]. To avoid changing these qualities, it is important to identify characterization methods that do not require dilution of the original sunscreen. Both the titanium dioxide raw materials and the finished sunscreen products were characterized in terms of particle size distribution. The purpose of this study was to determine the particle size and particle size distribution of several commercially available titanium dioxides as raw materials and to determine whether the size distribution changes (e.g., agglomeration or deagglomeration) when the titanium dioxide is formulated into a sunscreen.

Materials and methods

Samples

Three titanium dioxide raw materials were utilized to manufacture sunscreen products. The blank sunscreen, uncoated nano TiO_2 sunscreen, coated nano TiO_2 sunscreen, and submicron TiO_2 sunscreen were manufactured according to a similar BASF formulation[26]. Characteristics of the titanium dioxide raw materials are shown in Table 1, and the sunscreen formulation ingredients are shown in Table 2. All sunscreens, including the blank sunscreen, contained magnesium aluminum silicate (1.5%) that contained approximately 3% titanium dioxide.

Table 2. Sunscreen formulation.

Phase	Ingredients
A	Dibutyl adipate, $C_{12–15}$ alkyl benzoate, cocoglycerides, sodium cetearyl sulfate, lauryl glucoside, polyglyceryl-2 dipolyhydroxystearate, glycerin, cetearyl alcohol, octyl methoxycinnamate, tocopheryl acetate
B	Titanium dioxide
C	Glycerin, disodium EDTA, allantoin, xanthan gum, magnesium aluminum silicate, water
D	Phenoxyethanol, methylparaben, ethylparaben, butylparaben, propylparaben, isobutylparaben

Briefly, the formulation procedure consisted of the following steps:

- Heat Phase A (see Table 2) to 80°C.
- Add Phase B and homogenize for 3 minutes. (For the blank sunscreen, the homogenization for 3 minutes is carried out even in the absence of Phase B.)
- Heat Phase C to 80°C and stir into Phase A+Phase B while homogenizing.
- Cool to about 40°C, add Phase D, and homogenize.

Instrumentation

In this study, particle size distribution of titanium dioxide raw materials and the finished sunscreen products containing the titanium dioxide were analyzed using scanning electron microscopy (SEM), laser scanning confocal microscopy (LSCM), and X-ray diffraction (XRD). In a previous study, several techniques such as X-ray disc centrifuge (XDC), acoustic attenuation spectroscopy (AAS), dynamic light scattering (DLS), laser diffraction, centrifugal separation analysis, and Raman chemical microscope imaging were evaluated as potential techniques to investigate the particle size and distribution of titanium dioxide and zinc oxide in 'neat', as is commercially available sunscreens. Several of the techniques such as XDC, AAS, laser diffraction and DLS required that the samples be diluted. Centrifugal separation analysis required that the particles be extracted and purified. The sunscreen sample exhibited a strong Raman signature using Raman chemical microscope imaging; however, the particles were not resolvable in the imaging data.

Table 1. Titanium dioxide raw materials.

Raw material	Brand	Particle size as advertised (nm)	Crystallinity as advertised
Uncoated nano titanium dioxide (titanium dioxide)[27]	Degussa Aeroxide P25	21	80% anatase and 20% rutile
Coated nano titanium dioxide (titanium dioxide, aluminum hydroxide, dimethicone/methicone copolymer)[28,29]	BASF T-Lite SF	50	Rutile
Submicron titanium dioxide (titanium dioxide, aluminum hydroxide)[30]	Ishihara Corporation TIPAQUE CR50	250	Rutile

Electron microscopy

Electron microscopy analysis was performed on a JEOL model GSM 6320F. All the sunscreen samples were dried in a vacuum of 10^{-6} torr at room temperature, which enabled characterizing the samples using SEM with a reasonable resolution. (No solvent was used for the SEM sample preparation.)

Laser scanning confocal microcopy

All measurements were taken on a Zeiss model LSM510 reflection laser scanning confocal microscope equipped with a He–Ne laser (543 nm). Solutions containing ~10 wt% of TiO_2 raw material in deionized water (nano-uncoated and submicron) or isopropanol (nano-coated) were examined to provide a size reference for particles embedded in sunscreens. Images are two-dimensional projections of a Z series; at 150×, the z step was 0.25 μm.

X-ray diffraction

Samples were examined with a Bruker D8 Discover XRD. Titanium dioxide raw material powder samples were placed in a standard powder holder and flattened gently with a glass coverslip to obtain a smooth surface. Sunscreen formulations were transferred to a 1 mm thick glass slide and smoothed with a metal spatula.

The size was calculated using line-broadening analysis. Data were smoothed and corrected for background using Bruker analysis 'EVA' software. All samples were processed with the same parameters (Smooth: Max 1.54045, Min 0.0503483, Factor 0.25, Background: Threshold 0.5, Curvature: 1.5). Peak matching was performed using EVA software to obtain crystal phase identification. In some cases, the raw data were also analyzed without background or smoothing corrections. For size analysis, the full width at half maximum (FWHM) was calculated using EVA and exported to Excel. The reflections used for crystallite analysis were 101 for ZnO, 110 for rutile TiO_2, and 101 for anatase TiO_2. In order to obtain instrumental broadening for all angles, the reflections of NIST ZnO reference material 674a was used to construct a plot of $FWHM^2$ versus $\tan(\theta)$ and the coefficients of the quadratic of best fit to the graph were determined in order to extract instrument broadening parameters for all angles.

Results

Titanium dioxide powders

Uncoated nano titanium dioxide

SEM image of the uncoated nano titanium dioxide powder revealed that the sample contained spherical and/or cubic particles ~30–50 nm in size, with an average particle size of about 40 nm (Figure 1A). The particle size was confirmed with transmission electron microscopy (TEM) (data not shown).

LSCM images of the uncoated nano TiO_2 raw material sample showed that individual particles as well as larger aggregates can be distinguished (Figure 1B).

Particle size from XRD line-broadening calculations for the uncoated nano TiO_2 raw material indicated the primary particles to be 26 nm.

Coated nano titanium dioxide

SEM image of the coated nano titanium dioxide powder indicates that the sample consisted of needle-like particles 20–30 nm in diameter and ~50–150 nm in length (Figure 2). The particle size was confirmed with TEM (data not shown).

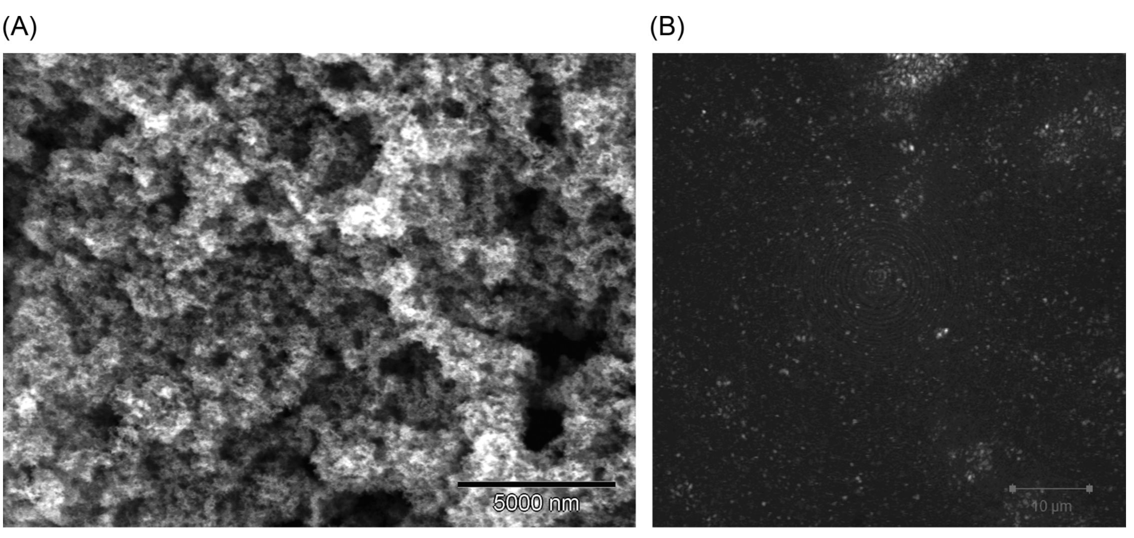

Figure 1. Uncoated nano titanium dioxide SEM image (A), LSCM image, 150× (B). (The circular diffraction rings seen in LSCM image are due to interference with the glass coverslip.)

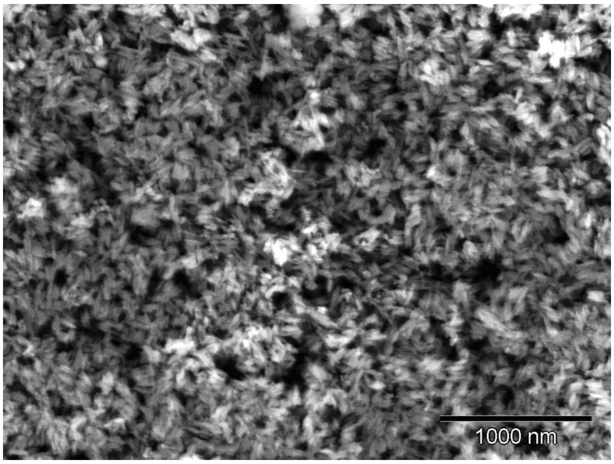

Figure 2. SEM image of coated nano titanium dioxide.

The particles appeared elongated in the LSCM images of the coated nano TiO_2 raw material sample. Individual particles may be observed. Particles appeared to be the smallest of the raw materials.

Particle size from XRD line-broadening calculations indicated the primary particles to be 19 nm.

Submicron titanium dioxide

A SEM image of the submicron titanium dioxide powder showed that the sample consisted of spherical and/or elongated particles ~300–500 nm in size, with an average particle size of about 400 nm. The SEM image showed some particles (several tens of nanometers in size) were attached on the surfaces of the submicron particles (Figure 3A). The particle size was confirmed with TEM (data not shown).

Individual particles were present in the LSCM images of the submicron TiO_2 raw material sample, although aggregates also appear to be present (Figure 3B).

Since XRD lines are not broadened by particles larger than about 100 nm, particles size could not be determined for this sample.

Formulated sunscreens

Blank

SEM images at two different magnifications showing surface morphology for the blank sunscreen sample (no TiO_2 particles) are provided in Figure 4A.

On the LSCM image of the blank sunscreen, bright spots may arise from the 1.5% magnesium aluminum silicate, which includes residual TiO_2. Other sunscreen components accounted for the weaker background signal (Figure 4B).

Uncoated nano titanium dioxide sunscreen

Although nano TiO_2 particles were observed in the uncoated nano titanium dioxide sunscreen sample, the SEM images showed that most of the nanoparticles are agglomerated to form clusters of different shapes. The distribution of the nanoparticles is rather uniform over the surfaces of the sample (Figure 5A). Based on the measurements from the SEM images, the sizes of the nano TiO_2 particles range from 30 to 50 nm with the average size of 40 nm, which is the same as the size distribution of the nano TiO_2 particles observed in the powder form (Figure 1A).

According to the LSCM images of the uncoated nano TiO_2 sunscreen, there was a relatively even distribution of particles (Figure 5B).

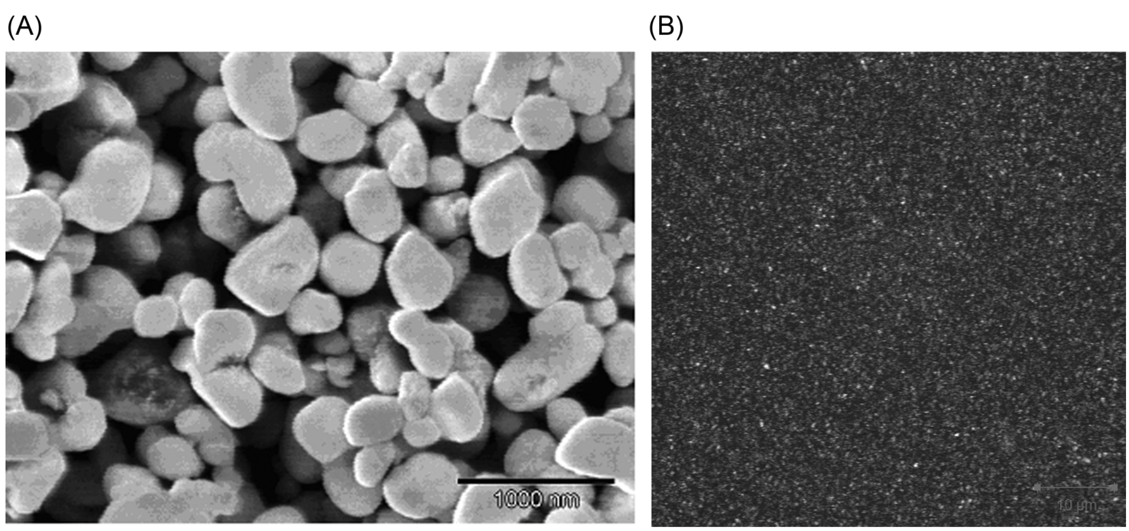

Figure 3. Submicron titanium dioxide SEM image (A); LSCM image, 150× (B). (The circular diffraction rings seen in LSCM image are due to interference with the glass coverslip.)

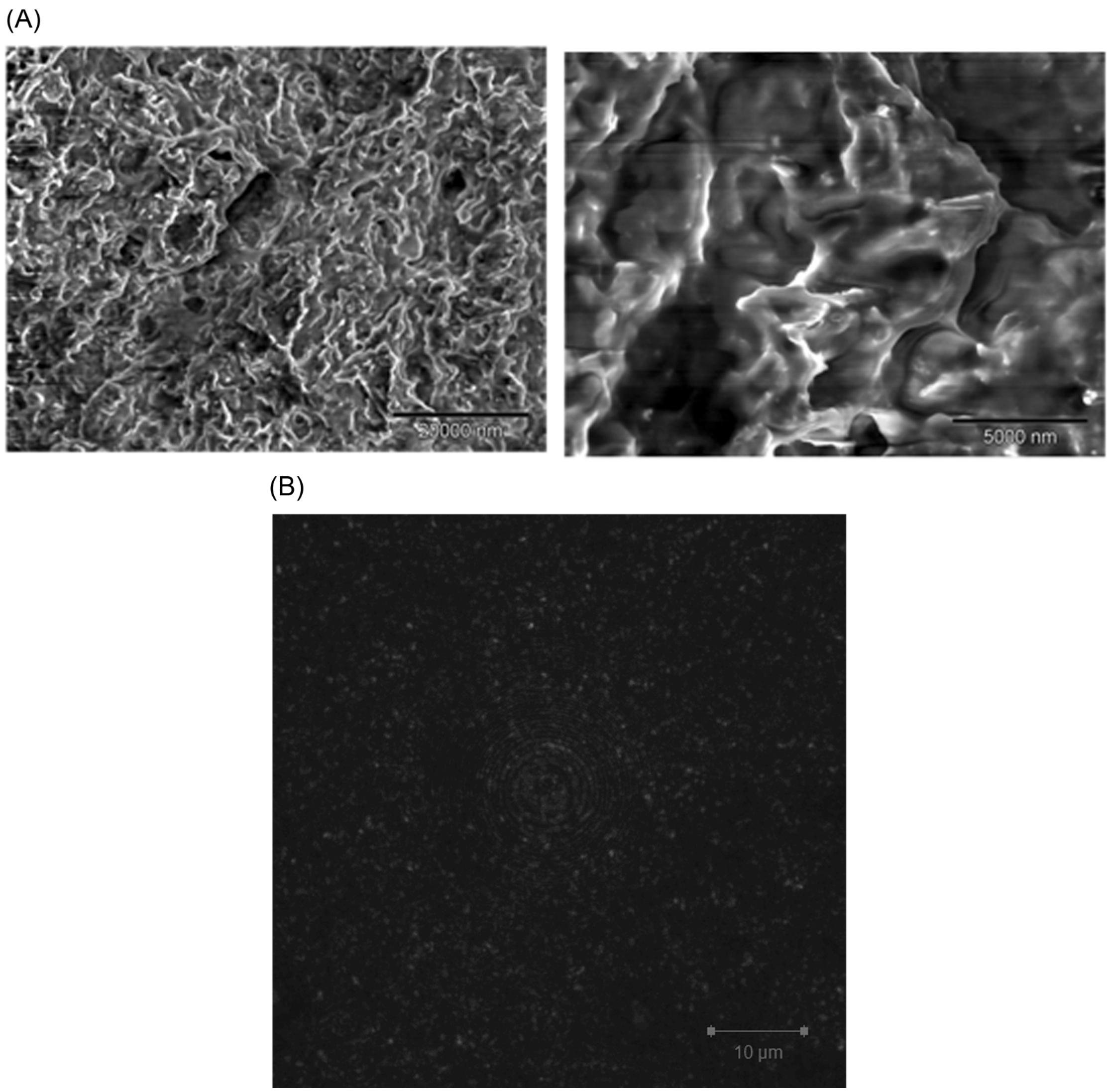

Figure 4. Blank sunscreen SEM images (A), LSCM image at 150× (B). (The circular diffraction rings seen in LSCM image are due to interference with the glass coverslip.)

Particle size from XRD line-broadening calculations indicated that the uncoated nano TiO_2 sunscreen contained 30 nm primary particles (Figure 5C).

Coated nano titanium dioxide sunscreen

An SEM image showed that the coated nano titanium dioxide sunscreen sample contains needle-like nanoparticles with a nonuniform distribution (Figure 6A). In some areas, the density of nano-needles was high, while other areas of the sample were devoid of TiO_2. The SEM image also showed how the needle-like nanoparticles are agglomerated in the areas of high density. Based on the measurements of the SEM images, the needle-like particles in the coated nano titanium dioxide sunscreen are about 20–30 nm in diameter and ~50–150 nm in length, which are the same dimensions as were obtained from measurement of the raw material (Figure 2).

The LSCM images of coated nano titanium dioxide sunscreen confirm the uneven distribution of the particles observed using SEM and that the particles appear primarily as aggregates (Figure 6B).

Particle size from XRD line-broadening calculations indicated the coated nano TiO_2 sunscreen contained 24 nm primary particles (Figure 6C).

Submicron titanium dioxide sunscreen

The surface morphology of the sunscreen formulated with submicron titanium dioxide is shown at two magnifications in Figure 7A. From these images, it appears the TiO_2 particles are uniformly distributed over the surface and range in size from 300 to 500 nm with an average particle size of about 400 nm, which is the same as that observed from the corresponding SEM images for the raw material sample (Figure 3A). This suggests that the

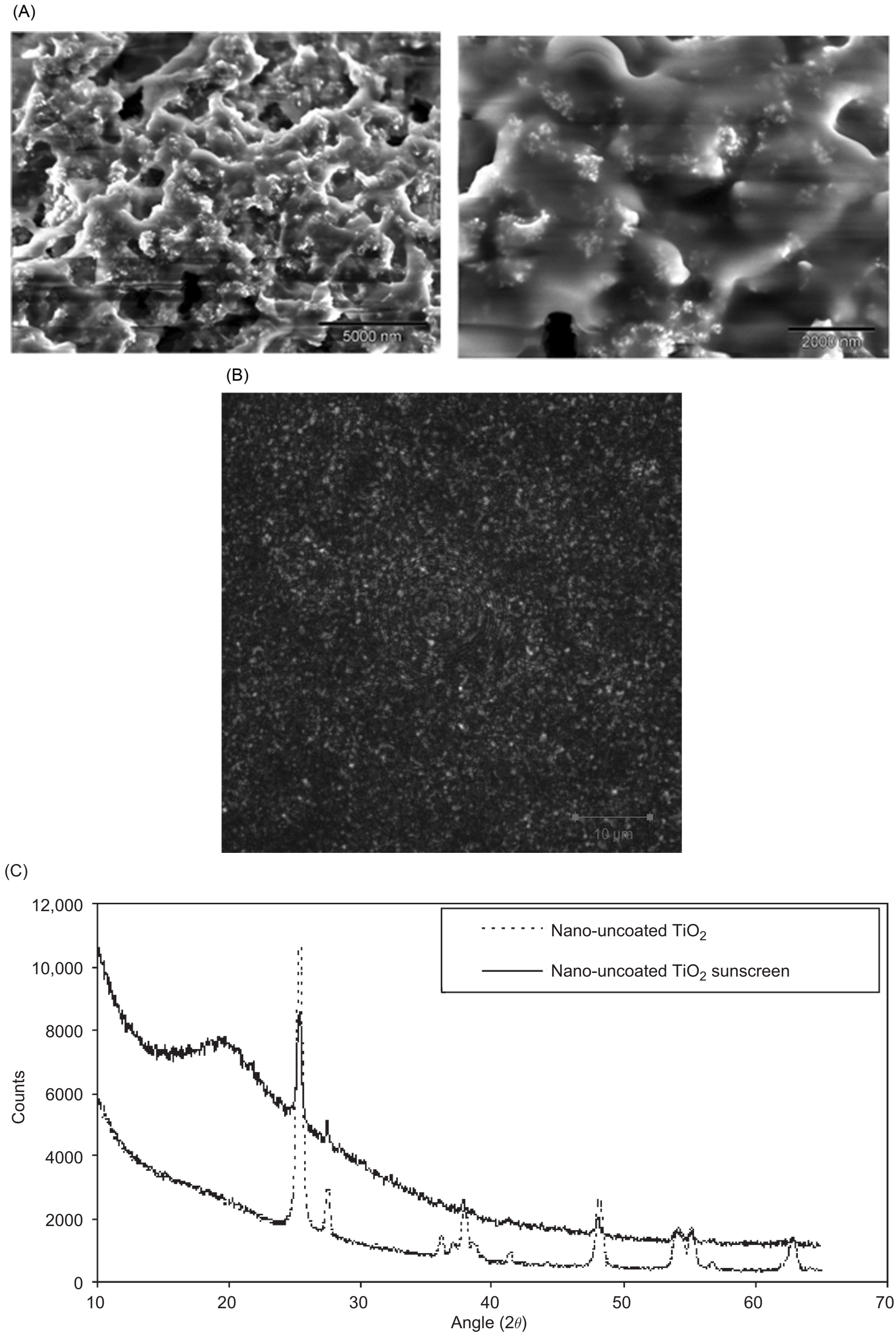

Figure 5. Uncoated nano titanium dioxide sunscreen SEM images (A); LSCM image at 150× (B). (The circular diffraction rings seen in LSCM image are due to interference with the glass coverslip.) XRD of uncoated nano titanium dioxide and uncoated nano titanium dioxide sunscreen (C).

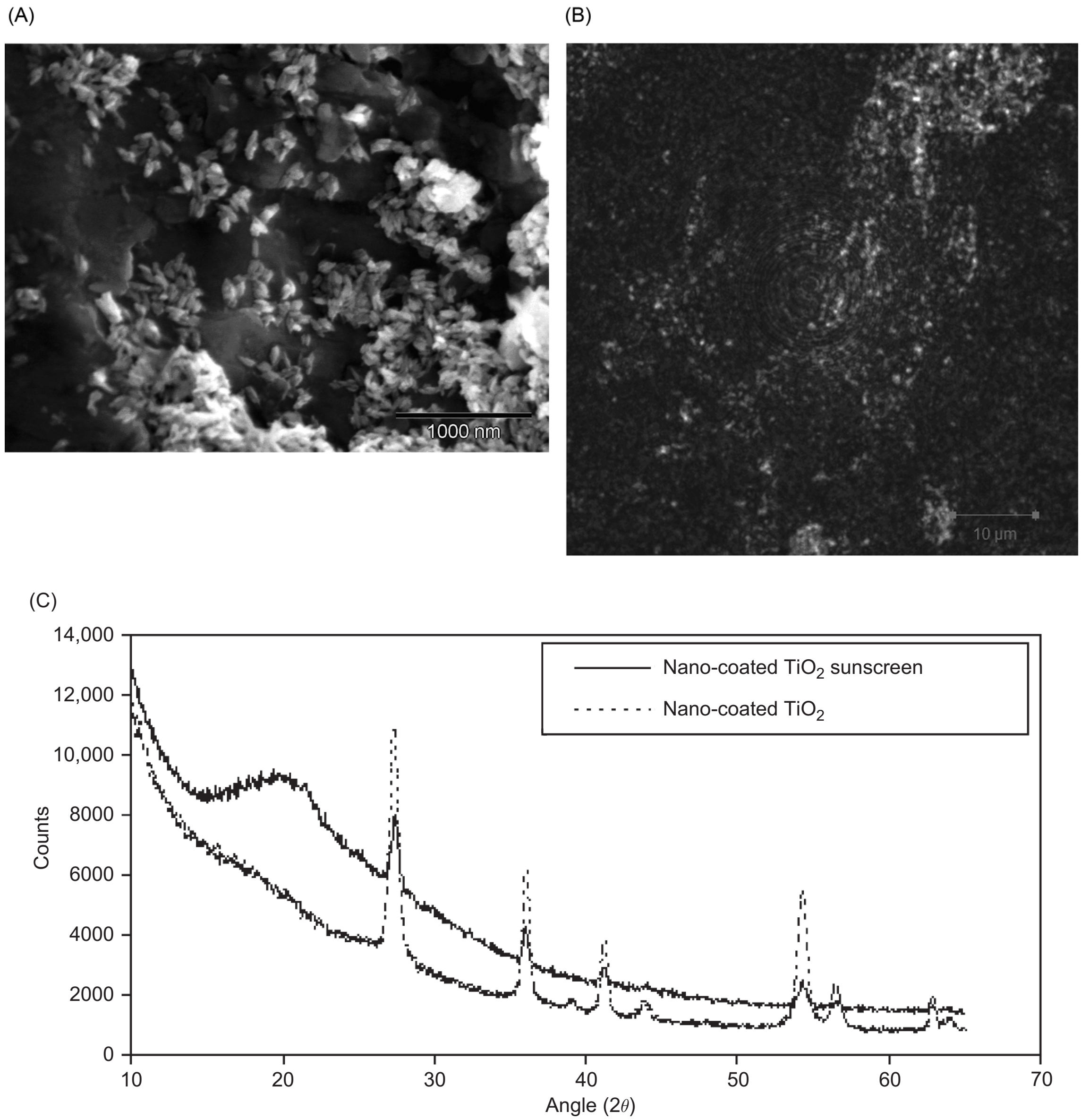

Figure 6. Coated nano titanium dioxide sunscreen SEM images (A); LSCM image at 150× (B). (The circular diffraction rings seen in LSCM image are due to interference with the glass coverslip.) XRD of coated nano titanium dioxide and coated nano titanium dioxide sunscreen (C).

TiO_2 particles were not affected by the formulation process employed although the degree of aggregation is difficult to assess since the SEM image also showed that some of the TiO_2 particles have agglomerated to form TiO_2 clusters (Figure 7A). Small agglomerates consisting of two to four primary particles (~600–700 nm) are observed in these images but there are also some very large agglomerates of over 2 μm. SEM image of the TiO_2 particles from the submicron titanium dioxide sunscreen indicates that the particles have rounded or elongated shapes.

A relatively even distribution of particles was observed in the LSCM images of the submicron TiO_2 sunscreen (Figure 7B).

Since XRD lines are not broadened by particles larger than about 100 nm, particles size could not be determined for this sample (Figure 7C).

Results for particle size as determined by SEM and XRD for all samples are summarized in Table 3.

Discussion

In this study, particle size distribution of titanium dioxide raw materials and the finished sunscreen products containing the titanium dioxide were analyzed using SEM, LSCM, and XRD. In a previous unpublished study[31], several techniques such as XDC,

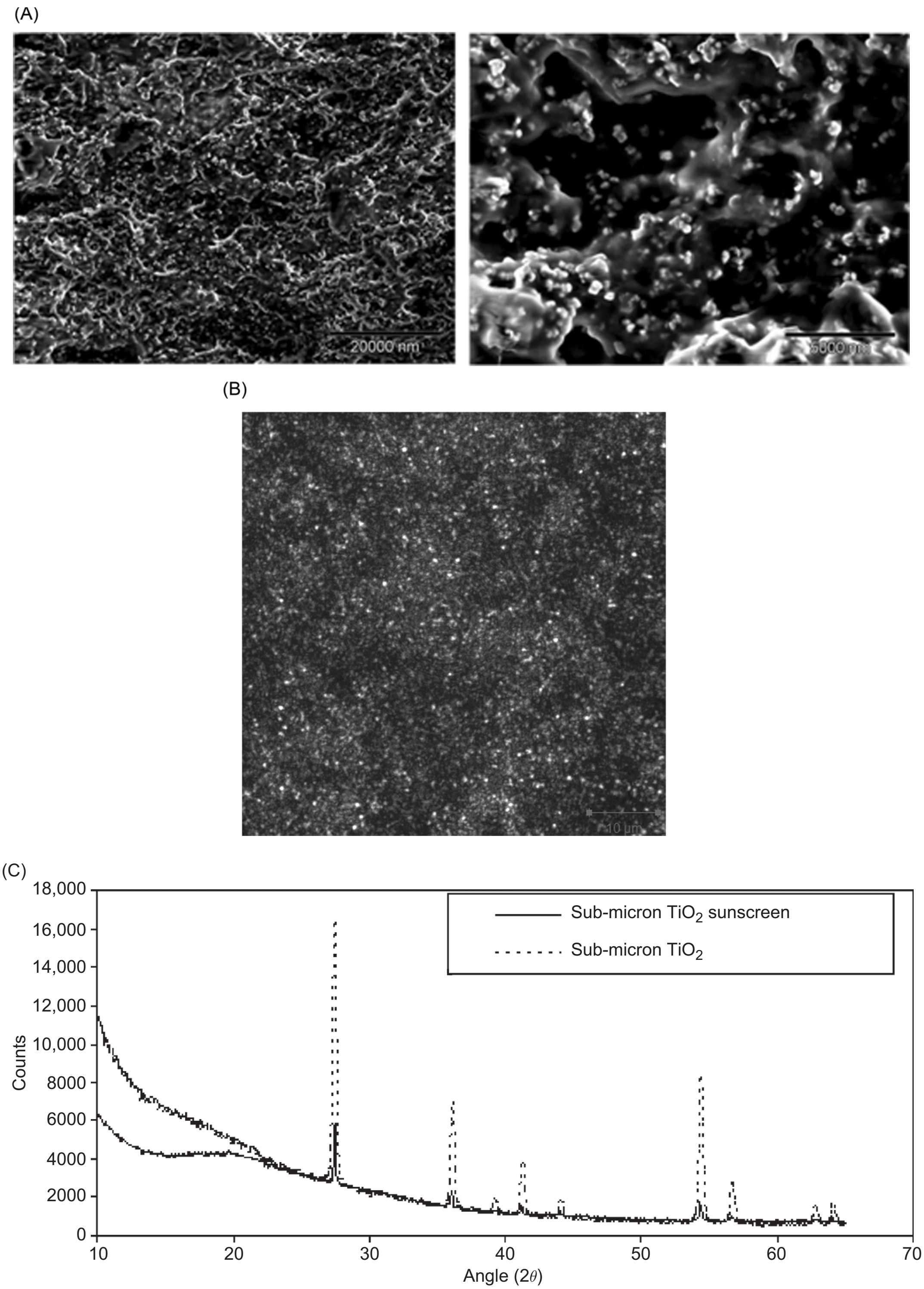

Figure 7. Submicron titanium dioxide sunscreen SEM images (A); LSCM image at 150× (B). (The circular diffraction rings seen in LSCM image are due to interference with the glass coverslip.) XRD of submicron titanium dioxide and uncoated nano titanium dioxide sunscreen (C).

AAS, DLS, laser diffraction, centrifugal separation analysis, and Raman chemical microscope-imaging were evaluated as potential techniques to investigate the particle size and distribution of titanium dioxide and zinc oxide in commercially available sunscreens. However, in that study, no technique was able to determine the particle size without dilution or otherwise changing the sample. Different particle sizing

Table 3. Particle sizing results of titanium dioxide raw materials and formulations containing titanium dioxide.

Sample	Particle size by SEM	Particle size from XRD line-broadening calculations
Uncoated nano TiO_2	30–50 nm	26 nm
Uncoated nano TiO_2 formulation	30–50 nm	30 nm
Coated nano TiO_2	20–30 nm in diameter and about 50–150 nm in length	19 nm
Coated nano TiO_2 formulation	20–30 nm in diameter and about 50–150 nm in length	24 nm
Submicron TiO_2	300–500 nm	Could not be determined
Submicron TiO_2 formulation	300–500 nm	Could not be determined

techniques yield different sizes for the same particles because they measure a different property of the particle[32–34]. This does not necessarily mean that any of the techniques are 'wrong'—just that a different property of the particle is being measured and the result is expressed in different terms[32]. Even when a result is obtained, some techniques may not be able to distinguish that 'the result' is solely titanium dioxide particles. Regardless of the techniques applied, careful consideration should be given to sample preparation procedures, equipment limitations, and measurement protocols to ensure that reliable data are obtained[25].

The observed line broadening in the XRD lines can be used to estimate the average size. When crystallites are less than approximately 100 nm in size (which is the range of the NNI definition of nanotechnology), appreciable line broadening in the XRD lines will occur[35]. Since the X-ray diffractometer is not sensitive to changes on crystallite sizes from 100 to 10,000 nm, other methods need to be used to calculate size[36].

The LSCM technique provided a direct method for characterizing the particle dispersion in sunscreen samples without dilution. Due to the resolution limits of optical microscopy, nanoparticles could not be accurately sized using LSCM although the method allows their detection. Reflection LSCM provided contrast based on differences in the refractive indexes of components in the formulation. Since TiO_2 has a much higher refractive index than the bulk formulation, it appeared as bright dots in the images; nanoparticles having a refractive index not significantly different from the bulk sunscreen formulation would not be visible using this method. Additional methods would be needed to fully characterize all nanoparticles in sunscreen formulations.

Although there are limitations in using LSCM as a probe for nanoparticles in sunscreen formulations, there are also some benefits of using this method. Little or no sample modification was needed before LSCM analysis, and the confocal method permits depth analysis of the sample. This allows dispersion profiles to be determined throughout the sample, not just on the surface, as is the case for SEM.

Conclusion

This study demonstrated that electron microscopy is a useful technique to characterize TiO_2 raw material as well as sunscreens containing titanium dioxide. The EM characterization showed that TiO_2 particles in the sunscreens had their original dimensions (sizes and shapes) as was observed in the powder samples, suggesting that the formulation process did not affect the sizes and shapes of the TiO_2 particles used in the sunscreens. LSCM can be used to verify that observations made from SEM images are not solely surface effects. To date, we have found no instrument capable of sizing nanoparticles in undiluted, unmodified formulated sunscreens; it appears that more than one method is needed to adequately determine particle size in formulated sunscreen products.

Characterization of nanomaterials is challenging due to the size of the particles as well as the complexity of the system. Characterization of nano-sized raw materials may not appropriately represent properties of the final product; therefore, it is also desired to characterize the materials in unmodified, finished formulations; this is necessary for the control of the quality of the product. By measuring particle size of the raw material only and not also of the end-use product, inappropriate conclusions could be drawn.

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