International Journal on Advanced Science Engineering Information Technology

Vol.11 (2021) No. 4
ISSN: 2088-5334

Titanium Dioxide in Commercial Sunscreens: the Morphological Characterization and the Quantification

Indah Primadona[a,*], Fitri Dara[a], Agustina Ircha Winda Pratiwi[a], Indriyati[a], Fahmi Idzni[a], Dedi[b], Muhamad Nasir[a]

[a] *Research Unit for Clean Technology, Indonesian Institute of Sciences, Bandung 40135, Indonesia*
[b] *Research Center for Electronics and Telecommunications, Indonesian Institute of Sciences, Bandung 40135, Indonesia*
*Corresponding author: *indahprimadona99@gmail.com*

***Abstract*—Due to nanotechnology's advancement, the application of nanomaterials in commercial products, including in sunscreens, has been increased rapidly. Physical sunscreens employ Titanium dioxide (TiO_2) or Zinc oxide (ZnO) nanoparticles as UV filter materials. Indonesian National Agency of Drug and Food Control regulates that TiO_2 rutile polymorph, size distribution ≥30 nm, and maximum concentration of 25% are criteria for physical sunscreen marketed in Indonesia. However, most of these products do not indicate the detailed inorganic material information in the product ingredients, resulting in the increasing concern of nanoparticle's risk to human health and the environment. Therefore, the size, type of crystal structure, and amount of TiO2 or ZnO must be closely monitored. In this work, we investigated the morphological structure of TiO_2, including quantified its concentration in some commercial sunscreens marketed in Indonesia. TiO_2 was characterized using different characterization techniques. XRD analysis revealed that some studied sunscreens employed anatase TiO_2, which is not suggested to be added in a sunscreen product. HRTEM analysis proved that the sizes of materials in sample S1-S3 are below 50 nm, and silica-coated TiO_2 was observed in S4. Quantification of Titanium using GF-AAS yielded Ti's concentration in the range of 1400-7800 μg g^{-1} (0.14-0.79%). To the best of our knowledge, this is the first study to report the physical properties and the concentration of TiO_2 nanoparticles (NPs) in commercial sunscreen marketed in Indonesia.**

***Keywords*— Nanoparticle; nanotechnology; sunscreen; titanium dioxide; UV-blocking materials.**

Manuscript received 21 Jun. 2020; revised 15 Feb. 2021; accepted 2 Mar. 2021. Date of publication 31 Aug. 2021.

I. INTRODUCTION

Titanium dioxide (TiO_2) has been widely used in many commercial products such as textiles, coating, packaging, food additive, and various personal care products [1]–[6]. Due to its unique properties, including chemically inert, relatively non-toxic, and the ability to absorb a broad spectrum of UV radiation, this material is become popular to be applied as a physical sunscreen for many years [7], [8]. TiO_2 can reflect and scatter both UVA (320–400 nm) and UVB (290–320 nm) radiation coming from the sunlight efficiently lead to prevent a sunburn [9], [10]. In addition, TiO_2 material has a high refractive index [11], [12] which allows the substance to give a whitening effect. However, this property also provides an opaque appearance upon application lead to cosmetically unattractive and less liked among consumers. Since the 1990s, nanosized versions of TiO_2 sunscreens were introduced to the market with better properties than the older versions. This nanoscale oxide is transparent and pleasant to touch, thus resulted virtually invisible when applied to the skin [8]. Besides, it also shows more excellent UV protection.

TiO_2 exists in three main crystalline forms: rutile, anatase, and brookite. Among these, rutile is the most common and stable form in nature. Both the anatase and rutile are widely applied as photocatalysts and semiconductors with band-gap energies of about 3.2 eV and 3.0 eV, respectively [13], [14]. Under UV light irradiation, electrons can excite from the valence band (vb) to the conduction band (cb), producing negatively (e–) and positively charged spaces called holes (h+). After that, in a saturated aqueous environment, electrons and holes react with oxygen and hydroxyl ions, respectively, generating hydroxyl radicals [15], [16]. The ability of TiO_2 to produce reactive radical species leads to a new concern regarding the photocytotoxic effects. Dunford et al. have demonstrated that TiO_2 particles isolated from commercial sunscreen products generated the reactive oxygen species, which induced DNA strand-breaks in human cells [17]. Consequently, TiO_2 in sunscreen formulations can initiate or lead to photo-oxidative damage to the skin. Compared to the rutile, anatase is more photoactive [13], [18]. Therefore, rutile should be the suggested form of TiO_2 for application in sunscreen products.

Besides the crystal type of TiO_2, particle size also affects the photocatalytic properties [19]. As mentioned above, due to several advantages, the nanosized TiO_2 is currently used in sunscreen products. However, because of the small particle size that increases the possibility of cell penetration, this new formulation raises a new concern regarding the safety of human health and the environment. Some reports and regulations have shown the effect of using TiO_2 NPs on the human body. For example, Scientific Committee on Consumer Safety reported that TiO_2 NPs could penetrate the skin, lead to lung toxicity and inflammation, and be possibly carcinogenic to humans [20], [21].

Moreover, the National Institute for Occupational Safety and Health (NIOSH) suggests that the exposure limit of ultrafine TiO_2 is 0.3 mg/m^3 for up to 10 h per day [22]. Those regulations thus limit the usage of TiO_2 NPs directly in contact with the human body. According to European Commission (EC) regulation No. 1223/2009, to protect consumers, the European Parliament requires a label on cosmetic products containing NPs. The label must include the name of the chemical in IUPAC, size, physicochemical properties, and toxicological information [23]. Particle size, agglomeration state, shape, surface area, composition, surface chemistry, surface charge, and solubility/dispensability were listed as the physicochemical parameters. In addition, crystal structure form, size and concentration of TiO_2 NPs have been regulated as well in Indonesia through the National Agency of Drug and Food Control (NADFC) regulation No. 23/2019. Accordingly, rutile polymorph, size distribution ≥30 nm, and maximum concentration of 25% are criteria for sunscreen marketed in Indonesia [24]. However, previous publications found that some commercial sunscreens contain anatase or a mixture of the two anatase and rutile and do not mention the size of TiO_2 in the product packaging [10], [25]. Therefore, to assess the safety, monitoring the inorganic UV-blocker contained in the sunscreens available in Indonesia is imperative.

In this work, the combination of x-ray diffraction (XRD), high-resolution transmission electron microscopy (HRTEM), energy dispersive x-ray spectroscopy (EDS), and particle size analyzer (PSA) were used to characterize the properties of TiO_2 NPs incorporated in commercial sunscreens. First of all, the crystal phase was obtained from the XRD analysis result. Then, we used PSA to know the mean size and size distribution of TiO_2 NPs. HRTEM coupled with EDS mapping were utilized to study morphology and elemental composition of particles. Finally, graphite furnace atomic absorption spectrometry (GF-AAS) with pyrolytic graphite tube was utilized to quantify Ti metal. To the best of our knowledge, study the physical properties and analyze the concentration of TiO_2 NPs in commercial sunscreen marketed in Indonesia is the first work to be carried out.

II. MATERIALS AND METHOD

A. Materials

All chemicals and reagents were used as received without further purification unless otherwise stated. Similarly, all aqueous solutions and reagents used in the analysis were prepared using deionized water purified by the MilliQ system. Nitric acid (HNO_3) supra pure, Fluoric acid (HF) 40%, Sulphuric acid (H_2SO_4) 95%, Ethanol, n-hexane, Isopropanol, Acetone, and Methanol were purchased from Merck (Darmstadt, Germany). Atomic absorption calibration standard for Ti was obtained from SCP Science (Baie-D'Urfe, Canada). Five commercial sunscreen creams containing Inorganic materials, particularly TiO_2 (Table 1) were obtained from the domestic cosmetic stores and those were selected based on the most widely used by the community in Indonesia. One product was made in France and four products were made in Indonesia. However, three products made in Indonesia were licensed by USA, Japan, and France. We also purchased TiO_2 powder from Merck that consists of anatase and rutile for the crystal structure analysis.

TABLE I
INORGANIC INGREDIENTS OF COMMERCIAL SUNSCREENS STUDIED IN THIS WORK

Name of Product	Origin	Ingredients		SPF
		TiO_2	ZnO	
S-1	USA	✓	✓	35
S-2	Indonesia	✓	Not listed	Not listed
S-3	France	✓	Not listed	50
S-4	France	✓	Not listed	50
S-5	Japan	✓	Not listed	20

B. Characterization of TiO_2 NP in Sunscreen

1) X-Ray Diffraction (XRD): Before the XRD analysis, a portion of the sunscreen sample was poured into the tube and then sequentially added by n-hexane, isopropanol, acetone, and methanol to remove the organic matrix contained in the sunscreen cream (pre-treated sample) [10]. After that, the precipitate was dried in the oven blower at 46°C to get the powder form. XRD patterns were obtained at room temperature using a Bruker D8 ADVANCE (Germany), equipped with Cu Kα radiation. All samples were analyzed under the same operating parameters: primary optic: 0.6; scanning speed; 0.2 steps/s; scan 2θ range; 10°-100°. Generated data were matched for crystal-phase determination using DIFFRAC.SUITE EVA software.

2) Scanning Electron Microscopy (SEM): Like the XRD experiment, all sunscreen samples were pre-treated with various organic solvents to get powder form before getting into the SEM experiment. A slight powder sample was placed on a carbon tape for SEM and EDS (Jeol type IT300, Japan) analysis. The surface morphology and particle size were analyzed at an acceleration voltage of 30 kV and imaged at 1,000-30,000x magnification.

3) High-Resolution Transmission Electron Microscopy (HRTEM): In this experiment, a few milligram sunscreen samples were suspended in ethanol without any pretreatment (un-treated sample). Some drops of the resulting dispersions were loaded directly onto a 200-mesh carbon-coated copper grid, then air-dried at room temperature. The particles' detailed morphology and mapping of elemental composition were examined by TEM Hitachi H9500 – EDAX (Krefeld, Germany) at an acceleration voltage of 300 kV and imaged at 20,000-100,000x magnification.

4) Particle Size Analyzer (PSA): The particle size distribution was measured by the Dynamic Light Scattering (DLS) instrument (Zetasizer Nano-ZS Malvern, UK). Before the measurement, the sample suspension in deionized water was sonicated for 5 minutes to break up the agglomerates. The sample was then examined in the same conditions as follows: 25°C measurement temperature, 4.65 mm measurement position, and 97.7 kcps count rate.

5) GF-AAS Quantification in Sunscreen: Sample preparation for GF-AAS experiment followed the modified standard method American Public Health Association (APHA) 3000. The modification was at the heating time and temperature. First, each sample was accurately weighed as much as 0.1 g in a vessel. Then, 10 mL of HNO_3 and 1 mL of H_2SO_4 were added. The solution was left for 10-15 minutes. Afterward, the digestion was carried out in Microwave Digestion Ethos Easy Milestone SK-15 (Italy) for 40 minutes at 200°C, 100 bar, and 1200 watt. The solution after digestion was cooled down to room temperature and dissolved in deionized water to a volume of 100 mL. This clear digestion solution was then tested for Ti total concentration by GF-AAS instrument (Agilent, United State). Limit detection (LOD) and limit of quantitation (LOQ) values for verification were achieved by digesting the blank using the same acid and parameter conditions mentioned above. Validation of the method was performed using Ti free sunscreen sample, which was added by 5 mL of 1000 mgL^{-1} Ti standard.

III. Results and Discussion

A. Physicochemical Properties of TiO_2 NP in Sunscreens

The XRD experiment was carried out to characterize the crystal structure of inorganic materials in the sunscreen samples. Anteriorly, the organic materials in the sample were extracted by various organic solvents to prevent amorphous peaks in the spectrum, distracting the spectrum interpretation. Previous literature has shown that to protect the skin; sunscreen products add inorganic materials such as TiO_2 and ZnO as sunlight blocking [26], [27]. As we know, TiO_2 presents in three crystalline structures: anatase, rutile, and brookite. Rutile is the most common and stable form in nature. Generally, compared with anatase, rutile has a higher UV absorption and low toxic [28]. However, more recent studies revealed that anatase TiO2 showed lower toxicity than rutile TiO_2 [29]. Figure 1 shows the spectrums of five commercial sunscreens studied in this work. According to that figure, TiO_2 exists in all products, and only product S1 contains both UVA (ZnO) and UVB (TiO_2) absorbing materials. This result is following the ingredients information given by the products (Table 1). Furthermore, TiO_2 material in samples S1, S2, and S3 have a rutile crystalline structure, while S4 and S5 products possess anatase forms.

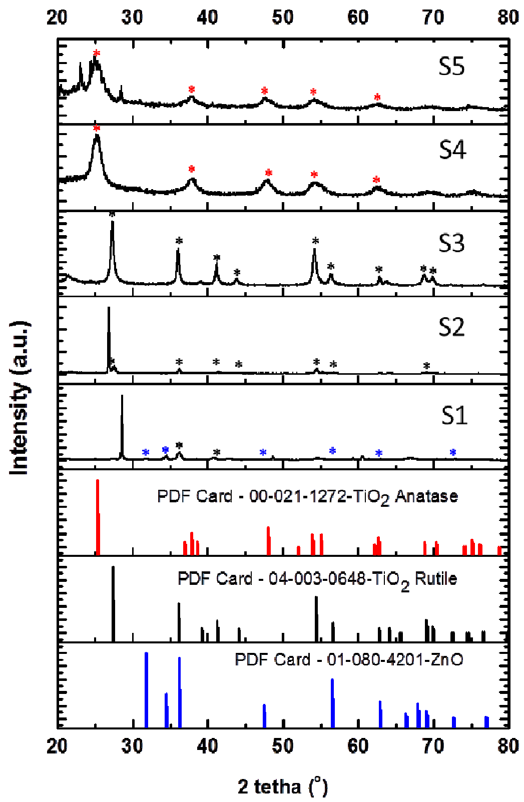

Fig. 1 XRD spectrum of TiO_2 nanoparticles in commercial sunscreens compared with database spectrum TiO_2 anatase (PDF Card 00-021-1272), TiO_2 rutile (PDF Card 04-003-0648), and ZnO (PDF Card 01-080-4201). The red, black, and blue stars denote the peak for TiO_2 anatase, TiO_2 rutile, and ZnO, respectively.

SEM and HRTEM characterized the morphology of a particle contained in the commercial sunscreen. Moreover, each of those analyses was combined by EDS mapping to determine the samples' elemental composition. In the beginning, the SEM images were acquired using the untreated samples, as shown in Figure 2.1a-1e. The results (Figure 2.1a-1e) indicated a high aggregation and huge cover of particles in the cream matrix, causing difficulty in determining particles' size and shape. Therefore, to remove the matrix, all samples were sequentially pre-treated by various organic solvents, including n-hexane, isopropanol, acetone, and methanol. The SEM images of pre-treated samples (Figure 2.2a-2e) show that particles' morphology characteristic is visually more apparent. The sphere particles below 500 nm were observed in sample S1-4 (Figure 2.2a-2d), while sample S5 possesses the particles with the flake shape and the size above 500 nm (Figure 2.2e). The EDS results (Figure 2.3a-3e) using pre-treated samples verify the UV filter materials incorporated in the product (Table 1). Ti was detected in all samples, but only in S1 (Figure 2.3a), Zn was observed, and it was in agreement with the packaging label displayed on each product. Besides Ti and Zn, the compositional analysis demonstrated silicon (Si) presence that might come from silica (SiO_2) and some other minor elements.

Some studies revealed that to diminish photo reactivity and minimize the toxicity, UV filter materials (TiO_2 or ZnO) surfaces have to be coated by SiO_2 [30]–[32]. In order to analyze the layer by layer of metal oxide composites, HRTEM coupled with an EDS mapping experiment was suggested.

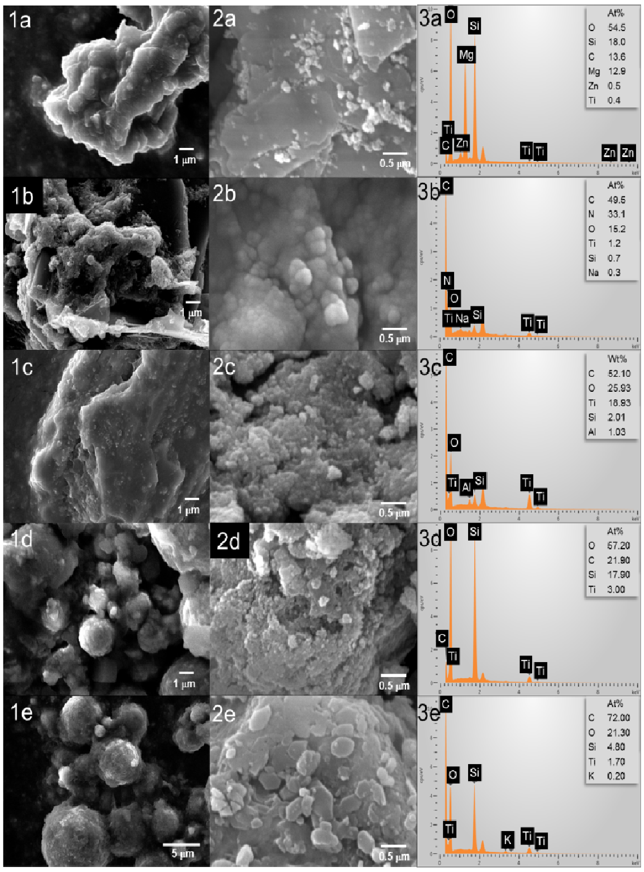

Fig. 2 SEM image of un-treated and pre-treated commercial sunscreen products as well as EDS spectrum of pre-treated sunscreen products: S1 (1a-3a); S2 (1b-3b); S3 (1c-3c); S4 (1d-3d); S5 (1e-3e).

In this experiment, the untreated sample was employed to prevent the information loss of material conformation added in the sample. The sample only needs to be diluted in ethanol before HRTEM/EDS analysis. The HRTEM image and EDS mapping (Figure 3) provide complete information from SEM analysis. According to the results, the size, shape, conformational, and composition of metal oxide particles in the cream matrix varied between the samples. The HRTEM images clearly show the size of particles below 50 nm for S1, S2, and S3 (Figure 3a, 3b, and c, respectively) and in the micron size range for samples S4 and S5 (Figure 3d and e, respectively).

Differences in particle shape were also observed among samples; for instance, sample S1 appears to have both spherical and needle-shaped particles (Figure 3a), S2 has a mixture of spherical and rod-shaped particles (Figure 3b), needle-shaped particles were found in S3 (Figure 3c), and spherical particles were identified in S4 and S5 (Figure 3d and e). Using EDS mapping analysis, the results (Figure 3f-j) were not really under generated by EDS coupled with SEM (Figure 2.3). It might be due to the inhomogeneity of metal particle distribution in the sample. According to Figure 3f-j, the characterization of the detailed structure of metal oxide composites was not successfully, except for sample S4 (Figure 3i), wherein Si particles which act as a core and is coated by metal layer (Ti, Al, and Cu), and not vice versa. This result is contrary to reports [30], [32] mentioned in the previous paragraph.

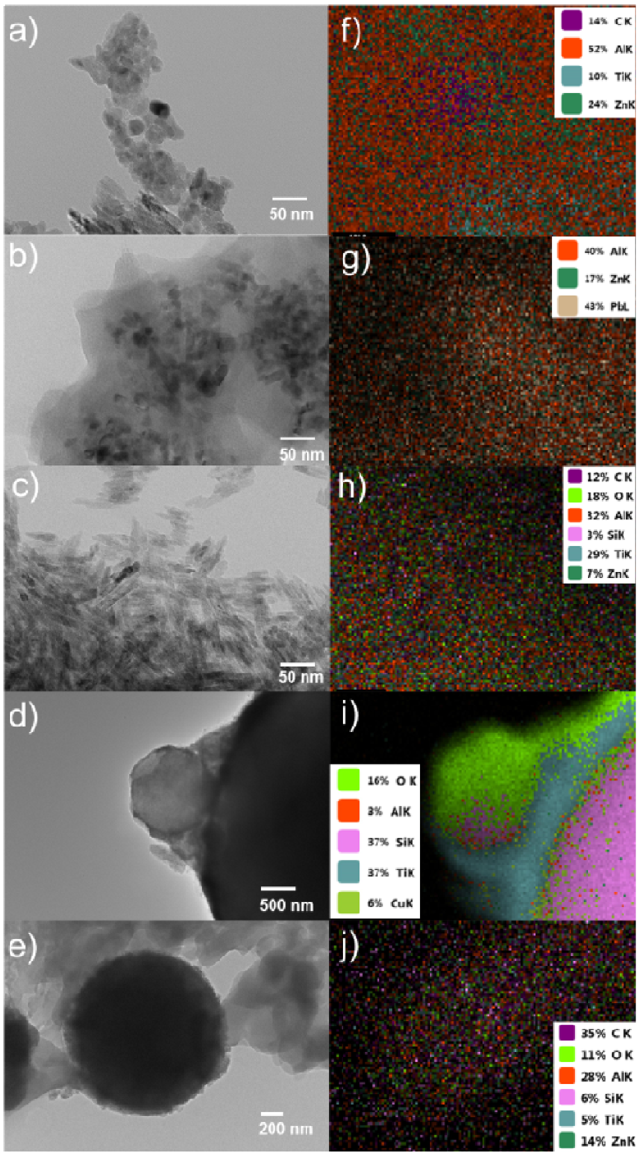

Fig. 3 TEM image and EDS mapping of unpre-treated commercial sunscreen products: S1 (a) (f); S2 (b) (g); S3 (c) (h); S4 (d) (i); S5 (e) (j).

PSA was utilized to determine the size and distribution of particles in samples. According to Figure 4, the mean size of particles in all samples is below 500 nm. Sample S1, S2, and S3 have a smaller particle size than S4 and S5 (Figure 4), and these results are under the HRTEM data (Figure 3). However, there is a difference in size value between HRTEM and PSA analysis results for S1, S2, and S3. HRTEM image demonstrated that samples S1, S2, and S3 (Figure 3a, b, and c) have a particle size smaller than 50 nm, while PSA analysis resulted in the particle size of 168, 152, and 189 nm for S1, S2, and S3, respectively. Those differences might be due to the aggregation of particles, as we can see as well from the SEM images (Figure 2.2a, 2b, and 2c) and Pdi value (Figure 4) which indicated the high relative polydispersity of particles (Pdi > 0.1). The PSA (Figure 4, the green and red line) and HRTEM (Figure 3d and e) analysis results of sample S4 and S5 were almost similar, wherein the average size of particles is above 200 nm.

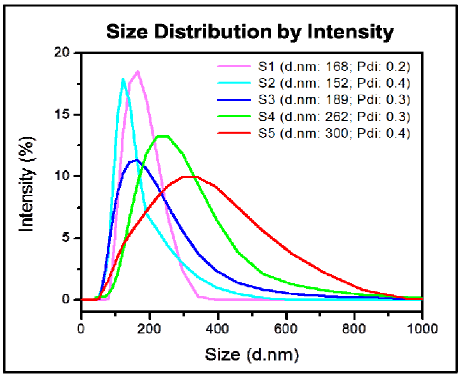

Fig. 4 Size distribution of particles in un-treated commercial sunscreens. The magenta, cyan, blue, green, and red represent sunscreen S1, S2, S3, S4, and S5.

B. *Quantification of Ti in Commercial Sunscreen by GF-AAS*

We developed a GF-AAS method for Ti quantification in commercial sunscreen products, in which microwave-assisted digestion was used to speed up the digestion process. Standard solutions of titanium, ranging from 0 to 500 μgL^{-1}, were used for the calibration. The calibration graph was linear over this concentration range, and the coefficient of determination (R2) was >0.99 in all cases. Table 2 displays the verification data of GF-AAS for Ti determination in the sunscreen products. The relative standard deviation at each concentration of Ti standard solution (0, 40, 80, 100, 200, 300, and 500 μgL^{-1}) were found to be less than 5%, which means that the instrument has a high precision for Ti quantification at that range concentration. The detection limit (LOD) was calculated to be 5.55 μgL^{-1}, while the limit of quantitation (LOQ) was approximately 10.00 μgL^{-1}. The method accuracy was examined at the Ti standard concentration of 10 and 250 μgL^{-1} and yielding the percent recovery of 95.45% and 102.34%, respectively, which are satisfactory.

TABLE II
VERIFICATION DATA OF GF-AAS FOR TITANIUM DETERMINATION.

Parameters	Value
Calibration Range (μgL^{-1})	0-500
Relative Standard Deviation	<5%
Correlation Coefficient	0.99
LOD (μgL^{-1})	5.55
LOQ (μgL^{-1})	10.00
% Recovery	95.45 ~ 102.34%

The quantitative data presented in Table 3 is the concentration of Ti present in the sunscreen sample. According to Table 3, all sunscreen analyzed contain Ti metal/TiO_2 in their formulation. Sample S3 and S4 have a higher concentration of Ti (0.53 and 0.79 %, respectively) compared with the rest three, and this result corresponds to the SPF value listed on their package (Table 1). The lowest Ti is owned by sample S1 (0.14%), even though based on the SPF value (Table 1), the one that should have the lowest Ti concentration was sample S5 with the SPF value of 20. High SPF value of S1 (SPF 30) might be contributed by another UV protection materials contained in the product such as ZnO as shown by XRD (Figure 1), EDS (Figure 2.3a) analysis results, and product label, which reveal that TiO_2 and ZnO incorporated in S1 as UV protection materials. However, in general, the concentration of Ti in all sunscreen studied are below the regulation published by NADFC [22] and United State Food and Drug Administration (US-FDA) [33].

TABLE III
THE CONCENTRATION OF TI IN STUDIED COMMERCIAL SUNSCREEN

Product's Code	Ti Concentration		RSD
	(μg g^{-1})	(%)	(%)
S-1	1452.58	0.14	4.59
S-2	2958.64	0.30	15.89
S-3	5332.23	0.53	6.97
S-4	7881.95	0.79	4.09
S-5	2532.99	0.25	17.78

IV. CONCLUSION

In summary, we have demonstrated the success of a combination of XRD, HRTEM, EDS, PSA, and GF-AAS analysis to characterize and quantify TiO_2 in sunscreen products. Those instruments gave complementary information regarding the physicochemical properties and the concentration of TiO_2 NPs. XRD spectrum revealed that two out of five studied sunscreens contain anatase TiO_2, while HRTEM was able to confirm the particle's size, shape, and homogeneity. EDS mapping coupled with HRTEM is a powerful method to elucidate the composition of the nanocomposite. However, there is a limitation for small nanoparticles (<50 nm) and thermally unstable material. GF-AAS can do quantification of TiO2 in sunscreen matrix with high precision and accuracy. Overall, the results revealed that all studied sunscreens marketed in Indonesia contain TiO2 in nanometer size with a concentration much lower than standard NADFC regulation.

ACKNOWLEDGMENT

This work is supported by a grant from INSINAS Riset Pratama Individu project 2019, Ministry of Research Technology and Higher Education of Indonesia. The authors are obliged to the Research Unit for Clean Technology, Indonesian Institute of Science (LIPI) for supporting facilities.

REFERENCES

[1] A. J. Haider, Z. N. Jameel, and I. H. M. Al-Hussaini, "Review on: Titanium Dioxide Applications," *Energy Procedia*, vol. 157, pp. 17–29, 2019.

[2] D. Ziental *et al.*, "Titanium Dioxide Nanoparticles: Prospects and Applications in Medicine," *Nanomater. (Basel, Switzerland)*, vol. 10, no. 2, p. 387, Feb. 2020.

[3] N. Veronovski, "TiO2 Applications as a Function of Controlled Surface Treatment," in *Titanium Dioxide - Material for a Sustainable Environment*, D. Yang, Ed. Rijeka: IntechOpen, 2018.

[4] A. Philippe, J. Košík, A. Welle, J.-M. Guigner, O. Clemens, and G. E. Schaumann, "Extraction and characterization methods for titanium dioxide nanoparticles from commercialized sunscreens," *Environ. Sci. Nano*, vol. 5, no. 1, pp. 191–202, 2018.

[5] Z. Chen, S. Han, D. Zhou, S. Zhou, and G. Jia, "Effects of oral exposure to titanium dioxide nanoparticles on gut microbiota and gut-associated metabolism in vivo," *Nanoscale*, vol. 11, no. 46, pp.

22398–22412, 2019.
[6] I. Ahmad, C. Kan, and Z. Yao, "Photoactive cotton fabric for UV protection and self-cleaning," *RSC Adv.*, vol. 9, no. 32, pp. 18106–18114, 2019.
[7] S. L. Schneider and H. W. Lim, "A review of inorganic UV filters zinc oxide and titanium dioxide," *Photodermatol. Photoimmunol. Photomed.*, vol. 35, no. 6, pp. 442–446, Nov. 2019.
[8] M. P. Abuçafy, E. B. Manaia, R. C. K. Kaminski, V. H. Sarmento, and L. A. Chiavacci, "Gel Based Sunscreen Containing Surface Modified TiO_2 Obtained by Sol-Gel Process: Proposal for a Transparent UV Inorganic Filter," *J. Nanomater.*, vol. 2016, p. 8659240, 2016.
[9] B. Dréno, A. Alexis, B. Chuberre, and M. Marinovich, "Safety of titanium dioxide nanoparticles in cosmetics," *J. Eur. Acad. Dermatology Venereol.*, vol. 33, no. S7, pp. 34–46, Nov. 2019.
[10] P. J. Lu, S. W. Fang, W. L. Cheng, S. C. Huang, M. C. Huang, and H. F. Cheng, "Characterization of titanium dioxide and zinc oxide nanoparticles in sunscreen powder by comparing different measurement methods," *J. Food Drug Anal.*, vol. 26, no. 3, pp. 1192–1200, 2018.
[11] J. Musial, R. Krakowiak, D. T. Mlynarczyk, T. Goslinski, and B. J. Stanisz, "Titanium Dioxide Nanoparticles in Food and Personal Care Products—What Do We Know about Their Safety?" *Nanomaterials* , vol. 10, no. 6. 2020.
[12] S. A. Jalil *et al.*, "Fabrication of high refractive index TiO2 films using electron beam evaporator for all dielectric metasurfaces," *Mater. Res. Express*, vol. 5, no. 1, p. 16410, 2018.
[13] K. Chalastara, F. Guo, S. Elouatik, and G. P. Demopoulos, "Tunable Composition Aqueous-Synthesized Mixed-Phase TiO2 Nanocrystals for Photo-Assisted Water Decontamination: Comparison of Anatase, Brookite and Rutile Photocatalysts," *Catalysts,* vol. 10, no. 4. 2020.
[14] W. Xie, R. Li, and Q. Xu, "Enhanced photocatalytic activity of Se-doped TiO 2 under visible light irradiation," *Sci. Rep.*, vol. 8, no. 1, p. 8752, 2018.
[15] S. Sharma *et al.*, "Fueling a Hot Debate on the Application of TiO(2) Nanoparticles in Sunscreen," *Mater. (Basel, Switzerland)*, vol. 12, no. 14, p. 2317, Jul. 2019.
[16] A. M. Abdullah, M. Á. Garcia-Pinilla, S. C. Pillai, and K. O' Shea, "UV and Visible Light-Driven Production of Hydroxyl Radicals by Reduced Forms of N, F, and P Codoped Titanium Dioxide," *Molecules,* vol. 24, no. 11. 2019.
[17] R. Dunford *et al.*, "Chemical oxidation and DNA damage catalysed by inorganic sunscreen ingredients," *FEBS Lett.*, vol. 418, no. 1, pp. 87–90, 1997.
[18] T. Luttrell, S. Halpegamage, J. Tao, A. Kramer, E. Sutter, and M. Batzill, "Why is anatase a better photocatalyst than rutile? - Model studies on epitaxial TiO 2 films," *Sci. Rep.*, vol. 4, no. 1, p. 4043, 2014.
[19] D. Li *et al.*, "Effects of Particle Size on the Structure and Photocatalytic Performance by Alkali-Treated TiO2," *Nanomaterials,* vol. 10, no. 3. 2020.
[20] SCCS (Scientific Committee on Consumer Safety), "OPINION for clarification of the meaning of the term 'sprayable applications/products' for the nano forms of Carbon Black CI 77266, Titanium Oxide and Zinc Oxide," 2015.
[21] E. Baranowska-Wójcik, D. Szwajgier, P. Oleszczuk, and A. Winiarska-Mieczan, "Effects of Titanium Dioxide Nanoparticles Exposure on Human Health—a Review," *Biol. Trace Elem. Res.*, vol. 193, no. 1, pp. 118–129, 2020.
[22] NIOSH (National Institute for Occupational Safety and Health), "Current Intelligence Bulletin 63: Occupational Exposure to Titanium Dioxide," 2011.
[23] European Union, "European parliament and of the council of 30 November 2009 on cosmetic products," Regulation (EC) number 1223, 2009.
[24] Badan Pengawasan Obat dan Makanan (BPOM), "Persyaratan teknis bahan kosmetika," Peraturan Badan Pengawasan Obat dan Makanan, no. 23, 2019.
[25] P.-J. Lu, S.-C. Huang, Y.-P. Chen, L.-C. Chiueh, and D. Y.-C. Shih, "Analysis of titanium dioxide and zinc oxide nanoparticles in cosmetics," *J. Food Drug Anal.*, vol. 23, no. 3, pp. 587–594, 2015.
[26] M. Geppert *et al.*, "Interactions of TiO2 Nanoparticles with Ingredients from Modern Lifestyle Products and Their Effects on Human Skin Cells," *Chem. Res. Toxicol.*, vol. 33, no. 5, pp. 1215–1225, May 2020.
[27] L. T. Ngoc, V. V Tran, J.-Y. Moon, M. Chae, D. Park, and Y.-C. Lee, "Recent Trends of Sunscreen Cosmetic: An Update Review," *Cosmetics,* vol. 6, no. 4. 2019.
[28] V. De Matteis, M. Cascione, V. Brunetti, C. C. Toma, and R. Rinaldi, "Toxicity assessment of anatase and rutile titanium dioxide nanoparticles: The role of degradation in different pH conditions and light exposure," *Toxicol. Vitr.*, vol. 37, pp. 201–210, 2016.
[29] Q. Yu, H. Wang, Q. Peng, Y. Li, Z. Liu, and M. Li, "Different toxicity of anatase and rutile TiO2 nanoparticles on macrophages: Involvement of difference in affinity to proteins and phospholipids," *J. Hazard. Mater.*, vol. 335, pp. 125–134, 2017.
[30] D. L. Slomberg *et al.*, "Aqueous aging of a silica coated TiO2 UV filter used in sunscreens: investigations at the molecular scale with dynamic nuclear polarization NMR," *RSC Adv.*, vol. 10, no. 14, pp. 8266–8274, 2020.
[31] M. Canta and V. Cauda, "The investigation of the parameters affecting the ZnO nanoparticle cytotoxicity behaviour: a tutorial review," *Biomater. Sci.*, vol. 8, no. 22, pp. 6157–6174, 2020.
[32] S. Ortelli, C. A. Poland, G. Baldi, and A. L. Costa, "Silica matrix encapsulation as a strategy to control ROS production while preserving photoreactivity in nano-TiO2," *Environ. Sci. Nano*, vol. 3, no. 3, pp. 602–610, 2016.
[33] Food and Drug Administration, "Subchapter: Drug for human use. Part: Sunscreen drug products for over-the-counter human use," *Federal Register US Government*, 2019. [Online]. Available: https://www.federalregister.gov/documents/2019/02/26/2019-03019/sunscreen-drug-products-for-over-the-counter-human-use. [Accessed: 21-Feb-2021].