

Accurate Determination of TiO_2 Nanoparticles in Complex Matrices using the Agilent 8900 ICP-QQQ

Application note

Environmental, food, cosmetics, materials

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Introduction

Titanium dioxide (TiO_2) nanoparticles (NPs) are widely used in paints, food colorants, cosmetics, pharmaceuticals, and many other applications. Due to their high refractive index, TiO_2 NPs are common ingredients in sun protection products used to guard against UV exposure. However, the fate of NPs in the environment and the potential for toxic effects once absorbed into the body remain largely unknown. Many researchers have investigated different methodologies to measure TiO_2 NPs in cosmetic or food samples [1, 2, 3, 4].

TiO_2 NPs have three principal levels of structure, beginning with nanoscale crystallites. These crystals fuse to form 'hard' nanoscale aggregates, which in turn associate to form microscale agglomerates [5]. When aqueous dispersions of TiO_2 NPs are prepared, the particle sizes observed are the aggregation or agglomeration sizes, which are usually different from (larger than) the primary (crystal) particle

sizes [5, 6]. Typically, the primary size is measured by transmission electron microscopy (TEM) or X-ray diffraction (XRD), and the dispersion size is measured by laser diffraction spectrometry (LDS) or dynamic light scattering (DLS).

The relatively recent development of Single Particle ICP-MS (spICP-MS) now provides a powerful tool to characterize the NP content of dispersed samples. spICP-MS is used to measure the target element signals generated from individual NPs in the solution analyzed. This approach allows the simultaneous determination of the number, concentration, and size of particles present, as well as the dissolved element concentration.

In practice, however, there are some challenges for the measurement of TiO₂ NPs using conventional single quadrupole ICP-MS (ICP-QMS). Many real samples may contain P, S, Ca, Si and C, and all these elements cause interferences that hinder the measurement of Ti. Also, the most abundant isotope of Ti, ⁴⁸Ti (73.7% abundance), suffers an isobaric interference from ⁴⁸Ca; therefore, the less interfered isotopes ⁴⁷Ti or ⁴⁹Ti are typically measured. However, the less abundant isotopes provide lower sensitivity, which limits the detection of smaller-sized TiO₂ NPs by ICP-QMS.

The Agilent 8900 Triple Quadrupole ICP-MS (ICP-QQQ) can operate in MS/MS mode to resolve the spectral interferences on Ti, including the isobaric interference from ⁴⁸Ca on ⁴⁸Ti. The 8900 ICP-QQQ is a tandem mass spectrometer, meaning that it has an additional mass spectrometer with unit (1 u) resolution, positioned before the collision/reaction cell. This extra mass filter selects the ions that can enter the cell, providing control of the reaction chemistry when reactive cell gases are used. ICP-QQQ with MS/MS provides an elegant and effective approach for solving the most challenging spectral overlaps [7].

In this study, TiO₂ NPs in sunscreen were measured in spICP-MS mode using the Agilent 8900 ICP-QQQ in MS/MS mode. The optional Single Nanoparticle Application Module software for ICP-MS MassHunter was used for method setup and data processing.

Current regulations

The methodologies used to evaluate the properties of nanomaterials are not yet considered to be finalized and approved, which may be impeding the introduction of specific regulations relating to NPs. In June 2014, the USA Food and Drug Administration (FDA) issued guidance on the safety assessment of nanomaterials in cosmetic products [8]. As part of the FDA, the Center for Drug Evaluation and Research (CDER) is examining the safety of titanium dioxide (and zinc oxide) nanomaterials for sunscreen use as part of an ongoing regulatory process to establish a final monograph for over-the-counter (OTC) sunscreen drug products [9].

Currently, the European Union Scientific Committee on Consumer Safety (SCCS) considers that it is safe to use TiO₂ NPs as a UV filter at a concentration up to 25% in sunscreens. Manufacturers must respect this limit according to European legislation (annex VI list of UV filters) of the EU regulation on cosmetic products; regulation EC 1223/2009 [10]. The regulation was amended in 2016 to state that in the case of combined use of titanium dioxide and titanium dioxide (nano), the sum shall not exceed 25% [11].

In 2016, following a request from the European Commission to the European Food Safety Authority (EFSA), the Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS) considered the safety of titanium dioxide (TiO₂, E 171) when used as a food additive [12]. The Panel will establish a health-based guidance value for acceptable daily intake (ADI) once more data is available on the reproductive toxicity of E 171.

Experimental

Reference materials and calibration solutions

The TiO₂ standard reference material (SRM) NIST 1898 Titanium Dioxide (Maryland, US) was used. The SRM contains crystal or primary sized particles <50 nm, but the size of particles dispersed in the aqueous phase range from 71 to 112 nm due to nanoscale aggregation [5]. The SRM was diluted with de-ionized water to a particle concentration that was calculated to give 500 – 2000 particle counts per minute, and sonicated to ensure sample homogeneity. A 1 ppb Ti ionic standard prepared in 1 % nitric acid was used to measure the elemental response factor for Ti. A gold NP RM with a nominal particle size of 60 nm (NIST 8013 Gold Nanoparticles) was used to measure the nebulization efficiency of the ICP-QQQ.

Sunscreen samples

Sunscreen products were bought in a local store in Tokyo, Japan. The samples were diluted with de-ionized water plus 0.1 % Triton™ X-100. The results obtained from an initial screening analysis using the spICP-MS method, showed the size-range of TiO₂ particles present in the different sunscreen samples varied. One of the samples contained particles <30 nm, while another product contained particles sized 30 to 200 nm. A sunscreen that contained TiO₂ NPs sized 30 to 100 nm was selected for further investigation. The selected sunscreen was prepared in various diluent matrices: de-ionized water; tap water; and a “matrix mixture” containing 100 ppm of P and S, 50 ppm of Ca and Si, and 0.1 % of ethanol. The matrix mixture was used to check the impact of matrix-based interferences on the measurement of Ti.

Instrumentation

An Agilent 8900 Advanced Applications configuration ICP-QQQ was used throughout. The instrument was equipped with the standard glass concentric nebulizer and quartz spray chamber, optional quartz torch with 1.0 mm i.d. injector, and standard nickel sampling and skimmer cones. Samples were introduced directly into the ICP-QQQ using the standard peristaltic pump and 1.02 mm i.d. pump tubing. Analyses were performed in fast Time Resolved Analysis (fast TRA) mode, using a dwell time of 0.1 ms (100 μ s) per point, with no settling time between measurements. The major titanium isotope, ^{48}Ti , was measured in MS/MS mass-shift mode, using a mixed cell gas containing oxygen and hydrogen to resolve all the polyatomic and isobaric interferences. Q1 was set to m/z 48 (the mass of the precursor ^{48}Ti ion) and Q2 was set to m/z 64 (the mass of the target product ion $^{48}\text{Ti}^{16}\text{O}$). O_2 and H_2 cell gases were used to promote the formation of the TiO^+ product ion, avoiding the on-mass interference from ^{48}Ca and matrix-based polyatomic ions that overlap ^{48}Ti . The operating conditions of the Agilent 8900 ICP-QQQ are detailed in Table 1.

Table 1. ICP-QQQ operating conditions.

Parameter	Value
RF power	1550 W
Sampling depth	8 mm
Carrier gas	0.70 L/min
Sample uptake rate	0.35 mL/min
Spray chamber temp.	2 °C
Dwell time	0.1 ms
Settling time	None
Acquisition mode	MS/MS (Q1: m/z 48, Q2: m/z 64)
Oxygen flow rate	0.15 mL/min (10% of full scale)
Hydrogen flow rate	7.0 mL/min
Axial Acceleration	1.0 V
Octopole bias voltage	-6 V
Energy discrimination	-15 V

The Single Nanoparticle Application Module of the ICP-MS MassHunter software was used for method setup and data analysis. Sample results for an entire batch are summarized in the interactive 'Batch at a Glance' table. Detailed graphical results are displayed for selected samples, permitting visual confirmation and optimization of parameters if needed.

Results and Discussion

Optimization of cell gas conditions using ionic Ti solution

Before measurement of the NPs, cell gas conditions were investigated. Ti reacts readily with oxygen, so can be measured as TiO^+ in oxygen mass shift mode. The first quadrupole (Q1) was set to pass only m/z 48, to allow $^{48}\text{Ti}^+$ (and any on-mass interferences) to enter the cell. The second quadrupole (Q2), which is located after the collision/reaction cell, was set to m/z 64 to pass the target product ion ($^{48}\text{Ti}^{16}\text{O}^+$) to the detector. Any potential native ion overlaps at m/z 64 (e.g. ^{64}Zn and ^{64}Ni) are rejected by Q1. Most of the primary interferences at m/z 48, such as $^{32}\text{S}^{16}\text{O}^+$, $^{30}\text{Si}^{18}\text{O}^+$, $^{31}\text{P}^{16}\text{OH}^+$, $^{12}\text{C}^{18}\text{O}_2^+$, can be avoided by measuring Ti as TiO^+ in oxygen cell gas mode. However, some of the ^{48}Ca ions also react with oxygen to form $^{48}\text{CaO}^+$, which interferes with the $^{48}\text{TiO}^+$ product ions at m/z 64. Adding hydrogen gas can eliminate the Ca interference by converting CaO^+ to CaOH^+ . TiO^+ does not react in the same way with H_2 cell gas, so remains as the TiO^+ product ion at m/z 64. Inter-isotope overlaps (such as $^{46}\text{Ti}^{18}\text{O}$ and $^{46}\text{Ca}^{18}\text{O}$) can affect the $^{48}\text{Ti}^{16}\text{O}$ measurement at m/z 64 when a single quadrupole or bandpass MS system is used. With MS/MS, however, these overlaps are avoided as the precursor ions (^{46}Ti and ^{46}Ca) are rejected by Q1 and so do not enter the cell to react.

Table 2 shows the quantitative results for Ti (measured as $^{48}\text{Ti}^+$ in no gas mode and $^{48}\text{TiO}^+$ in O_2/H_2 mode) in various matrices. The quantitative results obtained in no gas mode show a large positive error due to the interferences on ^{48}Ti . In contrast, O_2/H_2 cell gas mode effectively reduces the interferences including the potential CaO^+ product ion overlap formed from ^{48}Ca . This method enables the TiO^+ product ion from the most abundant isotope of Ti (mass 48; 73.7% relative abundance) to be measured, providing the sensitivity required for detection of small particles.

Table 2. Interference check results for ⁴⁸Ti in various matrices, with and without cell gas.

Cell gas mode	Sensitivity (cps/ppb)	Apparent concentration of Ti, measured as ⁴⁸ Ti ⁺ or ⁴⁸ TiO ⁺ (ppb)					
		100 ppm P	100 ppm S	50 ppm Ca	50 ppm Si	0.1% ethanol	Matrix mixture*
No gas	155,000	1.7	6.0	225	0.39	0.14	261
O ₂ + H ₂	79,000	0.010	0.001	0.18	0.054	0.001	0.23

*Includes all the matrices (100 ppm of P and S, 50 ppm of Ca and Si, and 0.1% ethanol).

Measurement of a TiO₂ NP reference material

NIST 1898 TiO₂ NP reference material was measured by ICP-QQQ in MS/MS mass-shift mode with O₂/H₂ reaction gas. The time resolved signal chart for NIST 1898 (Figure 1) shows clear NP peaks with a wide variation in intensity (peak heights). In single particle ICP-MS, the peak height for each particle signal “plume” is representative of the particle mass (size). Figure 2 shows the signal frequency distribution for NIST 1898 (upper), and the calculated particle size distribution (lower). The mean size of 71 nm agrees well with the results by LDS (71 ± 4 nm), X-Ray Disc Centrifugation (77 ± 7 nm), and DLS (112 ± 4 nm) according to the NIST certificate [5]. Note that DLS measures the hydrodynamic particle size, which includes the layer where the particle surface interacts with the solvent. Consequently DLS has been reported to give particle sizes that are larger than the value measured by other techniques [13].

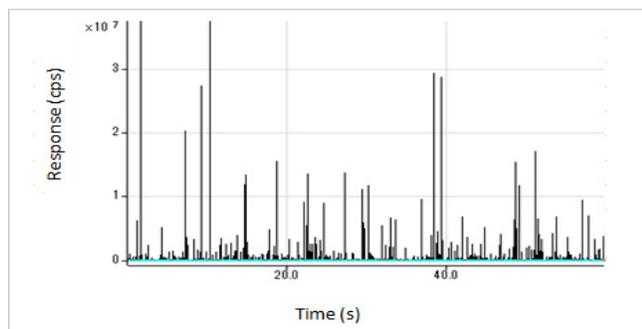


Figure 1. Time resolved signal for NIST 1898 TiO₂ NP reference material. The blue line represents a baseline automatically set by the MassHunter software function

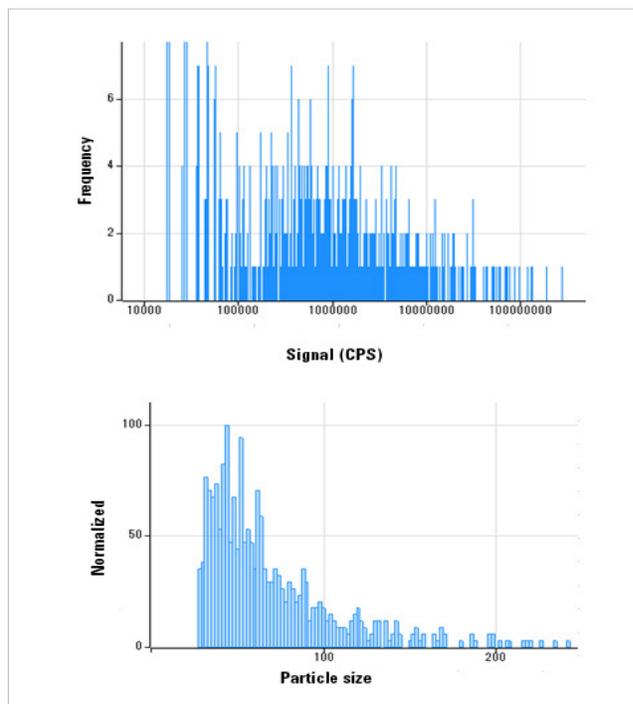


Figure 2. Signal frequency distribution (upper) and particle size distribution (lower) for NIST 1898 TiO₂ NP reference material.

Analysis of TiO₂ NPs in sunscreens

TiO₂ NPs were measured in a commercial sunscreen prepared (dispersed) in several different solutions and the results are presented in Figure 3. Figure 3-A shows the TiO₂ signal distribution and Figure 3-B shows the particle size distribution for the sunscreen dispersed in de-ionized water (plus Triton X-100). The mean particle size of TiO₂ was calculated as 77 nm. The same sunscreen was dispersed in tap water (Figures 3-C and 3-D), and a synthetic matrix mixture comprising 100 ppm of P and S, 50 ppm of Ca and Si, 0.1 % of ethanol (Figures 3-E and 3-F). These results show signal distributions that are almost the same as the ones

obtained for the sunscreen dispersed in de-ionized water. The mean particle sizes (79 nm for tap water and 84 nm for the matrix mixture) are similar. The particle size detection limit (the threshold between the baseline noise and particle signals) was about 30 nm for the dispersed sunscreens in all the matrices. The synthetic high matrix (Figure 3-E and 3-F) did not affect the size-DL or the accuracy of the particle size measurement.

The results show that TiO₂ NPs <100 nm diameter can easily be measured using the MS/MS capability of the 8900 ICP-QQQ, even in a high concentration matrix.

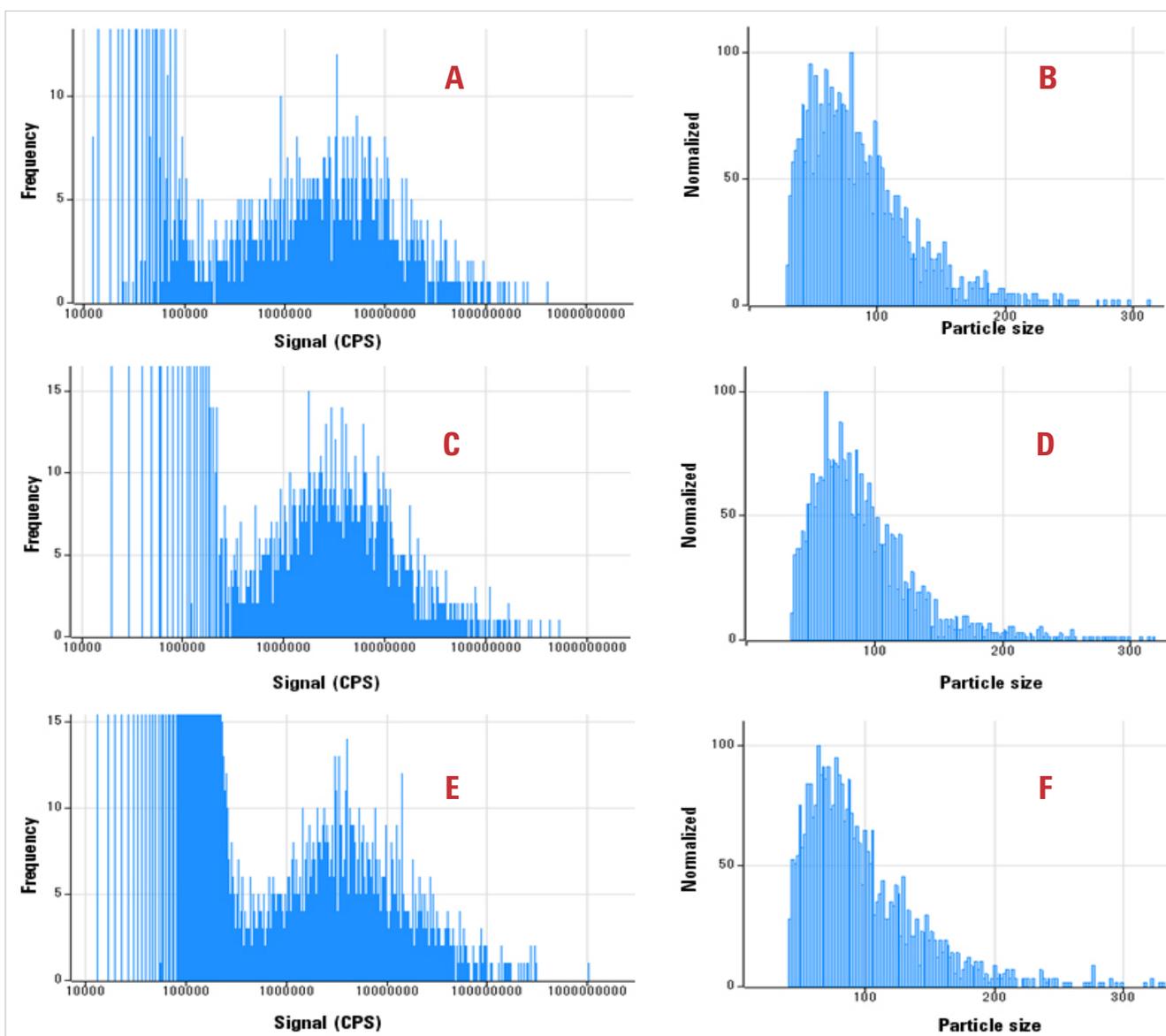


Figure 3. TiO₂ NP measurement of commercial sunscreen using ICP-QQQ. Signal distribution A) and particle distribution B) of sunscreen dispersed in de-ionized water. Signal distribution C) and particle distribution D) of sunscreen dispersed in tap water. Signal distribution E) and particle distribution F) of sunscreen dispersed in the matrix mixture.

Conclusions

The Agilent 8900 ICP-QQQ operating in MS/MS mode with O₂/H₂ cell gas was used for the successful determination and characterization of TiO₂ nanoparticles in various sample matrices. MS/MS mass-shift mode effectively resolved the polyatomic and isobaric ions that interfere with the measurement of Ti at its most abundant isotope. This unique MS/MS capability provided a particle size detection limit of ~30 nm.

Overall, the method delivered low background signals and excellent sensitivity, even in the presence of a high level of P, S, Ca, Si, and C matrix.

References

1. V. Nischwitz and H. Goenaga-Infante, *J. Anal. At. Spectrom.*, **2012**, *27*(7), 1084–1092.
2. C. Contado and A. Pagnoni, *Anal. Methods*, **2010**, *2*, 1112–1124.
3. I. López-Heras, Y. Madrid, C. Cámara, *Talanta*, **2014**, *124*, 71–78.
4. P. Lu, S. Huang, Y. Chen, L. Chiueh and D. Y. Shih, *J. Food and Drug Anal.*, **2015**, *23*, 587–594.
5. Standard Reference Material 1898 (Titanium Dioxide Nanomaterial) Certificate of Analysis, 2012.
6. Z. Magdolenova, D. Bilaničová, G. Pojana, L. M. Fjellsbø, A. Hudecova, K. Hasplova, A. Marcomini and M. Dusinska, *J. Environ. Monit.*, **2012**, *14*, 455–464.
7. G. Woods and E. McCurdy, *Spectroscopy*, **2015**, *30* (11), 18–25.
8. Guidance for Industry: Safety of Nanomaterials in Cosmetic Products, U.S. Department of Health and Human Services Food and Drug Administration Center for Food Safety and Applied Nutrition, June 2014, <https://www.fda.gov/Cosmetics/GuidanceRegulation/GuidanceDocuments/ucm300886.htm#introduction> (accessed July, 2017).
9. N. Sadrieh, Overview of CDER Experience with Nanotechnology-related Drugs, Slides for the August 9, 2012 Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, 2012.
10. Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products, <http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32009R1223> (accessed July, 2017).
11. Commission Regulation (EU) 2016/1143 of 13 July 2016 amending Annex VI to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products, <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32016R1143> (accessed July, 2017).
12. Re-evaluation of titanium dioxide (E 171) as a food additive, EFSA Journal 2016; 14 (9):4545, www.efsa.europa.eu/efsajournal, (accessed July 2017).
13. A. Dhawan and V. Sharma, *Anal. Bioanal. Chem.*, **2010**, *398* (2), 589–605.

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