Short communication

Non-destructive determination of TiO₂ concentration in cream formulation using Raman spectroscopy

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ABSTRACT

The concentration of TiO₂ in a cream formulation has been non-destructively measured using Raman spectroscopy without further sample pretreatments. The distribution of TiO₂ particles in a highly viscous cream may not be homogeneous on a microscopic scale and local aggregation of the particles is possible; therefore, acquisition of Raman spectra capable of representing the whole sample identity rather than the localized chemical information was critically necessary to ensure reliable quantitative analysis. A wide area illumination (WAI) scheme, applying 6-mm diameter laser illumination area (total coverage: 28.3 mm²) on a sample, was used to achieve representative sample presentation and improved accuracy. When Raman spectra were collected for the same sample using a conventional scheme with a much smaller laser spot (∼100 μm), the spectral reproducibility was degraded, as expected. The local aggregation of TiO₂ particles was confirmed by analyzing both SEM (scanning electron microscopy) and Raman images of a cream sample. When the WAI scheme was used, the resulting error in the determination of TiO₂ concentration was 0.03 wt%, while 0.17 wt% in the case of using the conventional scheme. The proposed Raman scheme would be advantageous over the conventional titration method that requires destructive incineration of the organic cream matrix, as well as a large consumption of chemical reagents.

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1. Introduction

TiO₂ nanoparticles have been extensively utilized in diverse pharmaceutical and cosmetic products for the purpose of UV (Ultra-Violet) protection, as well as whitening. To maintain its optimal function and meet required safety regulations, the concentration of TiO₂ must be accurately controlled and measured at the production stage. To determine TiO₂ concentration, a titration method conventionally has been used [1]; however, this method requires a long period of destructive sample preparation, such as total incineration of the organic cream matrix before the titration. In addition, the titration method requires a large consumption of chemical reagents. Consequently, there is a strong demand for a new analytical method that is capable of fast and non-destructive quantitative analysis. When rapid, non-destructive analysis becomes a critical analytical requirement, vibrational spectroscopy would be one of the excellent candidates to meet this goal.

We have studied Raman spectroscopy as a new analytical method that is capable of non-destructively determining the TiO₂ concentration in a cream formulation. Usually TiO₂-containing cream is a highly viscous emulsion in which oil and aqueous phases are simultaneously homogenized; therefore, there is a chance of inhomogeneous distribution as well as localized aggregation of TiO₂, especially on a microscopic scale (approximately in several hundreds microns). This possibility could lead to uncertainty in quantitative Raman analysis when a conventional Raman scheme of a small laser illumination area (50–200 μm in diameter) is used. The resulting Raman spectrum from such a small sampling area would fall short of representing the overall TiO₂ concentration in a cream sample. To improve the sample representation and lessen sub-sampling problem, spatially offset Raman spectroscopy (SORS) and transmission Raman spectroscopy have been developed [2]. The SORS involves the collection of Raman spectra from regions spatially offset on the sample surface from the laser beam interaction point, thereby leading to wider spread of photons interacting with deeper layers emerging onto the sample surface. Transmission Raman measurement is based on the collection of Raman signal at the opposition side of the laser illumination, so Raman spectra representing bulk content of samples can be acquired. In addition, wide area illumination (WAI) scheme, in which a laser simultaneously illuminates a large sample area such as 28.3 mm², has been used to enhance the sample representation for the analysis of diverse pharmaceutical samples [3–5].

To ensure the representative sampling of a TiO$_2$-containing cream in this study, the WAI scheme was used. Initially, the sample representations of TiO$_2$ cream that resulted from using both the conventional and WAI schemes were compared each. Raman spectra of TiO$_2$ cream were collected by randomly illuminating the laser onto different sections of the sample using each Raman scheme and then the resulting spectral features were examined. Next, to determine the concentration of TiO$_2$ using Raman spectra collected by both schemes, partial least squares (PLS) regression [6,7] was utilized and the resulting accuracies were compared. To check possible aggregation of TiO$_2$ particles in a cream, both SEM (scanning electron microscopy) and Raman images were examined.

2. Experimental

2.1. Samples

Eighteen TiO$_2$ creams were obtained from Amore-Pacific Corporation, R&D Center, Yongin-si, Korea. The concentration of TiO$_2$ in these samples ranged from 1.75 to 2.32 wt%, with the span of variation only 0.67 wt%. The organic cream matrix (except for the TiO$_2$) was composed of approximately 33 components, including water, decamethyl cyclopentasiloxane, tocopheryl acetate, stearic acid, and polyacrylate-13. A description of the detailed function and concentration of each component would not be important for this study. The organic cream matrix is an emulsion of homogenized aqueous and organic phases. The TiO$_2$ cream is white and highly viscous. Except for the spectral collection, the samples were always stored in a refrigerator.

2.2. Raman spectral collection

Raman spectra of TiO$_2$ cream samples were acquired using two different spectral collection schemes. First, the WAI (wide area illumination) Raman scheme, illuminating laser into a 6-mm diameter spot (Kaiser Optical Systems, Ann Arbor, MI, USA), was used. A detailed explanation of the WAI scheme can be found in our previously published article [3]. Additionally, a conventional small-spot scheme (non-contact Raman probe with a 10-mm focal length, beam size approximately 100 μm, Kaiser Optical Systems) was also used to collect Raman spectra of the same samples. As mentioned earlier, our approach was designed to investigate whether or not the sample representation of the WAI scheme would be superior
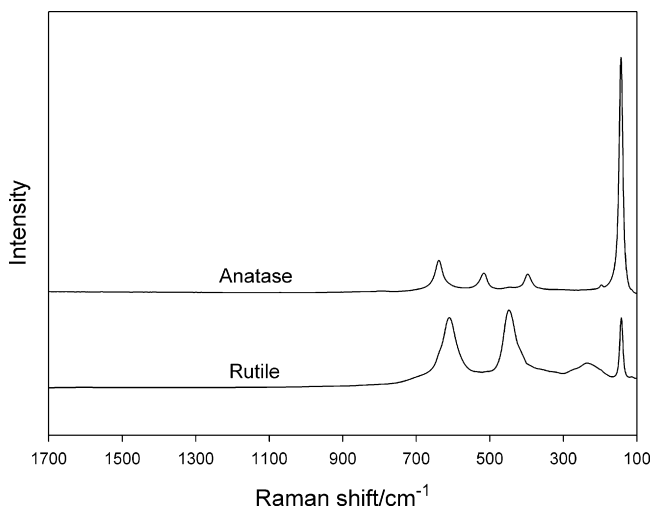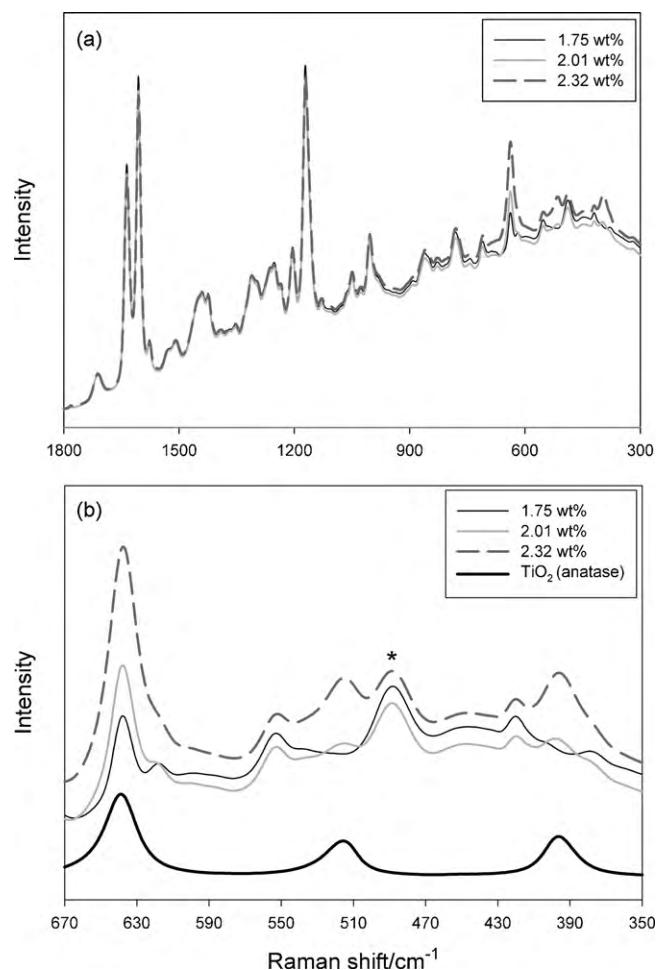

Fig. 2. Raman spectra of three different concentrations (1.75, 2.01, and 2.32 wt%) of TiO$_2$ creams in the 1700–300 cm^{-1} range (a). The spectra of the same three samples are highlighted in the 670–350 cm^{-1} range (b).

to the conventional scheme when determining the concentration of TiO$_2$ in cream.

In both schemes, TiO$_2$ creams were directly measured without manual sample transfer into other spectroscopic cells. The top surface of cream was flattened using a plastic spatula before the spectral collection. Due to high viscosity, a perfectly flat cream surface was difficult to generate. The cream surface was positioned at the focal point of both schemes, and triplicate spectra were collected for each sample. For the collection of triplicate spectra, three different spots on a cream surface were randomly illuminated. In both cases, Raman spectra were collected using a 785-nm laser with an exposure time of 10 s for 6 scans (total 60 s for acquisition, resolution 4 cm^{-1}).

All of the calculations, including baseline correction, intensity normalization, and partial least squares (PLS) regression, were done in Matlab version 7.0 (The Math-Works Inc., MA, USA).

3. Results and discussion

3.1. Raman spectral features of TiO$_2$ cream

The spectral features of the TiO$_2$ particle itself were initially examined. It is commonly known that TiO$_2$ has three different natural phases: anatase, rutile, and brookite. Fig. 1 shows the Raman spectra of anatase and rutile TiO$_2$ collected by the WAI scheme in the 1700–100 cm^{-1} range. In the case of anatase TiO$_2$, five bands are clearly observed at 639 cm^{-1} (E_g), 513 cm^{-1} (B_{1g}), 399 cm^{-1} (B_{1g}),

Fig. 1. Raman spectra of anatase and rutile TiO$_2$ collected by the WAI scheme in the 1700–100 cm^{-1} range. The spectra are offset for clarity.

197 cm^{-1} (E_g), and 144 cm^{-1} (E_g). In the case of rutile TiO_2, the bands at 610 cm^{-1} (A_{1g}), 446 cm^{-1} (E_g), 236 cm^{-1} (multi-photon process), and 142 cm^{-1} (B_{1g}) are clearly apparent. No significant Raman bands in the 1700–670 cm^{-1} range were observed. The observed band positions of both TiO_2 phases collected by WAI scheme are well-matched with those observed in previous publications [8–11].

Fig. 2(a) shows Raman spectra of three different concentrations (1.75, 2.01, and 2.32 wt%) of TiO_2 creams in the 1800–300 cm^{-1} range. The WAI scheme was used to collect these spectra. The cream samples used in this study were prepared using only anatase TiO_2. The overall spectral features are resultant from the combined features of TiO_2 and organic cream matrix. There were no significant spectral variations among the three samples in the 1800–670 cm^{-1} range, where only the spectral bands corresponding to the organic cream matrix are present. In contrast, the variation of TiO_2 bands was clearly observable in the 670–350 cm^{-1} range, where the spectral features of both TiO_2 and the cream matrix are simultaneously present.

Fig. 2(b) shows Raman spectra of the same three samples in the 670–350 cm^{-1} range. For the purpose of comparison, the Raman spectrum of TiO_2 (anatase) is also shown. Clearly, the intensities of three TiO_2 bands increase with concentration, while the intensity of the 488 cm^{-1} band (marked as an asterisk) that corresponds to one of the bands of organic matrix is quite unchanging. Compared to the range of variations in the TiO_2 concentration, the resulting Raman intensity varies quite sensitively because TiO_2 is a strong Raman scatter. If a typical organic compound with a concentration ranging from 1.75 to 2.32 wt% is measured, the resulting Raman intensity would not significantly vary as the TiO_2 bands do. Inherently, Raman spectroscopy is not a highly sensitive method for differentiating small concentration changes; however, the sensitive variation of the TiO_2 bands observed in Fig. 2(b) clearly demonstrate that sensitive Raman measurement is feasible even when narrow variations of TiO_2 concentrations occur. Obviously, the 670–350 cm^{-1} range should be more suitable than the full spectral range for quantitative analysis.

3.2. Examination of the microscopic homogeneity of urea cream

Raman spectra are normally collected by illuminating a focused laser onto a tiny spot of a sample and collecting the scattered radiation. In the case UV-protection cream, TiO_2 nanoparticles are dispersed in a highly viscous emulsion cream; therefore, their distribution may not be homogeneous relative to the size of the laser illumination. In addition, the chemical environment surrounding each TiO_2 particle could also vary. In this situation, there is a high chance of acquiring Raman spectra containing only local information rather than the whole sample composition.

To examine the sample presentation of TiO_2 cream by Raman measurement, 2.32 wt% TiO_2 cream was spread on an aluminum plate over a 3 cm × 3 cm area with a thickness of approximately 1.5 mm. Raman spectra were collected using both the conventional (non-contact Raman probe with a 10-mm focal length) and the WAI scheme. The size of the laser illumination spot in the conventional scheme is much smaller (approximately 100 μm in diameter) than that of the WAI scheme. Raman spectra were collected by randomly illuminating seven different spots over the sample. The resulting Raman spectra are shown in Fig. 3(a).

When the WAI scheme is employed, the resulting Raman spectra are similar to each other. Contrarily, when the conventional scheme is employed, the resulting Raman intensities are relatively more variable, with a slight change of band shape. Since the conventional scheme has a higher chance of yielding localized information, the variation of TiO_2 band intensity and shape indicates that the dispersion of TiO_2 particles would not be homogeneous on a micro-
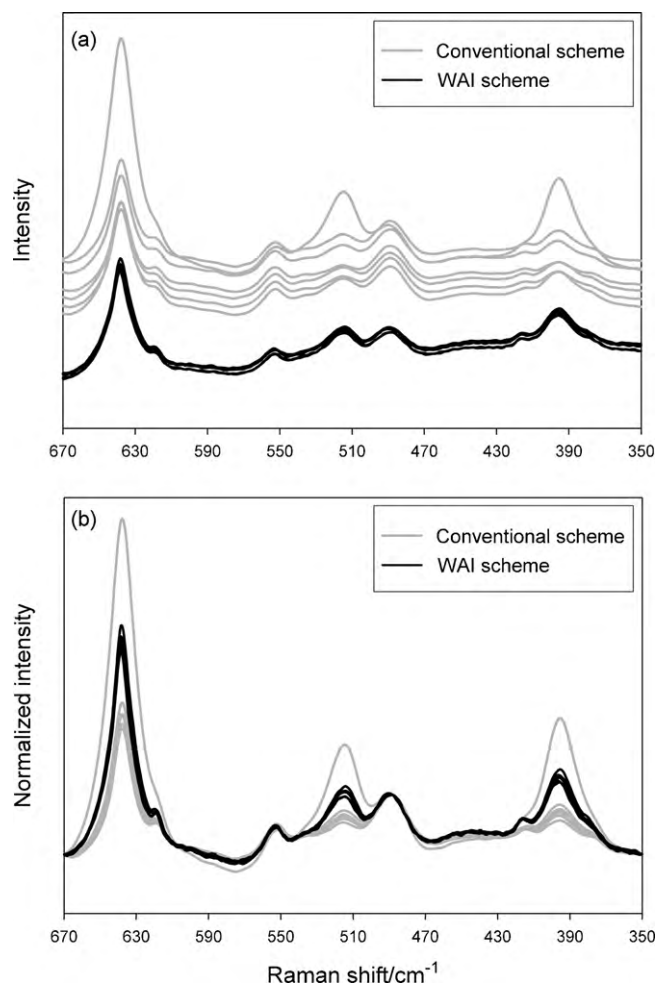

Fig. 3. Raman spectra collected using the WAI and conventional schemes by randomly illuminating seven different spots over 2.32 wt% TiO_2 cream (a). The spectra of each group are slightly offset for clarity. The corresponding normalized spectra are also shown (b).

scopic scale, which could explain the variation of TiO_2 bands in Fig. 3(a). One spectrum, in particular, collected using the conventional scheme, shows exceptionally high Raman intensity. It is presumed that TiO_2 particles are more aggregated at the location where the laser is illuminated.

To confirm the possible aggregation of TiO_2 nanoparticles in a cream matrix, SEM (scanning electron microscopy) image of 2.32 wt% TiO_2 cream as shown in Fig. 4 (field of view: 2050 μm × 1250 μm) was obtained by spreading the cream sample on a silicon wafer. The thickness of the cream sample is 80 μm approximately. As shown in the SEM image, the aggregations of TiO_2 particles can be observed. Some of the aggregations are marked by arrows in the image to help identification. The sizes of aggregation vary from 20 to 70 μm approximately. The aggregations are widely spread over the sampled area; while, these are also relatively more concentrated on top-left and bottom-right regions.

To further confirm the possible aggregation of TiO_2 nanoparticles in a cream matrix, Raman image of 2.32 wt% TiO_2 cream was also acquired. The sample was spread on a slide glass with a thickness of approximately 0.5 mm and then Raman mapping was performed over the sample area of 1000 μm × 750 μm. The point-to-point distance in x and y direction was 50 and 25 μm, respectively, thereby resulting in a total of 600 points (20 × 30 points). The same conventional Raman spectrometer as described
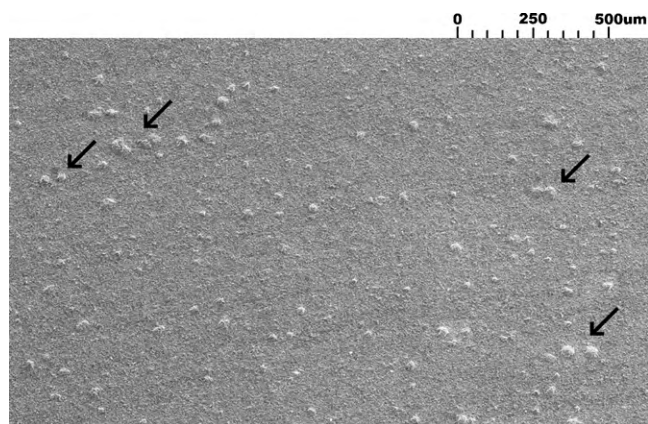
Fig. 4. SEM (scanning electron microscopy) image of 2.32 wt% TiO₂ (field of view: 2050 μm × 1250 μm).

in Section 2 was also used for the mapping by conjunction with a microscope (Leica microscope with objectives (10× N PLAN)).

To examine the distribution of TiO_2 nanoparticles, the area of 639 cm^{-1} band corresponding to the highest intensity of TiO_2 was used. Initially the baseline of spectra was corrected to zero at 663 and 612 cm^{-1}, and then peak area in the 663–612 cm^{-1} range was calculated. Out of 600 calculated areas from 600 spectra from each mapping point, the lowest area was assigned as one and then relative areas were obtained for the rest. Fig. 5(a) shows the three-dimensional surface map obtained from 2.32 wt% TiO_2 cream. As shown, two aggregates of TiO_2 nanoparticles are clearly observed, while the right one has the larger degree of aggregation. The maximum peak area at this aggregate is approximately 24 times larger than that of non-aggregated particle. To estimate the size of the aggregates, the colored contour map using the relative area was generated as shown in Fig. 5(b). As shown in the figure, the sizes of the larger and smaller aggregate are approximately 160 and 100 μm, respectively. As mentioned, the larger one shows the stronger Raman intensity due to the larger degree of aggregation.

Based on the above observation from SEM and Raman image, TiO_2 aggregates of different sizes clearly exist in cream matrix; therefore, the possibility of collecting Raman spectra containing localized information is difficult to exclude when laser is focused on the region of populated TiO_2 aggregations in the case of using the conventional scheme.

3.3. PLS regression

Partial least squares (PLS) regression was used to determine the concentration of urea in a cream matrix using both spectral datasets collected by the conventional and WAI schemes for the purpose of comparison. The 670–350 cm^{-1} range, where the bands of TiO_2 were clearly highlighted, was used for both cases. For PLS, 18 samples were divided into 13 samples (39 spectra, 1.75–2.32 wt%) for the calibration set, and five samples (15 spectra, 1.84–2.30 wt%) were used for the validation set. Before performing PLS, all of the spectra in Fig. 3(a) were normalized. Initially, baselines of the Raman spectra were corrected using the 4-point (670, 574, 466, and 350 cm^{-1}) polynomial method. Then, the baseline-corrected spectra were normalized to have the same intensity at 488 cm^{-1}, corresponding to the peak of the organic cream phase. The normalization is based on the assumption that the peak intensity at 488 cm^{-1} would be constant regardless of sample presentation or laser power change. The resulting normalized spectra are shown in Fig. 3(b) for both schemes. Through normalization, the possible Raman intensity variations resulting from an uneven sample surface or occasional laser power fluctuations could be compensated.
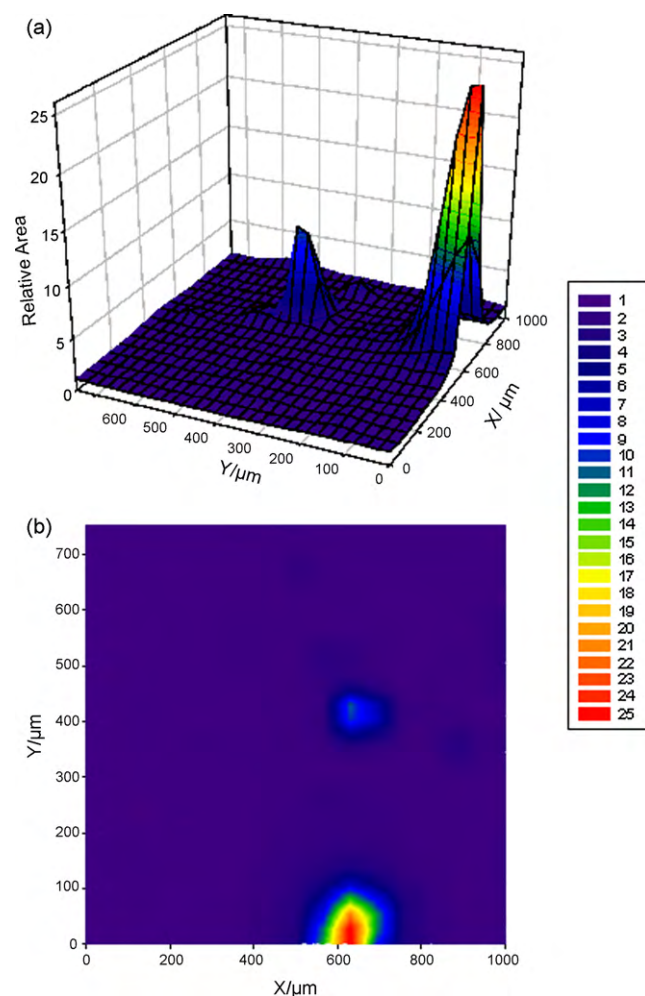

Fig. 5. Three-dimensional Raman surface map (a) and the corresponding colored contour map obtained from 2.32 wt% TiO₂ cream. The sample was spread on a slide glass with a thickness of approximately 0.5 mm and then Raman mapping was performed over the sample area of 1000 μm × 750 μm. The point-to-point distance in x and y direction was 50 and 25 μm, respectively, thereby resulting in a total of 600 points (20 × 30 points).

After normalization, the spectra from each scheme are closer to each other except for one spectrum with high intensity that was obtained from the conventional scheme.

The optimum number of factors was identified as the number of factors that gives a minimum SECV (standard error of cross-validation). The cross-validation was performed by dividing the calibration dataset into four segments. The use of two PLS factors provided the optimal calibration performance for both cases, resulting in a SECV of 0.07 and 0.04 wt% for the conventional and the WAI schemes, respectively. Using each PLS model, the spectra in the corresponding validation set were predicted, and then the SEP (Standard Error Prediction) was calculated for each case. The SEP was 0.17 wt% for the conventional scheme and 0.03 wt% for the WAI scheme. The relative percent error was 6.1% for the conventional scheme and 1.6% for the WAI scheme. The obtained relative percent error using the WAI scheme is acceptable for the practical QC application where the relative percent error below 2% is required for the determination of TiO_2 concentration.

Fig. 6 shows the corresponding PLS correlation plots for the determination of TiO_2 concentration resulted from the use of the conventional (a) and the WAI scheme (b). Filled and open circles correspond to the calibration and prediction data, respectively. As shown in the figure, the WAI scheme obviously leads to approx-
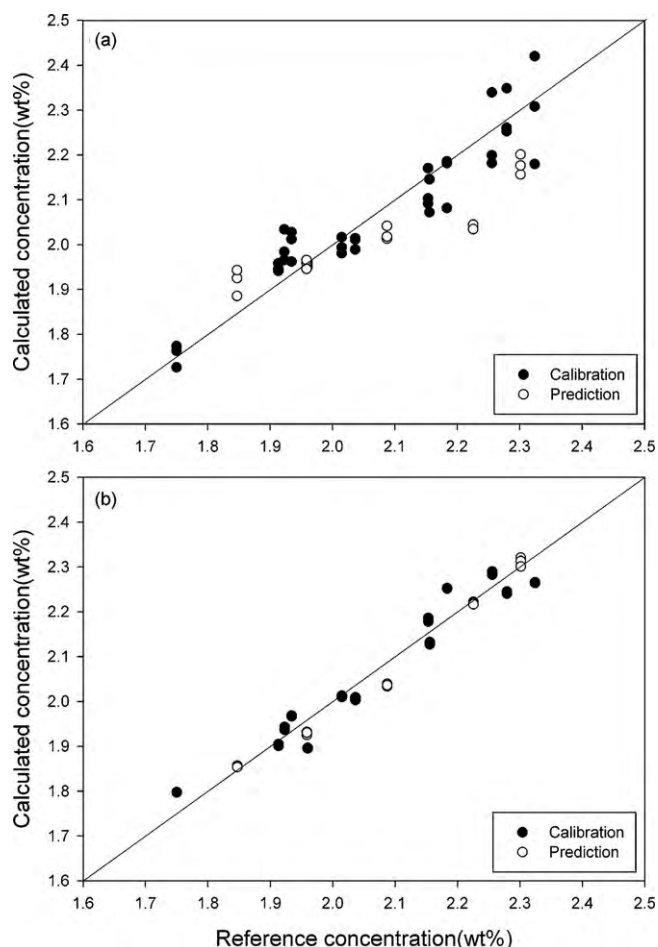
Fig. 6. Concentration correlation plots generated from the use of conventional (a) and WAI (b) schemes. Filled and open circles correspond to the calibration and prediction data, respectively. In both cases, a 2-factor PLS model developed in the 670–350 cm^{-1} range was used for the prediction.

imately sixfold more accurate prediction of TiO$_2$ concentration, as compared to the prediction using the conventional scheme. In addition, the triplicate data of each sample from the conventional scheme are scattered, while these are more repeatable for the WAI scheme.

4. Conclusion

With the help of SEM and Raman images of a TiO$_2$-containing cream, the localized aggregations of TiO$_2$ particles were clearly observed. This fact clearly demonstrated the requirement of large area sampling when Raman spectra are collected for TiO$_2$ creams. With the use of the WAI scheme, the more reproducible (representative) Raman spectra were collected and the resulting accuracy for the determination of TiO$_2$ concentration was superior to that of using the conventional scheme. Although the feasibility for determining the TiO$_2$ concentration has been demonstrated in this study, several issues require further investigation before introducing the proposed scheme into field QC labs. Major concerns are the possible Raman intensity variations that depend on TiO$_2$ particle size [12,13] and its interaction with the organic cream phase. In addition, simultaneous measurement of both anatase and rutile TiO$_2$ in a cream would be eventually necessary. The listed issues are currently under investigation.

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