

Effect of particle size distribution on Spatially and Angularly Resolved Diffuse Reflectance Measurement

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Introduction

In the chemical industry, more than 75% of materials processed are in particulate form in order to form a large variety of products such as pharmaceuticals, abrasives, paints etc. These particle behaviours, such as flow, dissolution, flocculation and sedimentation, are closely linked to particle characteristics such as particle shape, size, etc. - all of which can vary greatly. For this reason, particle size distributions (PSD) are of crucial importance, and particle size and shape parameters are therefore commonly used in product specifications. There is the need for particle size determination methods, for which ranges of in-situ and ex-situ techniques and processes have been developed.¹ The techniques allows for in-situ analysis are advantageous over ex-situ techniques because they eliminate the need for continuous process sampling. This eliminates the possibility of both large-scale time delays, changes in particle characteristics during the sampling process, and therefore allows for real time process analysis and optimisation, which can result in capital and running cost savings. Although the in-situ analysis most commonly outperforms ex-situ analysis, additional considerations into the characteristics of slurries are required due to the particles being in suspension when the analysis takes place.²

Most particles in industry vary in shape and often have rough surfaces. While bulk materials of a certain chemical composition can have identical properties (density, conductivity etc.), on a particulate level different crystalline structures and/or impurities may lead to variations in flow properties and appearances as well as it behaviour during processes such as sedimentation and sieving.¹ Traditionally, particle size measurements have been taken essentially by off-line techniques such as sieving, laser diffraction and microscopy. Sieving is an attractive method for in separating spherical or near-spherical particles in a broad particle size range in relative short time; particles of non-spherical shape often lead to peculiar results. In comparison, laser diffraction measurement is more widely accepted in many industries as a standard method for a wide range of particle size, typically between 0.1-3000 μm . Optical microscopes are often used alongside to get particles shape information. The particle size can then be estimated from the images acquired. However, the optical resolution of the particle limits the application to particles around and below micrometer size. Due to the off-line nature of all these analysers, errors can also be introduced during sampling or sample preparation and transport. More concerns can arise from the collecting a non-representative sample in the process due to process inhomogeneity, the difficulty to access the sample, or when frequent sampling is required. Therefore, in-line particle analysis presents an attractive option for complex processes where particulate substances evolve with process and/or vary with process conditions.

The most common techniques for in-line particle measurements include particle chord length measurement, microscopic imaging, and spectroscopy. Spectroscopy is the most prominent method for in-line process analytics. Depending on the application, there is a range of options for useful wavelength regions and modes of interaction between electromagnetic radiation and the sample. However, spectroscopic based techniques often can only probe chemical information for chemical systems containing little or no particulates, a significant challenge arises when applying spectroscopy to industry for manufacturing of high-value solid chemicals, such as agrochemicals, dyes and pharmaceuticals. The process in these industries typically deals with high solid content, and the presence of particulates causes light scattering effect, a universal phenomenon affecting all optical based spectroscopic techniques. It results in coupling of physical and chemical information in the spectra and breaks down the linear relationship between the spectral intensity and the concentration of the chemical species, causing significant errors in estimating accurately and reliably chemical information. Furthermore, valuable information about the particulate attribute hidden in the cofounded spectra is often discarded and currently there is no in-line measurement capable of monitoring chemicals of high solid content.

The Near-infrared (NIR) spectroscopy can be seen as the work horse for the field of Process Analytical Technology (PAT). Last decade saw NIR spectroscopy received significant interests from pharmaceutical sector owing to the US FDA and EU EMA Process Analytical Technology initiative that seeks to streamline drug manufacturing processes.³ The analysis in NIR spectra is the key factor driving the development and advancement of multivariate regression analysis and the scattering correction methods. Currently, the common approach to reduce the impact of light scattering is by using empirical scatter correction techniques to linearizing the chemical-related information or remove spectral variation due to scattering effect and/or other non-chemical effects.⁴ While the method is easy to apply, the effectiveness of the scatter method could vary from system to system, hindering the robustness and reliability of the multivariate calibration model built on the scatter-corrected spectra. An alternative approach for removing light scattering effects is to use the radiative transfer theory to extract the bulk absorption and scattering properties of the sample.⁵ Although the method is a promising approach to decouple scattering and absorption information in the spectra, the computational intensive method make the method less ideal for real-time process measurement.

We recently reported an innovative spatially and angularly resolved diffuse reflectance measurement (SAR-DRM) which combines unique measurement configurations and analysis strategy to produce reliable and robust calibration model performance for the samples of high turbidity.⁶ The SAR-DRM system collects diffuse reflectance in visible-NIR wavelength region using optical fibers which are arranged at different angular and distance relationship to the source fiber which delivers the illumination light. The multi-angle and multi-distance diffuse reflectance spectra collected contains differentiable information corresponding to the absorption and scattering properties of light travelled through different path in the sample. Unlike the conventional diffuse reflectance measurement, the additional information associated with the multi-angle and multi-distance features of the SAR-DRM can be further utilised in multivariate regression analysis. Here we will show examples of SAR-DRM analysis on particulate systems related to pharmaceutical applications, and the effect of the particle size distribution observed using the SAR-DRM.

Indigestion Remedy:

The SAR-DRM spectra were taken from two different brands (Brand A and B) of indigestion remedy purchased from the pharmacist counter. Both products contain the same amount of APIs which are in particulate forms with most of the supplementary ingredients being the same. None of the supplementary ingredients are light scattering components. Both brands produce two flavours (Flavour A & B) and use the same flavouring and colorant in the products. For Flavour B, Brand B also has a double strength product which contains twice of the APIs to the standard Brand B product and the same supplementary ingredients. As the APIs are the only light scatterers in the remedy suspension, we first investigate the effect of API concentration on the SAR-DRM spectra.

As shown in Figure 1(a), the reflected intensity decreases as the samples become diluted, however, the changes in the intensity are not linear. The overall profile of the SAR-DRM spectra is related to the wavelength-dependent, nonlinear light scattering effect of API with the drop in the intensity at 520 nm corresponding to the absorption of the colorant in the product. By analysing the intensity variation with the change of spatial relationship between the source and collecting fibers, it is found that the intensity decreases non-linearly with the increase of the fiber distances, and such relationship is unique to sample condition. For instance, comparison on Figure 1(b) and (c) shows that sample of 10% of the original API contents results in a sharper drop in the SAR-DRM intensity at wavelength of 700nm than the 100% sample when the distance increases from 0.3 to 0.6mm.

Another interesting findings observed from the indigestion remedy is that, while the amount of light scattering components (in this case, the APIs) are the same for both brands, the samples return different intensity in the SAR-DRM measurement, as shown in Figure 2. Visually, Brand A and B for Flavour B shows little difference in the appearance with the Brand B double strength sample appears similar to the standard strength samples. However, the SAR-DRM analysis on the samples show distinct differences between Brand A and B, with the Brand B double strength sample match the intensity level from Brand A. As the APIs is the only source to cause light scattering effect, and the amount and composition of the APIs are the same for both brands, the difference observed can only attribute to the differences in the scattering properties of the particulate APIs. The possible contribution to the APIs' light scattering properties could be differences in particle size (hence number of particles), size distribution and particle shape. The encouraging results from this study show the sensitivities for SAR-DRM to differentiate the variation of particulate components in a high turbidity samples.

Effect of PSD on SAR-DRM spectra

The effects of particle size and size distribution on the SAR-DRM spectra were investigated using polystyrene particle suspended in water as the model system. Polystyrene particle beads with diameter between 1-300 μm were synthesized by suspension polymerization reaction and were sieved into several particle size groups. The SAR-DRM spectra from the 5 wt% particle suspensions using different particle size group are shown in Figure 3(a)-(d). It can be seen that the differences in intensity between the samples vary with the source to detecting fiber distances used. In addition, instead of monotonically decreasing the SAR-DRM intensity as the particle size increases (hence the number of particle decreases), the largest particle group (180-300 μm) results in higher intensity than the particle group of 120-180 μm . This suggests the complexity of the light scattering effect in particle suspensions where the reflectance from the turbid suspension is not linearly and solely dependent on the particle size but the measurement configuration could have an effect on the

spectra obtained. Another measurements were carried out using mixtures of particles to vary PSD in the suspension with the same solid load (5 wt%). Figure 4(a)-(d) shows the SAR-DRM spectra from difference fiber distances for samples of different width in the PSD (sample conditions shown in Table 1). Figure 4(e) is the number weighted chord length distribution from in-line chord length measurement (FBRM, Mettler Toledo). In general, broadening the PSD increases the SAR-DRM intensity although the spectral response depends on the fiber distances used. A good correlation between the CLD count and SAR-DRM intensity can be seen. Our further analysis indicates that SAR-DRM can measure the polystyrene suspensions with higher solid load (at least up to 20 wt%) where the CLD measurement or in-line imaging see difficulties of obtaining reliable results.

Overall, the SAR-DRM system produces apparent respond to the variations in the particle size and distributions for particles in large range of diameter. Combining our previous studies on suspensions of particles of diameter between 100-500nm, the results from the unique SAR-DRM system shows promising features to measure highly turbid system for a large range of particle size, therefore could potentially be capable to be implemented in a wide variety of applications.

1. Merkus, H. G., *Particle Size Measurements - Fundamentals, Practice, Quality*. Springer Netherlands: 2009.
2. Weinstein, L. J.; Epstein, J. I.; Edlow, D.; Westra, W. H., Static image analysis of skin specimens: The application of telepathology to frozen section evaluation. *Human Pathology* **1997**, *28* (1), 30-35.
3. (a) U S Food and Drug Administration, Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance. Rockville, MD, 2004; (b) European Medical Agency, Guideline on the use of near infrared spectroscopy by the pharmaceutical industry and the data requirements for new submissions and variations. London, UK, 2014.
4. (a) Geladi, P.; MacDougall, D.; Martens, H., Linearization and Scatter-Correction for Near-Infrared Reflectance Spectra of Meat. *Applied Spectroscopy* **1985**, *39*, 491-500; (b) Martens, H.; Nielsen, J. P.; Engelsen, S. B., Light Scattering and Light Absorbance Separated by Extended Multiplicative Signal Correction. Application to Near-Infrared Transmission Analysis of Powder Mixtures. *Analytical Chemistry* **2003**, *75* (3), 394-404; (c) Barnes, R. J.; Dhanoa, M. S.; Lister, S. J., Standard Normal Variate Transformation and De-trending of Near-Infrared Diffuse Reflectance Spectra. *Applied Spectroscopy* **1989**, *43*, 772-777.
5. (a) Steponavicius, R.; Thennadil, S. N., Extraction of Chemical Information of Suspensions Using Radiative Transfer Theory to Remove Multiple Scattering Effects: Application to a Model Two-Component System. *Analytical Chemistry* **2009**, *81* (18), 7713-7723; (b) Steponavicius, R.; Thennadil, S. N., Full Correction of Scattering Effects by Using the Radiative Transfer Theory for Improved Quantitative Analysis of Absorbing Species in Suspensions. *Applied Spectroscopy* **2013**, *67* (5), 526-535.
6. Chen, Y.-C.; Foo, D.; Dehanov, N.; Thennadil, S. N., Spatially and angularly resolved spectroscopy for in-situ estimation of concentration and particle size in colloidal suspensions. *Analytical and Bioanalytical Chemistry* **2017**, *409*, 6975-6988.

Figure 1

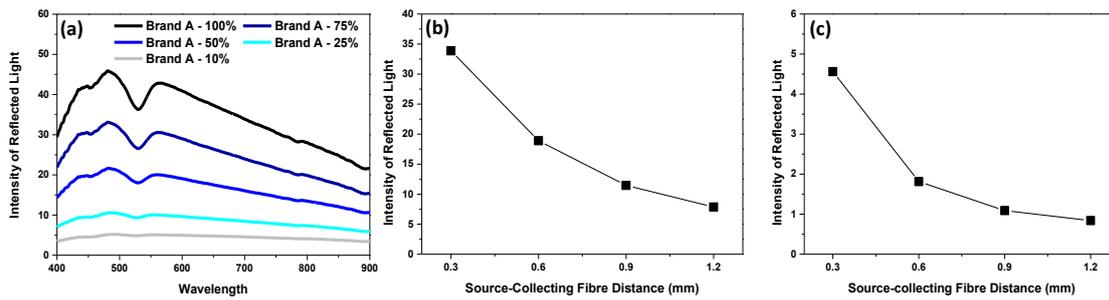


Figure 1: (a) SAR-DRM spectra from indigestion remedy collected from source to fiber distances at 0.3 mm. (b) and (c) corresponds to the SAR-DRM intensity of 100% and 10% Brand A product (Flavour A) from different source to collecting fiber distances at wavelength of 700 nm.

Figure 2

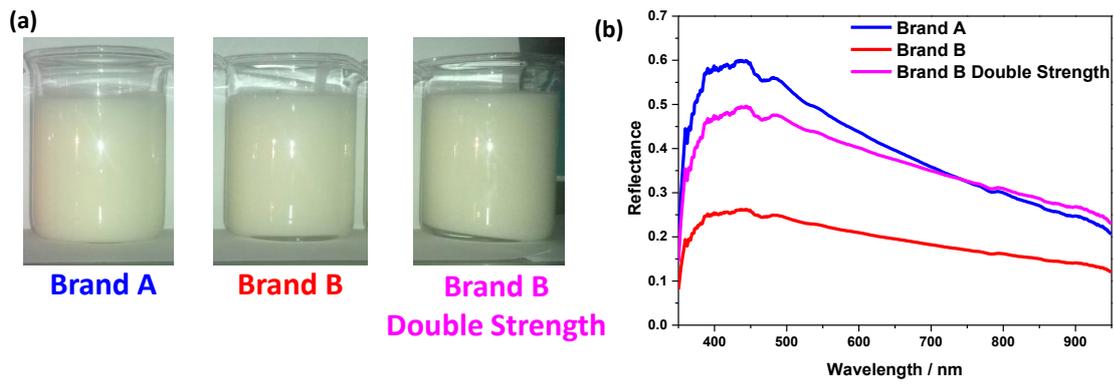


Figure 2: (a) Image of indigestion remedy (Flavour B) from both brands (including the double strength product from Brand B). (b) SAR-DRM spectra taken from samples in A with source to collecting fiber distance of 1.2 mm.

Figure 3

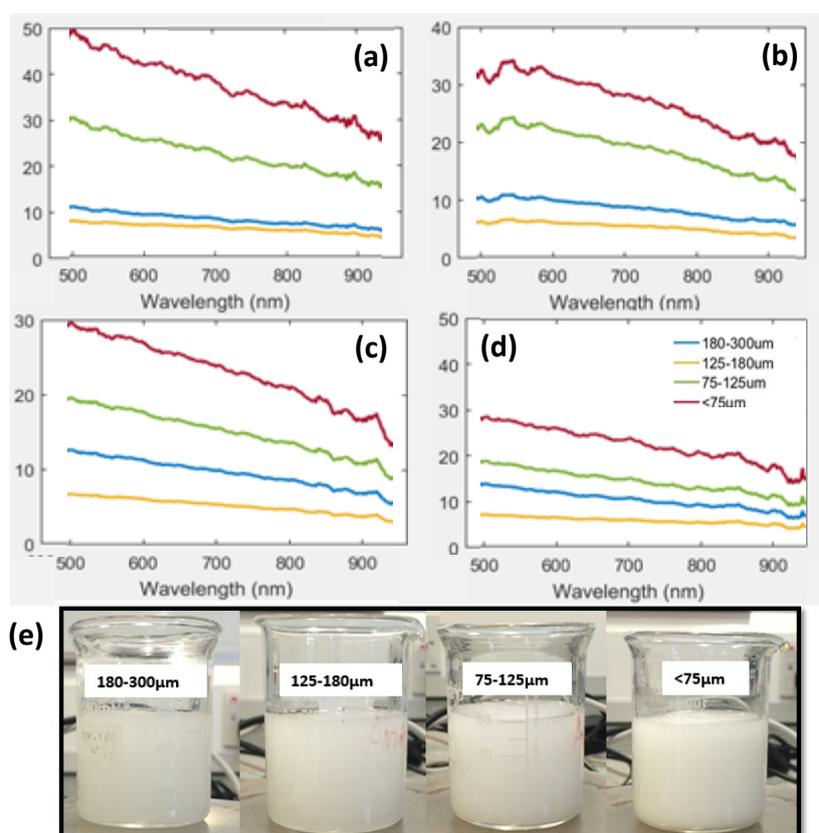


Figure 3: (a)-(d) SAR-DRM spectra from polystyrene suspensions in (e) using source to detector distances from 0.3, 0.6, 0.9 and 1.2 mm respectively. (e) Images of the polystyrene suspensions from different particle diameter group. All suspensions contain 5 wt% solid load.

Figure 4

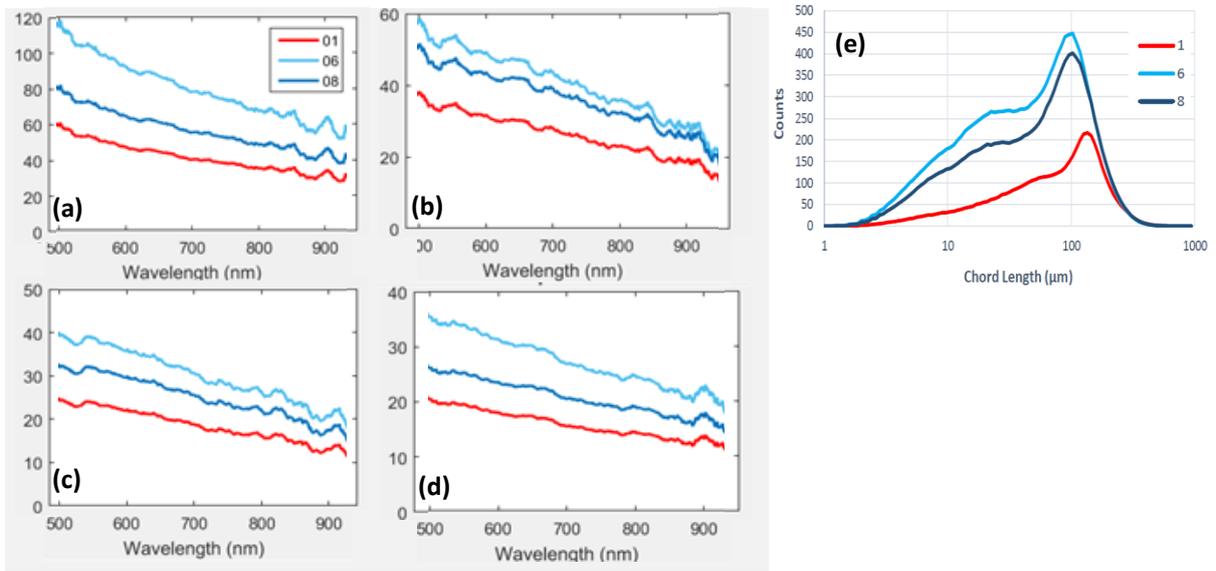


Figure 4: (a)-(d) SAR-DRM spectra from polystyrene suspensions corresponds to the conditions in Table 1. The spectra were collected using source to detector distances from 0.3, 0.6, 0.9 and 1.2 mm respectively. (e) CLD from the same samples in (a)-(d). All suspensions contain 5 wt% solid load.

Table 1

Table 1: Sample conditions for the study on the effect of particle size distribution on SAR-DRM spectra

Sample No.	Solid load (wt%)		
	<75 μm	75-125 μm	125-180 μm
1	0	5	0
6	2.5	2.5	0
8	1.66	1.66	1.66