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Polymers, Tablets and Tissue – The Third Way in Spectroscopy for Process Monitoring

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1. Introduction

Optical sensing technologies have tremendous potential in areas of high socio-economic significance such as in medical diagnostics, environmental and chemical process monitoring applications. Many recent advances in photonics have been motivated by the impact early diagnosis of cancers and tumours and monitoring physiological parameters will have on saving lives and improving quality of life through non-invasive methods. While the potential of optical techniques in non-invasive medical diagnostics is great, there has been very limited success in achieving a level of accuracy and reliability that is required for the techniques to be applied safely.

Optical technologies have also been used extensively in process and environmental monitoring applications. In these areas, optical sensors offer promise of rapid physical and chemical characterisation of process and effluent streams. By providing the ability to rapidly detect deviations from target quality, they could lead to efficient optimisation and control of processes thereby ensuring consistent quality of the final product. This will lead to enormous savings and aid in greener process operations. However, in applications involving monitoring of particulate systems such as slurries, there has been limited realisation of this promise.

The common feature linking these seemingly disparate areas is that the underlying physics of light propagation on which the measurements are based is the same and the fundamental problem of measurement and interpretation of data is similar. These challenges are mainly due to complications arising from the complex interplay between absorption and scattering effects on the propagation of light through a particulate sample. Different disciplines have addressed these problems in different ways. In many cases advances made by researchers in one area are relatively unknown to those in other areas even though the fundamental problems are the same.

Spectroscopic applications in medical diagnostics have focused primarily on new instrumentation technologies such as time resolved and frequency resolved measurements and optical coherence tomography. The focus in process monitoring using spectroscopic methods has been primarily in the interpretation of data by chemometrics (statistical learning) for chemical information and light

scattering theories for extracting physical information such as particle size, shape and microstructure from spectroscopic measurements.

We can thus broadly classify the research efforts into two approaches. One is the development of chemometric or "black-box" methods based on statistical learning. In this case, spectroscopic data from samples with known property values are collected and statistical models are built using them. In this approach, no attempt is made to use fundamental physical principles or mechanistic knowledge. Also in spectroscopic analysis, linear models are commonly used while the underlying phenomenon of light propagation in particulate systems is highly nonlinear. This approach has been very successful with liquid mixtures where the variations are well explained by linear models predominantly for estimating the chemical composition of samples. To apply to particulate systems, empirical correction techniques to remove light scattering effects were developed[1]. However, these have not proved to be effective especially if the sample-sample scattering properties have large variations, which is the situation that is commonly encountered in practical applications.

Researchers in the physical sciences have tackled this challenge in a completely different way. This involved the development of light propagation theories to describe light-matter interactions. While theories for multiple scattering of light were developed, the application of this approach to industrial slurries and emulsions has been limited to using the theory to situations where the suspensions were sufficiently dilute so that the single scattering approximation can be used to extract information regarding particle size and shape[2].

Thus chemometrics is mainly used to extract chemical information but runs into difficulties if this information has to be extracted from spectroscopic measurements of particulate samples. The approach treats light scattering effects as a nuisance, while in reality the nature of scattered light contains information regarding the particles. On the other hand, light propagation theories are useful in extracting information about the particle size and shape but require dilution of the samples which is not feasible for tissue and when continuous online monitoring of processes are required.

Why not combine the two approaches so that we can extract both composition and particle size information? Or at the very least, if we

can separate the effect of absorption (which is affected by chemical composition) and scattering (which is affected by particle size and shape), we can derive useful information of the bulk characteristics of the samples which in many cases is sufficient for making decisions regarding controlling and manipulation processes. Clearly this requires a multi-disciplinary approach.

My research programme pursues a unique approach that integrates advances in basic technologies for instrumentation with fundamental light propagation theories (physics), inversion methods (mathematics), multivariate calibration methods (chemometrics) and chemical knowledge of the system (chemistry) under consideration. The aim is to develop a suite of tools that can be used in a wide variety of applications, which includes chemical and petrochemical processing, food and agriculture sectors and medical diagnostics. For each application only a subset of the tools may be required but overall the suite of tools will cover the framework given in Figure 1 (page 4).

2. Radiative transfer theory

In the figure, it can be seen that the two central steps are the set of multi-wavelength spectroscopic measurements with different measurement configurations, for example a combination of reflectance and transmittance measurements and the radiative transfer equation (RTE). Before discussing the set of measurements and how we would obtain them, we will first look at the RTE which at each wavelength λ is given by[3],

$$\frac{d\mathbf{I}(\mathbf{r},\mathbf{s},\lambda)}{d\mathbf{s}} = -(\mu_a(\lambda)+\mu_s(\lambda))\cdot\mathbf{I}(\mathbf{r},\mathbf{s},\lambda)+\frac{\mu_s(\lambda)}{4\cdot\pi}\int_{4\pi} p(\mathbf{s},\hat{\mathbf{s}},\lambda)\cdot\mathbf{I}(\mathbf{r},\hat{\mathbf{s}},\lambda)\cdot d\omega \quad (1)$$

where $I(r,\mathbf{s},\lambda)$ is the specific intensity at a distance r from source along directional vector s, $\mu_a(\lambda)$ (cm-1) is the bulk absorption coefficient, (cm-1) is the bulk scattering coefficient, $p(\mathbf{s},\hat{\mathbf{s}},\lambda)$ is the phase function, which is a measure of the angular distribution of scattered light and ω is the solid angle. The phase function can be represented as a function of another optical property called the asymmetry factor $g(\lambda)$.

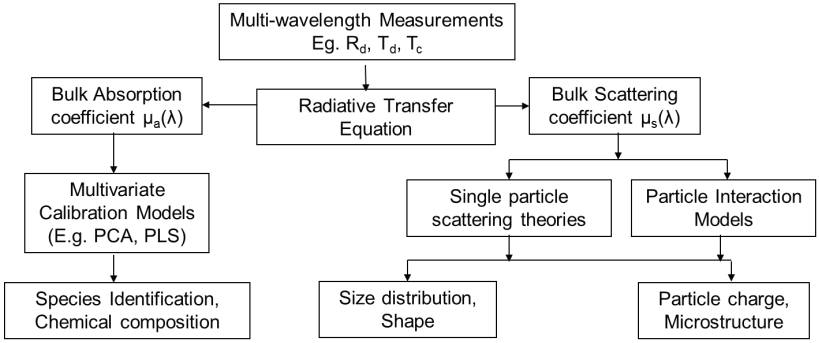

Figure 1. Radiative transfer theory based approach to extracting physical and chemical information from spectroscopic measurements

Essentially, equation 1 indicates that if we knew the optical properties $\mu_a(\lambda), \mu_s(\lambda)$ and $g(\lambda)$ we can solve the equation and predict how much light is reflected or transmitted. But we are interested in the "inverse problem" – Given a set of measurements, we want to use equation 1 to obtain the optical properties of the sample for the wavelengths at which the measurements were taken. Given there are three unknowns we would need at least three measurements. Of the three unknowns, two of them represent scattering effects and can be combined into one parameter (and thus one unknown), which is known as the reduced scattering coefficient $\mu_s'(\lambda) = \mu_s(\lambda)[1 - g(\lambda)]$. In this case, we need a set of two measurements at each wavelength.

Before we go further, the question we have to answer is what benefit do we get by extracting the optical properties? The main benefit is that when we use the raw spectrum that we measured to estimate the properties of the sample, the nonlinear scattering effect degrades the signal contributed by the composition information which manifests as variations in the absorption effect. The degradation is so much that the spectroscopic measurements do not provide reliable estimates and therefore not useful. By obtaining the bulk optical properties, we are effectively decoupling or separating the effects of scattering and absorption. Thus, the information regarding composition is contained in the bulk absorption coefficient without being corrupted by the presence of scattering effects while information regarding particle size distribution and shape, particle charge (if the suspension consists of charged particles) and microstructure (the way the particles arrange

due to interactions between them) are contained in the bulk scattering coefficient.

Currently we need two instruments – one to measure concentration of chemical species present in the suspension and one to measure the particle properties. Currently available commercial instruments are capable of measuring particle properties only in very dilute suspensions. In other words, samples are conditioned by diluting them typically by more than 1000 times. Through the separation of the absorption and scattering effects, we can obtain both composition and particle properties with one instrument and we would not require diluting the sample. This approach is particularly useful when we need to make online (in-situ) measurements and in non-invasive medical diagnostics applications.

We will now consider two instrument designs. One of them is useful only for offline measurements where a sample is placed in a sample holder. This set up is used by several research groups though such instruments are not commercially available. A second design is a fibre-probe based instrument and the version shown in this article is an improved design for which a patent application is in progress[4].

3. Instrument design

3.1 Integrating sphere set up

This set up is shown schematically in Figure 2 (page 6). Such an instrument allows the measurement of diffuse reflectance and diffuse transmittance spectra of the samples which can then be used to invert equation 1 to obtain the bulk absorption coefficient spectra and the reduced bulk scattering coefficient spectra[5].

As mentioned earlier, this instrument design is limited to offline measurements and is more suited to studies of sample properties in research labs. If we want to measure the properties of samples in-situ so that the dynamic changes in the sample over a period of time can be captured, for example during the course of a polymerisation reaction, then a fibre-optic probe design is essential.

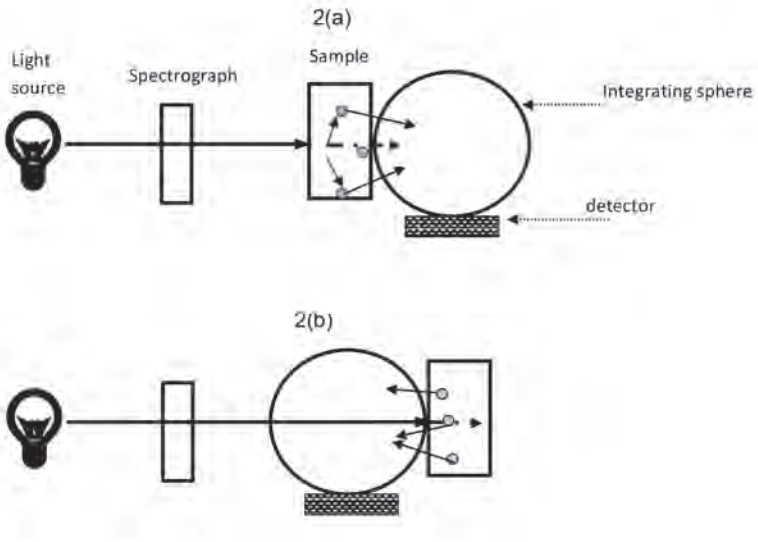

Figure 2. Integrating sphere set up. (a) Diffuse Reflectance and (b) Diffuse transmittance.

3.2 Spatially and angularly resolved diffuse reflectance (SARDR) measurements

This set up is shown schematically in Figure 2. Such an instrument allows the measurement of diffuse reflectance and transmittance spectra of the samples which can then be used to invert equation 1 to obtain the bulk absorption coefficient spectra and the reduced bulk scattering coefficient spectra. A version of this design which only includes spatially resolved measurements has been used by researchers in medical diagnostics applications[6]. This improved design provides additional dimensions by measuring spatially resolved light from light incident from different angles. This additional set of measurements could make the inversion of the measurements more accurate. This instrument is being tested in a number of applications such as characterising pharmaceutical suspensions and monitoring emulsion and suspension polymerisations. We will look at a simple case study involving pharmaceutical suspensions with the research focussing on the possibility of using this instrument for identifying counterfeit drugs[7] and to monitor the suspension quality during transit and storage.

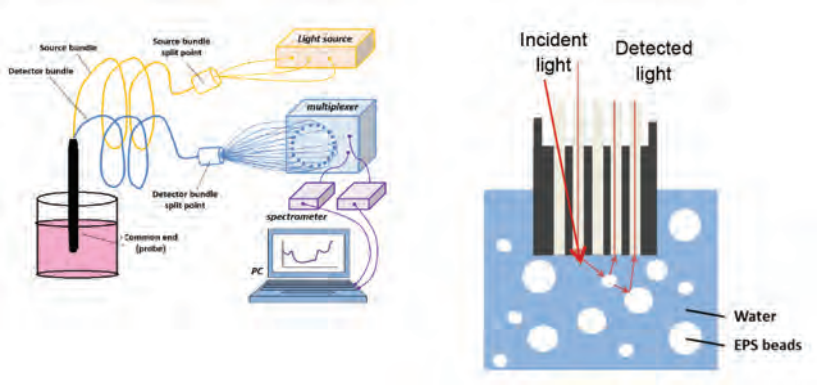

Figure 3. Spatially & angularly resolved diffuse reflectance fibre probe measurement system.

4. Case study: Analysis of equivalent pharmaceutical suspensions

4.1 Motivation

The pharmaceutical industry is facing big challenges in ensuring that counterfeit versions of their drugs are not being sold. In addition, regulatory bodies are also keen on stopping such drugs as they pose significant risks to consumers since they are produced by counterfeiters who do not follow regulatory procedures. The problem is particularly exacerbated by internet sales in the western hemisphere. Counterfeit pharmaceuticals may contain little or no active pharmaceutical ingredient (API) or the consumer becomes ill due to super-potent levels of API or due to the presence of dangerous ingredients such as arsenic[8].

To evaluate the feasibility of using Visible-NIR spectroscopy for counterfeit detection we used a set of "equivalent" pharmaceutical products. These are products made by different manufacturers that contain the same quantity and type of API. However, the supplementary ingredients vary depending on the manufacturer. In fact, if the API is in the form of particles, the products from different manufacturers can have different particle sizes. These equivalent products may look alike and thus differences cannot be visually perceived. Therefore we can use such products as a model system for studying how well the contrasts in the samples can be detected by spectroscopy.

4.2 Objectives of the initial study

The overall objective is to develop a counterfeit detection system based on UV-Vis-NIR measurements that is capable of identifying differences in particle characteristics (particle size distribution, shape) and concentration of the ingredients. As a first step, in this study we used our novel SARDR fibre probe measurement system to address the following questions:

1. Can we detect differences in equivalent pharmaceutical suspensions using Vis-NIR spectroscopy?
2. Is the ability to sense the differences better in the Visible or NIR region?
3. Is the sensitivity to contrasts in the samples dependent on incident light angle?
4. Is the sensitivity to contrasts in the samples dependent on source-to-detector distance?

Figure 4. "Equivalent" indigestion remedies used in this study.

4.3 Materials

Drugs for indigestion are manufactured as suspensions by different manufacturers to produce many equivalent products which are both branded and generic, and therefore used as a model system for this study to answer the questions raised above.

Two flavours of the products were chosen namely, the traditional aniseed flavour referred to as Flavour A and mint flavour which is referred to as Flavour B. The products used in this study are shown in Figure 4 and are referred to as Flavour A Brand 1, Flavour A Brand 2, Flavour B Brand 1 and Flavour B Brand 2. In addition, this study also included a product that had the same visual appearance as the Flavour B products and had the same chemical type of active ingredients and manufactured by the same company as Brand 2 but

the active ingredients were present in higher concentrations to the equivalent products. This product is referred to as Flavour B Brand 2 'DA'.

While there are differences in colour between the two flavours, within each flavour the different brands are not distinguishable. This is also the case with counterfeit products – they are visually indistinguishable from the authentic ones.

4.3 Experiments

The five products were placed in beakers which were filled to a constant mass of product. Each beaker was then chosen in a random order and SARDR measurements were taken by immersing the probe in the suspension (See Figure 3 for the setup, page 7). The reflected light was collected from each collection fibre sequentially for three different incident light angles. For each incident angle, reflectance spectra from four collection fibres each placed at different source-detector (spatial) distance were obtained.

4.4 Results and discussion

Data from the four different collection fibres for the three different incident light angles all showed that it was possible to use reflectance measurements to differentiate the equivalent visually similar products in both the visible and NIR region of the spectra. The spectral profiles of the products in the visible wavelength region collected at a source-detector distance of 0.3mm for two different angles of incidence (angle 1 = 90 degrees, angle 2 = 30 degrees) are shown in Figure 5 (page10). It is evident that for both angles clear differences can be seen between the samples considered here. However, it can be seen that angle 1 results in better contrast between the Flavour B products namely Brand 1 and Brand 2 DA suspensions particularly in the wavelength region 400–600nm.

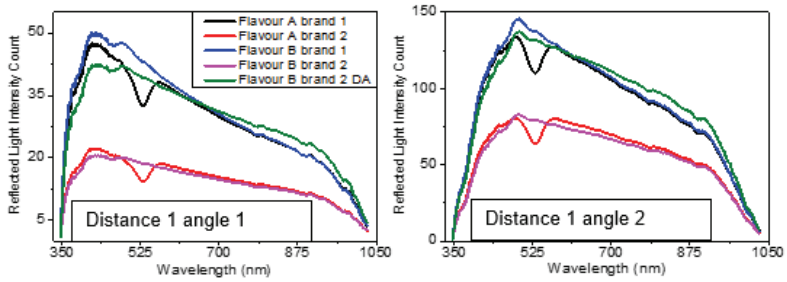

Figure 5. Visible spectra of different equivalent indigestion remedy suspensions for source-detector distance of 0.3mm taken at 2 angles (angle 1 = 90 degrees, angle 2 = 30 degrees)

The effectiveness of differentiating the products by collection fibres placed at different distances form the incident light emitting fibre was examined. It was seen that while the collection fibres with other source-detector distances also showed similar contrast, the best contrast was obtained with the source-detector distance of 0.3mm.

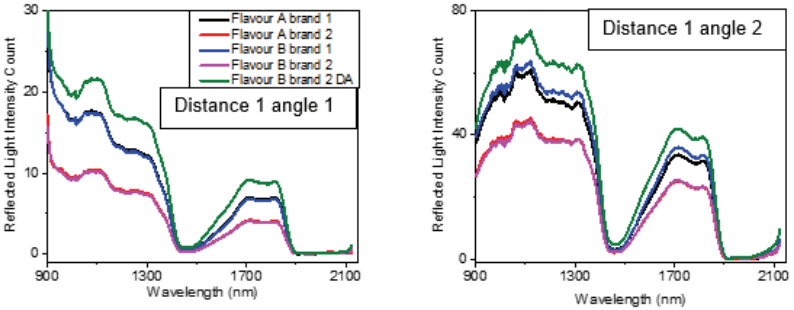

Figure 6. Near infrared spectra of different equivalent indigestion remedy suspensions for source-detector distance of 0.3mm taken at 2 angles (angle 1 = 90 degrees, angle 2: 30 degrees)

In the near infrared (NIR) wavelength region, we can see from Figure 6 the effect of angle of incident light on the ability to differentiate the products. Angle 1 shows that there is no visual difference between the same branded products, while angle 2 shows some difference in the magnitude of reflected light in the samples thus indicating that choosing the appropriate incident angle could enhance the differentiability of the products.

This preliminary study indicates that SARDR measurements can be used to distinguish visually similar equivalent pharmaceutical indigestion samples. This suggests the possibility of using such measurements to identify suspension quality and possible application in identifying counterfeit drugs. This measurement system can be used to identify optimal source-detector distance and angle of incidence for specific applications which can then be used to design a cheaper and simpler measurement system.

5. Ongoing and future work

The preliminary study indicates that a single source-detector distance and incident angle might be sufficient for identifying differences in equivalent products. However, better consistency in identification can be potentially obtained by inverting the SARDR measurement using the radiative transfer equation (equation 1, page 3) to obtain the bulk absorption and scattering properties. This will allow us to pinpoint whether the differences are chemical in nature, which will manifest as differences in absorption spectra, or whether they are due to particle size differences, which will manifest as differences in scattering spectra. Also the inversion is essential for applying this system to identifying changes in quality of the suspension during storage and transit. This work is currently being carried out. Currently an inversion method based on the diffusion approximation of the radiative transfer theory[9] is being developed and tested.

The SARDR system is also being studied as a monitoring tool for emulsion and suspension polymerisation reactions, milling operations in the paint industry and for characterising catalyst suspensions.

Future work will further extend the range of applications that will be investigated. One application that is being considered is the rapid testing of meat tenderness to aid in grading of meat. In the medical diagnostics application, interesting possibilities exist in the use of the SARDR system for cancer screening and for non-invasive glucose monitoring.

6. Acknowledgements

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He is co-inventor of 10 patents and has published about 30 refereed articles.