Key Issues

- **Real-time process monitoring and control for the FDA’s PAT initiative**
- **Analysis of the whole thickness of complex solid samples**
- **Enhanced Raman signal intensity**

Introduction

The Process Analytical Technology (PAT) initiative from the U.S. Food and Drug Administration (FDA) encourages pharmaceutical manufacturers to employ real-time analytical tools for detailed understanding of their processes. This serves two purposes: to enable real-time process control and to promote detailed process understanding for flexible quality control during the course of the process rather than only by analyzing the end product.

The development of techniques for real-time process analysis is a significant focus of recent work in pharmaceutical technology and analytical chemistry. Vibrational spectroscopic methods such as near-infrared (NIR) spectroscopy and Raman spectroscopy have gained favor because they can be deployed in a non-contact mode, and they give detailed chemical information with great potential for robust modeling.

Raman has proven to be especially useful in pharmaceutical process monitoring because it is not obstructed by the presence of water, which is a significant problem for infrared spectroscopies, and because it usually requires little to no sample preparation.

Of particular utility in pharmaceutical processing is the ability to analyze the entire depth of a complex layered solid simultaneously. This note describes the use of enhanced Raman reflection spectroscopy to accomplish this analysis on multi-layered samples similar to many pharmaceutical tablets. This work underpins current applications in the pharmaceutical industry.

Reflection and Transmission Raman

Raman spectroscopy can occur in both reflection and transmission modes. In the reflection mode (known also as backscattering mode) the light that is scattered back in the direction of the incident laser-light source is collected, often through the same lens used to focus the incident laser, whereas in transmission-mode Raman the collection probe is located on the opposite side of the sample from the laser to collect Raman-scattered photons that have exited the sample in that direction.

Under typical conditions the Raman intensities from reflection and transmission modes are related to the depth of the sample layer as shown in Figure 1, in which most of the Raman signal in reflectance Raman comes from very near the surface of the sample whereas in the transmittance mode most of the Raman signal originates from the middle of the sample. However, backscattering by a diffuse white reflectance target such as BaSO$_4$ can enhance the ability of reflectance Raman spectroscopy to probe deep into a sample as is observed with transmittance Raman. This note describes a proof of the concept that enhanced Raman reflection spectroscopy can generate strong Raman signal from throughout the depth of a sample, enabling analysis of the whole thickness of a complex solid sample similar to a pharmaceutical tablet.

![Figure 1](image-url)
Experimental

The analytical samples for this work were cylindrical discs consisting of layers of varying thicknesses of polytetrafluoroethylene (PTFE), cellulose paper, acetylsalicylic acid (ASA), or mannitol. BaSO₄ was used as a white diffuse-reflectance standard in some samples.

Both reflection-mode Raman spectra were collected with a RamanRxn Systems™ Raman analyzer from Kaiser Optical Systems, using a 785-nm Invictus™ laser. The scattered laser light was collected using a PnAT technology probe head. The sampling geometries for reflection- and transmission-mode Raman are shown in Figure 2.

Enhanced Reflectance Raman

A series of six experiments was performed on cylindrical samples of PTFE with cellulose paper. Experiments I through III involve tandem reflection and transmission Raman, whereas experiments IV through VI involve enhanced reflection Raman using a BaSO₄ backscattering layer.

Figure 3 shows the results from these six experiments. In the enhanced reflection Raman trials the Raman signal intensity of the PTFE layer is enhanced approximately three to four times regardless of its position relative to the paper layer and the BaSO₄ reflector. Since the Raman intensity of the PTFE Raman signal is not affected by its location within the sample, these results indicate that the entire bulk of the sample is analyzed uniformly.

In experiment IV a black background was compared to the enhanced Raman reflection technique. The results indicate a 3.5-time improvement of the PTFE intensity with respect to the PTFE intensity on the blank substrate.

Conclusion

When the total composition of the sample is of interest, enhanced reflectance Raman can be used to obtain spectral information from throughout the bulk of the sample.

This study shows that bulk analysis with enhanced Raman reflection spectroscopy is a powerful tool for process analytical technology in the pharmaceutical industry. In fact, applications of this technique are already finding their way to the pharmaceutical process line. Although depth profiling by transmission-mode Raman is possible, enhanced Raman reflection spectroscopy is much more easily integrated into current processes to allow real-time measurement and thus control because it can be used with existing equipment such as non-transmissive belts.

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Reference: