Non-invasive bulk analysis of pharmaceutical tablets and capsules using the transmission Raman method

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Introduction

In a number of analytical applications involving diffusely scattering media, the primary target of analysis can be the bulk content of the sample as in the probing of pharmaceutical tablets to identify their overall content. The need stems from the fact that it is the overall content of the product delivered during medical treatment that must be accurately known as any inappropriate heterogeneous components concealed within the interior of the tablet may have deleterious effects. Ideally, the content information should be obtainable non-destructively and on short timescales as is required in environments such as production lines. This need is emphasized by recent FDA's Process Analytical Technology (PAT) initiative that requires pharmaceutical manufacturers to improve the critical quality performance monitoring for ensuring final product quality. A similar need exists in the analysis of pharmaceutical capsules.

Raman spectroscopy holds a particular promise in this area. Presently, it is used overwhelmingly in backscattering mode for its instrumental simplicity and ease of use. However, in this mode the technique is limited to yielding only information from the surface layers. Here we report how this surface layer bias can be overcome by adopting the transmission Raman geometry [1] (see figure 1). An added benefit of this configuration is the ability to suppress fluorescence originating from surface layers of the analysed object in contrast with the conventional Raman approach.

The full account of this work is given in Refs [2,3]. A review of these techniques and their applications is also presented in Ref. [4].

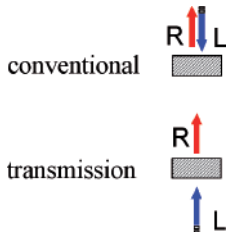

Figure 1. Illustration of the backscattering and transmission geometries.

Experimental section

The Raman spectra were obtained using a transmission Raman apparatus as follows. The probe beam was generated using a 115 mW temperature stabilised diode laser operating at 827 nm (80 mW). The laser spot diameter before the sample was ~4 mm. The beam was incident on the sample at ~45 degrees.

The Raman light was collected using a 50 mm diameter lens with a focal length of 60 mm. The scattered light was collimated and passed through a 50 mm diameter holographic notch filter (830 nm, Kaiser Optical Systems, Inc) to suppress the elastically scattered component of light. A second lens, identical to the first, was used to image, with magnification 1:1, the sample interaction zone onto the front face of a fibre probe. Two more filters (25 mm diameter holographic notch filter, 830 nm, Kaiser Optical Systems, Inc, and an edge filter, 830 nm, Semrock) were used just before the probe to suppress any residual elastically scattered light that passed through the first holographic filter. The fibre probe was comprised of 7 fibres placed tightly packed at the centre of the probe. The fibres were made of silica with a core diameter of 200 mm and a numerical aperture of 0.37. The bundle was custom made by C Technologies Inc. The Raman light was propagated through the fibre systems of length ~1 m to the linear fibre end oriented vertically and placed in the input image plane of a Kaiser Optical Technologies Holospec $f^{\#}$ = 1.4 NIR spectrograph with its slit removed. The Raman spectra were collected using a deep depletion liquid nitrogen cooled CCD camera (Princeton Instruments, SPEC10 400BR LN Back-Illuminated Deep Depletion CCD, 1340 × 400 pixels) by binning the signal from all 7 fibres vertically.

Results and discussion

The results shown in Figure 2 depict the conventional backscattering geometry applied to the two layered sample with the sample infront and behind the impurity and then in the transmission geometry for the corresponding orientations of the sample. It is evident that in the former case only the surface Raman signal is seen as evidenced from the spectra. In contrast, in the transmission geometry a gross insensitivity is observed to the location of the impurity layer. Irrespective of the orientation of the sample, ie whether the impurity is at the front or back of the sample the impurity is clearly detected and identifiable from the spectra at a more even proportion to the overall bulk signal of the tablet.

The consequence of this result is profound as it means that even if the paracetamol tablet had a thick layer of 'impurity' at the back of tablet of high Raman scattering cross section the conventional backscattering approach would not be able to detect its presence. On the other hand the transmission geometry is able to reveal the layer presence irrespective of whether it is located at the front or back of the sample.

For the tablet alone, the overall Raman signal intensity when going from the conventional backscattering to

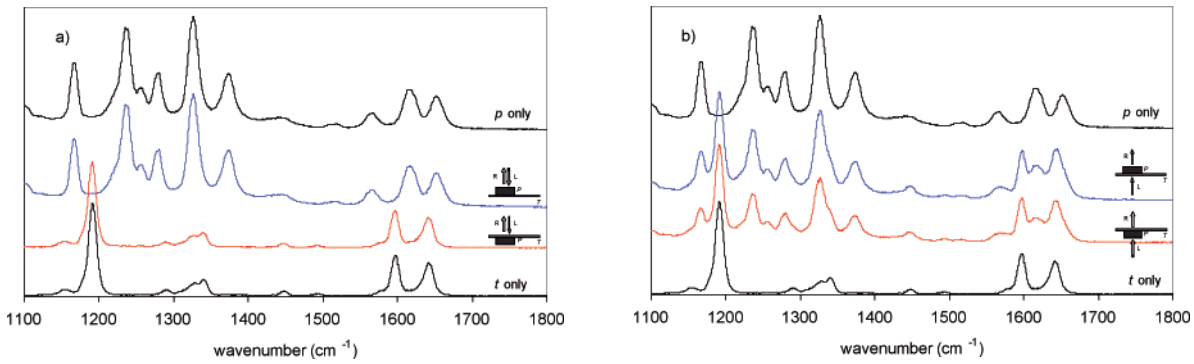

Figure 2. The Raman spectra obtained from the two-layer sample (3.9 mm thick paracetamol and 2 mm thick *trans*-stilbene powder layers) for a) conventional backscattering geometry and b) transmission geometry. The measurements are performed for two sample orientations, with paracetamol at the top and bottom of the *trans*-stilbene cell as indicated in the graphs. The top and bottom spectra are those of paracetamol and *trans*-stilbene, respectively, obtained in separate experiments and shown for comparison. The acquisition times were between 0.2 and 10 s. The spectra are offset for clarity. Legend: *P* - paracetamol, *T* - *trans*-stilbene, R- Raman light, L- laser beam.

transmission geometry was reduced by a factor of 12 and meant that short acquisition times could still be used with the transmission geometry. The large illumination areas applicable in transmission geometry with pharmaceutical tablets also make it possible to use substantially higher laser powers without damaging the sample. This would enable further reductions of exposure times if required.

In a number of analytical pharmaceutical applications there is a need to probe capsules or coated tablets non-invasively to monitor their composition. Although Raman spectroscopy can be used to probe some capsules non-invasively in some instances, in particular with darkly coloured capsules, intense fluorescence can severely reduce the technique's sensitivity. Here we also demonstrate how the transmission Raman geometry can dramatically reduce this surface layer interference.

Figure 3 shows the result of probing differently coloured sections of pharmaceutical capsules using both the conventional Raman backscattering approach and transmission Raman geometry. The spectra are shown in their raw form with no backgrounds removed. It was found that with a number of coloured capsule shell fluorescence was deteriorating significantly the signal-to-noise of the measured Raman spectra of the inner material held within the capsule. The deployment of the transmission Raman geometry eliminates to a large extent this interference enabling much more sensitive measurements of the Raman signal of material within the capsule.

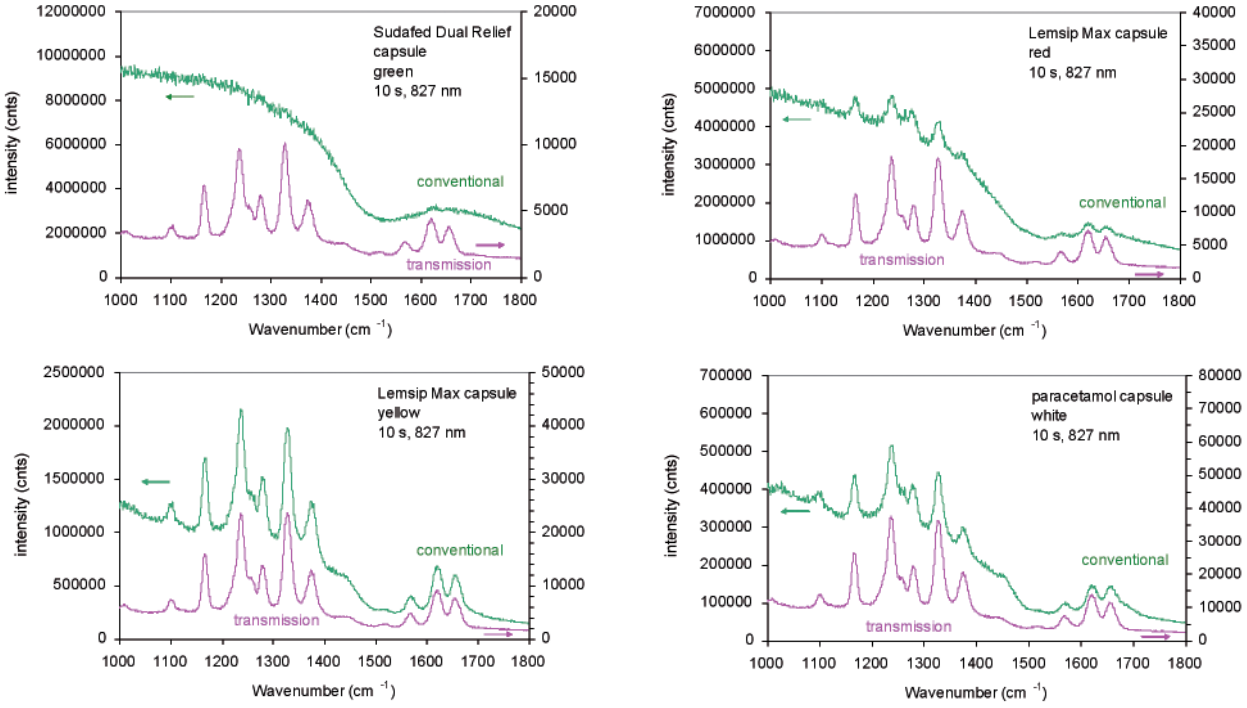

Figure 3. The comparison of performance of the conventional backscattering and transmission Raman geometries in probing various pharmaceutical capsules. The acquisition times were 10 s unless indicated otherwise.

We envisage that in combination with large area probes [5] the acquisition times could be shortened to well below 0.1 s permitting potentially non-invasive bulk analysis on production lines in quality control applications.

Conclusions

We have demonstrated that the largely neglected transmission Raman geometry is ideally suited for the non-invasive probing of pharmaceutical tablets and capsules providing bulk information on their content and reducing substantially surface fluorescence signals that often hamper similar measurements in conventional backscattering Raman geometry. We believe that these properties in combination with the technique's superb chemical specificity, speed and easy deployment make it particularly well suited for rapid analysis of the average content of pharmaceutical products on production lines.

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