Non-invasive detection of counterfeit drugs using Spatially Offset Raman Spectroscopy (SORS)

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Introduction

There is an increasing need for the non-invasive verification of the authenticity of pharmaceutical products on the market. The number of generic copies of popular and well-known drugs is steadily increasing worldwide. For example, the infiltration of the market by fake anti-malarial drugs currently presents a major crisis in eastern Asia [1]. Although the generic copy often has the correct molecule as its active pharmaceutical ingredient (API) the formulation of the drug can be very different affecting the effectiveness of treatment. The worst case and potentially life-threatening scenario is when the generic product does not contain the active ingredient at all. A very recent article in Lancet Infectious Diseases gives a general overview of the counterfeit drug problem together with examples and current methods of analysis [2].

Given the extent of the problem and its current trend, it is becoming increasingly important to verify the actual content of drugs throughout the entire supply chain. This task is complicated by the fact that once tablet packaging is opened, it cannot be marketed. Therefore a non-invasive method of analysis is needed to address the problem effectively. Ideally, the method should be fast and provide clear and easy-to-interpret results.

Raman spectroscopy holds a particular promise for its high chemical specificity. The method in its conventional backscattering form permits the interrogation of many pharmaceutical products through their coating or capsules as well as through blister packs and the technique has also been used to detect counterfeit drugs [3]. However, in many instances, and in particular with dark coloured coatings or capsules, or thicker packaging, the Raman signal of API can be heavily polluted with fluorescence and Raman signals originating from the coating, capsule, [4] blister pack or plastic bottle itself. These extra signals increase noise levels within the observed Raman spectrum of API and in some cases even preclude the observation of API and other ingredients held within the product altogether.

Recently, through collaborative efforts, we have developed a new form of Raman spectroscopy applicable to probing deep layers of turbid media, well beyond the reach of conventional Raman techniques such as confocal Raman microscopy. The method termed Spatially Offset Raman Spectroscopy [5], SORS, provides qualitatively a new capability to analyze non-invasively diffusely scattering media with much higher clarity than possible with conventional approaches.

The SORS approach [5,6,7,8] is based on the collection of Raman spectra from spatially offset regions away from the point of illumination on the sample surface and subsequent scaled subtraction of the spectra (or multivariate data analysis) to separate the signals of individual layers within the interrogated sample. Since the first demonstration of the SORS concept [5], the technique has been used in numerous applications including Raman tomography in turbid media by Morris *et al.* [7], the non-invasive Raman spectroscopy of bones on cadavers and animal samples by Morris *et al.* [8] and the first observation of human bone in vivo under safe illumination conditions by our collaborative team [8]. More recently a more sensitive variant, inverse SORS, has been developed [10,11]. The counterfeit work presented here was performed in the basic SORS point illumination and collection geometry [5] and its full account is given in Ref. [12].

Methods

The Raman spectra were measured using a SORS Raman apparatus described in detail earlier [8]. The probe beam was generated using an attenuated 115 mW temperature stabilized diode laser for Raman spectroscopy, operating at 827 nm (50 mW). The laser spot diameter at the sample was ~0.5-1 mm. The beam was incident on the sample at ~45 degrees. The spatial offset used throughout the SORS experiments was ~3 mm. Controlled conventional backscattering Raman measurements were performed using the same instrumentation with spatial offset set to zero.

Raman light was collected in backscattering geometry using a 50 mm diameter collection 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. The second lens, with the same parameters as the collection lens, was then used to image, with magnification 1:1, the sample interaction zone onto the front face of the fiber probe. The Raman light was propagated through the SORS annular fiber systems of length ~2 m to the linear fiber end oriented vertically and placed in the input image plane of a Kaiser Optical Technologies Holospec $f^{\#} = 1.8i$ NIR spectrograph. Raman spectra were collected using a NIR back-illuminated deep-depletion TE cooled CCD camera (Andor Technology, DU420A-BR-DD, 1024 × 256 pixels) by binning the entire chip vertically.

The Raman signal was collected using a fiber bundle probe made of 22 tightly packed active fibers at the centre of the probe. The spatial offset was introduced by altering the position of the incident laser beam on the sample as illustrated in Figure 1. The individual fibers were made of silica with a core diameter of 220 µm. The fiber numerical aperture was 0.37. The bundle was custom made by CeramOptec Industries, Inc. Acquisition times were 10 s.

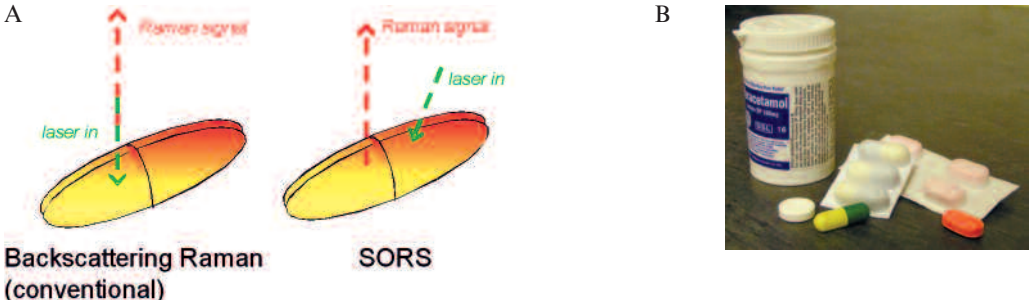

Figure 1. Schematic illustration of the laser illumination and the Raman collection geometry for (A, left) the conventional Raman and (A, right) the Spatially Offset Raman set-up. The photograph in (B) shows the two types of packaging and the corresponding drugs tested in the reported experiments.

Results and discussion

SORS spectra of paracetamol were obtained non-invasively through a wide range of typical drug packaging such as blister packs and white plastic bottles. In all the cases SORS showed superior performance by delivering spectra of drugs held within the packaging of substantially higher quality and purity. Figure 2 shows the non-invasive measurement of paracetamol tablets held within a white plastic container. Both conventional and processed SORS spectra are shown along with the tablet spectrum itself. The conventional Raman spectrum is dominated by the Raman signal of the plastic bottle which completely obscures the signal of paracetamol held within the bottle. In contrast, SORS, after a scaled subtraction of two spectra obtained at different spatial offsets to eliminate the residual surface contribution, provided a clean spectrum of the paracetamol inside.

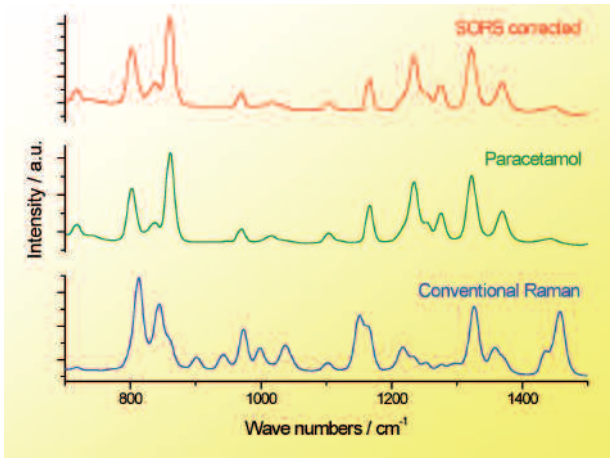

Figure 2. Raman spectra of plain paracetamol tablets held in a white diffusely scattering plastic jar (as shown in Figure 1B). Conventional Raman and SORS processed spectra are shown together with the tablets reference. The spectrum obtained using conventional Raman spectroscopy is dominated by the Raman spectrum of the jar itself hampering the analysis of the chemical constituency of the tablets held within.

Conclusions

The work demonstrates the improved sensitivity of the Spatially Offset Raman Spectroscopy (SORS) over the conventional backscattering Raman spectroscopy in the identity testing of pharmaceutical products through packaging. The new approach is particularly beneficial in situations where the conventional Raman backscattering method is hampered or fails because of excessive surface Raman or fluorescence signals emanating from the packaging, capsule shell, tablet coating or plastic container that contaminates the much weaker subsurface Raman signals of the active pharmaceutical ingredients and excipients held in the product with undesired noise. These interfering signals can be effectively suppressed by SORS.

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