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Non-invasive identification of incoming raw pharmaceutical materials using Spatially Offset Raman Spectroscopy

Matthew Bloomfield[a,*], Darren Andrews[a], Paul Loeffen[a], Craig Tombling[a], Tim York[a], Pavel Matousek[a,b]

[a] Cobalt Light Systems Limited, The Electron Building, Fermi Avenue, Harwell, Oxford OX11 0QR, United Kingdom
[b] Central Laser Facility, Research Complex at Harwell, STFC Rutherford Appleton Laboratory, Harwell, Oxford OX11 0QX, United Kingdom

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ABSTRACT

A new approach to verification of incoming raw materials through packaging in pharmaceutical manufacturing is proposed and demonstrated. The method is based around Spatially Offset Raman Spectroscopy (SORS) and permits a rapid chemical identity analysis of incoming materials to satisfy regulatory requirements but without the need to open the packaging. This dramatically increases the throughput of incoming raw materials into the pharmaceutical manufacturing chain and eliminates the need for a chemically safe sampling environment required for invasive inspection methods. Since the inspection is non-invasive the safety of the operators is ensured and the integrity of inspected material is not compromised by preventing exposure to the ambient atmosphere and cross contamination. The experiments presented here demonstrate the ability to accurately identify common pharmaceutical materials, typically in under 10 s acquisition time, through a range of frequently used packaging, including translucent plastic and paper sacks and coloured glass bottles, which can be challenging for conventional Raman spectroscopy as well as other optical spectroscopy methods. With the exception of metallic containers and cardboard drums all the tested packaging materials proved to be amenable to this technique. This demonstrates the viability of this new rapid verification method for non-invasive materials identification in pharmaceutical manufacture.

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1. Introduction

An independent verification of incoming raw materials is a basic regulatory requirement in pharmaceutical manufacturing [1]. At present this verification is typically achieved by invasive means whereby the packaged material is taken into a chemically safe environment, opened and inspected by conventional analytical techniques, for example, using FTIR-ATR or wet chemical methods. Where incoming chemicals have to be taken through this inspection area, with its limited throughput and resource-intensive manual inspection, this creates a major bottleneck in pharmaceutical manufacturing with associated high costs and a requirement for highly trained employees. Regulatory pressure to verify each unique item in a lot (100% inspection), instead of a small representative sample, will add further delays and highlights the need for rapid inspection tools. Additional complications may arise from the fact that some materials when exposed to ambient atmospheric conditions can undergo rapid degradation – for example, due to the uptake of moisture or oxygen from air, exposure to light or could be cross-contaminated by previously inspected materials or sampling tools.

A major benefit could therefore be brought about if such analysis could be performed through the packaging non-invasively and in situ. For this the portability or other type of mobility of the device is also important in order to be able to bring the device to the inspected containers within warehouse. In this area vibrational spectroscopy techniques such as NIR absorption and Raman spectroscopy have already been employed. Near-infrared (NIR) absorption spectroscopy is however often hampered by interfering signals from the packaging, a limited chemical specificity compared with other vibrational techniques and difficult training due to the influence of particle size, angle of probe contact and other physical properties. Raman spectroscopy has the potential to overcome these limitations but its use in this area has been mainly limited to probing opened packaging invasively or non-invasively probing packaging that is transparent or semi-transparent. Also, whereas colourless glass bottles tend to be amenable, any laser-induced fluorescence arising from colouring within the glass (especially with green glass) can mask the Raman signal of the contents.

* Corresponding author. Tel.: +44 1235 445377.
E-mail addresses: Matthew.Bloomfield@cobaltlight.com (M. Bloomfield), Pavel.Matousek@stfc.ac.uk (P. Matousek).

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Recent advances in non-invasive Raman spectroscopy [2] in the area of subsurface probing of turbid media led to the development of Spatially Offset Raman Spectroscopy (SORS) [3–5]. SORS provides the potential to considerably broaden the range of containers one can scan non-invasively from substantially transparent containers to translucent ones such as paper sacks, plastic bottles or highly fluorescing coloured glass bottles (e.g. green or amber glass) that would be otherwise challenging for conventional Raman spectroscopy. The SORS technique has been successfully demonstrated in many related areas, such as the detection of liquids and powders in bottles in security applications and counterfeit drug detection [2]. Here we propose and investigate the extension of its use into the raw materials verification in the context of pharmaceutical manufacturing. A range of common packaging materials and ingredients used in pharmaceutical manufacture are tested and the capabilities and limits of the technique established in the context of this specific application.

1.1. Spatially Offset Raman Spectroscopy

In a SORS measurement, Raman spectra are typically collected on the sample surface from two or more regions that are spatially separated from the laser illumination point by different amounts (see Fig. 1a). Such spectra contain different relative Raman contributions from the packaging and the content. Typically, a zero spatial offset and some non-zero spatial offset is used to interrogate a two layer system such as a bottle or sack with their contents. This is in contrast with conventional Raman measurements where only one Raman spectrum would be collected from the zone directly illuminated by the laser beam. Such a spectrum would typically be dominated and often overwhelmed in diffusely scattering containers by the surface Raman signal (bottle, packaging) and any fluorescence components, precluding the unambiguous inspection of their content. In contrast, SORS can yield pure Raman spectra of individual layers; in our case, those of the content and the container. In this measurement, two Raman spectra are obtained at different spatial offsets. These are then processed using a scaled subtraction of one from the other to yield pure Raman signatures of the individual layers [2]. Of particular interest to this application is the recovery of the pure Raman signature of the contents unobstructed by the Raman and/or fluorescence interference from the bottle or packaging. This processing approach can be fully automated and requires no a priori knowledge of the chemical composition of either the container or contents.

To also permit the inspection of transparent containers with a single illumination and collection geometry a special SORS optical arrangement has been used [6]. The need is brought about by the different nature of the propagation of light through such media. In transparent containers the light propagates in straight paths but in diffusely scattering media its direction is continuously randomised as the photons diffuse through the medium (see Fig. 1). The collection system therefore has to account for two different illumination situations and be effective in both. This can be satisfied by the illumination setup adopted here. In this configuration an obliquely angled laser beam is used to pass through transparent container walls spatially offset from the collection zone at an angle to intersect the Raman collection zone located below the wall within the probed medium (see Fig. 1b). When such a setup is presented with a diffusely scattering sample, e.g. an opaque plastic bottle, this configuration acts as a conventional SORS setup as the laser photons quickly lose memory of their direction of travel when encountering the diffusely scattering medium (e.g. the container wall). This setup also suppresses fluorescence and Raman signals originating from transparent container wall, e.g. green glass, as long as the spatially offset laser beam intersects the container wall out of sight of the Raman collection system.

As with conventional Raman and other types of optical spectroscopy, the technique is limited to non-metallic containers. Other restrictions include the limitation to contents that do not fluoresce at the excitation laser wavelength excessively and materials not excessively absorbing laser or Raman photons (e.g. black or very darkly coloured packaging materials such as cardboard drums). However, fluorescence originating from the packaging can be effectively suppressed with SORS as also demonstrated here [7].

To date, SORS has been used in various forms [2,7] in a range of applications including biomedical analysis, pharmaceutical analysis and aviation security. In the biomedical field it is under development to detect in vivo bone diseases [8] and cancer [9]. Elsewhere it is used to detect counterfeit and concealed drugs [10,11] or to quantitatively characterise drug mixtures in containers [12] in pharmaceutical analysis and in aviation security SORS to screen for liquid and gel explosives in bottles [6,13]. Recently, it has also been used to extend the applicability of Surface Enhanced Raman Spectroscopy (SERS) to detect signals deep within biological tissue (SESORS – Surface Enhanced Spatially Offset Raman Spectroscopy) [14–16].

2. Experimental

The SORS setup used here has been described earlier [17]. A 500 mW, 830 nm laser beam was delivered to the sample at an angle of ~40° to the collection optics onto a spot of a diameter 2.5 mm. A computer controlled motorised linear translation stage was used to set the spatial offset by moving the laser beam delivery optics to direct the beam onto sample at an appropriate point. Raman scattered light was collected using a lens (25 mm diameter, 40 mm focal

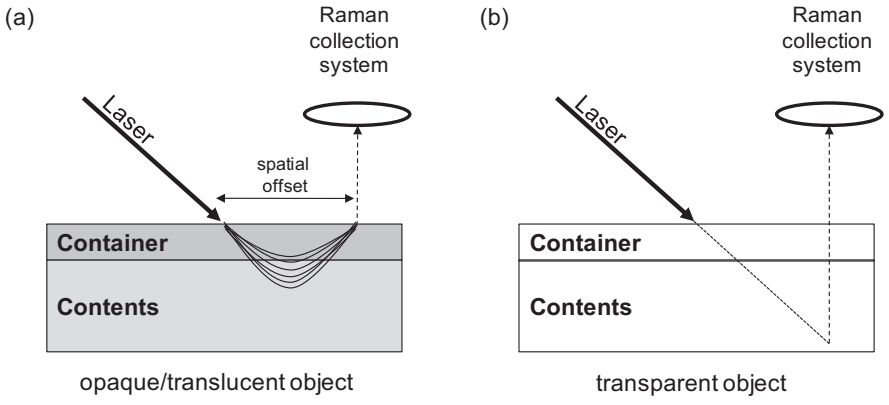

Fig. 1. A schematic illustration of SORS noninvasive concept with (a) opaque packaging and (b) transparent packaging.

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