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

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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.

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.

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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

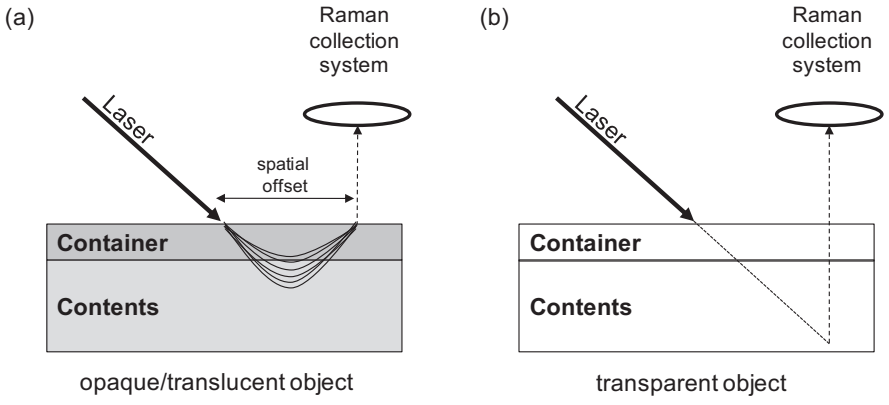

Fig. 1. A schematic illustration of SORS noninvasive concept with (a) opaque packaging and (b) transparent packaging.

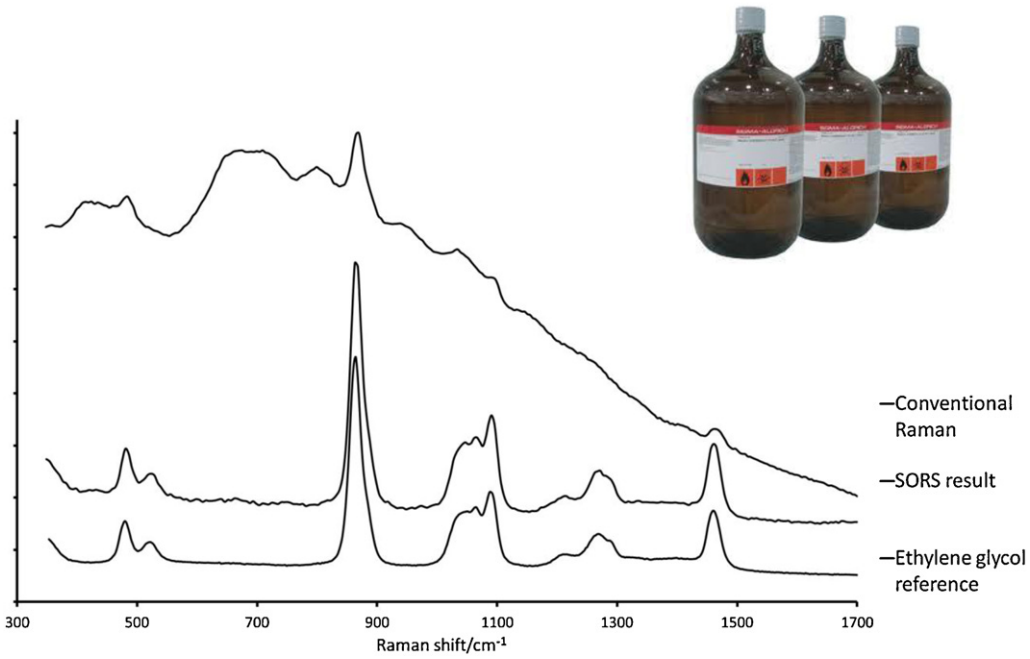

Fig. 2. SORS (middle) and conventional Raman (top) spectra of ethylene glycol measured through amber glass bottle. A reference spectrum (bottom) measured without the bottle is also shown. The spectra are offset for clarity.

length), filtered to reject elastically scattered light using a pair of long pass dielectric edge filters and imaged onto a fibre-optic bundle. The vertically oriented fibres at the other end of the bundle were placed at the entrance slit position of the spectrograph. The Raman spectra were detected using a back-thinned, deep-depletion CCD detector (Andor iDus, 1024 by 256 pixels). Acquisition times varied depending on the sample. Since the spectra acquired at the surface ("zero offset") are significantly more intense than the offset spectra, acquisition times are typically an order of magnitude greater at the offset position. Zero offset spectra were acquired in <0.5 s and offset spectra acquisition times ranged between 2 s and 10 s. Contents with poorer Raman responses or in more challenging containers required longer acquisition times.

The processing of SORS spectra included a standard scaled subtraction of the two Raman spectra acquired at a zero and non-zero (3–10 mm, depending on the container) spatial offsets to obtain a pure signature of the content cancelling the container Raman contribution. The process was semi-automated with a user-defined variable scaling tool in the SORS control and measurement software. In some examples, the fluorescence backgrounds were subtracted before the scaled subtraction by fitting a polynomial baseline. Automated software has subsequently been developed

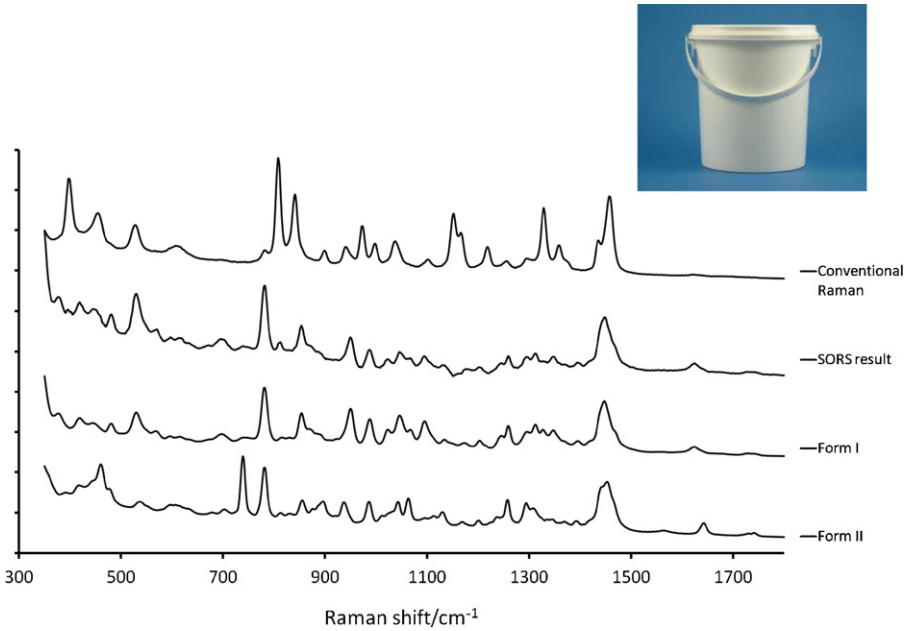

Fig. 3. SORS and conventional Raman spectra of active pharmaceutical ingredient (API) measured through opaque polypropylene container. The reference spectra of the two polymorphic form of API are also shown. The spectra are offset for clarity.

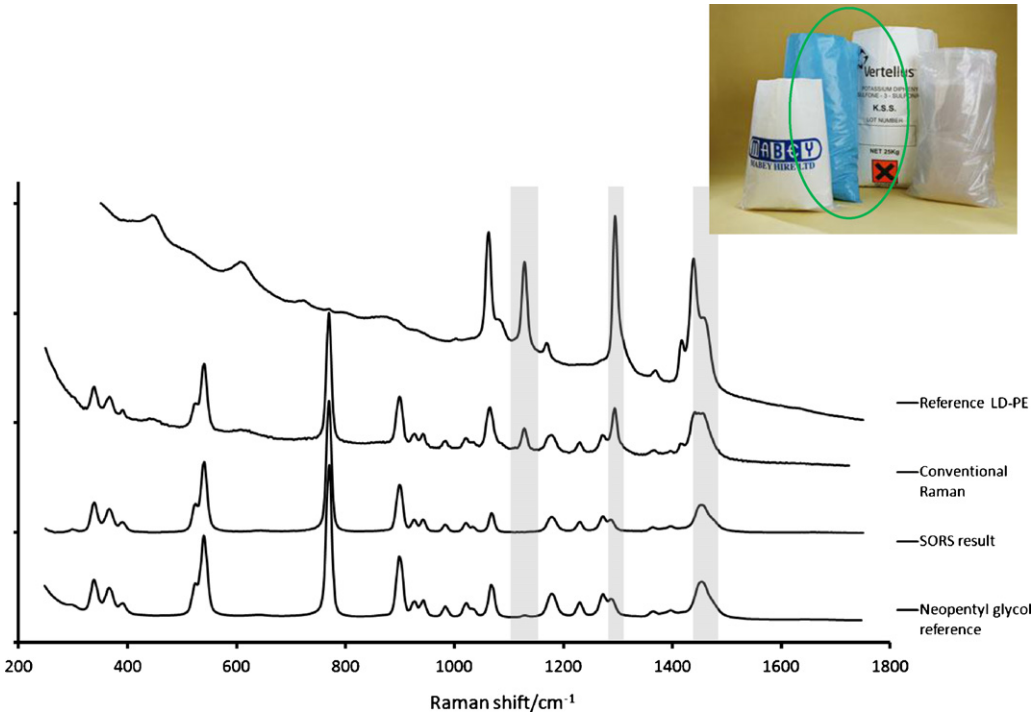

Fig. 4. SORS and conventional Raman spectra of neopentyl glycol measured through opaque polyethylene sack. Reference spectra of the sack (LD-PE) and neopentyl glycol measured without the sack are also shown. The spectra are offset for clarity. (For interpretation of the references to colour in text, the reader is referred to the web version of the article.)

for the application that iteratively fits a smoothing spline to remove fluorescent baselines, before subtracting automatically scaled spectra.

3. Results and discussion

Fig. 2 illustrates the results of the non-invasive probing of an amber glass bottle containing ethylene glycol, both with conventional and SORS configuration with a 3 mm spatial offset. Whilst the conventional Raman spectrum is polluted with a large fluorescence background and Raman components from the glass, the SORS spectrum yields a clean Raman spectrum of the contents as evidenced by comparing the SORS result with a conventional Raman spectrum of pure ethylene glycol.

The measurement of a polymorphic form of perindopril, an ACE inhibitor, through a 2 mm thick white plastic (HDPE) tub is shown in Fig. 3. There are two polymorphic forms of this active pharmaceutical ingredient (API) and for manufacturing it is naturally vital that the right form is correctly identified. Again, the results of SORS are compared with those obtained using conventional Raman

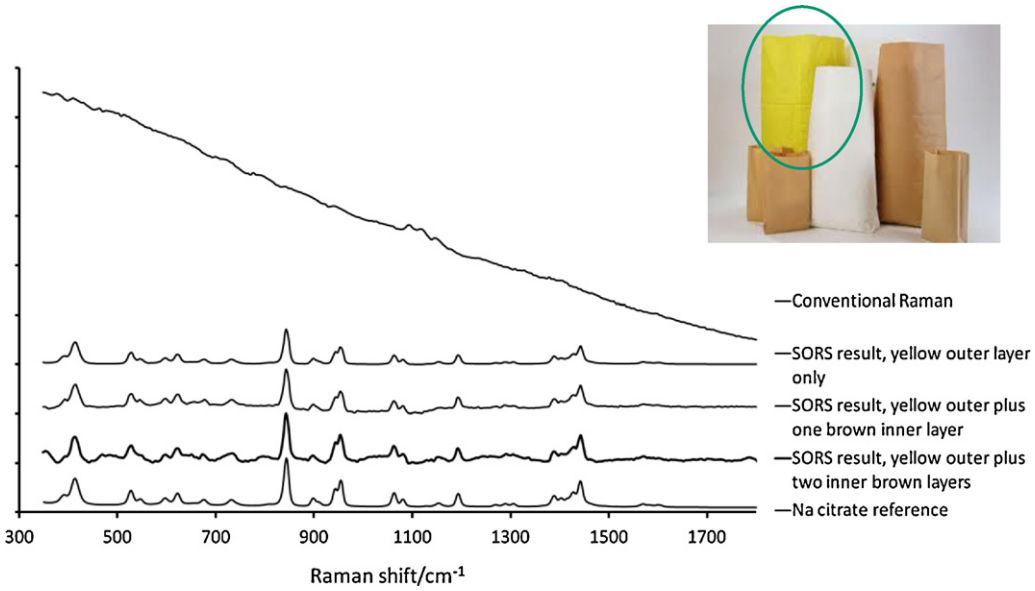

Fig. 5. SORS spectra of Na citrate measured through 1, 2 and 3 layers of paper sacking. A conventional Raman measurement through 3 layers of sacking is shown for comparison. A reference spectrum of Na citrate is also shown. The spectra are offset for clarity. (For interpretation of the references to colour in text, the reader is referred to the web version of the article.)

measurement. Processed SORS spectra show close correspondence with the reference Raman spectrum of Form I evidencing the nature of the content. In contrast, the conventional Raman spectrum is dominated by the Raman signatures of the container, making it an inappropriate method to identify the API and its form.

Fig. 4 shows the results of the measurement of a pharmaceutical reagent, neopentyl glycol, through the blue plastic sack indicated with a circle in the photograph. Although the conventional Raman spectrum contains components belonging to the contents it is again heavily polluted with the Raman signal of the container making the unambiguous identification of the content difficult. On the other hand, the processed SORS spectrum shows a close correspondence with the reference spectrum.

Fig. 5 illustrates the measurement of sodium citrate powder through a paper sack, indicated in the insert with an ellipse. Two inner brown paper layers are covered by an outer paper layer coloured yellow. The results are shown for 1, 2 and 3 layers of the packaging. Although with only the outer, yellow paper layer conventional Raman was capable of providing an adequate answer albeit with the presence of fluorescence and the cellulose Raman signature of the paper packaging material, when the second and third (inner brown paper) layers are introduced (shown), the sample becomes highly challenging or impossible for conventional Raman spectroscopy. In contrast, the processed SORS spectra exhibit close correspondence with the Raman spectrum of the contents, even through all three packaging layers, making the identification of the chemical content unambiguous and straightforward.

Overall the applicability of Raman spectroscopy has been considerably extended with the deployment of SORS including transparent and translucent plastic and coloured glass containers and paper and plastic sacks. Non-viable containers include metallic and thick cardboard packaging. The limits of detection cannot be always drawn accurately as it is blurred depending on the strength of the Raman signal of the content; for example very strong Raman scatterers could possibly be detected in some challenging containers. However, it is evident that a substantial extension of the applicability of non-invasive inspection in this area is achieved with the SORS technique.

4. Conclusions

A non-invasive, chemically specific inspection method has been demonstrated to be viable in materials verification within pharmaceutical manufacturing. The key benefits include the ability to perform the identification through packaging, thus eliminating need for opening the packaging, with its associated safety hazards, potential for sample degradation or cross contamination and the requirements for special chemical handling environments. The analysis can be performed within seconds and the device can be portable or mobile. Viable packaging materials include transparent and opaque plastic sacks and tubs, paper packaging and coloured glass bottles (e.g. green or amber glass). Packaging materials that could not be probed with this method include metallic containers and drums with thick cardboard walls. The concept demonstrates the viability of a new rapid, cost effective inspection of incoming materials in pharmaceutical manufacturing.

References

[1] FDA Code of Federal Regulations 21CFR211.84. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.84
[2] P. Matousek, M.D. Morris (Eds.), Emerging Raman Applications and Techniques in Biomedical and Pharmaceutical Fields, Springer, Heidelberg, 2010.
[3] P. Matousek, I.P. Clark, E.R.C. Draper, M.D. Morris, A.E. Goodship, N. Everall, M. Towrie, W.F. Finney, A.W. Parker, Subsurface probing in diffusely scattering media using spatially offset Raman spectroscopy, Appl. Spectrosc. 59 (2005) 393–400.
[4] P. Matousek, M.D. Morris, N. Everall, I.P. Clark, M. Towrie, E. Draper, A. Goodship, A.W. Parker, Numerical simulations of subsurface probing in diffusely scattering media using spatially offset Raman spectroscopy, Appl. Spectrosc. 59 (2005) 1485–1492.
[5] P. Matousek, A.W. Parker, Apparatus for Depth-Selective Raman Spectroscopy, US Patent 7,652,763, January 26, 2010.
[6] C. Eliasson, N.A. Macleod, P. Matousek, Non-invasive detection of concealed liquid explosives using Raman spectroscopy, Anal. Chem. 79 (2007) 8185–8189.
[7] K. Buckley, P. Matousek, Non-invasive analysis of turbid samples using deep Raman spectroscopy, Analyst 136 (2011) 3039–3050.
[8] M.V. Schulmerich, K.A. Dooley, M.D. Morris, T.M. Vanasse, S.A. Goldstein, Transcutaneous fiber optic Raman spectroscopy of bone using annular illumination and a circular array of collection fibers, J. Biomed. Opt. 11 (2006) 060502.
[9] P. Matousek, N. Stone, Emerging concepts in deep Raman spectroscopy of biological tissue, Analyst 134 (2009) 1058–1066.
[10] C. Eliasson, P. Matousek, Noninvasive authentication of pharmaceutical products through packaging using spatially offset Raman spectroscopy, Anal. Chem. 79 (2007) 1696–1701.
[11] W.J. Olds, E. Jaatinen, P. Fredericks, B. Cletus, H. Panayiotou, E.L. Izake, Spatially offset Raman spectroscopy (SORS) for the analysis and detection of packaged pharmaceuticals and concealed drugs, Forensic Sci. Int. 212 (2011) 69–77.
[12] W.J. Olds, S. Sundarajoo, M. Selby, B. Cletus, P.M. Fredericks, E.L. Izake, Non-invasive, quantitative analysis of drug mixtures in containers using spatially offset Raman spectroscopy (SORS) and multivariate statistical analysis, Appl. Spectrosc. 66 (2012) 530–537.
[13] P. Loeffen, G. Maskall, S. Bonthron, M. Bloomfield, C. Tombling, P. Matousek, Spatially offset Raman spectroscopy (SORS) for liquid screening, optics and photonics for counterterrorism and crime fighting VII, in: Lewis, Burgess, Zamboni, Kajzar, Szep, Gruneisen, Dusek, Rarity (Eds.), Optical Materials in Defence Systems Technology VIII, and Quantum-Physics-based Information Security, Proceedings of SPIE, vol. 8189, 2011, pp. 81890C-1-81890C-10.
[14] N. Stone, K. Faulds, D. Graham, P. Matousek, Prospects of deep Raman spectroscopy for noninvasive detection of conjugated surface enhanced resonance Raman scattering nanoparticles buried within 25 mm of mammalian tissue, Anal. Chem. 82 (2010) 3969–3973.
[15] N. Stone, M. Kerssens, G.R. Lloyd, K. Faulds, D. Graham, P. Matousek, Surface enhanced spatially offset Raman spectroscopic (SESORS) imaging – the next dimension, Chem. Sci. 2 (2011) 776–780.
[16] J.M. Yuen, N.C. Shah, J.T. Walsh, M.R. Glucksberg, R.P. Van Duyne, Transcutaneous glucose sensing by surface-enhanced spatially offset Raman spectroscopy in a rat model, Anal. Chem. 82 (2010) 8382–8385.
[17] P. Loeffen, G. Maskall, S. Bonthron, M. Bloomfield, C. Tombling, P. Matousek, Chemical and explosives point detection through opaque containers using spatially offset Raman spectroscopy (SORS), in: A.W. Fountain III, P.J. Gardner (Eds.), Chemical, Biological, Radiological, Nuclear, and Explosives (CBRNE) Sensing XII, Proceedings of SPIE, vol. 8018, 2011, pp. 80181E-1–80181E-9.