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Review

Recent advances in the application of transmission Raman spectroscopy to pharmaceutical analysis

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ABSTRACT

This article reviews recent advances in transmission Raman spectroscopy and its applications, from the perspective of pharmaceutical analysis. The emerging concepts enable rapid non-invasive volumetric analysis of pharmaceutical formulations and could lead to many important applications in pharmaceutical settings, including quantitative bulk analysis of intact pharmaceutical tablets and capsules in quality and process control.

Contents

1. Introduction

In a number of analytical applications in the pharmaceutical environment it is often desirable to characterise the bulk chemical constituency of intact samples rapidly, non-destructively and non-invasively. Raman spectroscopy holds a particular promise in this area due to its inherently high chemical specificity (substantially higher than that of its competitor: near-infrared absorption (NIR) spectroscopy), its ability to probe samples in the presence of water, and its potential for high penetration depth into non-absorbing or weakly absorbing turbid samples (similar to NIR absorption spectroscopy), such as those typically present within pharmaceutical formulations.

The higher chemical specificity of Raman spectroscopy compared with NIR absorption spectroscopy stems from the fact that NIR spectra consist of broad and overlapping bands which are typically high frequency overtone and combination bands of fundamental vibrational modes; the fundamental modes themselves are invisible to the technique. As NIR only detects combinations/overtones, it is only sensitive to anharmonic vibrations, i.e. predominantly *X*–H bonds. This is another reason for the lack of chemical information compared with MIR or Raman. In contrast, Raman spectroscopy permits the direct monitoring of fundamental vibrational modes (within the important finger print and phonon mode spectral regions) and exhibits much sharper bands [1]. Although the other main optical counterparts of Raman scattering

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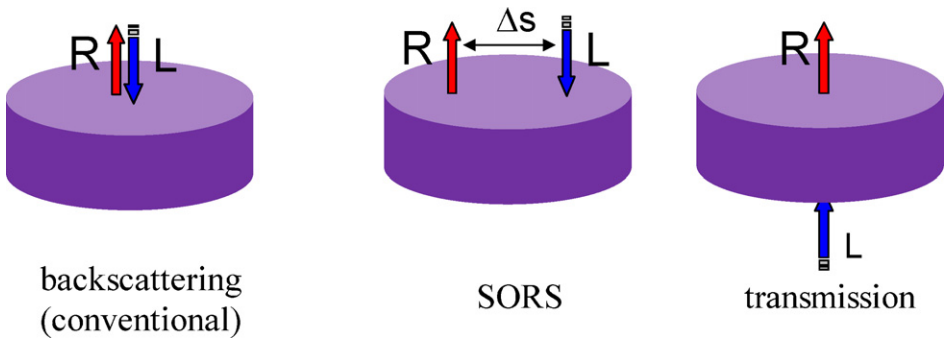

Fig. 1. Raman spectroscopy variants: conventional backscattering Raman, spatially offset Raman spectroscopy and transmission Raman spectroscopy. Legend: *R* – Raman light, *L* – laser beam and Δs – spatial offset.

(mid-infrared (MIR) and to some extent terahertz (THz) spectroscopy) also offer high chemical specificity, their applications are typically restricted to dry samples, due to strong water absorption impeding their applicability. In addition, MIR spectroscopy is in general only applicable to very thin layers of samples unless the samples are substantially diluted. On the other hand, the Raman technique suffers from sensitivity to fluorescence which can sometime swamp the much weaker Raman signal. This problem can, however, often be circumvented by using near-infrared excitation [1].

Until recently the volumetric analysis of pharmaceutical samples such as tablets and capsules with Raman spectroscopy was hampered by severe sub-sampling [2,3]. This limitation stems from the widely used backscattering Raman collection geometry in which most Raman instruments operate. In this mode Raman signal is collected from the sample directly at the laser illumination zone. This geometry is widely used for its instrumental simplicity and ease of deployment.

Recently, a range of Raman techniques capable of penetrating substantially deeper into the sample than possible with the conventional Raman backscattering approach have emerged. These developments permitted new important applications in a number of disciplines [4]. This review focuses on one of these methods, transmission Raman spectroscopy, as it has considerable potential to become a particularly important tool in pharmaceutical analysis.

1.1. Transmission Raman spectroscopy

The development of transmission Raman spectroscopy for pharmaceutical applications was a spin out from the recent development of spatially offset Raman spectroscopy (SORS) [5,6], a method for isolating Raman signals from chemically distinct layers deep within turbid media. It stems from earlier research into deep Raman ultrafast methods and Raman photon migration research and is finding applications across a wide range of disciplines [7–16]. Although the transmission Raman technique was demonstrated in the early days of Raman spectroscopy [17], until recently its benefits for the non-invasive probing of the bulk content of samples had not been recognised and exploited in pharmaceutical settings. Transmission Raman spectroscopy can be considered a special modality of SORS, in which the laser beam and the Raman collection zone are separated to the extreme, both being on opposite sides of the sample. It was shown that this configuration exhibits special properties compared with conventional Raman spectroscopy that are well suited for the determination of the bulk content of turbid samples such as pharmaceutical capsules and tablets [18]. Crucially, one can also effectively suppress the sub-sampling in the *z*-direction (depth) [3] which plagues conventional Raman spectroscopy (extreme oversensitivity to the signals from within the vicinity of the laser illumination zone on sample surface) as well as any surface-generated Raman and fluorescence signals to which conventional backscattering Raman spectroscopy is overly sensitive [19].

The sub-sampling problem presents a severe limitation to the applicability of conventional Raman spectroscopy to probing pharmaceutical tablets (and capsules) as these samples are often highly heterogeneous and can also contain surface coatings or layers giving rise to strong Raman and fluorescence signals that reduce technique's sensitivity to the inner content of the sample [3]. The problem of sub-sampling was partially addressed in lateral dimensions by Wikstrom et al. [20] who used a wide-illumination with a conventional Raman collection backscattering geometry although the sub-sampling problem in the *z*-direction (depth), albeit reduced, still remained. This technique and the reduction of sub-sampling was further explored by a group of Chung [21–24]. The transmission Raman geometry addresses the sub-sampling problem further in the *z*-direction (depth) permitting a rapid and effective monitoring of the bulk content of pharmaceutical formulations (Fig. 1).

The reduction of the sub-sampling problem in the transmission Raman geometry was first demonstrated computationally by Matousek and Parker [18]. Numerical Monte-Carlo simulations were performed of a pharmaceutical tablet like object with a thin 'impurity' layer inserted at different depths and with wide illumination and collection areas (6 mm diameter in both the cases). The results (illustrated in Fig. 2) indicate that transposing the impurity from surface to a depth of 3 mm within a 4 mm thick tablet diminishes the signal in conventional backscattering Raman spectroscopy by 4 orders of magnitude. At this point, such signal would be typically overwhelmed by the surface Raman signal preventing the detection of this impurity layer by conventional means. In contrast, the transmission geometry yields a Raman signal level largely invariant (in this case, to within ±50% accuracy) to the depth of impurity layer. This result was in agreement with experimental observations. The Monte Carlo simulations also indicated a weak bias towards signals from the inner part of the tablet (see Fig. 2a). Experimental studies of layered pharmaceutical tablets have confirmed these predictions e.g., Townshend et al. [25] and Johansson et al. [26].

Everall et al. [27] further investigated theoretically the spatial resolution of transmission Raman spectroscopy in both lateral and depth dimensions from a standpoint of tomographic applications. Apart from looking at the spatial origin of the measured Raman signals, the research investigated homogeneity of the probing as a function of experimental geometry. The study examined the effect of incident beam size, Raman collection aperture, sample thickness and transport length. In this study it was predicted that the lateral resolution should worsen linearly with sample thickness (typically the spatial resolution was about 50% of the sample thickness). The lateral resolution was better at the sample surfaces (essentially

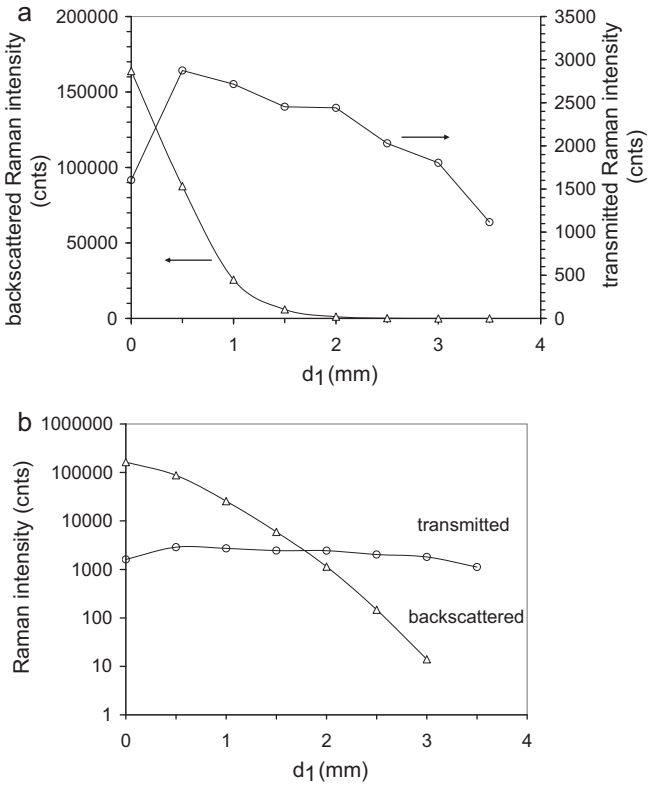

Fig. 2. Plot of calculated Raman intensities for the backscattering and transmission geometries versus depth (d_1) of the inter-layer (impurity) within a pharmaceutical tablet-like medium. The dependencies are the results of Monte Carlo simulations. The results are presented in (a) linear and (b) $\log_{10}$ plots.
Reprinted with permission from Matousek and Parker [18]. Copyright (2006). The Society for Applied Spectroscopy.

determined by the probe beam diameter or the collection aperture) than that for objects buried deeply in the sample. In line with earlier observations the signal biased towards the mid-point of thick samples in transmission sampling was also established. This effect is depicted in Fig. 3 showing the Monte Carlo simulated Raman signal intensity as a function of depth of its origin.

In a subsequent study Everall et al. [28] looked experimentally at the spatial resolution and sensitivity of Raman spectroscopy in backscatter and transmission modes in turbid media. For the first time under such conditions the width and intensity of the point spread function has been accurately measured as a function of sample thickness and depth below the surface. In transmission mode,

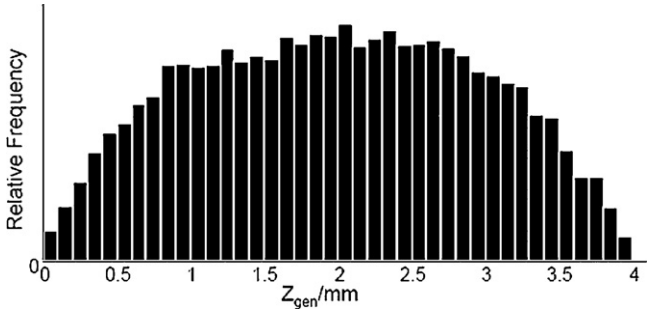

Fig. 3. Computed distribution of generation depths for all detected Raman photons assuming 4 mm thick sample, 0.5 mm probe beam, 1 mm collection zone and 80 μm transport length; the detected photons tended to be generated near the middle of the sample.
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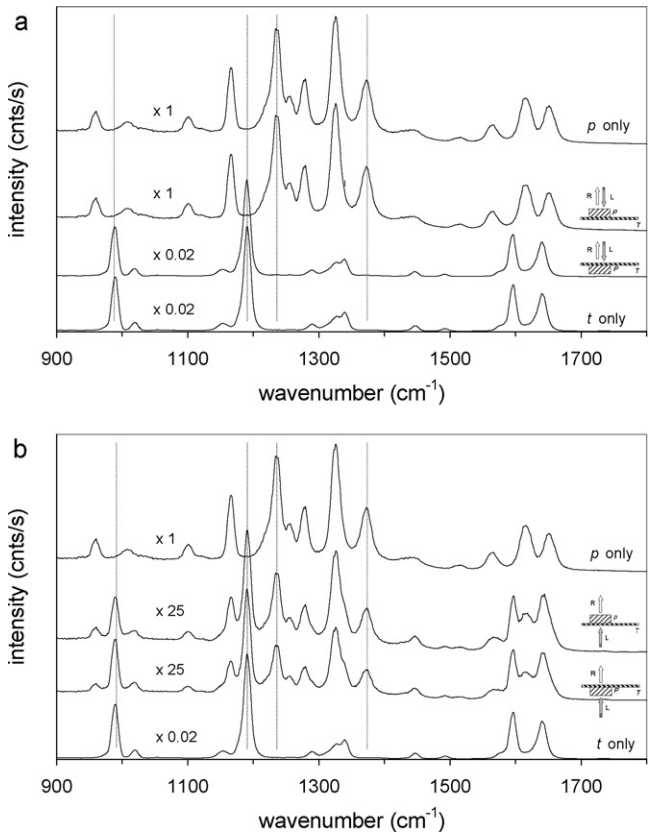

Fig. 4. The Raman spectra obtained from a two-layer sample (3.9 mm thick paracetamol tablet and 2 mm thick trans-stilbene powder layer) using (a) conventional backscattering geometry and (b) transmission geometry. The measurements are performed at two sample orientations, with paracetamol at the top and at the 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. The acquisition times were between 0.2 s and 10 s, with a laser power of 80 mW. The spectra are offset for clarity. Legend: p – paracetamol, t – trans-stilbene, R – Raman light, L – laser beam.
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the lateral resolution for objects in the bulk was shown to degrade linearly with sample thickness. The resolution was also shown to be much better for objects near either surface, being determined by the diameter of the probe beam and collection aperture irrespective of sample thickness. The objects in the bulk yielded higher signals than those at the surfaces in line with the preceding numerical simulations [27] and experimental findings [25–27]. The observations were also shown to be insensitive to the choice of transport length in the studied deep diffusion regime implying that a simple model can be used to predict instrument performance for given experimental conditions.

The ability of transmission Raman spectroscopy to access very deep areas of highly turbid samples and convey information on its bulk content was experimentally demonstrated by Matousek et al. [18] on a two-layer tablet-like sample of overall thickness ~6 mm. This is demonstrated in Fig. 4 where conventional backscattering and transmission Raman results are depicted. They were performed on a 3.9 mm thick tablet of paracetamol followed by a 2 mm thick layer of trans-stilbene powder. Whilst conventional backscattering Raman spectroscopy was capable of seeing only the surface layer presented to the instrument transmission Raman spectroscopy yielded signal contributions from both the layers within this thick and highly turbid sample. For a paracetamol tablet of 3.9 mm thickness the overall Raman signal strength was lower by a factor of 12 in transmission Raman geometry compared to the backscattering

measurement. Despite the reduced intensity of the signal, the transmission Raman configuration still permitted high quality Raman spectra to be acquired within seconds.

1.2. Raman signal enhancement using a 'photon diode'

Since signals can be substantially weaker in transmission Raman spectroscopy than in conventional backscattering Raman spectroscopy, it is often necessary to take steps to increase the signal-to-noise level and/or reduce the concentration detection threshold (limit of detection). These measures can include the optimisation of Raman collection system specifically for the transmission Raman geometry, the use of higher laser powers (permitted by considerably larger laser illumination areas in transmission Raman spectroscopy) or using longer acquisition times.

Another, more unconventional approach for boosting Raman signals by passive means, which is suitable for use with transmission Raman spectroscopy, was proposed and recently demonstrated by Matousek [29]. This concept uses a 'unidirectional' mirror placed in a close proximity of sample within the laser illumination zone to enhance the Raman signal. The role of this optical element is to prevent the loss of diffusely scattered photons lost from the sample at the laser coupling interface whilst permitting the laser beam to be transmitted through the optical element on the other side. The special mirror is effectively a multilayer dielectric optical bandpass or edge filter. The concept relies on the generic angular properties of dielectric filters for which the spectral profile shifts to shorter and shorter wavelengths as photons impact them at angles further from normal incidence. The increased coupling of laser radiation into the sample leads to a substantial boost of overall Raman signal generated within the sample. As the dielectric filters are typically produced as flat optical elements and the filters need to be in near-contact with the sample the sample should also be ideally flat, or at least not excessively curved. Ideal samples are therefore flat pharmaceutical tablets or powders. Although some curvature is acceptable its presence typically leads to the diminishment of the enhancement effect. Fig. 5 shows the performance of the enhancer with 6–7 mm thick powder formulation of paracetamol. An enhancement factor of 8.5 was achieved in this particular situation. The associated benefits to the signal-to-noise ratio is evidenced from the figure. The concept was also demonstrated to be viable with the SORS concept [30] as well as with conventional Raman and fluorescence spectroscopy [31].

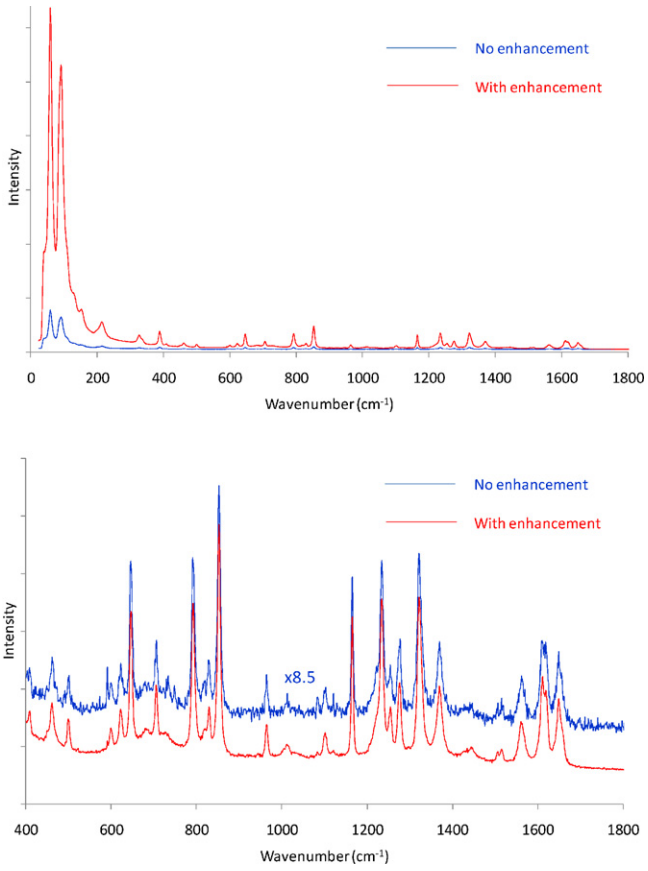

Fig. 5. The experimental demonstration of the enhancement of transmission Raman signal using a 'unidirectional' mirror ('photon diode') on a 6–7 mm thick powder sample of paracetamol. The Raman spectra were measured with and without the enhancing mirror. The acquisition time was 1 s.

2. Examples of pharmaceutical applications

2.1. Quantification of active pharmaceutical ingredients and excipients in pharmaceutical tablets and capsules

The quantitative analysis of pharmaceutical formulations is traditionally performed using HPLC. However, this technique is time and labour consuming as well as destructive to the sample. In many applications it would be highly advantageous to replace it with a bulk sensing method capable of rapid, non-destructive and non-invasive analysis. This requirement is addressed in some situations by NIR absorption spectroscopy although in a number of applications this method is hampered by technique's limited chemical specificity and a lack of robustness due to its high sensitivity to the physical properties of the sample (e.g., formulation particle size). Many of these deficiencies are largely suppressed or removed by Raman and, in particular, transmission Raman spectroscopy.

A complete displacement of HPLC methods by transmission Raman spectroscopy is unlikely to occur, as HPLC has a much lower concentration detection threshold and is capable of reaching trace level sensitivity. In contrast, Raman spectroscopy in general can typically detect species at concentrations of ~0.1% at best. However, the key advantages of Raman spectroscopy are that it is rapid and non-destructive, and is capable of providing information that is lost during the HPLC preparation process (e.g., information on the polymorphic content), it can also detect insoluble excipients. These factors can be crucially important in a number of quality control applications. These features are also likely to lead to a number of niche applications in the process control area.

The ability of transmission Raman spectroscopy to provide quantitative information on sample constitution was demonstrated experimentally by Johansson et al. [32]. In this study, 20 test tablets (3.3 mm thick) prepared in a laboratory environment were analysed. The quantity of the active pharmaceutical ingredient (API) was determined with a relative root mean square error of ±2.2% (see Fig. 6). The acquisition time in these measurements was 10 s and a laser power of 400 mW (785 nm) was used. The study was also performed in a conventional backscattering Raman geometry which yielded a lower relative accuracy (±2.9%) ascribed to the presence of sub-sampling. The transmission Raman method was also applied to pharmaceutical capsules yielding a relative accuracy of ±3.6%. The study indicated that the transmission Raman mode requires a leaner calibration model relative to conventional Raman spectroscopy and was capable of providing reasonably good accuracy even when based on only 2 or 3 calibration spectra (see Fig. 6).

In a parallel study Eliasson et al. [33] used a batch of 150 production line type formulations contained within white capsules prepared in a laboratory environment. The investigations showed that intense interfering Raman signals from the capsule shell were

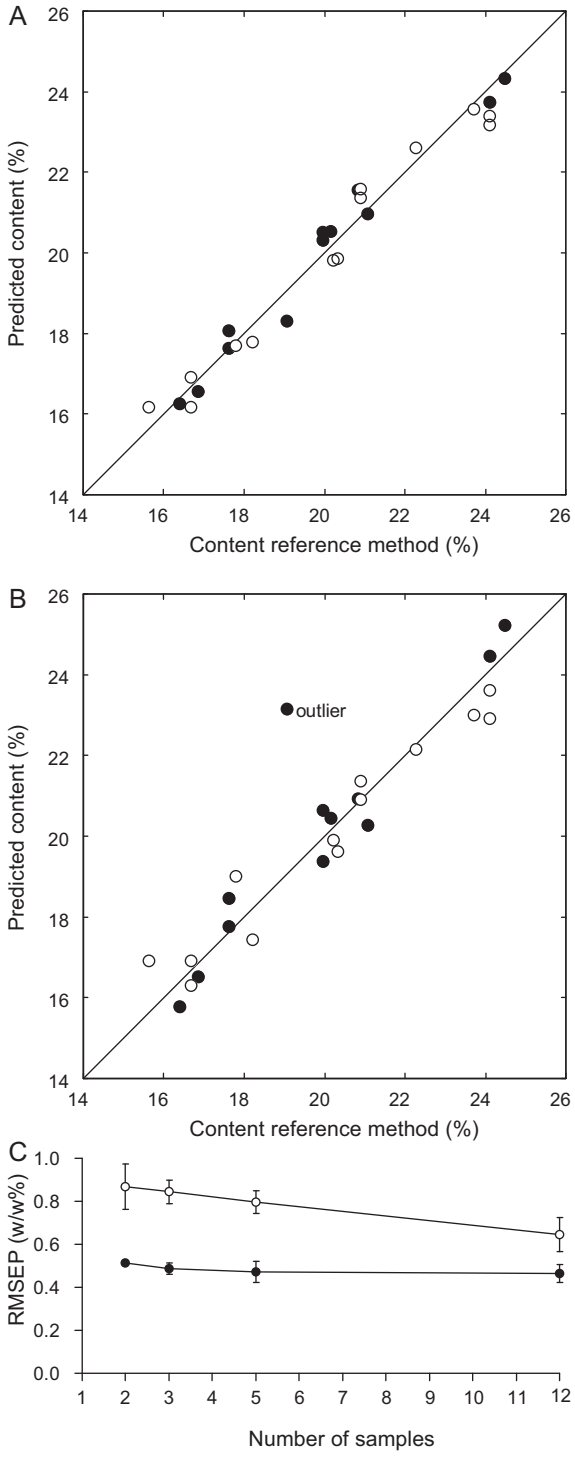

Fig. 6. Prediction of the concentration of propranolol tablets in two independent test sets; the original test sets (solid circles) and the exchanged test sets (open circles). Comparison of (A) Raman transmission (1 PLS component) and (B) Raman backscatter (1 PLS component). (C) Model robustness: the effect of reducing the number of samples in calibration models on the prediction errors for independent test sets. Solid circles represent the transmission mode while open circles represent the backscatter mode. The figure shows mean values of RMSEP for reduced models built on the original and the exchanged models, and the error bars show max and min values of RMSEP. The same test set was used for all reduced models originating from the same full model.
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suppressed in the Raman transmission mode by a factor of 33 relative to conventional Raman measurement. This permitted the accurate quantification of the API with a relative root mean square error of ±1.2% with 5 s acquisition time. In this study the laser power at the sample was 250 mW and the laser wavelength 830 nm. The beam spot diameter on the sample was ~3–4 mm.

The ability to use widely defocused beams in transmission Raman spectroscopy also permits to increase the laser power without risking sample damage compared with traditional Raman microscopy setups. This property is useful in situations demanding further improvement of Raman signal-to-noise ratio or where reduction of exposure time is desirable. An additional Raman signal boost can also be achieved with the aforementioned 'photon diode' mirror. The larger illumination and collection areas also dramatically reduce requirements for the alignment of the sample in front of the instrument and further contribute to the effective averaging of the signals throughput the sample.

The two studies above used predominantly binary mixtures. The ability to quantify more complex formulations was studied by Hargreaves et al. [34]. This study focused on a detailed characterisation of transmission Raman spectroscopy from the standpoint of rapid quantitative analysis of pharmaceutical capsules using production relevant formulations; these comprised active pharmaceutical ingredient (API) and 3 common pharmaceutical excipients. For the first time, it was shown that the technique is largely insensitive to the amount of material held within the capsules. A single calibration model was developed using capsules of one fill weight, 100 mg, to a relative error of typically <3%. This model was then used to predict API concentration of capsules with varying fill weights (100–400 mg) and different shell colours. The relative root mean square error of prediction of the concentration of API for the main sample set (nominal content 75% (w/w)) was 1.5% with a 5 s acquisition time. The quantity of API was also predicted using the same model for capsules prepared with different generations of API (i.e., API manufactured via different processes) with a relative error within ~3% indicating a high degree of robustness. The study suggests that there could be significant benefits for the pharmaceutical industry to using this approach; both in terms of resource requirements from method development and maintenance but also in terms of validation and regulatory activities.

2.2. Quantification of polymorphs in pharmaceutical formulations

Recently, Aina et al. [35] demonstrated the ability of transmission Raman spectroscopy to quantify the polymorphic content of pharmaceutical formulations. This study represents another step on the way to establishing this emerging analytical technique as a practical tool in the area of process and quality control, as the quantification of polymorphs (crystalline structure) is of particular importance. It cannot be accomplished using traditional HPLC methods that rely on dissolution of sample and therefore involve associated loss of information on the polymorphic form within the original formulation. Alternative methods such as X-ray diffraction, NMR or differential scanning calorimetry suffer from limited sensitivity, complexity with safety management or long data acquisition times. In the study, flufenamic acid, a non-steroidal anti-inflammatory drug, was used as a model compound. The transmission Raman method was shown to provide a true bulk measurement of the composition, in a sharp contrast with conventional backscattering Raman method which provided unsatisfactory results due to a severe sub-sampling problem. For a model-free fit, the transmission Raman method yielded R^2 of 0.996 compared to the backscattering value of 0.802; for a partial least squares fit with a single component the TRS method accounted

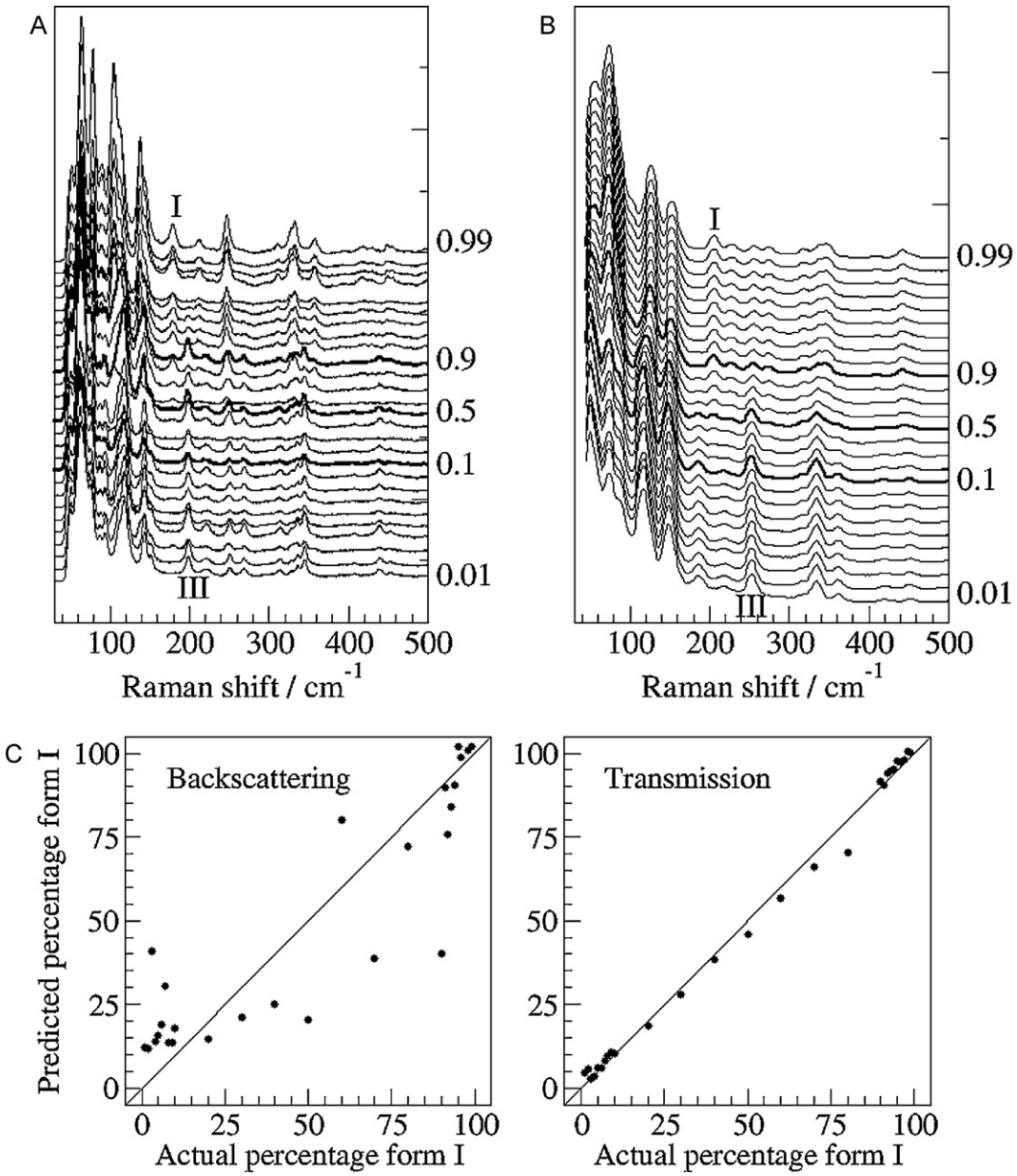

Fig. 7. Raman spectra of two polymorphic mixtures of flufenamic acid collected in (A) backscattering and (B) transmission geometry. Signature peaks for forms I and III are labelled. Composition (mole fraction of form I) is given on the right, spectra for 0.1, 0.5, 0.9 mixtures are in bold. The Raman spectra were recorded on different instruments with different spectral resolutions; full width at half maximum of the phenyl peak is 7 cm^{-1} for transmission mode and 4 cm^{-1} for backscattering). (C) Results of PLS analysis (validation plot, all data) for transmission and backscattering data.
Aina et al. [35], /http://dx.doi.org/10.1039/C0AN00352B – reproduced by permission of The Royal Society of Chemistry).

for 98.09% of the variance in the data compared to 89.65% for the backscattering method (see Fig. 7).

The study also looked at the likely cause of the variability of the backscattering spectra associated with a sub-sampling issue. A series of 20 spectra were recorded on different areas of polymorphic form I, form III and the 50:50 mixture using conventional Raman spectroscopy. For mixtures, the reproducibility of the measurement was expected to be considerably lower and the standard deviation of the measurement higher. Indeed much higher standard deviation was observed for the 50:50 mixture compared with the pure forms clearly indicating the presence of a sub-sampling problem. It was therefore concluded that the use of a Raman microscopy in conventional backscattering geometry, and the associated small sample volume, is not appropriate for accurately measuring the composition of bulk samples, even when great care is taken to reduce lateral sub-sampling problems, e.g. by co-milling samples prior to measurement to facilitate thorough sample mixing and by rastering the laser over a 50 $\mu m \times 50\ \mu m$ area.

Further scrutiny of the Raman spectra also revealed a systematic trend in which more of the spectra captured using the backscattering geometry resembled form III than form I. This systematic over-sampling of form III was suggestive of surface segregation of the mixed samples. Such surface segregation was confirmed by scanning electron microscopy (SEM) demonstrating that co-milling led to a greater size reduction of form III than form I. Crucially, the transmission Raman spectroscopy overcame all these issues by more effectively sampling the volume of the tablets.

In a recent study Fransson et al. [36] investigated the accuracy of the quantification of pharmaceutical tablets with transmission Raman spectroscopy as a function of the type of chemometric

method used to analyse data. Several multivariate approaches were investigated including partial least squares (PLS), multivariate curve resolution (MCR), classical least squares (CLS), curve fitting and peak ratios were included for comparison. MCR, CLS and PLS gave comparable results with relative prediction errors for an independent test set in the range of 2.4–3.4%. Curve fitting and peak ratios gave higher prediction errors, typically around 4 and 6%, respectively. The study also noted that the number of samples and concentration levels needed for calibration could be reduced down to four or even two without any major increase in prediction error. This effect was attributed to a higher chemical selectivity of Raman spectroscopy. For PLS, MCR and CLS, the use of very few samples and concentration levels shows the potential for making lean and rapid calibrations, using transmission Raman, early in the development of pharmaceutical formulations. With PLS data processing there is the added benefit that the selective Raman spectra coupled to a calibration model with few components results in easy to interpret loadings. For CLS, MCR and the curve-fitting methods, the interpretation is always straightforward since they use, or obtain, spectral components of pure drug substance and excipients.

2.3. Sample presentation and calibration transfer

Sample presentation can be a critical issue when applying spectroscopic techniques to solid formulations. This is a well studied issue with NIR spectroscopy [37]. In this context, the robustness towards sample presentation was investigated for both transmission and backscatter Raman geometries by tilting a tablet in the sample well by Sparen et al. [38]. The results demonstrate that a slight or moderate tilt does not have any significant effect on the predicted concentration, nor does turning the tablet upside down. However, when a heavy tilt is imposed the predictions can be severely affected. Similar results were obtained for backscattering mode concluding that the sample presentation can be considered to be robust in both the transmission and backscatter geometries.

Calibration transfer has also been extensively studied for NIR absorption spectroscopy [39–43]. With this method elaborate means are often needed to ensure accurate and precise performance after transferring a qualitative or quantitative calibration from one instrument to another. This desire is driven by global nature of manufacturing where a single drug can be manufactured at several sites across the world. In a feasibility study performed by Sparen et al. [38], the effect on the accuracy of quantification was investigated when transferring a calibration developed on one Raman instrument to another. Predictions from spectra measured on the second instrument, using a calibration developed on the first device, gave large prediction errors, mainly consisting of a bias. Applying a spectral pre-treatment, however dramatically reduced the prediction error. The feasibility study indicates that calibration transfer techniques, which are well established for NIR spectroscopy, may be directly applicable to Raman spectroscopy although more work is needed in this area.

3. Conclusions

A combination of the benefits of transmission Raman spectroscopy: the ability to yield highly chemical specific information, the ability to probe water containing samples and the ability to obtain quantitative volumetric data from thick and highly turbid samples, unlocks a range of new applications in pharmaceutical settings. These include rapid volumetric quantification of API/excipients and of polymorphs within intact tablets and capsules or powders. Perhaps most importantly, the technique is experimentally straightforward and can be combined with the existing multivariate techniques.

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