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Infrared imaging of laser-induced heating during Raman spectroscopy of pharmaceutical solids

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Abstract

Raman spectroscopy is finding increasing popularity as an analytical technique for the analysis of pharmaceutical powders and solid dosage forms. It is well known that illumination by the high intensity lasers used in Raman spectrometers can result in sample heating, however, the extent of the problem has not been assessed for pharmaceutically relevant materials. Using direct thermal imaging of compressed powders, the extent of heating for microcrystalline cellulose (MCC), vanillin, ibuprofen and stearic acid was measured as a function of laser intensity. MCC was found to be the most susceptible to sample heating while ibuprofen was least sensitive. At high laser powers (1.5 W), samples were heated by between 38 and 60 °C while at more moderate laser powers (0.7 W) the degree of heating was between 20 and 30 °C. The kinetics of the heating process were mathematically modeled for MCC and the derived constants were used to predict the rotation speed necessary to prevent a solid state transition in a heat sensitive compound, theophylline monohydrate. Experimental measurements at different rotation speeds verified that the estimated rotation speed reduced sample heating by the desired amount. In conclusion, the extent of heating is clearly of some concern for pharmaceutical materials but can be substantially reduced by sample rotation.

Keywords: Laser-induced heating; Raman spectroscopy; Infrared imaging; Pharmaceuticals

1. Introduction

Sample heating is widely recognized as a potential problem in Raman spectroscopy [1]. Various approaches have been taken in order to try and measure the extent of heating including monitoring of phase changes known to occur at a specific temperature and comparison of Stokes and anti-Stokes ratios [2,3]. The extent of heating appears to be variable and very dependent on both sample and experimental conditions. However, it is apparent that significant temperature rises can occur when using moderate laser powers, for example temperature rises of 50–100 K have been reported for samples at laser powers of around 300 mW [2,3].

Raman spectroscopy is finding increasing application in the field of pharmaceutical analysis [4]. Sample heating in materials of pharmaceutical

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interest may be particularly undesirable for a number of reasons. Drug substances are particularly prone to polymorphism and pseudopolymorphism (the inclusion of solvent molecules in the crystal lattice). Increasing the sample temperature may result either in a change in polymorphic form or a loss of the solvent molecule. In either case, the resultant spectrum will not be representative of the starting material which is unacceptable within a regulated environment. Further negative effects of sample heating also include the potential for sample degradation, melting of crystalline samples and recrystallisation of amorphous material. Some of these effects have been noted for pharmaceutical materials [5].

To our knowledge, none of the studies which have probed sample heating have investigated pharmaceutical materials to date. Indeed very little work appears to have been done in general on organic compounds, although many organic compounds have some absorptions at 1.064 μm and will, therefore, be susceptible to laser induced heating [1,6]. Moreover, the magnitude of the reported temperature increases at relatively low laser powers for other samples suggests that there is a need to assess the extent of heating in pharmaceutical materials. The aim of this work was to investigate sample heating in Raman spectroscopy using a number of model compounds which are representative of active pharmaceuticals and excipients. For this purpose two aromatic compounds, vanillin and ibuprofen were chosen as models of drug substances whilst stearic acid and microcrystalline cellulose (MCC) were selected as examples of excipients. Initial attempts to use the substance melting transition to monitor heating were found to be experimentally challenging, due to flow of the sample on melting with resultant loss of spectrum quality. Likewise, it was not possible to estimate the temperature rise from a ratio of the Stokes and anti-Stokes radiation due to poor sensitivity in the anti-Stokes spectral region. An alternative method would be to directly measure the temperature of the sample upon exposure to laser radiation using thermal imaging, a technique which has been applied successfully in many research fields, such as for medical applications [7]. However, to the authors knowledge, this method has not been used previously to monitor sample heating in Raman spectroscopy. Using this approach, we were able to monitor temperature changes in sample compacts as a function of laser power. Experimental models were developed for the different samples studied and the extracted empirical constants used to predict the degree of heating for additional samples. The model was validated using theophylline monohydrate, a compound known to be sensitive to laser induced heating [5]. The model was able to correctly predict the minimum sample rotation speed needed in order to avoid a heat-induced solid state transition.

2. Materials and methods

2.1. Materials

Stearic acid ($C_{18}H_{36}O_2$) came from Witco Corp. (Memphis TN), MCC $(C_6H_{10}O_5)_n$ was obtained from the FMC corporation (FMC Europe NV, Brussels), ibuprofen ($C_{13}H_{18}O_2$), vanillin ($C_8H_8O_3$) and theophylline monohydrate ($C_7H_8N_4O_2 \cdot H_2O$) were supplied by Sigma Chemical Company (St Louis, MO).

2.2. Methods

2.2.1. Thermal characteristics of the model substances

Using a Mettler Toledo 820 DSC system, the onset melting points of ibuprofen, vanillin and stearic acid were determined to be 75, 82 and 56 °C, respectively, using a heating rate of 10 °C min^{-1} and crimped aluminium sample pans. MCC according to the literature does not melt but undergoes charring at 260–270 °C.

2.2.2. Measurement of laser induced sample heating

Sample heating was investigated using a Biorad FTS 575C infrared/Raman spectrometer (Cambridge, MA, USA) equipped with a Nd:Yag laser operating at 1.064 μm (Spectra-Physics) and a liquid nitrogen-cooled germanium detector. For the experiments with the infrared camera, the

sample compartment collection optics and the sample compartment lid were removed. Samples, in tablet form, were mounted in a holder and the laser was deflected onto the sample by a gold plated mirror. The optical path length was similar to that experienced by the sample during routine data acquisition. An Agema 570 elite (FLIR Systems, Danderyd, Sweden) infrared camera was used to measure the laser induced temperature increase. The temperature accuracy of the camera was $\pm 2\%$. The camera was positioned normal to the tablet surface.

Flat 13 mm diameter tablets were prepared using a Perkin–Elmer hydraulic press. 600 mg of substance was subjected to a load of 3, 6.5 or 10 tons for 60 s. Thermographic images of the tablets following exposure to laser radiation were collected during two sets of experiments. Firstly, the laser power was raised in steps, starting from 300 mW with a stepsize of 100–200 mW. An image was collected at each laser power with the sample being allowed to reach thermal equilibrium prior to image collection. When the laser power was raised, the laser beam was blocked from the sample in order to avoid unnecessary heating. In the second set of experiments, the laser power was set to a fixed level and images were collected at 1 s intervals. After around 40 s, the laser was turned off and the cooling was monitored. This experiment was performed using at least two laser powers for each sample, 500 mW and a higher laser power, which was sample dependent.

The temperature scale of the thermal camera was calibrated for each sample. The tablets were placed in an oven, the temperature was monitored by means of a thermocouple and a thermal image was collected for each sample at 5 °C intervals. There was a linear correlation between the temperature recorded by the camera and the actual sample temperature, enabling calculation of a correction coefficient using linear regression analysis (R^2-values between 0.998 and 0.999 for the four different samples). An emissitivity value of 0.98 was found to be representative for all samples according to the calibration.

2.2.3. Spectral data acquisition

Spectra were acquired at a resolution of 4 cm^{-1} using the BioRad system described above. Spectra were obtained from tablets of theophylline monohydrate that were rotated at 0, 5, 10 or 25 rpm. The number of spectra collected varied so that the exposure time to the laser differed.

3. Results

Thermographic images of the samples with different constituents and compression forces, were recorded. In Fig. 1, an example of a thermographic image of an ibuprofen tablet is shown. The scale bar to the right shows the temperature scale within the image. The laser was focused to a beam diameter of about 0.5 mm close to the center of the tablet. As can be seen, the temperature at the laser illumination point was more than 50 °C using 1500 mW laser power for 35 s and this central area is termed the hot spot. Closer to the tablet edge, the tablet is still heated to about 30 °C, indicating that heat has been transported from the illumination point by heat diffusion (ambient temperature was 22 °C).

Heating as a function of laser power was investigated and is compared with the different compounds in Fig. 2. The temperature was retrieved from the hot spot in each recorded image. As can be seen from Fig. 2, the temperature at the hot spot shows a linear relationship with the laser power in all four cases. Moreover, each compound is heated to a different extent by the laser with the heating being most pronounced for MCC whilst ibuprofen is least affected.

The kinetics of the laser-induced heating was investigated in a second series of measurements. Thermographic images were recorded for the samples at time intervals of 1 s. First, the camera was started and, a few seconds later, the laser was switched on to monitor the heating process. After typically 40 s, the laser was switched off and the cooling process was monitored. Fig. 3 displays a typical heating profile where it can be seen that heating is initially rapid before approaching an equilibrium value. On removing the laser illumination, cooling is likewise initially rapid. The onset

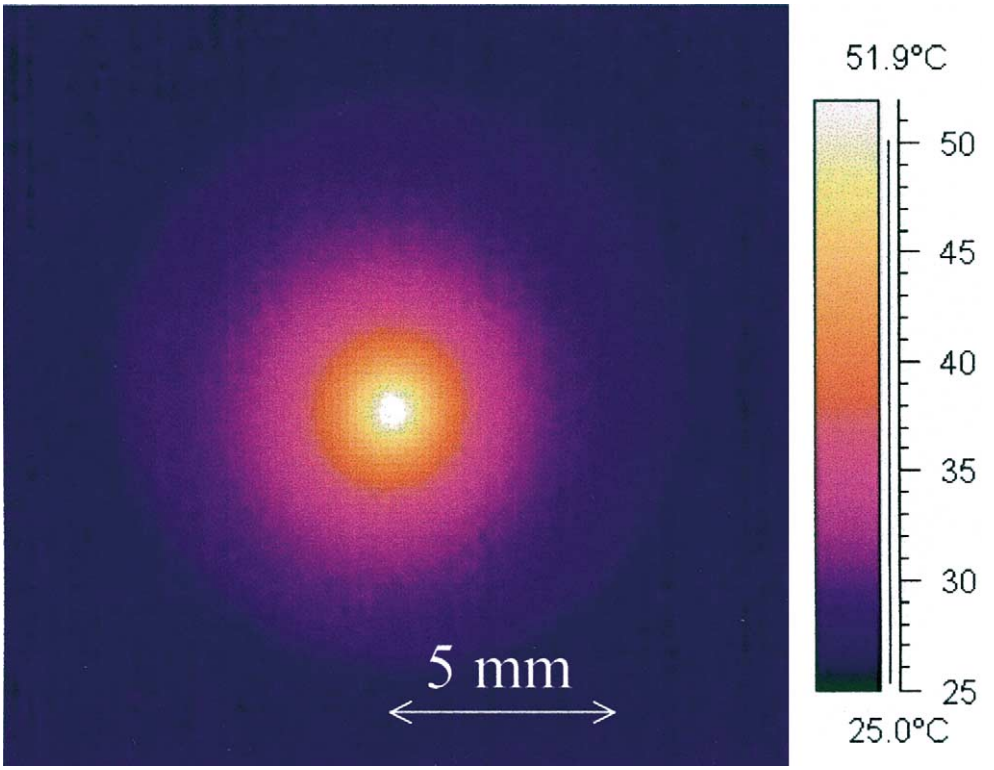

Fig. 1. Thermographic image of a 13 mm diameter ibuprofen tablet. The laser power was 1500 W and the laser duration was 35 s.

and termination of laser illumination is indicated with the notation a and b, respectively. Again, the displayed temperatures represent the hot spot of a complete recorded image. The data were fitted to an empirical function:

$$T = k_0 + k_1\sqrt{t} + k_2\left(\frac{1}{\sqrt{t}}\right) \quad (1)$$

where T (°C) is the temperature, t (s) is the time and k_0, k_1 and k_2 are fitted constants. The values for the best fit are shown for the four different samples in Table 1. Also included are the standard deviation of the fitting residual for each sample. As can be seen in Table 1, the agreement with the empirical function was good with very low fitting residuals. For the data shown in Table 1, the laser

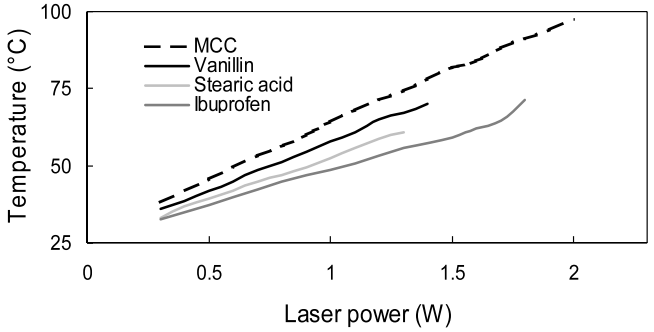

Fig. 2. The tablet temperature at 30 s exposure at different laser powers. The temperatures are the maximum values within each recorded image.

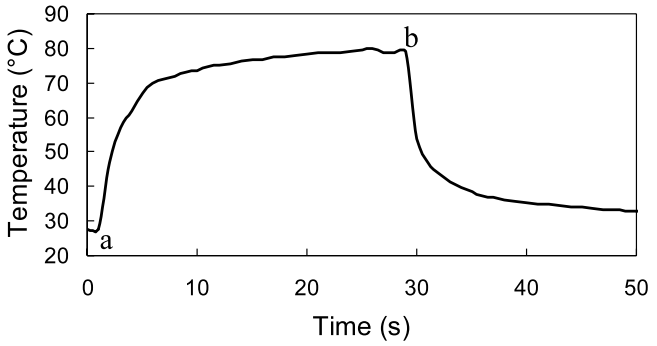

Fig. 3. An example of a heating/cooling kinetic profile. The laser was turned on shortly after the camera started recording (denoted a) and was switched off after about 30 s (b). The sample was a MCC tablet pressed with 6.5 tons and the laser power was 1800 mW.

power was 500 mW and the compression force was 6.5 tonnes. The same calculations were also performed for three different tablet compression forces, 3, 6.5 and 10 tonnes for ibuprofen tablets. The heating profiles of ibuprofen tablets using 1500 mW of laser power are displayed in Fig. 4. As can be observed, the heating profiles depend on the compression force with a faster and greater extent of heating for the tablet with the lowest compression force.

The heating kinetics reported above were studied by recording the temperature at the hot spot as a function of time. An alternative approach is to utilize the spatial information available from the IR images i.e. study the spread of heat outwards from the point of illumination. An example of this is shown in Fig. 5, where the temperature profile across tablets composed of the four model substances MCC, vanillin, ibuprofen and stearic acid are shown. The corresponding images were recorded after 40 s laser exposure to allow a substantial heat diffusion within the samples. As can be observed, the profiles from each samples differ in shape, indicating a variation in heat diffusion from the illumination point. For example, in the case of ibuprofen, the heat diffusion is comparatively efficient resulting in a broad heating profile, whereas for MCC it appears to be less efficient, resulting in a more intense localized heating of the sample. For the latter sample type, there is a higher risk of damage to the sample during Raman analysis because of the less efficient cooling of the heated area. There is probably also a correlation between the ability of the sample to disperse heat and the maximum temperature reached at the hot spot. Thus the samples which have the broader heating profiles also are heated to a lower extent (ibuprofen and stearic acid), whilst those with the sharper profile are also heated the most (i.e. MCC and vanillin).

Table 1
Numerical constants derived from the empirical heating profile Eq. (1), including one standard deviation of the fitting residual

Substance	Laser power (mW)	k_0	k_1	k_2	S.D. of residuals (°C)
Stearic acid	500	34.3	0.68	−6.07	0.15
	1000	38.4	1.48	−10.83	0.16
Ibuprofen	500	33.8	0.61	−7.46	0.15
	1500	48.7	1.44	−22.68	0.34
Vanillin	500	43.0	0.13	−16.18	0.21
	1200	62.2	0.27	−30.95	0.28
MCC	500	52.5	−0.73	−22.43	0.45
	1800	106.0	−1.97	−75.33	0.52

The compression force was 6.5 tonnes.

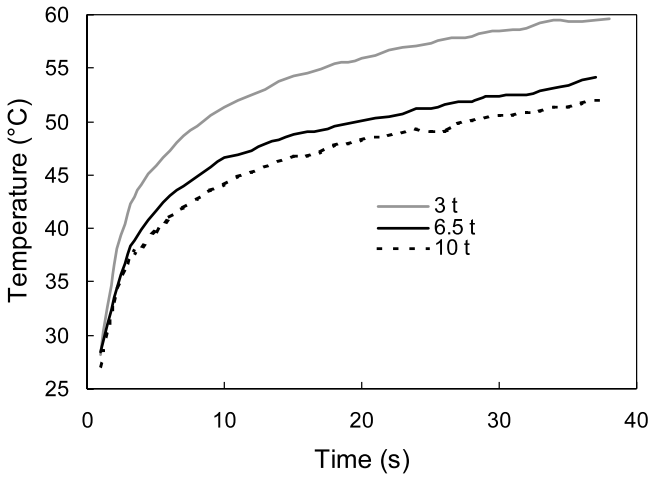

Fig. 4. The effect of compression force on the heating profile. The sample was an ibuprofen tablet and the laser power was 1500 mW.

Many pharmaceutical compounds undergo severe changes when exposed to heat, changes that can be recorded using Raman spectroscopy. In order to illustrate this problem, a theophylline monohydrate tablet was exposed to 1000 mW for 20 min. while Raman spectra were continuously recorded. A selected set of Raman spectra together with a spectrum of anhydrous theophylline, are shown in Fig. 6a. The effect of the excitation laser is clearly shown in the transformation of the spectrum towards a more anhydrous-like spectrum. Although the exposure time is fairly long (20 min) it should be pointed out that the laser spot is comparatively large, ~0.5 mm in diameter, which is substantially larger that most other systems. Thus, the power density of the Raman system is still fairly low even for 1000 mW laser exposure.

One way to avoid or reduce the sample heating is to move the sample during laser exposure, as previously reported in the literature [8]. In order to illustrate the benefit of moving the sample, another set of spectra were recorded from a rotated tablet of theophylline monohydrate. According to the literature, the transition from hydrate to

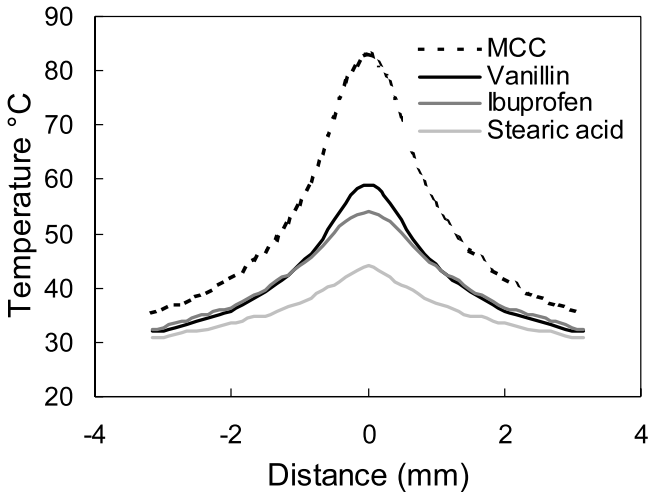

Fig. 5. Spatial heating profiles of MCC, vanillin, ibuprofen and stearic acid obtained after 40 s laser exposure.

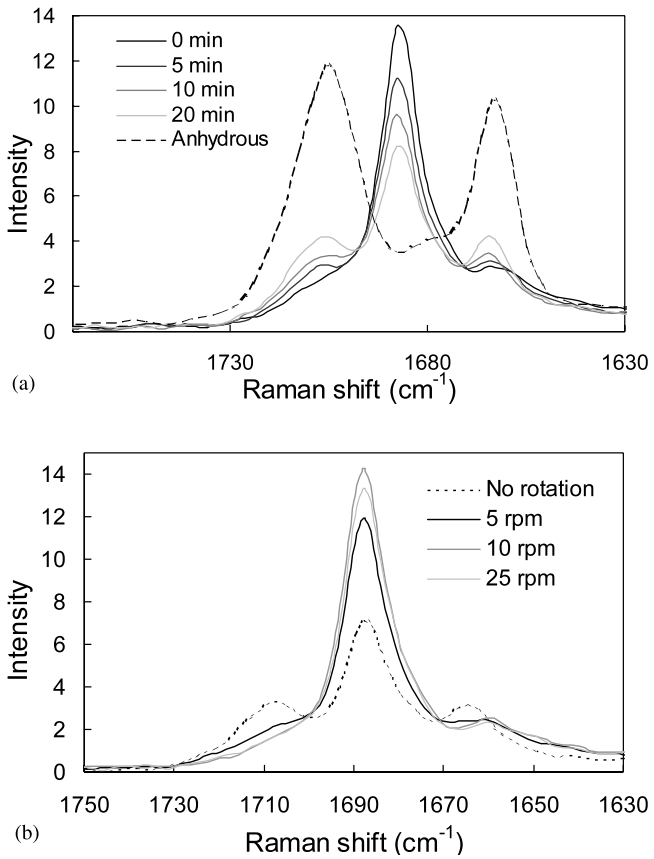

Fig. 6. (a) Spectra of theophylline monohydrate tablet collected over 20 min. using a laser power of 1000 mW compared with a spectrum of anhydrous theophylline. (b) Spectra of theophylline monohydrate tablet rotated at 0, 5, 10 and 25 rpm with a rotation diameter of 8 mm using a laser power of 1000 mW. The laser exposure time was 20 min.

anhydrate has an onset temperature of 45 °C [9]. Prior to the experiment, calculations were performed to establish a sufficient rotation speed to avoid sample dehydration, i.e. the rotation speed necessary to prevent the sample temperature reaching 45 °C. This was done using (Eq. (1)) and coefficients k_0, k_1 and k_2 corresponding to MCC, which was considered as a worst case. These were: $k_0 = 106$, $k_1 = -1.97$, $k_2 = -75.3$. The rotation diameter was set to 8 mm. The laser spot was approximated to a sharp circular area with a uniform laser power rotating around the front face center of the tablet. Assuming that heating occurs during laser exposure of a particular point at the tablet surface and cooling for the rest of the rotation cycle, a rotation speed of 8.4 rpm was calculated as being necessary to prevent the sample temperature rising to more than 45 °C. In a series of experiments, Raman spectra were recorded for theophylline monohydrate using sample rotation speeds of 5, 10 and 25 rpm,, as well as for no sample rotation. The corresponding spectra, shown in Fig. 6b, show a spectral feature at 1710 cm^{-1} indicative of an anhydrate transition. The 1710 cm^{-1} peak is clearly present in the case of no rotation and 5 rpm rotation while for a rotation speed of 10 rpm and higher the peak can not be found. These data support the validity of the

calculations, which suggested that a rotation speed of at least 8 rpm was necessary to avoid heating the sample to above the dehydration temperature.

4. Discussion

The heating of pharmaceutical solids during Raman spectroscopy has been investigated by means of a rather direct approach namely thermographic imaging. The infrared camera is sensitive in the spectral region between 7 and 13 μm. Since the laser emits at 1.064 μm, only the black body radiation from the samples was imaged by the camera. The use of direct imaging of sample temperature has obvious advantages. First, it provides spatial distributions of the temperature within the sample matrix. With heterogeneous samples such as pharmaceutical tablets, the spatial distribution takes into account that different excipients heat to a different degree. The importance of spatial distribution is discussed further below. Secondly, in thermographic imaging the IR response is linear with the sample temperature, which facilitates true quantitative measurements across a broad temperature region. Using the Raman signal from phase transitions of the excipients, only qualitative information can be attained. The use of temperature-sensitive additives has been reported in the literature [3], however, this approach suffers from possible perturbation of the sample heating properties, it can not be used for intact samples and is not feasible in a regulated production environment.

In this study we have investigated compacts of pure materials in order to facilitate the experimental measurements. However, realistically many samples will be presented to the laser in the form of powders. From our observations on the effect of compaction pressure on the extent of heating in the tablets, we would predict that heating would be much worse in powders as compared with compacts. Tablets compacted at a lower pressure experienced more heating than those produced at higher pressures (see Fig. 4). This can probably be explained by considering the porosity of the different samples since any air present between particles can act as an insulator and prevent heat dissipation. Thus under high compaction pressures, there is little void space filled with air and more particle–particle contact allowing conduction of heat. In contrast, for powders, there will be many more void spaces filled with air and thus it would be anticipated that heating would be both more pronounced and localized.

A considerable difference was noted between the various materials, in terms of their sensitivities to laser induced heating. This is probably due to a number of factors. Thermal conduction within each compact will vary depending both on the chemistry of the material and the mechanical properties of the powders, which will in turn influence the nature of the compact formed. Furthermore, the absorption of the laser will be dependent on the chemistry of the compounds which, although all organic, varies considerably between the test compounds including aromatic groups, a long hydrocarbon chain or an aliphatic compound with numerous hydroxyl groups. Interestingly, MCC, which contains numerous hydroxyl groups, is most sensitive to heating. Other factors, which are probably also influential, include the optical properties of the sample matrix, such as the light scattering coefficient.

Pharmaceutical tablets generally contain a number of components fulfilling different functional roles and the drug substance may only form a small proportion of the total. In such instances, it may not just be the tendency of the drug substance itself to heat on exposure to the laser which is important, but also the heating tendency of auxiliary ingredients since these may serve to transport heat to the drug. Indeed, it has been pointed out the substances in a matrix will be influenced by the matrix material [3]. It is, therefore, pertinent to point out that MCC, which was found to be most sensitive out of the model compounds to heating, is a very widely used ingredient in tablets.

The benefit of rotating samples as to avoid subsampling from non-representative loci within samples has been reported previously [10]. It was also reported in this publication that sample rotation will lower the problems associated with sample heating. In this report we provide an estimation of the extent of sample rotation necessary to avoid

sample heating. By using the empirical (Eq. (1)), it is easy to calculate the sample heating for a given movement of the sample. The material constants k_0, k_1 and k_2 can be approximately retrieved from the comparison of the four different compounds and the three different compression forces used in this report. Furthermore, the heating possesses a linear relationship with laser power. Thus, well chosen values of experimental parameters can be estimated for non-heating Raman spectroscopy of a different but similar substance. In the case of theophylline monohydrate, a rotation speed of 8 rpm was estimated to avoid temperatures higher than 45 °C for 8 mm rotation diameter. This calculation was also confirmed experimentally. Using a different laser the calculations have to be corrected for the laser focus profile. This presents a potential source of error since we here assume an even intensity distribution across the laser focus. In reality, the laser focus is at best Gaussian shaped and in most cases obscured by a diffraction pattern with microscopic hot spots. The laser focus spatial distribution is certainly instrument-dependent and that has to be taken into account when calculating the sample heating.

5. Conclusions

Sample heating following exposure to laser irradiation has been measured for a number of pharmaceutically relevant materials and found to both significant and linearly related to the laser intensity. The extent of heating was found to be dependent on the both the substance measured and factors related to sample presentation. The kinetics of heating could be mathematically modelled and used to predict the rotation speed necessary to minimize heating for an unknown sample. The results of this study suggest that potential heating of pharmaceutical samples during Raman analysis must be taken into consideration but can easily be minimized by sample rotation.

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