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Limiting Sample Damage in Laser Diagnostics

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Declaration

All experimental data was collected and analysed ourselves, using Spectrum, and Renishaw WiRE to measure and record spectra from tablets. Any other data from other sources is referenced. Experimental work, analysis and interpretation was divided equally between us; for a detailed guide to the division of labour between the four people involved please refer to the one page summaries of individual contributions which have been written separately to this report.

Contents

Acknowledgements

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Abstract

Tests conducted comparing the effect exposure of Paracetamol to a laser with oven heating a sample to a temperature above its melting point, $169^{\circ}C$, showed similarties. This implies that the primary cause of sample damage during Raman spectroscopy is heating. It was found that inserting a piece of glass between the sample and the microscope lens dramatically reduced the ability of the laser to damage samples. Computer models indicate that rotating a sample at 8 rotations per minute could be an effective method of limiting sample damage, and is a potential alternative to active cooling if this becomes financially and logistically viable in industry. Active sample cooling was investigated, but results proved inconclusive. This is a key area for any future research on the topic.

1. Introduction

The use of pharmaceutical drugs and medication is common place in modern society. Their extensive use requires the companies selling them to be confident in what they are producing. This requires the ability to test the chemical compositions of the products for quality control purposes.

The current favoured method of quality control testing is Raman spectroscopy; preferred for its non-destructive capabilities. This is used to map the composition of tablets. Currently, the quality control system used in industry is to remove one in every few hundred tablets from the production line, test its chemical composition using Raman spectroscopy, and then return it to the production line. However, it would be highly favourable for the manufacturers to test the composition of each tablet to ensure correct dosage and maintain high quality of product being produced.

In order to test the highest possible percentage of tablets, spectra must be taken quickly. To achieve this, a large amount of light must be incident on a tablet. The simplest way to do this is using moderately high powered lasers. However, if the laser is too powerful, it can damage the sample, rendering both the spectrum taken and tablet useless. This trade-off between the speed of collection of a spectrum, and the possibility of damaging samples is problematic in industry to companies such as Renishaw, a leading producer of Raman spectrometers, as pharmaceutical manufacturers want to be able to perform these analysis techniques efficiently and for the least possible cost. The subsequent benefit of this, to the pharmaceutical industry, is cheaper and more reliable product testing, whilst ensuring a higher standard of quality and, therefore, a safer and more effective product.

Therefore the project is concentrated on two aspects:

1. Ascertain why pharmaceutical products are damaged when high power laser light is incident upon them.

2. Find a way to reduce and stop this damage, whilst still allowing a high amount of light to reach the sample, such that it can be implemented alongside current Raman spectroscopy testing techniques.

To solve the issue of sample damage, it is first necessary to understand what is causing the pharmaceutical products to burn, or change their chemical structure.

This project aims to investigate the first part of the brief by looking at why pharmaceutical products burn or change their chemical structure through the difference between 'oven' heating and localised heat from a laser, with respect to the damage it caused the sample in order to understand the mechanisms which caused the degradation. This was done by using a near infrared laser and a heating stage, acting as an 'oven', and comparing the results to a sample irradiated by a 488nm laser.

Once the reasons behind this had been identified, the project went on to look at ways of reducing this effect: firstly, by experimentally exploring the cooling of the sample environment, and therefore the sample, when taking the spectrum; and, secondly, by running computer models to simulate the rotation of a sample during the testing procedure.

2. Theory & Background

2.1 Sample Testing in Pharmaceuticals

Traditional methods of analysing the chemical composition of pharmeceutical products often subject samples to crushing, dissolution and separation [1]. This means that the testing methods are time-consuming, labour-intensive and ultimately destructive. Therefore there is a growing need within the industry for fast, simple and non-destructive analysis of the products [2]. For example, in quality control, information is needed rapidly and non-destructively to identify the chemical composition of the products, dictated by the practical requirements of production lines where it must be obtained both efficiently and without wastage.

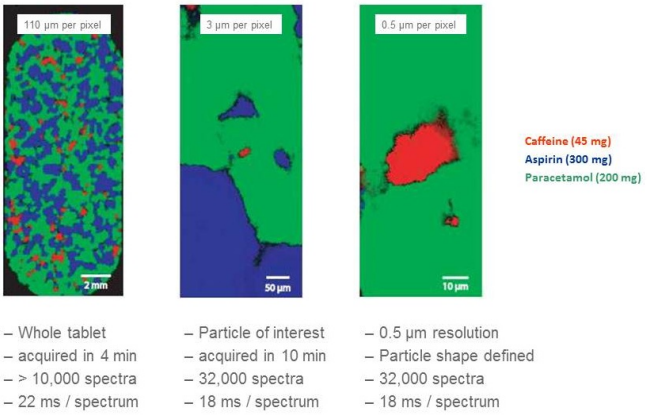


Figure 1: *An example showing the mapping of an Anadin tablet at three different scale sizes. Generated from StreamLine images with 785nm excitation, provided by Renishaw.*

There are several analytical methods which use non-invasive techniques to probe a sample; the most effective are spectroscopy techniques as they are both simple and fast [3]. Of these, Raman spectroscopy is the most popular as it requires virtually no sample preparation whilst producing spectra that provide a large amount of relevant information [1], this means it is possible to take Raman spectra of pharmaceutical products as they are still on the production line before they are packaged for distribution. There are alternatives such as X-ray or THz spectroscopy; however, these are currently not economically viable in industry [4]. Near infrared (NIR) spectroscopy or reflection spectroscopy (FTIR) can also be used non-invasively, but the information acquired is limited in comparison to Raman [5]. Consequently there is a growing interest in the use of Raman spectroscopy in the analysis of pharmaceuticals.

Figure 1 shows a mapping of an Anadin tablet using Renishaw's inVia Raman spectroscopy system. The combined images were taken over the course of 25 minutes and show increasing precision of mapping.

2.2 The Raman Effect

Raman Spectroscopy takes advantage of Raman scattering to analyse the vibrational and rotational transitions in molecules so that their chemical composition can be determined [6].

When light is incident upon a sample, photons are absorbed by an atom and excite the bonds in the molecule to a higher virtual energy state. By emitting a photon they then fall back down to a state whose energy differs from the initial state, shifting the emitted photon's wavelength either up or down. If the photon is emitted with less energy than the original, then the material absorbs energy, known as Stokes radiation; if the emitted photon is higher in energy, and the material loses energy, it is called Anti-Stokes radiation.

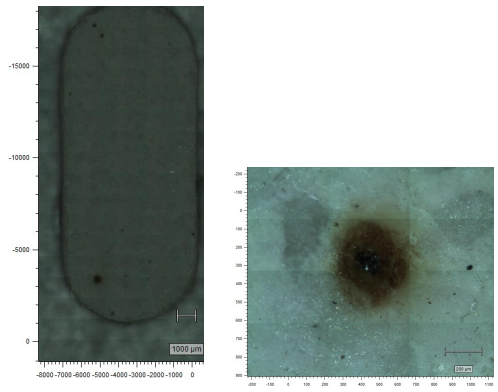
There are a number of aspects that affect Raman spectra of a tablet which can reduce the clarity and accuracy of determining the chemical composition of the sample. The temperature of the sample affects the peak structure seen in a spectra and at high temperatures the peaks corresponding to certain chemical bonds in the sample can be shifted in wavelength, reduced in height and even split due to vibrations in the bonds due to the increased heat energy [7].

2.3 The Industrial Process & the Issue of Sample Damage

Sample heating is widely recognised as a potential problem in the use of Raman Spectroscopy [8]. The current method of quality control within the pharmaceutical industry is to remove one tablet in every few hundred, test its chemical composition, and then return it to the production line. This method, however, only gives an average analysis on tablets, rather than on each individual product. It is employed due to the current industrial constraints on time and money; the process needs to run quickly, efficiently and inexpensively. The aim of the industry is to test the composition of each individual tablet to ensure the correct dosage of each product, not just a likely correct composition of the bulk. This would maintain a higher quality of product.

To achieve fast and accurate analysis high speed imaging is required. For this, there must be a large amount of light incident on a sample; this equates to using moderately high powered lasers producing around 100mW on the sample. The resulting laser power can, in some cases,

cause sample heating and localised damage sufficient to modify the sample structure or chemistry, making the spectrum collected meaningless and the tablet useless. It has been reported, in the testing of pharmaceutical tablets, that laser induced sample heating can significantly alter the make-up of the material being tested [9]. Therefore, the resulting spectrum is not indicative of the starting material, which is unacceptable in testing conditions. Figure 2 shows a Paracetamol tablet that has been damaged in Renishaw's testing procedure; it is possible to see the black scorch marks on the surface from burning caused by the laser.



(a) The whole tablet (b) The scorch mark

Figure 2: *An example of a damaged Paracetamol tablet, provided by Renishaw.*

Heating in pharmaceutical samples is therefore particularly undesirable. However, the amount this process heats the sample has proven difficult to quantify. It is variable from case to case and dependent on a number of factors; in particular, laser power, sample chemistry, and the efficiency of the heat dissipation through the surrounding medium [7]. Nevertheless, it is apparent that significant temperature rises can occur; for example, for laser powers close to 300mW there have been observations of temperature rises of 50 - 100K for the chemical ammonium nitrate, a white crystalline solid at room temperature [10].

2.4 Heat Transer

To be able to understand the effects of localised laser heating it important to understand how the heat moves through the sample. Heat is the transfer of energy in response to a temperature gradient [11]. It moves through a material according to Fourier's law [12],

$$\mathbf{q} = -k\nabla T \tag{1}$$

where $\mathbf{q}$ is the local heat flux density (the amount of heat energy which flows through a unit area per unit time), k is the material's thermal conductivity (how quickly the heat moves through a material), and ∇T is the gradient of temperature.

This shows that heat energy flows down the gradient of temperature; in other words, heat moves from hot to cold regions.

Combining Fourier's law, Equation 1, with the law of conservation of energy describes how thermal energy moves through a material [12]. This is the diffusion equation

$$\alpha_T \nabla^2 T = \frac{\partial T}{\partial t} \tag{2}$$

Where T is temperature, t is time, and α_T is the thermal diffusivity

$$\alpha_T = \frac{k}{\rho c} \tag{3}$$

The density of a material is ρ, and c is the specific heat. The thermal diffusivity gives the ratio of how quickly heat flows through a material to the ability of a material to store heat energy [12]. This can be taken to give a measure of how quickly a material will respond to temperature changes in its environment. A material with high α_T will respond quickly to any changes in environment, and quickly reach a new equilibrium condition, whilst a low α_T will cause a build-up in heat where any external change in temperature occurs.

2.4.1 Modelling the System Using the Diffusion Equation

The diffusion equation is an example of a partial differential equation. PDEs are a powerful tool for describing physical systems; however, they can be difficult to solve analytically; one analytical solution, the "fundamental solution", is found when temperature is a delta function at a known position at time $t = 0$. The solution to this is [13],

$$T(x,t) = \frac{1}{\sqrt{4\pi kt}} e^{-\frac{x^2}{4kt}} \tag{4}$$

Due to the precise conditions required to find an analytical solution, it is often more easily modelled using a computer simulation. A way to do this is via finite difference methods [14]; in such methods, functions are evaluated at discrete points in space and time. See Appendix A.

2.5 Sample Burning

There are many ways in which a material can be damaged when being exposed to a high energy laser.

The first of these is a phase change. When light is incident on a sample, it absorbs energy from the laser. The majority of this energy will be converted into heat, causing the sample to heat up, possibly to the point of melting or boiling.

Another mechanism which can cause damage is combustion, an exothermic chemical reaction between the sample and an oxidising agent; often oxygen from the air.

Photodecomposition is another possible cause of damage in samples. This occurs when chemical bonds are broken inside a material. If the energy of a photon of laser light incident on a sample is the same, or similar to that of a bond inside the target material, photodecomposition is much more likely to happen [15].

2.6 Sample Chemistry

The way that heat moves through a sample is also dependent on the chemistry of that sample. Pharmaceutical tablets contain not only the active drug, but also a coating on the outside of the tablet and often a bulking substance if only a small dosage of the active drug is needed. Therefore the response to heat of the carrier must also be taken into consideration, for example, the chemical microcrystalline cellulose, widely used in pharmaceutical tablets, is highly susceptible to heating due to exposure to laser light [16].

The porosity of a tablet will also affect how it reacts when laser light is incident upon it. Porosity is the ratio of volume of empty space to total volume in a material. The heat transfer equations for a porous solid are significantly more complex as the heat does not dissipate as evenly and the air pockets insulate areas inside the material [17]. The more porous a material is, the slower heat is transferred through it, which would translate to a higher localised temperature reached at the site the laser is incident.

This is analogous to the differences between tablets and powder; a powder will have many more air gaps between crystals than with a tablet, thus, hypothetically making it easier to damage (by the heat from the laser alone) than a tablet [16].

Depending upon the composition and chemical bonds in the sample, certain wavelengths of light will be absorbed more than others. The absorption of the electromagnetic radiation in the sample will also vary on both the chemical composition of the product being tested and the frequency of light being used.

2.7 Laser Theory & Optics

The wavelength and power of the laser used in experiments can dramatically affect the results.

When trying to limit damage to tablets, it is important to bear in mind the "penetration depth". This is a measure of how far light can penetrate into a material, and is defined by the depth at which intensity of radiation inside a material falls to $1/e$ of its original value. The Beer-Lambert law says that the intensity of an electromagnetic wave inside a material reduces exponentially from the surface [18]:

$$I(z) = I_0 e^{-\alpha_\lambda z} \tag{5}$$

Here, α_λ is the absorption coefficient, which can be described by [19]:

$$\alpha_\lambda = \frac{4\pi\kappa}{\lambda_0} \tag{6}$$

Where κ is the refractive index, and λ_0 is the wavelength of light in free space. This shows that absorption increases as wavelength decreases. Therefore, penetration depth will be lower with a shorter wavelength. If penetration depth is lower, then power from a laser is being concentrated into a smaller region of the target, so a high frequency laser beam will heat up a target more than a lower frequency laser would.

This means that an infra-red laser is less likely to burn a sample for a given laser power than a near-ultraviolet laser is.

In order to get a good output from Raman spectroscopy, it is very important to focus the sample correctly. Figure 3 shows the difference between a sharply focused, and unfocused laser beam. It is important to bear this in mind for any possible solutions to the sample damage problem.

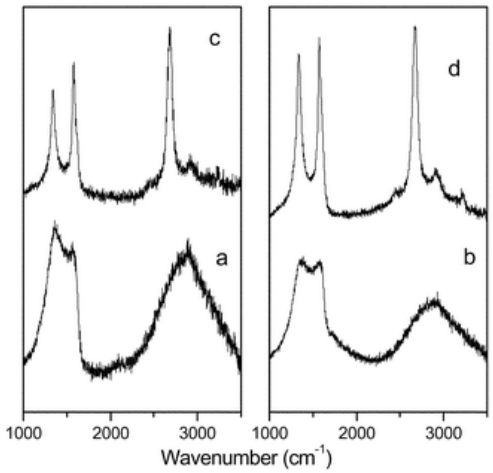


Figure 3: *An example showing Raman spectra for focused (top) and unfocused (bottom) laser beams [20]*

2.7.1 Fluorescence

If the wavelength of the laser corresponds to an electronic transition of either the sample or an impurity, there is a strong possibility that fluorescence will occur [8]. It is an additional source of noise where the peaks produced by fluorescence, in comparison to those from Raman, are often much stronger. Therefore, if present, fluorescence will act to mask the desired Raman signal and slow down the data acquisition, in some cases making it impossible to perform the Raman measurements.

Fluorescence is an issue in the use of Raman spectroscopy, as its presence can mean that there is no possibility of observing any Raman bands above the fluorescent background. The observation of fluorescence in the spectrum can be indicative of damage within the sample, if that fluorescence was not present before the irradiation. In addition, if a fluorescent spectrum is produced then the data collected is meaningless to the sample being tested, which is obviously not suitable in quality control processes.

2.7.2 Optics

Focusing the laser to a small point is important for the accuracy of Raman spectra, as shown in Section 2.7. Figure 4 is a diagram showing the difference between focusing a laser beam with thin and thick diameters. This clearly shows that if a laser beam has a thicker diameter, it is focused to a clearer, sharper spot. As the lasers used in this report are produced at around 1 *mm* in diameter, focusing this light can be a challenge.

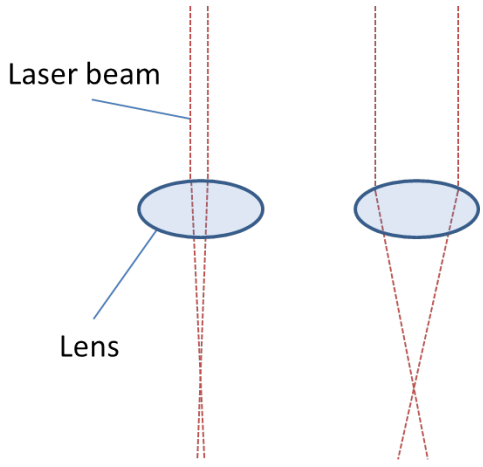


Figure 4: *Diagram showing the difference between focusing a beam of light with small diameter (left) and one with a larger diameter (right)*

The angle made between the normal to the lens surface and the laser beam (angle of incidence) is very small in the image on the left. In the image on the right of Figure 4, the angle of incidence is clearly greater than on the left. This allows the beam to be deflected more, and therefore a sharper focus is reached.

Due to the small beam diameter of a laser, when shone directly through a microscope lens, it is hard to properly focus the beam.

In order to erase this problem, a beam expander (a system of two lenses, as shown in Figure 5) can be used. This allows the entire microscope lens to be filled with laser light, giving a situation more simlar to that in the left hand diagram of Figure 4, and therefore a very sharp laser focus point.

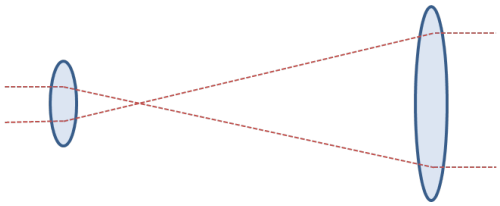


Figure 5: *Beam diagram showing how a simple beam expander works.*

3. Experimental

3.1 Sample Preparation

For the following experiments it was necessary to remove the outer coating of any pharmaceutical tablet being tested and create a flat, smooth side so that laser light could be correctly focused onto the surface of the sample. This was achieved using a scalpel to scrape the top bevelled side off the tablet and a fine sandpaper was then used to smooth this side down as flat as possible.

Experiments with powdered products required no specific preparation to the samples.

3.2 Initial Proposed Experiment

The following setup was designed and constructed to focus laser light from a 133mW DPSS laser onto any sample required; this experimental setup can be seen below in Figure 6.

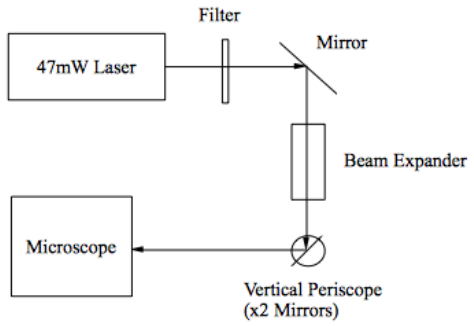


Figure 6: *Initial experimental design setup.*

The setup included a beam expander constructed from two plano-convex lenses (15.00mm and 150.mm focal lengths respectivly) to increase the beam diameter so that it completely filled the back aperture in the microscope objective lens. A vertical periscope was also constructed from two mirrors so that the beam could be correctly aligned into the microscope.

However, the original 133mW laser provided by Renishaw did not function once it had been set up and was instead replaced with a 47mW 532nm DPSS laser. After passing through the beam expander and other optics, shown in Figure 7, the 47mW laser, provided a maximum power on the sample of 11.3mW using a 50x objective lens. This produced a spot size with a diameter of 3 microns and thus gave a total power density of $400 \times 10^6 Wm^{-2}$ on the sample.

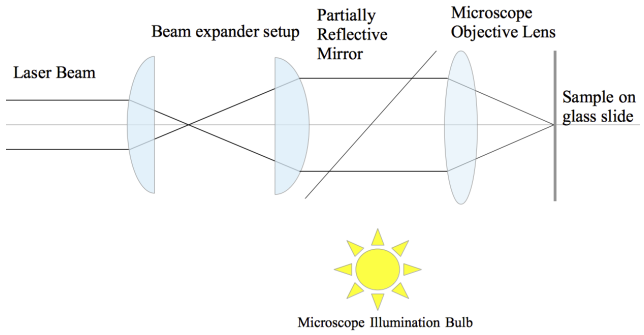


Figure 7: *Initial experimental design ray schematic (not to scale)*

After many experiments with the laser incident on samples of paracetemol and asprin in both powder and tablet form, for periods up to 30 minutes, no visible sample damage was seen on any sample.

3.3 NIR Laser Raman Spectroscopy

Due to the limitations of the designed experimental setup, alternative methods of obtaining relevant results had to be devised. A PerkinElmer RamanFlex 400 spectrometer, with a 350mW, 785nm, near infrared, diode laser, was used. The average observed power was measured to be 57.5W, when focused through the 50x/0.45 lens. Although lower than expected, was significantly greater than the observed power of the 532nm laser.

Despite this new system delivering a greater power onto the sample, this near infrared laser did not cause damage to any of the sample drugs - even when subjected to long exposures. In addition, photodecomposition is less likely to occur with this infrared laser due to the photon energy being inversely proportional to wavelength.

The main advantage of this experimental setup is that it allowed a direct comparison between samples under different conditions, and from the other experimental setups, without interfering with the results.

3.3.1 Investigating a Fixed Region

When investigating samples on different sets of apparatus, it was essential to ensure the same area of the sample was located when the sample was moved from one setup to another. Due to the highly collimated nature of laser light, the laser spot size was very small when focused through the microscope.

To easily identify the area being investigated, a thin cylinder of aluminium with a thickness of 1mm, a radius of 8mm with a hole of radius 0.3mm in the middle was crafted. This aluminium piece was fixed to a microscope slide with electrical tape. The sample could then be

crushed down to a fine powder, and brushed across the hole multiple times, until the hole filled up. Under the 50x/0.45 lens of the microscope, it was possible to identify a vertical and horizontal landmark round the edge of the hole, and align the crosshairs on these landmarks before focusing on the powder at the top of the hole. This is illustrated in Figure 8, where the crosshair is aligned with visible landmarks around the rim of the hole.

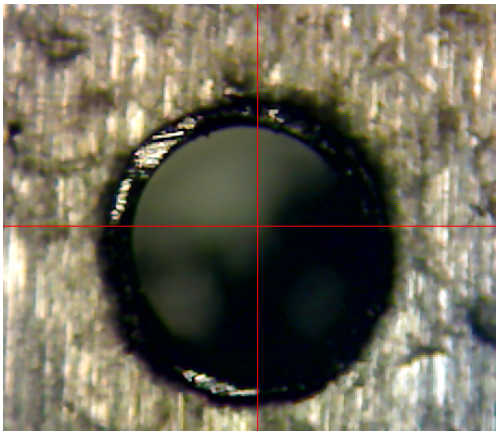


Figure 8: *An illustration of how the crosshairs were aligned with the hole to find the same region of the sample, when transferring between equipment.*

Although no visible sample damage was seen with the original laser setup, the chemical composition of the samples may be altered. To test for any changes, Raman spectra of the sample were taken using the PerkinElmer RamanFlex 400 spectrometer before and after exposure to the laser using the aluminium disc method outlined above. Even after exposure times of up to 15 minutes, no changes were seen between the spectra of aluminium or paracetemol before and after exposure. This shows that the 47mW 532nm laser does not provide a large enough power to damage samples and was therefore not used in any further experiments.

A spectrum was taken of the powder using the near infrared laser prior to it being transferred to a spectrometer with a 488nm visible laser attached. Due to this laser having a shorter wavelength than the infrared laser, its photons have higher energies and are capable of damaging the sample. Using the crosshairs of the microscope to relocate the previously identified landmarks, the same region of the sample was located. The sample was then exposed to the laser for a time period of 60 seconds. Immediately after the 60-second exposure the sample was returned to the NIR laser, as quickly as was possible, and the same region of the sample, within the aluminium frame was located. It was possible to take a new spectrum of the sample 90 seconds after the exposure to the laser. From this point, new spectra were taken every minute. These spectra of the sample, after it had been exposed to the 488nm laser, were then compared with the spectrum of the sample prior to the exposure.

Paracetamol was the drug used for this investigation. The NIR laser was calibrated before any data was taken, and each subsequent time that the laser was turned on.

3.3.2 Measuring Sample Damage Caused by Heating Stage

This experiment was designed to investigate the relationship between different temperatures and the spectra obtained from the sample. It can also be used to compare the effects of melting different samples with the observations made when exposing samples to the 488nm visible light laser. The microscope stage was replaced with a Linkam Instruments TMS 92 heating stage.

Several investigations were carried out to find the relationship between the temperature of the sample's environment and the spectra taken. Paracetamol, Aspirin, and Caffeine were studied. At intervals of 10°C, after an acclimatisation period of three minutes, spectra would be taken of the sample. Three minutes was chosen as an appropriate acclimatisation period, after initially taking spectra every thirty seconds after the oven was held at a certain temperature, and finding little change after two and a half minutes. One aspect, which was investigated in great detail, was how the spectra of each sample changed beyond the point at which the sample melted.

The movement and change in shape of all the samples, beyond the melting point, required the microscope to be refocused.

3.4 Visible Laser Spectroscopy

Equipment used in this section of the experiment was similar to that used in Section 3.2. A laser was directed, via mirrors, a beam expander and a microscope, onto a sample. The differences between this and the equipment from Section 3.2 are due to a different wavelength of laser, and the fact that this system was attached to a Renishaw Raman spectroscope.

The laser used in this case was a $488\,nm$ Argon Ion laser, with a power of $211\,mW$. The power incident on the sample was $13\,mW$ due to large power losses, especially in the beam expander. The laser beam was focused onto a spot of $2.0 \pm 0.3\,\mu m$ in diameter, giving a surface power density of $4.1 \pm 1.6\,GW\,m^{-2}$ on the surface of the tablet. Due to the laser having a lower wavelength than that used in Section 3.2, power from the laser is not spread too far

into the sample, as discussed in Section 2.7.

The Raman spectrometer attached to the equipment allowed spectra to be taken almost immediately after burning a tablet.

3.4.1 Cause of Sample Damage

The first aim of the project is to find the cause of the sample damage. Before doing this, however, a "normal response" to burning must be established. In order to do this, tablets, prepared as mentioned in Section 3.1, were damaged using the laser on full power for several seconds. Immediately following this, a spectrum of the tablet was taken and compared to a spectrum of an undamaged sample to observe any changes due to burning.

After the effect of damaging tablets was understood, the cause of damage could be investigated. This was be tested in two ways:

1. Heating Paracetamol using an oven heater, to see the effects this had on its spectrum, and comparing this to the spectra found by exposing the tablet to the laser.

2. Irradiating Paracetamol at various starting temperatures, and finding the time taken for Paracetamol to burn. If a warmer tablet burns faster than a cooler one, this suggests that temperature causes the damage.

Once the cause of sample damage had been found, a method to prevent damage could be investigated. Due to the fact that heat was suspected to cause sample damage, active sample cooling was investigated as a method to prevent burning.

3.4.2 Measuring the Damage with Active Sample Cooling

The aim of the investigation was to use 488nm laser, along with a Likham TMS 600 cooling stage to irradiate a sample at constant power to determine the time taken to display the normal response for decreasing environment temperature, to ultimately determine a temperature at which the sample heating was reduced or stopped completely.

The temperature stage was similar to that used in the oven heating experiments in Section 3.3.2; however the temperature range could be controlled by passing a coolant, liquid nitrogen, over the sample.

The system was calibrated by attempting to achieve the normal response at room temperature; this was observed to take significantly longer than expected even though very little power had been lost through the glass lid of the stage.

The investigation was carried out over the temperature range 20°C to −20°C. The environment was stabalised at 5°C intervals, the sample irradiated at maximum power, and a spectrum taken. This was repeated for increasing amounts of time until the normal response was observed.

3.5 Estimating the Thermal Conductivity of Paracetamol

To understand how heat moves through a sample, it is necessary to calculate its thermal conductivity. This was estimated for Paracetamol as this was the product used mostly in our experiment. A tablet of the sample was prepared using the method outlined in Section 3.1 so that it has two flat sides, one side was then attached to a thermocouple using a small amount of electrical tape, and the other side was then placed in the middle of a hot plate set at a certain temperature. The temperature of the side adjacent to the hot plate was then recorded at 10 second intervals until it appeared to plateau. The difference in the temperatures of both sides of the tablet was then recorded and used to calculate the thermal conductivity using Equation 1.

3.6 Modelling the System Using the Diffusion Equation

It is sometimes easier to model a system computationally than investigate it experimentally; therefore the tablets were investigated by modelling the diffusion equation using the relaxation methods detailed in Appendix A.

The program was used to investigate the standard Paracetamol tablet used throughout the project. This required the implementation of α_T for Paracetamol, Equation 3. The density was simply found by measuring the dimensions of a sample tablet, as well as its mass. A value of c was found from [21], taken as the value at room temperature and thermal conductivity was calculated using Equation 1, a value of heat flow from [22] and the temperature difference from the hot plate experiment in Section 3.5.

It was also necessary to evaluate the temperature at which the laser would irradiate the sample. Using the Stefan-Boltzmann law to approximate the laser as a blackbody [11], and using literature values to determine how much light the tablet will absorb at that wavelength [23], an approximate value could be found.

3.6.1 The 2D Surface Investigation

The first investigation was into how the heat spread out over the top surface of the tablet as a function of time, for which the surface was approximated as the flat top

of a cuboid tablet. For this simulation the nodes form a two-dimensional grid as shown in Figure 9.

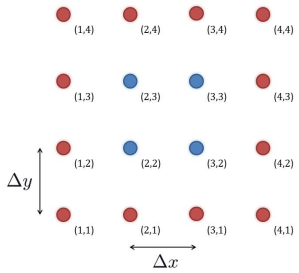


Figure 9: *A diagram showing the discretisation of a two dimensional grid with $m = 4$ in the x direction and $n = 4$ in the y direction. The grid is referenced by its i and j indices, such that the i index is in the x direction, and the j index is in the y direction.*

3.6.2 Investigate Rotating the Sample as a Method of Reducing Heating

The rotation of a sample as an effective method of reducing sample heating has also been reported [16]. However, this is hard to set up experimentally. Therefore it was decided that a computer simulation would be the best way to investigate this.

The system was modelled by rotating the 2D grid around the x-axis to simulate the surface of the tablet as a cylinder, as shown in Figure 10.

To simulate the rotation, the laser was set as stationary and the nodes were moved one place round after each iteration. This was then run until the system reached stability.

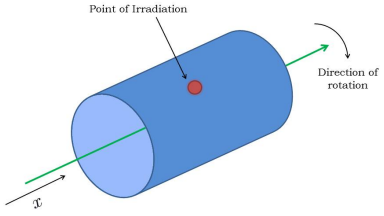


Figure 10: *A diagram showing the ring of nodes created by joining up the two ends of the line of nodes, as well as the direction of rotation.*

4. Results

4.1 NIR Laser Raman Spectroscopy

The near infrared laser operated at a temperature of $-50°C$. Scans made using the spectrometer were single exposures over a ten second interval. The spectra obtained from these scans, such as those shown below, had distinct peaks with low levels of noise.

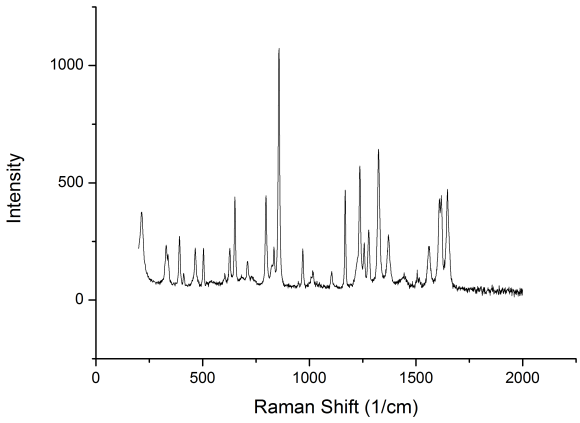


Figure 11: *Individual Paracetamol Spectra at 21 degrees.*

4.1.1 Investigating a Fixed Region

The black spectrum in Figure 12 was taken, at room temperature, of a freshly prepared Paracetamol sample in the aluminium disc. The red spectrum was taken of the same area of the sample 90 seconds after it had been exposed to the 488nm laser for 60 seconds.

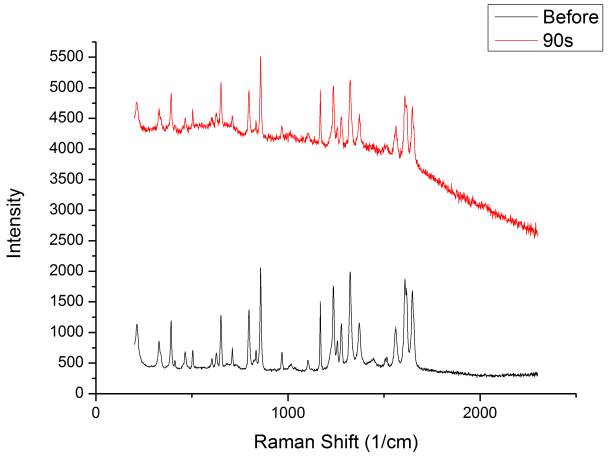


Figure 12: *Graph showing spectra taken of Paracetamol both before and after being exposed to the 488nm Laser.*

The red spectrum has peak intensities, measured in arbitary units, between approximately 4,500 and 5,700 and the intensity between peaks lies between 4,000 and 4,500. These are significantly higher than the original spectrum, which has peak heights ranging from roughly 750 to 2,000 and intensity between peaks of close to 500.

Another noticeable difference between the two spectra is the relative flatness between peaks of the black spectrum, compared with the slope between peaks of the red spectrum. The background intensity of the red spectrum decreases, with increased Raman shift.

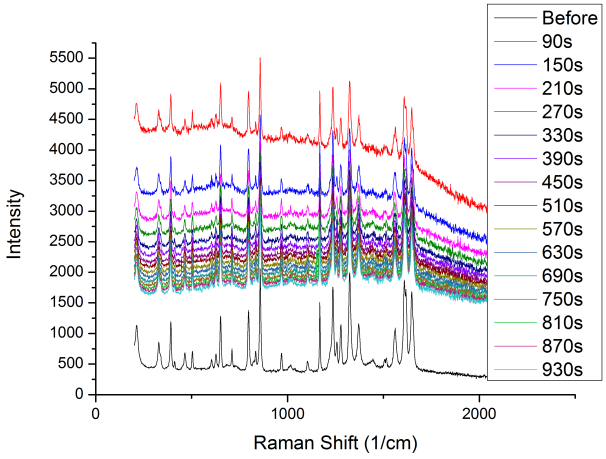


Figure 13: *Comparison of Paracetamol before and after exposure to 488nm laser with time.*

These changes from the original spectrum can be observed in the additional spectra, displayed in Figure 13, which were taken at 60 second time intervals after the red spectrum was measured.

In addition, it can be seen that the intensity of the spectra, taken after the exposure to the 488nm laser, decreases with time.

When investigating the decrease in intensity for these readings, for any single peak, the rate of decrease can be seen to decline exponentially with time after the exposure, as can be seen in Figure 14. The equation is given below, where I is intensity in arbitary units, and x is Raman shift in cm^{-1}:

$$I = 3100 + 3400e^{-0.0046x} \tag{7}$$

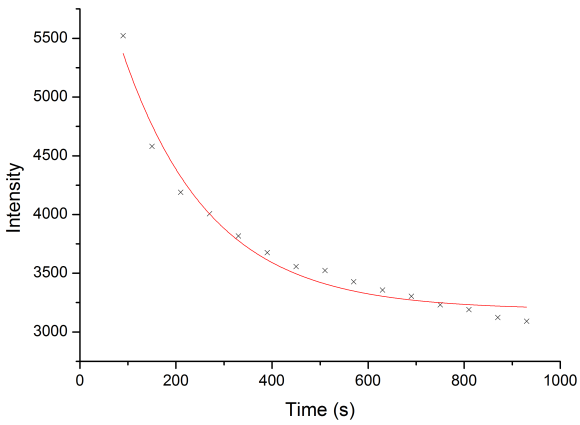


Figure 14: *Graph showing the change in peak intensity after exposure to the 488nm laser with time.*

4.1.2 Sample Damage Caused by Heating Stage

As the temperature of the Paracetamol sample is increased, using the heating stage, the intensity of the spectra taken decreases. When focusing on a single peak, as in Figure 15, this decrease in intensity can be clearly observed.

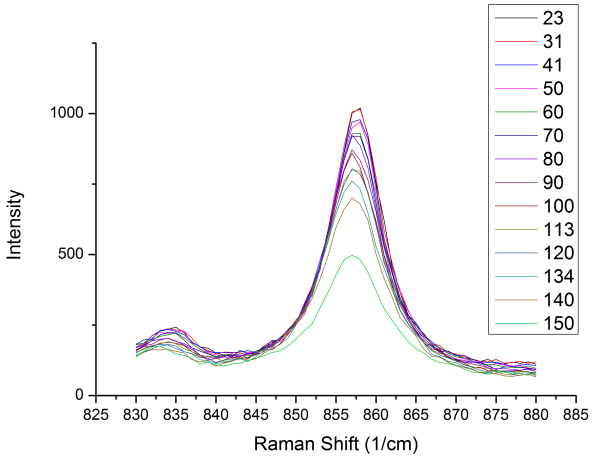


Figure 15: *Graph showing change in intensity of Paracetamol spectra, for a single peak, at different temperatures in degrees Celcius, listed in the included key.*

Figure 15 shows how a single peak of the Paracetamol spectra changes, as the Paracetamol sample is heated, in ten degree intervals. The intensities of this chosen peak, at a Raman shift of $857cm^{-1}$, can be seen to decrease at a gradient of -2.41 arbitary units of intensity per °C, as shown in Figure 16. This indicates that intensity is inversely proportional to temperature.

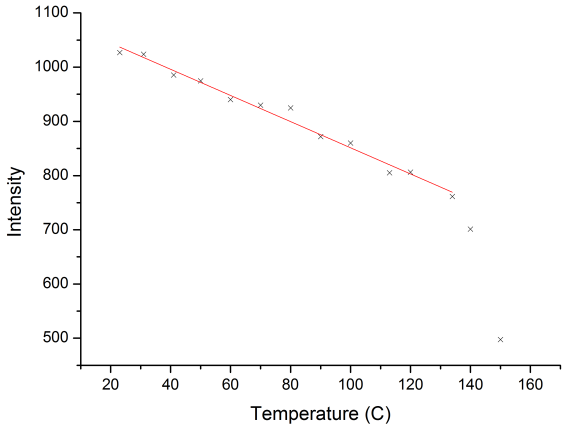


Figure 16: *Graph Showing how the intensity of a single peak changes with temperature.*

The peak intensities measured at 140°C and 150°C, in Figure 16, are anomalous readings which will be discussed in Section 5.1.2.

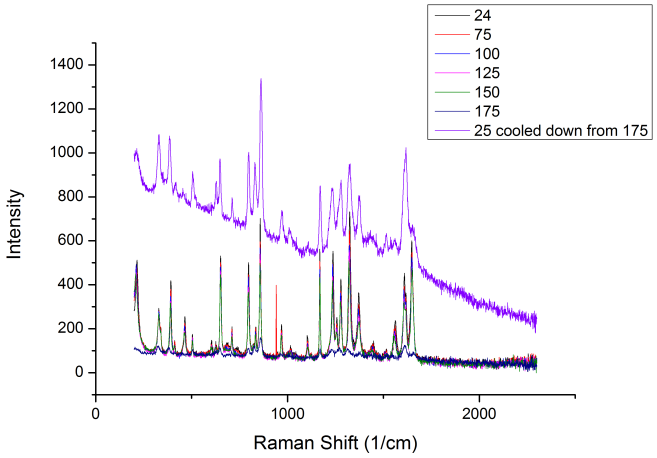


Figure 17: *Graph showing how the spectrum of Paracetamol changes with temperature.*

Figure 17 shows several spectra of another sample of Paracetamol taken at increasing temperatures. These results follow a similar trend to those shown in Figure 15, decreasing in intensity as temperature increases, with the exception of the spectrum labelled *25 cooled down from 175*. This spectrum has significantly higher intensities than the spectra measured at other temperatures. The background intensity of this spectrum between peaks is on a slope, decreasing with increasing Raman Shift, compared with the relatively flat background intensities of the other spectra. The spectrum taken at 175°C was an anomalous result, similar to those from Figure 16, which will also be

explained in Section 5.1.2.

Figure 18 shows this same set of results, but is focused on the same peak, at a Raman Shift of $857cm^{-1}$, as Figure 15.

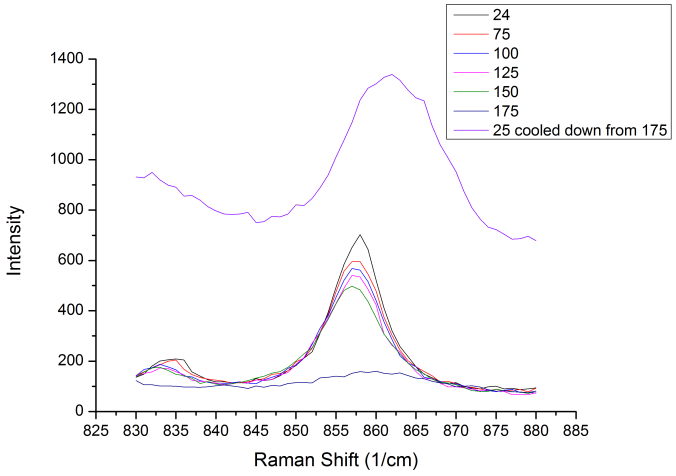


Figure 18: *Graph showing how a single peak of the spectrum of Paracetamol changes with temperature.*

The black square points in Figure 19 represent the peaks of each spectrum taken as temperature was increased to 175°C, including the anomalous result taken at 175°C itself. The circular red point indicates the intensity of the peak of the spectrum labelled *25 cooled down from 175*.

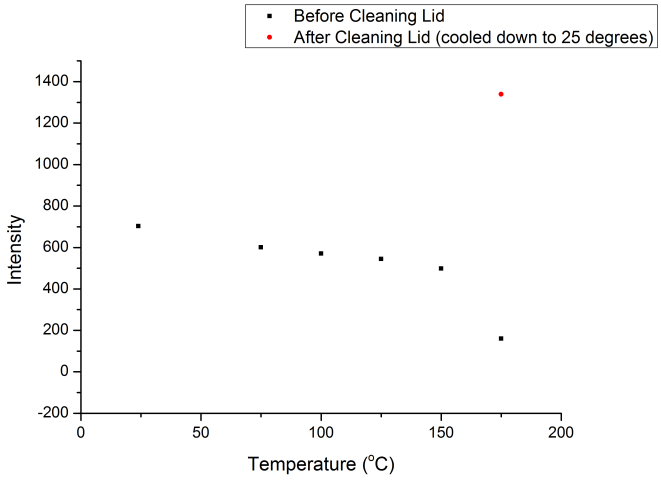


Figure 19: *Graph showing how a single peak of the spectrum of Paracetamol changes with temperature.*

4.2 Visible Laser Spectroscopy

In order to find out the reason tablets are damaged, spectra were first taken to find a "normal response" to burning.

Figures 20 and 21 show the difference between a spectrum of a tablet which hasn't been burnt, and one which has.

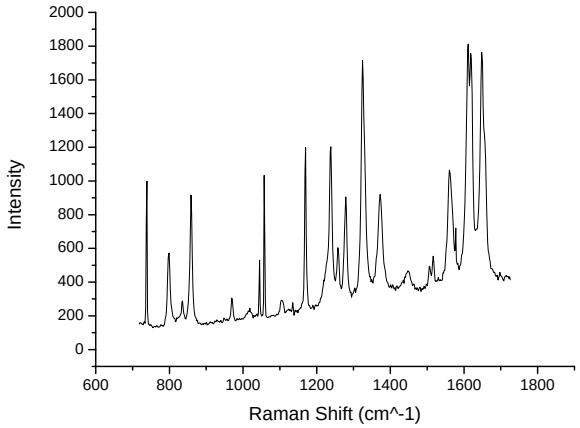


Figure 20: *Spectrum of Paracetamol taken before being burnt.*

The distinguishing feature in Figure 21 is the increasing background intensity. The peaks are much harder to make out, though the bigger peaks are still visible.

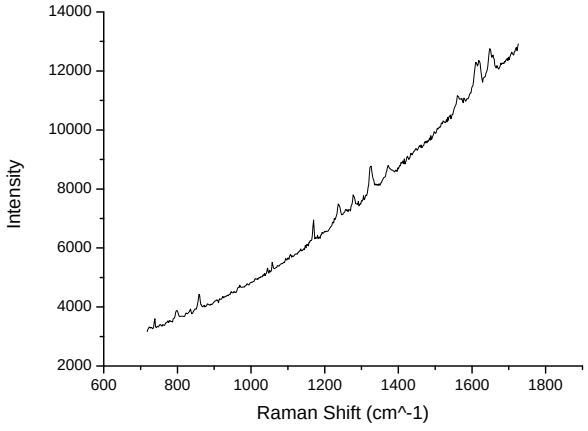


Figure 21: *Spectrum of Paracetamol taken after being damaged by the laser.*

This spatial background has distinct features of its own, as shown by a spectrum taken over a much larger range, such as in Figure 22.

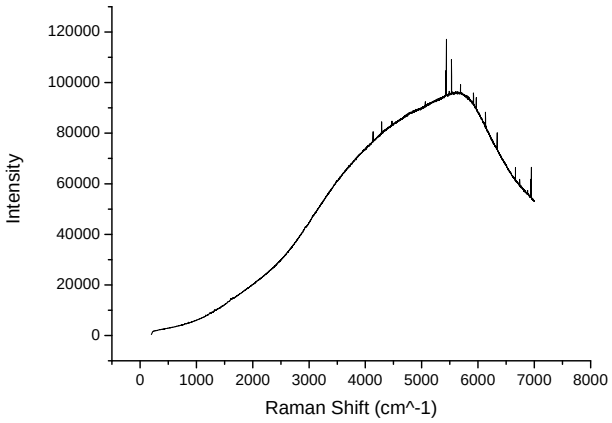


Figure 22: *Spectrum of Paracetamol taken after being damaged by the laser, using a large range of Raman shift values.*

A wide, gradual peak appears in the spatial background at around $5600cm^{-1}$. Taking this from the wavenumber of the laser, this correspondes to an observed transition at $672\,nm$.

In order to find out the cause of sample damage, a spectrum was taken using Paracetamol which had been melted previously, at 180°C, which can be compared to damage caused by the laser. In order to make melting easier, powdered Paracetamol was used for this test. A comparison between the two is given in Figure 23.

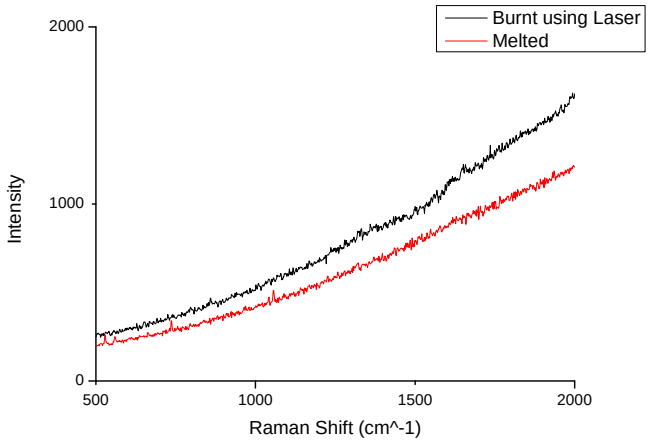


Figure 23: *Spectra comparing metled Paracetamol, and Paracetamol damaged by the laser.*

These two graphs follow a very similar pattern.

Another experiment which was carried out to investigate this was to vary the starting temperature of the tablets, using a Linkam Instruments TMS 92 heating stage. The time taken for damage to occur to a tablet via laser radiation at each temperature was recorded. Due to focusing issues using the heating stage, this experiment provided inconclusive data.

4.3 Measuring the Damage with Active Sample Cooling

When using the cooling stage, the maximum power of the laser was found to be $211mW$. By the time it has passed through the glass lid the power was found to be $10.3mW$. The system was calibrated by irradiating a Paracetamol tablet at room temperature, 27.8°C. The normal response was observed after an average time of 45 seconds. The sample was then cooled to 20°C and exposed to the laser for 5 minutes; no change was observed in the spectrum. This was repeated for several spots on the sample and no changes were observed. Any change would be expected to happen relatively quickly, so it was assumed that there was never likely to be any damage.

4.4 Experimentally Estimating the Thermal Conductivity

The dimensions of the tablet tested were $x = 0.016m$, $y = 0.008m$ and $z = 0.004m$, with mass $= 0.56g$. Therefore, the density could be calculated as $\rho = 1054kgm^{-3}$. The temperature difference between the two sides of the tablet was found using graphs such as Figure 24 and an average taken. This temperature difference was then used and the following values calculated:

$$k = 0.84Wm^{-1}K^{-1}$$
$$c = 1147.5Jkg^{-1}K^{-1}$$

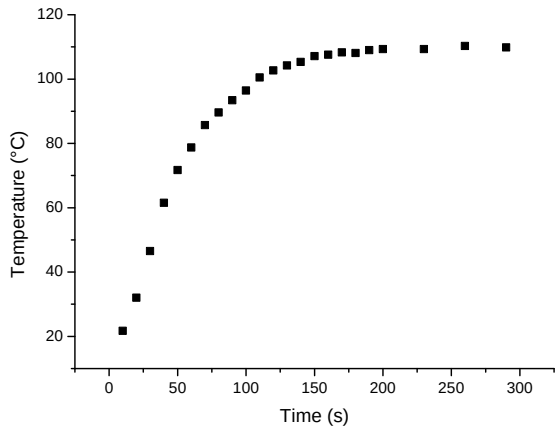


Figure 24: *Graph showing the tempurature increase for Paracetemol on the hot plate.*

4.5 Modelling the System Using the Diffusion Equation

As mentioned in Section 3.5 a value was needed for α_T to be able to model the diffusion equation. This meant that using Equation 3 a value of α_T was approximated to be $7 \times 10^{-7}\ m^2 s^{-1}$.

The simulations were run for the 488nm laser; this was worked out to have a power of 13mW on the sample, the absorption was found to be 0.05%, and the temperature incident on the sample was modelled to be 3000K.

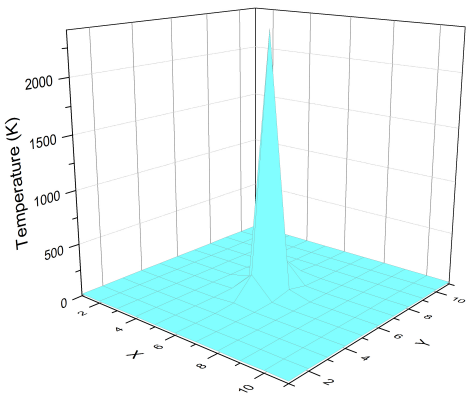
4.5.1 The 2D Surface Investigation

For this investigation the number of nodes was set to 11 in both directions and the time step was set to 0.1 seconds. The system was then modelled for a total time of 50 seconds and the evolution is shown in Figure 25.

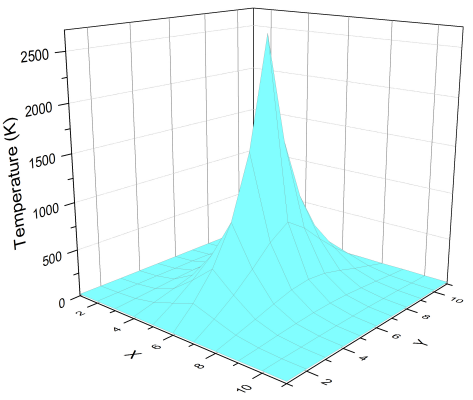
4.5.2 Investigate Rotating the Sample as a Method of Reducing Heating

Literature values suggest that rotating the sample at 8 rotations per minute is an effective method of reducing sample heating [16], therefore the programme was modelled for a time step of 0.24 seconds and a total time of 480 seconds.

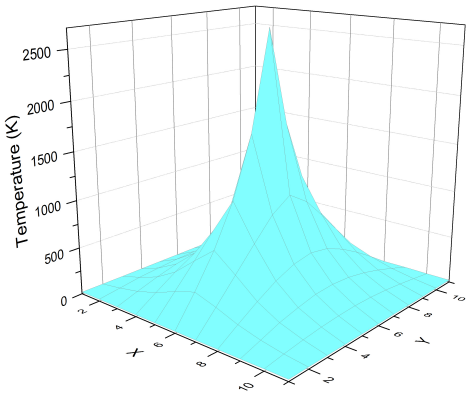
The test was to show how the temperature of a point in space changed with time for four different points, this is shown in Figure 26. Figures 26(a) to 26(c) show how the temperature of the surface changes within the first rotation of the sample, the graphs show the surface area of the cylinder flattened out on one plot, such that the ends of the y axis would be joined up. It can be seen that as soon as the node moves away from the point of irradiation it begins to cool down, and only heats up again just before being irradiated by the laser again. Figure 26(d) shows the evolution in time of 4 points on that surface, given by their co-ordinates.



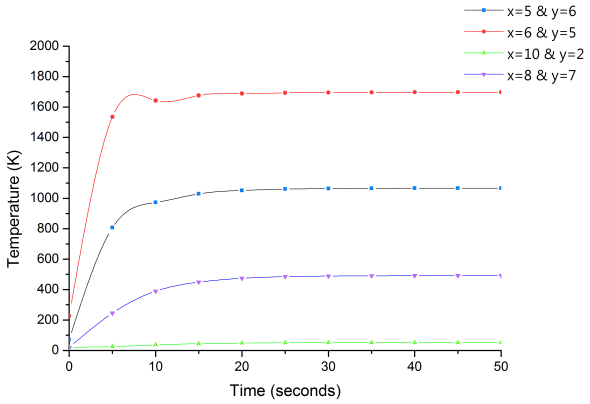
(a) After 0 seconds



(b) After 5 seconds

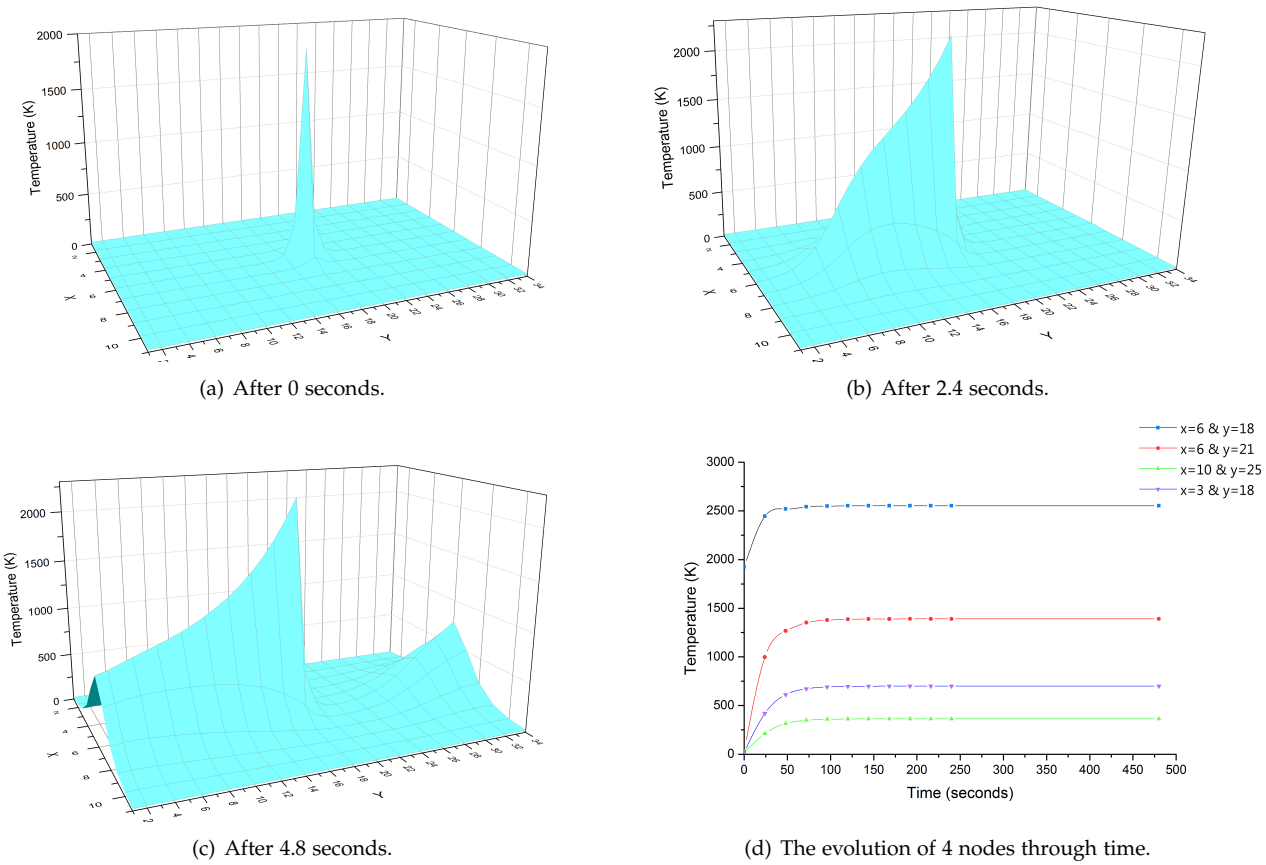


(c) After 50 seconds



(d) The evolution of 4 nodes through time

Figure 25: *A graph showing the evolution of heat through the 2D surface as a function of time.*



(a) After 0 seconds.

(b) After 2.4 seconds.

(c) After 4.8 seconds.

(d) The evolution of 4 nodes through time.

Figure 26: *Graphs showing how the temperature as a function of time for different points in space.*

5. Discussion

5.1 NIR Laser Raman Spectroscopy

Three different drugs were used throughout these experiments: Paracetamol, Aspirin and Caffeine. Caffeine was used the least frequently, as it has a boiling point (178°C) lower than its melting point (238°C) [24]. This caused the caffeine to sublime at higher temperatures, which condensed on the lid of the heating stage.

An advantage of using Aspirin was that it had a melting point (136°C) [24] lower than the temperature at which the condensation began to affect the results.

Despite this, Paracetamol was the drug chosen for most of the experiments, due to the fact we had a powdered sample available, without an outer coating, and it produced the clearest spectra - as shown in Figure 11.

5.1.1 Investigating a Fixed Region

The dramatic change in intensity that can be seen, before and after the exposure of the sample to the 488nm laser, in Figure 12 could be attributed to fluorescence.

The decrease in intensity of the spectra taken after the exposure, shown in Figure 13, is of particular interest. As can be seen in Figure 14, the rate of this decrease itself decreases exponentially with time. There is little change in spectra taken from about 1000 seconds after the exposure onwards. However, there is still a clear permanent change compared with the spectra of the original sample. When the direct relationship between intensity and temperature, shown in Figure 16, is also considered, this provides a significant indication that the effect the laser has on the sample is similar to that caused by a change in temperature.

5.1.2 Sample Damage Caused by Heating Stage

As Figure 15 shows, the intensity of the spectra decreases as the sample is heated. The rate of this decrease, as displayed in Figure 16, is seen to be constant at a value of -2.41 arbitary units per °C, with the exception of the anomalous readings at 140°C and 150°C. The reason for these two peaks having significantly lower intenisities was due to the lid of the heating stage becoming obscured. A white layer gradually began to form on the inner surface of the lid at 140°C. By 150°C the layer across the lid was obscuring the spectrometer from taking accurate readings of the sample. These two readings were therefore rejected from the linear analysis, as they were misrepresentative of the data.

This effect can further be seen in Figures 17 and 18. The spectrum taken at 175°C appears to have completely broken down. However, once the inner surface was cleaned and the aforementioned layer was removed, a significantly changed spectrum could be observed, labelled *25 cooled down from 175*.

This layer that formed accross the inside of the lid is likely to be a result of condensation. Due to the high temperatures on the inner surface of the lid, and the significantly lower temperatures on the outer surface of the lid, condensation could form on the inner surface. Whether this is condensation of water vapour in the air, the evaporated carrier material, or the sample itself would need further investigation.

The differences observed in Section 4.1.2 between the *25 cooled down from 175* spectrum and the spectra taken at other temperatures, in Figure 17, are similar to the differences between the spectra taken after exposure to the 488nm laser, and the spectrum taken before the exposure in Figure 12. The *25 cooled down from 175* spectrum could indicate fluorescence.

The melting point of Paracetamol is known to be 169°C [24]. These results suggest that the effect that the 488nm laser has on the sample is akin to that of heating the sample above its melting point. This implies that the changes the sample undergoes when exposed to the 488nm laser are caused by heat transfer from the laser to the sample.

5.2 Visible Laser Spectroscopy

The increasing background intensity is likely due to fluorescence, which occurs when a transition within the target molecule shares the same, or close to the same, energy as that of the laser [25]. Photons are then absorbed and re-emitted at a different wavelength, rather than scattered as is the case in the Raman effect.

This suggests that after exposure to the laser, there is a different transition in the Paracetamol tablet, which was not there before being damaged.

It may be expected that this is due to the breakdown of the Paracetamol molecule, however, no significant peaks are removed from spectra after irradiation.

If Paracetamol molecules themselves have been broken down, it would be expected that Raman peaks from amorphous Carbon at $1380\,cm^{-1}$ and $1460\,cm^{-1}$ would be seen, as has been found by employees working at Renishaw using high powered lasers ($\sim 60\,mW$ incident on sample). Raman peaks at these wavenumbers were not found to appear, which suggests that the molecules are not breaking down.

It is possible for fluorescence to change due to phase changes in molecules [26], which is a possible cause of the fluorescence pattern seen after damaging tablets.

The other possible cause is a breakdown of the carrier

material in the tablets. As Paracetamol tablets are made of 90% active ingredient, this breakdown is unlikely to cause such a large change in the spectrum.

The time taken to damage a Paracetamol tablet using laser irradiation was $16 \pm 5\,s$. This error is extremely large due to the focusing of the laser on the sample.

Even after being sanded to a point where tablets were smooth to the touch, the tablets still appear quite rough under a 50x microscope objective lens. With the rough surface, it is likely that the laser light will be incident on the tablet at an angle, thereby decreasing power density, as opposed to hitting the tablet straight on. This will influence the time taken for a tablet to become damaged.

Figure 22 shows the peak in the spatial background at around $5600cm^{-1}$, giving a transition at $672\,nm$, with an energy of 1.84 eV. This transition could be due to a chemical change in the Paracetamol itself, or could be due to a change in the carrier materials. This is an avenue for future investigation.

Figure 23 shows the spectra of both Paracetamol powder which has been damaged via laser irradiation and by simply melting the powder with an oven-type heater at $180°C$ for one minute.

The two graphs are very similar in shape, although the laser irradiated graph has a slightly higher intensity throughout. As the units of intensity are arbitrary however, only the shape matters. The slight "wobble" on the black, laser irradiated graph is due to some signal being picked up from non-burnt Paracetamol as the laser only irradiates a tiny area. This isn't seen on the melted graph as the entire sample has been damaged.

On heating the sample to $180°C$, it is very unlikely that the Paracetamol molecules themselves have decomposed. At this temperature, the rate of decomposition (fraction of a substance which decomposes per unit time) is $2.61 \times 10^{-2}h^{-1}$ [27]. This means that in the minute of heating, only 0.044% of the molecules in the material will have decomposed.

The similarity of the graphs suggests that the same process has been undertaken in both situations, leading to the fact that heat is the primary cause of sample damage.

In order to confirm whether the sample damage is due to burning, samples were exposed to the laser at different starting temperatures. Using the microscope heating stage, it was extremely difficult to correctly focus the laser to burn tablets, as shown in Figure 27. The microscope stage uses a lid, with a glass plate allowing light to pass through it. The refractive index of this glass plate causes incident light from the laser to be focused at different points in the axis perpendicular to the surface of the sample.

Due to this, results were inconclusive.

Figure 27 shows that laser beams coming from two different angles, after passing through the microscope lens, will focus at different points in the z-direction when travelling through a glass plate.

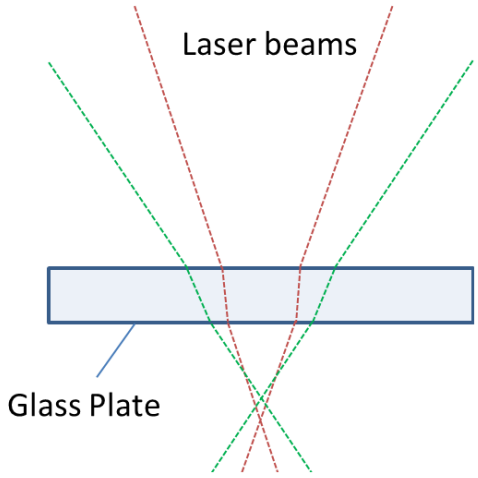


Figure 27: *Diagram demonstrating the difficulties faced when focusing a laser through a glass plate, such as that used to test active sample cooling.*

The same experiment was attempted without the lid on the heating stage, however, this meant that the temperature of the sample was very inconsistent, and results again were inconclusive.

5.3 Measuring the Damage with Active Sample Cooling

The difficulty in focusing the laser meant that it was not possible to get any experimental data to investigate the hypothesis that cooling the sample prevents the levels of degradation seen in the heating experiments. The inability to focus the laser on the sample was discussed in Section 5.2.

Even if the cooling stage had enabled this investigation, the results would only have acted as a theoretical proof of the phenomenon and would not have provided the industrial solution in the project brief. In industry cooled nitrogen would have to be blown over ever sample when testing them as discussed in Section 2.3; this is unlikely to be economically viable or time efficient.

The aim of the experiment was to find a temperature to which the sample needed to be cooled to limit sample damage, and then use this as a basis for investigations into ways to do this within the industrial limitations. However the laser power achieved on the sample from the 488nm laser was only 13mW. Industrially the aim would be to irradiate the sample with roughly 60mW, far greater than

this experiment was able to achieve. This meant that the best outcome would have been to find a solution which showed evidence that it could scale accordingly with increased power.

Nevertheless, it was found that by putting a piece of glass in between the laser and the sample it was possible to take a reasonable spectrum, quickly, and without burning the sample. Therefore it could be possible that this would also work for higher laser powers and is worth further dedicated investigation.

5.4 Modelling the System Using the Diffusion Equation

The code used to simulate the diffusion equation has some limitations; such as not accounting for heat loss, modelling an ideal surface and using an approximate value of α_T. In addition the laser spot size in these simulations is far larger than that used in the experiments, therefore experimental results would be far more localised than shown in the simulations. These restrictions mean that the simulations are not physical results but rather indications of the system.

The main aim of the code was to suggest how the heat might move through the sample in each situation. This is so that if the project was to be taken further or re-worked then these tests, if successfully modelled, could be implemented experimentally.

5.4.1 The 2D Surface Investigation

Figure 25 shows how the heat spreads out through the top surface of the sample as a function of time, again approximated without heat loss. The motivation for this simulation was to understand how heat moved along the surface. The diagram shows what would be expected, that the heat spreads out through the tablet from the point of incidence as the time it is exposed increases. It should be noted that the heat spreads out quicker in the y direction which is modelled as the shorter dimension of the tablet, this is because the heat has less of the tablet to diffuse into. If heat loss had been modelled then it is likely that the drop off in temperatre from the central point would have been much greater.

5.4.2 Investigate Rotating the Sample as a Method of Reducing Heating

It can be seen from the results of this simulation that the nodes within the ring irradited by the laser, $x = 6$, reach a maximum temperature at the point the laser is incident and then cool down to a minimum, before going through the cycle again. This minimum point does increase with time until it reaches a stable equilibrium, as shown in Figure 26(d) by the point $x, y = 6, 21$. However, once equilibrium has been reached a point in space remains at the same temperature, i.e. each node heats up to the same temperature at a specific point in the grid.

By the end of the simulation, the entire surface of the tablet is well above the melting point of Paracetamol, where it can be assumed damage has taken place. However, the simulation does not account for the heat loss from the surface to the particles of the tablet, and the heat loss at the end of the cylinder. This means that the temperatures shown are far higher than would be expected experimentally. What the simulation does show is that the spot at which the laser irradiates the sample is given an opportunity to cool down and therefore is less likely to sustain damage. Therefore if the project was to be continued or done again then it would be worth looking into investigating this experimentally

However whilst this simulation suggests that, if the project was taken forward, it would be beneficial to conduct this test experimentally, there are some industrial limitations which could prevent this from being a viable method of limiting sample damage. It is not cost effective or time efficient to test the samples as detailed in Section 2.3, where each sample is rotated individually whilst the spectrum is being taken. Therefore whilst theoretically rotating the tablet is a method of limiting sample damage, it may not be a solution to the project brief.

6. Conclusion

The cause of sample damage in laser diagnostics was investigated by comparing the effects of 'oven' heating on samples of Paracetamol, in tablet and powder form, and localised heating due to laser exposure. It was determined that the effects of melting the tablet were similar to those from exposing it to a laser and therefore heating within the sample is the cause of damage.

It was also determined that there was a linear relationship between temperature and decrease in intensity of Raman peaks, and above the melting point the spectra of the sample is found to show fluorescence.

Active sample cooling was investigated as a potential solution to sample damage and, whilst the results proved inconclusive, it is believed that this is a viable solution and would warrant further investigation. In addition, it was observed that inserting a piece of glass in between the laser and the sample acted to prevent the normal damage without any observed negative effects to the spectrum. This would merit dedicated investigation.

Finally, a computer model simulating the rotation of a sample, at 8 rotations per minute, during the diagnostic procedure appears to show that this is a possible solution. If it becomes economically and industrially viable, this would be worth investigating experimentally.

Appendix

A. Modelling the System using the Diffusion Equation

The diffusion equation is an example of a time-dependent partial differential equation; this is solved by letting the system reach equilibrium from some arbitrary initial state, also known as letting it 'relax' by iterating towards a final solution, subject to any boundary conditions placed on the system.

A stable method of computing the diffusion equation can be found by using the implicit equation

$$\frac{\phi'(x_i) - \phi(x_i)}{\Delta t} = \frac{\alpha}{h^2}[\phi'(x_{i-1}) + \phi'(x_{i+1}) - 2\phi'(x_i)] \tag{8}$$

The finite difference form uses the value of ϕ at a time t to evaluate the values of ϕ' at three neighbouring points at the next time step $t + \Delta t$. This is a known as a backwards time method. A solution is then possible for a one-dimensional system by splitting the problem into a line of nodes or for a two-dimensional grid of nodes. However the relaxation methods are the same for both. This technique involves implementing a few simple steps:

1. Define a regular spatial grid covering the region of interest,
2. Impose the boundary conditions by fixing the values of the nodes on the boundaries,
3. Set all non-boundary nodes to an initial condition,
4. Fix any node values that are to remain constant,
5. Apply the finite difference equations,
6. Iterate the equations at each node until the solution converges.

There are many ways of iterating towards the solution; here the Jacobi method was used as the form of iteration [14]. This is a good method for use in testing, as although it is fairly slow to converge it is accurate.

The finite equation 8 was then used to start from known initial conditions and evolve the node values forwards in time [14]. The spatial derivative on the right-hand side needs to be evaluated at time $t + \Delta t$. This is done by expressing the equation explicitly in the matrix form

$$\mathbf{A} \cdot \phi'(x_i) = \phi(x_i) \tag{9}$$

Therefore the linear system can be written as the matrix

$$\begin{pmatrix} 1 & R & 0 & 0 & 0 \\ L & C & R & 0 & 0 \\ 0 & L & C & R & 0 \\ 0 & 0 & L & C & R \\ 0 & 0 & 0 & L & 1 \end{pmatrix} \begin{pmatrix} \phi'(x_{i-2}) \\ \phi'(x_{i-1}) \\ \phi'(x_i) \\ \phi'(x_{i+1}) \\ \phi'(x_{i+2}) \end{pmatrix} = \begin{pmatrix} BC \\ \phi(x_{i-1}) \\ \phi(x_i) \\ \phi(x_{i+1}) \\ BC \end{pmatrix} \tag{10}$$

where BC are the boundary conditions and the coefficients are defined by:

$$C = 1 + 2\alpha\frac{\Delta t}{\Delta x^2} \tag{11}$$

$$L = -\alpha\frac{\Delta t}{\Delta x^2} \tag{12}$$

$$R = -\alpha\frac{\Delta t}{\Delta x^2} \tag{13}$$

It is also possible to use this matrix in a 2D system. For the system in Figure 9, equation 9 was adapted to include the new coefficients

$$\begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & B & 0 & 0 & L & C & R & 0 & 0 & T & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & B & 0 & 0 & L & C & R & 0 & 0 & T & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & B & 0 & 0 & L & C & R & 0 & 0 & T & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & B & 0 & 0 & L & C & R & 0 & 0 & T & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} \phi'(x_1, y_1) \\ \phi'(x_2, y_1) \\ \phi'(x_3, y_1) \\ \phi'(x_4, y_1) \\ \phi'(x_1, y_2) \\ \phi'(x_2, y_2) \\ \phi'(x_3, y_2) \\ \phi'(x_4, y_2) \\ \phi'(x_1, y_3) \\ \phi'(x_2, y_3) \\ \phi'(x_3, y_3) \\ \phi'(x_4, y_3) \\ \phi'(x_1, y_4) \\ \phi'(x_2, y_4) \\ \phi'(x_3, y_4) \\ \phi'(x_4, y_4) \end{pmatrix} = \begin{pmatrix} BC \\ BC \\ BC \\ BC \\ BC \\ \phi(x_2, y_2) \\ \phi(x_3, y_2) \\ BC \\ BC \\ \phi(x_2, y_3) \\ \phi(x_3, y_3) \\ BC \\ BC \\ BC \\ BC \\ BC \end{pmatrix}$$

these take into account the nodes on the boundaries of the grid which are equivalent to the nodes at either end of the one dimensional system. The new matrix is therefore

$$\begin{aligned} B &= -\alpha \frac{\Delta t}{\Delta y^2} \\ T &= -\alpha \frac{\Delta t}{\Delta y^2} \end{aligned} \tag{14}$$

In each case the model uses a spatial step and time step to iterate the temperature forwards in time. The value of the spatial step was found by dividing the length in either the x or y direction by the number of nodes; the time step was set for each test to display the desired data most efficiently.

The matrix equation was then solved using the LU Decomposition method [14], and functions from the GNU Scientific Library [28]. This method was chosen due to the diagonal nature of the matrix equation 9 and the algorithm's scalability and its efficiency.

The programme was first tested for an arbitrary equation

$$\phi' = e^x e^t \tag{15}$$

where the answers would be known, in order to test the stability and accuracy of the programme.

It was observed from the solution for the known case that there were marginal errors at each step; these are likely to be a combination of the errors arising from the precision involved in the programme and from errors resulting from the LU Decomposition function. For matrices of the size used in this investigation, it can be considered that the accuracy of the results only depends on the machine's precision. These errors were, however, not significant enough to be considered to affect the modelling ability of the programme.

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