Spectroscopic Imaging of the Compaction and Dissolution of Model Pharmaceutical Formulations

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A thesis submitted to Imperial College London in partial fulfilment of the requirements of the degree of Doctor of Philosophy
I would like to dedicate this thesis to my Family for all their support throughout my education and for showing me the value of learning.

“Concentrate and Work-Hard”

-Deborah Wray
PREFACE

This thesis is a description of the work carried out in the Department of Chemical Engineering, Imperial College London, between October 2007 and August 2011, under the supervision of Professor Sergei G. Kazarian. Except where acknowledged, the material is the original work of the author and no part of it has been submitted for a degree at any other university.
ABSTRACT

Orally administered compressed tablets are the most commonly used dosage form. Understanding the physical and chemical processes involved in drug release from tablets is critical for designing more effective formulations. Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) spectroscopic imaging is a powerful chemically specific and spatially resolved analytical approach. Effective uses for this technology have been found in the field of pharmaceutics, studying the compaction and dissolution of oral dosage formulations. However, the full potential of this technology is yet to be explored.

This thesis describes work that further explores the applications of FTIR imaging through the use of model pharmaceutical formulations. The work is broadly split into three sections: quantification of imaging data, dissolution of pH modified formulations and application to structured tablets.

The in situ compaction of model drug tablets with different polymer matrices was studied using ATR-FTIR imaging. The choice of polymer strongly affected the distribution of the drug at the tablet surface. X-ray tomography was used as a complementary technique, verifying the distribution of drug particles within the compacted matrices. Statistical analysis was applied to investigate obtaining quantitative data such as particle size and component loading from the image data.

Previous work using ATR-FTIR imaging has shown the ability of the approach to detect crystallisation of ibuprofen during dissolution. The dissolution of ibuprofen from HPMC matrices containing pH modifying compounds was studied. FTIR imaging showed that tablets containing acidic compounds slowed the dissolution of crystalline ibuprofen domains. The formation of soluble and insoluble salts of the drug was seen in tablets containing basic compounds.

As FTIR imaging supplies both chemical and spatial information it was applied to study structured tablets, both tablet-in-tablet structures and multilayer formulations, in conjunction with visible optical video analysis. The tablet-in-tablet structures were used to create delayed release formulations, in which both the core and shell materials were used to control release. pH resistant formulations were also developed for the release of pH labile drugs. FTIR imaging supplied vital information on the rate of ingress of water fronts, the movement of swelling polymers and the chemical state of the drug.

Multilayer formulations were investigated for studies of biphasic release and also in order to compare the dissolution performance of tablets in the custom ATR flow cell with that found in the industry standard USP tests.
ACKNOWLEDGEMENTS

Completion of this thesis and the work contained within would not have been possible without the help and support of many people. I would like to begin by thanking Professor Sergei Kazarian for introducing me to the exciting field of vibrational spectroscopy and the enthusiasm and interest he has shown in my work throughout. The enjoyment and achievement I have extracted from my PhD owes a great deal to his continued encouragement and input. I will be forever grateful to him for all of his guidance supervision and friendship throughout. I would also like to thank my collaborating academic, Professor Paul Luckham for his help and advice.

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A special debt of thanks is reserved for Mrs Susi Underwood and her husband John, whose help and support cannot be underestimated and who have been great friends to me throughout. The departmental support staff have all been of great help during my time here; Anusha Sri-Pathmanathan, Pim Amrit, Keith Walker, Tawanda Nyabango, Chin Lang and Nam Ly. Thank you also to the staff in the workshop, especially Richard who has helped me to make a number of items in the student workshop.

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<tr>
<td>$T$</td>
<td>Transmittance</td>
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<tr>
<td>$T_c$</td>
<td>Glass transition temperature</td>
<td>°C</td>
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<tr>
<td>wt%</td>
<td>Weight percent</td>
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<tr>
<td>X</td>
<td>2D matrix</td>
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<tr>
<td>$X_{F, \text{max}}$</td>
<td>Maximum Feret diameter</td>
<td>m</td>
</tr>
<tr>
<td>$X_{F, \text{min}}$</td>
<td>Minimum Feret diameter</td>
<td>m</td>
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<tr>
<td>Y</td>
<td>2D matrix</td>
<td></td>
</tr>
<tr>
<td>$z$</td>
<td>Vertical distance from ATR crystal</td>
<td>m</td>
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<tr>
<td>$\epsilon$</td>
<td>Deformation strain</td>
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<tr>
<td>$\varepsilon$</td>
<td>Molar absorptivity</td>
<td>L.mol$^{-1}$ .cm$^{-1}$</td>
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<tr>
<td>$\theta$</td>
<td>Angle of incidence</td>
<td>rad</td>
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<tr>
<td>$\theta_c$</td>
<td>Critical angle</td>
<td>rad</td>
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<tr>
<td>$\lambda$</td>
<td>Wavelength of light</td>
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<tr>
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<td>$\sigma_d$</td>
<td>Deformation stress</td>
<td>MPa</td>
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<tr>
<td>$\sigma_y$</td>
<td>Yield stress</td>
<td>MPa</td>
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**Greek Letters**

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<tr>
<th>Symbol</th>
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<tr>
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<td>Deformation strain</td>
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<tr>
<td>$\varepsilon$</td>
<td>Molar absorptivity</td>
<td>L.mol$^{-1}$ .cm$^{-1}$</td>
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<tr>
<td>$\theta$</td>
<td>Angle of incidence</td>
<td>rad</td>
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<td>$\theta_c$</td>
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<td>$\lambda$</td>
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<td>$\sigma_d$</td>
<td>Deformation stress</td>
<td>MPa</td>
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<tr>
<td>$\sigma_y$</td>
<td>Yield stress</td>
<td>MPa</td>
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# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>a.u.</td>
<td>Arbitrary Units</td>
</tr>
<tr>
<td>ADC</td>
<td>Analogue to digital converter</td>
</tr>
<tr>
<td>AFM</td>
<td>Atomic Force Microscopy</td>
</tr>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>ATR</td>
<td>Attenuated Total Reflection</td>
</tr>
<tr>
<td>CCD</td>
<td>Charge Coupled Device</td>
</tr>
<tr>
<td>CMC</td>
<td>Carboxymethylcellulose</td>
</tr>
<tr>
<td>CO</td>
<td>Corrective Optics</td>
</tr>
<tr>
<td>DESI-MS</td>
<td>Desorption Electrospray Ionization Mass Spectrometry</td>
</tr>
<tr>
<td>DTA</td>
<td>Doctoral Training Accounts</td>
</tr>
<tr>
<td>DTGS</td>
<td>Deuterated Triglycine Sulfate</td>
</tr>
<tr>
<td>EPSRC</td>
<td>Engineering and Physical Sciences Research Council</td>
</tr>
<tr>
<td>FA</td>
<td>Factor Analysis</td>
</tr>
<tr>
<td>FALLS</td>
<td>Forward Angle Laser Light Scattering</td>
</tr>
<tr>
<td>FaSSIF</td>
<td>Fasted State Simulated Intestinal Fluid</td>
</tr>
<tr>
<td>FeSSIF</td>
<td>Fed State Simulated Intestinal Fluid</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FOV</td>
<td>Field of View</td>
</tr>
<tr>
<td>FPA</td>
<td>Focal Plane Array</td>
</tr>
<tr>
<td>FT</td>
<td>Fourier Transform</td>
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<tr>
<td>FTIR</td>
<td>Fourier Transform Infrared</td>
</tr>
<tr>
<td>FT-NIR</td>
<td>Fourier Transform Near-Infrared</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>HPC</td>
<td>Hydroxypropyl Cellulose</td>
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<tr>
<td>HPMC</td>
<td>Hydroxypropyl Methylcellulose</td>
</tr>
<tr>
<td>HPMCAS</td>
<td>Hydroxypropyl Methylcellulose Acetate Succinate</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>MCC</td>
<td>Microcrystalline Cellulose</td>
</tr>
<tr>
<td>MCT</td>
<td>Mercury Cadmium Telluride</td>
</tr>
<tr>
<td>MIR</td>
<td>Mid-Infrared</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NA</td>
<td>Numerical Aperture</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>NIR</td>
<td>Near-Infrared</td>
</tr>
<tr>
<td>NIRS</td>
<td>Near-Infrared Spectroscopy</td>
</tr>
<tr>
<td>NME</td>
<td>New Molecular Entity</td>
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<tr>
<td>N-PLS</td>
<td>Multilinear Partial Least Squares</td>
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<tr>
<td>NSAID</td>
<td>Nonsteroidal Antiinflammatory Drugs</td>
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<tr>
<td>PARAFAC</td>
<td>Parallel Factor Analysis</td>
</tr>
<tr>
<td>PCA</td>
<td>Principal Component Analysis</td>
</tr>
<tr>
<td>PDMS</td>
<td>Polydimethylsiloxane</td>
</tr>
<tr>
<td>PEG</td>
<td>Polyethylene Glycol</td>
</tr>
<tr>
<td>PEO</td>
<td>Polyethylene Oxide</td>
</tr>
<tr>
<td>PLS</td>
<td>Partial Least Squared</td>
</tr>
<tr>
<td>PMMA</td>
<td>Poly(methyl methacrylate)</td>
</tr>
<tr>
<td>PVA</td>
<td>Polyvinyl Alcohol</td>
</tr>
<tr>
<td>PVP</td>
<td>Polyvinylpyrrolidone</td>
</tr>
<tr>
<td>RGB</td>
<td>Red Green Blue</td>
</tr>
<tr>
<td>SEM</td>
<td>Scanning Electron Microscopy</td>
</tr>
<tr>
<td>SNR</td>
<td>Signal-to-Noise Ratio</td>
</tr>
<tr>
<td>SORS</td>
<td>Spatially Offset Raman Spectroscopy</td>
</tr>
<tr>
<td>USP</td>
<td>United States Pharmacopeia</td>
</tr>
<tr>
<td>UV/Vis</td>
<td>Ultraviolet-Visible</td>
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</table>
CHAPTER ONE

INTRODUCTION
Chapter 1: Introduction

1 Introduction

1.1 Background

The pharmaceutical industry is one of the largest industries in the world, with sales in 2010 of around $825 billion, which are expected to cross the $1 trillion mark sometime around 2013-2014 (Gatyas and Savage, 2009, Berkot, 2010). The cost of bringing a new drug to market currently stands at around $1 billion, over the course of eight years on average (Tufts, 2010). Over the last 30 years the level of annual spending on research and development has increased drastically. In the U.S. alone the level of spending on research and development (adjusted for inflation) has risen from $4 billion each year in 1970 to $40 billion in 2005 as shown in Figure 1-1.

![Figure 1-1. Estimate of U.S. drug industry spending on research and development from 1970 to 2005, compared with approval rate for new molecular entities (NMEs) in the same period. Adapted from (CBO, 2006).](image)

Despite the large increase in spending on research in development, there has been no such change in the number of new drugs approved. Therefore the level of spending per drug has increased significantly. While a large part of this investment is spent on clinical trials, an important part of the development phase of any product is formulation design. Well designed formulations improve the efficiency and efficacy of a treatment, while failures in this design process can be extremely costly (Bauer et al., 2001).

The most commonly used delivery method for drugs are tablets, accounting for almost half of the drug products approved by the Food and Drug Administration (FDA), as they are simple, effective and robust. Formulation design is becoming increasingly more
important. The main aim of formulation design in tablets is to develop a tablet which will deliver the required amount of the drug to the patient at a rate which provides the maximum therapeutic benefit. Formulation scientists seek to develop novel formulations providing more control over the release of the drug in the patient. In order to do this they must understand the characteristics of the components involved. The active pharmaceutical ingredient (API) or drug is often mixed with a polymer, referred to as an excipient. The polymer can have several important functions. The first is to act as a carrier for the API. The API is mixed with the polymer, either mechanically or through a solvent preparation process where the drug is dispersed within the polymer. The polymers also serve as binders, allowing the formulation to be compacted into a tablet with sufficient mechanical integrity. Often the inherent dissolution characteristics of the pure drug compound are unsuitable for drug release and the polymer is used to enhance and control the release of drug.

The effects of the excipients on drug release are of great interest to pharmaceutical scientists designing controlled release formulations. Consequently there is significant interest in developing a better understanding of the physical and chemical processes which determine the release mechanisms of the drug.

Dissolution tests are the standard methodology for examining the dissolution profile of a tablet; however they provide little information concerning the behaviour of the matrix and processes within the matrix. Novel chemical imaging techniques promise to provide new insight into these processes. ATR-FTIR spectroscopic imaging is a powerful spatially resolved and chemically specific analytical approach. Using this methodology it is possible to analyse the concentration and spatial distributions of the components in a sample. It has been shown to be highly effective for studying the in situ compaction and dissolution of pharmaceutical formulations (Chan et al., 2005, van der Weerd et al., 2004, Kazarian and Chan, 2003). However, the full potential of applying this imaging approach to studies of tablet dissolution has yet to be realised.

1.2 Objectives

The main objective of the work presented in this thesis is to use model pharmaceutical formulations to further investigate and develop the applications of ATR-FTIR imaging
in the field of pharmaceutical science. Two facets of tablet behaviour were investigated, compaction and dissolution. One of the advantages of the ATR-FTIR imaging approach is the ability to use complementary analytical techniques. UV/Vis, X-ray microtomography and visible optical imaging were used to provide supplementary information, offering a more global view of the processes being studied.

The spatial and chemical information provided by using FTIR spectroscopic imaging in ATR mode with a diamond crystal provide a range of investigative opportunities. The major objectives of this work are presented below:

1. To study the *in situ* compaction of pharmaceutical formulations, to determine the ability of ATR-FTIR imaging to distinguish the compaction properties of different formulations.

2. The validity of FTIR imaging in ATR mode to study particles in compacted matrices was investigated. This was done by comparing FTIR data with 3D imaging data and through statistical analysis of particle size and component coverage at the surface of the samples.

3. The novel application of FTIR imaging to study the effects of modifying the pH microenvironment of a tablet matrix was tested. This was done by adding pH modifying compounds to the matrix to study the effect of the dissolution of domains of a weakly acidic drug.

4. The feasibility of using ATR-FTIR imaging to study the structure and dissolution of structured tablets, both multilayer and compressed coating formulations, was assessed. The chemical and spatial information provided by the approach was able to provide valuable information on how the ingress of water influenced the behaviour of the tablet sections and reveal the presence of any interactions between them.

5. The dissolution profiles of tablets in the custom flow through apparatus designed for FTIR imaging was compared with those of tablets dissolved in USP
dissolution apparatus. This may help facilitate an understanding of how valid it is to compare data gathered using these different methodologies.

In summary the main aims of this work are to further investigate the possibilities of using ATR-FTIR imaging to study pharmaceutical formulations. Both compaction and dissolution of these systems were investigated to understand and demonstrate the benefits that this powerful analytical approach can bring.

1.3 Thesis Outline

This thesis continues the application of ATR-FTIR imaging to pharmaceutical formulations. Chapters 2, 3 and 4 contain a review of relevant literature, which serve as a background for the research presented thereafter. Chapter 2 begins with an introduction to pharmaceutical formulations, specifically compaction and controlled release studies, before moving on to discuss pH modification and structured tablets. Chapter 3 covers the various relevant analytical approaches which have been applied to study pharmaceuticals, while Chapter 4 discusses FTIR spectroscopy and imaging. Chapter 5 then presents a general description of the experimental techniques and sampling methodologies used. The modifications made to these approaches for each section of work are discussed in the relevant chapters.

The presentation of results begins in Chapter 6, which is split into two sections. The first section covers the compaction of caffeine tablets with different polymer matrices, while the second section compared the FTIR data gathered at the surface with X-ray microtomography data of the tablet. Chapter 7 investigates the possibility of determining properties of a tablet such as component loading and particle size from FTIR imaging data, using statistical analysis to determine whether the data have achieved statistical significance. The work in Chapter 8 considers the application of FTIR imaging to studying the dissolution of crystalline ibuprofen from matrices containing pH modifying compounds and the effects of salt formation during dissolution. Chapter 9 demonstrates the use of FTIR imaging, in conjunction with UV/Vis dissolution profile data and visible optical imaging, to study the dissolution of tablet-in-tablet structured dosage forms. These tablets were used to create delayed release profiles and pH resistant formulations for the delivery of pH labile drugs.
Chapter 10 continues the work with structured tablets, presenting an investigation of multilayer formulations. The first section sees the use of these formulations to provide biphasic release, while the second section uses the structure of these tablets as a method to compare the dissolution profiles of tablets in the USP type I apparatus and the custom ATR-FTIR flow through cell. The thesis then concludes in Chapter 11 with a summary of the work and discussion of possible opportunities for continuation of this work in the future.
CHAPTER TWO

PHARMACEUTICAL FORMULATIONS
Chapter 2: Pharmaceutical Formulations

2 Pharmaceutical Formulations

2.1 Introduction

This chapter contains a review of pharmaceutical literature relevant to the topics covered in this thesis. The chapter starts with an introduction to tablet compaction, covering compaction processes and methods and the surface characteristics of compacted formulations.

Section 2.3 begins with an introduction to controlled release and its advantages for drug delivery. This is followed by a discussion of swellable polymers and their dissolution properties before introducing some models for drug release.

Sections 2.5 onwards discuss literature concerning the types of formulations studied for dissolution in the thesis. This includes, microenvironmental pH modification, ibuprofen dissolution and structured tablets specifically, tablet-in-tablet and multilayer formulations.

Drugs administered via solid oral dosage forms are almost never taken in an undiluted form. Instead the active pharmaceutical ingredient (API) is generally given in tablet form. Tablets generally consist of a mixture of the drug and other powdered components which are compressed into a solid tablet or compact (Nystrom and Karehill, 1996). The addition of the other components is designed to influence various characteristics of the final formulation (Jain, 1999). These additives are referred to as excipients. The most important functions of excipients are: guaranteeing the dosage, stability and bioavailability of the API (Pifferi and Restani, 2003). Excipients can also have many other properties, such as pH modifiers, disintegrants, release modifiers, flavour masking and lubricants (Pifferi et al., 1999).

2.2 Tablet compaction

Compaction is an important step in tablet processing. The mechanical strength and dissolution behaviour of the resulting tablets are strongly affected by the compaction properties of the ingredients, the compaction processes they undergo and the subsequent densities of the formulations produced.
Many drug compounds do not exhibit favourable compaction properties and therefore, it is important to choose excipients which form a strong coherent structure following compaction (Chan et al., 2005, Jain, 1999). The simplest method used for compaction of tablets is direct compression in which the constituent powders of the tablet are simply mixed and compacted, although drug content in these formulations is usually less than 30 wt% (Jivraj et al., 2000).

2.2.1 Compaction process

The first stage of compaction is to pour the powder material into a die cavity; at this stage the particles are loosely packed. A punch is then lowered into the die above the powder and compaction commences. Firstly the particles rearrange resulting in a decrease in volume due to a closer packing structure. This is then followed by elastic (reversible) and plastic (irreversible) deformation of the particles. As compaction progresses the density of the powders continues to increase due to continued particle deformation and particle fracture, depending on the properties of the powder (Jivraj et al., 2000). For example, microcrystalline cellulose (MCC) undergoes plastic deformation during densification, whereas in ceramic type materials, particles are usually either crushed or fractured (Cunningham et al., 2004).

The most important factor in determining how a powder blend behaves when being compacted into tablet form is the deformation behaviour (Jain, 1999). As discussed above this may take the form of elastic, plastic or brittle fracture deformations. These deformations have been characterised by a number of parameters, of which the Young’s modulus, yield stress and fracture toughness are important (Duncan-Hewitt and Weatherly, 1989). The way a material behaves following exposure to one of these deformation stresses, \( \sigma_d \), is a result of the on the deformation mode and the mechanical properties of a material (Rowe and Roberts, 1996). The Young’s modulus \( (E) \) is the ratio of the uniaxial stress to the uniaxial (deformation) strain \( (\epsilon) \) in the range of stress for which Hook’s law holds (Equation 2-1) and is therefore a measure of the elastic properties of the material (Cottrell, 1964).
Plastic deformation is dependent on yield stress and fracture toughness. When the yield stress, $\sigma_y$, is exceeded the particles no longer behave elastically and begin to flow and break as given by Equation 2-2 (Rowe and Roberts, 1996).

$$\sigma_d = \sigma_y$$  \hspace{1cm} \text{Equation 2-2}

For a plastic material yield stress is proportional to indentation hardness ($H$) Equation 2-3 (Rowe and Roberts, 1996).

$$\sigma_y = \frac{H}{3}$$  \hspace{1cm} \text{Equation 2-3}

The tendency of a material to undergo brittle fracture is dependent on the fracture toughness of the material. This is a measure of how much the contact areas between particles crush and fracture under compaction (Duncan-Hewitt, 1993). The brittle fracture stress is given by Equation 2-4 where $A_g$ is a constant dependent on geometry and the application of stress, $d$ is the particle diameter and $K_{IC}$ is the critical stress intensity factor, which describes how much stress would be needed to initiate catastrophic crack propagation. This is given by Equation 2-5 where $R$ is the fracture toughness of the material (Rowe and Roberts, 1996).

$$\sigma_d = \frac{A_gK_{IC}}{\sqrt{d}}$$  \hspace{1cm} \text{Equation 2-4}

$$K_{IC} = (ER_f)^{1/2}$$  \hspace{1cm} \text{Equation 2-5}

The type of deformation exhibited by a compound is dependent on the properties of the materials in the compact described above and the mechanism of compaction. Exact prediction of material behaviour is non-trivial however, the expected behaviour of pharmaceutical compounds based on the parameters described above has been summarised by Roberts and Rowe (Roberts and Rowe, 1987). Materials like microcrystalline cellulose, with low values for Young’s modulus, hardness and yield
stress can be described as soft. These materials will be ductile and will exhibit plastic flow whereas, drugs such as paracetamol and caffeine can be considered as moderately hard and are brittle. These materials will exhibit a mixture of fracturing and plastic flow under compaction (Roberts and Rowe, 1987).

Compaction of pharmaceutical powders can be strongly affected by environmental conditions. Humidity can have significant effects on pharmaceutical powder compaction, for example moisture present in the matrix can act as a lubricant or plasticiser, which will increase the resulting tablet density (Giordano et al., 1990, Elkhider et al., 2007, Khan et al., 1981). Formulations produced at a greater relative humidity will have different physical properties, such as exhibiting greater compaction densities or being mechanically stronger (Ahlneck and Alderborn, 1989), or in some cases capping (Khan et al., 1981). Other components specifically designed to lubricate the powders during compaction, such as magnesium stearate, can also be added to the matrix (Allen and Luner, 2000).

### 2.2.2 Analysis of surface characteristics

There has been great interest in the surface properties of compacted pharmaceutical tablets, and several methods have been used for studying the surface characteristics. Scanning electron microscopy (SEM) has been used to provide qualitative information about the surface. Karehill et al. used SEM to study double layer tablets following compression (Karehill et al., 1990). They established that the strength of bonding between the layers of the tablets reduced with decreasing surface roughness for plastically deforming components. Fracturing materials did not exhibit the same trend as the area of contact was at its greatest immediately following their initial fracturing (Karehill et al., 1990).

Atomic force microscopy (AFM) allows quantitative surface roughness data to be gathered with very high spatial resolution. This approach requires contact with the sample and can result in damage to the surface (Poon and Bhushan, 1995). Non-contact optical profilometry offers a non-destructive alternative for quantitative assessment of
surface characteristics. It requires minimal sample preparation and can produce spatial resolutions of approximately 1 µm (Silvennoinen et al., 1999).

While these approaches are very effective for generating spatial information regarding the surface of a tablet, they only provide data describing the surface roughness. No chemical information is provided, which is necessary for describing the distribution of components within the tablet matrix. In order to do this it is necessary to use chemically specific imaging approaches such as FTIR imaging or NIR imaging (Hilden et al., 2008, Chan et al., 2005, Elkhider et al., 2007). These approaches are described in greater detail in Section 3.5 and Section 4.2.

2.2.3 Lab scale compaction

Industrial tablet compaction systems use rotary presses which operate at high speed. However, on a lab scale using custom tablets, this is not feasible. During the development stages of a formulation single station presses are often used. When studying tablet dissolution using FTIR imaging, custom made tablet compaction systems have been used (Chan et al., 2005, van der Weerd et al., 2004). The pressures exerted on the powders in these cells can be as high as 120 MPa (Elkhider et al., 2007), which is relatively low compared to pressures of up to 500 MPa used in standard compaction in industry (Nystrom and Karehill, 1996). However, for controlled release systems it has been shown that a significant difference in the compaction force used, and consequently void fraction, between formulations will only manifest as a small difference in dissolution performance (Bettini et al., 1994).

2.3 Introduction to controlled release

A large number of drug delivery methods are available to formulation scientists; however tablets delivered via the oral route remain the most popular today (Fass et al., 2009). Controlled release tablets commonly consist of the drug or active pharmaceutical ingredient (API) and a polymer bulk as the two most important constituents. The polymer is normally a chemically inert component which is used to aid in the formation of the tablet and in controlling the release (Colombo et al., 2000). A significant amount of work has been done in the development of polymeric controlled drug release
formulations (Colombo, 1993). The aim of using controlled release systems is to improve the efficiency and effectiveness of the delivered drug in treating the patient (Uhrich et al., 1999).

Controlled release formulations have myriad advantages among which some of the most significant are reducing the toxicity of the drug, improving the efficacy, greater convenience and also better patient compliance (Uhrich et al., 1999). A common usage of controlled release is to produce sustained release formulations, which prolong the release of drug from the tablet matrix by slowing the erosion of the tablet and increasing the diffusion pathlength (Sung et al., 1996, Mitchell et al., 1993). Controlled release formulations can also be designed to have a range of other functions (Peppas et al., 2000), such as being, pH active (Badawy and Hussain, 2007) and environmentally responsive (Qiu and Park, 2001).

An example of a significant advantage of temporal controlled (sustained) release dosage forms is presented in Figure 2-1. This shows a comparison between the performance of controlled release formulations and non controlled release methodologies such as injections. The dosage of the controlled release formulation spends a much larger fraction of the time period within the therapeutic range (Langer and Peppas, 1983).

![Figure 2-1. Comparison of the performance of controlled release formulation (solid line) and repeated dosage (dashed line) in terms of drug concentration in blood plasma over time. The grey box denoted the therapeutic range.](image)

In the repeated dosage case in Figure 2-1 there is a peak immediately following administration of the dosage to toxic levels, which is subsequently falls rapidly to below the minimum effective level. The use of controlled release formulations benefits the
patient as not only does the dosage spend less time spent above the toxic level, but also above the minimum effective level (Uhrich et al., 1999, Lopina and Kanjickal, 2004). This is an example of one way in which controlled release systems can improve the reliability, patient safety and effectiveness of drug treatments.

2.3.1 Swellable polymers

In oral controlled release formulations, the polymer bulk of the tablet is used to create the controlled release properties of the tablet. Commonly these polymers are hydrophilic swellable polymers (Hogan, 1989). In drug delivery these polymers are often referred to as hydrogels, although they are technically not. Hydrogels are hydrophilic macromolecular compounds which maintain their shape following swelling due to permanent links in the molecular network (Lee, 1985). Swellable hydrophilic polymers are different in that they do not maintain their shape following swelling (Colombo, 1993). Swellable matrix systems in general take the form of compressed powders in monolithic tablet form (Colombo et al., 2000). The polymers used are often cellulose derivatives in which the controlled release properties are derived from their swelling behaviour. The swelling behaviour is caused by the formation of an expanding gel layer around the tablet on contact with water.

Of the many polymers used in controlled release, hydroxypropyl methylcellulose (HPMC) is perhaps the most important (Siepmann and Peppas, 2001). It is a water soluble cellulose ether, derived from cellulose (Colorcon, 2009b), the generalised chemical structure is shown in Figure 2-2. Reasons for its popularity are, that it is non-toxic, possesses favourable compaction properties and can be used in formulations with high drug loadings while still exhibiting controlled release (Pham and Lee, 1994). It is also nonionic and will not form complexes with ionic species such as metal salts, is stable over a wide range of pH (2.0 to 13.0) and it is metabolically inert (Colorcon, 2009b).
Chapter 2: Pharmaceutical Formulations

Figure 2-2. Image showing the chemical structure of HPMC. Where R represents –CH₃, a –CH₂CH(CH₃)OH group, or –H (Siepmann and Peppas, 2001).

The dissolution properties of HPMC are determined by three factors: (1) the methoxy group content; (2) the hydroxylpropoxy group content; (3) the molecular weight. The United States Pharmacopeia defines four types HPMC based on the methoxy group content and hydroxypropoxy group content. These are: HPMC 1828, HPMC 2208, HPMC 2906, HPMC 2910, where the first two numbers represent the –OCH₃ percentage and the second two numbers indicate the –OCH₂CH(CH₃)OH percentage (Siepmann and Peppas, 2001). These factors all influence the physicochemical properties of the polymer. This manifests itself primarily through differences in the behaviour of the gel layer. The greater the molecular weight of the polymer chains involved, the higher the viscosity of the gel formed (Colorcon, 2009a).

The glass transition temperature \(T_g\), which is very important to the dissolution properties has been reported as lying between 154 and 184°C (Johnson et al., 1991, Siepmann and Peppas, 2001). During dissolution the dissolution medium enters the polymer matrix. The solvent acts as a plasticiser, increasing the mobility of the polymer chains, causing them to transition from being in the glassy state to the rubbery state (Lee and Peppas, 1987). The solvent effectively lowers the glass transition temperature of the matrix, therefore compounds with a lower initial glass transition temperature require less solvent to undergo the glassy/rubbery transition.

2.3.2 Dissolution of swellable polymers

Dry HPMC exists as a glassy (amorphous) polymer. Upon contact with water HPMC based tablets will go through several processes:
1. Water intake into the matrix. The water serves as a plasticizer lowering the $T_g$ of the HPMC. As $T_g$ lowers the polymer transitions from being in the glassy state to the rubbery state.

2. The HPMC swells forming a gel and the dimensions of the tablet increase.

3. The presence of water facilitates dissolution of the drug which begins to diffuse out of the tablet. Only dissolved drug can diffuse, non-dissolved drug will not, though translocation of drug particles may occur due to the expansion of the polymer matrix.

4. As the water content rises the gel becomes more swollen and the diffusivity of the drug increases.

5. As the polymer becomes completely saturated with water it will begin to dissolve however, drug dissolution may long since have been completed.

The formation of the gel layer is the most important part of the controlled release process from tablets containing swellable polymers. The formation of the gel layer is what shapes the performance of drug release (Sung et al., 1996). If the initial gel layer forms too slowly water ingress through the matrix is rapid causing the matrix to disintegrate and the drug to dissolve prematurely. The gel layer is defined as the distance between the penetration and dissolution fronts (Harland et al., 1988).

It is for its gel forming properties that HPMC is seen as a suitable polymer for controlled release formulations, whereas polymers such as hydroxypropyl cellulose (HPC) and carboxymethyl cellulose (CMC) do not establish a gel layer in a sufficiently short space of time (Colombo et al., 2000). These polymers may be added to HPMC matrices to adjust the release properties, where HPC has been seen to increase the rate of release from HPMC matrices (Vueba et al., 2006) and CMC has been used to slow release (Dabbagh et al., 1999).
The major features of a dissolving swellable tablet are illustrated in Figure 2-3. The barrier of the gel layer serves to regulate water ingress and consequently drug dissolution and diffusion within the matrix. The gel begins to form upon contact with water; at this point the polymer chains are still highly entangled. Further outwards from the point of swelling onset the water content of the gel is much greater and the entanglement of the polymers is looser, this marks the onset of the diffusion layer of the gel, where full gellification has occurred. At the outer edge of the gel layer the water content of the gel reaches the extent at which full disentanglement of the chains occurs, this is defined as full dissolution of the polymer (Kazarian and van der Weerd, 2008, Narasimhan and Peppas, 1996, Colombo et al., 2000). The entanglement of the polymer chains at various stages is illustrated in Figure 2-4.

The exact determination of these fronts in certain systems is somewhat disputed with several groups postulating what they believe is the most correct interpretation (Gao and Meury, 1996, Bettini et al., 2001), the approaches to study these phenomena are compared in Section 3.4. However, most recently they have been explained by Kazarian.
and van der Weerd (Kazarian and van der Weerd, 2008), with the aid of FTIR imaging as follows (inside to outside):

1. True water penetration front exhibiting partial dissolution of the drug and only limited gelling of the polymer.
2. Total gellification of the HPMC, through which diffusion of the drug occurs.
3. Erosion/dissolution front of the polymer.

### 2.3.3 Drug release mechanism

In order for the drug within the matrix to dissolve out of the tablet and into the dissolution medium it must diffuse through the gel layer of the swelling tablet. Therefore the thickness and concentration of polymer in the gel layer are important factors in the release of the drug. The gel layer thickness is dependent on the rate of penetration of the dissolution medium, the disentanglement of the polymer chains and mass transfer of the polymer and drug in the dissolution medium (Pham and Lee, 1994).

Initially penetration of the dissolution medium into the matrix is the dominant process, while relatively little disentanglement of the polymer chains is seen. This leads to formation of the gel layer. As the thickness of the gel layer increases then the path length for diffusion increases, slowing the intake of the solvent. This leads to a slowing of the swelling as penetration and disentanglement rates begin to coincide. The thickness of the gel layer only begins to decrease once the majority of the polymer has entered the rubbery phase and the disentanglement/erosion rate begins to dominate. The lower the viscosity of the HPMC the faster it will both swell and erode (Pham and Lee, 1994). For highly soluble drugs diffusion through the gel layer is the dominant release process whereas, for insoluble drugs release mainly occurs due to erosion processes (Sung et al., 1996).

### 2.4 Modelling of drug release

As described above, the release kinetics from swellable erodible formulations are governed primarily by matrix erosion (polymer dissolution) and drug diffusion. Significant work has been done to model drug release from dissolving polymer systems.
The most well known model is probably the Higuchi model (Higuchi, 1961), which when presented in its most basic form is shown in Equation 2-6.

\[ \frac{M_t}{A_s} = \sqrt{D(2c_0 - c_s)c_s t} \]  

**Equation 2-6**

Where \( M_t \) is the cumulative drug released at time \( t \), \( A_s \) is the surface area of the controlled release system exposed to the dissolution medium. \( D \) is the diffusivity of the drug in the polymer, \( c_0 \) is the initial drug concentration and \( c_s \) is the solubility of the drug in the polymer. Equation 2-6 can be condensed to Equation 2-7.

\[ \frac{M_t}{M_\infty} = K\sqrt{t} \]  

**Equation 2-7**

Where \( M_\infty \) is the total amount of drug released given infinite time and \( K \) is a constant which is based on the design variables of the system (Siepmann and Peppas, 2001). The advantage of this model is its simplicity as the drug release fraction is proportional to the square root of time. However, it is not without its drawbacks and when it is applied then the following major assumptions should be considered, most of which make this model inappropriate for HPMC based systems: 1) Initial drug concentration must be much greater than the solubility of the drug. 2) There should be negligible swelling or polymer dissolution. 3) Perfect sink conditions are maintained. 4) Finally, drug diffusivity does not change (Siepmann and Peppas, 2001).

### 2.4.1 Power law model

An equation which has become very common for analysing controlled release formulations is that proposed by Ritger and Peppas as shown in Equation 2-8 (Ritger and Peppas, 1987a).

\[ \frac{M_t}{M_\infty} = k t^n \]  

**Equation 2-8**

It is a power law, much like the condensed version of the Higuchi model shown in Equation 2-7. However, in this equation \( k \) is a kinetic constant and \( n \) is a diffusional
exponent. The value of \( n \) can be varied for different geometries and release regimes and the equation is valid for the first 60% of drug released. For Fickian diffusion, depending on the aspect ratio of the tablet, the value of \( n \) can range between 0.43 and 0.50. For non-Fickian diffusion the value of \( n \) ranges between 0.43 and 1. These values are summarised in Table 2-1 (Ritger and Peppas, 1987b).

Table 2-1. Value of exponent \( n \) for various geometries and drug release mechanisms

<table>
<thead>
<tr>
<th>Diffusional exponent, ( n )</th>
<th>Drug release mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin Film</td>
<td>Cylindrical sample</td>
</tr>
<tr>
<td>0.5</td>
<td>0.45</td>
</tr>
<tr>
<td>0.50 (&lt; n &lt; 1.00)</td>
<td>0.45 (&lt; n &lt; 0.89)</td>
</tr>
<tr>
<td>1.0</td>
<td>0.89</td>
</tr>
<tr>
<td>Spherical sample</td>
<td></td>
</tr>
<tr>
<td>0.43</td>
<td>0.43 (&lt; n &lt; 0.85)</td>
</tr>
<tr>
<td>0.85</td>
<td>Case-II transport</td>
</tr>
</tbody>
</table>

The power law is still subject to many of the same limitations of the Higuchi model, such as negligible size change, constant diffusivities and perfect sink conditions. Equation 2-8 describes two physical effects on the dissolution of tablets. If \( n = 0.5 \) then dissolution is purely diffusion controlled however, if \( n = 1 \) then dissolution is governed by Case-II transport (for slab type geometry). In Case-II transport the relaxation of the polymer chains in the matrix governs the release of the drug (Ritger and Peppas, 1987b). If the value of the exponent \( n \) lies between the 0.5 and 1 then the release is termed as anomalous, meaning there is a contribution from both the Fickian and Case II transport modes. For cylindrical tablets containing HPMC it has been shown that the value of \( n \) is approximately 0.6 (Skoug et al., 1993). When the value of \( n \) is close to 1 a constant release rate (zero-order release) will be produced, which can be obtained in monolithic forms through careful polymer selection. This has been achieved using low molecular weight PVA. The value of \( n \) was found to be very close to 1.0 indicating erosion controlled release (Conte et al., 1988). Baveja et al. were able to obtain zero-order release from HPMC matrices by adding CMC to control swelling. It was found that the value of \( n \) was 0.89. The zero-order kinetics were attributed to the fact that a constant diffusional path length was maintained (Baveja et al., 1987).

A similar equation to that seen in Equation 2-8 has been introduced by Peppas and Sahlin in which the Fickian and non-Fickian contributions are separated into two terms as shown in Equation 2-9 (Peppas and Sahlin, 1989).
\[
\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m}
\]  
\text{Equation 2-9}

Where \( k_1 \) is the diffusional constant and \( k_2 \) is the relaxational constant and \( m \) is the diffusional exponent. The advantage of using this approach is that the relative contributions of diffusion and relaxation can be measured using Equation 2-10.

\[
\frac{R}{F} = \frac{k_2 t^m}{k_1}
\]  
\text{Equation 2-10}

Where \( R \) is the relaxational contribution and \( F \) is the Fickian contribution. This equation has been used by Bettini et al. to monitor the \( R/F \) ratios of drug release from cylindrical tablet matrices with impermeable caps on the top and bottom (Bettini et al., 1994). It was found that the \( R/F \) ratio was much larger for tablets with the impermeable coverings, indicating that the relaxational contribution is much more important for these formulations.

### 2.5 Microenvironmental pH modification

The performance of a dissolving drug can be modulated by adding acidic and basic compounds to the tablet matrix. This has the effect of modifying the pH of the tablet microenvironment.

#### 2.5.1 Selection of pH modifier

The selection of a pH modifier can be very complex as the concept of pH cannot strictly be applied to solid formulations (Badawy and Hussain, 2007). It has been suggested that a suitable means for selection of a pH modifier should be based on the pH of saturated solutions (Badawy et al., 1999). In that study it was found that fumaric acid and citric acid despite having similar \( \text{p}K_a \) values had distinctly different saturated pH values. The pH value of citric acid was found to be around 0.4 and fumaric acid 2.5. However, this is not necessarily representative of the pH within the matrix. It is a measure of what the highest pH would be, though this may just be with very small localised domains, but it is a standard by which to compare possible pH modifiers.
2.5.2 Measurement of pH in pharmaceuticals

Several methodologies have been used in attempts to measure the pH within pharmaceutical formulations. The slurry method uses a pH meter to measure the pH of a slurry of the formulation (Badawy et al., 1999). However, the measured pH of the slurry depends on the concentration of the slurry used and will obviously differ from the pH in the solid tablet form. Other methods used include pH microprobes (Doherty and York, 1989) and the addition of pH indicator dyes to the system (Zinchuk et al., 2005). The advantage of adding indicator dyes to the system is that it is a simple approach which gives an indication of pH within the matrix that can be observed with a standard video camera.

2.5.3 pH modification in controlled release formulations

There are many examples in literature of adding pH modifiers to tablet matrices to adjust the solubility of weakly basic drugs (Streubel et al., 2000a, Thoma and Zimmer, 1990, Tatavarti and Hoag, 2006). In these formulations, the addition of acidic compounds will increase the rate of release of the drugs from the formulations and the addition of basic compounds will result in diminished release. Thoma and Zimmer tested the effects of a range of acids on the dissolution of noscapine hydrochloride (Thoma and Zimmer, 1990). It was found that low solubility acids did not maintain a low enough pH, while highly soluble acids dissolved out of the matrix too rapidly. Succinic acid was found to be the most successful due to a solubility which allowed it to maintain a low pH environment without dissolving out of the formulation too rapidly (Thoma and Zimmer, 1990). Less work exists on the use of pH modifiers for controlling the release of weakly acidic drugs (Riis et al., 2007, Pygall et al., 2009, Rao et al., 2003, Fuder et al., 1997). It should, however, be equally effective.

Enteric polymers have been used to enhance the release of pH sensitive drugs. Polymers such as Eudragit and Carbopol exhibit pH dependent solubility and can be used to “program” formulations to release the drug at the correct point in the body. Indeed these polymers have their own effect on the pH of the matrix and it has been shown by Tatavarti et al. that this effect may be as significant in enhancing the release of drugs as the increased dissolution rate of the polymers (Tatavarti et al., 2004).
2.5.4 Dissolution of ibuprofen

Ibuprofen is one of the most commonly taken drugs in the world, the UK market alone for ibuprofen is £300 million a year. However, it is poorly soluble in water and may crystallise in the gut where these crystalline deposits can irritate the lining of the gut causing stomach ulcers (Lanza et al., 1979). In elderly patients, taking this drug over the long term can be a significant problem.

Several approaches have been used to enhance and control the release of ibuprofen. Ibuprofen can be dispersed in water soluble polymers such a polyethylene glycol (PEG) (Najib and Salem, 1987) or creating complexes with cyclodextrins (Mura et al., 1998).

The solubility of the compound increases above pH 5.5 (Levis et al., 2003) as ibuprofen is a weak acid and hence is much more soluble in basic conditions. It will even crystallize when dissolving in neutral pH (Kazarian and Chan, 2003). However, raising the pH of the tablet microenvironment may improve the dissolution of ibuprofen from solid tablet matrices.

Upon the addition of ionic species to the matrix, salts may be formed with oppositely-charged drugs, of both low solubility and high solubility (Feely and Davis, 1988). When using pH modified formulations, the pH is adjusted within the tablet matrix; therefore it is important to understand the behaviour of the drug within the matrix. This may take the form of increased or decreased solubility of the drug, or the formation of salts.

2.6 Structured tablets

As described above pharmaceutical tablets are generally simple monolithic structures. There may also be a thin coating on the formulation to improve the aesthetics or facilitate easy swallowing. Through the use of excipients, such as HPMC, these formulations can achieve controlled and extended release profiles as discussed in Section 2.3. In order to exert more control over the release of the API from the formulation it is possible to construct more complex tablet structures. Multilayer and tablet-in-tablet formulations will be discussed in detail below.
2.6.1 Tablet-in-tablet structures

Pharmaceutical tablets often have external coatings, which can be used for something as simple as masking the bitter taste of the API underneath; however, they are regularly used to control or enhance the release of the API in some way. Film coating systems have been used for coating tablets, although, this is not always a favourable technique due to the solvents used to prepare such tablets and legislation on exposure limits for workers (Bose and Bogner, 2007). Compression coating is an effective method for coating tablets, in which a shell section can be directly compacted around the core section carrying the drug payload (Ozeki et al., 2004). A schematic diagram of the formulation structure is shown in Figure 2-5.

![Figure 2-5. Schematic diagram of compression coated tablet form.](image)

Matsuo et al. used the outer shell as a protective barrier creating delayed release tablets (Matsuo et al., 1995). The in vitro dissolution of the tablets was monitored by UV/Vis spectroscopy and it was shown that the lag-time could be controlled by both particle size and amount of polymer in the outer shell. Ozeki et al. have also shown that it is possible to vary the lag-time by changing the thickness of the shell layer (Ozeki et al., 2004).

Ishino et al. have shown that rapid delayed release can be achieved by controlling the disintegration of the outer shell (Ishino et al., 1992), while Ueda et al. have used a spherical four layered formulation to achieve rapid drug release and programmed lag-times (Ueda et al., 1994). These studies have both produced dissolution profiles demonstrating the delayed release mechanism and the ensuing controlled release thereafter.
Ordered release can be achieved by using a tablet-in-tablet system, in which there is a central core wrapped in an outer layer. This technique has been used for biphasic fast/slow release by Lopes et al. (Lopes et al., 2007) to develop a biphasic release system and study the effects of a combined fast release coat with controlled release core. Ibuprofen was used as the model drug for both sections of the tablet. HPMC and ethyl cellulose (EC) were used as the excipients in the controlled release core. The excipient for the outer section was microcrystalline cellulose, mixed with sodium croscarmellose as a superdisintegration component. The tablets were formed using a lightly modified version of standard compaction methods. The dissolution was monitored using UV/Vis spectroscopy.

The shell structure of these tablets can be used as more than just a barrier to delay release. Indeed, Chan and Zhang used hydroxypropyl cellulose and sodium alginate to coat freeze dried cells, protecting them from the acidic environment of the stomach and enhancing the efficiency of their delivery to the large intestine (Chan and Zhang, 2005).

### 2.6.2 Multilayer and zero-order release tablets

Standard monolithic tablets containing a uniformly distributed drug generally provide continuously diminishing release rates (Siepmann et al., 1999a, Siepmann et al., 1999b). More complex tablet structures offer greater control and flexibility over the delivery of the drug in the patient and can create many different release regimes.

Tablets with a multilayered structure offer an opportunity to modify release profiles. One example is bimodal release, while this pattern of release can be achieved using other tablet geometries such as core-in-cup tablets (Sirkiä et al., 1994), Streubel et al. used Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS) based tablets (Streubel et al., 2000b) for pH dependent bimodal release.

The multilayer structure has been successfully applied to achieve biphasic delivery for the purpose of quick/slow release, which can simply be achieved by using one fast release layer and another controlled release matrix layer (Conte and Maggi, 1996). Uekama et al. used a double layer tablet for biphasic release of piretanide, with β-
cyclodextrin being used in the fast layer and ethyl cellulose and hydroxypropyl methylcellulose (HPMC) being used in the slow release layer (Uekama et al., 1990). Maggi et al. used double layer tablets for biphasic release of two different drugs, in which the speed of release from the fast release layer was determined by a super disintegrant added to the layer (Maggi et al., 1999).

Another common purpose of using multilayered tablets is to produce zero-order release tablets, which have the desirable property of exhibiting a constant release rate of drug (Chidambaram et al., 1998, Abdul and Poddar, 2004, Conte et al., 1993, Qiu et al., 1998, Krishnaiah et al., 2002). These multilayer formulations employ barrier layers as a method for limiting the area of the tablet exposed to the dissolution medium. However, zero-order release can also be attained using monolithic tablets (Baveja et al., 1987). Baveja et al. used non-ionic HPMC and anionic sodium carboxymethylcellulose in a carefully controlled ratio with each other and the drug. This led to the swelling and expansion of the HPMC being balanced by the erosion of the gel layer, maintaining a constant diffusion length for the drug. Zero-order release has also been demonstrated using doughnut shaped tablets (Kim, 1995).

Colombo et al. (Colombo et al., 1990) achieved a close to linear release profile by applying impermeable barrier coatings to the top and bottom face of HPMC based tablets to control the direction of swelling, restricting changes in the surface area for release. Further work found that manually applied film barriers could be replaced in favour of swellable HPMC barriers that would swell with the core maintaining the surface area of the exposed core (Conte et al., 1993).

### 2.6.3 Analysis methods for structured tablets

The dissolution of pharmaceutical tablets is often monitored using UV/Vis analysis which produces a profile of drug released over time. However, it is often important to understand how tablets behave during dissolution, particularly in the case of structured tablets. Therefore it can be advantageous to use imaging techniques to study their formation and dissolution. This has been done using a video camera to film layered tablets during the various stages of dissolution (Conte et al., 1993). However, this required the addition of coloured compounds to the dissolving matrix and photography
may not provide quantitative information regarding the concentrations of the components in a system.

When studying tablet compaction and dissolution particularly of structured tablets, it is desirable to investigate the distribution of various components within the formulation, as this will influence the chemical and physical properties of the tablet (Chan et al., 2003). Chemical imaging approaches such as FTIR, NIR and Raman imaging and mapping have been used for this (Chan et al., 2005, Clarke et al., 2001). Chemical imaging methodologies such as FTIR imaging have also been successfully applied to studying the dissolution of pharmaceuticals. FTIR imaging has been used to provide quantitative information regarding water ingress, component dissolution, polymer swelling as well as revealing phenomena such polymorphic transitions and salt formation (Kazarian and Chan, 2003, van der Weerd and Kazarian, 2005, Koenig, 2002). A discussion of relevant pharmaceutical analysis approaches follows in Chapter 3 and a discussion of infrared spectroscopy and imaging can be found in Chapter 4.
CHAPTER THREE

ANALYTICAL METHODS FOR PHARMACEUTICALS
3 Analytical Methods for Pharmaceuticals

3.1 Introduction

Chapter 3 reviews relevant analytical approaches that have been applied to study the formation and dissolution of pharmaceutical formulations. The chapter starts with a discussion of established in vitro dissolution approaches for solid dosage forms.

Section 3.3 introduces X-ray microtomography as a three dimensional imaging procedure used largely for analysis of static samples as well as covering MRI. Section 3.4 covers the topic of visible optical imaging for studying tablet dissolution.

Section 3.5 onwards then discusses the usage of spectroscopic techniques for investigating pharmaceutical formulations, including near-infrared spectroscopy including imaging and mapping.

3.2 Tablet dissolution

In vitro dissolution testing was originally used to investigate the amount and extent of drug release from solid dosage forms; but it is now used for studying many types of delivery forms (Siewert et al., 2003). Dissolution tests are used in the development of new products, determination of bioequivalence and quality control (Cohen et al., 1990). An important application is providing information on the dissolution properties of various candidate formulations, to find that which is most suitable for purpose. If the tests do not in some way reflect the in vivo performance then they may be irrelevant as a predictive tool (Löbenberg and Amidon, 2000). They are also used to establish in vitro/in vivo performance correlations and can be used in place of a large bioequivalence study (Dressman et al., 1998). As a result of this much work has been done to develop biologically relevant artificial dissolution media, such as Fed and Fasted States Simulated Intestinal Fluids (FeSSIF and FaSSIF) (Aiache et al., 1997) and other biorelevant dissolution media (Galicia et al., 1998, Nicolaides et al., 1999, Wei and Löbenberg, 2006). For conventional solid oral dosage forms four different dissolution apparatuses are used: Basket, paddle, reciprocating cylinder and flow-through cell (Siewert et al., 2003). The most commonly used pieces of apparatus are the basket and
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paddle methods, so called USP I and USP II (Azarmi et al., 2007) apparatuses shown in Figure 3-1.

![Figure 3-1. Schematic diagram of USP I (basket) and USP II (paddle) dissolution apparatus.](image)

The formulation is placed inside the basket or in the bottom of the flask for the paddle method and the chamber is filled with dissolution medium. The basket is then rotated and the concentration of the drug released into the dissolution medium is measured as a function of time. For these standard dissolution tests consistency of application is required for meaningful comparison, therefore there are very strict calibration settings, and modifications are made to the apparatus over time to help improve consistency (Beckett et al., 1996).

The method by which the concentration of the drug in the dissolution medium is determined is UV/Vis spectroscopy. This makes use of radiation in the region of the electromagnetic spectrum between 190 and 900 nm. Much like other spectroscopic techniques such as infrared spectroscopy, the concentration of the component is determined via absorbance at a characteristic frequency of absorption. Using the Beer-Lambert law, the absorbance is proportional to concentration of the species. However, as opposed to exciting molecular vibrations such as in infrared spectroscopy, UV/Vis spectroscopy is based on electronic transitions (Owen, 1996).

UV/Vis spectroscopic analysis is generally used in pharmaceutical science to produce a dissolution profile. In the case of the USP dissolution procedures this takes the form of
a plot of concentration of the component of interest in the dissolution medium as a function of time. This methodology is simple, effective and sensitive. However, dissolution analysis using UV/Vis spectroscopy with dissolution tests only provides information about the global dissolution rate of a sample and gives no information about the physical or chemical processes occurring within the sample (e.g. tablets).

### 3.3 X-ray microtomography

The bulk properties of a tablet, such as density and particle distribution are very important to dissolution properties of the formulation. X-ray microtomography provides a three dimensional non-destructive analytical approach with a wide range of applications, among which is the study oral dosage formulations (Stock, 2008). Previously, synchrotron sources of radiation were used to study particulate samples (Seidler et al., 2000, Richard et al., 2003). With the advent of portable microtomography equipment this is no longer necessary and successful application has been seen for the study of pharmaceutical formulations.

The first application of X-ray microtomography to pharmaceuticals was performed by Farber et al. to study the morphology and porosity of granules (Farber et al., 2003). It was found to be less effective than mercury porosimetry for determining pore size, due to limited spatial resolution. X-ray microtomography still supplied valuable information concerning the morphology of the pores, and their spatial distribution and interconnectivity (Appoloni et al., 2002). Sinka et al. were able to extract precise measurements of localised density variations within a tablet matrix (Sinka et al., 2004). Busignies et al. studied the density distribution in compacted cylindrical tablets to find that density throughout the tablets was highly non-uniform (Busignies et al., 2006) as shown in Figure 3-2.
Figure 3-2 shows that the density is not uniform throughout the tablet. It was found that the tablet was denser at the edges than in the centre. This was attributed to friction at the wall during compaction of the tablet. X-ray tomography has also been used to study density distribution within structured tablets. Ozeki et al. used it to study the density distribution within dry coated tablets to determine the density of the core section (Ozeki et al., 2003). Yang and Fu studied the compaction and mixing of MCC particles, in order to deliver sufficient contrast in the images it was necessary to impregnate the particles of one of the materials with a high X-ray attenuation coefficient substance (lead acetate) (Yang and Fu, 2004). If there is a significant difference in density between the surrounding matrix and particles distributed within it, then X-ray microtomography can be used to distinguish the particles. This has been shown for citric acid particles (Hancock and Mullarney, 2005). X-ray microtomography has been used to study tablet dissolution by Karakosta et al. and clearly showed changes to the void structure within the tablet (Karakosta et al., 2006). However, the contrast of images between the polymer and the ingressing water was low and image acquisition required around 40 minutes.
A schematic representation of X-ray microtomography is shown in Figure 3-3. The X-rays are emitted from the source and pass through the sample on the way to the detector which measures the intensity of the transmitted beam, creating a two dimensional shadow image. The greater the mass density of the material and the path length of the X-rays in the material, the greater the absorbance of X-rays will be (Sasov and Van, 1998). The sample is then rotated in front of the source and two dimensional images are acquired from multiple angles. A Fourier analysis technique based on the Radon transform is used to compare the images from each rotational step and from this a three dimensional density map can be constructed (Hancock and Mullarney, 2005).

As shown in Figure 3-4 the spatial resolution of X-ray microtomography can be very good, up to around 4 μm (Zeitler and Gladden, 2009). However, on smaller portable machines the spatial resolution is often much lower, around 50 - 80 μm (Kohout et al., 2006).
3.4 Imaging of tablet dissolution

Imaging of tablet dissolution can help to improve the understanding of the physical and chemical mechanisms involved in tablet dissolution, and multiple approaches have been used to investigate these processes. Imaging methodologies are advantageous because they provide supplementary information about the tablet dissolution that would otherwise be unseen in the industry standard USP dissolution tests. In this section MRI and visible optical imaging will be discussed, although, numerous other approaches have been applied such as confocal laser scanning microscopy (Cutts et al., 1996) and cryo-SEM (Melia et al., 1993) but are outside scope of this review.

Magnetic resonance imaging (MRI) is a three dimensional imaging approach and consequently has several advantages. A sample can be completely immersed in dissolution medium while a slice image through the sample is taken, whereas many other approaches require constraining of the sample in two dimensions. However, the chemical sensitivity of non-spectroscopic MRI is low. Quantification of drugs and their release from formulations is only possible through use of a marker such as fluorine (Fyfe and Blazek-Welsh, 2000). MRI images of pharmaceutical solids are generally not conducted directly; instead, the signal of the water interacting with a dissolving polymer is measured (Zeitler and Gladden, 2009), for example investigating the formation of the gel layer of a dissolving HPMC tablet (Rajabi-Siahboomi et al., 1994). MRI does have the advantage that it can be used in conjunction with the existing USP IV apparatus without major modification (Fyfe et al., 2000).

Optical photography has been applied to study the dissolution of polymer based tablets. This is done through the addition of coloured drugs to the dissolving matrix; however, quantification of component concentration from the data gathered via this approach is not possible. Several groups have used this approach to determine the formation of fronts during dissolution. Colombo and co-workers, using buflomedil pyridoxal phosphate as a coloured drug defined three boundaries: 1) The glass transition boundary, where the gel matrix begins. 2) Drug diffusion boundary, the point at which the drug starts dissolving and diffusing. 3) The erosion boundary where the matrix completely breaks down due to erosion or dissolution (Bettini et al., 2001). Gao and
Meury defined somewhat different boundaries. 1) True penetration front, little or no swelling has occurred, but water has ingressed through pores. 2) Phase transition front, the glassy material becomes a transparent gel matrix. 3) Dissolution front, matrix has completely disappeared through erosion or dissolution (Gao and Meury, 1996). Visible optical imaging was used in conjunction with FTIR imaging by Kazarian and van der Weerd (Kazarian and van der Weerd, 2008) (discussed further in Section 4.6.3), which confirmed the work by Gao and Meury. It is important to note that these optical imaging approaches display sharp fronts more clearly than FTIR imaging. The fronts seen using these approaches are sharp, unlike the smooth gradients predicted by Fick’s law, or shown by FTIR imaging. This is indicative of the fact that they do not display quantitative data, rather they identify effects that occur at certain concentrations, such as changes in refractive index which reduces the scattering of light from the material (Kazarian and van der Weerd, 2008). This approach has also been applied to study the dissolution of structured tablets as shown in Figure 3-5 (Conte et al., 1993).

![Figure 3-5](image)

**Figure 3-5. Photographic image of cross-section of press coated tablet following four hours of dissolution (Conte et al., 1993).**

As shown in Figure 3-5, in order to obtain information concerning the internal processes of the tablet during dissolution it was necessary to remove the tablet from the dissolution medium in order to cross-section it. These images also provide little in the way of chemical information and the contrast between sections was poor. In order to improve contrast it was necessary to add coloured compound to sections of the matrix, as shown in Figure 3-6.

![Figure 3-6](image)

**Figure 3-6. Photographs taken in situ of dissolving multilayer tablets (Conte et al., 1993).**
Melia and co-workers used a fluorescent dye (Congo Red) to study the early stages of gel formation in HPMC (Bajwa et al., 2006). The fluorescence of the dye selectively increased when bound to β-D-glucopyranosyl sequences. This allowed imaging of the structural changes of the hydrating polymer as the gel layer formed. It was found that upon contact with the dissolution medium, the medium was drawn into pores in the surface of the tablet. The morphology of the particles of HPMC then changed as they swelled in a columnar fashion, forming the gel layer.

3.5 NIR spectroscopy

As described in Section 4.1 the near-infrared (NIR) region of the electromagnetic spectrum lies between the visible region and the mid-infrared (MIR) region. Near-infrared spectroscopy (NIRS) has gained significant popularity, especially within the pharmaceutical industry (McClure, 1994). This is because NIRS has several advantages over some other analytical techniques, it requires little or no sample preparation, remote measurements can be made using fibre optics, while chemical and physical properties of the sample can be predicted from one spectrum and it is relatively inexpensive (Reich, 2005, Herkert et al., 2001, Roggo et al., 2007).

MIR spectra usually contain well defined peaks that can be directly analysed using univariate analysis methods. However, NIR spectra often require multivariate processing using chemometric methodologies (Gendrin et al., 2008). This is due to the fact that the absorption bands of MIR and NIR spectroscopy have slightly different origins. The absorbance in MIR is a result of excitation of the fundamental vibrations within molecules. In NIR the bands are caused by combinations and overtones of –CH, –NH, –OH and –SH fundamental vibrations (Reich, 2005). Despite making the chemical information in NIRS slightly harder to elucidate, this does have certain advantages in sampling. As with MIR several sampling methodologies can be used, the most commonly used methods in NIR are transmission and diffuse reflectance. Due to the weaker absorbance of these overtones and combination bands, samples analysed using NIRS usually require little or no sample preparation (such as dilution), and samples can also be analysed through glass as it contains no X–H bonds. The detectors used do not require cooling, which make NIRS ideal for in-line analysis of industrial
pharmaceutical processes. As with MIR spectroscopy NIRS can be coupled with an FPA detector to provide chemical imaging capabilities (Koehler et al., 2002, Lewis et al., 2001).

### 3.5.1 Multivariate analysis

Univariate analysis uses one spectral band to produce chemical images and it is a simple and direct method for producing images. In systems with a large degree of overlap of the spectral bands, this method of analysis is not always possible and image artefacts can be induced (Chan et al., 2005). Rather than using a single band, multivariate analysis employs information from a range of spectral data. This allows the spectral properties and spectral distribution of components to be analysed.

Principal component analysis (PCA) and partial least squares (PLS) are the two most commonly used algorithms (Gendrin et al., 2008). The aim of using PCA is to reduce the dimensionality of the data matrix. This is done by removing correlation between variables. The data produced in chemical imaging can be thought of as a three dimensional matrix, \( D \), containing spatial data on two axes and spectral data on the third axis, \( n_a \times m_b \times \lambda_c \), where \( n_a \) and \( m_b \) are the number of pixels in the x and y axes and \( \lambda_c \) represents the spectral data points. The data are then unfolded to form a two dimensional matrix \( X \), such that \( X = i \times \lambda_c \), where \( i = n_a \times m_b \). The data are then projected onto a new component subspace and the principal components known as loadings are calculated. The principal components are chosen such that the first explains as much of the data as possible, while the second explains as much of the remainder as possible while remaining orthogonal to the first. The data projections onto the principal components are known as scores. The first principal components normally describe the most important information, whereas the later components mostly describe noise. By rejecting these noisier components, the dimensionality is reduced. The data are then folded back into the same spatial arrangement as in matrix \( D \), such that the loadings are in the correct spatial arrangement. While PCA is very useful for identifying components' differences from subtle spectral changes, it does not provide chemical information as the data produced are not spectra and the PCA loading will also describe negative values.
Factor Analysis (FA) is a similar approach to PCA, however, while PCA produces loading vectors, FA attempts to generate single component absorption spectra. Therefore, PCA is used to reduce the data into a smaller number of components and FA is used to determine what the components are which underpin the data. PLS is a different approach in which the aim is to establish a linear relationship between the spectral data of matrix $X$ and a matrix $Y$ containing reference data. This is done via a calibration step, using data for which the values of $X$ and $Y$ are well known. The data must then be validated using known values. The model can then be used for prediction, such as revealing the concentration of a component in each pixel of an image.

Having processed the data the final step is to extract useful information from the distribution map displayed. This can be as simple as applying a rainbow colour scale showing the distribution of a component in which red is high and blue is low concentration, or showing how similar to one of the generated factors the data in a pixel may be. RGB colour analysis can be used in which one colour is assigned to each component to show their distributions simultaneously. Image binarization aims to clearly separate the component of interest from the rest of the material in a sample to produce an image showing where a component is and is not present within a two colour image. This methodology does lose any dynamic information as the data are presented in a purely binary fashion. This requires thresholding of the data, which often requires the user to determine where the threshold will be set (Hilden et al., 2008).

### 3.5.2 Pharmaceutical applications of NIRS

NIRS has a large range of applications within the pharmaceutical industry. Analysis of intact solid dosage forms has largely focused on content determination (Chalus et al., 2005, Trafford et al., 1999), hardness (Morisseau and Rhodes, 1997), coating thickness (Moes et al., 2008) and prediction of dissolution rates (Freitas et al., 2005). Component identification may even be performed through blister packs by using NIR in transmission as shown by Maesschalk and Van den Kerkhof when they used NIRS in conjunction with a PLS based chemometric method to verify whether tablets were placebos or not for clinical trial tablets (De Maesschalck and Van den Kerkhof, 2005). Polymorphism is more commonly studied using MIR and Raman spectroscopy,
although, NIRS has been shown to be applicable to study these phenomena as well, for example Blanco et al. studied the polymorphisms of miokamycin (Blanco et al., 2000). NIRS can be used for particle sizing of powders (Frake et al., 1998), whilst simultaneously providing chemical information. When NIR light scatters from diffusely reflecting materials, this can result in a non-uniform or offset baseline. One of the variables upon which these scattering effects are dependent is particle size. It has been seen that there is an inverse relationship between reflectance and mean particle size (O'Neil et al., 1998). Moffat and coworkers compared the results of Forward Angle Laser Light Scattering (FALLS) with NIRS and found that using relatively simple chemometrics it was possible to accurately measure the median particle size using NIRS. Good calibration was also achieved from both sieved and bulk samples (O'Neil et al., 1998).

3.5.3 Pharmaceutical applications of NIR imaging

NIR imaging also has great potential for studying pharmaceutical formulations. In an early application Koehler et al. used NIR imaging to show and quantify the distribution of API in a tablet using PCA (Koehler et al., 2002). This showed that the API was distributed in clumps. Least squares regression using pure component spectra allowed them to quantify the amount of drug in the sample (Koehler et al., 2002). This approach has applications in many facets of pharmaceutical science (Dubois and Kidder, 2010, Gendrin et al., 2008).

An effective application of the imaging capabilities of NIR imaging has been seen in particle size analysis in solid dosage forms. Hilden et al. used NIR image analysis to determine the size and distribution of tartaric acid particles in a tablet matrix (Hilden et al., 2008). A principle component analysis was used for the separation of the tartaric acid particles from the surrounding matrix, by choosing the principle component spectrum which was most closely related to the difference between the tartaric acid spectrum and the excipient spectrum. Particles were then identified using contour delineation, a threshold was applied to create a binary image. It was found for this process that choice of a threshold level was non-trivial. When two particles lay in close proximity distinguishing between particles became difficult, and the results were very sensitive to the chosen threshold level as shown in Figure 3-7. A fine and coarse
threshold were chosen. When the contour level was set to fine, closely spaced large particles were well differentiated. Small particle fragments, which may have previously been part of the larger particle, which had fractured off and detached under compaction, were counted as individual particles. It also appeared that as a result of this thresholding some “real” particles were lost from the fine threshold level. When a coarse contour level was used large nearby particles were not well differentiated.

![Image of particle distribution](image)

**Figure 3-7.** Images showing particle distribution of tartaric acid using a fine contour level (left image) and coarse contour level (right image) (Hilden et al., 2008).

The particles in powder batches were sized using laser light scattering which produces particle sizes as mean equivalent diameters. The mean equivalent diameter approximates the diameter of the particles to that of a circle which occupies the same area. This is a fast and simple measurement of the particle size as long as the particles are roughly spherical. However, powdered materials often have non-spherical particles. The particle sizes in the batches used experimentally are also often determined by particle sieving. Sieving could in theory let through a particle with a very wide aspect ratio, i.e. a very long, narrow particle, for which the equivalent spherical diameter would be very different from the sieve diameter. Sieve diameter is often better approximated using other sizing methods, such as Feret’s diameter (Walton, 1948).

FT-NIR mapping has been combined with Raman mapping as a complementary technique to study heterogeneous pharmaceutical formulations (Clarke et al., 2001). Two samples were studied, one was used to verify the methodology, while the second was used to visualise the entire formulation. In the second formulation the drug and the inorganic binder were identified using Raman spectroscopy, while the diluent
disintegrant and cellulose derivative were identified using NIR spectroscopy. NIR and Raman maps were gathered from the same areas of the samples. The sampling aperture for NIR was set to 20 µm × 20 µm, while the spot size of the Raman laser was 5 µm. Therefore in order that the data could be overlaid, the X and Y direction step size was set to 20 µm for both. The data were used to identify tableting problems in the formulation, showing that the particle size and distribution of the binder was causing problems with tablets sticking to compaction punches.

Overall, NIRS and NIR imaging have been shown to be powerful vibrational spectroscopic techniques for the study of pharmaceuticals. Chapter 4 continues the discussion of spectroscopic approaches introducing and discussing FTIR spectroscopy and imaging.
CHAPTER FOUR

MID-INFRARED SPECTROSCOPY
4 Mid-Infrared Spectroscopy

Infrared spectroscopy has long been a useful analytical tool for studying pharmaceutical formulations. It has the potential to reveal much chemical information for both static samples and dynamic systems such as tablet dissolution. It provides complementary data to that obtained by conventional methods, such as the industry standard USP dissolution tests. These only produce a global dissolution profile, but do not provide any information concerning the internal processes within the sample. Therefore, a significant number of applications of FTIR spectroscopy have been developed to study such processes (Wartewig and Neubert, 2005).

4.1 Introduction to infrared spectroscopy

Infrared spectroscopy is the study of how radiation in the infrared region of the electromagnetic spectrum interacts with matter. It is a form of absorption spectroscopy and looks at the difference in the intensity of the light across a frequency range in the infrared region before and after interaction with the sample.

The range of wavelengths defined as the infrared region lies between 800 and 3×10^5 nm as shown in Figure 4-1. The unit of wavenumbers is commonly used in spectroscopy; it has the units of reciprocal distance (commonly cm^(-1)). It is the inverse of the wavelength, such that radiation with a wavelength of 10 μm will have a wavenumber value of 1000 cm^(-1).

The infrared region is split into three major regions, near-infrared, so called because it lies close to the visible region of the electromagnetic spectrum and is found between 12000-4000 cm^(-1), then mid-infrared, which is found between 4000-400 cm^(-1), and far-infrared which is found between 400-20 cm^(-1). The far-infrared region is in the low energy region and is used for studying rotational spectroscopy; the near-infrared is in the higher energy region and is used for studying molecular overtone and combination vibrations. Mid-infrared radiation is used for studying fundamental molecular vibrations.
The covalent bonds in molecules vibrate at characteristic frequencies. Absorbance of infrared light takes place when the frequency of the infrared light is the same as the natural frequency of vibration of the atoms in the molecule. The different vibrations are referred to as vibrational modes. In a molecule with N atoms, the number of vibrational modes (vibrational degrees of freedom) for a linear molecule is given by \(3N - 5\) and for a non-linear molecule by \(3N - 6\).

The vibrations for carbon dioxide are shown in Figure 4-2. These are all the possible vibrations of the carbon dioxide molecule. The two bending modes are the same but occur in different planes, therefore these vibrations are degenerate and absorb infrared light at the same frequency.

![Symmetric stretch - 1288cm\(^{-1}\)](image1)

![Asymmetric stretch - 2349cm\(^{-1}\)](image2)

![Bending mode - 667cm\(^{-1}\)](image3)

**Figure 4-2. Vibrational modes of carbon dioxide (Atkins and de Paula, 2002)**

Not all of these modes are infrared active, meaning infrared light will not excite every vibration. The activity of these modes is dependent on selection rules. In order for a
mode to be infrared active the motion must be accompanied by a change in the dipole moment of the molecule. Therefore, the symmetric stretch is not infrared active.

The frequency of vibration depends upon the force constant of the molecular bonds, the mass of the atom(s) attached and the type of the vibrational mode. Therefore, when a functional group is attached to a molecule, that group can be identified as it will absorb infrared light at a characteristic frequency. Many of these vibrations lie within the mid-infrared region of the spectrum, which allows many compounds to be identified, making this region of the electromagnetic spectrum a powerful characterisation tool.

4.1.1 Fourier Transform Infrared (FTIR) spectroscopy

Before the advent of powerful desktop computers, a less computationally intensive method was required for acquiring spectra. This took the form of a dispersive grating spectrometer. These spectrometers used diffraction gratings to disperse the infrared light into a range of wavelengths and the detector measured the brightness of the radiation at each wavelength. Therefore, only a small portion of the beam was measured by the detector at any one time, this resulted in poor signal to noise or long acquisition times.

Modern spectrometers no longer use this principle; instead they are Fourier Transform (FT) systems. The key component of any FT system is the interferometer, as shown in Figure 4-3, was first introduced by Albert Michelson in 1880. It was not employed in spectroscopy until much later, as the calculations required are computationally intensive. It was not until 1965 when Cooley and Tukey developed the Fast Fourier Transform algorithm that FTIR systems became commercially viable (Cooley and Tukey, 1965).
Infrared radiation is emitted from the source and travels towards the beamsplitter. At the beamsplitter, the beam is split in two, half proceeds to the fixed mirror, while half proceeds to the moving mirror. As the mirror moves a varying path distance is introduced to half of the beam, such that when the split beams recombine at the beamsplitter there is a phase difference between them. Therefore, the beams interfere with each other in an either constructive or destructive manner depending on the phase difference that has been introduced. The difference in phase is a function of the difference in optical path length. The results for a polychromatic and monochromatic source are shown in Figure 4-4. These are plotted as interferograms, which show the intensity of the signal at the detector with change in optical path. Figure 4-4 (b) shows a peak in intensity when the optical path difference is zero and fully constructive interference of the beams is seen, this is the centreburst.
The interferogram is a plot of beam intensity measured by the detector against path difference. Therefore, it is necessary to use the Fourier transform to convert this into a plot of infrared intensity against wavenumber as illustrated in Figure 4-5. In order to eliminate any instrumental or environmental influences on the spectral data gathered, a background scan must be gathered in an empty system which is then ratioed against data from the system gathered with the sample in place using Equation 4-1. This produces a result in terms of percentage transmittance ($\%T$), and is a ratio of the intensity of the system with a sample in the beam ($I$) to the intensity of the system measured without a sample in the beam ($I_0$).

\[
\%T = \frac{I}{I_0}
\]  \hspace{1cm} \text{Equation 4-1}

This transmittance can also be converted to absorbance ($A$), Equation 4-2, this is necessary for quantitative analysis.

\[
A = -\log_{10} T
\]  \hspace{1cm} \text{Equation 4-2}

Figure 4-5. Conversion of interferogram into single beam spectrum using the Fourier transform. (Smith, 1996)
4.1.1.1 **Advantages of FTIR spectroscopy**

One of the most important aspects of the performance of any spectrometer is its signal to noise ratio. Any spectrum will contain random points of noise. The signal to noise ratio, is the ratio of the magnitude of those noise peaks to real peak data.

The dispersive systems reject a large amount of the light, whereas in an FTIR system all the light hits the detector at once so the detector sees the maximum amount of light throughout the whole scan. This is known as the throughput or Jacquinot advantage. The second advantage is due to the fact that all wavenumbers are detected at once, therefore if a system is set to scan for 10 minutes then an FTIR system will obtain data at all points for the whole 10 minutes, whereas in the dispersive system only a small amount of that time is spent observing the response at each wavenumber. Increased scan time will improve the signal to noise ratio, the relationship between number of scans and signal to noise ratio (SNR) is given by Equation 4.3.

\[ SNR \propto (\text{Number of Scans})^{1/2} \]

Equation 4.3

As the FTIR system can acquire more scans in a given period amount of time then it can achieve a significantly better signal to noise ratio. This is known as the multiplex or Fellgett advantage (Smith, 1996).

4.1.2 **Quantitative analysis**

FTIR spectroscopy is a well established technique for the acquisition of quantitative data (Wurster *et al.*, 1993, Farinas *et al.*, 1994). The transmitted intensity of infrared light through a sample is found to be dependent on: the concentration of the species, the path length of the radiation through the sample and the molar absorptivity of the sample. This is described in Equation 4.4 by the Beer-Lambert law, where \( \varepsilon \) is the molar absorptivity, \( l \) is the path length.

\[ I = I_0 10^{-\varepsilon l c} \]

Equation 4.4

\[ A = \varepsilon l c \]

Equation 4.5
Based on Equation 4-2, the Beer-Lambert law becomes Equation 4-5. Assuming a constant path length, the absorbance \((A)\) is proportional to the molar concentration \((c)\) of the component. Therefore, if the molar absorptivity is known, or using samples of known concentrations to produce a calibration curve, it is possible to calculate the concentration of a component in a sample.

### 4.1.3 Sampling methods

Several different infrared sampling methodologies are commonly used; these are transmission, diffuse reflectance and attenuated total reflection. Diffuse reflectance based infrared spectroscopy uses diffusely scattered infrared light, and is often used when a sample scatters strongly but absorbs only weakly. It is often used for studying solid particulate samples as little preparation is required, however, solid samples require grinding and diluting with materials such as KBr which are non-absorbing. As the signal collected using this sampling approach is usually very low, long acquisition times are needed to produce an acceptable SNR. To compare the data between two samples reliably the particles in the sample need to be of similar size distribution.

Transmission mode is the most well known form of infrared spectroscopy. A beam of infrared light passes through a sample as shown in Figure 4-6. Examination of the resulting radiation can determine which frequencies of infrared light have been absorbed. The advantages of this methodology are that the SNR is good and the accessories necessary are relatively cheap. It is also the most straightforward approach for quantitative analysis, as the path length of the beam in the sample is the same as the effective path length used in quantitative analysis (see Section 4.2.8). A disadvantage of this approach is that the sample must be thin enough to allow the radiation to pass through, but it must also be thick enough such that a reasonable amount of absorbance occurs. This can often require very careful sample preparation. A suitable thickness is usually between 5 and 20 μm for studies in the mid-infrared region. The form of the chosen sample is also an important factor, fluids are simple to prepare as cells with fixed path lengths can be used, whereas, working with solid samples is often non-trivial. Powders cause random reflections of the light as it passes through the sample, thus the beam can become too scattered or they will be too opaque for sufficient signal transmission. Solid samples will often require mixing with other non-absorbing
materials such as KBr to a concentration of around 0.2-0.5 wt% of the sample. The KBr and the sample are ground together and pressed into a disc.

![Schematic diagram of transmission sampling.](image)

**Figure 4-6. Schematic diagram of transmission sampling.**

Attenuated Total Reflection (ATR) is a significantly more versatile sampling methodology which is described in detail by Harrick (Harrick, 1967). This technique relies on the principle of total internal reflection. A material with a high refractive index such as diamond which has a refractive index of 2.4 or zinc selenide, which has a similar value of refractive index, is often used in the form of an inverted prism. The sample is placed on the top surface of the crystal; the infrared radiation enters the crystal and approaches the top surface of the crystal at an angle greater than the critical angle. Although total internal reflection occurs at the interface between the crystal and the sample, the radiation does penetrate a few micrometers into the sample, in the form of an evanescent wave, where absorption of by sample attenuates the beam. This is illustrated in Figure 4-7.

![Diagram illustrating refraction below the critical angle and internal reflection above the critical angle.](image)

**Figure 4-7. Diagram illustrating refraction below the critical angle and internal reflection above the critical angle, where \( n_1 \) and \( n_2 \) are the refractive indices of media 1 and 2, \( n_1 > n_2 \) and \( \theta_c \) is the critical angle.**
Figure 4-8. Exponential decay of evanescent field into the medium with lower refractive index. $d_p$ is the depth at which the field amplitude has decayed to $1/e$ of its initial value at the interface.

The penetration depth of the evanescent wave into the next medium $d_p$, which is defined as the distance in which the amplitude of the electric field falls to $1/e$ of its initial value at the surface, can be calculated using Equation 4-6, where $\theta$ is the angle of incidence, $\lambda$ is the wavelength of light and $n_1$ and $n_2$ are the refractive indices of media 1 and 2.

$$d_p = \frac{\lambda}{2\pi n_1 (\sin^2 \theta - (n_2/n_1)^2)^{1/2}}$$

Equation 4-6

The depth of penetration in Equation 4-6 is dependent on several factors listed above. Longer wavelengths have greater depth of penetration, the consequences of this will be discussed further in Chapter 7. The expected depth of penetration using common polymeric materials with refractive indices of around 1.5, is usually in the range 1 to 5 μm when working in mid-IR (Gupper et al., 2002).

To measure a sample in ATR mode, it must be placed on the surface of the crystal, therefore sample preparation can be very simple. The sample must be pressed onto the crystal with sufficient force to ensure comprehensive contact between the two media because of the shallow penetration depth of the evanescent wave. The crystal must be transparent to infrared radiation and have a high refractive index. Zinc selenide crystals are brittle and easily scratched but a large, optically consistent crystal can be obtained.
relatively cheaply. Diamond is another option however; it is expensive and absorbs certain frequencies of infrared radiation, especially at high temperatures. The main advantages of diamond are that it is able to endure high pressures, its chemical resistance and it is exceptionally hard making it scratch resistant.

A general perception about ATR spectroscopy is that a high level of force is required to achieve a good contact between sample and ATR crystal, which is often not the case. Adequate contact can be achieved with liquid samples simply by covering the top of the crystal with the sample, although, when working with polymeric materials, some compaction force is required to achieve sufficient contact. The required force can be minimised as flat surfaces help facilitate the contact, while malleable samples require minimum force in compaction. When working with some pharmaceutical polymeric materials in dissolution experiments, the formation of a gel upon contact of the polymeric sample with water greatly improves the contact of the polymer (van der Weerd and Kazarian, 2004b). Although the compaction force used for compacting tablets of the ATR crystal is significantly lower than in industrial tablet presses, the image data obtained using these in situ compaction methods show good contact for pharmaceutical formulations. This demonstrates that the force used to compact tablets in situ is sufficient to achieve good contact. Nevertheless, while compaction with a diamond as an ATR crystal is not an issue, it can be harder to achieve a satisfactory compaction on some other crystals, such as zinc selenide, without incurring damage to the crystal.

4.2 FTIR spectroscopic imaging

Conventional FTIR spectrometers are single detector devices. One spectrum is obtained which averages information from the total measured volume of the sample, no spatial information is acquired. Previously, image production was only possible using mapping techniques, which involved gathering spectral data in a grid pattern from localised areas of the sample to build up a spatially resolved map of the system. This was advanced with the introduction of linear array detectors which gather a line of data at a time, and move across the sample. Focal Plane Array (FPA) detectors use a grid array of detectors which collect spatially resolved spectral information from all regions of the sample simultaneously. When acquiring the image, each detector gathers a full spectrum with
every scan, and therefore every point is measured at the same time. The FPA detector can be used in conjunction with a standard interferometer and source. As a 64 × 64 system records 4096 spectra with each scan, a large amount of data are produced. In early systems, to reduce the computationally intensive nature of this process, step scan mode was implemented, where the moving mirror changed position in discrete steps. This allowed the computer time to process the data. With modern, more powerful systems and better detectors, continuous scan mode is used, in which the mirror moves smoothly and continuously. This gathers data much more rapidly.

Today FPA detectors are available in a number of sizes. The most commonly used sizes range from 32 × 32 up to 256 × 256 pixels. In this thesis two detectors are used, both with 64 × 64 pixel arrays. The earlier model used a detector with a pixel size of 60 µm × 60 µm, producing an unmagnified image size of 4 mm × 4 mm, though these had relatively slow response times. The newer versions of the detectors have a pixel size of approximately 40 µm × 40 µm producing an unmagnified image size of 2.6 mm × 2.6 mm.

4.2.1 Introduction to spectroscopic imaging

The subject chosen for this description of the imaging process is a model pharmaceutical tablet consisting of caffeine and hydroxypropyl methylcellulose (HPMC), a cellulose based polymer. A schematic diagram of the imaging process is presented in Figure 4-9.

Figure 4-9. Schematic diagram showing the collection of spectra using an FPA detector to produce images showing the distribution of two different components in the sample.
Each pixel in the grid collects a full infrared spectrum, with a spectral range of 4000 to 900 cm\(^{-1}\). The concentration of a component is proportional to its absorbance as stated by the Beer Lambert law. The absorbance of a particular spectral band can be calculated by integrating the area under a spectral band. By plotting the absorbance values of a component spatially it is possible to generate a relative concentration map. A band must be found for each material which is well-separated from the bands of other materials for univariate image analysis. For this reason the band highlighted between 2750 and 3000 cm\(^{-1}\) was chosen for HPMC and the band between 1670 and 1730 cm\(^{-1}\) was chosen for caffeine in Figure 4-9. By plotting the values of integrated absorbance in a grid matching that of the detector array (taking into account the aspect ratio of the images obtained with macro ATR using an inverted prism) concentration maps of HPMC and caffeine within the tablet can be constructed as shown in Figure 4-9.

The two images generated in Figure 4-9 represent the same spatial region. One plots the distribution of the absorbance of the corresponding band of caffeine, the other plots the distribution of the absorbance of HPMC and hence they show their corresponding distribution within the imaged area of the sample. Red and pink domains correspond to regions of high concentration, whereas blue domains correspond to regions of low concentration. It can be seen that these images are complementary, i.e. where there is a high concentration region of caffeine there is a relatively lower concentration region of HPMC. There are some regions where low concentration in registered for both, this is most likely a void within the tablet structure, or an impurity.

### 4.2.2 Transmission FTIR imaging

Spectroscopic imaging can be performed in both transmission and ATR modes, however, as explained in Section 4.1.3, transmission requires significantly more sample preparation.

As transmission measurements apply through the whole the sample, in imaging mode only an average through the thickness of the sample is seen (Kazarian and Chan, 2006). This can have some significant effects when studying heterogeneous samples. A large particle seen in an image may in fact not be a large particle, but instead consist of two
separate particles at different depths that slightly overlap in the path of the beam as shown in Figure 4-10. Therefore the sample thickness should be less than the domain size in order to avoid misleading images.

Figure 4-10. Schematic diagram showing the effect of “averaging” through the sample when imaging in transmission. (a) Front view of sample showing overlapping particles, (b) sample at an angle showing separate particles, (c) side view of sample. (d) and (e) transmission images of (a) and (c) respectively.

4.2.3 ATR-FTIR imaging

ATR imaging with visible light can be demonstrated by pressing a finger against a glass of water, the parts of the fingerprint in contact with the glass can be seen, the remainder of the light, in the areas of the valleys in the fingerprint, undergoes total internal reflection. At the points where there is contact between the skin and the glass this total internal reflection is destroyed and thus the fingerprint is visible. This effect was demonstrated by Harrick, through the use of a prism (Harrick, 1967). The finger was pressed against the surface of the prism and the light focused onto a photo film, producing an image of the fingerprint. In the ATR-FTIR imaging approach used in this thesis, rather than focusing visible light onto a photo film, infrared light will be focused onto an FPA detector (Kazarian and Chan, 2003).
Figure 4-11. Effect of probing depth in ATR imaging on imaged particle size.

ATR imaging is a surface technique and usually does not suffer from the “averaging” issue seen in transmission; however, there are some considerations that must be made as the spectroscopic data obtained are sampled from the surface layer of the sample. The probing depth is around several micrometers, however, the individual particles in most powder based pharmaceutical formulations are much larger than this. Therefore, a relatively small fraction of total volume is imaged and only “the tip of the iceberg” may be seen. This effect is demonstrated in Figure 4-11 where, although the particles all have the same maximum diameter, there are some much smaller domains visible. These smaller visible domains are actually a small fraction of a much larger particle, of which, a large part lies outside the ATR field of view. Nevertheless, both transmission and ATR mode have uses and an appropriate choice must be made based on the analytical requirements as they differ on many aspects such as spatial resolution, field of view and the possibility of leaving artefacts (Chan et al., 2003, Sommer et al., 2001).

4.2.4 Spatial resolution

The spatial resolution of an ATR system is limited by the wavelength of the radiation being used, the pixel size of the detector and the numerical aperture of the objective being used. The resolution is determined by diffraction, when light enters a slit, diffraction occurs; the diffraction pattern is shown in Figure 4-12. This is described by the Rayleigh criterion, shown in Equation 4-7, which can be used to calculate the
theoretical distance required between two adjacent points in order for them to be just resolved.

\[ r = \frac{1.22\lambda}{2NA} \] \hspace{1cm} \text{Equation 4-7}

\[ NA = n \sin \theta \] \hspace{1cm} \text{Equation 4-8}

Where \( r \) is the distance between two adjacent point that are just resolved, \( \lambda \) is the wavelength of the radiation, \( NA \) is the numerical aperture of the system, defined in Equation 4-8, with \( n \) being the refractive index of the imaging medium between the objective and the sample and \( \theta \) being half the angular aperture.

![Diffraction pattern diagram](image)

\textbf{Figure 4-12.} Schematic diagram of the diffraction pattern of light.

In order to resolve two points completely from each other, the separation required is a minimum of \( 2r \). In practice this cannot be achieved due to practical imperfections such as optical aberrations within the system. A microscope is required to realise the highest spatial resolution that can be achieved in infrared, which Chan and Kazarian found to be about 4 \( \mu \)m using light of wavelength 6 \( \mu \)m. In the case of a diamond Golden Gate™ accessory, 13 \( \mu \)m is the demonstrated spatial resolution (Chan and Kazarian, 2003). However, careful alignment of the optical systems is required to achieve the maximum spatial resolutions, as due to optical aberrations in the system and throughput issues the resolution can be limited to around 15 – 20 \( \mu \)m (Bailey et al., 2000).
4.2.5 Acquisition of ATR-FTIR images

Before the advent of FPA detectors various mapping techniques were applied in order to obtain image data. Many of these involved translation of the crystal under the sample, although this could result in smearing of the sample and physical damage, reducing the quality of the image data. Separating the sample from the ATR crystal between each measurement and moving to the next point greatly increased the time required to acquire the mapping data. Various attempts have been made to overcome these issues, Esaki et al. developed a V-shaped hexagonal crystal which can be moved with the sample in place to gather mapping data without damage to the sample (Esaki et al., 1993a). This crystal was able to map an area of ca. 2 mm × 7 mm. As this required a custom designed crystal it is not as widely available as hemispherical crystals (Esaki et al., 1993b). The use of a germanium hemisphere for non-destructive mapping of soft materials has been demonstrated by Lewis et al. (Lewis and Sommer, 2000). However, this still remained a relatively slow method of acquisition.

Linear array imaging systems make use of a linear array of pixels as opposed to a single element detector system or full grid like an FPA (Patterson and Havrilla, 2006). This system has some advantages, as the spectral range of the detector is greater, being able to go down to 700 cm\(^{-1}\), and a flexible imaging size, whereas the image size produced by the FPA is usually determined by the size of the FPA detector and the optics being used. However, there are disadvantages, as the inability to capture all the data simultaneously is a limitation when studying dynamic systems, while the spatial resolution and depth of penetration are not consistent across the imaging area. It has been shown by Patterson et al. that a combination of using an FPA with a translating ATR crystal it is possible to image a larger field of view (Patterson et al., 2007). However, there are limitations to this approach in the size of the area measured and the spatial resolution of the data. Kazarian and Chan have employed an imaging and mapping combination through which a large field of view can be imaged without sacrificing spatial resolution (Chan and Kazarian, 2008). However, this approach, as with all mapping approaches, is generally limited to the investigation of static or steady state systems.
4.2.6 Macro ATR-FTIR imaging

In this thesis the imaging data are predominantly acquired in macro mode using a diamond Golden Gate™ ATR-FTIR accessory from Specac, ltd. The internal optics are shown schematically in Figure 4-13. Based on the detector used and version of the accessory used the image size produced can range from ca. 570 µm x 530 µm to 1140 µm x 820 µm.

![Figure 4-13. Schematic diagram of the internal optics of Golden Gate™](image)

As can be seen from the diagram in Figure 4-13 the beam of infrared radiation undergoes total internal reflection at the interface of the ATR crystal with the sample. The angle at which the beam arrives at the interface is ca. 45°; therefore as opposed to being imaged with a circular beam, the sample area is imaged by an elliptical beam. As the angle is ca. 45° the resulting ratio of the height of the image to the width of the image is approximately 1:2.5 as shown in Figure 4-14, this aspect ratio must be taken into account when recording and displaying the images.

![Figure 4-14. (a) Schematic presentation showing the elliptical imaging area resulting in image stretching. (b) Resulting change in imaging aspect ratio (Chan and Kazarian, 2003).](image)

A diamond ATR crystal is used for several reasons. When working in ATR spectroscopy it is important to have a crystal with a high refractive index, which at 2.4 for diamond is relatively high. Diamond is also very hard, which is a very useful property, as described in Section 4.1.3 some force is required to achieve good contact.
between the sample and the crystal (Kazarian et al., 1999, Everall and Bibby, 1997). The hardness of the crystal also facilitates the in situ study of materials under high pressure (Flichy et al., 2002, Kazarian and Martirosyan, 2002). The diamond ATR accessory was not specifically designed for imaging, however, it has been shown to be capable of the acquisition of imaging data (Kazarian and Chan, 2004, Chan and Kazarian, 2003). As described previously the angle of incidence of the beam led to an elongated aspect ratio. The introduction of the Imaging Golden Gate™ (Specac, UK), minimised this effect as it was designed specifically for imaging purposes. The imaging accessory incorporates a set of corrective optics which consists of a wedge-shaped prism, which corrects the orientation of the focal plane and the anamorphic magnification of the imaged sample (Poulter and Thomson, 2004).

Attaining the highest spatial resolution is often of significant importance, though this will come at the expense of the size of the field of view leading to imaged areas that are rather small (e.g. ca. 64 µm × 64 µm when using a microscope). Using a ZnSe crystal with no magnifying optics, such as the Oil Analyser from Specac, can produce an image size of 2.6 mm × 3.6 mm. This is the same size as the detector with the aspect ratio of the beam taken into account. Accessories with optics which allow for a variable angle of incidence are also available (Chan and Kazarian, 2007a). For studies in which a larger field of view (FOV) is required it is possible to use a large ZnSe imaging prism with custom designed expanded optics. The experimental apparatus is analogous to that of a standard Golden Gate™, however concave lenses are also inserted which expand the beam (Chan and Kazarian, 2006a). The schematic for this system is shown in Figure 4-15. The area imaged by this accessory is ca. 15.4 mm × 21.5 mm; this enlarged FOV facilitates the measurement of multiple samples simultaneously, as the samples can be easily deposited directly on the surface of the crystal within the imaged area. This has been applied to acquire data from more than a hundred static samples in one image, while the dissolution of five samples has been studied simultaneously (Chan and Kazarian, 2006a). A disadvantage of imaging with an expanded FOV is a decrease of the spatial resolution. As the beam is expanded the projected area for each pixel in the detector increases, the beam expansion also leads to a reduction in the numerical aperture (NA) of the system. Thus, expanded field of view imaging cannot be used to obtain data concerning smaller features of the studied samples and therefore is only applied to situations for which an enlarged area of interest is necessary.
4.2.7 Micro FTIR imaging

Micro FTIR imaging employs an imaging system in conjunction with microscope optics to gather spectra from very localised regions (Sommer et al., 2001). This has an application in the analysis of heterogeneous samples with small domain sizes, and can be performed in both transmission and ATR modes. In practice the achievable spatial resolution of microspectroscopic mapping is limited to around 10-15 μm, which can be accounted for by the low throughput of the IR beam with small aperture sizes, though this can be improved by the use of a synchrotron (Dumas et al., 2004, Carr, 2001, Briki et al., 2000, Bantignies et al., 2000). This has allowed the collection of chemical maps of hair showing the medulla region (Briki et al., 2000, Dumas and Miller, 2003). However, despite the use of a 3 μm aperture, the fingerprint region has a wavelength of 6-11 μm resulting in spectra that would be “contaminated” by the spectral information from the surrounding materials because of diffraction.

As shown by Equation 4-7 the Rayleigh criterion is partially dependent upon the numerical aperture of the system. Therefore, by using an ATR crystal which has a much higher refractive index than air, it is possible to drastically improve the spatial resolution of the system. Chan and Kazarian were able to obtain a resolution of 4 μm using infrared light of wavelength 6 μm (Chan and Kazarian, 2003).

The increased spatial resolution has led to improved detection limits when looking for trace amounts of materials (Chan and Kazarian, 2006b). This is particularly useful when studying pharmaceutical formulations, as heterogeneities may be found in the micrometer scale.
4.2.8 Quantitative analysis

With the introduction of the FPA detector quantitative analysis can now be performed in imaging mode. This has been demonstrated with pharmaceutical tablets consisting of HPMC as the polymer matrix and niacinamide as a model drug (van der Weerd and Kazarian, 2004a). Concentration profiles were created using the partial least squares method to quantify the components. From these dissolution profiles it was possible to obtain a global view of the dissolution and link it to the physical processes occurring in the dissolving tablet for determination of the mechanism of dissolution.

FTIR imaging has also been applied to study in situ experiments concerning polymer interdiffusion using poly(vinylpyrrolidone) (PVP) and poly(ethylene glycol) (PEG) under high pressure CO₂ (Fleming et al., 2006). FTIR-ATR imaging is also being applied to aid the development quantitative models for drug dissolution as proposed by Jia and Williams (Jia and Williams, 2007) and now applied by Kimber et al. (Kimber et al., 2011). This is significant, since for real systems and those with complex granule structures, it is important to have experimental examples as case studies for validation and improving the accuracy of the model. It is also essential to understand what the effects of digitization may be in terms of introducing errors into the predicted behaviour of a system. Imaging can also be applied to quantitatively study the effects of contaminants in formulations (Roggo et al., 2005).

Quantitative analysis is based on the Beer-Lambert law shown in Equation 4-5. In transmission, the radiation passes straight through the sample and so the path length is merely the thickness of the sample. In ATR mode, due to the fact that the radiation interacts with the sample via the evanescence wave, the effective path length \( (d_e) \) is used. For non-polarised light this is calculated using Equation 4-9 (Chan and Kazarian, 2007a), where \( \theta \) is the angle of incidence, \( n_1 \) is the refractive index of the crystal and \( n_2 \) is the refractive index of the sample.
When performing quantitative studies it is important to note that even when analysing a homogeneous sample the absorbance may not always be homogeneous throughout the whole imaged area of the sample. Depending on the accessory used, the angle of incidence may not always be uniform across the imaging surface of the crystal (Wessel et al., 2006). This will have the effect of changing the effective path length across the imaged area and consequently the absorbance, despite a uniform distribution of the sample. Therefore, it is very important to ensure correct optical alignment of the system for imaging studies. It should also be noted that the mean angle of incidence is heavily dependent upon the alignment of each individual system and so may not match the specification of the manufacturer (Flichy et al., 2002). More sophisticated methods such as parallel factor analysis (PARAFAC) and multi-linear partial least squares (N-PLS) can be used to determine the amount of drug in a formulation as well (Matero et al., 2007).

**4.2.9 Detection limits of ATR-FTIR imaging**

When analysing samples with potentially very low concentrations of a component the sensitivity levels of the imaging approaches are very important. A high sensitivity means components with very low concentrations may be detected within the sample.

Conventional spectroscopy using a single element detector gathers one spectrum from a relatively large area, whereas in imaging, data are gathered from many very localised points in the sample. In heterogeneous samples this can lead to a significant increase in detection sensitivity, depending on the size of the sampling area, particle size, number of pixels in the array detector and the spatial resolution of the image. The sensitivity levels of conventional FTIR spectroscopy and FTIR spectroscopic imaging were compared for a model tablet made of polymer and drug. In this model system the detection limit for the drug was found to be 0.35 wt% for the conventional
Ricci et al. used micro ATR-FTIR imaging in combination with desorption electrospray ionization linear ion-trap mass spectrometry (DESI MS) to analyse counterfeit artesunate anitimalarial tablets (Ricci et al., 2007b). Micro ATR-FTIR imaging located and identified the domains of drug while DESI MS facilitated high-sensitivity drug detection.

Macro ATR-FTIR imaging was also used in conjunction with spatially offset Raman spectroscopy (SORS) (Ricci et al., 2007a). SORS was able to acquire Raman spectra of the tablets within their packaging materials. SORS identified the bulk of the constituents of the tablets and macro ATR-FTIR spectroscopic imaging revealed the spatial distribution of the drug and other components across the surface of the tablets and was able to detect drug concentrations below, the threshold for detection when using the SORS technique (Ricci et al., 2007a).

4.3 Applications of FTIR spectroscopy

FTIR spectroscopy is well suited to the study of polymorphism of drugs. The ability to distinguish between polymorphic forms is crucial to the pharmaceutical industry as each polymorphic form can be individually patented. Therefore, pharmaceutical companies must find all possible the polymorphs of the drugs they have developed otherwise competitors can use the same drug in another crystalline form as in the case of Cefdinir (Cabri et al., 2007).

The polymorphic state of the drug can have a large effect on the dissolution properties of a formulation. The amorphous form of a drug typically exhibits a much higher solubility than the crystalline forms. Moreover controlling the crystalline state of the API has significant implications in ensuring the safety and efficacy of the formulation.

Infrared spectra are highly sensitive to polymorphic changes in a compound. Polymorphic transitions will manifest in several forms of spectral change. Upon a transition from an amorphous state to a crystalline structure, the peaks in the spectrum
of the compound become sharper and more defined. A more quantifiable difference comes in the form of a peak shift, for example amorphous ibuprofen has a carbonyl peak at 1730 cm\(^{-1}\), whereas the carbonyl peak in the crystalline form shifts to ca. 1710 cm\(^{-1}\), because during crystallization hydrogen bonds will form between the drug molecules (Kazarian and Chan, 2003).

This sensitivity has led to the creation of many assays for classifying the crystallinity of a compound (Bugay et al., 1996, Kamat et al., 1988, Sarver et al., 1998, Agatonovic-Kustrin et al., 1999, Hartauer et al., 1992). For example, sulfamethoxazole has two distinct polymorphic forms, and, when studied in diffuse reflectance mode, distinct spectra can be identified which correspond to the different forms. However, in using diffuse reflectance mode, homogeneous samples must be used for validation and calibration, while particle size must remain consistent for all components.

Inhomogeneous calibration and validation samples can give incorrect values for IR absorption leading to errors in prediction, while variation in particle size can change the diffuse reflecting properties of a sample. However, an accuracy of 4\% is readily achievable when quantifying the crystallinity of a sample.

When preparing pharmaceutical formulations numerous methods may be used for embedding the drug within the polymer bulk. Solvent impregnation has been shown to be practical in preparing samples for which a molecularly dispersed and homogeneous distribution of the drug within the polymer is required. This can be done via particle formation by antisolvent precipitation, aerosolisation and rapid expansion of supercritical fluids (Alessi et al., 1996, Benedetti et al., 1997, Yeo et al., 1993). Kazarian and Martirosyan (Kazarian and Martirosyan, 2002) have applied ATR-FTIR spectroscopy to study the procedure of supercritical fluid drug impregnation using PVP as the polymer and ibuprofen as a model drug. It was shown that this process is capable of molecularly dispersing the drug in the polymer matrix (the drug is dissolved in polymer matrix at the molecular level). This was revealed by the shift of the carbonyl peak of ibuprofen from 1710 cm\(^{-1}\) to 1727 cm\(^{-1}\) within the PVP, indicating that the intermolecular bonds between drug molecules had been broken. This study also demonstrated the ability of ATR-FTIR spectroscopy to reveal specific interactions between the C=O groups of the PVP and CO\(_2\). ATR-FTIR spectroscopy using a
diamond crystal is particularly suited to this work as it is much stronger than other applicable materials such as zinc selenide, and thus it can endure the high pressures required to work with supercritical carbon dioxide (Kazarian et al., 1999).

### 4.4 General applications of FTIR imaging

With modern FPA detectors an image can easily be attained in as little as 10 seconds. In recent work, through careful optimisation of the imaging parameters, it was possible to acquire full FTIR images in a scanning time of 50 ms with a temporal resolution of 120 ms (Chan et al., 2011). Mapping methods which are not strictly imaging are also commonly used. The use of linear array detectors for the chemical mapping of polymeric materials (Zhou et al., 2009) and pharmaceutical samples (Pajander et al., 2008) has recently been demonstrated. Pajander et al. used mapping to study the dissolution of starch acetate tablets. As the mapping process required a significant amount of time, the samples were freeze dried prior to imaging (Pajander et al., 2008).

Since Mid-FTIR imaging was first introduced in 1995 (Lewis et al., 1995), the technique has been applied to study many different systems from all facets of science. One of the most popular areas of application has been in the field of polymeric materials (Bhargava et al., 1998, Oh and Koenig, 1998), studying samples such as polymeric blends (Gupper et al., 2002, Wilhelm et al., 2005) and multilayer films (Chernev et al., 2008) and their degradation (Nagle et al., 2010) as well as in situ diffusion and dissolution (Ribar et al., 2001, Snively and Koenig, 1999, Gupper et al., 2004). Recently this approach has found application in biomedical science (Salzer et al., 2000, Camacho et al., 2001), investigating samples including the imaging of live cancer cells (Kuimova et al., 2009), arteries (Palombo et al., Colley et al., 2004), proteins (Steiner et al., 2007) blood cells (Sommer et al., 2001) and stem cells (Randle et al., 2007). The approach has also been used to study drug diffusion through skin (Andanson et al., 2009) and in forensics (Ricci et al., 2007c). The ability of imaging to measure a large area simultaneously allows studies of many samples at once in high-throughput analysis (Snively et al., 2001, Kubanek et al., 2004, Chan and Kazarian, 2005), and applications in microfluidics (Kazarian, 2007) (Chan et al., 2011).
While this thesis will investigate the application of ATR imaging to pharmaceuticals, transmission imaging has been successfully applied to many materials (Artyushkova et al., 2001, Koenig and Bobiak, 2007, Miller-Chou and Koenig, 2003), including the study of pharmaceutical formulations (Rafferty and Koenig, 2002, Koenig, 2002). This will be further discussed in more detail below.

4.5 Pharmaceutical applications of FTIR imaging

4.5.1 Imaging of compacted pharmaceutical tablets

ATR-FTIR imaging is a useful tool for studying pharmaceutical tablets, as little or no preparation of the sample is required, and much valuable spectroscopic information can be extracted from imaging studies of these formulations. The minimal sample preparation is a useful property of the ATR methodology. While ATR-FTIR imaging allows for the study of many aspects of the tablets, the most important property of imaging is being able to assess the spatial distribution of different components within the sample (van der Weerd et al., 2004, van der Weerd and Kazarian, 2005, Chan et al., 2005). By taking several images of a sample, changes in the distribution can be studied, e.g. when undergoing compaction the positions of particles within the tablet rearrange, followed by the particles crumbling, the voids within the material then collapse resulting in a harder denser material (Duberg and Nystrom, 1985). This process can be studied in situ using ATR-FTIR imaging (Wray et al., 2008, Elkhider et al., 2007).

Figure 4-16. Schematic presentation of in situ imaging of tablet compaction.
A custom designed compaction cell has been developed to work in conjunction with a diamond ATR crystal and Golden Gate™ accessory that allows for in situ compaction of the pharmaceutical powders into model tablets (Chan et al., 2005). The operation of this cell is shown in Figure 4-16.

The brass cell is bolted into place over the diamond plating; the powder mixture is then poured into the hole in the cell, the cylindrical punch is then placed into the hole on top of the powder before the armature is lowered. A torque screwdriver is then used to wind down a compaction plating from the armature of the Golden Gate™ accessory onto the punch compacting the powder. Diamond is employed for this approach because when working with compaction only hard ATR crystals can be used. The feasibility of using this methodology for imaging tablet compaction has already been shown for model tablets consisting of starch and caffeine (Chan et al., 2003).

4.5.2 Micro ATR-FTIR imaging

Macro imaging, such as that using the Golden Gate™, is useful when a large field of view is required. However, sometimes it is necessary to investigate samples on a smaller scale in order to resolve details of smaller features. Micro-ATR imaging can be used to study compacted pharmaceutical tablets; however, it is not possible to perform in situ compaction on these samples so they have to be prepared ex situ. Micro-ATR imaging produces an image with a size of approximately 50 x 50 μm². This has been demonstrated by Chan and Kazarian using model formulations consisting of caffeine, starch and HPMC as shown in Figure 4-17 (Chan and Kazarian, 2003).

Figure 4-17. Micro ATR-FTIR images showing the distribution of caffeine starch and HPMC in a model tablet (Chan and Kazarian, 2003).
Figure 4-17 shows that the distributions of starch and HPMC are complementary, demonstrating the ability of micro ATR-FTIR imaging to spatially separate different chemical domains within a mixture on the micrometer scale. The quality of these images also shows that good contact was made between the micro-ATR crystal and the sample. The large particle seen in the caffeine image is approximately 10 μm in diameter; this would not have been visible using macro ATR imaging, demonstrating the effectiveness of being able to image samples on a much smaller scale. The smaller caffeine particles in the image only have a diameter of the order of 2-3 μm, despite this being very close to the limits of the spatial resolution of the system, they still clearly visible.

The manufacture of pharmaceutical solid dosage forms mixes drug compounds which are typically hydrophobic into hydrophilic polymer matrices in order to enhance the dissolution properties of the API. Therefore, during storage and manufacture these formulations may well absorb water from the atmosphere. This sorption of water can manifest itself in the form of undesirable effects on the dissolution and therapeutic properties of the formulation, hindering the bioavailability of the API. The sorption of water into the polymer powder can alter its compaction properties, which can then have an effect on the particle morphology within the formed tablet (Yoshinari et al., 2003). This has led to interest in studying the uptake of water into pharmaceutical formulations (Aso et al., 2002, Crowley and Zografi, 2002, De Brabander et al., 2003).

The application of conventional FTIR spectroscopy can only give an overall value of the quantity water absorbed into the sample; however, it is unable to display any heterogeneity of water sorption into different domains of the tablet. Previous studies have used solely polymer based formulations, whereas Kazarian and Martirosyan have shown that the composition of the formulation can affect the availability for water sorption (Kazarian and Martirosyan, 2002). FTIR imaging has been applied to study the heterogeneous distribution of water in pharmaceutical formulations. A controlled humidity cell was combined with FTIR imaging in transmission mode to study water sorption into different domains of the sample in situ as shown in Figure 4-18 (Chan and Kazarian, 2004b).
The tablets used consisted of polyethylene glycol and griseofulvin. The relative humidity was varied between 0.5 and 90% and the temperature maintained at 25°C. Images were produced to show the distribution of griseofulvin, PEG and water individually as shown in Figure 4-19.

![Schematic diagram of controlled humidity in FTIR transmission imaging mode](image)

**Figure 4-18.** Schematic diagram of controlled humidity in FTIR transmission imaging mode (Chan and Kazarian, 2004b).

![FTIR images of the PEG-griseofulvin mixture exposed to different relative humidities](image)

**Figure 4-19.** FTIR images of the PEG-griseofulvin mixture exposed to different relative humidities. The left (a) middle (b) and right (c) columns show the distribution of griseofulvin, PEG, and water, respectively. Adapted from (Chan and Kazarian, 2004b).

The work demonstrated that the water preferentially absorbed into the domains of the hydrophilic PEG, rather than the drug. It was also able to reveal that there was a
significant increase in the amount of water adsorbed in the formulation above a relative humidity of 70%, but no effect was seen on the spatial distribution of the components.

As described previously, humidity can affect the compaction properties of tablets. The controlled humidity approach has been applied to study the compaction of pharmaceutical formulations in ATR mode (Elkhider et al., 2007). Tablets consisting of ibuprofen and HPMC were exposed to relative humidities between 0 and 80% before being compacted into tablets. Results of this work are shown in Figure 4-20.

These data in Figure 4-20 show that at the same compaction pressure the sample exposed to the higher humidity shows a greater level of infrared absorbance of the corresponding components in the measured spectra. This is due to an increased density of the tablet resulting from a greater degree of compaction, showing increasing the humidity had a significant lubricating effect upon the formulation. FTIR imaging has demonstrated the ability to reveal information about the properties of compacted tablets. These data were quantitatively analysed via extraction of the absorbance values of the corresponding spectral bands, from which histograms were produced showing the range of absorbance values throughout the image.

![Figure 4-20](image.png)

**Figure 4-20.** a) Image showing FTIR results for compaction of HPMC at 120 MPa and 60% RH with histogram showing the number of pixels at a particular absorbance level b) Image showing FTIR results for compaction of HPMC at 120 MPa and 80% RH with histogram showing the number of pixels at a particular absorbance level FTIR Imaging of Tablet Dissolution. Adapted from (Elkhider et al., 2007).

The combination of macro ATR-FTIR imaging with a controlled environment accessory also allowed analysis of the stratum corneum, which is the uppermost layer of the skin, under controlled humidity (Chan and Kazarian, 2007b). The heterogeneous distribution of water in the stratum corneum was analysed with the aid of a multivariate approach. It
has also been shown that ATR-FTIR imaging provides information on the swelling of the stratum corneum as a function of humidity. This approach was also used to image the penetration of liquid ethanol into the skin (Chan and Kazarian, 2007b) and showed good potential for studying the transdermal delivery of drugs (Andanson et al., 2009, Boncheva et al., 2008).

4.6 FTIR imaging of dissolution processes

FTIR imaging has been applied successfully to study many relevant processes, such as: pH effects on tablet dissolution (van der Weerd and Kazarian, 2005), polymer behaviour under tablet dissolution (van der Weerd and Kazarian, 2004b), effects of the initial sample parameters on tablet dissolution (van der Weerd and Kazarian, 2004a, Kazarian et al., 2005), and the occurrence of polymorphic transitions (Kazarian and Chan, 2003, Chan and Kazarian, 2004a).

4.6.1 Transmission imaging of dissolution

Koenig and co-workers used FTIR imaging to analyse the dissolution of drug delivery formulations in transmission mode (Coutts-Lendon et al., 2003). Formulations consisting of testosterone as the API and poly(ethylene oxide) (PEO) as the polymer matrix were used. This technique was able to demonstrate the dissolution of the API from the hydrophilic matrix as shown in Figure 4-21.

This work was challenging due to the strong infrared absorption of water in the mid-infrared region. This necessitated the use of deuterated water as well as a very thin spacer, thus restricting investigation to very thin samples (ca. 10 µm). These samples did not fully represent real tablets as with the application of such thin spacer, the tablets had a very small thickness.
Figure 4-21. FTIR imaging of formulation dissolution in transmission (Coutts-Lendon et al., 2003). The arrows point to the polymer and drug dissolution fronts. Time is given below each pair of images in minutes:seconds.

4.6.2 ATR imaging of static dissolution

ATR imaging has the advantages that the path length is independent of the sample thickness and that the depth of penetration of the infrared light into the sample is rather small. Therefore, the dissolution, in water based media, of thicker tablets which more closely approximate real world samples can be studied, as opposed to thin artificially prepared samples.

The possibility of using macro ATR-FTIR imaging to examine the dissolution of polymer/drug formulations in contact with water was first demonstrated in a study by Kazarian and Chan (Kazarian and Chan, 2003). The macro ATR-FTIR imaging approach, developed in that work, allowed them to simultaneously study the spatial distribution of both polymer and drug in contact with water as a function of time. The most important finding in that study was that crystallization of the initially molecularly dispersed drug occurred upon contact with the dissolution medium. This was important because crystallization slows overall drug dissolution. These phenomena would not be detected by the conventional dissolution tests and demonstrated that ATR-FTIR imaging can provide important insight into the mechanisms of drug release. The study also demonstrated that the ATR-FTIR imaging approach can study the dissolution of
inclusion complexes of ibuprofen with cyclodextrins which prevented drug crystallization (Kazarian and Chan, 2003).

Another example of ATR-FTIR imaging of dissolution involved formulations of nifedipine in PEG (Chan and Kazarian, 2004a). Different amounts of crystalline nifedipine were dissolved in molten PEG (MW = 8000) at 70 °C to produce samples of 5, 10 and 20 % drug. The samples were allowed to cool and solidify before being powdered. The powder was then transferred to the surface of the ZnSe ATR crystal which was heated to 60 °C to re-melt the formulation. The sample was then covered with a glass slide, using a spacer to create a space in which a sample of uniform thickness could form. The sample was then allowed to cool further before the addition of water. FTIR images were then acquired at five minute intervals as shown in Figure 4-22.

![Figure 4-22. Dissolution of nifedipine and PEG. Top row shows drug dissolution, bottom row shows the polymer dissolution (Chan and Kazarian, 2004a).](image)

The results show that there was a change in the morphology of the drug as it recrystallized. This occurred within the polymer matrix upon contact with water, but FTIR imaging shows that this happened in regions in which the water had not yet reached. This suggested that water vapour had ingressed through microchannels in the formulation initiating crystallisation; therefore the concentration was below the limit of the measurement equipment. This demonstrated a different trigger for crystallization compared to ibuprofen which exhibits crystallization on direct contact with the
dissolution medium (Kazarian and Chan, 2003). The data also showed that an increase in the drug loading led to much increased crystallization at the same conditions. This work utilised the potential of FTIR imaging to reveal more information about the dissolution of pharmaceutical formulations (Chan and Kazarian, 2004a).

### 4.6.3 Flow-through dissolution studied with FTIR imaging

In order to study flowing dissolution using ATR imaging a refinement of the simple compaction cell was employed. The cell was developed such that the tablet could be compacted in situ as shown in Figure 4-23, and the dissolution medium could flow through the cell without the need to move the sample. The construction is similar to the standard compaction cell; however, surrounding the punch is a retractable metal bolt which is raised after compaction creating a chamber through which the dissolution medium flows as shown in Figure 4-23 (van der Weerd et al., 2004).

![Figure 4-23. Schematic representation of the flow dissolution cell combined with ATR accessory.](image)

The dissolution cell has a similar experimental set up to that of the compaction cell as shown in Figure 4-16. It is bolted into place over the diamond plating, the only difference being the off-centre punch hole and the retractable bolt. There are also flow pipes attached to the side of the block, through which the dissolution medium is pumped.
This equipment is particularly useful for studying the dissolution of model pharmaceutical tablets, as it brings the spatially resolved chemical specificity of FTIR spectroscopic imaging to flow processes. It allows for the study of the ingress of water into the tablet, the formation of polymer gel layers and ultimately the dissolution of the drug itself. By taking images at regular time intervals, time-resolved chemical information of the dissolution can be obtained. The dissolution cell was also designed with the punch aligned slightly off centre relative to the diamond, such that the tablet only covers half the face of the imaged area. This sets the interface between the tablet and the dissolution medium as the centreline of the image, while also providing space for any potential gelation and expansion or dissolution of the polymer to be observed.

Figure 4-24. FTIR images showing dissolution of tablet containing HPMC and caffeine (van der Weerd et al., 2004).

Figure 4-24 reveals the extent of the information that can be obtained using this method. The sample was a model tablet consisting of HPMC and caffeine (van der Weerd et al., 2004). The caffeine and HPMC are shown to have only covered half of the image as expected. It can also be seen that the images were complementary; there are two circular domains of low concentration in the HPMC image, which are matched by the positions of two domains of higher concentration in the caffeine image. Water was shown to have filled the empty space on the unoccupied side of the interface, as this image was taken shortly after dissolution commenced and water had not yet started to ingress into the bulk.

The in situ compaction and dissolution cell is used in conjunction with the diamond Golden Gate™ ATR accessory producing images that are 1 mm² or smaller. These images were obtained with a high spatial resolution (ca. 15 μm) which is useful for studying crystallisation and small changes in the structure of the tablet. This FOV only
facilitates the study of a relatively small area of small tablets, however, sometimes it is necessary to have a larger field of view to study larger areas of tablets, and the processes of dissolution that occur a larger distance from the original boundary of the tablet (Chan et al., 2003, Kazarian and Chan, 2003). For this a larger ATR crystal must be used. ZnSe is suitable for this purpose, but it is not as hard as diamond and so compaction cannot be performed in situ. Therefore, the tablets must be compacted ex situ and then dissolution studied in situ. This creates the possibility of leakage of the dissolution medium into the interface between the sample and the surface of the cell if care is not taken. In the compaction and dissolution cell, as the formulation is compacted onto the diamond, leakage is very unlikely (van der Weerd et al., 2004), the swelling of polymers such as HPMC further helps to prevent this ingress (van der Weerd and Kazarian, 2004b). When using the ZnSe crystal the sample can be formed in situ if the polymer has a low melting point, and this has been used to study the dissolution of PEG based formulations (Chan et al., 2005). A schematic diagram of the ZnSe dissolution cell can be seen in Figure 4-25.

A recent example of the application of ATR-FTIR imaging to dissolution and drug release is the simultaneous FTIR imaging and visible optical photography of an HPMC based tablet (Kazarian and van der Weerd, 2008). A custom designed cell was built, which was attached to the standard diamond ATR accessory and had a transparent window for visual observation of the top surface. The tablet was compacted ex situ and then placed between a diamond crystal and the window. The cell had pipes built in to the sides, which allowed the dissolution medium to flow through the chamber inside the cell. Thus, visible images were acquired using a CCD camera from the top surface of
the tablet simultaneously with ATR-FTIR images measured from the bottom surface during the dissolution of the tablet. This combined approach allowed the study of the moving fronts observed during dissolution. The assignment of the fronts had been a contentious issue as different explanations for the fronts were provided. Consequently, this new imaging approach was applied to a previously studied system which consisted of a coloured drug (buflomedil pyridoxal phosphate) and HPMC (Kazarian and van der Weerd, 2008). Previous assignment of the dissolution fronts for this tablet based on optical photography was not convincing because photography does not provide a quantitative value for concentrations of the drug, polymer and water. Effects such as changes in the materials’ refractive indices due to intake of water and gel formation will change the scattering properties of the medium, which can affect the interpretation of the visible imaging data. The ATR-FTIR imaging approach provided reliable interpretation of varying concentration of the components across the system. These were then compared with the appearances of the fronts in visible photography. The three fronts observed in the dissolution of the studied tablets were assigned to: true water penetration, total gelification of HPMC and the erosion front (Kazarian and van der Weerd, 2008). Significantly, due to the information provided by ATR-FTIR imaging the front assignment was seen to be different to those postulated by Melia et al., Colombo et al. (Melia et al., 1992, Bettini et al., 2001), and instead was in line with that postulated but Gao and Meury (Gao and Meury, 1996). This assignment of the fronts is crucially important for understanding the mechanism of drug release in HPMC based tablets. This understanding may help in the designing of new and better drug delivery products. That Perspex cell also provides the opportunity to study samples which cannot be compacted in situ. As it is Perspex, alignment of the sample relative the imaging crystal can be viewed and controlled as the cell is bolted into place, while it is capable of working with samples which are not necessarily cylindrical tablets with flat surfaces (Velasco et al., 2011).

4.6.4 **ATR-FTIR imaging for high-throughput analysis**

Imaging in macro ATR mode is a very useful tool for high-throughput technology, especially applied to pharmaceutical formulations. This fast screening of many samples could drastically reduce the time required to investigate a range of formulations.
Chan and Kazarian used a micro-drop system to deposit a range of over 100 formulations directly onto the surface of the ATR crystal. Formulations with different compositions were created by varying the number of drops dispensed from each head to the same point in the sample (Chan and Kazarian, 2005). A controlled humidity cell was used to control the environment, studying the performance of all samples under uniform conditions simultaneously (Chan and Kazarian, 2005). The micro-drop system had 2 dispenser heads, the first was loaded with the drug sample (nifedipine or ibuprofen) and the second was loaded with pure PEG. ATR-FTIR images showing an array of samples of drug and polymer created for high throughput analysis is shown in Figure 4-26.

![ATR-FTIR images showing an array of samples](image)

**Figure 4-26. Images showing the distribution of (a) PEG and (b) ibuprofen in an array of samples. Adapted from (Chan and Kazarian, 2005).**

High through put analysis was also used to investigate the effects of temperature on the stability of formulations. A range of stable formulations was found along with evidence that hydrogen bonding between ibuprofen and the polymer results in improved stability of the formulations at higher temperatures (Chan and Kazarian, 2006d). The use of a multi-channel grid facilitated studying the dissolution of several formulations simultaneously (Chan and Kazarian, 2006a), while high throughput analysis using macro ATR-FTIR imaging was applied to study protein crystallisation (Chan et al., 2009).
4.7 Summary

The applications presented here have illustrated the potential of FTIR imaging for studying pharmaceutical formulations. The use of an FPA detector facilitates the acquisition of both spatial and spectral information with a short measurement time.

Macro and micro ATR imaging allow for studies to be carried out at a range of fields of view. ATR-FTIR imaging is not necessarily a destructive technique, therefore samples can be extracted and reanalysed using complementary techniques to support the investigation of the sample. Although the dissolution procedures are obviously destructive, other analysis techniques, such as UV/Vis spectroscopy or visible optical analysis, can be used in conjunction.

FTIR imaging is a valuable analytical tool for the studying pharmaceutical and has clear advantages over the standard pharmaceutical analysis tools such as the USP dissolution tests, as it reveals information about the physical and chemical processes occurring within a dissolving tablet.
CHAPTER FIVE

EXPERIMENTAL APPARATUS
5 Experimental Apparatus

5.1 Introduction

In the work described in this thesis a number of different experimental apparatuses in various configurations were used. This chapter contains a general description of the major pieces of equipment and tools used and their applications.

Table 5-1 and Table 5-2 also contain a summary of the properties of the various optical arrangements used for FTIR imaging throughout the work. Particular experimental modifications and specifications are detailed as appropriate in each chapter.

5.2 FTIR imaging

![Figure 5-1. Photograph of Bruker FTIR imaging system including a) IFS 66 spectrometer, b) microscope, c) macro chamber (large sample accessory), d) a diamond Golden Gate™ ATR accessory.](image)

The data presented in this thesis were primarily acquired using two continuous scan FTIR imaging systems from Bruker (Germany). One system used an IFS 66 spectrometer connected to an external microscope and macro chamber (shown in Figure 5-1). The other used an Equinox 55 connected directly to an external macro chamber. Some measurements were also acquired using an imaging system from Varian Inc now part of Agilent Technologies, USA. The measurements on the Varian system made use of both the microscope optics (UMA 600) and the Large Sample Accessory. The IFS 66 spectrometer shown in Figure 5-1 is a conventional spectrometer and contains a single element DTGS detector and has space for a single-element Mercury Cadmium Telluride
(MCT) detector. The source was a silicon carbide Globar source and the interferometer used a germanium coated potassium bromide beamsplitter. When acquiring data using the microscope (both imaging and non-imaging), the source and interferometer of the spectrometer unit were utilised and the beam was directed out of a port on the right of the spectrometer, through a light box and into the microscope. In order to gather imaging data using the macro chamber, the beam was directed to bypass the microscope optics and passed into the macro chamber. The FPA detector was then incorporated into these external sections where needed. The FTIR imaging data were all gathered using FPA detectors with 64 × 64 pixel arrays (Santa Barbara Focalplane, USA), which acquired 4096 spectra simultaneously. A range of different optical arrangements and FPA detectors were used over the course of the work. The general properties of each arrangement are displayed in Table 5-2 and will be detailed as appropriate throughout the thesis. As the FPA detectors are MCT based detectors, they require cooling with liquid nitrogen to operate. Proper safety procedures for the handling of cryogenic materials were followed, such as the wearing of appropriate protective clothing and the usage of the correct transportation vessels.

5.2.1 Acquisition process

When acquiring data it is important to ensure that the system has been configured correctly. The important aspects of image acquisition are outlined below.

5.2.1.1 Co-addition of scans

As a standard 64 × 64 FPA detector records 4096 spectra simultaneously, then a large amount of data are produced. In the first application of these detectors this meant using the FTIR spectrometer in step scan mode to allow the computing hardware time to gather the data. With the advent of faster FPA detectors and more powerful computers the system can be run in continuous scan mode, such that the mirror in the interferometer moves in a smooth continuous fashion rather than moving in discrete steps. In order to improve the SNR several scans are co-added. For studying static systems fast measurement time is not necessary, therefore hundreds of scans can be co-added to improve the SNR. However, for dynamic systems such as dissolution measurements acquisition time is very important. An image with good spectral quality can be gathered in fewer than ten scans, however, for the work in this thesis normally
20 to 32 scans were co-added depending on the requirements of the system being studied and the performance of the equipment being used. The older FPA detectors with a pixel size of 60 µm × 60 µm had a significantly slower measurement performance than the newer FPAs with 40 µm × 40 µm pixels.

### 5.2.1.2 Spectral resolution

An important aspect of any dataset is the spectral resolution: the number of data points which make up the spectrum. On the imaging systems used in this work, spectral resolution was typically set to 8 cm⁻¹, although it was possible to gather data at higher and lower resolutions. In order to gather data at higher resolutions the mirror in the interferometer must move through a greater distance. This requires a longer acquisition time and generates larger datasets.

### 5.2.1.3 Spectral range

The spectral range for FPAs when working in mid-infrared was generally set to 4000 cm⁻¹ to 900 cm⁻¹. The FPA detectors have a cut-off below 900 cm⁻¹ meaning no measurements are possible in the region lower than this wavenumber. However, depending on the coating of the window in the Dewar holding the FPA it was possible to extend the spectral range into the near-infrared above 4000 cm⁻¹. When working with the prototype imaging Golden Gate™, the spectral range was limited to the fingerprint region (2000 – 900 cm⁻¹) as the coating on the lenses of the internal optics did not allow wavenumbers above 2000 cm⁻¹ to pass through. Reducing the spectral range will also decrease the measurement time as there will be fewer points in the resulting interferogram. However, a suitable low pass filter is required to prevent spectral artefacts.

### 5.2.1.4 Gain and frame rate

The intensity of the infrared radiation at the detector is often below the maximum available given the dynamic range of the analogue to digital converter (ADC). In order to maximise the dynamic range of the system, the electronic gain can be set such that the maximum intensity of the centreburst is close to the top of the dynamic range, without exceeding it. At the “wings” of the centreburst, the intensity is much lower,
therefore increasing the gain maximises the number of discrete levels used upon analogue to digital conversion. This can significantly increase the SNR of the spectra produced (Bhargava et al., 2001).

The signal measured by the detector can be increased by decreasing the framerate, this increases the exposure time. The greater the exposure time, the higher the intensity of the signal measured and the better the SNR. However, increasing the exposure time too much will result in increased temporal smearing of the data, as the mirror of the interferometer will have moved a significant distance during the exposure time. This will add more noise to the data, which would need to be rectified by slowing the scan speed.

5.2.1.5 Sample alignment

The imaging FOV is usually smaller than the surface area of the ATR crystal. When dealing with dissolving tablets it is important to ensure that the FOV is aligned with the region of interest of the dissolving tablet. As the diameter of the imaging area for the diamond is approximately 500 µm across, it is important to check that the sample has been positioned correctly. Sample position may be checked through acquisition of an image however, if the sample position is incorrect then the sample position must be adjusted and another image recorded in order to check this. Fine adjustment of the sample position can be a fairly lengthy process using this methodology, therefore a faster process is required.

![Figure 5-2. Live images showing intensity of light falling on FPA detector, where white is high intensity and black is low. a) no sample on ATR crystal b) sample positioned to half cover imaging area.](image)
This is most simply done using the live scan, which shows the intensity of the IR light reaching each pixel of the FPA detector. The first item to note in Figure 5-2a is that the illumination is heterogeneous. This is due to several factors; the first is that the Globar source provides a heterogeneous distribution of radiation; the second is that the sensitivity of each pixel varies slightly and the third is that the optics of the system does not provide a completely even distribution of radiation across the imaging area. In Figure 5-2b it can be seen that while the overall distribution of intensity is very similar to that in Figure 5-2a there is a darker red region in the lower part of the image. This darker region denotes an area in which something is in contact with the crystal, slightly attenuating the IR signal. By using the live scan in this way it is possible to ensure the sample has been positioned correctly before acquisition of any image data.

5.2.2 Macro chamber

The macro chamber or large sample accessory was used for achieving fields of view (FOV) with dimensions ranging from approximately 0.5 mm to 4 mm depending on the accessory used (though larger FOVs may be achieved using other optical configurations). For these measurements the IR beam was directed from the source in the spectrometer through to the macro chamber using a series of motorised mirrors. The macro chamber serves as a housing device for a range of spectroscopic accessories, which can be exchanged depending on the application. The accessories in combination with the FPA produce a different FOV and spatial resolution, and depending on the crystal within the accessory, can be used in conjunction with custom designed cells for compaction and dissolution of samples. The work in this thesis mainly used a Golden Gate™ diamond ATR accessory (Specac Ltd, UK) (Figure 5-3) which was originally designed for supercritical fluid analysis, the internal optics for this are presented in Figure 4-13. As shown in Figure 5-3c this accessory has a set of threaded holes around the diamond plating, by which cells for dissolution and compaction may be affixed. In the middle of the armature of the gate a threaded bolt can be seen. This bolt was used to press down the punch in the in situ compaction cells. A range of anvils could also be attached to the bottom, which were used to press the sample onto the ATR crystal, in the absence of a compaction cell.
5.3 Data acquisition

The data acquired in this thesis were gathered using the ATR approach, for which the sampling procedure is relatively simple. The sample must be placed in contact with the crystal. In order to produce reliable and repeatable data, good contact between the sample and the crystal must be achieved. This is not an issue with liquid, wet or relatively soft samples, whereas in the case of hard or fragile samples achieving good contact can be more difficult. For samples with low melting points, contact may be improved by heating the measuring surface until the bottom of the sample softens slightly. In the case of samples where this is not possible, a set of in situ compaction and dissolution cells have been designed which help to press the sample onto the crystal.

5.3.1 Compaction cell

In order to study in situ tablet compaction on the diamond ATR accessory, a compaction cell was used as shown in Figure 5-4a (Elkhider et al., 2007). The cell was mounted on the accessory and the constituent powders of the tablet were poured into the cell. A punch (Figure 5-4b) was then inserted into the cell and the armature of the Golden Gate™ accessory was lowered. The anvil was then brought into contact with the top of the punch and a torque screwdriver was used to control the amount of compaction force applied to the sample. The force used in the formation of tablets using this methodology was up to an order of magnitude smaller than that usually used in...
industry; nonetheless this formed tablets with a good structural integrity. The torque screwdriver (Figure 5-4c) was calibrated to produce a known compaction force on the sample. The range of the compression force applied on the diamond ranged from ca. 270 – 850 N which is corresponded to ca. 50 – 120 MPa for a 3 mm diameter tablet.

![Figure 5-4](image)

*Figure 5-4. Photographs showing a) compaction cell with screw fixings at corners, b) punch which is inserted into the central hole and c) torque screwdriver, the first application of this cell was described by Elkhider et al. (Elkhider et al., 2007).*

### 5.3.2 Compaction and dissolution cell

The compaction and dissolution cell allows for compaction and dissolution of a tablet to be studied *in situ* (van der Weerd *et al.*, 2004). The compaction and dissolution cell bolts onto the diamond ATR accessory in much the same way as the standard compaction cell. However, in order to allow flowing dissolution to occur, it had pipes to allow dissolution medium to flow both into and out of a central chamber. The dissolution chamber was created by a central bolt which could be partially lifted out of the central chamber exposing the tablet to the dissolution medium. The bolt was only lifted for dissolution, during compaction the bolt remained down, as in the down position it served as the compaction chamber for the tablet. The compaction of the tablet was off-centre from the middle of the diamond crystal, such that when imaged half of the imaged area was covered by the tablet and the other half by the dissolution medium.
5.3.3 Visible optical dissolution cell

A transparent dissolution cell has been designed, such that the dissolution of samples may be studied using a video camera while simultaneously acquiring FTIR images (Kazarian and van der Weerd, 2008). The cell consists of a rectangular section of Poly(methyl methacrylate) (PMMA), with flow holes drilled through it to allow the flow of dissolution medium. The sample is placed on the diamond ATR crystal and a rubber O-ring is placed around the sample. The dissolution cell is then bolted into place on top of the sample, sealing against the O-ring to create a chamber for dissolution. As the bottom of the cell is a flat piece of PMMA, this cell has the advantage that it may be used with samples that cannot be formed inside the standard compaction/dissolution cell. This is particularly useful when careful alignment of the system is required as the position of the sample may be monitored by the operator at all times.

Figure 5-6. Photograph of visible optical dissolution cell. The cell is affixed by the four screws in the corners, the pipes can be seen passing through the PMMA into the chamber created by the rubber ring between the cell and the diamond plating. The tablet can be seen dissolving within the chamber. This was first described by van der Weerd et al. (van der Weerd and Kazarian, 2004b).
5.3.4 Micro ATR imaging

![Photographs of a Varian microscope system](image)

**Figure 5-7. Photographs of a Varian microscope system a) Infrared microscope, b) micro ATR objective, c) Germanium ATR crystal.**

For analysis of some static samples a high spatial resolution was required. In this case it was necessary to use the FTIR microscope (Figure 5-7) which produced images with a field of view of 64 µm × 64 µm with a spatial resolution of 4 µm. The area of interest of the sample was located using visible microscopy, before switching to infrared. The microscope used a germanium crystal which was attached to a removable mounting (Figure 5-7c), which was moved into position when taking measurements (Figure 5-7b). The crystal was held in place and the sample was lifted into contact with the crystal, with sufficient force to achieve adequate contact. Compaction cannot be conducted *in situ* when using a microscope objective, therefore samples are prepared *ex situ* before measurement in the microscope system. The micro ATR system as of yet has not been used for studying dissolution.

5.3.5 Properties of ATR crystals

As discussed in Section 5.2.2 the majority of the FTIR imaging measurements in this thesis were conducted using diamond ATR accessories; although zinc selenide and germanium ATR crystals were also used. The zinc selenide was large and facilitated the acquisition of data with a larger FOV, while the microscope was fitted with the germanium crystal. Each crystal has different properties, for example, although large
zinc selenide crystals can be grown relatively easily, zinc selenide is brittle and susceptible to acidic and basic erosion. The general properties of the materials used in this work for ATR crystals are summarised in Table 5-1.

Table 5-1. Properties of ATR crystals.

<table>
<thead>
<tr>
<th>Material</th>
<th>Refractive Index (at 1000 cm⁻¹)</th>
<th>Spectral Range (cm⁻¹)</th>
<th>Other Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc Selenide (ZnSe)</td>
<td>2.4</td>
<td>20000 - 500</td>
<td>Insoluble in water, however is brittle, easily scratched and is attacked by acids and bases</td>
</tr>
<tr>
<td>Germanium (Ge)</td>
<td>4</td>
<td>5500 - 870</td>
<td>Insoluble in water, however is brittle and easily scratched</td>
</tr>
<tr>
<td>Diamond (C)</td>
<td>2.4</td>
<td>4500 - 2500, 1650 - &lt;200</td>
<td>Very hard, can withstand high pressure</td>
</tr>
</tbody>
</table>

5.4 Conventional FTIR spectroscopy

In order to obtain spectra of the components which were used in a sample, the pure forms of the components were measured using a conventional (non-imaging) ATR-FTIR spectrometer before sample preparation. In order to ensure a good comparison could be made between the spectra extracted from the imaging datasets and the conventionally acquired spectra, both were measured at the same spectral resolution, which was normally set to 8 cm⁻¹.
Two spectrometers were used for this, a Bruker Vector 22 and a Bruker Alpha-P, which is shown in Figure 5-8a. The Vector 22 used a standard Golden Gate™ ATR accessory. The Alpha-P system was a portable spectrometer and used a lever to lower the anvil onto the sample pressing against the ATR crystal to ensure good contact. The detectors for these systems were able to operate at room temperature as they used deuterated triglycine sulphate (DTGS) detectors.

5.5 X-ray microtomography

X-ray microtomography was used as a complementary technique for sample analysis Figure 5-9. This was done using a Skyscan 1074 Portable X-ray microtomograph (Skyscan, Belgium). The data were captured using the Skyscan 1074 data capture software, which recorded the data as greyscale transmission images with a resolution of 720 × 576 pixels. These two dimensional images were reconstructed into three dimensional data using the Skyscan Dataviewer program. Unless otherwise stated, the step scan angle was set to 0.9º and the sample was rotated through 360º. The exposure time was set to 2 ms, and each image extracted was an average of 10 frames.

Figure 5-9. Photograph of Skyscan 1074 portable X-ray microtomograph

Figure 5-10. Photograph of interior of X-ray microtomograph showing, a) plinth, b) sample and modelling clay, c) detector.
The interior of the microtomograph contained a rotating plinth, on which the samples to be measured were positioned as shown in Figure 5-10a. They were fixed in place using a small amount of modelling clay (Figure 5-10b), the platform was then adjusted to the correct height ensuring the sample was in the middle of the detector’s field of view (Figure 5-10c).

5.6 UV/Vis spectroscopy

In order to measure the amount of drug dissolved into dissolution media it was necessary to connect a UV/Vis spectrometer to the effluent stream of the dissolution cell as shown in Figure 5-11 (van der Weerd and Kazarian, 2004a).

![Figure 5-11. Schematic diagram of UV/Vis flow system.](image)

It was not possible to simply connect the UV/Vis detector directly to the effluent stream as there was very large pressure drop across the detector used. This would have resulted in the system being very susceptible to leakages. Therefore the dissolution system was separated into two sections. In the first section dissolution medium was drawn out of Reservoir 1 and was pumped through the dissolution cell at atmospheric pressure and into Reservoir 2. In the second section dissolution medium was drawn out of Reservoir 2 and pumped via Pump 2 through the UV/Vis spectrometer into the effluent tank. Reservoir 2 employed a small vial suspended above and within a larger beaker. The residence time of the fluid in the vial was approximately 2 minutes for a flow rate through Pump 1 of 1 ml/min. Pump 2 was run at 90% of the flow rate of Pump 1, such that the vial constantly overflowed into the beaker. This was designed so Reservoir 2 never ran dry, while there was only a small amount of averaging of the concentration in the dissolution medium over time.
The UV/Vis detector was also used in a single pump configuration, as shown in Figure 5-12, in which the dissolution medium was continually recirculated. This system was used for the work comparing the dissolution performance of the FTIR flow cell system to the USP dissolution apparatus in Chapter 7. This was because in the two pump system the tablet is constantly dissolving in fresh dissolution medium, whereas in the USP dissolution apparatus the tablet dissolves in a bath, the recirculating system more closely mimics this system. The size of the reservoir used in this configuration was 900 ml.

![Figure 5-12. Schematic diagram of single pump UV/Vis flow system.](image)

In the configuration shown in Figure 5-12, the UV/Vis spectrometer was positioned after the pump and before the dissolution cell. There were two reasons for this; there was a large pressure drop across the spectrometer, while the flow cell was susceptible to leaks when operating at high pressure. This system was designed to measure the concentration of the bulk of the fluid in the reservoir. If the spectrometer had been placed after the dissolution cell, the spectrometer would have measured the bulk concentration plus the material which had just been dissolved.

These pumping systems were capable of achieving a flow rate of 9.99 ml/min. Pump 1 was a Merck-Hitachi L-6200 (Hitachi, Japan) and Pump 2 was a Kontron 320 (Kontron, USA), both systems were originally used for high pressure chromatography. The detector used was a Kontron 332 UV/Vis detector; the wavelength used for analysis will be specified in each chapter containing UV/Vis data where appropriate.

### 5.7 Hardware properties

Table 5-2 contains a summary of the imaging and experimental capabilities of the various ATR arrangements used in the work.
Table 5-2. Summary of properties of imaging hardware and configurations used in this work.

<table>
<thead>
<tr>
<th>Macro or Micro imaging approach</th>
<th>Macro Imaging</th>
<th>Micro Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATR crystal type</td>
<td>Diamond</td>
<td>Germanium</td>
</tr>
<tr>
<td>Spectrometer type</td>
<td>Bruker: IFS 66</td>
<td>Varian: 670 FT-IR</td>
</tr>
<tr>
<td>Accessory</td>
<td>Non-imaging Prototype imaging (CO*)</td>
<td>Oil Analyser 10x micro ATR objective</td>
</tr>
<tr>
<td>Detector pixel size (µm)</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>Spatial Resolution (µm) (approx)</td>
<td>20-30</td>
<td>15</td>
</tr>
<tr>
<td>Field of view (µm x µm)**</td>
<td>800 × 1100</td>
<td>1800 × 2500</td>
</tr>
<tr>
<td>In situ compaction capable</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Suitability for studying dissolution</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Combination with UV/vis detector</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* Corrective Optics (CO) incorporated into imaging Golden Gate™ creating an aspect ratio close to 1:1
** FOV size calculated based on using a 64 × 64 pixel detector

5.8 Materials and samples

The materials used throughout this thesis were model pharmaceutical powders and were therefore potentially harmful. Powders were all handled while wearing appropriate safety clothing, such as, lab coat, gloves and safety goggles.
CHAPTER SIX

COMPACTION OF PHARMACEUTICAL TABLETS WITH DIFFERENT POLYMER MATRICES STUDIED BY FTIR IMAGING AND X-RAY TOMOGRAPHY
Chapter 6: Compaction of Pharmaceutical Tablets with Different Polymer Matrices studied by FTIR Imaging and X-ray Tomography

6 Compaction of Pharmaceutical Tablets with Different Polymer Matrices studied by FTIR Imaging and X-ray Tomography

This chapter presents the application of ATR-FTIR spectroscopic imaging to study the compaction of model pharmaceutical formulations. As discussed in the literature review, the spatial and chemical specificity of this imaging approach have been exploited to analyse the distribution of different components in various formulations. ATR-FTIR imaging is a surface analysis methodology which analyses a relatively thin (a few micrometers thick) surface layer of the sample, therefore when studying pharmaceutical formulations it is important to understand the relationship between the data gathered at the surface layer and the bulk properties of the formulation.

6.1 Compaction of model tablets made of different polymer matrices

6.1.1 Introduction

The first section of this chapter sees ATR-FTIR imaging applied to study the compaction of model caffeine tablets made of two different commonly used polymer matrices, microcrystalline cellulose (MCC), hydroxypropyl methylcellulose (HPMC) and lactose (Reier and Shangraw, 1966, Bolhuis and Armstrong, 2006, Wu et al., 2005). The effective performance of a tablet depends upon the composition and the manufacturing process. The important parts of the process are the choice of the polymer matrix, the processing of the components and then the compression of the powder into a tablet.

While conventional attenuated total reflection spectroscopy has previously been used to study the surface layers of compacted tablets (Planinsek et al., 2006), imaging can reveal the distribution of different components at the surface layer of the tablet matrix (Chan et al., 2003, Chan et al., 2005).
As the penetration depth of the infrared radiation into the sample is relatively shallow, good contact between the sample and the ATR crystal is required. Good contact can be defined as a region in which band intensities remain constant across a homogenous sample (Buffeteau et al., 1996). Uniform contact usually requires a liquid or smooth sample. Particle based pharmaceutical powders therefore do not provide uniform contact and so a compaction force must be applied to ensure good contact for non-ideal samples (Zhao et al., 1987). When a tablet is compacted, initially the positions of particles rearrange. The particles crumble, and the voids then collapse into harder denser material. Elastic and plastic deformation, is followed by particle fragmentation, the particles then rearrange further into a closer packing structure reducing the volume (Duberg and Nyström, 1985, Duberg and Nyström, 1986), thereby improving contact with the ATR crystal. Therefore, during compaction, not only can relocation and fracturing of the particles be studied, but the increase in tablet density may also be assessed.

6.1.2 Experimental

6.1.2.1 Sample preparation

Tablets made of four different components were investigated in this study: caffeine (model drug) and three common excipients (HPMC, microcrystalline cellulose (MCC), and lactose) for the tablet matrix. HPMC was supplied by Colorcon. Microcrystalline cellulose and lactose were supplied by Merck Sharp & Dohme. The powders were sieved into a selection of particle size ranges. For the excipients, particles with size below 90 µm were used, while the drug particles were sieved to a size of 90-125 µm. Drug/polymer matrix mixtures were created by mixing an accurately weighed amount of drug and polymer in a small vial. The powder mixtures were blended together in a vial with a flat bottom with a spatula that was approximately as wide as the inner diameter of the vial. This ensured that any powder at the edges of the vial would become mixed in as well. Following mixing, the powders were compacted directly on the diamond surface where the ATR-FTIR image was measured.
6.1.2.2 **FTIR spectroscopic imaging**

The IFS 66 spectrometer was used in conjunction with the macro sample chamber to accommodate the diamond Golden Gate™ ATR accessory. FTIR images were acquired with a 64 × 64 FPA detector with 8 cm⁻¹ spectral resolution and 32 scans co-addition. This is described in Column 1 of Table 5-2. All images shown are 1100 µm × 780 µm.

6.1.2.3 **Compaction**

Compaction of the powder mixture was performed using a custom designed compaction cell. The cell, which was integrated with the diamond Golden Gate™ ATR accessory, was the same cell described in Section 5.3.1. The compaction force was controlled using a torque wrench. Following compaction, the force on the tablet was not released until the image data had been captured.

6.1.3 **Results and discussion**

The composition of each component was varied systematically to facilitate an understanding of the effect made by each individual component. The drug loading was varied between 10 and 30 weight percent (wt%) and the other components were varied accordingly. A full range of tablet compositions were tested, with concentration varied by 10 wt% at each step. The data presented here are representative and convey the major results. The presented formulations are given in Table 6-1.

<table>
<thead>
<tr>
<th>Lactose</th>
<th>HPMC</th>
<th>MCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 wt% Caffeine</td>
<td>Tablet 1.1</td>
<td>-</td>
</tr>
<tr>
<td>20 wt% Caffeine</td>
<td>Tablet 1.2</td>
<td>Tablet 2.2</td>
</tr>
</tbody>
</table>

The strength of the diamond allowed the compaction and the imaging measurement to be performed *in situ*, thus providing a means to study the effect of pressure on tablet compaction without the need for removal of the tablet from its die. Therefore the same tablet could be studied at several different levels of compression force, while at the
same time ensuring a good contact between the ATR crystal and the tablet surface which is important in ATR-FTIR measurement. The range of the compression force applied on the diamond ranged from ca. 270 – 850 N which is corresponded to ca. 50 – 120 MPa for a 3 mm diameter tablet.

In order to obtain a good contact between the tablet and the surface of the diamond, a minimum force of 610 N (86 MPa) was required as shown by the poor contact in Figure 6-1 at 40 MPa. Nevertheless, measurements were taken from 370 N to assess the effect of increasing pressure on the formation of the tablets. Images of the tablet were then taken at compression forces of 610 N (86 MPa) to 850 N (120 MPa) at 120 N intervals, these pressures were relatively mild when compared to those used in industry because the maximum torque that can be applied by the torque wrench used was limited. Further improvement to the compaction cell with a stronger press with calibrated pressure is possible and could be investigated in future developments.

The absorption bands at 1562 – 1518 cm\(^{-1}\), 1153 – 1127 cm\(^{-1}\), 3007 – 2774 cm\(^{-1}\) and 1118 – 1088 cm\(^{-1}\) were used to generate images showing the distribution of caffeine, lactose, HPMC and MCC respectively. The images of the same substance all share the same colour scale, across all datasets, such that they can be compared directly.

![Figure 6-1](image.png)

**Figure 6-1.** An image showing the relative surface changes in caffeine and lactose content of the surface layer of the tablet with increasing pressure for a 10 wt% drug loading of caffeine (tablet 1.1). The images size is 1100 \(\mu\)m \(\times\) 780 \(\mu\)m.
Between the two sets of images shown in Figure 6-1 and Figure 6-2, the caffeine concentration is doubled from 10 wt% to 20 wt%. This is reflected by the increasing intensity and area occupied by the caffeine for the tablet with a higher caffeine concentration. The caffeine (top row) and lactose (bottom row) images are not totally complementary as in some areas the images show low concentration for both components. This is an indication of the presence of a large void in the tablet and as expected there is a greater presence of voids at the surface of the tablet at low compaction pressures. For example, by comparing the images of caffeine and lactose shown in Figure 6-1 at 40 MPa there are large areas of the image in which there is no presence of either component.

This in situ compaction study provides an opportunity to obtain a series of chemical images representing the distribution of different chemical components from the same area of a tablet when compaction pressures are increased. The effect of pressure on the distribution of different components can be studied. When the compaction pressure increases, the absorptions of caffeine and lactose also increase due to the reduction of voids in the tablet and at the surface of the ATR crystal and better contact of the with the crystal tablet is achieved. However, there was not much change in the distribution of the two components analysed which is expected since lactose is a low fragmentation propensity material (Bolhuis and Armstrong, 2006). This can be clearly observed by the increase in absorption of all tablet components in the series of images shown in Figure 6-1 and Figure 6-2.

There is also a much greater percentage change in the apparent concentration of lactose across the image range. The caffeine images in Figure 6-1 and Figure 6-2 are almost stable above 95 MPa, however there is a noticeable increase in absorbance for lactose even between the images for 112 and 120 MPa. This indicates that lactose continued to move within the matrix with increasing compaction force, and that, were the compaction force to be increased further changes in the matrix would continue to be seen in the images.
Figure 6-2. An image showing the relative surface changes in Caffeine and lactose content of the surface layer of the tablet with increasing pressure for a 20 wt% drug loading of caffeine (tablet 1.2). The images size is 1100 µm × 780 µm.

The images of caffeine and lactose remained not completely complementary even when the pressure reached 120 MPa. This made the assessment of drug homogeneity in the tablet more challenging. While this accessory was not originally designed for imaging purposes or for compaction studies, modifications to enable the study of tablet compaction were made to the apparatus. A higher compression force would further eliminate voids, such that the images would become complementary. While this was not possible with the existing equipment, the opportunity for modification to allow this exists in potential further work.

Nevertheless, comparing the tablet that contains more caffeine (20 wt%) to the tablet with less caffeine (10 wt%), Figure 6-2 which presents the result of the tablet with a greater loading of caffeine appears to give a stronger average lactose absorption than Figure 6-1 even though the lactose is actually in lower concentration in that tablet. This was due to a greater void reduction which must be as a result of higher caffeine concentration. A previous study has shown a similar effect when a small amount of magnesium stearate, which is a known lubricant, was added to the formulation of a HPMC tablet (Chan et al., 2005). This suggests that the caffeine acts as a lubricant for the lactose making it more compactable. It is therefore possible to apply this approach to detect the possibility of unexpected lubricating effects of the drug on the polymer and
vice versa. This is very important to the pharmaceutical industry because the final density of the tablet, which can be a strong function of its dissolution properties, may be affected by the lubrication of the powders during compaction.

The imaged area has a width of approximately 500 µm. Drug particles of 90-125 µm in size (largest particles from sieving) would be expected to occupy approximately 1/5 the width of the image at their maximum width. In Figure 6-1 and Figure 6-2 the largest particles are almost exactly this size which indicates the particle size of caffeine used for this tablet coincides with the maximum domain size of the caffeine. These data show that it may be possible to use FTIR imaging to obtain particle size information from compacted tablets, this is discussed further in Chapter 7.

Figure 6-3. An image showing the relative surface changes in caffeine and HPMC content of the surface layer of the tablet with increasing pressure for a 20 wt% drug loading of caffeine (tablet 2.2). The images size is 1100 µm × 780 µm.

Figure 6-3 and Figure 6-4 illustrate the polymer (80 wt%) and drug (20 wt%) distribution in the tablet with polymer matrices of HPMC and microcrystalline cellulose. The drug and polymer images from these tablets are more complementary than those shown in Figure 6-1 and Figure 6-2 even for those compacted with low compaction pressure (40 MPa) suggesting that these polymers have very good compaction properties (Bolhuis and Armstrong, 2006). This results in the appearance of larger drug domains.
As in Figure 6-1 and Figure 6-2 there is a greater percentage change in the apparent concentration of microcrystalline cellulose and HPMC across the image range in Figure 6-3 and Figure 6-4. The caffeine images stabilise with pressure quite rapidly, however the bulk of the polymer matrix continues to improve in contact even up to the maximum pressure applied. This is more clearly illustrated in the histograms in Figure 6-5.

![Caffeine and MCC images](image)

**Figure 6-4.** An image showing the relative surface changes in caffeine and MCC content of the surface layer of the tablet with increasing pressure for a 20 wt% drug loading of caffeine (tablet 3.2). The images size is 1100 µm × 780 µm.

Comparing the relative increase in absorbance of drug and polymer based on the change in the colour in the images, the relationship between compression force and the tablet density can be visualised immediately. However, this comparison is clearer when the absorbance is plotted as histograms which are presented in Figure 6-5.

The same approach has been previously used to assess the homogeneity of pharmaceutical formulations (Coutts-Lendon et al., 2003, Chan and Kazarian, 2004a). The histogram on the right hand side of Figure 6-5 shows that the absorbance of HPMC increased more with pressure than that of MCC. A previous study (Picker, 2004) has shown that HPMC exhibits a greater slope of porosity (density) over pressure than MCC which is consistent with the result shown.
Figure 6-5. Top two histograms showing change in apparent caffeine (left) and HPMC (right) absorption with increasing pressure (MPa, as indicated in the right-top corner of each graph) for tablet 2.2. Bottom two histograms showing change in apparent caffeine (left) and MCC (right) absorption with increasing pressure for tablet 3.2.

The histogram on the left hand side of Figure 6-5 reveals that a higher absorbance of caffeine can be observed when MCC was used as the polymer matrix. The absorbance of caffeine is more sensitive to the compression force and the distribution of absorbance is wider for the tablet with MCC. This demonstrates that the employed approach can reveal the effects of different types of polymer matrices on the distribution and the relative density of drug and polymer on the tablet.

6.1.4 Conclusions

In this part of the chapter it has been shown that during tablet formation, lactose compaction can be enhanced by the presence of caffeine particles. This has important implications for the pharmaceutical industry as the integrity of a tablet can have an
important influence over its dissolution properties. Statistical analysis of the data obtained with \textit{in situ} spectroscopic imaging for compaction of HPMC and MCC has shown that the polymers have very good compaction properties, whilst also demonstrating that HPMC will compact more at lower pressures than MCC.
6.2 Complementary use of FTIR imaging and X-ray microtomography

6.2.1 Introduction

Spectroscopic chemical imaging allows a high resolution two-dimensional “chemical image” to be created. The infrared radiation penetrates up to several micrometers into the sample. The chemical images are obtained from a thin surface layer of the tablet. There are several advantages to this. The sampling region where the data are gathered is very well defined; there is no averaging through the sample as there would be when imaging using the transmission approach. The sampling methodology can be applied to a range of samples types that might be more complicated to study using other sampling approaches, such as transmission, which for tablet studies would necessitate microtoming of the samples in order to achieve the required thinness (this is more clearly illustrated in Figure 4-10). As the diamond ATR crystal is hard, the compaction of the tablets can be studied in situ, while the short penetration depth of the evanescent wave facilitates dissolution studies as seen in Section 4.6. Most importantly for the work in this chapter, ATR-FTIR imaging is non-destructive allowing the samples to be reanalysed using complementary analytical techniques.

In order to verify the usage of data from this surface layer analysis approach, a complementary technique was used to analyse the samples in conjunction with ATR-FTIR imaging. X-ray microtomography, which is a more penetrative technique, was chosen. As it uses X-rays which pass through the sample, a three-dimensional image of the sample can be generated, showing the density distribution within the tablet. The results obtained were compared to ATR-FTIR images obtained from the thin surface layer of the tablet. As X-ray microtomography can only distinguish different samples based on density differences, it cannot distinguish between the different chemical compounds in a tablet as clearly as FTIR imaging. In order to ensure clear differentiation of the components in the tablets it was necessary to select components which had significantly different densities, in this case caffeine and microcrystalline cellulose were used. The results of this work show that X-ray tomography can be used.
in conjunction with FTIR spectroscopic imaging to produce a density map that verifies the chemical images obtained by FTIR imaging.

6.2.2 Experimental

6.2.2.1 X-ray microtomography

The X-ray data were acquired using a Skyscan 1074 Portable X-ray Microtomograph. The data were collected using the Skyscan 1074 data capture software, and were reconstructed using the Dataviewer program. The step scan angle was set to 0.9° and the tablet was rotated through 360°. The exposure time was set to 2 milliseconds and each extracted image was an average of 10 frames.

6.2.2.2 Sample preparation

The tablet samples were blended and compacted using the same methodology as described in Section 6.1.2.3. The density of caffeine crystals is 1.23 g/cm³ and the density of microcrystalline cellulose is 1.58 g/cm³ (IPCS, 1998, Sun, 2005). Upon exposure to a damp atmospheric environment MCC will absorb water influencing the final density of the compacted tablets (Sun, 2005). Therefore the samples were stored in a stable low humidity environment until usage.

6.2.3 Results and discussion

6.2.3.1 FTIR imaging and particle size

The effect of particle size on the measured domain size of caffeine on the compacted tablet was also investigated. Caffeine with particle sizes of 100-125 µm and 125-150 µm were mixed with MCC at 30 wt% and compacted into tablets with 120 MPa of compaction pressure. Examples of the distributions of caffeine at the surface of the compacted tablets are shown in Figure 6-6.
Figure 6-6. An image showing the relative surface changes in caffeine content of the surface layer of the tablet with increasing particle size for a 30% drug loading of caffeine and a 70% loading of MCC. The images size is 1100 µm × 780 µm.

The maximum domain size of caffeine shown in Figure 6-6 varied according to the particle size of the drug used. However, there are many domains of caffeine shown in each of the images that are smaller than the particle size of caffeine used. This is possibly due to the fact that some of the caffeine particles may have fragmented during the process of compaction despite the relatively mild pressure used. Another possibility is that since the evanescent wave of the IR radiation (one of the features of ATR measurement) only probes into the sample for a few micrometers (Harrick, 1967), then the full size of the domains of caffeine may only be revealed with more penetrative measurements. The smaller particles seen in the images are most likely merely the tips of relatively unfragmented particles. This is more clearly illustrated in Figure 4-11. The image illustrates how particles, which all have the same diameter, with a tablet matrix can present significantly different sizes in the resulting ATR image. In Figure 4-11 the measured particle size is dependent on the point of intersection of the particle with the surface of the tablet. In a real system the varying measured particle size would be produced by the non-spherical nature of the particles, or the degree of deformation of the particles at the surface of the tablet.

The images in Figure 6-6 also display some domains of caffeine which appear to be larger in one dimension that the stated particle size. There are several possible reasons for this, the most likely is post sieving agglomeration, such that either in the sieve pan or during the subsequent mixing and compaction procedures, two particles either adhere to one another or arrive in very close proximity to one another in the final tablet matrix,
appearing as one larger particle in the final image. Sieving selects particles based on a two-dimensional projection of the shape, therefore particles which possess an aspect ratio significantly greater than 1 may fall though the sieve on their smallest diameter but present in the images with their larger diameter visible.

6.2.3.2 Comparison with X-ray data

X-ray microtomography was used as a complementary method to construct three dimensional spatially resolved images of materials of different density. Following the in situ compaction of the tablet and acquisition of an ATR-FTIR image, the tablet was retrieved and imaged using the X-ray microtomographic approach. The data are presented in Figure 6-7.

Figure 6-7. Images showing the data obtained with ATR-FTIR spectroscopic imaging which are compared with images from X-ray tomography. The top set of images shows the results for the 100-125µm particle size. The bottom set shows the data for the 125-150µm particle size. The FTIR data are shown on the right hand side, the key area of the X-ray tomography is shown in the middle, and the FTIR is layered over the X-ray data for comparison on the left hand side. The FTIR images are 1100 µm × 780 µm in size.
Chapter 6: Compaction of Pharmaceutical Tablets with Different Polymer Matrices studied by FTIR Imaging and X-ray Tomography

The images in Figure 6-7 show X-ray images extracted from the surface layer of the tablet overlaid with the ATR-FTIR images for comparison. The X-ray microtomography images were able to distinguish the caffeine particles based on the density difference between HPMC and caffeine. The image shown in Figure 6-7 reveals large caffeine particles (150-200 µm) embedded in the tablet which are not shown in the ATR-FTIR images. However, due to the limited spatial resolution of the X-ray microtomograph used in this study (ca. 80 micrometers (Kohout et al., 2006)), the smaller particles of caffeine are not shown clearly and it is probable that these larger particles were either a collection of smaller particles which averaged to appear as one large domain or were slightly beyond the penetration depth of the ATR images.

It was possible to compare the two sets of results by directly overlaying the two images from the FTIR-ATR approach and X-ray microtomography approach based on the pattern of the distribution of caffeine in the tablet. The results are shown in Figure 6-7. The distribution of caffeine did not match exactly due to the fact that the two methods have different sampling volumes and spatial resolutions. However, the similarity between the two caffeine distribution patterns suggests the results are showing the same measured area.

Figure 6-8. Coronal, sagittal and transverse cross sections through tablet with caffeine particle size 100-125µm. The particles of caffeine distributed in the sagittal and transverse planes are circled in red.
As ATR imaging is a surface layer analysis technique, when studying samples of any thickness, such as pharmaceutical tablets, it is important to understand whether the image seen at the surface is representative of what may be found in the bulk of the sample. It is illustrated in Figure 4-11 that the measured particle diameter may be less than the maximum diameter of the particle, however if the distribution of particles throughout the tablet matrix is relatively even and similar to that found at the imaging surface, then the ATR data can be seen as representative of the tablet as a whole. The image in Figure 6-8 is a significant result in conjunction with the data in Figure 6-7, as it shows the distribution of caffeine through the depth of the tablet. As would be expected, there was a relatively even distribution, as particles can be seen at all depths, indicating that as long as one is aware of the assumptions being made regarding particle size etc., the data seen at the surface of the tablet can be applied to the bulk of the tablet. This result helps to validate an assumption that must be made when using ATR-FTIR spectroscopic imaging to study pharmaceutical tablets.

This is the first time that X-ray microtomography has been used in combination with ATR-FTIR imaging. As X-ray microtomography relies on the density difference between the drug and the polymer in order to distinguish between the two substances, it would be challenging to analyse a multi-component system containing more than two substances. Based on the success of this combination of X-ray microtomography with ATR-FTIR imaging, a feasible future study would be to explore the possibility of assigning the presence of different components to the colour scale in the X-ray tomography image based on the result obtained from the comparison between the ATR-FTIR imaging and X-ray microtomography for a 3D-multicomponent analysis.

### 6.2.4 Conclusions

The work showed that data obtained with ATR-FTIR imaging can give a good indication of the particle size being investigated. However, the validity of this information is limited by the relatively short penetration depth of the infrared light into the sample. Therefore, more penetrative supplementary techniques must be used to fully determine this parameter of a system.
It was also shown that X-ray tomography can be used in conjunction with FTIR imaging to produce a density map of the tablets that verifies the data from the FTIR imaging. However, as it is only a density map, this technique relies on a system containing only two different species with distinctly different densities and may be too limited for complex mixtures such as those found in commercial tablet formulations.

This chapter has described an investigation into studying particle distribution within compacted tablet matrices using FTIR imaging. This work is continued in Chapter 7 which evaluates the possibility of obtaining quantitative information from the FTIR imaging data, such as particle size and component loading.
CHAPTER SEVEN

METHODOLOGIES FOR STATISTICAL ANALYSIS OF PHARMACEUTICAL FORMULATIONS
7 Methodologies for Statistical Analysis of Pharmaceutical Formulations

7.1 Introduction

ATR-FTIR imaging has been shown to be highly applicable to pharmaceutical formulations. It is an excellent approach for studying physical phenomena during dissolution, such as drug crystallization (Kazarian and Chan, 2003). Its application to achieving quantitative data from dissolution tests has also been shown (van der Weerd and Kazarian, 2004a). However, the application of this approach to gathering quantitative data regarding particle size and component loading from dry tablet matrices is less established.

Three factors were studied: An assessment of the ability to determine the relative concentration of a component from FTIR images, particle size analysis and statistical analysis of the data to determine the number of images required for the mean of these parameters to satisfy required confidence levels.

Similar analyses have been performed with spectroscopic techniques previously; however, this has mostly been with NIR spectroscopy (Clarke, 2004, Hilden et al., 2008, Lyon et al., 2002, Clarke et al., 2001). While surface analysis of binary mixtures of powders to quantify the appearance of components at the surface layer has been conducted using ATR-FTIR spectroscopy (Planinsek et al., 2006), there has been no application of imaging to similar studies. The application of ATR-FTIR imaging to spherical objects has been investigated (Everall et al., 2009), which could be seen as an analogous system to tablet particulates. However, the spheres studied were intact glassy samples, whereas pharmaceutical powders undergo deformation and fracture during compaction.

The work presented here aims to investigate how changes in particle size affect the measured values of component area fraction that may be extracted from the FTIR imaging data, whether particle size can be determined from ATR-FTIR images and finally what is a statistically significant amount of data.
Chapter 7: Methodologies for Statistical Analysis of Pharmaceutical Formulations

7.2 Materials and methods

7.2.1 Sample preparation

For these model tablets acetaminophen (paracetamol) and caffeine were chosen as the two components for these binary samples as they had similar Young’s moduli (Duncan-Hewitt and Weatherly, 1989, Roberts et al., 1991), densities (Haisa et al., 1976, Duncan-Hewitt and Grant, 1986, Roberts et al., 1991) and indentation hardnesses (Duncan-Hewitt and Weatherly, 1989, Jetzer et al., 1985), whilst being spectroscopically distinct. The similarities in these mechanical properties result in the deformation behaviour of the two components being similar (Jain, 1999). Therefore, changes in the compaction behaviour seen in the FTIR images were largely due to the desired control variable of particle size.

The two components were ground and sieved. Caffeine was sieved to the size range 90-125 µm, while paracetamol was sieved to six size ranges, <75 µm, 75-90 µm, 90-125 µm, 125-150 µm, 150-180 µm, >180 µm. Tablet formulations were blended with a 20 wt% loading of paracetamol and each tablet used 10 mg of powder. Tablets were compacted in situ using the same compaction cell described in Section 4.5.1 to a pressure of 120 MPa. 40 tablets were compacted for each size interval. The formulations used are shown in Table 7-1.

Table 7-1. Formulations studied for compaction

<table>
<thead>
<tr>
<th></th>
<th>Batch 1</th>
<th>Batch 2</th>
<th>Batch 3</th>
<th>Batch 4</th>
<th>Batch 5</th>
<th>Batch 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paracetamol</strong></td>
<td>Loading (wt%)</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Particle Size (µm)</td>
<td>&lt;75</td>
<td>75-90</td>
<td>90-125</td>
<td>125-150</td>
<td>150-180</td>
</tr>
<tr>
<td><strong>Caffeine</strong></td>
<td>Loading (wt%)</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Particle Size (µm)</td>
<td>90-125</td>
<td>90-125</td>
<td>90-125</td>
<td>90-125</td>
<td>90-125</td>
</tr>
</tbody>
</table>

7.2.2 Particle analysis

To ensure correct sieving size and investigate particle shape visible light microscopy and X-ray microtomography were used.
7.2.2.1 **X-ray microtomography**

Samples were measured using the Skyscan 1074 X-ray microtomography described in Chapter 5. The step scan angle was set to 0.9° and the tablet was rotated through 360°. The exposure time was set to 2 milliseconds and each extracted image was an average of 10 frames.

7.2.3 **FTIR imaging**

Images were acquired in the macro chamber of the Bruker Equinox FTIR imaging system described in Column 3 of Table 5-2. The accessory used was the diamond ATR accessory (Prototype Imaging Golden Gate™ without the correcting mirror). The condenser lens of the ATR accessory was modified with the addition of an aperture which modified the average angle of incidence of the system to 47° (Chan *et al.*, 2008, Kazarian and Chan, 2010). This minimised any possible gradient in absorbance across the imaging area caused by possible non-uniform depth of penetration.

7.3 **Results and discussion**

7.3.1 **Particle size investigation**

The first step in analysis was to study the size and shapes of the particles following sieving, as the particles were unlikely to be spherical and this would have a significant effect on measurement of the particle diameter. Therefore, the particles were scanned in three dimensions using X-ray microtomography.

7.3.1.1 **X-ray data**

The paracetamol particles shown in Figure 7-1 were scattered in a dispersed fashion on a flat surface before being imaged. This allowed for an approximate analysis of particle shape and size in three dimensions.
Figure 7-1. Coronal, Sagittal and Axial views of paracetamol particles in the size range 180-150 µm. The profile line marks out the density profile from which Figure 7-2 was generated.

Figure 7-1 clearly shows that the particles were highly non-spherical. As a result the importance of choosing the correct diameter for measurement is seen in Figure 7-2.

Figure 7-2. Intensity profile through three particles sieved to 150-180 µm as highlighted in Figure 7-1. The red and blue lines mark out the 10% intensity cut-off for two of the particles. The y-axis represents the intensity of radiation falling on the detector.

The data in Figure 7-2 illustrate the importance of choosing the correct diameter to measure when sizing the particle. This profile approximately cut through the middle of all three particles; however, the results are significantly different. The smaller particle had a measured diameter of 157 µm, while the larger particle had a measured diameter of 310 µm. This is not a truly fair comparison as the spatial resolution of the equipment was only around 80 µm.
A consistent sizing methodology was needed which reflected the method by which the particles were separated into their size categories and the methodology by which the particle size data were acquired from the FTIR images. In this case the particles were to be sized using image analysis. There are many examples of methods by which to size particles from imaging data, such as chord size (Heath et al., 2002), equivalent circle diameter (Kobayashi et al., 1997), Martin diameter, Krumbein diameter (Yasuo, 1996) and Feret’s diameter (Walton, 1948). Feret’s diameter is often used in sieve analysis. In this case the minimum Feret diameter will be used as illustrated in Figure 7-3. The Feret diameter serves as an approximation of the smallest gap through which the particle can fit and therefore is similar to the sieve diameter.

Figure 7-3. Illustration of Feret’s diameter on non spherical particle. \( X_{F, \text{min}} \) represents the minimum Feret diameter, which is the smallest distance between two parallel lines which are tangential to the surface of the particle and do not intersect with any part of it. \( X_{F, \text{max}} \) is the maximum Feret diameter which represents the largest distance between two parallel lines which are tangential to the surface of the particle and do not intersect with any part of it.

### 7.3.1.2 Microscopy data

Images of particles were obtained on a visible microscope. In order to size these particles, image processing was required to produce binary image data. The data were imported into the imageJ image processing software. The images were then converted to greyscale and the threshold was set to 10% of the maximum intensity. Auto thresholding was available; but it was found that the resulting particle size was very sensitive to small changes in the threshold value. Particles with holes resulting from the thresholding process were filled. Small particles less than 10 µm in diameter were discarded from analysis. This process is summarised in Figure 7-4.
Following this image processing the particles were then sized using the Feret’s diameter algorithm built in to imageJ. The results are shown in Figure 7-5.

Figure 7-5 shows a very good correlation between the sieved sizes and those calculated by the minimum Feret diameter. It can be seen that there is a slight bias towards the values of the Feret diameter being high. This is probably a result of the fact that the holes in the sieve are square. Therefore, a sieve with 125 µm spacing has a diagonal of 177 µm allowing larger particles to fall through. It has been shown previously that this leads to two dimensional image analysis producing an over estimate of particle diameter (Fritts, 1937).
7.3.2 Parameters for FTIR image preparation

When performing quantitative analysis of samples using ATR-FTIR spectroscopy, choice of the characteristic band used for analysis is a significant factor. This has been shown to change the measured size of glassy hard spheres in ATR-FTIR imaging (Everall et al., 2009). As shown by Equation 7-1 the depth of penetration, \( d_p \), of the evanescent wave is dependent on wavelength.

\[
d_p = \frac{\lambda/n_1}{2\pi (\sin^2 \theta - n_{21}^2)^{1/2}}
\]

Equation 7-1

Where \( \lambda \) is the wavelength of radiation, \( n_1 \) is the refractive index of the ATR crystal, \( n_{21} \) is the ratio of the refractive index in the sample medium to the refractive index of the ATR crystal and \( \theta \) is the angle of incidence of the infrared beam. In the case of air as the adjacent medium \( n_2 = 1 \) and Equation 7-1 becomes Equation 7-2.

\[
d_p = \frac{\lambda}{2\pi (n_1^2 \sin^2 \theta - 1)^{1/2}}
\]

Equation 7-2

\( d_p \) is considered here as the point at which the field has decayed to \( 1/e \) times the value at \( z = 0 \) (the surface of the ATR crystal). The work in this chapter will be done based upon the depth at which the intensity has fallen to 10% of its value at \( z = 0 \) as the threshold value in image processing will be set to 10%. This will be denoted as \( d_t \) and has been shown to have a value of 1.15 \( d_p \) (Everall et al., 2009). The geometry of this calculation for the apparent size of a sphere in ideal conditions using hard spheres is shown in Figure 7-6.
Figure 7-6. Diagram showing how the depth of penetration of the evanescent wave \( (d_x) \) affects the perceived radius \( (S) \) of a sphere with radius \( (r_s) \). Adapted from (Everall et al., 2009).

Figure 7-6 shows the relationship between the actual radius of a sphere \( (r_s) \) and the apparent radius of a sphere \( (S) \) when measured in ATR mode. \( d_x \) is the depth of penetration and in this case can represent either \( d_p \) or \( d_t \). \( S \) can be calculated using Pythagoras as shown in Equation 7-3.

\[
S = (r_s^2 - (r_s - d_x)^2)^{1/2}
\]  

Equation 7-3

Figure 7-7. Comparison of the spectra of caffeine and paracetamol. The boxes highlight the possible ranges that could be used for univariate analysis. ● Caffeine: range 1721 - 1684 cm\(^{-1}\) centre at 1694 cm\(^{-1}\) ● Paracetamol: range 1513 - 1486 cm\(^{-1}\) centre at 1504 cm\(^{-1}\) ● Caffeine: range 1300 - 1274 cm\(^{-1}\) centre at 1285 cm\(^{-1}\) ● Paracetamol: range 1122 - 1091 cm\(^{-1}\) centre at 1108 cm\(^{-1}\).

Figure 7-7 highlights four possible characteristic bands of paracetamol and caffeine which could be used for image generation, spread throughout the spectral range. Each of these bands will exhibit a different mean depth of penetration. For consistency it was necessary to choose bands for caffeine and paracetamol which would produce depths of
penetration with as little discrepancy as possible. The theoretical case for hard spheres was calculated using Equation 7-2 and Equation 7-3 the data are presented in Figure 7-8. The colours of the lines in Figure 7-8 correspond to the colours used to highlight the bands in Figure 7-7.

Figure 7-8. Comparison of measured diameter and true diameter for hard spheres. The wavenumbers of the centre of the bands above are shown in the legend. The dashed lines are caffeine bands, the solid lines are paracetamol bands.

Figure 7-8 shows an almost 25% discrepancy in the measured size across the spectral range. It is clear that the caffeine and paracetamol bands with the closest result for measured size are the bands at 1694 cm$^{-1}$ and 1504 cm$^{-1}$. Therefore these bands were used for analysis of the data.

### 7.3.3 Analysis of component area fraction

The paracetamol and caffeine were mixed in a 20:80 mass ratio. Therefore if all the compaction properties of the two components were equal, the ratio of the surface areas occupied by the components in the imaged area should have been approximately 20:80. The ATR-FTIR images of the compacted tablets were processed in the same manner as the optical images as shown in Figure 7-9.
Figure 7-9. Image processing from colour FTIR image to black and white threshold images for particle analysis. The size of the images is 500 µm × 700 µm.

A randomly selected image from each size batch shown in Table 7-1 is shown in Figure 7-10. From this presented dataset it appears as through the percentage of the image area in which paracetmol was present was higher at lower particle size, while also there appears to have been a large amount of particle agglomeration, despite thorough mixing, at lower particle size.

![Paracetamol 125-90 µm](image)

Colour FTIR data

Greyscale FTIR data

Black and white FTIR data

Figure 7-10. ATR-FTIR images of caffeine and paracetamol following extraction and thresholding of the data for each size category of paracetamol. The size of the images is 500 µm × 700 µm.

As there were 40 images measured for each size interval, the mean value for each dataset of 40 images was calculated and the results are shown in Figure 7-11. It can be seen from Figure 7-11 that the measured fraction of the imaging area covered by paracetamol was not consistent across the range of size intervals studied. When the sieved particle size of paracetamol was in the 90-125 µm size range, i.e. the same size as the caffeine particles, then the area faction was very close to 20% indicating that the inconsistency in measured area across the range was due to differences in particle size.
The data showed a strong trend of exhibiting higher than expected surface area when paracetamol particle size was small and a lower than expected surface area when the particle size was large.

![Plot of sieved particle size of paracetamol against measured area fraction the image covered by paracetamol for each size interval. Error bars were generated based on the standard deviation of each dataset.](image)

The data showing the area fraction of the images covered by caffeine showed the opposite trend to that for paracetamol as shown in Figure 7-12. The area fraction occupied in the imaging data by paracetamol increased with increasing particle size of paracetamol, i.e. as the caffeine particle size became smaller relative to the particle size of the paracetamol. Also plotted in Figure 7-12 is the summation of the caffeine and paracetamol surface area contributions at each size interval.

In the case of a perfect system with no void space this should be equal to 1 at each size interval. In this case the average value was around 0.97, and although there was some variation between points the overall trend across the range was flat. This indicated that the integration ranges used for processing the FTIR images were relatively unaffected by spectral influences from the other component. The value of 0.97 does not suggest a void fraction of 3%, indeed it is probably slightly larger than this at the surface as the spatial resolution in the x and y directions is at best around 15 µm, therefore increasing the perceived surface area slightly due to blurring.
Figure 7-12. Plot of sieved particle size of paracetamol against measured area fraction of caffeine for each size interval. The graph also shows the summation of the values for caffeine and paracetamol. Error bars for caffeine were generated based on the standard deviation of each dataset. Error bars for the total are based on the larger error bar from either the caffeine or the paracetamol data.

The reason for this discrepancy across the range is most likely due to the fact that ATR-FTIR imaging measures at the surface layer of the sample. The smaller particles pack in around the larger particles. A series of many thin cross sections measured through the bulk of the tablet would still produce an 80:20 surface area ratio of the particles. However, due to the spaces between larger particles at the surface any smaller particles would pack in between the larger particles present producing an over estimate of surface area Figure 7-13.

Figure 7-13. Arrangement of particles at surface of ATR crystal before compaction.

The arrangement of particles would then lead to the smaller particles deforming under the large particles following compaction. This would lead to a greater overestimate of the amount of the smaller particles at the surface as shown in Figure 7-14.
These data show that ATR-FTIR imaging can give an approximation of component loading in a formulation with some caveats. When gathering these data one must be aware of the size of the particles involved and their properties under compaction. As ATR-FTIR imaging is a surface layer approach the data are susceptible to changes in these properties. However, if these are understood then it may be possible to draw meaningful conclusions from these data as long as one is aware of the assumptions being made.

7.3.4 Statistical testing of data

When analysing image data it is very important to understand whether or not the data truly represent the overall characteristics of the sample. ATR-FTIR imaging with a diamond crystal has good spatial resolution and can be used to study the compaction of tablets in situ; however it images a relatively small area of the sample.

For the dissolution studies reported previously (Kazarian and Chan, 2003, van der Weerd et al., 2004) and seen elsewhere in this thesis, absolute statistical significance is less of an issue. These studies investigate the application of FTIR imaging to study physical phenomena such as crystallization, salt formation or mechanisms of drug release. As these are model formulations, the absolute values obtained are less important as they provide proof of concept and key mechanistic information. In the case of determining component concentration or particle size the absolute values are important, however the standard deviation of the values obtained can be quite large.
Ideally there would be an infinitely large test dataset from which values for many different samples could be extracted. In practice this is not possible. Therefore, a relatively large dataset must be obtained and the data can be analysed carefully.

It is possible to follow the mean and standard deviation as a series of data samples are taken; when the inclusion of several further data points leaves these quantities unaffected, one can be confident that a good approximation to these values has been obtained. However, this entails human judgement and is very dependent upon the nature of the samples taken and especially upon the order in which the data are supplied.

It is more useful to have a statistically rigorous value for how many samples to take in each case. An asymptotic approximation to such a number can be derived from a single dataset using the technique of bootstrap resampling (Adèr, 2008). Here, the dataset is randomly resampled to simulate a larger dataset; it can then be seen how many samples are necessary to calculate a good approximation to the mean. A set of scripts was written to determine how many samples must be taken to obtain an estimated value of the mean with 95% confidence for a variety of confidence intervals. The process used for this is outlined in Figure 7-15.

![Figure 7-15. Simplified flow chart showing data processing methodology used for establishing statistical significance for each size batch. The blue and green boxes represent subroutines which are detailed in Figure 7-16.](image)

Figure 7-15 presents the basic outline of the script used to determine a sample size which produces statistically relevant data. There were three inputs to the process. The confidence level (CL) which was set at 95%. The confidence interval (CI*) which was set to 20, 10 or 5% of the mean values presented in Figure 7-12 and Figure 7-11. Finally the raw surface area values for each size batch as defined in Table 7-1, where \( X_i \) is one of size batch 1 to 6. These data were then passed to the Confidence Testing (CT) subroutine, which randomly selected data points from the chosen size batch until there
were a sufficient number of data points (images) used to achieve a 95% confidence that the mean value was within the chosen confidence interval ($CI^*$). This process was repeated 50 times. The number of images required for each of the 50 repeats was then passed to the second subroutine which calculated their means and standard deviations. Assuming a normal distribution of values, 95% of all measurements should fall within two standard deviations of the mean, 97.5% of measurements will satisfy the required confidence level.

The subroutine “CT” shown in Figure 7-16 details the confidence testing section of the script. As gathering thousands of images would have been an unfeasibly lengthy process, 40 images of data were used. In this subroutine the data were randomly resampled to simulate an infinitely large dataset. The first step read a surface area value from dataset $X_i$ into a new set $Y_n$. The point standard deviation and mean of $Y_n$ were then calculated. Based on this the confidence interval for a confidence level of 95% was calculated. If this value was greater than the chosen confidence interval $CI^*$ then the first loop was followed. This added another image to the set $Y_n$, increasing the value of the number of images used ($P_n$) by one. This was repeated until confidence interval was less than $CI^*$. Once this condition had been satisfied the process was repeated until $n=50$, i.e. there were 50 $Y$ datasets each with a number of images required until the $CI \leq CI^*$. The number of images required for each $Y$ was then printed.

The subroutine “Mean + 2 Standard Deviations” shown in Figure 7-16 was the final step of the script. This subroutine read the values $P_n$ for the number of images required for each $n$ in subroutine “CT”. The mean and standard deviation ($\bar{P}_n$ and stdev($P_n$)) of these values were then calculated. The number of images required was then defined as $\bar{P}_n + 2\cdot$stdev($P_n$), finishing the script. This process was then repeated in triplicate for each size batch for both caffeine and paracetamol, for 5, 10 and 20% confidence intervals.
Figure 7-16. Flow diagrams detailing the subroutines “CT” and “Mean + 2 Standard Deviations” as presented in Figure 7-15.

The data presented in Figure 7-17 show an example set of the confidence interval testing outlined in subroutine “CT” in Figure 7-16. The graph shows data for 20 different repeats of loop \( n \). It can be seen that as the data were selected randomly, some measurements settle rapidly, requiring only a couple of images to achieve the desired confidence interval, whereas some required as many as 20 images. The sample mean was 10 images, with a standard deviation of 4.85, therefore these data would suggest that gathering 20 images would suffice.
The data summarising the number of images needed to satisfy the required confidence level for paracetamol are presented in Figure 7-18. Within each confidence interval the values are relatively consistent across the range of particle sizes tested. Using a 20% confidence interval required just 8 to 10 images and a 10% confidence interval 20 to 25 images. However, satisfying a 5% confidence interval was much more expensive in terms of number of images required, with around 60 images required on average. This also shows that repeating the confidence tests in subroutine “CT” 50 times was sufficient as the 3 repeats for each data point in Figure 7-18 are almost all overlapped.

Figure 7-19 replots the data as presented in Figure 7-18, but for the surface area of caffeine. The results presented in Figure 7-19, as expected, largely reflect those for the
paracetamol seen in Figure 7-18. Only around 10 images were required for a 20% confidence interval, while 25 were required for a 10% confidence interval. 5% was again much more expensive, requiring around 70 images. There is one significant difference, the data for a paracetamol size of >180 µm present a discontinuity with the rest of the data. This is most likely due to the fact that the particles of >180 µm were significantly larger than 180 µm, and presented as only one particle in each image. Therefore although the percentage variation in paracetamol surface area was relatively consistent, the variation in caffeine area was much smaller as the area percentage of paracetamol was only around 8%.

These data have shown that it is possible to gather information that can be considered as satisfying a 95% confidence level with an interval of 10% and 20% of the sample mean, using the macro diamond ATR accessory in relatively few images. As seen in Figure 7-18 and Figure 7-19, this is highly dependent on the confidence interval chosen.

The data presented here are for a model system containing paracetamol and caffeine sieved to controlled particle sizes. Therefore, the absolute values cannot simply be transposed to other formulations which may be studied. However, these are two relatively typical pharmaceutical ingredients and serve as a model formulation. More importantly the statistical analysis methodology presented can be applied to other formulations.
7.3.5 Particle size analysis

In Section 7.2.2 the Feret diameter was used for analysis of the diameter of uncompacted particles. In this section Feret’s diameter was used for analysis of the diameter of particles within a compacted tablet matrix. The same thresholding process as seen in Section 7.2.2 was applied. A particle was defined as an individual domain of paracetamol. There were a certain number of small particles which were probably a result of small fragments of original particles breaking off during mixing and compaction of the powders. Particles below 10 µm in size were discarded. Only the size of the paracetamol particles were analysed as it was only a 20 wt% loading, therefore the caffeine mostly presented as a continuous phase as seen in Figure 7-10.

The first results of the particle size analysis are presented in Figure 7-20, which plots measured particle size against the sieved particle size of paracetamol. Rather than presenting as a straight line with a positive gradient as may be expected, the graph exhibits a clear “U” shape. On the high end of the graph the data behaves as expected, but on the low end the measured particle size increases. This effect can be seen in Figure 7-10, with a smaller particle size there were a greater number of paracetamol particles present at the surface of the ATR crystal which led to overlap at the edges of the particles. Therefore, these data were very sensitive to the threshold used and ratio of particle sizes, and to the loading of the two components in the formulation.

![Figure 7-20](image-url)

*Figure 7-20. Graph showing measured particle size against sieved particle size for caffeine across all size batches. The data were all thresholded to 10% and the loading of paracetamol was 20 wt%.*
The other issue with this analysis method was that it was largely automatic following initial establishment of the threshold levels. The data were not interpreted in any way so although it may appear as though there were clearly a large number of well separated particles in the colour images in Figure 7-9, when processed the separate particles may merge. The reason for this is that the colour images have a greater dynamic range than those in greyscale, making them easier to interpret by eye. However, it was necessary to convert to greyscale for the image processing and apply a blanket threshold. In order to try and improve the particle sizing a second set of batches was prepared, with a 10 wt% loading of paracetamol as opposed to a 20 wt%, while a 20 percent threshold was applied which may have made maximum particle size slightly smaller. The cut off for smaller particles was raised to 15 µm. The data for this are presented in Figure 7-21. These data show a trend much closer to the positive gradient that would be expected. Although the higher threshold level may have reduced the mean size of the particles, the increased cut-off size maintained the mean value across the size batches as approximately consistent with that seen in Figure 7-20.

![Figure 7-21. Particle size analysis in formulations with 10 wt% loading of paracetamol, thresholding value of 20% and particle size cut-off of 15 µm.](image)

These data were then run through the statistical analysis script described in Section 7.3.4 in order to determine how many particles and images were needed to satisfy a 95% confidence level with a 10% confidence interval. These data are presented in Figure 7-22. The data presented there show that the number of particles required was fairly consistent through the size batches except for the largest size batch, although this is most likely as it is an unbounded size category (>180 µm). The number of images...
required increased with paracetamol particle size as there were fewer particles contained within the imaged area, although for most particle sizes only a few images were needed.

![Graph showing the number of particles and images required to achieve statistical significance for size batches presented in Figure 7-21 using a 10% particle size confidence interval.](image)

Importantly these data show that relatively standard particle analysis methods can be applied to extract information from compacted pharmaceutical formulations using ATR-FTIR images. However, this methodology was very sensitive to the parameters of the processing methodology employed. The sensitivity of this approach to changes in particle size was also not very high. Ideally Figure 7-21 would have presented as close to $x=y$, however, the gradient of the line was only around 0.12. This was almost identical to the average gradient of the lines presented in Figure 7-8 for the case of hard spheres. The data in Figure 7-21 do have a positive offset of around 10 µm, most probably due to particle deformation under compaction. However, it does show that the approach is applicable when the user is aware of the properties of the analysis system.

### 7.4 Conclusions

The work presented in this chapter has covered three aspects of compacted tablet analysis. The first stage was studying the effect on the observed surface area fraction of a component in ATR-FTIR images with changing particle size. It was found for the two component model system studied here, that when the particle size of paracetamol was the same as the size of the bulk caffeine particles that the observed surface area fraction matched very closely with the actual volume fraction of paracetamol. However, when
the paracetamol particle size was smaller than that of caffeine the surface area fraction of paracetamol was larger than the bulk volume fraction and when the particle size of paracetamol was larger than that of caffeine the surface area was an underestimate compared to the bulk volume fraction.

The second part of the chapter dealt with investigating how much data was required to achieve a set confidence level. It was found that for these model samples it was found that 10 – 20 images was sufficient to gather surface area coverage in 2D imaging data to within a small confidence interval, while only a few images were needed for determination of particle size.

The final section investigated the application of this approach for assessing particle size within compacted matrices using FTIR imaging. It was found that this is possible; however, it was very sensitive to the parameters of the sample and analysis methodology. However, through the use of more advanced particle identification techniques this should become more feasible.
CHAPTER EIGHT

APPLICATION OF FTIR IMAGING TO STUDY THE EFFECTS OF MODIFYING THE pH MICROENVIRONMENT ON THE DISSOLUTION OF IBUPROFEN FROM HPMC MATRICES
Chapter 8: Application of FTIR Imaging to Study the Effects of Modifying the pH Microenvironment on the Dissolution of Ibuprofen from HPMC Matrices

8 Application of FTIR Imaging to Study the Effects of Modifying the pH Microenvironment on the Dissolution of Ibuprofen from HPMC Matrices

8.1 Introduction

The work in this chapter investigates the effects of modifying the pH in the tablet microenvironment on the dissolution of ibuprofen, studied with FTIR spectroscopic imaging. Previous work on the dissolution of ibuprofen using FTIR imaging was used to study polymer/drug interactions while the formulations were in contact with aqueous media (Kazarian and Chan, 2003). That work showed that while polyethylene glycol could be used to maintain the ibuprofen in a molecularly dispersed state when dry, the ibuprofen would form crystalline deposits as the water soluble polymer dissolved. These crystalline deposits can irritate the lining of the gut causing stomach ulcers, (Lanza et al., 1979) and as ibuprofen is one of the most commonly taken drugs in the world, these side can effects pose significant problems.

Previous work by Kazarian and Chan using FTIR imaging has demonstrated that this approach is fully capable of monitoring the crystallisation of the drug (Kazarian and Chan, 2003). The next logical step is to use this methodology to investigate ways to control and mitigate these issues. Several approaches have been used to enhance and control the release of ibuprofen. Ibuprofen can be dispersed in water soluble polymers such a polyethylene glycol (PEG) (Najib and Salem, 1987) or form complexes with cyclodextrins (Mura et al., 1998). While these methods do enhance dissolution of the drug, their effects are relatively small in magnitude compared to those of pH change and as in the case of PEG particularly, become ineffective once the polymer has dissolved, causing the drug to recrystallise.

As ibuprofen is a weak acid, the solubility will increase above the pKa of the drug (Levis et al., 2003) therefore by adding alkaline compounds to the tablet matrix it should be possible to increase the rate of dissolution, or by adding acidic compounds retard the dissolution rate. At high pH ibuprofen can react with the basic compounds to
form salts which can have both positive and negative effects on the dissolution performance of the drug.

The aims of the research reported in this chapter are to study and understand the effects of adding pH active compounds to mechanically mixed HPMC and ibuprofen tablet matrices. The gelling of the HPMC layer provided controlled release of the ibuprofen from the tablet, while manipulating the local pH within the tablet controlled the physical stability of ibuprofen.

8.2 Experimental

8.2.1 Sample preparation

Sodium biphthalate powder, designed to produce a buffer of pH 4 when dissolved in aqueous media and sodium carbonate and sodium bicarbonate powders blended to produce a pH 10 buffer when dissolved in aqueous media were supplied by Sigma Aldrich. Citric acid and calcium hydroxide were both supplied by VWR International. HPMC K4M was used as the bulk excipient for the tablets and was supplied by Colorcon. The powders were sieved to 90-125 µm in diameter to ensure particle size consistency. The formulations presented here were mixed to have a 10 wt% loading of drug, 10 wt% loading of pH modifying compound, with the remainder consisting of HPMC. In the case of the formulations containing basic modifier compounds molar loadings are important due to possible interactions between the species. In each tablet there were 4.85×10^{-5} moles of ibuprofen. In the calcium hydroxide tablets there were 1.75×10^{-4} moles of pH modifier and in the sodium carbonate based tablets there were 5×10^{-5} moles of both sodium carbonate and bicarbonate. Ibuprofen was supplied by Whitehall International.

8.2.2 FTIR spectroscopy

An Alpha T FTIR spectrometer (Bruker, UK), as detailed in Section 5.4, was used to measure the ATR–FTIR spectra with a single element detector and a spectral resolution of 8 cm^{-1} and 32 co-added scans.
8.2.3 FTIR spectroscopic imaging

The work in this chapter used a 64 × 64 FPA to acquire the images at a spectral resolution of 8 cm⁻¹, with 20 co-added scans for each image. The non-imaging Supercritical Fluid Analyser accessory with a diamond ATR crystal was used (Specac Ltd., UK) as detailed in Column 1 of Table 5-2. Acquisition of each image required approximately 2 minutes. All images shown are 1100 µm × 780 µm. The tablets were positioned such that they half covered the imaging area, allowing the ingress of water to the matrix and swelling at the tablet edge to be imaged.

8.2.4 Compaction and dissolution

The in situ dissolution/compaction cell as described by van der Weerd and Kazarian (van der Weerd et al., 2004) was used for in situ compaction and dissolution of the tablet. The compaction force was applied using a torque wrench and the compression force applied to the sample on the diamond was 850 N which corresponded to 120 MPa for the 3 mm diameter tablet used. The dissolution medium used was deionised water and the flow rate was set to 60 ml/h. Each experiment was run for 3 hours. Water was used as the dissolution medium, rather than phosphate buffer in order to isolate the effects of pH modifiers added to the matrix.

8.2.5 Visible optical procedure

Visible optical video analysis was used, similarly to that introduced previously (Kazarian and van der Weerd, 2008), to study retention of the pH modifying compounds in the matrix during dissolution. A transparent Perspex dissolution cell was used, as schematically shown in Figure 8-1a. The tablets were compacted using the same method as before, however they were then removed from the compaction cell, and placed on the measuring surface of the diamond crystal with the Perspex dissolution cell bolted into place on top. The CCD video camera was mounted above the system as shown in Figure 8-1b to capture visible optical images of the dissolution. Images were captured every 10 minutes at a resolution of 720 × 576 pixels and an image size of 6 mm × 4.5 mm. As the pH control compounds were the same colour as the rest of the tablet, universal indicator
(supplied by VWR, UK) was added to the dissolution medium, which in a basic environment was blue in colour, and red in acid.

![Diagram](image.png)

**Figure 8-1.** (a) Schematic of Perspex dissolution cell showing a top down view. The sample is placed half covering the top surface of the ATR diamond crystal. (b) Schematic of the optical dissolution assembly. The camera is mounted above the dissolution cell looking down on the sample, which is sandwiched between the Perspex cover and the diamond.

### 8.3 Results and discussion

#### 8.3.1 Imaging of tablet dissolution

The first set of images in Figure 8-2 show the changing distributions of the three major components (water, HPMC and ibuprofen) over time following contact between the side of the tablet and the dissolution medium. This was the control tablet which contained no pH modifying compounds. The characteristic spectral band used for analysis of the free acid ibuprofen was the carbonyl band in the range 1740 - 1670 cm\(^{-1}\), the band used to plot the distribution of the HPMC was in the range 1162 - 945 cm\(^{-1}\) and the band used to plot the distribution of water was in the range 3800 - 3000 cm\(^{-1}\).
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Figure 8-2. Overview of dissolution data for main tablet constituents. The top row shows the ingress of water with time, while the expansion and gelation of HPMC can be seen in the middle row and the distribution of the ibuprofen can be seen in the bottom row of images as a function of time. No pH modifier compounds were used in this tablet. The images are 1100 µm × 780 µm.

The data shown in Figure 8-2 served as a control experiment which was performed with no pH modification to illustrate the poor dissolution of ibuprofen from this type of formulation in a neutral pH tablet microenvironment and aqueous media. The data clearly differentiate all components of the system simultaneously in situ.

Some domains of drug did dissolve, although there was also a significant amount of recrystallisation. Region (a) in Figure 8-2 (10 minute image in row 3) is a domain of depositing crystalline ibuprofen. Where the crystalline deposits formed on the surface of the imaging diamond, a corresponding region of low concentration of HPMC or water developed as the ibuprofen replaced the other components on the ATR crystal.
Figure 8-3. Spectra showing a comparison of the spectrum of crystalline ibuprofen and a spectrum extracted from domains of crystallising ibuprofen in Figure 8-2. The spectrum of crystalline ibuprofen is shown to have the peak of the carbonyl band located at 1705 cm\(^{-1}\), whereas the crystallizing spectrum has a shoulder located at 1705 cm\(^{-1}\) corresponding to the presence of some crystalline material (the broad band at ca. 1640 cm\(^{-1}\) corresponds to the bending mode of water).

The spectrum of pure crystalline ibuprofen shown in Figure 8-3 was used as a reference and the spectrum of crystallising ibuprofen was extracted from region (a) of the ibuprofen image at 10 minutes in Figure 8-2. The reference spectrum of crystalline ibuprofen displays a prominent carbonyl band which is positioned at ca. 1705 cm\(^{-1}\). This has been validated in previous work as corresponding to the crystalline form (Kazarian and Chan, 2003). The spectrum of crystallising ibuprofen, extracted from the ten minute image of row 3 of Figure 8-2, shows a small band at around 1705 cm\(^{-1}\) which can be assigned to the carbonyl of depositing crystalline ibuprofen. In Figure 8-2 this cloudy region becomes more defined over time and is still present after 180 minutes of dissolution.

### 8.3.2 Comparison of evenly loaded formulations

Figure 8-4 presents data for tablets each with a 10 wt% loading of ibuprofen and a 10 wt% loading of one of the four pH modifying compounds.
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Figure 8-4. Figure showing ibuprofen (in free acid form) dissolution performance for tablets with 10 wt% loadings of pH modifying compounds and ibuprofen. Row 1: 10 wt% loading of calcium hydroxide; Row 2: 10 wt% loading of citric acid; Row 3: 10 wt% loading of sodium carbonate based modifier; Row 4: 10 wt% loading of sodium biphthalate. These images were generated based on the carbonyl band of ibuprofen 1740 - 1670 cm⁻¹. The images are 1100 µm × 780 µm.

Initially the data presented in Figure 8-4 appear to show that the compounds with basic pH modifiers exhibited faster dissolution of the ibuprofen than those with acidic pH modifiers. Indeed the presence of crystalline ibuprofen in the basic tablets was almost completely diminished after 180 minutes. In the acidic tablets there was a large presence of crystalline ibuprofen after 180 minutes of dissolution.

The effects of using HPMC as the polymer are also apparent in Figure 8-4. Translocation of the particles with the swelling matrix is seen to some extent in all of the images. Indeed in row 3 of Figure 8-4 there was a slight increase in the overall distribution of the drug at 180 minutes, however, this was due to the expansion of the
HPMC polymer moving drug particles from deeper within the tablet matrix into the imaging field of view.

### 8.3.2.1 Dissolution profiles based on FTIR spectroscopic imaging

In order to summarise the dissolution of the ibuprofen domains seen in Figure 8-4 a mass balance was performed on the imaging data. The processing method for these data is illustrated in Figure 8-5.

![Figure 8-5. Data processing of absorbance values for ibuprofen dissolution from tablet loaded with basic buffer.](image)

The absorbance values for the ibuprofen integration for each pixel were extracted from the imaging datasets for each time step and arranged in size order, pixel 1 to 4096. These were then plotted as seen in Figure 8-5. The large positive values correspond to pixels displaying part of an ibuprofen domain. A significant fraction of the values are close to zero in value as the tablet only half covers the imaging area. The negative values could be caused either by contaminants which produce a negative value when integrated for ibuprofen, which is unlikely as none were found in the images, or they are a result of non-uniform illumination of the detector. These values are erroneous and were discarded from the data processing. The remaining data were then averaged for each image individually and normalised against the highest concentration value seen for
each dissolution test. This produced a mass balance over time for the amount of ibuprofen present. The data are shown in Figure 8-6.

![Graph showing the fraction of ibuprofen in free acid form remaining in the image at each time-step from Figure 8-4 and Figure 8-2. These graphs use eight data points in each line. The time-steps are dry, 0, 10, 40, 80, 120, 150 and 180 minutes. The dry measurement and the time zero reading are both plotted at t = 0, therefore each line has two data points for 0 minutes. The data presented here are an average of three runs, error bars are based on the standard deviation.](image)

The basic tablet formulations in Figure 8-6 showed a faster rate of removal of the free acid of ibuprofen from the dissolving matrices than those with the acidic additives. The magnitude of the difference between the acidic formulations is small because the solubility of ibuprofen in aqueous media plateaus below pH 4, as this is below the pKa of ibuprofen (Levis et al., 2003). Therefore, the decrease in pH from the sodium biphthalate to citric acid was unlikely to have altered the dissolution of the ibuprofen significantly. The dissolution performance of the control formulations was between the acidic and basic formulations although notably closer to the acid modified tablets.

It can be seen that for some of the formulations the maximum amount of ibuprofen is seen at the 10 minute time point. This is a result of the fact that contact between the sample and the ATR diamond improves upon wetting of the formulations. This leads to an increase in absorbance by the ibuprofen in the tablet matrix.

The magnitude of the error bars in the early stages of dissolution of the basic formulations was much larger than in the latter parts. This was a result of the increased
rate of disappearance of the free acid form in the basic conditions. It is proposed that the basic environment of the mechanically mixed tablet enhanced the dissolution rate of the ibuprofen; such that when a domain of drug was wetted it dissolved relatively quickly, causing the fraction of ibuprofen remaining to drop rapidly between the two time steps, resulting in greater variation between experimental repeats. This is shown in row 3 of Figure 8-4 as large domains of ibuprofen were seen to have dissolved rapidly.

Conversely, the smaller error bars seen for the tablets containing the acidic pH modification compounds demonstrated that the acidic modification worked effectively. The presence of these compounds retarded the rate of dissolution of the ibuprofen. Therefore ibuprofen domains dissolved slowly, resulting in less variation between repeats.

### 8.3.2.2 Formation of calcium salt during dissolution

In previous studies of the dissolution of formulations containing ibuprofen using FTIR spectroscopic imaging, a large degree of recrystallisation of ibuprofen was observed (Chan and Kazarian, 2006c). In these formulations the addition of calcium hydroxide apparently prevented this as the ibuprofen appeared to dissolve well over the course of 180 minutes (Figure 8-4, row 1). However, ibuprofen is a weak acid and will form salts at high pH (Kararli et al., 1989).

In order to investigate the formation of this salt, super saturated solutions of ibuprofen and calcium hydroxide were prepared. As seen in Figure 8-7 these took the form of fine particulate suspensions. The pH of the calcium hydroxide based suspension was around 12 while the ibuprofen solution registered around pH 5. The two suspensions were then mixed and almost immediately formed the ibuprofen Ca\(^{2+}\) salt seen in the third image in Figure 8-7. The particulates in this suspension were much larger and were very insoluble, even in the presence of a very large amount of excess dissolution medium which agrees with data found in the literature (Levis et al., 2003).
Following formation of this salt, it was extracted and analysed using conventional FTIR spectroscopy. The results showing the spectral changes associated with this reaction are given in Figure 8-8. The formation of the salt is characterised by the removal of the carbonyl and the appearance of the carboxylate band at 1550 cm\(^{-1}\). These spectral changes were similar to those which occur during the formation of the magnesium salt (Kararli \textit{et al.}, 1989). The images of ibuprofen dissolution in Figure 8-4 were generated based on the carbonyl of the crystalline ibuprofen. As this was replaced by the carboxylate carbonyl at 1550 cm\(^{-1}\) these images presented an apparently increased dissolution rate.

![Figure 8-7](image)

**Figure 8-7.** Laboratory prepared suspensions of calcium hydroxide, ibuprofen and the ibuprofen Ca\(^{2+}\) salt. The particulates in the calcium hydroxide and ibuprofen suspensions are very fine, whereas the particulates in the ibuprofen salt are much larger.

![Figure 8-8](image)

**Figure 8-8.** Comparison of the spectra of ibuprofen, calcium hydroxide, HPMC and the calcium salt of ibuprofen in the range 1800 cm\(^{-1}\) to 1300 cm\(^{-1}\). The carbonyl of the crystalline ibuprofen can be seen at 1705 cm\(^{-1}\) whereas in the spectrum for the calcium salt of ibuprofen the carbonyl band has been replaced by a carboxylate band at 1558 cm\(^{-1}\).
Figure 8-9. ATR-FTIR images showing the formation of the calcium salt of ibuprofen with water ingress in ibuprofen tablet with 10 wt% loading of ibuprofen and calcium hydroxide. Image size is 1100 µm x 780 µm. The water images were generated based on the intensity of the ν(OH) band at 3800 - 3000 cm⁻¹, the salt images on the carboxylate band at 1580 - 1545 cm⁻¹ and the salt + ibuprofen images using the range 1440 - 1390 cm⁻¹.

The data in row 1 of Figure 8-9 show the presence of the calcium salt in the dissolving tablet loaded with calcium hydroxide from Figure 8-4 row 1. During the course of the dissolution there was a great deal of salt precipitation within the tablet matrix. This was therefore an unsuitable formulation for modifying the release of the drug, despite the apparently increased dissolution rate shown in Figure 8-4.

The spectra in Figure 8-10 were chosen to illustrate the conversion of the ibuprofen into the calcium salt within the matrix. The spectrum given in Figure 8-10a was extracted from the top edge of the area covered by the salt, while the spectrum given in Figure 8-10b was extracted from within the matrix where the salt was still forming. The spectrum given in Figure 8-10b clearly exhibits the carboxylate peak at 1550 cm⁻¹ (shown by box), although the bands are not as sharp or as well defined at those seen in Figure 8-8. This is most likely because there was still a large presence of unreacted ibuprofen present as evidenced by the presence of the crystalline carbonyl at around 1705 cm⁻¹ seen in the spectrum given in Figure 8-10c. There was also still a large amount of HPMC present in this spectrum, shown by the contribution of the...
C-O-C stretching band presented in the spectrum given in Figure 8-10d at 1058 cm\(^{-1}\). This evidence suggests that within the matrix the crystalline salt was still forming at the time of extraction of the spectrum given in Figure 8-10b. The spectrum given in Figure 8-10a has much sharper more defined peaks, while there is almost no presence of the original ibuprofen carbonyl at 1705 cm\(^{-1}\), the contribution from the C-O-C band of the HPMC is also much reduced relative to the spectrum given in Figure 8-10b. This suggests that the extracted the spectrum given in Figure 8-10a was from a much purer more crystalline domain of the salt.

Figure 8-10. Spectra from Figure 8-9 and comparative pure spectra a) spectrum extracted from point (a) in Figure 8-9, b) spectrum extracted from point (b) in Figure 8-9, c) spectrum extracted from pure, dry domain of ibuprofen in Figure 8-9, d) extracted spectrum of pure dry HPMC from Figure 8-9.

These data suggest that the ingress of water initiated the formation of the salt crystals within the matrix. While the effect of water to increase the rate of this kind of interaction has been seen before (Wright and Carstensen, 1986), the images in Figure 8-9 show that the salt formation occurred with the ingressing water front.
Chapter 8: Application of FTIR Imaging to Study the Effects of Modifying the pH Microenvironment on the Dissolution of Ibuprofen from HPMC Matrices

The images in the middle row of Figure 8-9, which show the presence of both the salt and the crystalline ibuprofen, were generated using the range 1440-1390 cm\(^{-1}\) in which both the ibuprofen and the salt present bands. Due to differences in the shape of the band between the two species, this row of images presents the distribution of the two components only qualitatively. While the salt did primarily form around the initially present ibuprofen crystals, these domains went on to form seed points around which more of the calcium salt crystallised. The insoluble salt forming around these nucleation points remained present in the images for the full three hours of the experiment. Over the course of the dissolution, the amount of salt increased, indicating dissolved ibuprofen was reacting with the calcium hydroxide forming an insoluble layer on the diamond.

8.3.2.3 Formation of sodium salt during dissolution

The formulation containing the sodium carbonate based pH modifier also formed an ibuprofen salt during dissolution (Figure 8-11). As the modifying compound in this case was sodium based, this was less of an issue for as the sodium salt was soluble. A secondary product of the reaction between the carbonates in the pH modifying compounds and the ibuprofen would have been the production of carbon dioxide. The volume produced would have been small relative to the total volume of the swollen matrix, and due to the buoyancy of the bubbles formed they would have floated to the top of the matrix. As a result there is no evidence of this in the images in Figure 8-4.

The spectrum shown in Figure 8-11 extracted from the salt deposit seen in the images above. Based on the position of the band at 1550 cm\(^{-1}\) and the bands at 1396 cm\(^{-1}\) and 1357 cm\(^{-1}\), the salt formed as expected was sodium ibuprofen dihydrate (Lee and Wang, 2009). The sodium salt of ibuprofen is significantly more soluble than the calcium salt and so this aids in the dissolution of the ibuprofen. This is highlighted in Figure 8-11 as the salt only appears to a slight degree in the middle of the dissolution before rapidly dissolving.
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Figure 8-11. Formation of sodium salt during dissolution of tablet with 10 wt% loading of basic buffer, with extracted spectrum of salt (a). These images were generated based on the intensity of the carboxylate band at 1550 cm\(^{-1}\). The images are 1100 µm × 780 µm.

As the sodium salt was highly soluble the images produced using univariate analysis, seen in Figure 8-11, do not show a clear image of the salt. Therefore following identification of the presence of the sodium salt, the data were analysed using factor analysis. By using factor analysis it was possible to check whether any other as yet undetected species had formed during dissolution. The first step was to process the data to produce factors. Factors were produced which corresponded to the HPMC, water, ibuprofen and the sodium salt of ibuprofen. The factors for ibuprofen and the sodium salt are presented in Figure 8-12.

Figure 8-12. Factors extracted from dissolution of tablet loaded with pH 10 buffer. (a) Factor corresponding to crystalline ibuprofen – the large band at 1700 cm\(^{-1}\) corresponds to the carbonyl of crystalline ibuprofen. (b) Factor corresponding to sodium ibuprofenate – the band at 1540 cm\(^{-1}\) is caused by the carboxylate band of the salt.
These factors were then plotted as score images (Figure 8-13 and Figure 8-14), in which the score was a measure of how similar the spectra in those images were to the factors presented in Figure 8-12, rather than the concentration based images seen in Figure 8-4.

**Figure 8-13.** Score images of crystalline ibuprofen showing the change in the distribution of ibuprofen during the course of the dissolution.

The data presented in Figure 8-13 show the distribution of crystalline ibuprofen during the dissolution of the tablet loaded with pH 10 basic buffer. These images present the same distribution seen in Figure 8-4 in which the ibuprofen dissolution proceeds rapidly over the course of the dissolution.

**Figure 8-14.** Score images of sodium ibuprofenate showing the change in the distribution of the salt during the course of the dissolution. The images are 1100 µm × 780 µm.

The images presented in Figure 8-14 present a much clearer representation of the formation and subsequent dissolution of the sodium ibuprofenate during the dissolution of the tablet than Figure 8-11. The images at 10 and 40 minutes in particular show that the amount of salt in the matrix increased up to 40 minutes, however, it had begun to dissolve by 100 minutes and by 180 minutes dissolution was almost complete.
Overall, these imaging data demonstrate that the presence of the calcium hydroxide was detrimental to the dissolution of ibuprofen, while the sodium carbonate based modifier serves to improve the dissolution significantly. Citric acid slowed the dissolution of the ibuprofen to the greatest degree, although similar performance was seen from the sodium biphthalate. This coincides with other data gathered for microenvironmental pH modification in which operating above the pKa increases the rate of drug release, while operating below reduces it (Pygall et al., 2009). The FTIR imaging data has provided information on dissolution within the tablet matrix. As expected the difference in performance is tied to the solubility performance of ibuprofen at various pHs.

8.3.3 Salt formation in storage conditions

It has been recorded previously that solid state interaction between calcium oxide and ibuprofen took several months of storage at 55 ºC (Kararli et al., 1989). It is interesting to note that this interaction occurred much more rapidly for calcium hydroxide in the presence of only ambient humidity. After about twelve hours at ambient conditions much of the ibuprofen had converted into the salt as shown in Figure 8-15. The fresh preparation, measured approximately five minutes after preparation of the sample, displayed a prominent carbonyl at 1705 cm⁻¹. After twelve hours of storage at ambient conditions, the carbonyl had diminished significantly and the carboxylate band had become far more prominent. Indeed the changes following three weeks further storage were minimal, with only a small further reduction in the intensity of the carbonyl band.

It was found that if powders were desiccated before preparation of the samples, the propensity of the components to react was significantly reduced. This suggests that a small amount of water that was present in the powders due to ambient humidity served to facilitate the reaction. It is proposed that water served as a medium through which a small amount of the drug and calcium hydroxide could diffuse and react. The products of this reaction were the salt and more water which would help the reaction to propagate more rapidly. Similar conclusions were drawn when investigating the solid state interaction of sodium bicarbonate and benzoic acid derivatives (Wright and Carstensen, 1986).
As it was determined that the rate of this reaction was highly dependent on the amount of water present in the samples, the powders were stored in dry conditions and experiments were performed immediately following preparation of the tablet batches.

### 8.3.4 Gel layer stability

Previous studies using other methods demonstrated that the addition of ionic species to the tablet matrix may have adverse effects on the formation of the HPMC gel layer around the dissolving tablet (Pygall et al., 2009, Bajwa et al., 2006, Mitchell et al., 1990). However, as seen in seen in Figure 8-16 any interruption to the gel layer in this case was minimal.
Chapter 8: Application of FTIR Imaging to Study the Effects of Modifying the pH Microenvironment on the Dissolution of Ibuprofen from HPMC Matrices

Figure 8-16. a) Comparison of the amount of swelling of HPMC for the formulations presented in Figure 8-2 and Figure 8-4 unloaded tablets. The presented images show the degree of swelling after 40 minutes approximately even in magnitude across the three formulations. b) Spectra extracted from area denoted by the grey box in each image. The HPMC band at 1065 cm\(^{-1}\) contains the same features for each formulation as the control and a constant height ratio between that band and the water bending mode at 1645 cm\(^{-1}\). The images are 1100 µm × 780 µm.

The extent of HPMC swelling in each image of Figure 8-16a is consistent across all formulations. This indicated swelling was not inhibited by the presence of control compounds to a degree which could otherwise overshadow the effects of pH on the solubility of the drug. The consistency in the ratio of the intensities of the HPMC and water bands seen in Figure 8-16b shows that HPMC hydration was consistent across the formulations. This is further supported by the consistency in the shape HPMC band between the control sample and the pH modified samples. These spectral features were very similar to those of the spectrum extracted from the gelling region by van der Weerd and Kazarian (van der Weerd and Kazarian, 2005).
8.3.5 Visible optical analysis of dissolving tablets

The dissolution of the pH modification compounds is a very important factor in affecting the dissolution of the ibuprofen. As seen in Figure 8-4, relative to the ibuprofen or the polymer matrix, the pH modification compounds were very soluble. HPMC was chosen as the polymer as it forms a gel layer, which would help retaining the pH modifying compounds within the polymer matrix. As the profiles shown in Figure 8-4 displayed differing performance throughout the entire period of dissolution this suggested that the pH modifying compounds remained within the matrix over the full course of each dissolution. Further confirmation of this is shown in Figure 8-17.

Figure 8-17. Visible optical imaging of distribution of active pH modifying compound within dissolving tablet matrices. The tablet in row 1 contained a 10 wt% loading of citric acid. The indicator became pink in acidic conditions; therefore pink colour indicates the presence of acidic media in the image. The tablet in row 2 contained a 10 wt% loading of the sodium carbonate based buffer. The blue regions in the image indicate an area of high pH.

Figure 8-17 shows the visible optical video images of the dissolving tablets over the course of three hours. As the dissolution medium (which contained universal indicator) came into contact with the pH modifying compounds in the matrix of the tablets, the indicator became pink in the presence of acid and blue in the presence of a basic compound. In row 1 of Figure 8-17, the pink colour remained throughout the experiment showing that there was still a large amount of the acid within the matrix at the end of the experiment. At the edges of the tablet, there was fainter pink colour, which was caused by the presence of citric acid in the gel layer and indicated pH control would be exerted over the drug up to the point of delivery from the matrix into the GI
The indicator around the tablet in row 2 was blue. The blue colour revealed that the pH within the tablet matrix was higher than 7 due to the presence of the basic modifier. The colour remained for the entire 3 h of the experiment. The blue colour was also present in the dissolving gel layer of the tablet.

### 8.4 Conclusions

In this chapter of the thesis it was demonstrated that the dissolution of ibuprofen from a mechanically mixed, model tablet can be adjusted by the addition of pH modifiers to the tablet matrix. The controlled release is dependent on the acidity or basicity of the additives. The relative insolubility of ibuprofen at low pH leads to the addition of acids slowing drug dissolution. The sodium carbonate based buffer was able to solubilise the ibuprofen via formation of a sodium salt to the extent that it is released more quickly, while the calcium hydroxide formed the largely insoluble calcium salt. This is the first time that salt formation has been seen within the matrix as a result of micro-environmental pH modification using FTIR imaging. Using these data it was also shown that as water enters the matrix during dissolution, salt formation occurs at the ingressing water front, demonstrating the role of the dissolution medium in facilitating this reaction.

FTIR imaging has provided information on the internal dissolution processes of the tablet, showing that the addition of these pH modifiers changes the rate at which the ibuprofen particles within the tablet dissolve. The use of visible optical analysis along with the addition of universal indicator to the dissolution medium has shown that the HPMC polymer matrix was able to retain the soluble pH modifiers for at least three hours.

This work has demonstrated the applicability of FTIR imaging to studying such formulations. Ibuprofen is one of a large number of weakly acidic poorly soluble drugs, while long term usage of the drug can have side effects such as stomach ulcers. The methods used here could be applied to study other pH sensitive formulations.
CHAPTER NINE

DISSOLUTION OF TABLET-IN-TABLET FORMULATIONS
9 Dissolution of Tablet-in-Tablet Formulations

Until now published reports have used ATR-FTIR imaging to study monolithic formulations, which are representative of a large fraction of tablets which have simple structures. However, ATR-FTIR imaging has the potential to study and reveal new information about the dissolution of more complex structures with multiple sections. The high chemical specificity of FTIR imaging is well suited to studying multiple components simultaneously. The high spatial resolution can show section boundaries in great detail and also reveal interfacial effects that may occur during dissolution. Multilayer systems have been commonly used to achieve multiphasic and zero-order release, though this will be investigated further in Chapter 10. This chapter presents the novel application of ATR-FTIR imaging for studying tablet-in-tablet structures, firstly for delayed release and secondly for delivery of pH labile drugs.

9.1 Delayed release formulations

9.1.1 Introduction

This tablet structure, shown in Figure 2-5, can be used for ordered release, in which the drug in the central core is wrapped in an outer layer which also contains drug. This technique has also been used for biphasic fast/slow release (Hamza and Aburahma, 2010, Lopes et al., 2007). This work applies similar principles to achieve delayed controlled release. Ueda and others have developed and applied a Time-Controlled Explosion System (Ueda et al., 1994, Hata et al., 1994). This produces a burst of drug release. The lag-time (time by which release is delayed) has been controlled by barrier thickness (Spencer et al., 2008, Ueda et al., 1994), the addition of water soluble excipients and the molecular weight of any swelling excipients (Matsuo et al., 1996).

The tablets in this chapter use a core consisting of the model drug caffeine and HPMC, with a microcrystalline cellulose and glucose shell section. Previous studies have largely focused on studying the release profile of the drug from the dissolving system. As this work uses ATR-FTIR imaging it will be possible to learn much more about the internal physical and chemical dissolution processes of the tablet structures. The work
in this section of the thesis will investigate the processes of the components at the interface between tablet sections during tablet dissolution.

X-ray microtomography, UV/Vis spectroscopy and visible optical video images were used as complementary techniques to study the dissolution, providing a complete analysis of the tablet breakup and drug release.

9.1.2 Materials and methods

9.1.2.1 Batch preparation

Tablets consisting of four components were studied in this investigation. The core of the tablets contained caffeine (model drug) and HPMC. The core was mixed to a ratio of 30 wt% caffeine and 70 wt% HPMC. HPMC was supplied by Colorcon (UK) and caffeine by Sigma-Aldrich (UK). The shell section of the tablet contained microcrystalline cellulose which was supplied by Merck Sharp & Dohme (UK) and glucose by Sigma-Aldrich (UK). The shell components were mixed in ratios varying from 100 wt% microcrystalline cellulose to 100 wt% glucose in steps of 25 wt%. The powders were sieved such that all powders were below 90 µm in size. The core of each tablet had a mass of 18 mg and the shell of each tablet had a mass of 42 mg.

9.1.2.2 Compaction procedure

In order to prepare these tablets in the lab, a custom ex situ compaction cell was designed in order to form the tablets as shown in Figure 9-1. The tablets were 5 mm in diameter and the core was 2.5 mm in diameter.
Figure 9-1. Tablet-in-tablet compaction cell. The compaction cell consists of four separate pieces which fit together in order to form a compaction mould for the sections of the tablet.

The tablets were compacted in two stages; the outer shell was compacted first, before the core powder was then compacted into the middle, the procedure was as follows:

1. The first step was to form the space for the outer shell by inserting the outer shell template (section 2 in Figure 9-1) and the punch (section 4) as guides into the base (section 1) before pouring the shell powder into the space created.

2. The outer shell punch (section 3) was then inserted on top of the powder compacting it to form the shell section of the tablet.

3. The punch was then removed leaving the compacted powder ring in place and the outer shell template with the outer shell punch were removed together from the base with the tablet shell still inside.

4. The assembly was then clamped on a flat surface and the core powder was poured into the central hole in the template piece and the middle of the powder ring.
5. The punch was then inserted and the core was compacted inside the ring, this compaction firmly secured the core within the shell.

Although the compaction of the tablets was performed *ex situ* it was important to maintain consistency with the procedures reported in the other chapters. As the surface area of the outer shell was roughly 2.8 times larger than that of the core a larger compaction force was required to achieve the same pressure. The pressure used for both sections was 120 MPa as this maintains consistency with procedures performed using *in situ* compaction (Wray *et al.*, 2008). The precision of the manufacturing of the cell was also of great importance as variations in the thickness of the shell section around the tablet have been seen in standard manufacturing techniques (Ozeki *et al.*, 2003).

**9.1.2.3 X-ray microtomography**

The X-ray microtomography was carried out using the Skyscan 1074 Portable X-ray microtomograph described in Section 5.5. The step scan angle was set to 0.9° and the tablet was rotated through 360°. The exposure time was set to 2 milliseconds and each extracted image was an average of 10 frames.

**9.1.2.4 FTIR spectroscopic imaging**

FTIR images were acquired with a 64 × 64 FPA detector with 8 cm⁻¹ spectral resolution and 20 scans co-addition. The accessory used was a non-imaging Golden Gate™ diamond ATR accessory (Supercritical Fluid Analyser, Specac Ltd., UK) described in Column 1 of Table 5-2. Image size was 1100 μm × 780 μm.

**9.1.2.5 Dissolution procedure**

The transparent Perspex dissolution cell described in Section 5.3.3 was used for tablet dissolution. The tablets were compacted using the same method described in Section 9.1.2.2, they were then placed on the surface of the diamond crystal and the Perspex dissolution cell was bolted into place on top (Figure 9-2). A CCD video camera was mounted above the system to capture visible optical images of the dissolution (Kazarian and van der Weerd, 2008), the setup is illustrated in Figure 9-2. A UV/Vis detector was
then connected online, in the two pump configuration described in Section 5.6, to measure the concentration of the drug in the effluent stream. The dissolution medium used was deionised water and the flow rate was set to 1 ml/min.

Figure 9-2. Tablet inside Perspex dissolution cell, showing flow pipes for dissolution and effluent stream to be sent for UV/Vis analysis

The tablets were positioned such that the FTIR image produced was at the interface between the layers as shown in Figure 9-3. Correct alignment of the tablet interface with the centre of the imaging area was non-trivial as the tablet fully covered the diamond crystal. Therefore a template was designed that fitted on the top surface of the dissolution cell, allowing the tablet to be aligned with a good degree of reliability by eye.

Figure 9-3. Positioning of tablet relative to the top surface of the ATR crystal. Schematic of underside of the dissolving tablet showing the imaging area aligned with the interface between tablet sections.
9.1.3 Results and discussion

9.1.3.1 X-ray tomography

In order to verify the quality of the tablets produced by the manufacturing process, X-ray microtomography was used to non-destructively construct a three dimensional density map of the tablet. This ensured that the tablets had consistent density distributions within each section of the tablet, that there were no large voids anywhere, and that the two sections had compacted together properly. The data from this verification are shown in Figure 9-4.

![Figure 9-4. X-ray density map of tablet overlaid onto three-dimensional structure of tablet. Red and purple domains are regions of high density and the blue domains represent areas of lower density](image)

The resulting structure of the tablet is clearly shown in Figure 9-4, this image shows that the core of the tablet was less dense than the shell region around it. For this test formulation a lower than normal compaction force was used to form the core in order to improve the contrast between the sections of the tablet in this image. The image shows that there was an approximately homogeneous density distribution throughout each section of the tablet. There is seen to be a slight gradient on the front face in the shell layer, however, this is not significant as the artificially applied colour range was set to cover a very narrow range of densities. Importantly, the image reveals that even with the reduced compaction force used to form the core of the tablet, the two sections compacted together seamlessly.

Figure 9-4 shows that the core of the tablet was exposed; this was to allow for analysis of the dissolution of both tablet sections using ATR-FTIR imaging. In practice this type
of tablet would be applied for delayed release, however, with the core exposed this would not create a delayed release profile. If this formulation were to be studied in a standard dissolution test or for in vivo studies, the tablet core would be sealed. More shell material would be compacted onto the exposed faces of the tablet as shown by Lopes et al. (Lopes et al., 2007). The exposed faces allowed for FTIR images of the tablet interior to be obtained from the underside of the tablet and for visible optical images to be gathered from above. During the dissolution the “caps” were replaced with the tablet being sealed between the diamond and its tungsten carbide surround at the bottom and the dissolution cell at the top.

### 9.1.3.2 ATR-FTIR imaging setup

The alignment of the interface between the two sections of the tablet with the ATR crystal was important. An example image showing the location of the shell material is shown in Figure 9-5.

![Figure 9-5. FTIR image generated at the interface between the tablet sections, showing both core and shell material.](image)

The thickness of the barrier layer was 1.25 mm, whereas the imaging area of the diamond was only slightly over 1 mm across. It would have been possible to use an imaging crystal with a larger FOV such as zinc selenide, however; this would have required sacrificing spatial resolution. As the area of interest in these experiments was the interface between the tablet sections, a high spatial resolution was essential for accurately tracking the speed of water ingress and any subsequent interfacial processes. Therefore, the imaging field of view was aligned such that the interface between tablet
sections was visible. This did result in the outer edge of the tablet not being visible, however, the visible video camera mounted above the dissolving system had a larger FOV in which the full diameter of the tablets could be seen.

The band between 3600 – 3000 cm\(^{-1}\) was used to generate images for the distribution of water, which was the largest component of the dissolution medium. The caffeine images were generated using the band between 1676 – 1724 cm\(^{-1}\) and the HPMC images were generated using the band between 1088 – 1030 cm\(^{-1}\). The integration range used to track the microcrystalline cellulose was 961 – 924 cm\(^{-1}\) and the band used for glucose was between 1183 – 1224 cm\(^{-1}\). As glucose was applied in these tablets merely to increase the solubility of the shell, it will not be shown in the FTIR images, MCC data will be used to track the integrity of the shell.

9.1.3.3 Presented formulations

The experiments were conducted at a range of shell MCC concentrations, varying in 25 wt% steps. FTIR imaging, optical imaging and UV/Vis spectroscopic data will only be shown in detail for the 75 wt% and 25 wt% MCC shell content formulations as demonstrations of the types of release mechanism obtained. The range of formulations studied is shown in Table 9-1, with presented formulations highlighted in grey.

Table 9-1. Formulations studied in this chapter, with presented examples highlighted in grey.

<table>
<thead>
<tr>
<th>Shell Contents wt%</th>
<th>Tablet 1</th>
<th>Tablet 2</th>
<th>Tablet 3</th>
<th>Tablet 4</th>
<th>Tablet 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC</td>
<td>100</td>
<td>75</td>
<td>50</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Glucose</td>
<td>0</td>
<td>25</td>
<td>50</td>
<td>75</td>
<td>100</td>
</tr>
<tr>
<td>Core Contents wt%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPMC</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Caffeine</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

The various formulations used were designed to cause the shell section of the tablets to break up at different times. The core section was designed to then provide controlled release of the drug following the breakdown of the shell. Similar controlled release
sections have been applied in other studies (Maggi et al., 1999, Lopes et al., 2007). These studies applied them to biphasic release, which would have been possible from these formulations by adding a second drug to the shell section of the formulation. However, as the focus of this study was at the interface of the sections and the behaviour of the core, the formulations were constructed to achieve delayed release. Glucose is normally used as a sweetener or diluent (Ash and Ash, 2007), however, it is also highly soluble. In this case, it was paired with microcrystalline cellulose which was chosen for its binding and disintegrant properties (Inghelbrecht and Remon, 1998). Varying the loading of glucose was used to increase or decrease the rate of water ingress, changing the disintegration rate of the shell. Rather than using the shell thickness to control water ingress time (Spencer et al., 2008, Ueda et al., 1994), this work used changes to the formulation of the shell to control the rate of water ingress.

9.1.3.4 Dissolution of Tablet 2

The FTIR images in Figure 9-6 show the various components of Tablet 2, the first of the two presented formulations as specified in Table 9-1, during dissolution.

Figure 9-6. FTIR images of the dissolution of sample with 75 wt% MCC and 25 wt% glucose in the shell (Tablet 2). The MCC coating is shown in the top row of images. The core components are shown in the second and third row, while the dissolution medium is shown in the bottom row. Image size is 1100 µm × 780 µm.
The first row of images in Figure 9-6 shows the distribution of the MCC in the shell section. The apparent breakup and dissolution of this layer was seen to take three hours. However, even following three hours of dissolution this layer had not dissolved, but had been moved out of the field of view. The MCC image at 170 minutes shows that the MCC layer had moved upwards, towards the periphery of the imaged area. This was explained by the behaviour of the HPMC in the core. At 50 minutes when the dissolution medium had only just penetrated to the imaged area the shell section remained fully intact. It was not until 110 minutes that the ingressing water concentration in the interfacial region of the matrix became significant. It was at this point that wetting of the HPMC in the core occurred. Upon wetting the HPMC began to form a gel and expand, this resulted in a significant change being seen in the HPMC images. This expansion of the inner section of the tablet caused the shell to be forced outward, displacing it from the imaging field of view as demonstrated in Figure 9-7d.

The tablets were constructed from separately compacted structures, an inconsistency of which was, that there was a small discrepancy in the heights of the sections following compaction as shown in Figure 9-7a. Ordinarily in ATR imaging of HPMC based tablets, formation of the gel phase improves contact with the imaging surface (van der Weerd and Kazarian, 2004a). However, as the core became wet and the HPMC gel formed, the gel lubricated the interface between the sections so they were no longer compacted firmly together and could move independently.

![Figure 9-7. Schematic diagram showing the effects of the swelling core on the images of the shell and core sections in Figure 9-6. (a) core and shell structure displaying slight discrepancy in heights (b) water ingress through shell (c) vertical movement of core due to restricted swelling of HPMC (d) outwards expansion of the core displacing the shell from the imaging area.](image-url)
Due to the discrepancy in the heights of the sections and their lubricated interface there was a small amount of vertical gelling space and the dry region of the core was lifted a short distance from the ATR diamond Figure 9-7c. As the penetration depth of the evanescence wave is a few micrometers then the core was lifted outside the ATR sampling volume. This lifting effect offered an effective method for tracking the inward progression of the water front into the core of the tablet. This is discussed further in Section 9.1.3.1.

The caffeine images in the third row of Figure 9-6 show that the caffeine was distributed within the core and as the water caused the HPMC to expand, resulting in translation of the caffeine particles and providing controlled release properties for the formulation (Adler et al., 1999). However, the field of view of the ATR images was small and the expansion of the core resulted in the breakup of the shell and the dissolution of the drug being outside this domain. FTIR imaging provided important chemical and spatial information about the interface between the tablet sections; however, complementary techniques were also used to give a fuller description of the dissolution processes occurring. Visible optical video images, from the camera mounted above the system, of the dissolution are shown in Figure 9-8.

![Figure 9-8](image)

**Figure 9-8. Visible optical images for sample with 75 wt% MCC and 25 wt% glucose shell. Time is given in minutes below. Image size is 6.5 mm × 5 mm.**

The images in Figure 9-8 show the dissolution of the tablet with 75 wt% MCC coating captured by a video camera. The field of view of these images is approximately 6.5 mm × 5 mm. While this technique lacks the chemical specificity of FTIR imaging it was
able to study a much larger area of the dissolution procedure simultaneously with FTIR imaging. The two sections of the tablet were clearly defined; the core was slightly lower than the surrounding shell material (c.a. 0.2 mm), indeed it is still in focus despite the small depth of field of the camera. It is important to note that the thickness of the shell section was uniform around the whole tablet, this is important as variations in shell thickness have been shown the significantly affect lag-time (Ozeki et al., 2004, Spencer et al., 2008).

The ingress of water into the shell, in the image at ten minutes in Figure 9-8, is seen as darker regions of the tablet matrix around the edge of the shell. The ingressing water took 50 minutes to approach close to the core, which was in agreement with the FTIR imaging data. The image at 110 minutes highlights one of the advantages of using the chemically specific FTIR imaging approach. At this point in the optical images it did not appear that any water had penetrated the core, whereas, the FTIR images clearly show that it was this point at which the HPMC began to swell.

At 110 minutes there was very little breakup of the shell of the tablet; this was not unexpected as there was a high concentration of MCC in the shell and this would have dissolved slowly. At 170 minutes two large cracks appeared in the shell, while at the same point there was significant wetting and expansion of the core. The shell material was pushed outward on the left of the tablet where the wetting of the HPMC was the greatest. This expansion of the core and the fracturing of the shell continued as more water ingressed into the core. Very little of the shell dissolved and the major route of exposure of the core to the flowing dissolution medium was through the cracks in the shell.

Figure 9-9 shows the UV/Vis delayed release profile for the tablet with 75 wt% MCC coating. The data were normalised to give values between 0 and 1. The data are shown to the point where the lag-time and release mechanism had been established. This profile shows that no caffeine is released for the first 2.1 hours of the dissolution, giving a lag-time for this sample of approximately 130 minutes. Establishment of the dissolution profile required around 45 minutes.
Figure 9-9. Graph showing dissolution profile for sample with 75 wt% MCC and 25 wt% glucose shell. Establishment of the dissolution profile is indicated by the grey box. The lag-time is defined as being from $t = 0$ to the first response in the UV/Vis profile, at the left edge of the grey box.

This coincided well with the information gathered from the optical and FTIR data. At 170 minutes in the FTIR images in Figure 9-6 the MCC coating had been displaced outward significantly by the core due to the HPMC expansion. In the visible optical images (Figure 9-8) major cracks started to appear in the shell, exposing the core to the flowing dissolution medium and providing a route for the caffeine to be released. At first the cracks in the shell were small leading to only a slow rate of release. As the HPMC continued to expand the cracks in the shell became more severe leading to an increased dissolution rate. It was this slow breaking of the shell that led to the gradual establishment of the dissolution profile.

These data show that, for tablets with high MCC content shells, the lag-time was controlled by the ingress of water to the core causing the expansion of the core and the fracturing of the shell. As the inelastic shell fractured, however, rather than exhibiting burst release, this formulation featured a gradual establishment of the release profile as shown in Figure 9-9.

**9.1.3.5 Dissolution of Tablet 4**

The FTIR imaging data for the sample with a shell formulation containing 25 wt% MCC and 75 wt% glucose (Tablet 4) are shown in Figure 9-10. The most apparent difference between the Tablet 2 coating and Tablet 4 was that the dissolution of the
shell sample occurred much more rapidly in Tablet 2 (Figure 9-10 row 1). The shell section of Tablet 4 had disappeared from the FTIR image field of view in 30 minutes. This also significantly reduced the time taken for the water to reach the core. In the Tablet 4 the dissolution medium penetrated the shell in 30 minutes compared to 110 minutes for Tablet 2. The shell of Tablet 4 broke up before there had been any significant expansion of the core. The high loading of glucose (75 wt%), which was highly soluble, encouraged rapid water ingress and facilitated a much more rapid breakup of the shell and hence a drastically reduced lag-time.

The speed ingress of the water front into the core was also much more rapid (Figure 9-10 row 4), achieving a similar level of core hydration to Tablet 2 at 290 minutes in approximately half the time. The definition of the water front is clarified in Section 9.1.3.1. The subsequent speed of water ingress into the core was also different between Tablets 2 and 4. The rate of water ingress through the core in Tablet 2 was found to be approximately 2.5 µm/min, whereas in Tablet 4 it was found to be approximately 4 µm/min. This broadly agrees with values found in the literature for monolithic HPMC tablets (van der Weerd and Kazarian, 2004b, Bettini et al., 2001), although the additional loading of drug in this case makes direct comparison impossible. It does show that the remaining shell material in the tablets with greater MCC loading did impede water ingress. The increased rate of core hydration combined with the rapid rate of shell dissolution led to rapid and unconfined core expansion (Figure 9-10 row 3). The gelling core material expanded to the edge of the field of view in 80 minutes, whereas this event occurred at 200 minutes for Tablet 2. Indeed, without the protection of the shell section, there was a greater exposure of the core to the flowing dissolution medium causing the HPMC to swell more rapidly.

This was reflected in the dissolution behaviour of the caffeine seen in row 3. As in Tablet 2 the caffeine particles in the core moved with the expansion of the HPMC gel. However, there was a decrease in the absorbance corresponding to the amount caffeine in these domains towards the top of the image suggesting they were being dissolved. In Figure 9-6 there was no significant decrease in the absorbance of the caffeine domains during the course of the experiment.
Figure 9-10. FTIR images of the dissolution of sample with 25 wt% MCC and 75 wt% glucose shell (Tablet 4). The MCC coating is shown in the top row of images. The core components are shown in the second and third row, the dissolution medium is shown in the bottom row. Image size is 1100 µm × 780 µm.

In Figure 9-10 the vertical swelling of the HPMC, seen in the HPMC data from Figure 9-6, which lifted the core from the surface of the ATR diamond, was not present. This can be explained by the fact that the outer shell had lost any significant structural integrity by the time the water reached the core. This allowed the HPMC to expand outwards freely, without it being forced to expand vertically, so the dry unexpanded regions of the core were no longer lifted from the face of the diamond. The data in Figure 9-11 confirm and explain the observations made in the FTIR images.

The images in Figure 9-11 show the dissolution of Tablet 4, captured using the video camera mounted above the dissolution cell. The dissolution process of this tablet was significantly different to that of Tablet 2. The highly soluble glucose caused the water to move through the shell in approximately 10 minutes, by which time the shell had started to dissolve throughout. The shell continued to rapidly dissolve through to 30 minutes, wetting the core, and only the region close to the core still maintained any structure. This observation is consistent with the data from the FTIR images in Figure 9-10.
Figure 9-11. Visible optical visible images for sample with 25 wt% MCC and 75 wt% glucose shell (Tablet 4). Time is given in minutes below. Image size is 6.5 mm × 5 mm.

As in the FTIR images, significant wetting of the core was seen at 30 minutes and by 50 minutes there was a dark ring around the core. This ring shows the formation of the translucent HPMC gel. The dark colour was due to the tungsten carbide plating below the tablet being visible through the gel. The HPMC continued to swell over time and expand outwards. The white powder at the outer edge of the ring was the remnants of the shell; it remained present as it was trapped in the outer layers of the gel. At 50 minutes the integrity of the shell was compromised, exposing the dissolving core to the dissolution medium.

These data show that this tablet had a different mechanism of drug release to Tablet 2. In Tablet 2 the release of the drug was governed by the speed of ingress of dissolution medium through the shell of the tablet and the subsequent expansion of the core material breaking the shell layer of the tablet, exposing the core. The mechanism of release in Tablet 4 was controlled by the breakup and dissolution rate of the shell section.
Figure 9-12. Graph showing dissolution profile for sample with 25 wt% MCC and 75 wt% glucose shell (Tablet 4).

The dissolution profile in Figure 9-12 shows that the lag-time for Tablet 4 was greatly reduced compared to Tablet 2 coating tablet, taking under 1 hour. The transition to establishing a consistent release profile was significantly sharper than for Tablet 2. These effects were due to the more rapid breakdown of the shell, resulting in a shorter time to the initial exposure of the core to the dissolution medium and thereafter a more rapid establishment of a stable dissolution regime. The absolute release rate of the drug from this formulation after the lag-time was also significantly faster than for Tablet 2. The amount of drug released in the first hour after dissolution was approximately ten times larger from Tablet 4 than Tablet 2.

These data confirm the dissolution of the drug from this formulation was controlled by another mechanism of release for this tablet type. The lag-time was determined by the disintegration of the shell layer, as opposed to the MCC rich shells in which the lag-time was determined by the ingress of water through the coating and the expansion of the HPMC core causing the shell layer to break open.
9.1.3.1 **Analysis of HPMC swelling front**

In order to determine the time at which the dissolution medium reached the core (penetration time), it was necessary to define a concentration of water which could be referred to as the ingressing front.

![Figure 9-13. Analysis of water front showing extracted images from Figure 9-6 showing (a) water distribution at 110 minutes and spectral extraction points and (b) swelling front of HPMC at 110 minutes (c) water spectra in the region of the water stretching vibrations extracted from corresponding extraction points, legend denotes extraction point](image)

The water images in Figure 9-6 show that the concentration of the water did not have a sharp decrease, by which to determine an ingressing front. Extraction of spectra along
the line in Figure 9-13a, shown in Figure 9-13c revealed a gradual increase in water concentration across the image. The intensity of these peaks was plotted in Figure 9-14 and water ingress presented in the images as a smooth gradient across the image, with a plateau towards the as yet unwetted core. It was not possible to pick a water front based on water concentration alone. However, as seen in Figure 9-13b, point 6 of extraction was at the swelling front of HPMC. The intensity of the HPMC band as a function of extraction point was plotted alongside that of water in Figure 9-14.

![Figure 9-14](image)

**Figure 9-14.** Integrated absorbance the corresponding spectral bands of HPMC and water spectra from Figure 9-13 (a) and (b) plotted as a function of extraction point.

Therefore, the concentration of water at which HPMC gelation commenced was determined as the front concentration. It was necessary to determine this water concentration, as not all of the formulations exhibited this lifting phenomenon, as shown in Figure 9-15.

![Figure 9-15](image)

**Figure 9-15.** HPMC distribution in formulations at time point when water concentration had reached swelling concentration in the core. Formulations given by MCC:Glucose concentrations below each image. Image size is 1100 µm × 780 µm.
The imaging time step, at which the water concentration in the HPMC reached the swelling concentration seen in Figure 9-13, is shown for each formulation in Figure 9-15. This shows that only the formulations with a 75 wt% and 50 wt% (Tablets 2 and 3) loading of MCC in the shell exhibited this phenomenon. The reason for this is explained by Figure 9-16; the tablet with a 100 wt% loading of MCC (Tablet 1) in the shell of the tablet showed no height difference between the shell and the core sections Figure 9-16. Due to the high solubility of glucose in water, the shell section of the tablet with a 100 wt% loading of glucose in the shell, dissolved very rapidly. Therefore, upon wetting of the core the shell section was so disintegrated that it did not serve as a swelling barrier to the core, such that no vertical swelling occurred.

9.1.3.2 Comparison of formulation performance

As stated previously, these experiments used a range of different shell concentrations and the two formulations analysed in detail here, have been shown in order to explain the numerous processes occurring during the dissolution in a fully comprehensive manner. These two experiments only show that there was a difference between the low and high MCC concentration shell, however, in order to study the trend, the lag-time data for the whole range of concentrations analysed is shown in Figure 9-17.
Figure 9-17. Graph showing comparison of lag-time (time taken before a response is seen in UV/Vis dissolution profile) and penetration time (time taken for dissolution medium to reach core). Data points are shown as the mean value of three experiments with error bars generated based on standard deviation.

Figure 9-17 compares the penetration and lag-times for the full range of shell concentrations. The lag-times were obtained from the UV/Vis dissolution profiles recorded for each dissolution experiment. The penetration times were obtained by finding the exact time at which the dissolution medium had penetrated the shell of the tablet and reached the core, from the FTIR data, as explained in Section 9.1.3.1. FTIR imaging shows a small region of the total core circumference, whereas the video images in Figure 9-8 show the entire circumference. It was decided not to use the video images for this as in the analysis of Figure 9-6 and Figure 9-10 it was demonstrated that the FTIR data detected the presence of water much more sensitively.

The data showed, as expected, that with increasing MCC shell concentration both lag-time and penetration time became larger. As the MCC concentration increased the penetration time of the dissolution medium increased, as without the presence of the soluble glucose the shell was less soluble, permeable and had better structural integrity. The most notable observation is that for tablets of 50 wt% MCC shell concentration and below, the lag-time and penetration time are very similar. This is because glucose is very soluble, so when it was present in high concentrations it caused the shell to disintegrate very quickly as it became wet and was dissolved. The result of this was that by the time the dissolution medium had reached the core then the integrity of the shell
outside it was already reduced significantly. The disintegrated state of the shell was confirmed by the video images in Figure 9-11. The lack of integrity of the shell then allowed the dissolution of the drug in the core to proceed.

It was also seen in Figure 9-17 that when the concentration of MCC was above 50 wt% the values for lag-time and penetration time started to deviate significantly from one another. This was because; the mechanism of drug release changed significantly with high MCC concentrations. The dissolution medium penetrated the core however, before drug release was seen, the expanding core material had to break the shell. When the MCC concentration was higher the shell layer was stronger, requiring a greater expansion force to be broken and longer time for water ingress to soften it. This led to a longer time for the required swelling to occur for the HPMC to break the shell. The insolubility of shell combined with its greater structural integrity, are what lead to the deviation between the lag-time and penetration time.

9.1.4 Conclusions

The work in this section of the chapter has studied the dissolution of delayed-release pharmaceutical tablet formulations using ATR-FTIR spectroscopic imaging.

For the tablet-in-tablet structured tablets studied, two release mechanisms were established. The first was seen for tablets in which the shell concentration of MCC was low. In these tablets the release was dependent upon the rapid dissolution of the shell which was facilitated by the high concentration of glucose. It was established that the lag-time and the penetration time were identical up to a shell MCC concentration of 50 wt% for these formulations.

The second type release mechanism was found in tablets with a high concentration of MCC in the shell. The lag-time was controlled by the rate at which the dissolution medium progressed through the shell and also by the subsequent expansion of the core and the amount of force required to break the shell.
This type of tablet is important, as adjustment of the concentrations of the shell components could allow for very fine control over the *in vivo* release point and mechanism of the drug, resulting in more targeted delivery.

FTIR spectroscopic imaging played a very important role in this work of accurately determining the swelling of the HPMC core and its relation to the rate of water ingress. This was essential in determining the release mechanism of the drug, information which would otherwise have been unobtainable.
9.2 pH resistant formulations

9.2.1 Introduction

Previous work discussed in Chapter 8 has shown that the addition of basic buffer to a tablet matrix containing ibuprofen can raise the solubility of the drug within the matrix. However, once the basic compound in that area of the formulation has been neutralised by any acidic environment through which it may pass, the solubility of the drug in those areas is no longer enhanced.

One method by which to deliver drugs such as ibuprofen, which crystallises in low pH conditions causing ulcers, or pH labile drugs which may be damaged by acidic conditions, is to deliver them straight into the large intestine. This has been done through the use of enteric coatings such as Eudragit® S, which dissolves above pH 7 due to deprotonation of its carboxylic acid groups (Van den Mooter and Kinget, 1995).

These formulations can be very effective and have been used for a wide range of applications including delivery of insulin (Touitou and Rubinstein, 1986, Dew et al., 1982). These formulations do have some control issues, as variations in the pH of the digestive system can delay the breakup point (Rubinstein, 1990) and poor site specificity has been demonstrated (Ashford et al., 1993).

This chapter proposes a pH resistant formulation for the delivery of NSAIDs such as ibuprofen based on the tablet-in-tablet structure seen in Section 9.1. However, the formulations in this section of the chapter use a pH modified barrier layer with a PEG and ibuprofen core. The pH active compound used was the sodium carbonate based buffer that was found to be effective at enhancing the solubility of ibuprofen in Chapter 8. The buffer in these formulations was designed to work in two ways: 1) to neutralise the acidic environment in which the tablet was dissolved and 2) to enhance the solubility of the ibuprofen contained in the core section.
9.2.2 Materials and methods

9.2.2.1 Batch preparation

The tablets studied in this work consisted of five components. The core of the tablets contained ibuprofen (Whitehall International, UK), used as a model drug, Poly(ethylene glycol) (PEG) (Sigma-Aldrich, UK), the molecular weight of the PEG used was 4000. The core was mixed to a ratio of 20 wt% ibuprofen and 70 wt% PEG. The shell section of the tablet contained HPMC (Colorcon, UK), the same sodium carbonate buffer used in Chapter 8, and glucose (Sigma-Aldrich, UK). The powders were ground and sieved such that all powders were below 90 µm in size.

9.2.2.2 Tablet formation

The compaction procedure was the same as that described in Section 9.1.2.2 for the first three steps. The core was then formed using a novel injection method. The assembly was placed on a flat surface and a shorter outer shell punch was inserted, this served as a guide for the injected core, and ensured the outer edges of the tablet were sealed leaving only the inside walls of the shell exposed.

Figure 9-18. Schematic of injection method of core preparation

The mixture for the core was prepared by melting the PEG and ibuprofen, the still molten formulation was then injected into the core space of the compacted shell, as shown in Figure 9-18 and was left to solidify. Once the formulation had cooled the tablet was then extracted from the compaction cell.
This chapter presents data from two of the formulations studied, one of which was used as a control and contained no pH active compounds, while the second formulation contained basic buffer, as shown in Table 9-2. The difference between the two formulations was made up by glucose.

### Table 9-2. Control and pH active formulations

<table>
<thead>
<tr>
<th></th>
<th>Tablet 6</th>
<th>Tablet 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shell Contents wt%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPMC</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Glucose</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>Basic Buffer</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td><strong>Core Contents wt%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

### 9.2.2.3 Experimental

The experimental procedure was much the same as that described in Section 9.1.2.5. However, the dissolution medium used was pH 2 hydrochloric acid, in order to replicate stomach conditions; this was then changed after 2 hours to pH 6.8 phosphate buffer to replicate post stomach conditions.

### 9.2.2.4 FTIR imaging

The FTIR imaging data of the dissolving tablets were acquired using the same imaging set up as described in Column 1 of Table 5-2. The images measured of the dissolving PEG/ibuprofen melt, were measured on a Varian imaging system with a 64 × 64 array detector with a zinc selenide accessory producing a field of view of 3 mm × 2 mm as described in column 4 of Table 5-2.

### 9.2.3 Results and discussion

#### 9.2.3.1 FTIR spectroscopic imaging

Six different compounds were used in these experiments: PEG and ibuprofen for the core, HPMC, buffer and glucose for the shell and water for the dissolution medium.
FTIR data of the dissolution of the excipients are shown for PEG in the core, HPMC in the shell alongside the FTIR data for water. This will suffice to demonstrate the location and any physical changes that occur to the core, shell and dissolution medium.

The integration ranges used were 980 – 900 cm\(^{-1}\) for the PEG, 1080 – 1008 cm\(^{-1}\) for HPMC and 3600 – 3000 cm\(^{-1}\) for water. The crystalline state of the ibuprofen was monitored by examining the position of the carbonyl peak.

FTIR imaging has been used to study the spatial distribution of the crystalline and amorphous forms of ibuprofen previously (Kazarian and Chan, 2003). A position of around 1730 cm\(^{-1}\) corresponds to the non-crystalline form, in this case molecularly dispersed in PEG. A band at 1705 cm\(^{-1}\) corresponds to the crystalline form. The integration ranges used were 1730 - 1685 cm\(^{-1}\) for the wet crystalline and 1740 - 1720 cm\(^{-1}\) for the non-crystalline as shown in Figure 9-19.

### 9.2.3.2 Dissolution of Tablet 6

Figure 9-20 shows the dissolution of the various sections of the control tablet (Tablet 6). The dissolution process of the shell can be seen in the first row of images. Removal of the shell section from the imaging FOV required approximately one hour, this process was expedited by the addition of glucose to the shell layer.
Figure 9-20. FTIR images showing the dissolution of control sample (Tablet 6). The first line of images show the dissolution of the HPMC shell, the second line shows the ingress of water into the tablet while the bottom line shows the dissolution of the PEG in the core. Image size is 1100 µm x 780 µm.

The dissolution medium reached the core after 50 minutes and rapidly dissolved the PEG from the core section of the tablet. As this tablet had no pH modification and PEG dissolved fairly rapidly, it would be expected that the ibuprofen may crystallise. The dissolution of the ibuprofen is shown in Figure 9-21.

Figure 9-21 FTIR images of the presence of amorphous ibuprofen (row 1) and crystalline ibuprofen (row 2) during dissolution of Tablet 6. Image size is 1100 µm x 780 µm.

The dissolution images of the ibuprofen from Tablet 6 in Figure 9-21 show that initially the amorphous form was homogeneously distributed throughout the core section of the
tablet. The core remained relatively unchanged until 50 minutes when the dissolution medium initially penetrated the shell. While the concentration of the PEG remained high, crystallisation of the ibuprofen did not occur in significant quantities. By 90 minutes the dissolution medium had achieved a much greater degree of penetration into the core as shown in row 2 of Figure 9-20. In row 1 of Figure 9-21 the coverage of amorphous ibuprofen is much reduced, with only a small amount remaining near the bottom of the image. However, the population of the crystalline species had increased drastically across the image. This trend continued till the end of the experiment when there was no remaining trace of the amorphous form of the drug, while a large amount of the insoluble crystalline material had formed.

These data demonstrated that as expected this formulation is unsuitable for delivery of ibuprofen in acidic conditions due to the low solubility of the large amount of crystalline material.

9.2.3.3 Dissolution of Tablet 7

Tablet 7 included the basic buffer as a pH modifier to protect the pH labile drug payload of the formulation from the acidic environment in which the formulation was being dissolved. The same components of dissolution will be shown for this tablet as for Tablet 6 in Section 9.2.3.2, but the time steps shown are slightly different. The dissolution of this formulation required more time as the buffer material was not as soluble as the glucose by which it was replaced in Tablet 6.

The distributions of the HPMC, PEG and water components during the dissolution are shown in Figure 9-22. The behaviour of these components was very similar to that seen in Figure 9-20. However, dissolution to the same stage of completeness required 40 minutes longer. The HPMC in the shell was removed from the imaging area by 210 minutes; while the PEG was fully dissolved by 250 minutes and full water ingress required 250 minutes.
Figure 9-22. FTIR images showing the dissolution of pH modified sample (Tablet 7). Row 1 shows the dissolution of the HPMC shell, row 2 shows the dissolution of PEG while row 3 shows the ingress of water into the tablet. Image size is 1100 µm × 780 µm.

As Tablet 7 had the basic buffer in the shell section it should be expected that there would have been improved dissolution of the drug as seen in Chapter 8. This was indeed the case in Figure 9-23. The ibuprofen, which was molecularly dispersed in the PEG, dissolved roughly in line with the PEG in Figure 9-22. The same behaviour for the amorphous species was seen in Figure 9-21; however, the crystalline behaviour was significantly different in this formulation.

Figure 9-23. FTIR images of the presence of amorphous ibuprofen (row 1) and crystalline ibuprofen (row 2) during dissolution of Tablet 7. Image size is 1100 µm × 780 µm.

In Figure 9-21 a large amount of crystalline material is seen to deposit, whereas in Figure 9-23 no crystalline material is seen to form. This suggests that not only had the
basic buffer neutralised the acidic dissolution medium, but that it had raised the pH in the core somewhat above neutral, as ibuprofen dissolving in neutral conditions from PEG dispersions will still crystallise as shown by Kazarian and Chan (Kazarian and Chan, 2003) using PEG 8000. This experiment was repeated with PEG 4000 as used in Tablets 6 and 7 and the results are shown in Figure 9-24.

![Figure 9-24. Dissolution of ibuprofen from PEG 4000 in water. Ibuprofen loading was 20 wt%. Images show PEG and crystalline ibuprofen. Image size is 3 mm × 2 mm.](image)

The ibuprofen was not soluble in the pH neutral aqueous media used and readily crystallised as the PEG dissolved. The completeness of the dissolution of the PEG and ibuprofen core in Tablet 7 is further demonstrated through the video images of the dissolution acquired.

![Figure 9-25. Visible optical images of the dissolution of the shell and core material for Tablet 7. Image size is 6.5 mm × 5 mm.](image)
Chapter 9: Dissolution of Tablet-in-Tablet Formulations

The data in Figure 9-25 illustrate that by 250 minutes of dissolution the core of Tablet 7 had dissolved to such an extent that the diamond underneath the tablet was visible to the camera mounted above the system. The advantage of having a tablet made of a PEG and ibuprofen melt is that the drug is molecularly dispersed, however, this system exhibits relatively uncontrolled release and the ibuprofen will readily recrystallise. The addition of the shell structure containing the basic buffer and HPMC minimised this effect. The rate of release of the drug from the tablet would have been controlled by the rate at which it diffused through the HPMC gel (Matsuo et al., 1996, Ozeki et al., 2004). Through this the ibuprofen inherited the controlled release properties of the HPMC.

The data thus far have implied that the pH neutralisation did indeed work as intended, however, there has been no direct evidence. In order to verify this, a similar methodology to that seen in Chapter 8 for investigating pH change in the matrix was applied. The acidic dissolution medium was dosed with universal indicator, turning it red, which, as neutralised by the buffer, should have turned green in colour. The results are shown in Figure 9-26.

![Figure 9-26. Video images of dissolving tablet with basic buffer. As the HPMC formed the gel it became translucent, which against the dark background of the diamond plating, made it difficult to see therefore, a 20 wt% loading of MCC was added to the matrix to improve contrast. Image size is 6.5 mm × 5 mm.](image)

In the images in Figure 9-26, it is clear that the pH neutralisation worked effectively. The gel layer appears cloudier than that in Figure 9-25, this is due to the addition of MCC, which was added to the tablet matrix to improve the visibility of the colour of the indicator. The image at 20 minutes shows a clear pink colour of the outer edge of the matrix. However, by 50 minutes, following a greater degree of establishment of the gel layer, the pink colour had faded and the matrix had a slightly green tinge, indicating neutralisation of the acid within the matrix.
9.2.4 Conclusions

This work has developed a formulation specifically for the improved delivery of ibuprofen. FTIR spectroscopic imaging provided a methodology by which to accurately track the multiple dissolving components of the tablets. It also confirmed the effectiveness of the formulation, through monitoring of the crystalline state of the drug.

The use of the PEG based core and basic HPMC shell prevented the crystallisation of the ibuprofen upon dissolution. The tablet structure also ensured that the drug was carried in a molecularly dispersed state, while also exhibiting controlled release.

This formulation could easily be transferred to work with other NSAIDs such as flurbiprofen which can be dispersed in PEG. The formulation could also be modified to carry other pH labile drugs for oral ingestion. Moreover this tablet form should also help mitigate the long-term side effects of using NSAIDs, such as stomach ulcers by reducing crystallisation in the gut.
CHAPTER TEN

BIPHASIC AND ZERO-ORDER RELEASE FORMULATIONS
Chapter 10: Biphasic and Zero-Order Release Formulations

10 Biphasic and Zero-Order Release Formulations

The work presented in Chapter 9 showed the potential information that FTIR imaging can provide when studying structured tablet formulations. The work in this chapter sees the novel application of ATR-FTIR spectroscopic imaging to study the formation and dissolution of multilayer pharmaceutical tablets. Multilayer formulations were used to create biphasic and zero-order release formulations. The work on zero-order formulations was then extended to investigate the effects of flow regime and geometry in the custom ATR flow cell.

10.1 Biphasic release formulations

10.1.1 Introduction

The multilayer structure has been successfully used to achieve biphasic delivery for the purpose of quick/slow release, which can simply be achieved by using one fast release layer and another controlled release matrix layer (Uekama et al., 1990). There are multiple types of tablet structure that can be used for this type of delivery, Lopes et al. have made use of a tablet-in-tablet structure in which a slow release compressed core was formed and coated in a fast release compressed shell (Lopes et al., 2007).

This chapter focuses on the use of FTIR imaging to study these fast/slow release formulations. Uekama et al. used cyclodextrin in the fast release layer and HPMC in the slow release layer (Uekama et al., 1990). Maggi et al. used double layer tablets for biphasic release of two different drugs in which the behaviour of the quick release phase was determined by the addition of a super disintegrant to the layer (Maggi et al., 1999).

In this work FTIR imaging was used to study the processes which occur during dissolution at the interfaces between the tablet sections, in order to understand how the more soluble layer affected water ingress into the less soluble layer, and hence the release of the drug.
10.1.2 Materials and methods

10.1.2.1 Tablet formulations

The biphasic tablets were designed to release the two different soluble drugs, buflomedil (Lisapharma SpA, Italy) and nicotinamide (Sigma Aldrich, UK) from separate halves of the tablet. Each half of the matrix also contained microcrystalline cellulose (Merck Sharp & Dohme, UK) and glucose (Sigma Aldrich, UK) in varying amounts to produce differing dissolution properties for each half. The mass fraction of drug was 20 wt% in each section of the tablet, while the full range of concentrations of the remaining components used is shown in Table 10-1.

Table 10-1. Tablet formulations studied for biphasic release. Concentration of components of studied formulations are given in wt%.

<table>
<thead>
<tr>
<th>Buflomedil Side</th>
<th>Tablet A</th>
<th>Tablet B</th>
<th>Tablet C</th>
<th>Tablet D</th>
<th>Tablet E</th>
<th>Tablet F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>0%</td>
<td>0%</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
<td>40%</td>
</tr>
<tr>
<td>MCC</td>
<td>80%</td>
<td>80%</td>
<td>70%</td>
<td>60%</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>Nicotinamide Side</td>
<td>Glucose</td>
<td>40%</td>
<td>10%</td>
<td>30%</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>MCC</td>
<td>40%</td>
<td>70%</td>
<td>50%</td>
<td>60%</td>
<td>70%</td>
<td>80%</td>
</tr>
</tbody>
</table>

10.1.2.2 Tablet compaction

The powders were all ground down and sieved to particle sizes of less than 90 µm, and then mechanically mixed. For the purpose of compaction a custom designed compaction cell was created as shown in Figure 10-1. The cell consisted of three sections:

1. The cell block, which was a square piece of metal with a 3 mm × 2 mm section cut out of it for inserting and compacting the tablet powders.
2. The punch, a 3 mm × 2 mm rectangular punch.
3. The faceplate, which bolted onto the face of the compaction cell to create the compaction chamber, and could be removed, simplifying extraction of the tablets.

The tablets created by the cell were 3 mm wide and 2 mm deep, with each half of the tablet weighing 10 mg.
The tablets were compacted with a total pressure of 120 MPa, however, in order to ensure good adherence of the tablet sections the pressure was applied in stages. The first section of the tablet was compacted with 60 MPa, then the powder for the second section of the tablet was added and everything was compacted to 120 MPa.

10.1.2.3 FTIR spectroscopic imaging

The FTIR images were acquired with a 64 × 64 FPA detector with 8 cm⁻¹ spectral resolution and 32 scans co-addition. The Golden Gate™ diamond ATR accessory (Supercritical Fluid Analyser, Specac Ltd., UK) was used. The field of view was 690 μm × 610 μm as shown in Column 2 Table 5-2. An FTIR microscope with a Ge objective was also used for checking the integrity of the interface, it was a 64×64 FPA detector with an image area of approximately 64 μm × 64 μm as described in column 5 of Table 5-2.

The characteristic bands use for generating the images were as follows: buflomedil: 1166 – 1088 cm⁻¹, nicotinamide: 1412 – 1374 cm⁻¹, glucose: 922 – 903 cm⁻¹, MCC: 1026 – 1010 cm⁻¹, water: 1665 – 1620 cm⁻¹.

10.1.2.4 Dissolution procedure

A transparent Perspex dissolution cell was used. The tablets were compacted ex situ, they were then placed on the imaging crystal and the Perspex dissolution cell bolted into place on top. The tablets were positioned such that the FTIR image produced was of the
interface between the layers while also showing some of the dissolution medium as shown in Figure 10-2. Images of the dissolving tablet were acquired every 2.5 minutes throughout the duration of the experiments. The dissolution medium used was deionised water and the flow rate was set to 1 ml/min.

![Image](image.png)

**Figure 10-2.** Position of tablet relative to ATR diamond and the images produced using this arrangement. The images show one drug on the left of the image, and the other on the right. The top half of the images is left empty in order to show the dissolution medium.

### 10.1.3 Results and discussion

#### 10.1.3.1 Compaction validation

In order to verify that the custom compaction cell had formed tablets with a defined interface and consistent structure, both FTIR imaging and X-ray tomography were used to study the interface.

![Image](image.png)

**Figure 10-3.** Non-uniform tablet interface

It was found, following the initial compaction procedure that the interface produced was not straight as shown in Figure 10-3. This was a result of the compaction face of the
punch not being completely flat. Due to the relatively small imaging area used, this non-uniformity manifested in the FTIR images which are aligned at the interface of the tablet sections, as seen in the first row of images in Figure 10-4. Therefore it was necessary to manually adjust the interface to be straight.

![FTIR images of tablet interface showing before correction (row 1) and after correction (row 2). In the formulations used for dissolution, the polymer in each half of the tablet was MCC, however, in order to highlight the interface, one half of this tablet was made using HPMC as the polymer. Image size is 690 µm x 610 µm.](image)

The interface of the tablet was straightened using a razor blade. After the first section of the tablet had been compacted, the faceplate of the cell was removed and the blade was used to cut away excess material. The tablets were weighed before and after and the loss due to cutting was approximately 2% of the mass of the tablet.

![X-ray image of bilayer tablet. Denser parts of the tablet are darker in colour.](image)
Figure 10-5 shows both halves of the tablet, the section which appears as the lower half of the tablet in the image was intentionally compacted using 80% of the force of that used on the upper half in order to produce contrast for the X-ray data. The data demonstrate that a tablet with relatively uniform density in each section was formed.

![Figure 10-5](image)

**Figure 10-5.** Shows both halves of the tablet, the section which appears as the lower half of the tablet in the image was intentionally compacted using 80% of the force of that used on the upper half in order to produce contrast for the X-ray data. The data demonstrate that a tablet with relatively uniform density in each section was formed.

The data demonstrate that a tablet with relatively uniform density in each section was formed. The interface shown in Figure 10-5 is relatively sharp, although some gradient can be seen. This is because the spatial resolution of the X-ray microtomograph was relatively low (~80 µm (Kohout et al., 2006)), as shown in Figure 10-6. In order to study the particles at the interface with higher spatial resolution, it was necessary to use the infrared microscope. These data are shown in Figure 10-7.

![Figure 10-6](image)

**Figure 10-6.** Density profile through interface of tablet shown in Figure 10-5. Interface is shown by step change in density between 300 and 400 µm on the x-axis.

The interface shown in Figure 10-5 is relatively sharp, although some gradient can be seen. This is because the spatial resolution of the X-ray microtomograph was relatively low (~80 µm (Kohout et al., 2006)), as shown in Figure 10-6. In order to study the particles at the interface with higher spatial resolution, it was necessary to use the infrared microscope. These data are shown in Figure 10-7.

![Figure 10-7](image)

**Figure 10-7.** FTIR microscope images of tablet section interface. Image size is approximately 64 µm x 64 µm, with spatial resolution 4 µm. This tablet was created using MCC as the polymer in the right of the images and HPMC in the left of the image. The images were generated based on the absorbance of MCC in the range 961 – 924 cm⁻¹.

The microscope images in Figure 10-7 show a well defined interface between the two sections of the tablet with no intermixing seen. The deviation at the bottom of the
second image was purely a result of the interlocking geometry of the particles which had all been sieved down to < 90 µm in size.

10.1.3.2 Dissolution of Tablets A and B

As described in Section 10.1.2.1 the tablets were designed to release two different readily soluble drugs, buflomedil and nicotinamide, although nicotinamide is more soluble than buflomedil. The rest of the bulk of the tablets consisted of microcrystalline cellulose (MCC) and glucose. The MCC was used to slow tablet dissolution due to its low solubility and good binding properties, whereas the glucose was used as a highly soluble agent, which expedited water ingress and caused the tablet to breakup more rapidly. Each tablet contained buflomedil in one half of the tablet and nicotinamide in the other and as such the halves of the tablet will be referred to as either the nicotinamide or buflomedil sections.

As shown in Figure 10-2 the tablet was positioned such that the imaging area showed the interface between the tablet sections and the edge of the tablet. This allowed investigation of how the two drug release mechanisms proceeded simultaneously and their interactions with each other.

Although a full range of formulations was tested, the data for Tablets A and B will be presented in detail (highlighted in Table 10-1). These formulations represent the extremes of the formulation range. Tablet A had a low loading of glucose in the buflomedil section of the tablet, while the nicotinamide section had a high loading of glucose. This formulation should highlight the effect of interference between the behaviour of the tablet sections. Tablet B contained a relatively low loading of glucose in both sections of the tablet and so serves to compare against the performance of Tablet A.
Figure 10-8 shows the dissolution of buflomedil, nicotinamide and glucose from the matrix of Tablet B. It is clear from the images that the buflomedil was entirely located in one half of the tablet while the nicotinamide was clearly confined to the other half. It is also seen that the glucose was distributed in the nicotinamide half of the tablet as would be expected by the formulation’s constitution. The nicotinamide dissolved slightly faster than the buflomedil. This was approximately in line with the dissolution of the glucose from the tablet.

In Figure 10-9 the dissolution of the drugs and glucose from Tablet A’s matrix can be seen. This formulation had a high loading of glucose in the nicotinamide section of the tablet. It appears in the images as though there is less nicotinamide in the sample than buflomedil. This was actually not the case, as shown by in Table 10-1 there was an equal loading of both drugs. The uneven distribution of the nicotinamide was a result of the mechanical mixing of the formulation, of which this image only displays a small portion.
Figure 10-9. Dissolution of nicotinamide, buflomedil and glucose from Tablet A. Buflomedil side – glucose: 0 wt% / MCC: 80 wt%, Nicotinamide side – glucose: 40 wt% / MCC: 40 wt%. Image size is 690 µm × 610 µm.

It is immediately apparent from the data that the nicotinamide dissolved out of the matrix very rapidly; there was nothing left of the nicotinamide in the imaging field of view after five minutes. This was much faster than the buflomedil in the other section of the tablet, or the nicotinamide in Tablet B.

The buflomedil section of the tablet was not completely unaffected by this and indeed the buflomedil did dissolve more rapidly. The buflomedil in tablet A only required 20 minutes to completely dissolve whereas 40 minutes were required for dissolution of buflomedil from Tablet B. These data indicated that the high loading of glucose in Tablet A not only increased the dissolution rate of the nicotinamide, but also increased the dissolution rate of the buflomedil. In order to fully understand why this difference occurs it is necessary to investigate the behaviour of the water and polymer components of Tablets A and B.
The dissolution of the polymer shown in Figure 10-10 shows that the microcrystalline cellulose swelled slightly. It also reveals that a channel in the nicotinamide half of the matrix opened up towards the end of the dissolution. If compared to glucose dissolution in Figure 10-8 it can be seen that this region corresponds to a void created in the matrix by the dissolving glucose. The images in row 2 of Figure 10-10 show that this void promoted the ingress of water into the tablet bulk, expediting the dissolution of the nicotinamide. As for the ingress of water it is clear that in this tablet the water ingressed into the more soluble nicotinamide half (containing the glucose) more rapidly than into the less soluble section. Indeed it appears that the water ingress rates for each section were relatively decoupled.

**Figure 10-11.** Polymer dissolution and water ingress for tablet A. Buflomedil side – glucose: 0 wt% / MCC: 80 wt%, Nicotinamide side – glucose: 40 wt% / MCC: 40 wt%. Image size is 690 \( \mu \text{m} \times 610 \mu \text{m} \).
The dissolution performance seen in Figure 10-11 was significantly different to that seen in Figure 10-10. While the polymer did still undergo some expansion on the less soluble side of the tablet, it can be seen that by the end of the experiment the polymer in the nicotinamide section of the sample had been severely eroded. The buflomedil section of the tablet had somewhat more eroded compared to Tablet B.

The greater level of disintegration was due to the greatly increased rate of water ingress. As would be expected water ingress happened much more rapidly on the nicotinamide half of Tablet A, however, faster water ingress was also seen in the buflomedil section relative to the buflomedil section of tablet B. In Tablet B the water ingress in each half of the tablet appeared quite independent. Whereas in Tablet A, probably due to the longer period for which the tablet interface was wetted, there was a significant movement of water moved across interfacial line into the buflomedil section. This had the effect of significantly increasing the rate of overall water ingress into the buflomedil section.

As the increase in glucose loading increased the rate of water ingress, which ultimately led to faster disintegration of the tablet, it is important to compare the water ingress rates for the two formulations in both tablet halves. As seen in Figure 10-11 there was lateral movement of the water within the tablet matrix. Therefore it was not possible simply to record the time taken for ingressing water to reach the top of the imaged area. Water ingress was measured by the wetted fraction of the matrix. This was calculated based on the initial area of the tablet section before the initiation of dissolution and the remaining unwetted area at each timepoint. Wetted was defined as the point at which the intensity of the water band between 1665 – 1620 cm$^{-1}$ reached 50% of the maximum value of the band in the lower half of the image in which there was no polymer. The results of this analysis are shown in Figure 10-12.
Figure 10-12. Comparison of wetted fraction for the buflomedil and nicotinamide sections of Tablets A and B. Data generated by extracting the wetted area as a function of time from Figures 6 and 7.

Figure 10-12 clarifies the various rates of water ingress seen in Figure 10-11 and Figure 10-10. The most significant difference between the formulations was that the rate of water ingress into the nicotinamide section of the tablet was greatly increased in Tablet A over Tablet B. This led to approximately a 50% reduction in the time required for water ingress to cover the entire visible area of the tablet half.

It is also seen from Figure 10-12 that the increase in the amount of glucose in the nicotinamide side of the tablet had a significant effect on the buflomedil dissolution. Indeed the 40% increase in the rate of water ingress into the buflomedil half of the tablet from Tablet B to Tablet A was almost as much as that for the nicotinamide half. This was because as can be seen in Figure 10-10 and Figure 10-11, the increased water ingress in the nicotinamide section of Tablet A almost doubled the wetted perimeter of the buflomedil section.

These data have shown that the rate of the dissolution of the two drugs in these formulations can be controlled. Most importantly though, it has shown the importance of gathering ATR-FTIR images with high chemical specificity and spatial resolution at the interfacial region of the tablets for the assessment of the dissolution of such formulations.
10.1.3.3 Dissolution performance summary

Following the detailed comparison of Tablets A and B it is important to analyse the behaviour of the rest of the formulations from Table 10-1. The data plotted in Figure 10-13 are the time taken for total water ingress into a tablet section and the time taken for total dissolution of the drug from that section for formulations A, C-F. Complete water ingress was defined as the time at which the wetted fraction of that tablet half reached 1. Complete drug dissolution was defined as the point at which the maximum absorbance of the drug in the image was less than 20% of the maximum absorbance value in the dry image.

The graph in Figure 10-13 illustrates that the rate release of each drug was controlled despite the interference seen in Figure 10-11. The concentrations of glucose for the formulations in Figure 10-13 varied inversely such that when the glucose loading in the buflomedil section was low, it was high in the nicotinamide section and vice versa.
Overall the nicotinamide dissolved much faster than the buflomedil due to it being more soluble, hence the dissolution times for both drugs are plotted on separate axes. Tablets A and F had a 40 wt% loading of glucose in one tablet section and a 0 wt% loading in the other. Therefore these formulations posed the greatest chance for interfacial interference, as one half dissolved rapidly potentially leaving the internal face of that tablet section exposed to the dissolution medium. Nonetheless the dissolution rate of the drug was controlled across the range of formulations with the maximum release rate for each drug seen with the highest glucose loading and conversely the slowest release seen with the highest loading.

The glucose, despite being in the same loadings as the buflomedil halves, had a less significant effect on the rate of dissolution due to the high intrinsic solubility of nicotinamide. Indeed there was no significant change in the dissolution performance of nicotinamide until the glucose loading reached 30 wt%.

It is clear from Figure 10-13 that, as expected for two soluble drugs, the time taken for the drugs to dissolve and the time taken for the water to ingress across the whole of the imaged area for the tablets were linked, as both sets of curves are roughly parallel. Indeed for the nicotinamide the curves are overlapped for all but a zero loading of glucose. This indicates the nicotinamide dissolved almost instantaneously (within the sampling rate of the images) upon contact with the dissolution medium. The match was less exact for the dissolution of buflomedil; there was a consistent lag of approximately 5 minutes between complete water ingress and complete dissolution of the drug.

The FTIR imaging data here demonstrate the applicability of this approach to studying these formulations. This work has shown that FTIR imaging can study the release of these two drugs from the tablet simultaneously. It has also shown that FTIR imaging has provided important information concerning the complex break up mechanisms of these structured formulations, such as cross-diffusion of the dissolution medium and identifying the dissolution front of the drug.
10.1.4 Conclusions

ATR-FTIR spectroscopic imaging has been successfully applied to study the release of drugs from multilayer formulations. Bilayer tablets were applied to study biphasic release of drugs. It was found that FITR imaging served as a useful approach for effectively studying the complex process of water ingress into structured formulations where the dissolution performance of one side could have an effect on the performance of the other.

In formulations with high loadings of glucose in one half of the tablet and low loadings in the other, the increased rate of water ingress into the more soluble section of the tablet caused it to dissolve rapidly. The high rate of dissolution increased the surface area of the less soluble section exposed to high concentrations of the dissolution medium. This led to an increased rate of dissolution being seen from the slow release section.

It was also established that despite the level of interfacial interference a sufficient degree of control could be achieved in order to control the dissolution rate of each section independently.
10.2 Zero-order release

10.2.1 Introduction

The USP industry standard dissolution tests are the most commonly used approaches for assessing the dissolution profiles of formulations in pharmaceutical science (Achanta et al., 1995). These important tests were specifically designed as a necessary step in determining drug bioavailability and product performance (Cohen et al., 1990).

The biphasic release studies showed ATR-FTIR imaging is an approach which can obtain direct insight into the complex drug release mechanisms and water ingress through structured tablets. However, such a layered structure can also produce tablets which exhibit zero-order release profiles. Colombo et al. (Colombo et al., 1990) achieved a close to linear release profile by applying impermeable barrier coatings to the top and bottom face of HPMC based tablets to control the direction of swelling, restricting changes in the surface area for release. Further work found that manually applied film barriers could be replaced in favour of swellable HPMC barriers that would swell with the core maintaining the surface area of the exposed core (Conte et al., 1993).

While FTIR imaging has great potential for studying the release of drugs from tablets, it is still a relatively specialised niche option for studying tablet dissolution. One of the reasons for this is that it is hard to compare the release data gathered from this method to that obtained from the industry standard USP dissolution tests. The major differences are found in the flow regimes and the geometry in the systems. The USP I and USP II type apparatuses are stirred tank systems, whereas the custom ATR dissolution cell is a flow-through system (van der Weerd and Kazarian, 2004b). In the USP systems the tablet is exposed to the dissolution medium on all sides, whereas in the ATR flow cell it is sandwiched top and bottom restricting the surface area, similar to a barrier layered tablet.

This section of work for the first time links the UV/Vis dissolution profile data that can be gathered from the apparatus, to the industry standard dissolution tests.
10.2.2 Materials and methods

10.2.2.1 Monolithic/barrier layer tablet formulations

A monolithic tablet and a barrier layer tablet were constructed for dissolution in USP I type apparatus; the formulation of the core of the barrier layer tablet was the same as the monolithic tablet: 45 wt% buflomedil (Lisapharma SpA, Italy), 35 wt% HPMC K4M (Colorcon, UK), 20 wt% MCC (Merck Sharp & Dohme, UK). The tablets were compacted to be 10 mm in diameter, the monolithic tablet and the middle section of the multilayer tablet weighed 222 mg. The barrier layered tablet also had two outer layers of HPMC (100 mg each) compacted onto the flat faces of the middle section. These formulations are shown in Figure 10-14.

![Figure 10-14 Formulations used for studies dissolution in USP I apparatus. a) Barrier layer formulation with cutaway showing ingredients of each layer b) Monolithic tablet formulation.](image)

For comparison a tablet with the same percentage component loadings as the monolithic tablet above was dissolved using the FTIR flow-through apparatus. This tablet was 3 mm in diameter and contained 7 mg of buflomedil.

10.2.2.2 FTIR imaging

The FTIR imaging equipment used for this work was the same as that described in Section 10.1.2.3. The formulations were positioned differently as seen in Figure 10-15. The tablets were positioned, such that the tablet half covered the diamond.
10.2.2.3 Dissolution procedures

The larger tablets were then dissolved using a USP I dissolution test with rotation speed set to 50 rpm. The smaller tablet was dissolved in the ATR flow cell at two flow rates, 1 ml/min and 9 ml/min. Rather than using the two pump configuration shown in Figure 5-11, the single pump system as used, as shown in Figure 5-12.

10.2.3 Results and discussion

10.2.3.1 FTIR and USP dissolution procedures

As the USP dissolution tests are the standard and most widely used dissolution tests throughout the industry, it is important to compare the dissolution performance of the dissolution cell apparatus used with the ATR-FTIR imaging approach with standard USP dissolution apparatus.

The differences between the methodologies are highlighted in the schematic diagrams of the ATR flow cell and USP I dissolution apparatus, which are shown in Figure 10-16. In the ATR flow cell, the tablet is sandwiched between the Perspex cell and the ATR diamond, while a rubber ring is used to seal the system, so the tablet is only exposed to the medium on its vertical side. In the USP I dissolution apparatus, the tablet is placed in the basket and is rotated during the whole dissolution test, so the tablet is totally exposed to the medium.
Figure 10-16. Comparison of design of USP dissolution cell and ATR flow through cell. The tablet in the FTIR dissolution cell is sandwiched between the cell and the diamond plating creating two barriers, whereas the tablet in the USP system is by virtue of the wire mesh of the basket, exposed on all sides to the dissolution medium.

It has been demonstrated that tablet geometry plays a significant role in governing the dissolution profile of a drug from a tablet (Conte and Maggi, 1996, Kim, 1995). As can be seen in Figure 10-16 the effective geometry of the tablet in each case is significantly different, which should manifest itself in distinct differences in the dissolution profile. The Perspex cell and the diamond plating in the ATR flow cell can be approximated as barrier layers which have in particular been used for establishment of zero-order release profiles (Colombo et al., 1990) with swellable polymers in place of the hard surfaces. Therefore dissolution of a monolithic tablet, with a similar composition to the middle section of a barrier layered tablet designed to produce zero-order release in the USP dissolution apparatus, may be expected to yield a release rate which tends towards constant in the ATR flow cell with the correct flow conditions.

10.2.3.2 Dissolution of formulations in USP I

The first step was to construct and dissolve a monolithic and a barrier layer tablet in the USP I dissolution apparatus. The formulations used are shown in Table 10-2.
Table 10-2. USP I dissolution tablet formulations.

<table>
<thead>
<tr>
<th></th>
<th>Buflomedil</th>
<th>HPMC</th>
<th>MCC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monolithic Tablet</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constituents (wt%)</td>
<td>45</td>
<td>35</td>
<td>20</td>
</tr>
<tr>
<td><strong>Layered tablet</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Core Constituents (wt%)</td>
<td>45</td>
<td>35</td>
<td>20</td>
</tr>
<tr>
<td>Barrier Constituents (wt%)</td>
<td>-</td>
<td>100</td>
<td>-</td>
</tr>
</tbody>
</table>

The monolithic tablet contained a soluble drug mixed with a swellable matrix of HPMC, a formulation which should have resulted in a tablet exhibiting a non-linear release profile for the drug (Lapidus and Lordi, 1966), while the addition of swellable barriers to the outside of the layered tablet should have yielded a more linear release profile (Conte et al., 1993).

![Figure 10-17](image)

**Figure 10-17.** UV/Vis dissolution profiles for monolithic and barrier layer tablets in USP I dissolution apparatus. The data in this graph were also fitted using the model in Equation 10-1.

The data for the monolithic tablet in Figure 10-17 show as expected a non-linear release profile, whereas the release profile for the barrier layer tablet exhibited a significant shift towards constant release rate of the drug. These data are in good agreement with dissolution profiles seen in other studies using similar formulations (Colombo et al.,...
1990, Conte et al., 1993). The release rate of the barrier layered formulation was also obviously much reduced as the surface area exposed to the dissolution medium was much smaller. The dissolution profile from the ATR flow cell would be expected to be more similar to the barrier layer tablet than the monolithic sample.

### 10.2.3.3 Dissolution of tablets in ATR flow cell

The formulations tested for dissolution in the ATR flow cell had the following composition: 45 wt% buflomedil, 35 wt% HPMC, 20 wt% MCC and had a total mass of 15 mg.

![Graph](image)

**Figure 10-18.** UV/Vis dissolution profiles for tablets dissolving in ATR flow cell at low flow rate (1 ml/min) and high flow rate (9 ml/min). The data in this graph were also fitted using the model in equation 1.

The dissolution in the ATR flow cell was performed at two different flow rates. A low flow rate of 1 ml/min still resulted in a rather non-linear dissolution profile; however, an increase in flow rate to 9 ml/min caused the release rate to shift towards constant as shown in Figure 10-18.
10.2.3.4 Modelling of dissolution profiles

The data from these experiments were fitted using a model developed by Peppas and Sahlin which separated the Fickian and non-Fickian components of release, shown in Equation 10-1 (Peppas and Sahlin, 1989).

\[
\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m}
\]

Equation 10-1

Where the term on the left hand side is the fraction of drug released at time \( t \) and the first term on the right hand side describes the Fickian contribution to dissolution and the second term describes the relaxational (non-Fickian) contribution. This equation has its limitations as it fails to take into account the effects of moving boundary conditions; it is a simplistic model, but can give an indication as to the level of contribution from each, via the magnitude of the \( k_1 \) and \( k_2 \) terms. The \( m \) term is the diffusion exponent and is dependent on the aspect ratio of the sample, with the value for cylindrical samples, such as the monolithic tablet dissolved in the USP I apparatus, being 0.45 (Peppas and Sahlin, 1989). The tri-layered tablets and those in the ATR flow cell had restricted geometries, therefore the value for the cylinder was no longer appropriate. Indeed these formulations were closer to slab geometries and so a value of 0.5 was used for \( m \). The \( k \) values for the fitted curves in Figure 10-17 and Figure 10-18 are shown in Table 10-3.

Table 10-3. Summary of \( k \) values for fitted dissolution curves

<table>
<thead>
<tr>
<th></th>
<th>( k_1 )</th>
<th>( k_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>USP Dissolution</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monolithic fit</td>
<td>0.16</td>
<td>0.094</td>
</tr>
<tr>
<td>Tri-layer fit</td>
<td>0.00024</td>
<td>0.0362</td>
</tr>
<tr>
<td><strong>FTIR-ATR Flow Cell</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low flow-rate fit</td>
<td>0.11</td>
<td>0.044</td>
</tr>
<tr>
<td>High flow-rate fit</td>
<td>0.0045</td>
<td>0.11</td>
</tr>
</tbody>
</table>

From Table 10-3 it can be seen that for the monolithic tablet the Fickian term was large indicating that it was diffusion of drug out of the tablet that was the dominating process for release. However, as this was a swelling and eroding tablet, there was a significant contribution from the polymer relaxation term. For the tri-layer tablet the results were
markedly different, as would be expected for the data which so closely approximates a straight line, the Fickian contribution was small compared to the non-Fickian term, indicating the relaxational contribution dominated.

The results from the ATR flow cell were similar to those from the USP dissolution apparatus, the low flow system produced a largely diffusion dominated result, while the high flow rate system produced a release profile in which release was controlled more by the relaxational term. Direct comparison of $k$ values is not possible as the units are not the same, $k_1$ has units of $s^{-m}$ and $k_2$ has units of $s^{-2m}$. Therefore a better way to compare the dissolution data are to use Equation 10-2 which plots the fraction of release due to Fickian diffusion (Peppas and Sahlin, 1989), the results of which are shown in Figure 10-19.

$$F = \frac{1}{1 + \frac{k_2}{k_1} t^m}$$  \hspace{1cm} \text{Equation 10-2}

![Graph showing fraction of drug released by Fickian diffusion against total drug released. This graph illustrates the relative importance of the drug release mechanisms to the linear and Fickian release profiles. The fit of the model is only valid up to 60% release.](image)

The release of the drug from the zero-order formulations shown in Figure 10-19 was much more dependent on polymer relaxation. The release of the drug from the non-
zero-order formulations relied significantly more on Fickian diffusion to release the drug. However, for the non-zero-order formulations, it can be seen that over time the contribution of Fickian diffusion dropped significantly over the course of the dissolution of the tablets. At the beginning of the dissolution the release was diffusion controlled as there had been little swelling, so this was the rate determining feature. However, once matrix swelling occurred the regime of release shifted towards being swelling controlled as the drug was released from the relaxing polymer matrix (Siepmann and Peppas, 2001), it is this which caused deviation from the standard square root of time kinetics (Korsmeyer et al., 1983, Urtti et al., 1985).

10.2.3.5 Zero-order release from barrier layered tablet

The mechanisms producing zero-order release for the barrier layer tablet and the ATR flow cell at high flow rate were not identical, although the similar geometries played a role in producing similar release profiles. The barrier layers of the tri-layer tablet in the USP dissolution apparatus initially reduced the surface area for interaction of the drug and the dissolution medium and therefore the rate of water ingress into the core (Conte et al., 1993, Conte and Maggi, 1996). The barrier layers restricted the swelling of the core to being primarily in the axial direction. Following this, as the polymers began to gel, swelling and erosion processes started to dominate. The core of the barrier layer tablet swelled leading to an increase in the diffusion path length of the drug through the swollen polymer slowing drug release. This was partially limited by erosion of the gel layer while the polymer barrier layers also began to erode, increasing the area of the core exposed to the dissolution media. These two effects counterbalanced the increased diffusion path length and as the effects were controlled and balanced correctly it was possible to generate zero-order release (Conte et al., 1993).

10.2.3.6 Dissolution of monolithic tablets in the ATR flow cell

In the case of the ATR flow cell, while the flow cell and diamond plating acted as barrier layers, they were not erodible as in the case of the HPMC in the barrier layers; therefore the mechanism for maintaining zero-order release was slightly different. While the barriers still had the same effects as the swellable barriers, of restricting water ingress and resulting in only axial swelling, they did not erode. Therefore erosion of the
radially swelled gel surrounding the core was more important, which is why zero-order release was only seen at higher flow rates when the rate of gel erosion was higher. This maintained the effective thickness of the gel layer through which the drug had to dissolve as being roughly constant with respect to time, resulting in a close to zero-order profile (Möckel and Lippold, 1993). It is for this reason that at a low flow rate, zero-order release was not achieved, as there was little erosion of the gel layer and so the diffusion path length became increasingly long for the drug.

A comparison of the effects on polymer swelling can be seen in Figure 10-20. The increased flow rate, shown in the second row of images, is seen to erode the polymer faster than the lower flow rate, as total dissolution of the polymer from the field of view occurred about an hour earlier in the high flow-rate system.

![Figure 10-20. FTIR images of dissolution of tablets in ATR flow-cell at low and high flow rates. The data show the initial 15 minutes of swelling ad gel formation, and the last 3 hours of final erosion of the swollen gel. Image size is 690 µm x 610 µm.](image)

Dissolution in the FTIR-ATR flow cell does share some similarities with the dissolution profile features of barrier layered tablets. While the mechanisms responsible for the zero-order release were not identical, the similarities between the geometries of the two systems were important. At low flow rates the level of Fickian diffusion involved in drug release was very similar to that of a monolithic tablet, whereas at high flow rates the dissolution profile did shift towards being linear.
10.2.4 Conclusions

In this section of this chapter zero-order release formulation were explored as an analogue to the constricted geometry of the ATR-FTIR flow through system. The barrier layered formulations exhibited a similar geometry to the custom ATR flow through cell. The ATR flow through dissolution cell had the dissolution cell and diamond plating above and below the tablet. These acted as barrier layers similar to those seen in zero-order release formulations

Based on the comparison of the levels of Fickian and non-Fickian release from the formulations studied in this section of the chapter, it was found that in low flow-rate conditions the dissolution performance of a tablet in the ATR flow cell did not differ significantly the performance of a monolithic tablet in a standard USP dissolution apparatus. The Fickian and non-Fickian contributions to the drug release mechanism were in roughly equal magnitude. However, it was found that higher flow-rates the dissolution performance did shift towards that of a barrier layered zero-order release formulation due to an increase in the role played by polymer gel erosion.
CHAPTER ELEVEN

CONCLUSIONS AND FUTURE WORK
11 Conclusions and Future Work

11.1 Conclusions

The results presented in this thesis discussed novel applications of FTIR imaging to the study of pharmaceutical formulations. The work contains three major research themes:

1. Validation of the approach, through the use of complementary techniques and comparison with existing methodologies.

2. ATR-FTIR imaging was applied to study the dissolution of pH modified, biphasic and delayed release formulations.

3. The novel application of ATR-FTIR imaging to study tablets with multilayer and tablet-in-tablet structures.

FTIR spectroscopic imaging is a powerful and versatile analytical approach for which the potential applications to studying pharmaceuticals have yet to be fully realised. This work sought to exploit the chemically specific and spatially resolved information provided by ATR-FTIR imaging to study model tablets. The ability to use this approach with complementary techniques such as UV/Vis spectroscopy and X-ray microtomography was also leveraged where applicable.

The work began with studies of tablet compaction, where it was found that the compaction of lactose can be improved by the presence of caffeine particles. Statistical analysis of the FTIR imaging data demonstrated that ATR-FTIR imaging was also able to reveal changes in the distribution of the components in matrices based on HPMC and MCC. This work has shown the applicability of FTIR imaging to study the effects of formulation and compaction pressure on component distribution and the density of the compacts.

It was also shown that X-ray tomography can be used in conjunction with FTIR imaging to produce a density map of the tablets that verifies the data from the FTIR imaging. As X-ray tomography can only differentiate components based on density, this
necessitated the use of simple two component systems. Analysis of tablets with many components required the use of a technique with greater chemical specificity.

A more thorough analysis of compacted tablets was then conducted, in which two aspects of the tablet properties were investigated: the relationship between component loading and observed component fraction at the surface layer with varying particle size and the ability of ATR-FTIR imaging to determine particle size. A model two component system consisting of paracetamol as the minor and caffeine as the major component was studied. When the particle size of paracetamol was smaller than that of the caffeine, the surface area fraction paracetamol was over estimated relative to component loading, whereas when the particle size of paracetamol was larger than that of the bulk, the surface area was an underestimate compared to the overall volume fraction. It was also determined that ATR-FTIR imaging is capable of differentiating samples based on differences in particle size. However, it was found that the accuracy of this information was highly sensitive to the loading of drug in the sample, and analysis parameters such as the thresholding values used for image processing.

By adding basic and acidic pH modifiers to HPMC based ibuprofen tablets, it was shown that the solubility of the drug within the matrix could be adjusted. Acidic additives lowered the pH, slowing the dissolution of the drug. The basic additives reacted with the acidic drug to both increase and decrease the rate of dissolution through the formation of salts. This was the first time that salt formation had been seen within the matrix as a result of micro-environmental pH modification using FTIR imaging. The retention of the pH modifiers for the length of the dissolution experiments was also verified, through the use of a visible imaging using a CCD camera to monitor the dissolution and the addition of universal indicator to the matrix.

The next section of work investigated tablet-in-tablet structures to create delayed release and pH resistant formulations. For the delayed release formulations studied, two release mechanisms were seen. For the first mechanism, lag-time was dependent upon disintegration of the shell section of the tablet. For the second type of release mechanism, lag-time was determined by the time taken for the dissolution medium to reach the core and also by the resulting expansion of the core which then broke through the shell section. FTIR imaging accurately monitored the swelling of the HPMC core
and was used to determine the point at which water ingress reached the core. This work represented the first application of FTIR imaging to studying structured tablets. Although these were model tablets, this work indicates that FTIR imaging can provide information which could help design formulations exhibiting fine control over the release point of the drug providing highly targeted delivery.

Using the information gathered studying tablets containing pH modifiers, a formulation was developed which was designed to mitigate the solubility issues of ibuprofen in low pH environments. FTIR spectroscopic verified the ability of this formulation to minimise ibuprofen crystallisation by monitoring presence of the crystalline form of the drug. Complementary analytical approaches were used to check the structure of the resulting tablets and confirmed the neutralisation of the acidic dissolution media. The PEG based core maintained the drug in a molecularly dispersed state, while the pH modified HPMC shell raised the solubility of the drug and provided controlled release. This formulation served as a model, the concepts of which could be applied to the delivery of other NSAIDs and pH labile compounds. The principles employed in this formulation could help to reduce the side effects of long term use of NSAIDs such as stomach ulcers by minimising the amount of crystalline material deposited in the gut.

Continuing the theme of studying structured tablets, bilayer tablets were studied. ATR-FTIR imaging was able to monitor the progression of water into structured tablets, the independent breakdown of the sections and the influence that the dissolution performance of one section had on the adjacent section. HPMC based barrier layered tablets were also used to replicate some aspects of the dissolution cell geometry in a USP I type apparatus. At low flow-rate conditions the dissolution performance in the ATR flow cell was similar to the performance of a monolithic tablet in a standard USP dissolution apparatus. At higher flow-rates the dissolution performance did shift towards that of a barrier layered zero-order release formulation due to an increase in the role played by polymer gel erosion.

To conclude, the chemical specificity and imaging capabilities of ATR-FTIR imaging have been used in conjunction with a number of complementary approaches to investigate a range of model pharmaceutical formulations. The applicability of the approach to studying pharmaceutical formulations has been further demonstrated.
through studies of compacted pharmaceutical formulations. This has highlighted the fact that image data gathered at the surface layer is representative of the bulk as long as certain assumptions are considered. Previous work highlighting the utility of ATR-FTIR imaging to studying poorly soluble drugs has been extended by investigating the mitigation of these issues. Structured model tablets were then investigated to demonstrate the power of leveraging spatially resolved nature of the data acquired to study the dissolution of these formulations. The data presented in this thesis have furthered the investigation of using FTIR imaging to study the compaction and dissolution of pharmaceutical formulations for the future.

11.2 Future work

The main goal of this thesis has been to further the application of FTIR imaging to pharmaceutical formulations through the use of model tablets. This work could also serve as a platform for new investigative opportunities in this field, potentially providing new insight into pharmaceutical technologies. Through the continued development of this approach to study pharmaceuticals, FTIR imaging is fully capable of becoming an important tool for product development to the pharmaceutical industry. Some recommendations for future research based on this work are outlined below.

- In order to confirm the mechanisms behind changes seen in the surface area fraction of the components and particle sizes, it would be useful to combine the experimental data with modelling. A particle packing algorithm combined with a discrete element based particle deformation model could help to explain the processes of particle arrangement and compaction during the tabletting process at the surface layer of the tablet.

- A logical continuation of the work regarding the solubility of ibuprofen would be to study ibuprofen dispersed in polymers such as polyethylene glycol (Kazarian and Chan, 2003) or complexed with cyclodextrins (Mura et al., 1998) mixed with a controlled release polymer such as HPMC. This work could also be extended to study other NSAIDs such as flurbiprofen and ketoprofen.

- The tablet-in-tablet structure was effectively applied to create controlled release and pH resistant formulations. Ideally these properties could be combined with
targeted drug delivery through the application of enteric coatings (Weiβ et al., 1993).

- The bilayer tablet structure was used to demonstrate the capability of FTIR imaging to simultaneously study the dissolution of two drugs and monitor the effects of water ingress. An interesting study would be to place components in each half that may react at the tablet interface upon wetting, before proceeding to investigate methods to minimise the issue, such as an intermediate layer or enteric coatings.

- Polymorphic transitions present a significant problem to the pharmaceutical industry. It is possible to detect these transitions using FTIR imaging as shown for ibuprofen. Various aspects of the environment can be controlled in situ, such as temperature, humidity and compaction pressure. It is also possible to study the stability of drugs in their final product form within the tablet matrix in order to determine formulation stability. It would be advantageous to carry out this process on multiple samples simultaneously. High throughput methodologies offer the opportunity to do this (Chan and Kazarian, 2006d). High throughput applications could also be extended to study flowing dissolution of multiple samples. This would require the design of a custom multichannel dissolution system constructed from a material such as PDMS.

- When studying tablet-in-tablet structures in order to preserve the spatial resolution of the images, only the interfacial region was studied, while video analysis was used to provide a global view. Larger crystals such as zinc selenide and silicon in accessories with expanding optics could be applied to investigate the entire tablet structure in each image (Chan and Kazarian, 2006a).

- An important factor in the dissolution of drugs is the dissolution medium used. In order to more closely mimic the in vivo performance of a drug, the use of more biorelevant media such as FeSSIF and FaSSIF would be applicable (Aiache et al., 1997). Indeed an advantage of the flow through dissolution system primarily used in this thesis, is the option to vary the dissolution medium throughout the experiment. This could be used to develop a replica of the
changes in dissolution medium encountered by a tablet as it passes through the digestive system.

- Throughout this thesis the work has been performed with model tablets which, were designed to investigate some facet of the formulation using FTIR imaging. It would be important to apply the information learned here to study commercial samples which share some of the same properties.

- For studying static samples measurement time is not as important as it is for dynamic samples such as dissolution. For these samples it is possible to study larger fields of view without sacrificing spatial resolution, using the imaging and mapping methodology (Chan and Kazarian, 2008). This could be used for particle and surface area fraction analysis to obtain data from a greater area of the tablet, reducing the total number of tablets that would need to be studied.
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