Soluble Drug Release from a Non-Swelling Polymer Matrix Studied by Magnetic Resonance and Other Imaging Methods

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This thesis is dedicated to my beloved sister, Thani. A great sister, a treasured friend and my support in life. To my sister who used to say to me

"Αδέλφη, don't worry about a thing cause every little thing is going to be alright"

Σ' αγαπώ πολύ αδελφόθα μου και μου ζείπες ακόμα περισσότερο. Θα σε θυμάμαι πάντα.
Abstract

Research in the area of controlled drug release is increasingly important in the pharmaceutical industry both from quality of life and commercial perspectives. One form of controlled release is of active components incorporated in solid polymer matrices. Understanding the nature and control of drug release is focal to the effective control and targeting of drugs. This will allow the prediction and modelling of new delivery systems. The aim of this thesis is to determine the principal manufacturing parameters affecting the release of a soluble drug from a non-swelling polymer matrix and so to understand better the dissolution mechanism. The matrix chosen for study is Eudragit and the chosen drug is Diltiazem Hydrochloride. Magnetic Resonance Imaging (MRI) experiments on Eudragit tablets with different levels of compression, drug loading and particle size exposed to water were made in order to observe the ingress of the water into the tablets. Nuclear Magnetic Resonance (NMR) spectroscopy was used to assess the amount of drug released. Stimulated-echo pulsed-field-gradient diffusion measurements of drug and water mobility in Diltiazem Hydrochloride solutions were made so as to estimate the self-diffusion coefficient of drug and water. Additional X-ray Computed Microtomography (\(\mu\)CT) and optical microscopy experiments were used to characterise the tablet microstructure.

Experimental evidence shows that there is a rapid capillary uptake (\(\leq 10\)mins) of water into the initial pore space of a tablet ahead of the primary dissolution. This porosity is very small, less than 4\% for pure compact Eudragit and even less for a drug loaded tablet. There is a slow subsequent dissolution characterised by a sharp diffusion front which separates the invaded and un-invaded regions. The water ingress proceeds linearly with the square root of time, \(t^{1/2}\). It is observed that water ingresses faster into tablets with small drug particle size and higher drug loading. Swelling of the whole tablet at intermediate drug loadings is seen as water ingresses into the system. However, no comparable swelling for either 100\% polymer or 100\% drug tablets is observed. There is evidence that as water ingresses into the tablet, air voids start to accumulate and ripen within the sample. Theoretical models are developed based on the experimental results in terms of diffusion and solubility parameters and the measured microstructure. In particular, a dimensionless time is introduced to best reflect the competition between dissolution and diffusion. This parameter is defined as the ratio of the time required for water to diffuse across the tablet and the time for the drug to dissolve.
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Chapter 1

1 Introduction

Controlled release may be defined as a technique by which the active components are made available to a target at a rate and duration so as to produce a desired effect [Singh and Fan, 1986]. Control release is central to many existing and foreseen technologies including agriculture, for the slow release of pesticides and fertilisers; food, for release of different flavours and additives; industrial protective coatings, for self-clean or self-repair paints; and pharmaceuticals. This last area is probably the most important as pharmaceutical industries try to improve the methods of delivering therapeutic doses of medicines that will improve both the end user benefit for the quality of life and their own commercial advantage. The primary objectives of controlled drug release systems are to ensure safety, to improve efficacy of drugs and improve patient convenience. Understanding the nature and control of drug release is central to the effective control and targeting drugs. However, in many instances development of devices remains a black art. The central purpose of this thesis is to advance understanding of the principal factors affecting release from just one system: a soluble drug release from a compact polymer matrix. The study takes advantage of modern non-destructive and non-invasive imaging methods including Magnetic Resonance Imaging (MRI) and X-ray Computed Microtomography (μCT) in particular.

1.1 Controlled release systems

Controlled release systems can be constructed from either polymer matrices, polymer encapsulating drugs or pumps. Pumps are larger and more costly than polymer matrices and polymer encapsulating drugs delivery systems. Externally worn and implantable pumps have been developed and in both cases the release rate is controlled dynamically; the driving force is the pressure difference such devices are also known as osmotic pumps. On the other hand, the small size and low cost of the polymer matrices and the polymer encapsulating drugs make these systems the most widely used controlled release system. The implementation of such drug delivery systems was first introduced in the 1970s, from polymer synthesised with lactic and glycolic acid [Kashyap et al., 2004]. Today, polymeric materials still provide the most important source for release system primarily because of their ease of processing and the ability to readily control their chemical and physical properties via molecular synthesis. The basic controlled
release formulation consists of a polymer, either natural or synthetic, which is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner over a long period of time [Brannon-Peppas, 1997]. The advantages of such systems include the localised drug delivery, the temporally uniform dose delivery, in order to eliminate the potential for both under- and overdosing, the need for fewer administrations, to reduce any side effects and the improved drug and patient compliance. Controlled release systems exist in many forms including specially-designed tablets that can be taken orally, injectable microspheres or implants, and transdermal patches.

Oral ingestion has long been the most convenient and commonly used route of drug delivery. For this reason, design and manufacture of oral formulations such as tablets and capsules is a very important aspect of drug delivery in the pharmaceutical industry. Systems can exists as both drug encapsulants and drug carriers by either protecting an active agent during its passage through the body until its release, or by just controlling its release. These form the two broad categories of polymer systems: the reservoir devices and the matrix devices. In the former the drug is surrounded by a polymer membrane, such as capsule or microcapsule, which acts as a barrier to release, whereas in the latter the drug is uniformly distributed through the polymer network (matrix).

Matrix systems are perhaps the most common of the drug controlled release devices. This is probably because they are relatively easy to manufacture, compared to reservoir systems, and there is not the danger of an accidental high dosage that could result from a fracture of the membrane of a reservoir system. In the matrix system the drug dispersed throughout the polymer matrix, and they are typically formed by the compression of a polymer/drug mixture or by dissolution or melting. A soluble drug may be incorporated into a water insoluble waxy or polymer matrix (non-swelling matrix) from which it is slowly released or it can be dispersed in a hydrophilic polymer which swells, forming a gel-like viscous layer through which the drug can be diffused. An insoluble drug may be released from a swelling soluble matrix as its combination with a non-swelling polymer is not useful.

Figure 1-1: (a) Polymer reservoir system and (b) polymer matrix system
1.2 Mechanisms of Controlled Drug Release

Over the years a lot of effort has been made in order to understand the release mechanisms from various polymer drug delivery systems. The literature survey carried out as part of this work revealed that the underlying rate-controlling mechanisms of these systems are complex and they fall into three fundamental categories: diffusion, polymeric degradation and solvent-activation. As a consequence, a lot of work was put in experimental research and mathematical modelling in order to predict and design new controlled release patterns.

In the diffusion controlled system, water diffuses into the membrane or matrix so as to dissolve the drug, which migrates from its initial position in the polymeric system to the polymer's outer surface and finally diffuses out of the polymer. It is the most common release mechanism. In a reservoir system, the rate determining step is associated with the diffusion of water through the polymer encapsulation. The release rate is constant and proportional to the initial concentration of the drug. On the other hand, in a matrix system the rate of release depends upon the amount of drug present at a particular time. Therefore, it is time dependent [Thrash, 1995].

![Drug dissolved or dispersed in polymer](image)

Figure 1-2: Polymer matrix: Diffusion controlled system.

In the polymeric degradation systems the drug is contained within a polymer membrane or matrix. The polymer is designed to degrade and release drug, which is related to the phenomena of matrix erosion. The polymer degradation can be distinguished by three dissolution mechanisms: (i) water soluble polymers are made insoluble by cross-linking them together and when this is broken the polymer dissolves, (ii) water insoluble polymers are made soluble by hydrolysis or ionisation of the side groups and (iii) water insoluble polymers are made soluble by backbone-chain cleavage to small soluble molecules [Langer, 1993]. Many degradation systems use a combination of these systems.
drug dissolved or dispersed in polymer

\[ t=0 \]

\[ t \]

Figure 1-3: Polymer matrix: Degradation system.

Solvent activation system involves either the swelling of the polymer or osmotic effects. In the first case the drug is entrapped in the polymer and upon exposure to water (or other solvent) it swells allowing the release of the drug whereas in the latter water may permeate the drug/polymer systems as a result of osmotic pressure, causing pores to form resulting in the release of the drug [Langer, 1990]. The most common form of osmotically controlled release system involves a semi-permeable membrane containing a small, laser-drilled hole. An osmotic agent, either the drug itself or a salt is contained within the membrane. Water enters the tablet through the membrane at a constant rate and drug is forced out through the hole due to the increased pressure [Thrash, 1995].

Figure 1-4: Solvent activation system: (a) Swelling of polymer matrix and (b) osmotically controlled system.

Combinations of all the above mechanisms are possible but having systems with different release mechanisms has the advantage that each can achieve different goals. In any case it is essential to understand the nature of these mechanisms in order to be able to construct effective drug delivery systems.

Diffusion is the most important mechanism used to control drug release. It is related to the transport phenomena of a liquid into a solid material. In particular, the diffusion of liquid molecules in polymers has been studied for at least 40 years. In 1966, Alfrey and co-workers proposed two distinct diffusion behaviours of liquids into glassy polymers: Fickian and Case II. In Fickian diffusion, smooth concentration profiles are observed. These vary with the square root of
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time. This is also the case even if the liquid diffusion coefficient is a strong function of concentration. In Case II diffusion a sharp liquid front, separating an inner glassy phase from an outer swollen rubbery region, ingresses into the polymer linearly with time. Behind the front, the liquid concentration is usually uniform. Both diffusion processes can be described by a single parameter. Fickian diffusion is controlled by the diffusion coefficient and Case II by the constant velocity at which the boundary between the swollen polymer and the glassy phase advances towards the centre of the polymer. If it is assumed that the mass of the liquid in polymer at time $t$ is $m = kt^n$, with $k$ and $n$ constants then according to above $n = 1/2$ for Fickian diffusion and $n = 1$ for Case II diffusion. Between the two ($1/2 < n < 1$) lies an anomalous diffusion regime which occurs when diffusion and relaxation rates are comparable [Crank, 1975].

The form of drug release studied in this thesis is that of the active component dispersed in a solid polymer matrix system where the matrix is formed by the compression of a polymer/drug mixture. The literature survey is mainly but not exclusively focuses on such drug delivery system.

During the past years a lot of experimental studies have been carried out in order to determine the release of the drug from polymer matrices. Primarily, these experiments rely on measurements of the temporal increase in drug concentration in the surrounding dissolution medium or on gravimetric analysis using a range of standardised protocols, equipment and dissolution media. Studies of drug release from swelling controlled delivery systems were conducted using the United States Pharmacopeia (USP) dissolution test [USP, Dissolution<711>, 1995] where the tablet is immersed in a media bath and the total amount of the drug released into solution is measured as a function of time. The relationship between the fraction of drug released and time is used to determine the diffusion process. An example would be the work of Debbagh et al. [Debbagh et al., 1996] who used dissolution analysis and differential scanning calorimetry in order to investigate the effect of drug/polymer ratio, viscosity grades and compaction pressure on the drug release rate in a combination system of ethycellulose/hydroxypropylmethylcellulose (HPMC)/propranolol hydrochloride. Munday and Cox [Munday and Cox, 2000] used swellable hydrophilic natural gums (xanthan or karaya gum) loaded with either caffeine or diclofenac sodium, as model drugs, and determined the degree of hydration as well as gum and drug erosion by gravimetric means (mass balance). Gravimetric analysis and USP dissolution method are routinely used in pharmaceutical industries for studying the release of drug from polymer systems. Dissolution testing has been used in conjunction with other analytical techniques for example high performance liquid chromatography (HPLC) [Sung et. al., 1996] and Ultraviolet (UV) spectroscopy [Cox et al., 1999] to determine the release rate of the drug. However, the methods traditionally applied to follow liquid transport in polymers provide only limited information. There is still an overall lack of understanding about the release mechanisms as dissolution tests cannot probe the drug present within the swollen matrix and do not provide

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information on the relative importance of the two mechanisms of drug release, which include the
diffusion through the swollen polymer and the release of drug at the edges of the tablet through
erosion. In addition, as the drug and solvent concentration profiles are not available from these
experiments it is not possible to test the results with theoretical models. A lack of understanding
of these mechanisms leads to difficulties in predicting formulations and drug delivery designs.

More detailed information on the swelling and erosion of a release system has been obtained in
the past by measuring dimensional changes and more recently it has been monitored optically
[Sujja-areevath et al., 1998], including spatially resolved Rayleigh light scattering [Gao and
Meury, 1996]. Adler et al. [Adler et al., 1999] used fluorescent microspheres as non-diffusing
markers to follow localised deformation within hydrating hydrophilic matrix tablets. They used
confocal scanning microscopy to study the differential swelling. Ion-beam analysis has also been
used to study the molecular diffusion into various drug release polymers [Jenneson et al., 1998].
However, these techniques are generally indirect as they require doping or contrasting agents and
are often invasive or destructive.

Drug delivery design has become imperative but is constrained by a restricted understanding of
the mechanisms of dissolution. With such understanding would come the ability to confidently
model the behaviour of current and new delivery systems. Although there has been much work,
designing polymer matrix controlled release systems remains something of a black art. The
pharmaceutical industry in particular is keen to see research carried out turned into predictive
capability. There is an urgent need to apply advanced experimental techniques capable of
obtaining spatially resolved information to probe the dissolution phenomenon and drug release at
a molecular level.

Several spectroscopic and imaging methods are currently available to determine drug distribution
in a polymer matrix non-invasively, including Fourier Transform infrared (FT-IR) spectroscopy
[Kazarian and Chan, 2003] and Raman spectroscopy [Vergote et al., 2002]. However, in some
cases the polymer matrix can only be studied in the form of a thin film. Another restriction
involving the Raman spectroscopy is the sample heating due to the absorption of the laser
radiation, which might lead to polymorphic changes. Even though these techniques provide non-
invasive analysis, the two methods that have the ability to provide internal images of the materials
under study and visualise the sample in 3D over a time course are X-ray Computed Tomography
(CT) [Sinka et al., 2004] and Magnetic Resonance Imaging (MRI) [Melia et al., 1998]. X-ray CT
is an imaging technique, which has recently advanced in the area of drug development as it can
also provide cross-sectional images in different planes through the sample. However, it is
sometimes limited by long image acquisition times and in situ experimental conditions. Of all
these methods, MRI is today central to measurements of drug distribution in polymer systems. It
is a powerful imaging technique that provides internal images of materials on a microscopic and
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Macroscopic scale. Although it has been used extensively for medical imaging it has rapidly gained in interest and used successfully in different fields of research for mapping of liquids in solid objects. This is really important in studying controlled release systems as the liquid transport in one of the key role mechanisms.

1.3 Magnetic Resonance Imaging and X-ray Computed Tomography in Controlled Drug Release

Magnetic Resonance Imaging (MRI) is a powerful technique that offers non-invasive and non-destructive time-resolved spatial mapping of water transport in porous materials. Image contrast is based on composition, molecular mobility and local microstructure. It is versatile, as a wide range of NMR modalities can be accessed, and 2D and 3D imaging can be undertaken. MRI has become an increasingly popular probe of diffusion in polymer as it avoids experimental limitations of the aforementioned techniques. It has been used by numerous groups to study liquid ingress into polymers. Rothwell et al. [Rothwell et al., 1984] used the technique to study the absorption of water in glass-reinforced epoxy resin composites, and were able to obtain images of the water distribution where the water uptake was only 1% by weight. Blackband and Mansfield [Blackband and Mansfield, 1986] studied the diffusion of water into solid blocks of nylon 6,6 and were able to determine the diffusion coefficient and its concentration dependence in a non-destructive manner by NMR imaging. The transport was Fickian in nature. Weisenberger and Koenig [Weisenberger and Koenig, 1990] have used MRI to investigate diffusion and desorption of methanol in partially swollen poly(methyl methacrylate) (PMMA) rods, observing Case II diffusion. NMR imaging also allows the study of the mobility of polymer chains as demonstrated by the work of Tabak and Corti [Tabak and Corti, 1990] on PMMA and polystyrene bars exposed to vapours of deuterated chloroform and carbon tetracloride. Knorgen et al. [Knorgen et al., 2000] used MRI technique to study the diffusion of organic solvents in polymeric materials like natural rubber, nematic-like networks, and hydrogels and observed the changing of the materials during the swelling processes. Fyfe et al. [Fyfe et al., 1993] have studied the absorption and desorption of water in nylon 6,6. Hyde et al. [Hyde et al., 1995] studied the diffusion of decalin in ultra-high molecular weight poly(ethylene), and observed high degrees of swelling, and Fickian diffusion. The above review illustrates the range of liquid-polymer systems that MRI has been applied to, and the capability the technique provides for studying a wide range of transport kinetics and swelling behaviour. It proves that MRI is a central technique for spatial resolved examination of diffusion processes in polymer networks in real-time conditions. These features make MRI ideal for studying both the penetration of polymeric controlled drug release matrices by water, and the
subsequent release of drug as the technique has enormous potential to elucidate important mechanisms that might contribute to understanding the drug release process.

In the last few years, MRI has started playing an increasingly important role in the pharmaceutical industry. Due to its non-invasive nature it represents a fundamental tool for interpreting key processes involved in the controlled drug release mechanisms and it has an evolving role as an investigative procedure to assist product development. Apart from being a non-destructive method- hence it does not require slicing of the sample which could induce changes to water distribution, it is possible to conduct experiments in situ, depending on the system under study. It can offer a chemical-selective analysis such that specific components in the system can be selectively imaged. It can be spatially selective to a certain region of the sample and it can give the relative concentration as a function of spatial location, thus the technique is not limited by the sample geometry. The method is far from being a routine application as the behaviour of each system is dependent on the material, the matrix or the solvent and can be observed by different NMR parameters (e.g. T₁, T₂), which have to be chosen very carefully for the different purposes.

MRI has been used to study internal mechanisms underlying in vitro drug release behaviour in dosage forms and to monitor events within pharmaceutical processes. Hydration underpins the system of many solid pharmaceutical dosage forms, and most studies have utilised MRI to observe and measure the internal events unfolding as a consequence of solvent penetration. Penetration of aqueous fluids into such systems (dosage forms) often results in drug dissolution, and the release rate of the drug is usually determined by the kinetics of water penetration and the polymer-water interaction. Contrary to other methods, for the investigation of the diffusion process of solvents into polymer matrices MRI, provides information relating to the nature of the diffusion process in a polymer matrix on a spatial resolved level. It interprets the ingress of solvent into polymers by mapping non-invasively the liquid concentration in the polymer as a function of time.

MRI has successfully been used as an investigative method by different research groups in order to monitor drug release. Bowtell et al. [Bowtell et al., 1994] monitored the formulation of the gel layer in hydrating HPMC tablets and HPMC tablets containing insoluble calcium phosphate particles or diclofenac. Rajabi-Siahboomi et al. [Rajabi-Siahboomi et al., 1996] characterised the water mobility in the gel layer of HPMC tablets and measured the spatial distribution of self-diffusion coefficient and T₂ relaxation across the gel layer by MRI. Kojima et al. [Kojima et al., 1998] looked at the differences between swelling of micronised low-substituted hydroxypropylcellulose (HPC) tablets and swelling of HPC and HPMC tablets. They demonstrated that MRI was sensitive enough to distinguish between gel layer formed and the core of the tablet. Fyfe and Blazek-Welsh [Fyfe and Blazek-Welsh, 2000] studied the release of fluorinated drugs trifluperazine-HCl and 5-fluorouracil from HPMC tablets using MRI. By
applying $^1$H and $^{19}$F imaging techniques they managed to determine (i) water and drug concentration profiles and (ii) diffusion coefficients that may be used in predicting mechanisms of drug release from other swelling matrix systems. Fahie et al. [Fahie et al., 1998] demonstrated how MRI technique can be used to help in the development of new matrices where the internal structure was designed such as to provide predictable drug release. Milroy et al., [Milroy et al., 2003] used MRI and scanning microbeam nuclear reaction analysis to monitor the water ingress into the polyglycolide disks during degradation.

The literature survey carried out as part of this work revealed that X-ray CT is good in characterising the density distribution in dry powder compacts. Sinka et al., [Sinka et al., 2004] measured the material density distribution in pharmaceutical tablets non-invasively by X-ray CT. The tablets were manufactured using microcrystalline cellulose. Yoon et al. [Yoon et al., 2004] reported the first use of in situ Raman spectroscopy and microfocus X-ray CT to probe and assess the diffusion behaviour of CO$_2$ in PMMA matrices. Ozeki et al., [Ozeki et al., 2003] used X-ray CT to compare the physical properties, compression characteristics, and internal structures of tablets containing $\alpha$-lactose monohydrate, cornstarch, hydroxypropylcellulose as high polymer binders, and ascorbic acid as a model core medicine. The technique can successfully be used to image the microstructure of a sample and detect any irregularities in the internal structure that can be liked to the manufacturing procedures. In this thesis X-ray CT has been used as a complementary technique to follow the ingress of water into the system in real-time and gain information about the dissolution process in a microscopic scale.

1.4 Theoretical models

Diffusion, swelling and erosion are the most important rate-controlling mechanism of commercial available controlled release systems. The behaviour of pharmaceutical systems containing a drug and a polymer can be analysed by a mathematical model which can predict the drug release, the swelling and dissolution of the system. The problem of tablet dissolution is one of the great importance in pharmaceutical science, as dissolution is the limiting step of the release of drug into the system. In the development of controlled release systems, especially in oral applications, it is necessary that the in vitro release and the in vivo delivery are compatible. Therefore, a mathematical and physical analysis of matrix dissolution becomes an important pharmaceutical research subject [Harland et al., 1988a].

Modelling of controlled release of drugs from polymeric devices has been a subject of considerable research in the past years. The dissolution of polymer in a solvent involves two transport processes, the solvent penetration and the chain disentanglement. When the rate limiting
step is diffusion then the solvent diffusion during dissolution process obeys Fickian second law of diffusion where the solvent ingress proceeds as a square root of time, $t^{1/2}$.

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} \tag{1-1}$$

where $D$ is the diffusion coefficient, $c$ is the concentration of the drug within the matrix as a function of position, $x$, and $t$ is the time. Most of the models that have been developed today are based on solutions of the Fickian diffusion equation. If the $D$ is a function of concentration then

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x} \left( D \frac{\partial c}{\partial x} \right) \tag{1-2}$$

There are many instances where the rate controlling step is due to matrix swelling or matrix erosion. In these cases a zero order release is achieved which means that the solvent advances linearly with time, $t'$ (Case II diffusion), into the polymer matrix.

Numerous studies have been reported in the literature investigating the release mechanisms from various polymeric drug delivery systems. Various mechanistic models including water diffusion into a polymer matrix, swelling, polymer dissolution, drug diffusion in swollen polymer and drug dissolution have been established by different research groups principal amongst these are Singh and Fan [Singh and Fan, 1986], Harland et al. [Harland et al. 1988a], Narasimhan [Narasimhan and Peppas, 1996 and Narasimhan, 2001], Peppas et al. [Peppas et al., 1994] and Brazel and Peppas [Brazel and Peppas, 2000].

A model that predicts polymer dissolution in the absence of embedded drug is that of Narasimhan et al. [Narasimhan et al., 1999]. They applied MRI to study the dissolution of swollen, noncrystalline poly(vinyl alcohol) in water. They suggested that polymer dissolution models can be developed by (i) using phenomenological models and Fickian equations, (ii) using external mass transfer as the controlling resistance to dissolution, (iii) using stress relaxation and (iv) analysis using anomalous transport models for solvent transport and scaling laws for actual polymer dissolution [Narasimhan et al., 1999]. Their model is based on anomalous transport and scaling laws. An one dimensional water diffusion is followed by chain disentanglement in amorphous, uncrosslinked, and linear polymers. The equation for the swollen polymer is determined to be

$$\frac{\partial \nu_1}{\partial t} = \frac{\partial}{\partial x} \left[ D_{12} \frac{\partial \nu_1}{\partial x} \right] + \frac{\partial}{\partial x} \left[ \frac{D_{12} \bar{V}_1 \nu_1}{kT(1-\nu_1)(1-2\chi \nu_1)} \frac{\partial \sigma_{xx}}{\partial x} \right] \tag{1-3}$$

$$\frac{\partial \sigma_{xx}}{\partial t} = \frac{\sigma_{xx}}{\eta} + \frac{E}{(1-\nu_1)^2} \frac{\partial \nu_1}{\partial t} \tag{1-4}$$
where \( \nu_J \) is the volume fraction of solvent in the swollen polymer, \( D_{12} \) is the solvent-polymer mutual diffusion coefficient, \( V_J \) is the molar volume of the solvent, \( R \) is the gas constant, \( T \) is the temperature, \( \chi \) is the solvent-polymer interaction parameter, \( \sigma_{xx} \) is the \( xx \) component of the viscoelastic stress tensor of the polymer, \( \eta \) is the viscosity of the polymer, and \( E \) is the tensile modulus of the polymer.

The coupled model equation for diffusion boundary with constant thickness, \( \delta \) is expressed as

\[
\frac{\partial \nu_2}{\partial t} = \frac{\partial}{\partial x} \left[ D_p \frac{\partial \nu_2}{\partial x} \right] \frac{dS}{dt} \frac{\partial \nu_2}{\partial x}
\]

where \( \nu_2 \) is the polymer volume fraction, \( S \) is the position of the rubbery-solvent interface, and \( D_p \) is the polymer self-diffusion coefficient in the diffusion boundary. In this model the polymer dissolution involves the determination of many parameters. The model also neglects the pore space within the polymer matrix. This model is typical of many in the polymer dissolution literature.

One model that predicts the drug release from swellable polymer systems is that of Siepmann et al. [Siepmann et al., 1999a]. Their mathematical model describes drug release from dissolving HPMC matrices by considering cylindrical devices and accounting for both radial and as well as axial transport. The water and drug diffusion are based on Fick's second law. Diffusion coefficients of water and drug are taken to be concentration dependent following a generalised free volume theory

\[
\frac{\partial c_k}{\partial t} = \frac{\partial}{\partial r} \left[ D_k \frac{\partial c_k}{\partial r} \right] + \frac{\partial}{\partial r} \left[ D_k \frac{\partial c_k}{\partial r} \right] + \frac{\partial}{\partial x} \left[ D_k \frac{\partial c_k}{\partial x} \right]
\]

where \( c_k \) and \( D_k \) are the concentration and diffusion coefficient of the diffusing species \( k = 1: \text{water}; k = 2: \text{drug} \), respectively, \( r \) is the radial coordinate, \( z \) the axial coordinate and \( t \) the time. According to the free volume theory of diffusion, exponential dependence of the diffusivities of water and drug \( D_1 \) and \( D_2 \), was considered.

\[
D_1 = D_{1eq} \exp \left( -\beta_1 \left( 1 - \frac{c_1}{c_{1eq}} \right) \right) \quad \text{and} \quad D_2 = D_{2eq} \exp \left( -\beta_2 \left( 1 - \frac{c_2}{c_{2eq}} \right) \right)
\]

where \( \beta_1 \) and \( \beta_2 \) were dimensionless constants, characterising the concentration dependence. Also, \( c_{1eq} \) was the concentration of water, \( D_{1eq} \) and \( D_{2eq} \) the respective diffusion coefficients of water and drug in equilibrium swollen of the system. The diffusion coefficient of water and drug were determined by fitting a simplified theory (neglecting polymer dissolution) to adequate experimental data [Siepmann et al., 1999a]. The dissolution of polymer was based on the reptation theory [Narasimhan and Peppas, 1996]. A critical polymer concentration is considered
below which disentanglement processes begin to dominate, resulting in convection-controlled transport of chains. A dissolution constant, \( k_{\text{diss}} \), is defined to describe the velocity of dissolution per unit area and can be controlled by either the rate of disentanglement or by diffusion through a boundary layer, adjacent to the HPMC-water interface. A mass balance for the polymer chains is written as

\[
M_t = M_0 - k_{\text{diss}} A_t t
\]

where \( M_t \) was the mass of the dry matrix at time \( t \), \( M_0 \) was the mass of the dry matrix at \( t = 0 \), and \( A_t \) was the surface area of the system at time \( t \). This model predicts the release kinetic of a drug from soluble polymer matrix. However, it neglects the initial pore space of the matrix and it does not account the effect of the component particle size on dissolution. It is confusing due to many parameters used to describe the mechanism even if one dimensional diffusion is considered.

Another model relevant to this study is that reported by Harland et al. [Harland et al., 1988b]. This is because it introduces a dimensionless parameter to classify different dissolution regime limits. They developed a new model to account for the kinetics of drug release from porous, non-swelling polymeric particles in the case where both drug dissolution and diffusion mechanisms control the overall release process. They considered a spherical particle made from non-swelling polymeric material and a water-soluble solid drug dispersed in the polymer. The spherical system is placed in contact with water and the water-soluble drug starts to dissolve and diffused through the pores of the polymer out of the system. The model incorporates a linear first order dissolution term in the Fickian diffusion equation. The equation describing the drug dissolution and diffusion is the following generalised differential equation

\[
\frac{\partial c}{\partial t} = D \left( \frac{\partial^2 c}{\partial r^2} + \frac{2 \partial c}{r \partial r} \right) + k (c_s - c)
\]

where \( c \) is the concentration of the drug, \( r \) is the radial position in the sphere, \( D \) is the drug diffusion coefficient, \( \varepsilon \) is the system void fraction, \( c_s \) is the drug saturation concentration in the system, \( k \) was the first order dissolution constant (in units of s\(^{-1}\)) and \( t \) is the release time. They defined a dissolution/diffusion dimensionless number, \( D_t \)

\[
\frac{\text{dissolution}}{\text{diffusion}} \text{ number, } D_t = \frac{k R^2}{D}
\]

where \( R \) is the initial radius of the spherical particle. Note that the parameter \( k \), which is the dissolution rate (in units of s\(^{-1}\)) is defined differently to the parameter \( k \) used later in this work (see page 15 in this chapter and Chapter 6, Sections 6.2 and 6.3.1). In Harland’s work the dimensionless number, \( D_t \), indicates the relative importance of the mechanism in the overall release and it is possible to identify regions of linear time dependence of the drug released.
However, the model cannot predict the time when the dispersed drug is fully dissolved. The diffusion coefficient \( D \) is referred to the drug diffusivity in water, which is assumed to be independent of drug concentration as seen in equation 1-9. No supporting experimental data is shown.

Finally, Droin et al. [Droin et al., 1985] studied the drug release in synthetic gastric liquid using sheets made from Eudragit RS as the polymer binder, and sodium salicylate as the drug. A double transfer has been observed when exposed to liquid. The liquid invaded the matrix, dissolved the drug which then diffused out of the system. Both these transfer mechanisms obeyed Fickian diffusion, with a constant diffusivity for the drug and a concentration dependent diffusivity for the liquid. The polymer matrix swelled because of higher rate of transfer for the liquid, but without affecting the stability and solidity of the sample matrix. The matter transfer was modelled based on numerically explicit method with finite differences. The model was able to take into account different laws for diffusivity and amounts of materials transferred at equilibrium, and it could be used for various sizes and shapes of the controlled release system [Droin et al., 1985]. In this model the matrix is considered as a thin plane sheet, it neglects the initial pore space of the matrix and the effect of the component particle size on dissolution.

1.5 Scope of the Thesis

The process of dissolution and drug release from solid dispersions of drugs in polymers is related to diffusion of water into the polymer/drug matrix followed by phenomena such as polymer swelling, polymer dissolution, diffusion of drug, and drug dissolution. These phenomena largely control the drug release process, but the overall process may be very complex and many factors affect the release mechanism. Interaction between polymer, drug and solvent are considered to be primary factors for the release control. Furthermore, the rate of drug release from a polymer matrix is dependent upon various other formulation variables, such as type of polymer, drug, polymer grade, polymer/drug ratio, particle size of drug and polymer, drug solubility, porosity and compaction pressure. All these can influence drug release rate to greater or lesser extent.

The aim of this study is to determine the principal manufacturing parameters affecting the release of a soluble drug from a non-swelling polymer matrix and so to understand better the dissolution mechanism. The matrix chosen for study is Eudragit. It is a copolymer of acrylic and methacrylic acid ester with low content of quaternary ammonium groups. The chosen drug is Diltiazem Hydrochloride (HCl), which is highly soluble in water. Both materials are widely used in research of controlled release systems. This methacrylic resin appears particularly attractive due to its high chemical stability, good compactability properties and there are a large variety of products available on the market with different physicochemical characteristics. Eudragit is commonly
used in the preparation of matrix tablets for oral sustained release, in tablet coatings and in microencapsulation of drugs [Azarmi et al., 2002]. Diltiazem HCl is widely used in treatment of arrhythmia and hypertension [Kristmundsdottir et al., 1996]. De Filippis et al. [De Filippis et al., 1995] studied the effect of Eudragit on the dissolution behaviour of different drugs using solid dispersions prepared by drying a mixed solution of polymer and drug. Kristmundsdottir et al. [Kristmundsdottir et al., 1996] used dissolution tests to study the release of Diltiazem HCl from Eudragit particles prepared by spray-drying.

The sample used in this thesis is in the form of the tablet prepared by direct compression of the powdered polymer and drug combination. The physical characterisation and preparation of the tablets are discussed in Chapter 3. The tablet is exposed to water and the drug release is monitored using a combination of techniques such as Nuclear Magnetic Resonance (NMR), MRI, X-ray μCT, optical microscopy and UV spectroscopy. Amongst these the foremost method in this thesis is MRI. For this reason Chapter 2 is dedicated to explaining the fundamental principals of MRI and the theory behind the measurements carried out in this thesis. It also includes a brief description of the complementary methods used, X-ray μCT and UV spectroscopy. The different instrumentation of each imaging method together with experimental procedures, sample preparation for each experiment and data processing are detailed in Chapter 3.

Spectroscopic characterisation of the raw materials is conducted, which contributes to the interpretation of spatially resolved MR data. These experiments are presented in Chapter 4 and involve the determination of $^1$H NMR $T_1$ and $T_2$ relaxation times of water swollen, equilibrated Eudragit powders at two different NMR frequencies, 20MHz and 400MHz. For both frequencies the $T_1$ and $T_2$ measurements show single component relaxation for $T_1$ whereas $T_2$ shows a double component relaxation attributed to water and polymer respectively. CYCLICROP $^{13}$C-edited spectroscopy is applied on concentrated Diltiazem HCl solution. This method has the ability to select a specific $^{13}$CH$_3$ group in the molecule while suppressing all proton resonances, which do not arise from the desired molecular groups. The objective of this method is to map drug concentrations in partially swollen system in imaging studies. The principle of this technique is described in Chapter 3. Three different CH$_3$ groups in the drug molecule are assigned. Based on these groups the self-diffusion coefficient of drug and water are estimated by conducted stimulated-echo pulsed-field-gradient diffusion measurements of drug and water mobility in Diltiazem HCl solutions.

In the following chapter, Chapter 5, the release of Diltiazem HCl from Eudragit tablets when exposed to water and the evolving micro-structure of the system during dissolution is investigated using non-destructive imaging techniques. The effect of drug release is studied in respect to different manufacturing parameters including different drug loading, levels of compaction,
particle size, matrix type and dissolution environments so as to enable the understanding of the dissolution mechanism of the sample matrix. MRI is used to follow the water ingress, the matrix swelling and dissolution. The amount of the drug release is obtained from NMR and UV spectroscopy. X-ray μCT and optical microscopy are used to gain information about the overall porosity of the system.

In Chapter 5 it will be shown that when the matrix is exposed to water there is rapid capillary uptake (≤ 10mins) of water into the initial pore space of a tablet ahead of the primary dissolution. This porosity is very small, less than 4% for pure compact Eudragit and even less for drug loaded tablet. The water then ingresses at a much slower rate with dissolution characterised by a sharp diffusion front which separates the invaded and un-invaded regions. The water ingress proceeds linearly with the square root of time, \( t^{1/2} \). The rate of water ingress is affected by the drug load and the drug particle size. As water continues to ingress into the system there is a swelling of the tablet at intermediate and high drug loadings. However, it will be shown that this is not primarily due to the materials as there is no comparable swelling for either 100% Eudragit or 100% Diltiazem HCl tablets. An important observation made in this thesis, which affects the release of the drug, is the accumulation and ripening of air voids within the sample matrix as water ingresses into the tablet. This phenomenon was both observed by MRI and X-ray μCT. The high spatial resolution of the X-ray μCT system allowed the air-void size distribution to be quantified as it changes over time.

In Chapter 6 a simple model is proposed suggesting that the ripening of the air-voids occurs via a combining process of air voids, which possibly involve little motion or some local diffusion. Also, a simple mathematical model of the dissolution mechanism of the matrix is presented in the same chapter. The experimental results are modelled in terms of diffusion and solubility parameters and the measured microstructure. In particular, a dimensionless time, \( \tau \), is defined as the ratio of the timescale of diffusion and the timescale of dissolution

\[
\tau = \frac{L^2 k}{D_w r_0}
\]

where \( L \) is the tablet thickness (cm), \( r_0 \) is the drug particle size (cm), \( k \) is the dissolution constant (cm/s) and \( D_w \) is the water diffusion coefficient (cm\(^2\)/s). This parameter compares the time taken for water to diffuse across the tablet with that for a drug particle to dissolve. It is found that for \( \tau \gg 1 \), diffusion is the dominant mechanism leading to a sharp diffusion front which progresses as a square root of time, \( t^{1/2} \). For \( \tau \ll 1 \) dissolution dominates and smooth water profiles are predicted. This parameter helps describe the effect of particle size on dissolution mechanism.
The dimensionless parameter defined by Harland et al., [Harland et al., 1988b] in equation 1-10 \(D_i = kR^2/D\) uses different definition of \(k\). He defines \(k\) to have units of s\(^{-1}\) whereas here \(k\) has units of cm/s. However, it implicitly only includes a single length scale \(R\), which is equivalent to the tablet size \(L\) defined in equation 1-11. It does not include the size of the drug particle \(r\), which in this analysis would require the typical dimension of a pore within the microstructure and, due to the different definition of \(k\), also the total internal surface area of porous microstructure. Therefore, Harland cannot discuss the time for dissolution as effectively as in the current work.
Chapter 2

2 Basic Principles of Imaging

In this thesis the release of the soluble drug from a non-swelling polymer matrix was studied using different imaging techniques. Each contributed to the collection of data used to understand the dissolution mechanism of the sample matrix. The most important was Magnetic Resonance Imaging (MRI). It was complemented by X-ray Computed Tomography (CT) to study the microstructure of the system, Ultraviolet (UV) spectroscopy to determine the amount of the drug released from the system and optical microscopy to examine the surface and particle size of the matrix. This chapter is a summary of general MRI theory explained with a judicious mix of classical and quantum physics. The basic principles of X-ray CT and UV spectroscopy are also briefly described.

2.1 Historical Background of Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a powerful imaging technique that is an extension of the phenomena of Nuclear Magnetic Resonance (NMR), a spectroscopic method related to the study of molecular structure and dynamics. In 1937 Isidor Rabi [Rabi et al., 1938] discovered the NMR phenomenon during an ion beam experiment. He was awarded by the Nobel Prize for Physics in 1944 for his invention of the atomic and molecular beam magnetic resonance method of observing spectra. It was not until 1946 where two different groups, one led by Purcell [Purcell et al., 1946] at Harvard University and the other by Bloch [Bloch et al., 1946] at Stanford University, who independently succeeded in demonstrating the phenomena of NMR in liquids and solids for the first time. They were awarded the Nobel Prize for Physics in 1952. Since then, nuclear magnetic resonance has become a routine tool for physicists and chemists to probe molecular structure. It has been widely used for the analysis of small samples, showing that different materials resonate at different magnetic strengths.

In 1971 Raymond Damadian [Damadian, 1971] reported differences in nuclear magnetic relaxation times (T_1 and T_2) of normal and cancerous tissues, thus motivating scientists to consider magnetic resonance as a potential diagnostic technique. In 1973 Lauterbur [Lauterbur, 1973] and Mansfield and Grannell [Mansfield and Grannell, 1973] independently proposed methods of imaging, based on the shift in resonant frequency that results from a change in the
magnetic field imposed on the object. This was the beginning of MRI. After that, development has been remarkably rapid, from the first demonstration of MRI of the whole body in 1977 [Damadian et al., 1977], the beginning of clinical trials of the first MR imaging prototypes in 1980 until the achievement of the spin-warp imaging technique [Edelstein et al., 1980] and real time imaging methods such as echo-planar imaging (EPI) [Mansfield, 1977], now commonly known as Fourier imaging, which form the basis of almost all modern MRI. Nowadays MRI has become an essential tool in medicine and it is routinely used in hospitals for diagnostic purposes and in 2003, Lauterbur and Mansfield were awarded the Nobel Prize in Medicine for their pioneering work. Due to the increasing progression of the technique, MRI has managed to find vast applications in other areas including material science. The sensitivity of NMR for molecular diffusion processes was marked in Hahn’s [Hahn, 1950] publication on spin echoes in 1950. He reported that self-diffusion influenced the spin-echo amplitudes. In 1954 Carr and Purcell [Carr and Purcell, 1954] introduced multiple echo pulse sequences to alternatively minimise diffusion attenuation effects in samples with mobile components or to measure self-diffusion coefficients in liquids by applying a constant magnetic field gradient. The pulsed field gradient technique developed by Stejskal and Tanner [Stejskal and Tanner, 1965] in 1965 demonstrated a novel way for determining diffusion coefficients and forms the basis of today’s diffusion weighted imaging methods, which is widely used in the study of materials. The basic principles of diffusion MRI were introduced in 1985 by Taylor and Bushell [Taylor and Bushell, 1985]. They combined NMR imaging principles with those introduced earlier to encode molecular diffusion effects in the NMR signal by using bipolar magnetic field gradient pulses [Stejskal and Tanner, 1965]. Throughout the years various techniques have been considered for studying materials including Stray Field Magnetic Resonance Imaging (STRAFI) introduced by Samoilenko et al. in 1987 [Samoilenko et al., 1987] being amongst the most prominent. Consequently, MRI is clearly a young, but growing science. Over the years the technique has evolved into a complex, interdisciplinary science, which has seen major breakthroughs and innovation until present research.

2.2 The Fundamental Physics of MRI

MRI is a development of NMR and is a logical extension of the basic principles of magnetic resonance. There are essentially two approached in explaining the fundamentals of MRI; the quantum physics and the classical.

2.2.1 The Quantum Physics Approach

Magnetic resonance is a phenomenon that has its origin in the magnetic properties of atomic particles such as electrons, protons, neutrons, which form building blocks of atoms and molecules.
According to quantum theory an atomic nucleus with either an odd number of protons or neutrons or both possess a property called intrinsic angular momentum or “spin” of magnitude

$$|J| = \sqrt{I(I+1)}\hbar$$

(2-1)

where $I$ is the nuclear spin quantum number and $\hbar$ is equal to the Plank’s constant ($\hbar = 6.6262 \times 10^{-34}$Js) divided by $2\pi$. When a nucleus contains an even number of protons and neutrons, the individual spins of these particles pair off and cancel out and the nucleus is left with zero spin, $I = 0$. In a nucleus containing odd number of protons or neutrons, pairing is incomplete and the nucleus has a net spin of $I = 1/2$ or greater. All such nuclei undergo NMR but the hydrogen atom, consisting of a single proton ($I = 1/2$), is regarded as the most suitable to use for MRI due to its high NMR sensitivity and natural abundance and also because of the high concentration of water in the human body.

A nucleus can be considered as a charged sphere spinning about its own axis. According to the laws of electromagnetism a spinning sphere of charge generates a magnetic dipole moment, $\mu$, which is proportional to the spin angular momentum

$$\mu = \gamma J$$

(2-2)

where $\gamma$ is the gyromagnetic ratio rad/s/T and is a characteristic constant for each magnetic nucleus. For the hydrogen proton $\gamma = 42.56$MHz/T. Each hydrogen proton is spinning, creating a magnetic field and acts very much like a tiny bar magnet (dipole).

In the absence of an external magnetic field, the magnetic moments of the hydrogen nuclei in a macroscopic sample are randomly oriented and are considered to have a net magnetisation of zero. When placed in an external magnetic field, $B_0$, applied along the z-axis the magnetic moments of the hydrogen nuclei are trying to align with this field. The energy of the magnetic moment, $\mu$, in the external magnetic field is given by

$$E = -\mu \cdot B_0 = \gamma J_z B_0$$

(2-3)

where $B_0$ is (traditionally) taken as defining the z-direction. The z component of the angular momentum ($J_z$) can have $m_I\hbar$ values where $m_I$ is the magnetic quantum number which can take the values $m_I = -I, -(I-1), \ldots, (I-1), I$. This creates $(2I+1)$ energy levels known as Zeeman levels. So, the hydrogen proton with spin $I = 1/2$ it has two Zeeman energy levels with $m_I = \pm 1/2$. Quantum theory states the proton can adopt only one of the two possible orientations relative to the direction of the magnetic field. The preferred orientation has the magnetic moment aligned parallel (spin $m = +1/2$) to the field. The other has it aligned anti-parallel to the applied field (spin $m = -1/2$) [Westbrook and Kaunt, 1998]. The energy of low and high energy states is $E_{m_I} = -\gamma \hbar B_0 / 2$ and $E_{m_I} = +\gamma \hbar B_0 / 2$, respectively. For normal field strengths this difference in
energy is small and at room temperature the preference for the lower level is very small: about one part on $10^6$.

![Figure 2-1: The Zeeman energy levels of hydrogen proton in a magnetic field $B_0$. The lower energy state with $m=+1/2$ where magnetic moment parallel to $B_0$ and higher energy state with $m=-1/2$ and magnetic moment anti-parallel to $B_0$.](image)

The levels are separated in energy by $\Delta E = \gamma h B_0$. This is the energy required to induce a transition from the lower to the higher energy state. The energy separation of the states depends linearly on the strength of applied magnetic field $B_0$.

The transition of the nucleus between the two energy levels is accompanied by absorption of a photon. The energy of this photon must exactly match the energy difference between the two states. The energy, $E$, of a photon is related to its frequency, $\omega$, by Plank's constant, $\hbar$:

$$\Delta E = \gamma h B_0 = \hbar \omega$$

where $\omega_0$ is the Larmor resonance frequency in rad/s and $B_0$ is the external magnetic field in Tesla (T). The physical origin of magnetic resonance is the observation of the transitions (spin slips) induced between the energy levels.

The spins in thermal equilibrium are distributed among the two states according to the Boltzmann distribution, which is the ratio of spins in the higher energy level, $n^r$, to the number of spins in the lower level, $n^r$, given by

$$\frac{n^-}{n^+} = e^{-\Delta E / k_BT} = e^{-\gamma h B_0 / k_B T}$$

where $k_B$ is the Boltzmann's constant and $T$ is the absolute temperature. For the $^1$H nuclei at room temperature and normal laboratory field strength there is a small excess in the number of spins in
the lower energy level with respect to the higher level. It is the population difference that gives rise to a net magnetisation (magnetic moment per unit volume) \( M \), that can be detected by NMR. The net magnetisation of the sample is the difference of the two distributions multiplied by the magnetic moment

\[
M = (n^+ - n^-) \mu \tag{2-6}
\]

As the total number of spins of \( n = n^+ + n^- \) it can been shown that

\[
n^+ - n^- = n \left( \frac{1 - e^{-\gamma h B_0 / k_B T}}{1 + e^{-\gamma h B_0 / k_B T}} \right) \tag{2-7}
\]

At room temperature, \( \gamma \hbar B_0 << k_B T \) and the exponential terms may be approximated by \( 1 - \gamma \hbar B_0 / k_B T \). So from equations 2-6 and 2-7

\[
M = n \frac{\gamma^2 \hbar^2 B_0}{4k_B T} \tag{2-8}
\]

The significance of this relation is that the magnetisation depends primarily on the applied magnetic field \( B_0 \), the temperature \( T \) of the system, and the distribution of the spins through the volume. The remaining parameters are intrinsic constants.

While quantum physics completely describes particle dynamics in a magnetic field, it is cumbersome to describe a large collection of particles. The classical physics perspective is considered to examine the effect of magnetic fields on the bulk magnetisation of many atomic nuclei.

### 2.2.2 The Classical Physics Approach

An alternative approach to explaining magnetic resonance is to consider the classical motion of a magnetic moment in a uniform magnetic field, \( B_0 \), under the conditions of constant total energy. The magnetic moment experiences a torque due to the magnetic field, which tends to align it perpendicular to the applied field

\[
T = \mu \times B_0 \tag{2-9}
\]

The law of conservation of angular momentum states:

\[
\frac{dT}{dt} = \frac{dJ}{dt} \tag{2-10}
\]

So for \(^1\)H nucleus the only contribution to the angular momentum comes from its spin. Hence, combining equations 2-9 and 2-10

\[
\mu \times B_0 = \frac{dJ}{dt} \leftrightarrow \frac{d\mu}{dt} = \gamma \mu \times B_0 \tag{2-11}
\]
So the torque exerted produces a change in angular momentum perpendicular to both $B_0$ and $\mu$ and thus perpendicular to the angular momentum $J$. The result corresponds to a rotation of the direction of $\mu$ in a cone-shape fashion about the $z$-axis of the $B_0$. Such a movement, which is analogous to the motion of a gyroscope, is referred to as precession and in such instances it is known as Larmor precession [Harris, 1986].

![Figure 2-2: Precession of magnetic moment about $B_0$](image)

The precessional frequency is given by [Banwell and McCash, 1994]

$$\omega_0 = \frac{\text{magnetic moment}}{\text{angular momentum}} \times B_0 \quad \Rightarrow \quad \omega_0 = \frac{\mu B_0}{J}$$

Replacing $\mu$ from equation 2-2 then

$$\omega_0 = \gamma B_0$$

This equation is called the Larmor equation and the frequency of precession, $\omega_0$, is known as Larmor frequency. The angular frequency of the precession is identical to the Larmor frequency derived in the quantum mechanical description above equation 2-4. The Larmor equation is important because it is the frequency at which the nucleus will absorb energy. The absorption of that energy at that specific frequency is referred to as resonance and it will cause the proton to alter its alignment.

This describes the motion of a single magnetic dipole under the influence of the static magnetic field. If there are a large number of dipoles, that is a collection of spins, in the sample it is possible to define a net magnetic moment or magnetisation, $M$ (as in equation 2-6), for the sample, which is the resultant of the nuclear magnetic moments

$$M = \sum_i \mu_i$$
As the magnetic field is applied along the z-axis it is convenient to determine the conventional coordinate system used in NMR. The z axis is known as the longitudinal direction and the xy-plane perpendicular to the magnetic field is the transverse plane. So in the presence of the static magnetic field the z-component of each magnetic dipole will add to give a detectable net magnetisation, \( M_z \). At thermal equilibrium this is non-zero because there is a slight difference in the population of spins pointing one way versus spins pointing another (given by the Boltzmann distribution). The net magnetisation along z is: \( M_z = M_0 \), whereas there is no bulk magnetisation at thermal equilibrium for \( M_x \) and \( M_y \): \( M_x = M_y = 0 \).

![Figure 2-3 Thermal equilibrium of spin distribution results in a net magnetisation along the z-axis.](image)

As the net magnetisation is in a magnetic field \( B_0 \), it will experience a torque and similar to the equation 2-11 of motion for \( \mathbf{M} \) can be written

\[
\frac{d\mathbf{M}}{dt} = \gamma \mathbf{M} \times \mathbf{B}_0
\]

In MR imaging, the energy that is transferred is radio frequency waves (RF) and like all electromagnetic radiation, it has electric and magnetic components. When the magnetic components of a RF pulse are applied perpendicular to an external magnetic field with a frequency equal to the Larmor frequency, this causes the net magnetisation to tilt away from the external magnetic field, \( B_0 \). This energy input has two effects on the protons. Firstly, the individual nuclei absorb energy that forces them to change from the low energy state to the high energy state, a process known as excitation. This results in the decrease of the longitudinal (z-axis) magnetisation due to the reduction in difference in population between the spins in the two states. Classically, this serves to reorient the direction of the net magnetisation. Secondly, the RF pulse induces all the protons into a coherent precession around the static field \( B_0 \) (z-axis) with a frequency equal to the Larmor frequency, resulting in the increase of the transverse (xy-plane) magnetisation.

If the RF pulse is applied in the form of a time varying field \( B_1 \), applied perpendicularly to \( B_0 \) and oscillating at \( \omega_0 \) then the equation of the field \( B_1 \) acting on the sample is derived by considering
only the circularly polarised component of \( B_1 \) rotating in the same direction as the precessing magnetisation in the xy-plane [Callaghan, 1993]. The component that rotates in the opposite direction to the nuclear precession is ignored provided that \( B_1 \ll B_0 \). The B field acting on the sample is

\[
B_{\text{total}}(t) = B_1 \cos \omega_0 t \mathbf{i} - B_1 \sin \omega_0 t \mathbf{j} + B_0 \mathbf{k}
\]

where \( \mathbf{i}, \mathbf{j} \) and \( \mathbf{k} \) are unit vectors along the x, y and z axes, respectively. Thus, during the pulse from equation 2-15 of motion the magnetisation of each x, y and z component can be expressed as

\[
\frac{dM_x}{dt} = \gamma \left[ M_y B_0 + M_z B_1 \sin \omega_0 t \right] \\
\frac{dM_y}{dt} = \gamma \left[ M_z B_1 \cos \omega_0 t - M_x B_0 \right] \\
\frac{dM_z}{dt} = \gamma \left[ -M_x B_1 \sin \omega_0 t - M_y B_1 \cos \omega_0 t \right]
\]

If a starting condition (for \( t = 0 \)) \( M(0) = M_0 \mathbf{k} \) is defined, then the solutions for \( M \) are

\[
M_x = M_0 \sin \omega_1 t \sin \omega_0 t \\
M_y = M_0 \sin \omega_1 t \cos \omega_0 t \\
M_z = M_0 \cos \omega_1 t
\]

where \( \omega_1 = \gamma B_1 \). This implies that by applying a rotating magnetic field of frequency \( \omega_0 \), the net magnetisation simultaneously precesses about the magnetic field \( B_0 \) at an angular frequency \( \omega_0 \) and about the \( B_1 \) field at a frequency \( \omega_1 \). This results in a spiral motion of the net magnetisation down and around the z axis as shown in Figure 2-4(a).

In order to simplify descriptions it is convenient to picture the excitation process in a frame of reference, \( (x'y'z') \) plane, which rotates about the z-axis at frequency \( \omega_0 \) (or in more general case at \( \omega \)). Initially, the equilibrium magnetic moment, \( \mathbf{M} \), is aligned parallel to the applied magnetic field, \( \mathbf{B}_0 \) (laboratory frame). The magnetisation is moved away from the equilibrium by a smaller magnetic field \( \mathbf{B}_1 \), which is applied as an RF pulse. In this frame, known as rotating frame, \( \mathbf{B}_0 \) is zero when \( \omega = \omega_0 \) (resonance), \( \mathbf{B}_1 \) is stationary along, for example, the \( x' \)-axis and this time the magnetisation precesses around \( \mathbf{B}_1 \) instead of \( \mathbf{B}_0 \), at a frequency equal to \( \omega_1 = \gamma B_1 \). After the pulse the magnetisation precesses around \( \mathbf{B}_0 \) in the transverse plane at the Larmor frequency, \( \omega_0 \). However, when \( \omega \neq \omega_0 \) (off-resonance) then the situation becomes more complicated and in the rotating frame there is a residual field that takes the value \( (B_0 - \omega_0 \gamma) \) along the z direction [Callaghan, 1993]. Therefore, the magnetisation precesses, in the rotating frame, about this residual field and \( B_1 \).
In an NMR experiment the $B_1$ field is applied as a short RF pulse. If the duration of the pulse is $t_p$ (a few $\mu$s long) then the magnetisation will rotate by an angle $\theta = \gamma B_1 t_p$. The RF pulse used to describe the energy needed to rotate the magnetisation from the longitudinal plane ($z$-axis) into the transverse plane ($xy$-plane) is referred to as $90^\circ$ pulse while the pulse that inverts the magnetisation is known as $180^\circ$ pulse. The direction of the pulse is also specified.

Following excitation, as the magnetisation rotates in the $xy$-plane of the laboratory frame about the $z$-axis it will induce a current in a coil of wire placed around the sample with its symmetry axis perpendicular to $B_0$. This signal from the coil is the NMR signal. The signal appears to die away with time and the plot of the signal intensity against time is referred to as Free Induction Decay (FID). The Fourier Transform of the NMR signal, recorded in the time domain, will produce the absorption line in the frequency domain. The coil that detects the NMR signal is the same one used for the excitation. A simple diagram of the detection of the NMR signal by a radiofrequency receiver is shown in Figure 2-5.
Chapter 2: Basic Principles of Imaging

\[ S(\omega) = \int_{-\infty}^{\infty} s(t) \exp(-i\omega t) dt \]  

The integration assumes \( s(t) \) as a continuous function over all of time. Note that the result of this integration is a complex function of frequency and that it will have real and imaginary coefficients.

![Figure 2-6: FID and its Fourier transform for (a) resonance signal and (b) off-resonance signal.](image)

The figures are drawn with reference to the demodulated signal, i.e. for the rotating reference frame.

2.2.2.1 Relaxation Theory

Since the application of a resonant RF pulse disturbs the spin system, there must subsequently be a process, known as relaxation, of coming back to equilibrium. There are two main relaxation processes associated with Magnetic Resonance (MR). The first involves the exchange of energy between the spin system and its surroundings. Such a process is called spin-lattice relaxation. It is the rate at which equilibrium is restored and it is characterised by the spin-lattice or longitudinal relaxation time, \( T_1 \). It is the rate at which nuclear spins align with the direction of the magnetic field and hence achieve thermal equilibrium with their surroundings. It defines the possible repetition rate of experiments. The spins however do not only exchange energy with the surrounding lattice, but also among themselves. This is the second process called spin-spin relaxation and is characterised by the spin-spin or transverse relaxation time, \( T_2 \). It is the rate at which coherently precessing nuclei dephase relative to each other after excitation and hence achieve thermal equilibrium amongst themselves. It is always a faster, or equally fast process than spin-lattice relaxation. The detection of these processes forms the basis of the MRI signal.
After a 90° pulse, the spins will tend to return to their equilibrium distribution, in which there is no transverse magnetisation, $M_x$ and $M_y$, and the longitudinal magnetisation, $M_z$, is at its maximum value and oriented in the direction of the static magnetic field.

Nuclear spin relaxation arises from the static and dynamic interaction of nuclear spins amongst themselves and with their surroundings. The relaxation rates depend critically on the magnitude of the interactions and also on the rate of their fluctuation. In this way both $T_1$ and $T_2$ relaxation times are very sensitive to molecular environment and motion. Both $T_1$ and $T_2$ relaxation times are very sensitive to local molecular motion. To a first approximation, $T_1$ depends on the amount of molecular motion at the MR experimental frequency which is usually in the 10MHz – 1GHz range. It varies significantly with MR frequency and depends on the correlation time of molecular motion, $\tau_c$. $T_2$ depends on low frequency molecular motion typically in the kHz range. A careful study of the frequency dependence of the relaxation times can reveal considerable detail about molecular motion of a wide frequency range. The theoretical link between relaxation and motion was first made by Bloembergen, Pound and Purcell [Bloembergen et al., 1946], after whom the model is commonly named the BPP theory. According to this theory, $T_1$ is long (typically 1-10s) for both very mobile liquids and very rigid solids whereas it is a minimum (typically ms) for an intermediate state with molecular motion characterised by intermediate correlation time, $\tau_c$, of the order of the inverse MR frequency, $\omega_0^{-1}$. Indeed it is a minimum when the average rate of molecular motion ($\tau_c^{-1}$) matches the NMR frequency $\omega_0$, i.e. $\omega_0\tau_c = 1$. $T_2$ is sensitive to the amount of motion at low frequency which increases as $\tau_c$ increases. Hence, $T_2$ is usually very short in solids ($\mu$s) so that $T_1<T_2$ whereas for liquids $T_2 \approx T_1$ and is of the order of seconds. The schematic dependence of both $T_1$ and $T_2$ on $\tau_c$ according to BPP theory is shown in Figure 2-8.
Figure 2-8: The dependence of T1 and T2 on the correlation time \( \tau_c \). For short \( \tau_c \) (\( \omega_0 \tau_c \ll 1 \)), T1 and T2 are equal. The fluctuations of the spins are averaged to zero known as extreme motional narrowing. At \( \omega_0 \tau_c = 1 \) T1 passes through a minimum. For long \( \tau_c \) (\( \omega_0 \tau_c > 1 \)), characteristic form less mobile samples a rigid lattice limit is reached and T2 attains a constant value.

2.2.2.2 Bloch equations

The master equations that govern the spin relaxation are the well-known Bloch equations [Bloch, 1946]. The Bloch equations provide a phenomenological description of the dynamics of nuclear spins. They summarise the interaction of nuclear spins with the external magnetic field (B₀) and its local environment (B₁). If at time t, following an RF pulse, the magnetisation has components \( M_x, M_y, \) and \( M_z \), then the rate of change of the magnetisation combined with the Larmor precession (equation 2-15 and 2-17) in the laboratory frame is described by:

\[
\frac{dM_x}{dt} = \gamma [M_y B_0 + M_z B_1 \sin \omega_0 t] \frac{M_x}{T_2}
\]

\[
\frac{dM_y}{dt} = \gamma [M_z B_1 \cos \omega_0 t - M_x B_0] \frac{M_y}{T_2}
\]

\[
\frac{dM_z}{dt} = \gamma [-M_z B_1 \sin \omega_0 t - M_y B_0 \cos \omega_0 t] \frac{M_z - M_0}{T_1}
\]

In the rotating frame these equations would be modified as:
In the laboratory frame, the longitudinal magnetisation returns toward the equilibrium value, $M_0$, with a time constant $T_1$ and the transverse magnetisation decays toward zero with a time constant $T_2$. Therefore, $T_2$ defines the MR signal lifetime.

### 2.2.2.3 Spin-lattice relaxation time $T_1$

The spin-lattice relaxation time $T_1$ can be determined by two distinct methods, the inversion recovery and the saturation recovery method [Haacke, 1999].

The inversion recovery experiment, also known as 180°-90° method, consists of a combination of two RF pulses. The first pulse, a 180° pulse inverts the longitudinal magnetisation, that is all the protons that were responsible for the net magnetic moment pointing upwards (+$z$ axis), now point downwards ($-z$ axis). In the absence of any further perturbation, the longitudinal magnetisation slowly reverts back up to its equilibrium direction. However, in order to acquire a signal a second pulse, 90° is applied after a time $\tau$. This pulse flips the longitudinal magnetisation existing at the time it is applied, into the transverse plane ($xy$-plane) where it rotates about the $z$-axis resulting in a FID signal, which can be measured. The amplitude of the signal is proportional to the magnitude of the $z$ magnetisation. The signal amplitude depends on the time between the 180° and the 90° pulse, which is known as inversion time, $\tau$ (pulse gap). Therefore, in order to measure $T_1$ it is necessary to vary $\tau$ and repeat the measurement. Measurements are repeated at a repetition delay (RD) interval long compared to $T_1$. Clearly, the optimum RD (approximately $5T_1$) is chosen by experience and trial experiment. A simple schematic representation of an inversion recovery sequence is presented in Figure 2-9 (see next page).

For short $\tau$, the longitudinal magnetisation immediately after the 90° inspection pulse ($t=0$) is equal to the negative of the equilibrium value

$$M_z(0) = -M_0$$  \hspace{1cm} 2-22

The recovery back to $+M_0$ is exponential and described by the Bloch equation the solution of which is

$$M_z(\tau) = M_0 \left(1 - 2e^{-\tau/T_1}\right)$$  \hspace{1cm} 2-23
The inversion recovery sequence is written as

\[ \text{[P}_{180} \tau \text{P}_{90} - \text{FID}] \]

Figure 2-9: The Inversion Recovery Sequence for measuring T₁, is the combination of two RF pulses applied in a number of repeated sequences for different τ values, each measurement separated by a delay RD.

The alternative process for measuring the T₁ relaxation time is the saturation recovery (SR) sequence. It a quicker method and consists of a chain of 90° pulses at relative short repetition times. Before the initial pulse is applied the longitudinal magnetisation, M₀, is at its maximum value, M₀. The first pulse disturbs the equilibrium and rotates the longitudinal magnetisation onto the xy-plane, perpendicular to the main magnetic field. At this point the M₀ is zero whereas the transverse magnetisation, Mₓy, is at a maximum value. Because M₀ equals zero, the nuclear spins are said to be saturated. For a long repetition time (5T₁) the saturated spins would fully recover resulting in FIDs of equal amplitudes each time [Bushong, 1996]. The M₀ magnetisation recovers with the T₁ relaxation time according to the formula derived from the Bloch equations

\[ M_z(\tau)=M_0(1-e^{-\tau/T_1}) \]

The saturation recovery sequence is written as

\[ \text{[(P}_{90} \tau \text{P}_{90})_n - \text{FID}] \]

2.2.2.4 Spin-spin relaxation time T₂

The spin-spin relaxation, T₂, can be measured by using “Spin-Echo” sequences. As mentioned earlier the application of a 90° pulse generates the precessing coherent transverse magnetisation,
As explained previously, due to magnetic field inhomogeneities and inter-nuclear interaction individual spins precess at different frequencies so that they gradually lose their phase relationship by fanning out (dephase). Therefore, the $M_{xy}$, hence the signal, reduces until eventually the spins are uniform distributed in the transverse plain and the signal disappears. The FID decays exponentially and the time constant that determines the rate of decay is $T_2$, derived from the Bloch equations.

$$M_{x,y} = M_0 e^{-t/T_2}$$  \hspace{1cm} (2-25)

However, by application of a 180° pulse the dephasing spins are inverted so that phase coherence is again established for a short time and a spin-echo signal is obtained. A schematic of echo formation is shown in Figure 2-10.

![Figure 2-10: Spin-echo sequence.](image)

It is necessary to separate relaxation due to inhomogeneity of the magnetic field, which is equipment specific (in the case of an inhomogeneous magnet or applied field gradient) or sample specific (in the case of an inhomogeneous sample like a porous medium) and that due to molecular motion which is again sample specific and is due to nuclear interaction. For rapidly relaxing components due to strong molecular interaction it is sufficient to excite the sample with a single pulse and to monitor the subsequent FID decay. For slower relaxing components a CPMG [Callaghan, 1993] sequence is used. In this sequence 180° pulses are regularly applied to refocus dephasing due to magnet inhomogeneity but not molecular interactions. The true decay is thus seen in the peak amplitudes of a train of echo signals.

In the CPMG sequence a 90° pulse is applied followed by a train of 180° pulses each separated by $2\tau$. This will obtain many spin-echoes and $T_2$ can be measured by tracing the decay of the echo sizes. In this case there is a 90° phase shift in the rotating frame of reference between the initial
90° pulse and the subsequent 180° pulse to reduce phase errors which are accumulated during the 180° pulse train.

The CPMG sequence can be written as

\[ [P_{90} \tau (P_{180} \tau \text{ echo } \tau)_n] \]

Two factors contribute to the decay of transverse magnetisation. (i) molecular interactions (said to lead to a pure $T_2$ molecular effect) (ii) variations in $B_0$ (said to lead to an inhomogeneous $T_2$ effect). The combination of these two factors is what actually results in the decay of transverse magnetisation. The combined time constant is called $T_2^*$ and is given the symbol $T_2^*$. The relationship between the $T_2$ from molecular processes and that from inhomogeneities in the magnetic field is as follows.

\[
\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_{2\text{inhomo}}} \quad 2-26
\]

### 2.3 Magnetic field gradients

In an NMR experiment, a measurement of the frequency of precession of the magnetisation gives information on the field experienced by that group of spins. In an MRI experiment spatial information about the spins in the sample can be obtained by the use of magnetic field gradients. A spatially varying magnetic field makes the frequency of the NMR signal depend upon position. The magnetic field gradients refer to an additional magnetic field applied using specially designed coils. They are usually applied as a series of pulses during an imaging study. The principle field direction remains along the same direction as the external magnetic field, $B_0$, but it varies in strength in any one of the direction is applied, $x$, $y$ and $z$. The field from a magnetic field gradient is not uniform throughout the sample. Actually, the strength of the field varies linearly with distance. Therefore, the amplitude of the signal at a particular frequency indicates the number of protons at a particular position. Magnetic field gradients can be applied in any direction

\[
G_x = \frac{dB_x}{dx}, \quad G_y = \frac{dB_y}{dy}, \quad G_z = \frac{dB_z}{dz} \quad \text{where } B_0 = B_z \quad 2-27
\]

where $G_x$, $G_y$ and $G_z$ are the linear applied gradients along the $x$, $y$, or $z$ directions. So in the presence of a magnetic field gradient, the local applied magnetic field is given by:

\[
B_0(r) = B_0 + G \cdot r \quad 2-28
\]

where $B_0$ is the applied field from the magnet and $G$ is the applied gradient along a position $r$. Given that the magnetic field varies linearly along $r$, the Larmor frequency now depends on the position of the spins within the sample:

\[
\omega_0(r) = \gamma (B_0 + G \cdot r) \quad 2-29
\]
This simple linear relation between the precession frequency $\omega$ and the nuclear spin coordinates, $r$, is of fundamental importance for the understanding of the imaging principle. According to the Larmor equation the magnetic field gradient causes identical nuclei to precess at slightly varied frequencies. A spatially variant magnetic field will lead to a spatially variant distribution of resonant frequencies.

Mansfield and Grannell (1973) introduced the concept of reciprocal space, called $k$-space. $k$-space does not correspond to the image. It is where the MR signal is stored and is an array of numbers whose Fourier transform is the MR image. $k$ is known as the wave number which refers to the number of a complete wave cycles that exist in one meter of linear space (units cycles m$^{-1}$).

$k$ is defined as the Fourier conjugate to the nuclear spin coordinate $r$ and for a constant magnetic field gradient is

$$ k = \frac{1}{2\pi} \gamma G t $$

where $t$ is the time for which the gradient is applied.

The NMR signal acquired in the time domain in the presence of imaging gradients in all directions may be written as

$$ S(k) = \int \int \rho(r) \exp(i 2\pi k \cdot r) \, dr $$

where $\rho(r)$ is the spatial distribution of spin density within the sample and the integral is over all sample volume, neglecting any relaxation decay. Performing inverse Fourier transform in all three directions of this sampled $k$-space data gives a description of the spatial distribution (or image) of spin density of the space scanned by $r$

$$ \rho(r) = \int \int S(k) \exp(-i 2\pi k \cdot r) \, dk $$

In other words, $S(k)$ is measured in the time domain while its Fourier transform yields $\rho(r)$ in the frequency domain. In this sense, it is valid to say that there is a correspondence between the real space and frequency, and between the reciprocal space and time [Callaghan, 1995]. So acquisition in the time domain, the signal is usually visualised as sampling $k$-space.

Depending on their function, the gradients are known as (i) slice select gradient, (ii) frequency encoding gradient and (iii) phasing encode gradient. The slice selection gradient is used to acquire an MR image from a particular location in the sample and with a particular thickness. The frequency and phase encode gradients are used to encode spatial information within the slice. A typical example of two-dimensional $k$-space imaging sequence is shown in Figure 2-11. The structure is common to many schemes for NMR imaging of an object slice.
Figure 2-11: Pulse sequence diagram of a two-dimensional spin-echo imaging experiment. The echo occurs at time $2\tau$ known as echo time, $T_E$. The slice gradient $G_S$, the phase encode gradient $G_P$ and the frequency encode gradient $G_R$ are shown.

- Slice selection

Slice selection is a technique to isolate a single plane in the object being imaged, by only exciting the spins in that plane. To do this a shaped RF pulse (selective pulse), which only affects a limited part of the NMR spectrum, is applied, in the presence of a linear magnetic field gradient, $G_S$, along the direction which the slice is to be selected. This results in the excitation of only those spins whose Larmor frequency, which is dictated by their position, is the same as the frequency of the applied RF pulse. The thickness of the slice is determined by the magnetic field strength across the sample and the length of the RF pulse. The Fourier transform of the RF pulse determines the profile of the excited slice. In Figure 2-11 the slice select gradient is applied at the same time as the initial RF pulse. The negative gradient is used for the same duration as the pulse to re-phase the spins of the excited slice at the start of the subsequent encoding. For a transverse image, $G_S$ is applied in the $z$-direction: $G_S = G_z$.

- Phase encoding

After the slice selection, a phase encoding gradient, $G_P$, is applied along for example the $y$-direction ($G_P = G_y$) for a fixed period of time and before the main acquisition time of the FID. The phase encoding gradient does not change the frequency of the acquired signal because it is not on during signal acquisition. However, it modulates the initial phase of the detected signal. By
repeating the experiment a number of times with different gradient amplitudes, it is possible to generate data that may be Fourier transformed to determine signal position [Keevil, 2001].

- **Frequency encoding**

The frequency encode gradient is applied linear and in a direction perpendicular to the slice select gradient, conventionally is applied along the x-direction, \( G_x \). It is turned on during NMR signal acquisition and for this reason it is also known as readout gradient \( G_R \) (\( G_R = G_x \)). As the readout gradient tends to dephase the coherences before the echo is formed, an extra gradient pulse is applied before the 180° pulse in order to compensate the first half of the read gradient as shown in Figure 2-11. After the application of the readout the resonance frequency of the spins responsible for the signal becomes a linear function of their position along the gradient direction. The Fourier transform of the acquired signal determines the amount of signal at each frequency and thus at each position. If only the read-out gradient is applied, a one-dimensional image, usually termed as profile, is obtained. In Figure 2-11 the compensate gradient has a positive magnitude because of the presence of the 180° pulse.

### 2.3.1 Image contrast

The contrast in an MR image is strongly dependent upon the way the image is acquired. By adding RF or gradient pulses, and by careful choice of timings, it is possible to highlight different components in the object being imaged.

The spin density throughout an object is directly related to the image contrast as if there are no spins present in a region it is not possible to get an NMR signal at all. In medical MRI, imaging is associated with the hydrogen nuclei in the mobile water and the image contrast comes most often from the degree of water mobility. In fact, as the water becomes less mobile, so the imaging becomes more difficult. For instance solid tissues (bones) give almost no signal because the water is relative immobilised and thus appear dark by contrast with soft tissues. An alternative imaging technique can be used such as X-ray CT for these purposes. However, as there is a small difference in proton spin density between most soft tissues in the body due to similar water content, other suitable contrast mechanisms must be employed. These are generally based on the variation in the values of \( T_1 \) and \( T_2 \) for different tissues.

The relaxation times \( T_1 \) and \( T_2 \) are very important in imaging, as they have the greatest effect in determining contrast. When describing the effect of the two relaxation times on image contrast, it is important to distinguish between relaxation time maps, and relaxation time weighted images. In the former the pixel intensities in the image have a direct correspondence to the value of the relaxation time, whilst in the latter the image is a proton density image which has been weighted by the action of the relaxation. The \( T_2 \) relaxation contrast is indeed a natural consequence of the
spin-echo imaging sequence. Only nuclei with a T₂ of the order of, or greater than the echo time contribute to the echo and so to image intensity. Shorter T₂ components decay away before the echo is formed and so they do not appear in the image.

Magnetic resonance images suffer from a number of artefacts. An image artefact is any feature which appears in an image which is not present in the original imaged object. The quality of the image can also be affected by various parameters such as magnetic field inhomogeneity and motion of spins during experiment.

2.4 Diffusion

Diffusion is the process through which small molecules are transported from one part of a system to another as a result of random molecular motions of the individual molecules. On average the molecules are transferred by diffusion from the region of higher to that of a lower concentration of the system. This process was recognised by Fick in 1855, who put diffusion on quantitative basis by adopting the same equation as that derived a few decades ago by Fourier (1822) for heat conduction [Crank, 1975]. The mathematical theory of diffusion for an isotropic substance is related to the rate of transfer of diffusing substance through unit area of a section that is proportional to the gradient of concentration measured normal to this section

\[ F = -D \frac{\partial c}{\partial x} \]  

where \( F \) is the rate of transfer of the diffusing substance per unit area of section, \( c \) is the concentration of the diffusing substance at position \( x \), \( \frac{\partial c}{\partial x} \) is the concentration gradient and \( D \) is the diffusion coefficient. If the \( F \) and the concentration are expressed with the same unit of quantity then the diffusivity is independent of this unit and has dimensions of \((\text{length})^2(\text{time})^{-1}\) or \( \text{cm}^2/\text{s} \). Equation 2-33 is applicable to the diffusion in the steady state, that is when the concentration does not vary with time. On the other hand, Fick's second law describes the nonsteady state transport process, where the concentration within the diffusing volume changes with respect to time.

\[ \frac{\partial c}{\partial t} = D \left( \frac{\partial^2 c}{\partial x^2} \right) \]  

This is the case where \( D \) is independent of concentration. In one-dimensional diffusion the concentration gradient is found only in one direction along for example the \( x \)-axis. In systems where \( D \) depends on the concentration of the diffusing substance then equation 2-34 becomes
\[
\frac{\partial c}{\partial t} = \frac{\partial}{\partial x} D \left( \frac{\partial c}{\partial x} \right)
\]

where concentration profiles can be measured with MRI.

### 2.4.1 NMR Diffusion

As mentioned, diffusion is a transport property of molecules. Translational diffusion across a nonzero concentration gradient is one such case; if the concentration gradient is zero (i.e., homogeneous with respect to concentration), then the translational diffusion process is referred to as self-diffusion. The study of diffusion reduces ultimately to the study of molecular motions—or dynamics—and can therefore provide valuable physical information.

In 1965 Stejskal and Tanner [Stejskal and Tanner, 1965] demonstrated that pulsed magnetic field gradients could be used in NMR to probe the displacement of protons in a sample. A standard pulsed gradient spin-echo (PGSE) and a stimulated echo pulsed field gradient sequence, is shown in Figure 2-12.

**Figure 2-12:** (a) Pulse gradient spin-echo sequence, (b) Stimulated echo pulsed field gradient sequence.

The PGSE sequence consists of a spin-echo sequence with two magnetic field gradients on each side of the 180° RF pulse. The first gradient imposes a phase shift on the nuclear spins in a sample, which depends upon position according to
\[ \phi = \gamma g \cdot r_1 \delta \]

where \( g \) is the gradient strength, \( r_1 \) is the position of the spin and \( \delta \) is the duration of the pulse. This phase shift is reversed by the 180° RF pulse. If the spins do not move during the diffusion time, \( \Delta \), the second PFG pulse exactly reverses the effect of the first and the NMR signal has intensity equal to that in the absence of the PFG pulse pair. However, if the spins do move to a different spatial position, \( r_2 \), then the second PFG pulse is unable to exactly reverse the effect of the first and the spins have a residual phase shift of \( \gamma \delta g \cdot (r_1 - r_2) \), where the negative sign arises from the refocusing effect of the 180°, at the echo formation time \( 2\tau \). Averaged over all of the nuclei results in an attenuation of the echo signal which is depend on the diffusion coefficient, \( D \), the diffusion time, \( \Delta \), and the duration and strength of the gradient. So, this sequence uses the difference in the position dependant phase shifts on the precession of the resonant nuclei in the sample to measure their movement during the diffusion time, \( \Delta \). The phase shift increases according to how far spins in the sample have moved during the diffusion time. As the gradient pulses are stepped up in strength, causing the phase shift imparted by the gradient pulses to increase, for each spin and hence attenuation of cumulative signal for all of them, the magnetisation decays according to:

\[
S_{(g)}/S_{(0)} = \exp \left[ -\gamma^2 g^2 \delta^2 D (\Delta - \delta/3) \right]
\]

where \( D \) is the diffusion coefficient, and \( S \) is the signal intensity. This indicates that the signal will also decay as the diffusion time is increased. The self-diffusion coefficient, \( D \), can be obtained from the semilogarithmic plots of \( S \) versus \( \gamma^2 g^2 \delta^2 (\Delta - \delta/3) \).

In the case where \( D \) is small and \( T_2 << T_1 \), an alternative of this method can be used with three-pulsed stimulated echo variant as shown in Figure 2-12(b) [Tanner, 1970]. Two 90° RF pulses are used instead of a single 180° RF pulse to prevent spin-spin relaxation of the sample magnetisation during the diffusion time; the second 90° RF pulse stores the magnetisation along the longitudinal axis. The stored magnetisation is recalled at later time by a third 90° RF pulse and rephrased in a stimulated echo (echo generated by sequence of three 90° RF pulses). This still allows the possibility of spin-lattice relaxation during the indicated gap, \( \tau \) between the 90° RF pulses with \( T_1 \) is generally slower than \( T_2 \) [Callaghan, 1995].

Very small diffusion coefficients require either very strong gradients or long diffusion times. The use of high-gradient system is related with the technique of Stray Field Magnetic Resonance Imaging (STRAFI). Stray Field Magnetic Resonance Imaging (STRAFI) exploits the very large magnetic field gradient in the order of 60T/m available in the fringe or stray field of a superconducting magnet. A fringe-field diffusion measurement of small diffusion coefficients has seen much development in recent years and the strong peripheral gradient has made possible the
study of diffusion coefficients as small as $10^{-11}\text{cm}^2\text{s}^{-1}$ in a variety of polymer melts and solutions [Kimmich et al., 1991].

2.5 X-ray Computed Tomography

In 1973 Hounsfield [Hounsfield, 1973] first developed the computerised axial tomography, which is nowadays referred to as computed tomography or CT. Hounsfield’s scanner consisted of a finely collimated source defining a pencil beam of X-rays, which is then measured by a well collimated detector. MR also owes a debt to computed tomography (CT) as it was initially developed on the back of CT. When Lauterbur [Lauterbur, 1973] first demonstrated magnetic resonance imaging in 1973 he used a back projection technique to reconstruct the images similar to that originally used in CT. The impact that CT had in the medical community is not to be disregarded as it stimulated interest both of clinicians and manufacturers to the potential impact of the MRI technique. It had already demonstrated the advantage of tomographic sections through the head or body of a patient allowing diagnosis of disease processes in a non-invasive way.

X-ray CT is a technique that uses x-rays to produce images of thin slices. It is a non-destructive, non-invasive imaging technique, which provides cross-sectional images in different planes through a component. In this thesis a third-generation cone-beam X-ray CT scanner was used, illustrated in Figure 2-13. An X-ray source and an X-ray detector are placed at opposite sides of a sample which sits on a precision mechanical turntable. The X-ray detector is used to measure the intensities of the X-ray beam transmitted through the sample, as the sample is rotated in the cone-beam.

![Figure 2-13: Schematic diagram of the third-generation cone-beam X-ray CT system](image)

The X-ray cross-sectional images are generated by processing the transmitted intensities. A mathematical algorithm is then used to generate (or reconstruct) the CT images from the measured transmitted intensities. A 3D CT data can be obtained from a single rotation of the component and cone beam reconstruction algorithms are then needed to compute the 3D CT dataset. The reconstruction of the X-ray CT images is discussed later in Chapter 3. In both CT and
MRI, physical characteristics of a volume element or "voxel" of the sample are translated by the computer into a two dimensional image composed of picture elements or "pixels". The pixel intensity in CT reflects the electron density of the material whereas in MRI, as already seen, the signal intensity reflects the density of mobile hydrogen nuclei modified by the chemical environment, that is, by the magnetic relaxation times, $T_1$ and $T_2$, and by motion. Therefore, X-ray CT is a suitable choice for skeletal imaging or solid materials that have low proton spin density.

The resultant CT images are true cross-sectional images, and show the geometry of the component in the plane of the cross-section. If an X-ray source with a very small size (microfocus source) is used, then the spatial resolution achievable can be very high (circa. 10µm for mm sized components) [Burch et al., 2004]. At any instant of time during the scan, the beam of x-rays is attenuated by the sample: different parts of the beam are attenuated by varying amounts, depending on the types and amounts of the materials the x-rays pass through. Materials which attenuate the x-rays more strongly appear lighter (whiter) in the image and others which are less attenuating appear darker (black). The CT image values known as grey-levels give information on the material x-ray attenuation at each point in the image. The CT grey levels can be converted to values which are directly proportional to the local material density.

Apart from the clinical use of X-ray CT the technique has found a vast application in studying materials. In this thesis X-ray CT has been used to study the microstructure of the system as it provided spatial resolution of 10µm.

### 2.6 Ultraviolet (UV) Spectroscopy

UV-Vis spectroscopy probes the electronic transitions of molecules as they absorb light in the UV and visible regions of the electromagnetic spectrum (UV = 200-400nm, Visible = 400-800nm). Any species with an extended system of alternating double and single bonds will absorb UV light, and anything with colour absorbs visible light, making UV-Vis spectroscopy applicable to a wide range of samples. For organic compounds in solution the visible region is of less importance as most of the organic compounds are colourless. UV spectra used for determination of structures are commonly obtained in solution.

A basic UV spectrophotometer consists of an energy source, a sample cell, a dispersing device (prism or grating) and a detector.
Chapter 2: Basic Principles of Imaging

Radiation source  Sample  Dispersing device or prism  Slit  Detector

Figure 2-14: Simple schematic diagram of a UV spectrophotometer.

The drive of the dispersing device is synchronised with the x-axis of the recorded so that the latter indicated the wavelength of radiation reaching the detector via the slit. The prism will bend the light in different degrees according to the wavelength. The signal from the detector is transmitted to the y-axis of the recorder indicating the amount of radiation absorbed by the sample at any particular wavelength. Most instruments use double-beam where the absorption of a reference cell, containing only solvent for example if the sample is dissolved in water it will contain only water, is subtracted from the absorption of the sample cell. The energy source, the materials from which the dispersing device and the detector are manufactured must be appropriate for the range of wavelength scanned and as transparent as possible to radiation.

The absorbance of a solution increases as attenuation of the beam increases. Absorbance is directly proportional to the length of the sample cell, \( b \), and the concentration, \( c \), of the absorbing species. Beer's Law states that \( A = ebc \), where \( e \) is a constant of proportionality, called the absorbitivity. Different molecules absorb radiation of different wavelengths. An absorption spectrum will show a number of absorption bands corresponding to structural groups within the molecule.
Chapter 3

3 Materials and Methods

In this chapter the materials and experimental methods used in this study are presented. The chapter is organised in two sections. The first is associated with the physical and chemical characterisation of the materials under study. The second is focused on describing the experimental methods used to obtain the information on the dissolution of the sample matrix. The methods included the spectroscopic characterisation of the materials and the imaging studies of drug release from the solid polymer matrix.

3.1 Materials

The solid matrix chosen in this study was Eudragit RSPO and the chosen active drug was Diltiazem Hydrochloride (HCl). Both the polymer and drug were supplied by Napp Pharmaceuticals Research Ltd manufactured by Degussa Rohm Pharma Polymers, Germany.

Eudragit RSPO is a copolymer of acrylic and methacrylic acid ester. It is a solid substance in the form of white powder. It is insoluble in aqueous media, as taken from manufacturers data sheet, but it is permeable, plasticised and has pH-independent release profile. The permeability in water is due to the presence of quaternary ammonium groups in its structure, which are present as salts [Haznedar and Dortunc, 2004]. Omari et al. [Omari et al., 2004] and Oth and Moes [Oth and Moes, 1989] suggested that Eudragit RS was capable of swelling in digestive fluid independently of pH. In this thesis 100% Eudragit tablets were exposed to water and experimental evidenced showed virtually no swelling of the tablet.

Eudragit RSPO is commonly used in film coating of tablets, granules and other small particles and also in matrix formulation. It is a high molecular weight polymer, MW: 150 000, and tablets consisting of Eudragit as binder exhibit some advantages as hardness, palatability, strength and stability [Droin et al., 1985]. The chemical structure of the polymer is shown in Figure 3-1.
The active drug, Diltiazem HCl, is a calcium ion influx inhibitor, slow channel blocker or calcium antagonist widely used in the treatment of angina pectoris, cardiac arrhythmia and hypertension [Kristmundsdottir et al., 1996]. It is a solid substance in the form of a white to off-white crystalline powder with a bitter taste. It is soluble in methanol, chloroform and water and it is odourless. It has a molecular weight of 450.98 [The Japanese Pharmacopoeia, 2001]. The chemical structure of the active drug is in Figure 3-2.

Figure 3-1: Chemical structure of Eudragit RSPO (redrawn from manufacturer data sheet).

Figure 3-2: Chemical structure of Diltiazem Hydrochloride -(2S,3S)-5-[2-(Dimethylamino)ethyl]-2,3,4,5-tetrahydro-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazepin-3-yl acetate monohydrochloride (redrawn from [Glaser and Sklarz, 1989]).
3.2 Methods

3.2.1 Magnetic resonance spectroscopy and imaging studies

In this study magnetic resonance spectroscopy and imaging experiments were carried out using a 400MHz spectrometer and a 9.4T superconducting magnet. The magnet was equipped with room temperature shims for improving the heterogeneity of magnet and x,y,z gradient sets with strength up to 80G/cm for spatial localisation of signals in imaging and diffusion experiments. The shim and gradient coils started to heat up as current passed through and in order to avoid the overheating of the coils a cooling system comprising of a water pump was used. The sample was placed in a NMR sample probe, which contained a built-in radiofrequency (RF) coil that was as close around the sample as possible. The RF coil has two purposes: (i) to transmit RF pulse into the sample so as to excite the nuclear spins and (ii) to detect the magnetic fields created by the precessing magnetisation. The sample was placed into the NMR probe so that the area of interest was within the coil. A computer was used to send the signal to initiate the pulse sequence and to receive and process the data that the instrument acquired. A detail description of the apparatus set up and principles can be found in [Leach, 1992]. A simple schematic diagram of a MRI system is shown in Figure 3-3.

![Figure 3-3: Block diagram of the MRI system used for the imaging experiments.](image)

The MRI equipment at the University of Surrey (Figure 3-4) consists of a 400 $^1$H MHz Chemagnetics Infinity Spectrometer (Varian Solid State Office, UK) coupled to a Magnex 9.4T (89mm diameter bore) superconducting magnet (Magnex Scientific, Oxon, UK). The
radiofrequency was amplified by a Higher Voltage Power Supply from Creative Electronics (Los Angeles, California) for the proton, $^1$H, spectrum and Chemagnetics Power Supply for the carbon, $^{13}$C. The imaging gradients and Matrix Shim Set were supplied by Resonance Research Instruments, USA. A double tuned $^{13}$C-$^1$H probehead (IBMT, Fraunhofer Institute, Germany) was used for the CYCLCROP experiment (see Section 3.2.2.2) and a $^1$H microscopy probe from the same manufacturer was used for $^1$H imaging and spectroscopy experiments.

![Figure 3-4: $^1$H MRI microscopy (9.4T) facility at the University of Surrey.](image)

The magnetic resonance spectroscopy and imaging experiments were controlled from Spinsight version 4.1 (Chemagnetics NMR products, Otsuka electronics, USA), which is a data acquisition and processing software. The acquired data were saved in the form of ASCII files, single raw data, and processed using code written in IDL version 5.5 (Research Systems Inc., Colorado, USA) with incorporated standard processing for the Fourier Transformation. Details on acquisition parameters for each experiment are discussed in the following sections.

$^1$H NMR $T_1$ and $T_2$ relaxometry measurements were also acquired using a bench-top 20 $^1$H MHz Maran permanent magnet (0.5T) spectrometer from Resonance Instruments. The resulting data were plotted in xMgr version 4.1.2 graphing program where the $T_1$ and $T_2$ relaxation times were calculated.

All the graphs presented in this thesis were plotted in Microsoft Office Excel 2003.
3.2.2 NMR Characterisation of Raw Materials

All the experiments described in the following sections were conducted at least two times apart from the T₁ and T₂ measurements of the equilibrated Eudragit tablets in Section 3.2.2.1. Results are discussed in Chapter 4.

3.2.2.1 T₁ and T₂ characterisation of equilibrated Eudragit samples

Experiments were carried out to optimise experimental procedures and characterise the materials under study. The ¹H NMR T₁ and T₂ relaxation times of water swollen, spatially and temporally equilibrated Eudragit samples at two different NMR frequencies, 20MHz and 400MHz were determined.

Samples of known concentrations were prepared each containing 3.00gr of Eudragit variously swollen by milli-Q water ranging in amount from 0.0ml to 0.9ml. The samples were made up in NMR tubes. The exact amount of water was first put in the tubes followed by the weighed powder. The tubes were carefully sealed by wrapping the NMR cups with paraffin film to prevent water evaporation and the weight of each one was recorded. The samples were shaken thoroughly and left to equilibrate. Complete spatial equilibration took approximately six weeks during which the samples were held vertically in an oven at up to 60°C. Throughout this period measurements of T₁ and T₂ were made to optimise the experimental parameters and to check on the equilibration by recording the changes in the measured values. From time to time samples were re-weighed so as to check for any loss of water. The “definitive” measurements were made after seven weeks at which point T₁ and T₂ results were not evolving noticeably further. All the measurements were conducted at room temperature. The resulting water mass fraction for each equilibrated Eudragit sample is listed in Table 3-1.

<table>
<thead>
<tr>
<th>Sample (ml H₂O / 3.0gr Eudragit)</th>
<th>Mass fraction of H₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.00</td>
</tr>
<tr>
<td>0.1</td>
<td>0.03</td>
</tr>
<tr>
<td>0.2</td>
<td>0.06</td>
</tr>
<tr>
<td>0.3</td>
<td>0.09</td>
</tr>
<tr>
<td>0.4</td>
<td>0.12</td>
</tr>
<tr>
<td>0.5</td>
<td>0.14</td>
</tr>
<tr>
<td>0.6</td>
<td>0.17</td>
</tr>
<tr>
<td>0.7</td>
<td>0.18</td>
</tr>
<tr>
<td>0.8</td>
<td>0.21</td>
</tr>
<tr>
<td>0.9</td>
<td>0.23</td>
</tr>
</tbody>
</table>
The low frequency measurements were recorded using a bench-top $^1$H 20MHz permanent magnet, whereas the high frequency measurements were carried out at $^1$H 400MHz using a Chemagnetics Infinity spectrometer with vertical bore super conducting magnet, both described in Section 3.2.1. For both NMR frequencies, the $T_1$ was measured using the inversion recovery method, whereas the $T_2$ was determined from the 90°-Free Induction Decay (FID) pulse sequence and the CPMG sequence. A schematic diagram of the pulse sequences used and the data parameters are summarised in Figure 3-5 and Table 3-2.

Figure 3-5: (a) Inversion recovery pulse sequence for measuring $T_1$ and (b) 90°-Free Induction Decay (FID) pulse sequence and the CPMG sequence for measuring $T_2$ both at 20MHz and 400MHz.
Table 3.2: Summary of data used to measure $T_1$ and $T_2$ at $^1$H 20MHz and 400MHz.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Method</th>
<th>Sequence</th>
<th>$P_{90}$ (µs)</th>
<th>$\tau$ (pulse gap)</th>
<th>RD*(s) Averages</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_1$ relaxation</td>
<td>Inversion</td>
<td>$[P_{180} \tau P_{90} - FID]$</td>
<td>3.7</td>
<td>0.02s &lt; 2s</td>
<td></td>
</tr>
<tr>
<td>time</td>
<td>recovery</td>
<td></td>
<td>3.6 (0.9ml H$_2$O)</td>
<td>0.05s &lt; 3s</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.8 (0.2ml H$_2$O)</td>
<td>(0.7,0.8,0.9ml H$_2$O)</td>
<td></td>
</tr>
<tr>
<td>$T_2$ relaxation</td>
<td>FID</td>
<td>$[P_{90} - FID]$</td>
<td>3.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>time</td>
<td></td>
<td></td>
<td>3.6 (0.9ml H$_2$O)</td>
<td></td>
<td>10 16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.8 (0.2ml H$_2$O)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CPMG</td>
<td>$[P_{90} \tau (P_{180} \tau echo \tau)_{13C}]$</td>
<td>3.7</td>
<td>128µs</td>
<td>10 16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.8 (0.2ml H$_2$O)</td>
<td>256µs</td>
<td></td>
</tr>
</tbody>
</table>

*RD=repetition delay

3.2.2.2 $^{13}$C-$^1$H CYCLCROP spectroscopy of Diltiazem HCl concentrated solution

Experiments were conducted on concentrated Diltiazem HCl solution in order to selectively obtain MR signals from specific --CH$_3$ groups in the molecule and their corresponding protons and importantly to suppress the water signal. For this purpose cyclic $J$ cross polariisation (CYCLCROP) technique was applied which allowed the indirect detection of $^{13}$C nuclei coupled to $^1$H nuclei with the high NMR sensitivity of protons and therefore considerably better signal-to-noise compared to direct $^{13}$C NMR. The experiments were carried out using CYCLCROP $^{13}$C-edited spectroscopy on a 9.4T superconducting magnet (Section 3.2.1).

The principle of the CYCLCROP [Heidenreich et al., 1998] editing sequence involved the selection a single resonance from a specific location of a molecule while suppressing all other resonances from the sample. The sequence consisted of two successive polarisation processes where the magnetisation was transferred within the selected group from the $^1$H to the $J$ coupled $^{13}$C nucleus ($^1$H→$^{13}$C) and backward to the $^1$H nuclei ($^{13}$C→$^1$H). The transfer began by applying a radiofrequency (RF) pulse (90°) followed by a spin lock pulse (SL) on the primary side ($^1$H nuclei) and a contact pulse (CP) applied on the secondary side ($^{13}$C nucleus). At the intermediate stage of the polarisation transfer cycle a combination of $^1$H radiofrequency and gradient pulses were applied so as to saturate all the uncoupled protons [Kunze et al., 1993], [McDonald et al., 1994].
The desired magnetisation was fully transferred and stored to the $^{13}$C nuclei. The outcome of the CYCLCROP editing sequence was a FID signal in time domain.

Polarisation took place when SL & CP were matched according to the Hartmann/Hann condition [Kunze and Kummich, 1994]

$$\gamma_C B_{1\text{,eff},C} = \gamma_H B_{1\text{,eff},H}$$  \hspace{1cm} (3-1)

where $\gamma_C$ and $\gamma_H$ were the gyromagnetic ratios of $^{13}$C and $^1$H respectively and $B_{\text{eff,H}}$ and $B_{\text{eff,C}}$ were the magnetic fields effective in the doubly rotating frame. A schematic representation of the CYCLCROP editing sequence is shown in Figure 3-6.

In order to obtain a strong signal for the drug a highly concentrated solution was required. The solution was prepared by gradually dissolving Diltiazem HCl powder in milli-Q water (in house). Initially, 2ml of milli-Q water were put in an NMR tube and small amounts of the drug were added progressively, mixed and dissolved until the solution became saturated. The final concentration of the drug solution was 29% (w/v), containing 0.8gr powder in 2ml of water. Above this concentration the drug could not dissolve in solution. The $^1$H and $^{13}$C spectra of the 29% (w/v) Diltiazem HCl solution were recorded at a set frequency of 400MHz and 100MHz respectively, with a 90° pulse of 27μs for both spectra, (for pulse sequence see Figure 3-5(b) the 90°-(FID) sequence) in order to select a specific -CH$_3$ group in the molecule and conduct the CYCLCROP editing sequence. Due to $^{13}$C natural abundance it was necessary to centre the proton

![Figure 3-6: The CYCLCROP editing sequence.](image-url)
and carbon channels at the respective frequencies yielding a better signal-to-noise. The
CYCLCROP spectrum was obtained with typical parameters of: contact time of 4.5ms; 90° pulse
of $21\,\mu s$ ($t=$contact time + 90° pulse, see Figure 3-6); gradient time of 3ms; and saturation time of
about 38ms. The NMR measurements usually required between 15 and 60mins for a typical $^1$H
analysis and a few hours for the $^{13}$C. For a complete CYCLCROP editing sequence the time
required was dependent on the parameters set. All measurements were conducted at room
temperature.

3.2.2.3 Self-Diffusion measurements of drug and water mobility in Diltiazem HCl
solutions

Drug solutions of various concentrations were prepared in order to determine the self-diffusion
coefficient of the actual drug, Diltiazem HCl, and water using the spectroscopically resolved
stimulated-echo pulsed-field-gradient method (Chapter 2, Section 2.4.1).

![Figure 3-7: Stimulated-echo pulsed-field-gradient sequence.](image)

The pulse sequence is similar with that discussed in Chapter 2, Figure 2-12. They only differ in an
extra gradient pulse that was put before the start of the actual pulse sequence as shown in Figure
3-7. The extra pulse served no purpose other than to “warm-up” the amplifiers and compensate
against “pulse droop”. In these experiments the drug was dissolved in a 2ml solution containing
95% D$_2$O / 5% H$_2$O. Deuterated water (D$_2$O) [Sigma-Aldrich Chemicals] was used in order to
reduce the dominant water signal intensity to levels typical of the drug. The samples studied are
listed in Table 3-3.

<table>
<thead>
<tr>
<th>% Drug concentration (w/v)</th>
<th>Drug weight (gr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.1</td>
</tr>
<tr>
<td>13</td>
<td>0.3</td>
</tr>
<tr>
<td>20</td>
<td>0.5</td>
</tr>
<tr>
<td>26</td>
<td>0.7</td>
</tr>
<tr>
<td>29</td>
<td>0.8</td>
</tr>
</tbody>
</table>
Typical parameters in standard notation for the diffusion stimulated-echo PFG experiments were: gradient pulse length, $\delta = 5\text{ms}$; pulse gap, $\tau = 10\text{ms}$; repetition delay $= 8\text{s}$; and the number of averages $n = 128$. The diffusion data were obtained using an array of field gradient strengths varied between 2 and 80G/cm in steps of 1G/cm and at diffusion times, (gradient pulse separation), $\Delta$, of 30 and 120ms. The resulting spectra were obtained from the FT of the recorded signal. All measurements were carried out at room temperature.

3.2.3 Imaging studies of drug release from a solid polymer matrix

All the experiments described in the rest sections were conducted at least two times. Results are discussed in Chapter 5.

3.2.3.1 Magnetic resonance imaging studies of drug release from a solid matrix under static dissolution conditions

MRI experiments on water exposed samples were conducted to follow the water ingress, the sample swelling and dissolution, and the drug release in order to understand the dissolution mechanism of the sample. The sample matrix was prepared by mixing the two components. The mixture was compressed in an instrumented single-punch tablet machine (IP Technical Services, UK) equipped with 9mm flat-faced punches in order to obtain tablets weighing $240 \pm 2\text{mg}$, $3.0 \pm 0.2\text{mm}$ in height and compressed at 2tons (0.303GPa). The tablets were placed into 9mm external diameter NMR tubes exposing both of its surfaces to lightly copper sulphate (CuSO$_4$) [Fisher Scientific] doped water ($3.7 \times 10^{-4}\text{M}$). The purpose of CuSO$_4$ in the water was to reduce the nuclear spin-lattice relaxation time of pure water, which normally is in the order of some seconds to a few hundred milli-seconds. This led to an improved signal averaging capability as the shorter relaxation time allowed higher number of repetitions. The above experimental set up corresponded to a static dissolution experiment and a schematic diagram of the sample in the magnet is shown in Figure 3-8, where the tablet was supported by a teflon sleeve, which is $^1\text{H}$ MRI invisible. In the rest of the thesis the copper sulphate (CuSO$_4$) doped water is referred to just water for convenient purposes. This applies only for the static dissolution experiments.
The $^1$H MRI 2D images of a vertical slice were acquired on the 400 $^1$H MHz superconducting magnet (9.4T) (see Section 3.2.1). A standard spin-echo imaging sequence (Chapter 2, Section 2.3) was used with echo time of 4ms, repetition delay of 4s and number of averages 2. The NMR signal was sampled 512 times during the acquisition period and the phase-encoded gradients were stepped in 64 repeats. A sine-bell apodisation was applied both in read direction and phase direction. In the phase it corresponded to both the static magnetic field direction and to the vertical direction in the tablet and in the second it corresponded to the horizontal direction. The slice was at the centre of the tablet with thickness of 1mm. The image quality is defined by its resolution. The pixel resolution is given by field-of-view (FOV) divided by the number of data points acquired. The FOV determines the size of the region scanned according to

$$\text{FOV}_{\text{read}} = \frac{1}{\Delta k_{\text{read}}} \quad \text{and} \quad \text{FOV}_{\text{phase}} = \frac{1}{\Delta k_{\text{phase}}}$$

where $\Delta k_{\text{read}} = \gamma G_{\text{read}} \Delta t$ and $\Delta k_{\text{phase}} = \gamma G_{\text{phase}} \Delta r$ where $t$ is the time of gradient applied in the read-direction and $r$ is the time of gradient applied in the phase-direction. The resultant magnitude Fourier transformed image field-of-view (FOV) was 15×24mm$^2$. The actual image resolution (after apodisation) was a few pixels. The in-plane pixel resolution was calculated from

$\text{Pixel size}_{\text{read}} = \frac{\text{FOV}_{\text{read}}}{\text{scan matrix}_{\text{read}}}$

$\text{Pixel size}_{\text{phase}} = \frac{\text{FOV}_{\text{phase}}}{\text{scan matrix}_{\text{phase}}}$
Hence the image pixel size was 29x375μm². The total time required to obtain an image varied from 4 to 34mins depending on the number of averages accumulated and the phase-encoded gradient steps.

The MRI experiments were performed as a function of manufacturing parameters including drug loading, compaction level, different particle size components for both polymer and drug and more which are fully described in the following sections. All experimental data were obtained for tablets primary compressed at 2tons, and exposed to water under static dissolution conditions. The ¹H MRI images were acquired at room temperature with similar pulse sequence and parameters set described above.

3.2.3.2 Water ingress into polymer, drug and polymer incorporating drug tablets

MRI experiments on water exposed Eudragit tablets incorporating different drug loadings were carried out in order to observe the effect of drug load to water diffusion and dissolution of the sample matrix. The drug loaded Eudragit tablets were prepared as described above containing a wide range of drug concentrations ranging from 5% up to 85%.

Similar, MRI experiments on 100% Eudragit and 100% Diltiazem HCl compressed tablets (prepared as in Section 3.2.3.1) were conducted to observe the effect of water on the tablets. For the 100% Eudragit tablets the images of samples prepared at two different compression levels, 0.1 and 3tons (0.015 and 0.455GPa) were also obtained. Moreover, T₁ weighted images of those were acquired from a saturation recovery sequence. The primary use of the saturation recovery sequence was to measure T₁ relaxation time. As already discussed in Chapter 2 Section 2.2.2.3, saturation recovery sequence consisted of multiple 90° RF pulses at relatively short repetition times (delay). The RF pulse tilted the magnetisation of the spin system into the xy-plane perpendicular to the main magnetic field and the spin system was saturated. Applying a T₁ saturation delay time, τ, on a standard saturation recovery sequence it was possible to obtain a T₁ weighted image. A simple diagram of the sequence is shown in Figure 3-9.

![Figure 3-9: Diagram of pulse sequence used to acquire a T₁ weighted image.](image)

Typical parameters include P90 of 85μs, echo time of 10ms, repetition delay of 1000ms and number of averages 4. The NMR signal was sampled 128 times during the acquisition period, the phase-encoded gradients were stepped in 16 repeats and the slice thickness was 1mm. The T₁
weighted image was obtained for an array of saturation delay times ranging from 50ms to 4000ms.

### 3.2.3.3 Water ingress into drug loaded Eudragit tablets with different particle size components

Tablets with different particle size components for both polymer and drug were examined in order to observe the effect of particle size on dissolution. The $^1$H MRI images of the tablets were acquired with similar parameters as before for samples listed in Table 3-4.

Table 3-4: Drug loaded Eudragit tablets having different particle size fractions for both polymer and drug.

<table>
<thead>
<tr>
<th>% Drug concentration (w/w)</th>
<th>Polymer particle size ($\mu$m)</th>
<th>Drug particle size ($\mu$m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>&lt;45</td>
<td>100-180</td>
</tr>
<tr>
<td>45</td>
<td>100-180</td>
<td>&lt;45</td>
</tr>
<tr>
<td>45</td>
<td>100-180</td>
<td>45-100</td>
</tr>
<tr>
<td>25</td>
<td>45-100</td>
<td>45-100</td>
</tr>
</tbody>
</table>

### 3.2.3.4 Water ingress into drug loaded Eudragit tablets incorporating a third component in the sample matrix

A third highly soluble component was incorporated into the sample matrix in an attempt to achieve faster dissolution of the drug. The third component used was Sucrose [Sigma-Aldrich Chemicals] due to its high solubility (1gr in 0.5ml water), its ready availability in various particle sizes from large granular to fine powder and the fact that it has been used in pharmaceutical formulations as a channel former in matrix systems. The three component tablet had similar structure as the one described for the two component system. The $^1$H MRI 2D images were recorded with analogous parameter sets as done before. The amount of sucrose into the tablet varied from 5%, to 30% and the ratio of polymer/drug was always kept 55/45. It is noted that sucrose was ground to a dry fine powder prior to mixing with the other components.

### 3.2.3.5 Water ingress into drug loaded Eudragit tablets exposed to water using Eudragit RLPO as polymer

MRI experiments were conducted on drug loaded Eudragit samples using Eudragit RLPO as polymer rather than Eudragit RSPO. The structure of Eudragit RSPO and RLPO differ only in the extent of the quaternary ammonium substitutions, with RSPO containing much less than RLPO. The ammonium groups are present as salts and are believed to make the polymer more permeable. So, water can permeate more freely into Eudragit RLPO than RSPO, due to the relative hydrophilicity of the RLPO polymer, and their permeability to water is unaffected by pH [Azarmi
et al., 2002]. The tablets were prepared according to method in Section 3.2.3.1 and images were acquired with parameter sets mentioned in the same section.

### 3.2.4 Magnetic resonance imaging studies of drug release from solid polymer matrix exposed to different dissolution environment

The effect on the dissolution mechanism was observed by changing the surrounding environment to which the tablet was exposed to. Different experimental conditions were investigated details of which are described in the following sections.

#### 3.2.4.1 Magnetic resonance imaging studies of drug release from a solid polymer matrix under dynamic dissolution conditions

In these experiments the $^1$H MRI 2D images of the samples were recorded while tap water was continuously flowing over the tablet surface. This assessed the feasibility to observe the effect of water flow, over the surface of the tablet, on dissolution and to determine the concentration of drug released. The experimental set up of such system is shown in Figure 3-10.

![Diagram of the dynamic dissolution cell.](image-url)

**Figure 3-10: Diagram of the dynamic dissolution cell.**
In the dynamic dissolution experiments the samples were made up of a layer of 55% (w/w) drug loaded Eudragit tablet above a 100% Eudragit layer as shown in Figure 3-10. The lower Eudragit layer was to provide structural integrity as experiments proceeded. Tap water was passed through a capillary tube, over the surface of the drug loaded Eudragit tablet and diffused into the system so as to dissolve the drug. The drug was released from the polymer and collected with the water that came out of the system, as shown in Figure 3-10. Analysis of that water gave the opportunity to gain information, such as the rate at which the drug was diffused out of the tablet and the amount of the drug present in the water, from a different perspective and correlate the results with those obtained from static measurements. The amount of drug in the water sample collected at different time points from the dynamic dissolution experiments was estimated using UV spectroscopy, which is discussed in Section 3.2.6. Moreover, dynamic experiments were carried out using different water flow rates in order to examine any change in the release rate and also any effect in the images. The $^1$H MRI 2D images of the samples were recorded using a similar acquisition method as in static dissolution experiments except the repetition delay was changed to 10s due to tap water).

3.2.4.2 Magnetic resonance imaging studies on drug loaded Eudragit tablets exposed to phosphate buffer pH 7.4

$^1$H MRI 2D images were recorded for samples exposed to phosphate buffer solution pH 7.4, under static dissolution in order to observe any different behaviour in the system (swelling). The phosphate buffer was prepared as follows; 1.38grams of disodium hydrogen phosphate [Sigma-Aldrich Chemicals], 0.19grams potassium dihydrogen phosphate [Fisher Scientific Chemicals], 0.20grams of sodium azide [Fisher Scientific Chemicals] and 8.0grams of sodium chloride (NaCl) [Sigma-Aldrich Chemicals] were dissolved in 1ltr of milli-Q water and the final pH of the buffer was adjusted to 7.4 using concentrated hydrochloride (HCl) (typically 2M) [A.S. Clough, private communication. Similar preparation method was found in www.thelabrat.com/protocols/3.shtml, viewed on 01/09/05]. The $^1$H MRI 2D images were acquired with similar parameter (repetition delay of 8s) as before.

Drug loaded Eudragit tablets were also exposed to aqueous sodium chloride solution (NaCl) of 0.2M and 2M concentrations and similar MRI experiments were conducted.

3.2.4.3 Magnetic resonance imaging studies on polymer tablets exposed to concentrated drug solution

MRI experiments on 100% Eudragit tablets exposed to concentrated drug solution were carried out in order to observe any swelling effect of the solid matrix due to the presence of dissolved drug. The concentration of the drug solution was 29% (w/v), which was the maximum
concentration of drug in solution as discussed in Section 3.2.2.2. The experiments were conducted under static dissolution conditions with similar imaging parameters as in Section 3.2.3.1.

3.2.5 X-ray Computed Microtomography (μCT)

High spatial resolution (10μm) imaging experiments were conducted using a bench-top third-generation cone-beam X-ray μCT scanner. A detailed description of the apparatus set up and principles can be found in [Jenneson et al., 2004]. In this system an X-ray source and an X-ray detector were at opposite sides of the sample which was placed on a precision mechanical sample table. The X-ray detector measured the intensities of the X-ray beam transmitted through the sample, as the sample rotated in the cone-beam. The X-ray cross-sectional images were generated by processing the transmitted intensities. The resulting CT image values known as grey-levels gave information on the microstructure of the sample in the plane of the cross-section. The third-generation cone-beam X-ray μCT system at the University of Surrey is shown in the Figure 3-11.

![Third-generation cone-beam X-ray CT system at the University of Surrey.](image)

The X-ray detector was a Hamamatsu C7942 flat-panel CMOS (complementary metal oxide semiconductor) array and the X-ray source a Hamamatsu L6731-01 microfocus x-ray tube with a focal spot size of 5μm, X-ray energy of 55kVp and a filament current of 0.1mA. The distance between the source and the sample was 50mm whereas the distance of the sample and the X-ray detector was 450mm. The mechanical sample table was a computer controlled rotational stepper motor with a resolution of 0.01°. The sample was rotated through 360° producing a series of 2D
projected images of 512×512 pixels. The X-ray projections contained superimposed images of the entire sample, which were recovered into a three-dimensional data set by COBRA version 4.9.5 (Exxim Computing Corporation, Pleasanton, USA) reconstruction program using the filtered back-projection algorithm known as the Feldkamp technique [Feldkamp et al., 1984]. For each sample 900 projections were recorded giving a total acquisition time of approximately 8hrs. The reconstructed X-ray μCT image was essentially a set of consistent grey-scale values with 10μm pixel spatial resolution.

### 3.2.5.1 X-ray μCT of water ingress into drug loaded Eudragit tablets

High resolution X-ray μCT experiments on drug loaded Eudragit tablets were conducted in order to gain information on the microstructure of the sample. In order to achieve 10μm spatial resolution the size of the sample was reduced and as a consequence the drug loading was reduced to prevent the rapid dissolution of the drug when exposed to water. Therefore, a new sample die was purchased that produced 3mm diameter tablets. The sample was placed in a specially designed cell as shown in Figure 3-12 made from teflon.

![Figure 3-12: Schematic diagram of the sample cell placed on the third-generation cone-beam X-ray CT system.](image)

All experiments were conducted on 25% (w/w) drug loaded tablets prepared according to method in Section 3.2.3.1. The tablet weight was 32 ± 4mg with 3mm in diameter, 3.5 ± 0.5mm in thickness and compressed at 0.1tons (0.137GPa) (greater pressure could damage the sample die). The images were recorded using a third-generation cone-beam X-ray μCT scanner as discussed in Section 3.2.5 and the wet samples were exposed to distilled water. The system was calibrated with the three components: drug and polymer compressed tablets and water in order to produce histograms, which provided information on the component fractions in the sample. The X-ray μCT experiments on drug loaded Eudragit tablets were acquired under static and dynamic dissolution conditions. In all experiments and dissolution conditions, the image of the completely dry tablet was initially acquired prior to exposing it to water.
In the static dissolution condition two sets of experiments were obtained. In the first one, the scans of the wet tablet were taken after it was left to soak in water for 2 days. In the second set the tablet was initially exposed to water for 60mins. Then the surrounding water was taken out and scans of the sample were acquired to observe the effect of the drying process to the morphology of the sample.

In the dynamic dissolution experiments the images of the wet tablet were acquired with water going in the tablet in real-time. The water above the tablet was refreshed every 50mins in order to avoid drug saturation.

The set up and acquisition parameters for both dissolution conditions were the same as discussed in Section 3.2.5. However, in the static experiments for each sample 900 projections (20 frames summed for each projection) were recorded giving a total acquisition time of approximately 8hrs, whereas in the dynamic experiments for each sample 450 projections (2 frames summed for each projection) were recorded giving a total acquisition time of approximately 47mins. The resulting images had 10\(\mu\)m pixel spatial resolution.

### 3.2.6 Determination of drug content in solution using spectroscopic techniques

The amount of the drug released from the sample matrix over time was estimated using UV spectroscopy and \(^1\)H NMR spectroscopy. The UV experiments were conducted on a Perkin-Elmer Lambda 9 UV/VIS/NIR spectrophotometer and the \(^1\)H NMR on a 400MHz spectrometer as shown in Section 3.2.1.

Siepmann et al. [Siepmann et al., 1999b] investigated Diltiazem HCl and theophylline in ethyl cellulose and Eudragit® RS 100 films containing various plasticizers. They detected Diltiazem HCl using UV spectroscopy at wavelength, \(\lambda = 236\)nm. Standard solutions of known drug concentration were prepared and their UV absorbance was measured between 200-400nm. The UV absorbance of the water samples collected from the MRI dynamic dissolution experiments (see Section 3.2.4.1) were again recorded between 200-400nm and compared with the standard solutions in order to estimate the percentage of drug in solution over the period of time. UV results were correlated with NMR spectroscopy experiments. A static dissolution experiment was set up by exposing the top surface of 55% (w/w) drug loaded Eudragit tablets to water. The sample was placed in the magnet so as only the water above the surface was within the MRI coil. The \(^1\)H NMR spectrum (for pulse sequence see Figure 3-5(b), with 90° pulse of 11\(\mu\)s) of the solution was recorded periodically (over five days) in order to determine amount of drug released over that period.
3.2.7 Optical microscopy

Optical microscopy experiments were used to characterise the tablet microstructure using a Zeiss axiolab-A microscope. The optical micrographs obtained under reflected and transmitted illumination and the distances were calibrated using a graticule.

3.2.7.1 Observation of sample matrix under an optical microscope

Drug loaded Eudragit and 100% polymer tablets, and just polymer and drug powders, were examined under an optical microscope at different magnifications under reflected and transmitted illumination. The drug loaded and polymer tablets were both observed dry and after they were immersed in water for 1hrs and 11hrs, respectively, in order to observe any changes in their surface.

3.2.7.2 Dissolution of a single drug particle in water

A single drug particle was placed under an optical microscope. The particle was exposed to water and the time required for the particle to fully dissolve was recorded. The particle size against the time required for the single particle to dissolve was plotted and the gradient of line was used to estimate the dissolution constant of the drug. This information was used for modelling the dissolution mechanism.
Chapter 4

4 NMR Characterisation of Raw Materials

In this chapter, experiments to optimise experimental procedures and characterise the materials under study are presented. The results were subsequently used to aid the interpretation of spatially resolved MR data. The $^1$H NMR $T_1$ and $T_2$ relaxation times of water swollen, spatially and temporally equilibrated Eudragit samples at two different NMR frequencies, 20MHz and 400MHz were determined. For both frequencies $T_1$ data was best fit by a single component exponential recovery whereas $T_2$ required a double exponential decay fit with a short and long component corresponding to polymer and water respectively. CYCLCROP $^{13}$C-edited spectroscopy was applied on a concentrated Diltiazem HCl solution (29%w/v) in order to select a specific $^{13}$CH$_3$ group in the molecule while suppressing all proton resonances, which did not arise from the desired molecular groups. This experiment assessed the feasibility of mapping drug concentrations in partially swollen system in imaging studies. Finally, the self-diffusion coefficient of the drug and water in various solutions of drug as a function of concentration were determined using the spectroscopically resolved stimulated-echo pulsed-field-gradient method. This information was subsequently used for modelling the drug egress.

4.1 $T_1$ and $T_2$ characterisation of equilibrated Eudragit samples

The $^1$H NMR $T_1$ and $T_2$ relaxation times of water swollen, spatially and temporally equilibrated Eudragit samples at two different NMR frequencies, 20MHz and 400MHz were determined. Experimental data showed that the spatial equilibration of samples took six weeks during which it was observed that the weight of each sample did not change significantly. For both frequencies, the $T_1$ was measured using the inversion recovery method, whereas the $T_2$ was determined by recording the FID and CPMG of each sample.

4.1.1 $T_1$ and $T_2$ determination at 20MHz

4.1.1.1 $T_1$ longitudinal relaxation time at 20MHz

Figure 4-1 shows an exemplar data set of a $T_1$ recovery curve for an equilibrated sample of swollen Eudragit prepared according to the method in Chapter 3, Section 3.2.2.1 and measured at
20MHz using the parameters listed in Table 3-2 of Chapter 3. The set shown is for a concentration of 3.0gr Eudragit and 0.1ml H$_2$O.

![Figure 4-1: T$_1$ measure of 0.1ml H$_2$O & 3.0gr Eudragit at 20MHz. Single component exponential fit.](image)

The data has been fitted with a single exponential recovery curve (black solid line) and a constant offset to account for the relative poor inversion achieved in the experiment, according to the formula

\[
M(t) = M_0(1 - 2\exp(-\frac{t}{T_1}))) + C_{offset}
\]  

4-1

The important fit parameter is T$_1$ and is shown as a function of concentration in Figure 4-3.

Figure 4-2 shows the same data set fitted to a double exponential recovery according to the equation 4-2.

![Figure 4-2: T$_1$ measure of 0.1ml H$_2$O & 3.0gr Eudragit at 20MHz. Double component exponential fit.](image)
\[ M(t) = M_0^a (1 - 2 \exp(-\frac{t}{T_{1a}})) + M_0^b (1 - 2 \exp(-\frac{t}{T_{1b}})) + C_{\text{offset}} \]  

The analysis showed that the data was well fitted by a single component exponential recovery and that there was insufficient experimental evidence to justify the two component fitting with the two relaxation constants \( T_{1a} \) and \( T_{1b} \). This can be seen in Figure 4-2, which is almost identical to the single component fit. Therefore, the spin-lattice relaxation, \( T_1 \), was taken to be a single component relaxation process for the whole range of the equilibrated samples.

Figure 4-3 shows the \( T_1 \) (±3ms) (estimation of error is shown later) values obtained according to equation 4-1 plotted against the water mass fraction of the equilibrated Eudragit sample (see Chapter 3, Table 3-1 for water mass fraction values).

![Figure 4-3: \( T_1 \) of equilibrated Eudragit samples vs. H\(_2\)O Mass Fraction at 20MHz.](image)

Figure 4-3: \( T_1 \) of equilibrated Eudragit samples vs. H\(_2\)O Mass Fraction at 20MHz.

It is observed that the \( T_1 \) of the samples increases as the water mass fraction increases.

### 4.1.1.2 \( T_2 \) transverse relaxation time at 20MHz

The \( T_2 \) transverse relaxation time was determined by recording the FID and CPMG of each sample. Figure 4-4 shows an exemplar of the FID data obtained at 20MHz for an equilibrated sample of 3.0gr Eudragit and 0.1ml H\(_2\)O concentration. The associated experimental method and parameter sets can be found in Chapter 3, Section 3.2.2.1 and Table 3-2 respectively.
The analysis showed evidence of two components in the samples, a short and a long component. The FID signal of the sample showed an initial sharp decay corresponding to the short component (polymer) followed by a slower decay corresponding to the fast component (water). As the signal did not go to zero the $T_2$ of the long component was better determined by CPMG as shown in Figure 4-5 (for parameter set see Chapter 3 Table 3-2).

The combination of the FID and CPMG results led to the estimation of the $T_2$ transverse relaxation time for the Eudragit equilibrated samples. The front end of the FID’s were fitted to Gaussian decay for the short component together with a constant offset to account the long component better measured by CPMG and any baseline offset according to the formula

$$M_{xy} = M_{0S} \exp\left(-\frac{t^2}{T_2^2}\right) + M_{0L} + C_{\text{Offset}}$$
where $T_{2S}$ is an indicative time constant or inverse rate for the short component. The Gaussian
decay of the FID is usually assumed to arise from inhomogeneous distribution static inter-nuclear
dipolar interactions. The CPMG data sets were fitted to a single exponential decay and constant
offset.

$$M_{x'/y'} = M_{0L} \exp\left(-\frac{\tau}{T_{2L}}\right) + C_{\text{Offset}}$$

Equation 4-4

Table 4-1 summarises the $T_2$ results obtained from the combination of the FID and CPMG
analysis. The experimental errors are also included the estimation of which is discussed later.

Table 4-1: $T_2$ double exponential recovery fit for the equilibrated Eudragit samples at 20MHz.

<table>
<thead>
<tr>
<th>Sample ml H$_2$O/3.0gr Eudragit</th>
<th>$M_{0S}$ (%magnitude)</th>
<th>$T_{2S}$ ($T_2$ of short component) (±2μs)</th>
<th>$M_{0L}$ (%magnitude)</th>
<th>$T_{2L}$ (T$_2$ of long component from CPMG) (±4ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>94</td>
<td>20</td>
<td>6</td>
<td>0.7</td>
</tr>
<tr>
<td>0.1</td>
<td>91</td>
<td>22</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>0.2</td>
<td>87</td>
<td>22</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>0.3</td>
<td>90</td>
<td>21</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>0.4</td>
<td>82</td>
<td>21</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>0.5</td>
<td>83</td>
<td>21</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>0.6</td>
<td>77</td>
<td>21</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td>0.7</td>
<td>77</td>
<td>21</td>
<td>23</td>
<td>34</td>
</tr>
<tr>
<td>0.8</td>
<td>78</td>
<td>19</td>
<td>22</td>
<td>43</td>
</tr>
<tr>
<td>0.9</td>
<td>76</td>
<td>20</td>
<td>24</td>
<td>50</td>
</tr>
</tbody>
</table>

The percentage intensities shown in Table 4-1 were derived from

% Intensity$_{\text{short}} = \frac{M_{0S}}{M_{0S} + M_{0L}} \times 100$ and % Intensity$_{\text{long}} = \frac{M_{0L}}{M_{0S} + M_{0L}} \times 100$.

The above data showed that the $T_2$ of the polymer ($T_{2S}$, short component) remained roughly
constant over the whole range of concentrations. On the other hand, the $T_2$ of water ($T_{2L}$, long
component) was consistent with the increasing water mass fraction of the sample, which was also
seen for its amplitude. Figure 4-6 shows plots of the amplitude of $T_2$ long component and $T_2$
relaxation times of short and long component in the sample to the water mass fraction from data
in Table 4-1.
Repeat measurements of $T_1$ and $T_2$ relaxation times for the equilibrated Eudragit sample of 3.0gr Eudragit and 0.9ml H$_2$O concentration were recorded to check the reproducibility of the results.
Chapter 4: NMR Characterisation of Raw Materials

and to obtain an estimate of the of random experimental error. Table 4-2 shows the values of these repeat experiments.

**Table 4-2: Repeat measurements of $T_1$ and $T_2$ for the equilibrated sample of 3.0gr Eudragit and 0.9ml H$_2$O concentration. The percentage magnitudes of the $T_{2S}$ and $T_{2L}$ are shown.**

<table>
<thead>
<tr>
<th>Sample measured five times</th>
<th>$T_1$ (ms) single component fit</th>
<th>$T_{2S}$ (short component)</th>
<th>$T_{2L}$ (long component from CPMG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>376</td>
<td>77% @ 19</td>
<td>23% @ 54</td>
</tr>
<tr>
<td>2</td>
<td>377</td>
<td>76% @ 20</td>
<td>24% @ 54</td>
</tr>
<tr>
<td>3</td>
<td>374</td>
<td>76% @ 20</td>
<td>24% @ 53</td>
</tr>
<tr>
<td>4</td>
<td>375</td>
<td>76% @ 20</td>
<td>24% @ 53</td>
</tr>
<tr>
<td>5</td>
<td>376</td>
<td>76% @ 20</td>
<td>24% @ 53</td>
</tr>
</tbody>
</table>

The results confirmed that the measurements were reproducible to within better than 5%. The data were in good agreement with the order of the $T_1$ and $T_2$ values obtained from the original measurement as shown in Table 4-1 for the $T_2$ of the sample and Figure 4-1 for the $T_1$ value (372ms). This suggested that the random experimental error was small for all relaxation times as already noted in the primary results (Table 4-1 and $T_1$ values).

The spatial homogeneity of the equilibrated samples with higher mass fraction of water was examined by determining the relaxation times of the samples at different height in the magnet. The NMR tubes of the samples were placed in the magnet at about 1cm to 2cm higher level than the original position. The results are summarised in Table 4-3.

**Table 4-3: $T_1$ and $T_2$ measurements of equilibrated Eudragit samples recorded at different sample height in the magnet. The percentage magnitudes of the $T_{2S}$ and $T_{2L}$ are shown.**

<table>
<thead>
<tr>
<th>Sample ml H$_2$O / 3.0gr Eudragit</th>
<th>$T_1$ (±3ms) single component fit</th>
<th>$T_{2S}$ (short component) (±2μs)</th>
<th>$T_{2L}$ (long component from CPMG) (±4ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.7</td>
<td>250</td>
<td>80% @ 20</td>
<td>20% @ 35</td>
</tr>
<tr>
<td>0.8</td>
<td>320</td>
<td>79% @ 21</td>
<td>21% @ 40</td>
</tr>
<tr>
<td>0.9</td>
<td>330</td>
<td>79% @ 21</td>
<td>21% @ 45</td>
</tr>
</tbody>
</table>

The data obtained showed faster $T_1$ and $T_2$ relaxation times compared to initial measurements of the samples (see Table 4-1 for $T_2$ and Figure 4-3 for $T_1$ results) and especially for the $T_1$ times. These results suggested that either the samples were not well mixed or that were dryer as it moved upwards. There was more water at the bottom that at the top of the tube.

### 4.1.1.3 $T_1$ and $T_2$ determination at 400MHz

The data obtained from the $T_1$ and $T_2$ measurements of the water swollen, spatially and temporally equilibrated Eudragit samples at 400MHz were interpreted similar to results at 20MHz. For the $T_1$, the data was fitted by a single component exponential recovery according to equation 4-1.
Figure 4-7 shows the resulting graph of the determined $T_1$ (±3ms) values with the water mass fraction of the samples (Chapter 3, Table 3-1).

![Graph showing $T_1$ of equilibrated Eudragit samples vs. H$_2$O mass fraction at 400MHz.](image)

The $T_1$ values of the samples did not increase substantially with water mass fraction in the same way as is seen for the 20MHz measurements in Figure 4-3. Here the $T_1$ value of the dry polymer powder gave a high value. There was an initial decrease in the $T_1$ value between the dry and the sample with 0.1ml water. Thereafter it began to increase slowly until it became almost constant for samples with higher amounts of water.

It is very unclear what is happening. One hypothesis is that the $T_1$ of the dry polymer and the water used in preparing the samples is very similar, circa 1s, so that they cannot be easily distinguished. However, the $T_1$ of the polymer with a very small amount of water is somewhat less, say 800ms. Therefore, the measurement reveals a weighted average of polymer with a small water fraction (likely <1%) and the bulk water between the grains. However, it is stressed that this is no more that a hypothesis. As will be seen in later chapters the situation is further complicates by the fact that a different $T_1$ is measured in imaging studies of pressed tablets exposed to water. It is observed that the $T_1$ relaxation times for both water and polymer were highly frequency dependent as the values obtained at 20 and 400MHZ were quite different.

The $T_2$ of the equilibrated samples was obtained from the combination of the FID and CPMG data analysis based on the equations 4-3 and 4-4 as shown at 20MHz. Table 4-4 summarises the results of the two component exponential decay fits with the percentage magnitudes and the associate plots are shown in Figure 4-8.
Table 4-4: T₂ double exponential recovery fit for the equilibrated Eudragit samples at 400MHz.

<table>
<thead>
<tr>
<th>Sample ml H₂O / 3.0gr Eudragit</th>
<th>M₂₅ (magnet.)</th>
<th>T₂₅ (T₂ of short component (±2μs))</th>
<th>M₂₅ (magnet.)</th>
<th>T₂₅ (T₂ of long component from CPMG) (±4ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>88</td>
<td>19</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>0.1</td>
<td>88</td>
<td>19</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>0.2</td>
<td>82</td>
<td>20</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>0.3</td>
<td>81</td>
<td>21</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>0.4</td>
<td>70</td>
<td>21</td>
<td>30</td>
<td>17</td>
</tr>
<tr>
<td>0.5</td>
<td>70</td>
<td>21</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>0.6</td>
<td>58</td>
<td>21</td>
<td>42</td>
<td>26</td>
</tr>
<tr>
<td>0.7</td>
<td>57</td>
<td>22</td>
<td>43</td>
<td>26</td>
</tr>
<tr>
<td>0.8</td>
<td>43</td>
<td>24</td>
<td>57</td>
<td>35</td>
</tr>
<tr>
<td>0.9</td>
<td>41</td>
<td>23</td>
<td>59</td>
<td>32</td>
</tr>
</tbody>
</table>

Data for the T₂₅ relaxation times of the samples compared well with the values obtained at 20MHz as seen in Table 4-1. The T₂₅ were difference especially for the high concentration samples and the correlation of water and component amplitudes did not follow a linear trend as in Figure 4-6(c).
Figure 4-8: (a) $T_2$ of short component (b) $T_2$ of long component and (c) Percentage amplitude of $T_2$ long component in equilibrated Eudragit samples at 400MHz.
4.2 $^{13}$C-$^1$H CYCLCROP spectroscopy of Diltiazem HCl concentrated solution

Cyclic $J$ cross polarisation (CYCLCROP) pulse sequence (Chapter 3 Section 3.2.2.2) was used to indirectly detect a $^{13}$C nuclei coupled to $^1$H nuclei in a drug solution and so determine the amount of drug in solution.

In order to select a specific methyl group (-CH$_3$) in the drug molecule the $^1$H and $^{13}$C spectra of a 29% (w/v) Diltiazem HCl solution, prepared according to the method in Chapter 3, Section 3.2.2.2, were first recorded at set frequency of 400MHz and 100MHz respectively. The parameter sets are mentioned in the same section. The $^1$H and $^{13}$C spectra allowed the peak labelling of the proton and carbon spectra lines corresponding to specific proton and carbon atoms in the molecule. Ananthanarayanan et al. [Ananthanarayanan et al., 1993] demonstrated the complete assignment of the proton resonances in the $^1$H-NMR spectrum of the drug and the chemical structure of Diltiazem showing the numbering of protons and carbons in the molecule as represented in Figure 4-9.

![Figure 4-9: Chemical structure of Diltiazem showing (a) the numbering of protons in the molecule and (b) the numbering of carbons in the molecule (Copied from [Ananthanarayanan et al., 1993]).](image)

In addition, Glaser and Sklarz [Glaser and Sklarz, 1989] assigned both the $^1$H and $^{13}$C NMR spectral parameters of Diltiazem HCl dissolved in Deuterated Dimethyl Sulfoxide ((CD$_3$)$_2$SO). Therefore, it was possible to assign three distinct methyl groups in the drug molecule that gave the best resonance. These were C(18)-H$_3$(9), C(23)-H$_3$(16) and C(20)-H$_3$(10) and the $^1$H and $^{13}$C spectra showing the labelling of the specific pair of proton and carbon atoms is shown in Figure 4-10.
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Figure 4-10: (a) $^{13}$C spectrum and (b) $^1$H spectrum of 29% (w/v) Diltiazem HCl solution.

Figure 4-10(b) is an enlarged area of the $^1$H spectrum of the drug obtained showing the resonances of the protons under study. However, comparing the full spectrum with that obtained by Ananthanarayanan et al. [Ananthanarayanan et al., 1993] it was observed that not all the peaks in the molecules were resolved. This suggested that some peaks were possibly covered by the broad base of the water resonance line and broadening was due to the concentrated nature of the solution.

The CYCLCROP spectrum of the concentrated drug solution was obtained for the three methyl groups in the molecule for a range of carbon frequencies in each case using parameters listed in Chapter 3 Section 3.2.2.2. The proton and the carbon frequencies were centred at the respective frequencies of the methyl group. Saturation pulses were set at the water frequency to suppress the water signal. Figure 4-11 shows an exemplar of the intensity data obtained from the CYCLCROP spectrum of the C(20)-H$_3$(10) methyl group at selected carbon frequencies.

Figure 4-11: CYCLCROP spectrum of C(20)-H$_3$(10). Intensity plots obtained at three different carbon frequencies.
The spectra of the CYCLCROP editing sequence showed a single peak corresponding to the selected methyl groups in the molecule and the complete suppression of the H$_2$O resonance line.

Experimental data revealed that the signal-to-noise of the $^{13}$C spectrum (Figure 4-10(a)), which took approximately 4hrs to acquire, was quite poor. On the other hand, CYCLCROP spectrum had faster acquisition time, less than 2hrs and it gave almost 10 times better signal-to-noise. In practice, the full acquisition time of the carbon spectrum corresponded to almost three complete CYCLCROP sequences. So by adding the three CYCLCROP spectra obtained in Figure 4-11, the resulting spectrum demonstrated the better signal-to-noise ratio of CYCLCROP compared to the normal $^{13}$C spectrum per unit acquisition time. The improvement was by a factor of the order of 10. This is represented in Figure 4-12.

![Figure 4-12: Total intensity of three CYCLCROP sequences C(20)-H$_3$(10).](image)

In order to validate the experiment and demonstrate the absence of any residual signal, which did not correspond to the selected methyl group, the $^{13}$C contact pulse was turned off. The sequence was re-run and Figure 4-13 is the intensity plots obtained from three CYCLCROP sequences (similar to Figure 4-12) when the $^{13}$C contact pulse was turned off.
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Intensity of three CYCLCROP sequences obtained for C(20)-H$_3$(10) when $^{13}$C contact pulse was turned off.

Figure 4-13: Intensity of three CYCLCROP sequences obtained for C(20)-H$_3$(10) when the $^{13}$C contact pulse was turned off.

The above plots showed clearly that no signal was acquired, as the magnetisation transfer did not take place. This data confirmed that the experiment was completed successfully as the signal in the spectrum of the concentrated drug was due to the cyclic polarisation transfer editing process.

Example spectra of the CYCLCROP editing sequence for the concentrated drug solution showing stacked plots of the intensity of another methyl group C(23)-H$_3$(16), obtained for an array of $^{13}$C frequencies, together with the spectra obtained when the $^{13}$C contact pulse was switched off are presented in Figure 4-14. Note that the H$_2$O peak was strongly suppressed. The small peaks observed were probably due to H$_2$O residues but they did not interfere with the resulting signal.

Figure 4-14: Example CYCLCROP spectra of C(23)-H$_3$(16) obtained for an array of $^{13}$C frequencies. The spectra show the $^{13}$C contact pulse alternately on and off.
4.3 Self-Diffusion measurements of drug and water mobility in *Diltiazem HCl* solutions

The self-diffusion coefficient of the drug and water from various solutions of drug as a function of concentration was determined using the spectrascopically resolved stimulated-echo pulsed-field-gradient method. Figure 4-15 shows exemplar spectra of a test solution with 26% (w/v) drug concentration prepared according to the method in Chapter 3 Section 3.2.2.3 and acquired using parameters listed in the same section. The spectra shown are for two different gradient strengths g=2 and 22G/cm. Based on the proton spectrum of the drug from Figure 4-10(b) the proton peaks, corresponding to specific methyl groups in the drug molecule, were assigned on the spectra. For the rest of the analysis these proton peaks are referred to as drug peaks.

![Example spectra of stimulated-echo pulsed-field-gradient sequence for a 26%(w/v) drug solution acquired at two different gradient strength g=2 and 22G/cm, showing the water and proton peaks of the drug molecule.](image)

The self-diffusivities of water and drug peaks were determined based on the Stejskal-Tanner equation [Stejskal and Tanner, 1965]

\[
\frac{S(g)}{S(0)} = \exp\left[-\frac{\gamma^2 g^2 \delta^2 D (\Delta - \delta/3)}{2}\right]
\]

where \(\gamma\) is the \(^1\)H gyromagnetic ratio, \(g\) is the gradient amplitude, \(D\) is the diffusion coefficient, \(\delta\) is the duration of the gradient pulses, \(\Delta\) is the separation of the gradient pulses and \(S\) is the signal amplitude.

Semilog plots of \(S\) against \(4\pi^2 \gamma^2 (\Delta - \delta/3) = \gamma^2 g^2 \delta^2 (\Delta - \delta/3)\) were used to determine \(D\). The intensity can be determined either from the amplitude or the area of the peaks. Figure 4-16 shows example plots derived the water and drug peak areas in the spectrum for different drug concentrated solutions. The resulting plots for the all the water peak areas showed strong evidence of two component decay whereas the drug peak areas were much closer to single component.
Figure 4-16: Natural log plot of the peak area against $4\pi^2 q^2 (\Delta-\delta/3)$ for (a) 20% (w/v) drug solution in 95%D$_2$O/5%H$_2$O, $\Delta=120$ms, Water peak area, (b) 26% (w/v) drug solution in 95%D$_2$O/5%H$_2$O, $\Delta=120$ms, Drug peak area of H$_3$(16) and (c) 13% (w/v) drug solution in 95%D$_2$O/5%H$_2$O, $\Delta=30$ms, Drug peak area of H$_3$(10).
The self-diffusion coefficient of the drug in each solution was determined from the gradient of the linear fitting of the data whereas for the water from the bi-exponential fit. All the results are summarised in Table 4-5 for data obtained at $\Delta=30\text{ms}$ and Table 4-6 for $\Delta=120\text{ms}$. The percentage amplitudes of the bi-exponential fits for all the water peak areas are also included.

Table 4-5: Self-diffusivities of water and drug estimated from the peak areas of spectra obtained from drug concentrated solutions at $\Delta=30\text{ms}$. The percentage amplitudes of the water peaks are shown.

<table>
<thead>
<tr>
<th>%Drug Concentration (w/v)</th>
<th>$D_{\text{H}_2\text{O}} \times 10^6$ (cm$^2$ s$^{-1}$)</th>
<th>$D_{\text{C}_2\text{D}_2\text{H}<em>5\text{O}</em>{10}} \times 10^6$ (cm$^2$ s$^{-1}$)</th>
<th>$D_{\text{C}_2\text{D}_2\text{H}<em>5\text{O}</em>{10}} \times 10^6$ (cm$^2$ s$^{-1}$)</th>
<th>$D_{\text{C}_2\text{H}_5\text{H}<em>3\text{O}</em>{10}} \times 10^6$ (cm$^2$ s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>27 (96% ±5%)</td>
<td>3.9 (4% ±4%)</td>
<td>4.3 (±4%)</td>
<td>4.4 (±4%)</td>
</tr>
<tr>
<td>13</td>
<td>17 (83% ±5%)</td>
<td>2.5 (17% ±4%)</td>
<td>3.3 (±4%)</td>
<td>3.3 (±4%)</td>
</tr>
<tr>
<td>20</td>
<td>19 (78% ±5%)</td>
<td>1.6 (22% ±4%)</td>
<td>1.5 (±4%)</td>
<td>1.4 (±4%)</td>
</tr>
<tr>
<td>26</td>
<td>11 (63% ±5%)</td>
<td>1.1 (37% ±4%)</td>
<td>0.9 (±4%)</td>
<td>1.2 (±4%)</td>
</tr>
<tr>
<td>29</td>
<td>1 (87% ±5%)</td>
<td>0.1 (13% ±4%)</td>
<td>0.1 (±4%)</td>
<td>0.1 (±4%)</td>
</tr>
</tbody>
</table>

Table 4-6: Self-diffusivities of water and drug estimated from the peak areas of spectra obtained from drug concentrated solutions at $\Delta=120\text{ms}$. The percentage amplitudes of the water peaks are shown.

<table>
<thead>
<tr>
<th>%Drug Load</th>
<th>$D_{\text{H}_2\text{O}} \times 10^6$ (cm$^2$ s$^{-1}$)</th>
<th>$D_{\text{C}_2\text{D}_2\text{H}<em>5\text{O}</em>{10}} \times 10^6$ (cm$^2$ s$^{-1}$)</th>
<th>$D_{\text{C}_2\text{D}_2\text{H}<em>5\text{O}</em>{10}} \times 10^6$ (cm$^2$ s$^{-1}$)</th>
<th>$D_{\text{C}_2\text{H}_5\text{H}<em>3\text{O}</em>{10}} \times 10^6$ (cm$^2$ s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>26 (98% ±5%)</td>
<td>4.1 (2% ±4%)</td>
<td>4.3 (±4%)</td>
<td>4.6 (±4%)</td>
</tr>
<tr>
<td>13</td>
<td>15 (80% ±5%)</td>
<td>1.8 (10% ±4%)</td>
<td>2.4 (±4%)</td>
<td>2.6 (±4%)</td>
</tr>
<tr>
<td>20</td>
<td>22 (81% ±5%)</td>
<td>1.5 (19% ±4%)</td>
<td>1.5 (±4%)</td>
<td>1.5 (±4%)</td>
</tr>
<tr>
<td>26</td>
<td>13 (84% ±5%)</td>
<td>1.0 (16% ±4%)</td>
<td>1.0 (±4%)</td>
<td>1.1 (±4%)</td>
</tr>
<tr>
<td>29</td>
<td>14 (75% ±5%)</td>
<td>1.3 (25% ±4%)</td>
<td>1.4 (±4%)</td>
<td>1.3 (±4%)</td>
</tr>
</tbody>
</table>

Consider first the water peak and in particular the 20% (w/v) drug solution at $\Delta=120\text{ms}$ as an example. This can be reasonably fitted to two exponentials as shown in Figure 4-16(a):

$$S = A_1 \exp(-D_1 q^2) + A_2 \exp(-D_2 q^2)$$

with $A_1=198$, $D_1=2.2\times10^{-5}\text{cm}^2\text{s}^{-1}$ and $A_2=49$, $D_2=1.5\times10^{-6}\text{cm}^2\text{s}^{-1}$. In particular note that $D_1$ was just a little less than the normal self-diffusivity of bulk water ($2.5\times10^{-5}\text{cm}^2\text{s}^{-1}$) and that the ratio $A_1$ to
$A_2$ was approximately 4:1. From Table 4-5 and Table 4-6 it was observed that for all the drug samples $D_1$ was closer to $D_{\text{bulk water}}$ and was therefore judged to reflect the water diffusion.

The sample (2ml of 95%D$_2$O / 5%H$_2$O; 0.5gr drug, Chapter 3, Section 3.2.2.3) contained approximately

$$\frac{2 \times 2 \times 0.05 \times A_w}{18.015}$$

hydrogen nuclei where $A_w$ is Avogadro's number (6.02214199x$10^{23}$mol$^{-1}$) and 18.015 was the water molecular weight and

$$\frac{3 \times 0.5 \times A_w}{450.98}$$

gives hydrogen nuclei in any particular -CH$_3$ group where 450.98 was the drug molecular weight. Hence, the water to any given -CH$_3$ group intensity in the spectrum was expected to be in the ratio 3.3:1 before spin relaxation and H-D exchange were taken into account.

Careful analysis of the NMR spectra previously presented in the CYCLCROP experiments (Figure 4-10(b)) suggested that a drug CH$_3$ line lie close to / underneath the water line. It seemed reasonable to assume that this peak contributed to the water peak, and manifested itself as the slow diffusing component within the water. It was however drug.

The diffusion coefficient for the three directly measured drug lines, C(23)-H$_3$(16), C(20)-H$_3$(10) and C(18)-H$_3$(9), in the same sample were $1.50 \times 10^{-6}$cm$^2$s$^{-1}$, $1.5 \times 10^{-6}$cm$^2$s$^{-1}$, and $1.5 \times 10^{-6}$cm$^2$s$^{-1}$, respectively (see Table 4-6 for 20% (w/v) sample) with a mean value of $1.5 \times 10^{-6}$cm$^2$s$^{-1}$. This was similar to the slow "water" component ($1.46 \times 10^{-6}$cm$^2$s$^{-1}$), supporting the argument that the bi-exponential water decay contained a hidden drug line. Moreover, the definite drug lines had a sensible average relative intensity compared to the slow component of the water line -the hidden drug line- of 1.2:1.

Given the need to incorporate relaxation, the ratios of 4:1 (derived from a water peak area calculation, equation 4-6) and 3.3:1 (from nuclei counting of the drug) compared well indicating the experiment agreed with theory. Moreover, the ratio of 1.2:1, from comparison of drug and water line-hidden drug line- was close to 1 so the analysis was supportive of the general argument of a methyl group -CH$_3$ underlying the water peak.

The self-diffusivities of the drug and water were also estimated from the decay of the amplitude of the peaks in the spectrum. Although the intensities derived from the amplitudes was a more rigorous procedure as the interference of overlaying peaks was less the resulting plots showed similar behaviour as the before. Figure 4-17 shows examples of a water peak with two component decay and drug peaks with a single component decay taken from different drug solutions.
Figure 4-17: Natural log plot of the peak amplitude against $4\pi^2 q^2 (\Delta-\delta/3) (s/cm^2)$ for (a) 20% (w/v) drug solution in 95%D$_2$O/5%H$_2$O, $\Delta=120$ms, Water peak intensity, (b) 26% (w/v) drug solution in 95%D$_2$O/5%H$_2$O, $\Delta=120$ms, Drug peak intensity of H$_3$(16) and (c) 13% (w/v) drug solution in 95%D$_2$O/5%H$_2$O, $\Delta=30$ms, Drug peak intensity of H$_3$(10).
The estimated diffusion coefficients of the water and drug are listed in Table 4-7 and Table 4-8.

### Table 4-7: Self-diffusivities of water and drug estimated from the peak amplitudes of spectra obtained from drug concentrated solutions at $\Delta=30\text{ms}$. The percentage amplitudes of water peaks are shown.

<table>
<thead>
<tr>
<th>%Drug Concentration (w/v)</th>
<th>$D_{\text{H}_2\text{O}}^{(\times 10^{-6})}$ ($\text{cm}^2\text{s}^{-1}$)</th>
<th>$D_{\text{CD}_3\text{CD}_2\text{H}_3}^{(\times 10^{-6})}$ ($\text{cm}^2\text{s}^{-1}$)</th>
<th>$D_{\text{CD}_2\text{CH}_2\text{H}_3}^{(\times 10^{-6})}$ ($\text{cm}^2\text{s}^{-1}$)</th>
<th>$D_{\text{CD}_2\text{H}_2\text{H}_3}^{(\times 10^{-6})}$ ($\text{cm}^2\text{s}^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>29 ($\pm 5%$) 4.5 ($\pm 4%$)</td>
<td>4.1 ($\pm 4%$)</td>
<td>4.1 ($\pm 4%$)</td>
<td>3.8 ($\pm 4%$)</td>
</tr>
<tr>
<td>13%</td>
<td>98 ($\pm 4%$) 2.4 ($\pm 4%$)</td>
<td>3.1 ($\pm 4%$)</td>
<td>3.1 ($\pm 4%$)</td>
<td>3.1 ($\pm 4%$)</td>
</tr>
<tr>
<td>20%</td>
<td>96 ($\pm 4%$) 4% ($\pm 4%$)</td>
<td>2.2 ($\pm 4%$)</td>
<td>1.8 ($\pm 4%$)</td>
<td>1.9 ($\pm 4%$)</td>
</tr>
<tr>
<td>26%</td>
<td>92 ($\pm 4%$) 8% ($\pm 4%$)</td>
<td>1.5 ($\pm 4%$)</td>
<td>1.5 ($\pm 4%$)</td>
<td>1.4 ($\pm 4%$)</td>
</tr>
<tr>
<td>29%</td>
<td>89 ($\pm 4%$) 11% ($\pm 4%$)</td>
<td>0.1 ($\pm 4%$)</td>
<td>0.1 ($\pm 4%$)</td>
<td>0.1 ($\pm 4%$)</td>
</tr>
</tbody>
</table>

### Table 4-8: Self-diffusivities of water and drug estimated from the peak amplitudes of spectra obtained from drug concentrated solutions at $\Delta=120\text{ms}$. The percentage amplitudes of water peaks are shown.

<table>
<thead>
<tr>
<th>%Drug Concentration (w/v)</th>
<th>$D_{\text{H}_2\text{O}}^{(\times 10^{-6})}$ ($\text{cm}^2\text{s}^{-1}$)</th>
<th>$D_{\text{CD}_3\text{CD}_2\text{H}_3}^{(\times 10^{-6})}$ ($\text{cm}^2\text{s}^{-1}$)</th>
<th>$D_{\text{CD}_2\text{CH}_2\text{H}_3}^{(\times 10^{-6})}$ ($\text{cm}^2\text{s}^{-1}$)</th>
<th>$D_{\text{CD}_2\text{H}_2\text{H}_3}^{(\times 10^{-6})}$ ($\text{cm}^2\text{s}^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>28 ($\pm 5%$) 3.8 ($\pm 4%$)</td>
<td>4.1 ($\pm 4%$)</td>
<td>3.9 ($\pm 4%$)</td>
<td>3.6 ($\pm 4%$)</td>
</tr>
<tr>
<td>13%</td>
<td>98 ($\pm 4%$) 1% ($\pm 4%$)</td>
<td>1.8 ($\pm 4%$)</td>
<td>2.5 ($\pm 4%$)</td>
<td>2.4 ($\pm 4%$)</td>
</tr>
<tr>
<td>20%</td>
<td>96 ($\pm 4%$) 4% ($\pm 4%$)</td>
<td>1.2 ($\pm 4%$)</td>
<td>1.7 ($\pm 4%$)</td>
<td>1.6 ($\pm 4%$)</td>
</tr>
<tr>
<td>26%</td>
<td>86 ($\pm 4%$) 13% ($\pm 4%$)</td>
<td>0.9 ($\pm 4%$)</td>
<td>1.2 ($\pm 4%$)</td>
<td>1.1 ($\pm 4%$)</td>
</tr>
<tr>
<td>29%</td>
<td>85 ($\pm 4%$) 15% ($\pm 4%$)</td>
<td>1.4 ($\pm 4%$)</td>
<td>1.5 ($\pm 4%$)</td>
<td>1.5 ($\pm 4%$)</td>
</tr>
</tbody>
</table>

The tables showed that results obtained from the amplitudes were in good agreement with those obtained from the peak areas. The diffusion coefficient of the slow "water" component was again in good comparison to the drug lines in each sample and the calculated ratio of the water peak amplitude to the drug amplitude was 1.01:1 confirming that the second water diffusing component was actually a hidden drug line as previously suspected.

The average diffusivity data for all results in the above tables for the peak areas and amplitudes is shown in Figure 4-18.
Figure 4-18: Average (a) $D_{self}$ as a function of concentration, peak area, and (b) $D_{self}$ as a function of concentration, peak intensity

Data confirmed again the good agreement of the results and show that $D_{self}$(drug) and $D_{self}$(H2O) were concentration dependant.

4.4 Discussion

The optimum $T_1$ and $T_2$ relaxation times of water swollen, spatially and temporally equilibrated Eudragit samples were determined at two different NMR frequencies, 20MHz and 400MHz. The spatial equilibration of the samples took a long time, approximately seven week and it was observed that the weight of each sample remained stable throughout the experimental period. For both frequencies, the spin-lattice relaxation, $T_1$, was a single component relaxation process along the whole range of the equilibrated samples. The experimental data were fitted to a single exponential recovery with a constant offset to account for the imperfect inversion. The low frequency $T_1$ times were sensitive to water content compared to the high frequency and they increased as the water fraction of the sample was increased. It was suggested that the $T_1$ results for the high frequency measurements gave a weighted average of polymer with a small water fraction (likely <1%) and the bulk water between the grains. The purpose for obtaining the $T_1$ values of water swollen, spatially and temporally equilibrated Eudragit samples was to use this data to interpret subsequent spatial resolved MRI data by determining water concentrations in the tablets.

The results obtained for spin-spin relaxation time were also affected by the above observations. The $T_2$ relaxation time required a double exponential decay fits with a short and long component broadly assigned to polymer and water respectively. The combination of the FID and CPMG results led to the final interpretation of the $T_2$ relaxation time for the Eudragit equilibrated samples. For both frequencies, experimental evidence showed that the $T_2$ times of the short component was low in the order of $\mu$s indicating a solid (polymer) and they remained approximately constant along the whole range of samples. The $T_2$ of the long component (in ms) was consistent with the water mass fraction of the sample as it was increasing with the water...
content. Finally, component amplitudes correlate with water mass fraction indicating a linear trend and corresponded particularly well at low frequency. The $T_1$ and $T_2$ relaxation times for both water and polymer were highly frequency dependent as the values obtained at 20 and 400MHz were relatively different.

CYCLCROP $^{13}$C-edited spectroscopy was applied on a Diltiazem HCl solution in order to select a specific $^{13}$CH$_3$ group in the molecule while suppressing all proton resonances, which did not arise from the desired molecular groups. This technique can reveal the amount of drug in solution and therefore it could enable drug concentration mapping in partially swollen matrices in imaging studies.

In order to obtain a strong drug signal a highly concentrated drug solution was required. The maximum concentration of drug in solution was 29% (w/v) (Chapter 3, Section 3.2.2.2). The $^1$H and $^{13}$C spectra of such solution were obtained and it was possible to assign specific methyl groups in the molecule; C(20)-H$_3$(10) and C(23)-H$_3$(16) as shown in Figure 4-10. The $^1$H spectrum (see Figure 4-10(b)) of the drug showed that the water peak had a very high resonance line compared to both H(10) and H(16) protons of the carbohydrate group, which suggested that it would be difficult to perform imaging on such sample. The CYCLCROP spectrum was acquired showing that it was a chemically specific method as it was possible to obtain signal for both the selected groups in the Diltiazem HCl molecule (Figure 4-11 and Figure 4-14). The spectrum showed that the H$_2$O was clearly suppressed and only the peak of the methyl group was acquired.

Therefore, the technique works at fixed carbon and proton frequencies. The CYCLCROP spectrum of Diltiazem HCl gave a 10 times better signal-to-noise compared to the $^{13}$C spectrum in significantly shorter acquisition time. The $^{13}$C NMR detection showed that the NMR sensitivity of $^{13}$C nucleus was relatively weak and it required either a large number of $^{13}$C nuclei within the sample or very long experimental times in order to improve the sensitivity. Consequently, for imaging studies only $^{13}$C enriched material should be used to give 100 times better signal-to-noise. The validity of the results were confirmed by turning off the amplitude of $^{13}$C cross polarisation. So the magnetisation transfer did occur and no signal was obtained.

The self-diffusion coefficient of water and drug was estimated from solutions of drug as a function of concentration, with maximum drug concentration of 29% (w/v), using spectroscopically resolved stimulated-echo pulsed-field-gradient method. The drug peaks on the spectra were assigned according to information obtained from the CYCLCROP experiments. The self-diffusivities of water and drug in each sample were estimated from either the amplitude or the areas of the peaks in the spectrum. For both cases evidence showed two component decay for the water peak, fast and slow, and a single component for the drug as shown in Figure 4-16 and Figure 4-17. The fast component in the water was assigned to "water" as the $D_{em}(H_2O-fast)$
compared well to bulk water and reduced as drug concentration increased as seen in Table 4-5 to Table 4-8. On the other hand, the slow component in water was assigned to a “hidden drug line” since its $D_{\text{self}(\text{H}_2\text{O}-\text{slow})}$ and the intensity of the peak were similar to the principal drug lines. This was also confirmed by careful analysis of the $^1\text{H}$ NMR spectrum of the drug based on Ananthanarayanan et al. [Ananthanarayanan et al., 1993]. Finally, Figure 4-18 revealed that both the $D_{\text{self}(\text{drug})}$ and $D_{\text{self}(\text{H}_2\text{O})}$ were much concentration dependant.

Attempts were made to measure the pore size distribution of the drug/polymer matrix using NMR Cryoporometry [Valckenborg et al., 2002]. This technique provides determination for pores in the range of a few nanometers to around 1-10 $\mu$m. However, the particle size of the components were big and so cryoporometry was not used to determine the porosity of the system.

4.5 Conclusions

In this chapter spectroscopic characterisation of the raw materials was conducted that will help the subsequent interpretation of spatially resolved MR data. The $T_1$ and $T_2$ relaxation times of water swollen, equilibrated Eudragit samples were determined at two different NMR frequencies. The $T_1$ was measured using the inversion recovery pulse sequence, whereas $T_2$ was determined by recording the FID and CPMG of each sample. For both frequencies $T_1$ showed a single component fit whereas $T_2$ a double which corresponded to a short and a long component, water and polymer respectively. For the high frequency measurements it was suggested that an effective $T_1$ of polymer and water was determined for the high concentration samples. CYCLCROP experiment on a 29%(w/v) solution of Diltiazem HCl was completed successfully as it was possible to obtain a signal for the selected methyl group in the molecule while totally suppressing the water signal and all the uncoupled or unselected $^1\text{H}$ resonances. This technique allows the indirect detection of $^{13}\text{C}$ nuclei coupled to $^1\text{H}$ nuclei with the high NMR sensitivity of protons and therefore considerably better signal-to-noise compared to direct $^{13}\text{C}$ NMR. However, it was concluded that $^{13}\text{C}$ enriched material was necessary to use as the natural abundance of $^{13}\text{C}$ gave a very low signal-to-noise. The technique is highly frequency selective and the magnetisation transfer is a relatively time consuming process.

Finally, the water and drug self-diffusivities in drug solutions were obtained. This is important information for modelling the drug egress.
Chapter 5

5 Imaging studies of drug release from a solid polymer matrix

In this chapter, results from parameters affecting the release of the soluble drug from a non-swelling polymer matrix are presented. MRI experiments on Eudragit tablets with different levels of compression, drug loading and particle size exposed to water were made in order to observe the ingress of water into the tablet. In addition, samples were exposed to different dissolution environments. NMR spectroscopy was used to assess the amount of drug released. The MRI technique was complemented by other chemical and physical structural methods, such as X-ray \( \mu \)CT, UV spectroscopy, optical microscopy to characterise the matrix microstructure. The data obtained provided the means to understand the swelling and dissolution mechanism of the sample matrix.

5.1 Water ingress into Standard System

The release of the soluble drug was studied on a system containing Eudragit RSPO loaded with 45% (w/w) Diltiazem HCl prepared according to the method in Chapter 3, Section 3.2.3.1 and compressed at 2 tons (0.303 GPa). For the rest of the study this is considered as the standard system. The tablet was exposed to water under static dissolution conditions (Chapter 3, Section 3.2.3.1). Figure 5-1 shows exemplar \(^1\)H 2D MRI images of a standard system acquired on the 400 \(^1\)H MHz superconducting magnet (9.4T) using the parameter sets listed in Chapter 3, Section 3.2.3.1. These are vertical slices (1mm thickness) taken from the centre of the sample and each took approximately 9 mins to acquire.
Figure 5-1: "H MRI 2D images of 45% (w/w) drug loaded Eudragit tablet exposed to water.

The bright areas corresponded to water above and below the tablet and the dark central band was the tablet. The spin-spin relaxation time ($T_2$) of the tablet was less than the echo time (4ms) and so the tablet was invisible. As time passed the colour of the dark band changed to light grey indicating that water was starting to penetrate the system and the $T_2$ of the tablet lengthened. The full penetration occurred after approximately 7.5hrs. Two observations can be made from this experiment. The first is that the water ingressed into the system with a sharp front and the second is that during the ingress of water the tablet was beginning to swell. The total change of tablet height over time was measured as shown in Figure 5-2. The height was determined by taking an average value of the increased height across the length of the tablet at each time point measured from the top surface of the tablet.

Figure 5-2: Increase of tablet size with time for 45% (w/w) drug loaded tablet.

The data analysis revealed that by the end of the experiment the tablet of 0.3cm in thickness swelled by about 20%. In order to understand the origin of the swelling similar MRI further experiments on 100% Eudragit and 100% Diltiazem HCl compressed tablets (prepared as described in Chapter 3, Section 3.2.3.2) were conducted.
Chapter 5: Imaging studies of drug release from a solid polymer matrix

5.1.1 MRI studies of water ingress into 100% Eudragit and 100% Diltiazem HCl compressed tablets

Figure 5-3 shows exemplar of $^1$H 2D MRI images of 100% Eudragit RSPO tablet exposed to water. Each image took approximately 17mins to acquire.

Figure 5-3: $^1$H MRI 2D images of 100% Eudragit tablet exposed to water.

Similar to Figure 5-1, the bright areas corresponded to water underneath and over the tablet whereas the dark band in between was the tablet itself. Figure 5-4 shows the vertical profiles extracted from the central region of the MRI images.

Figure 5-4: $^1$H MRI one-dimensional profiles extracted from the images shown in Figure 5-3 for the 100% Eudragit tablet (a) full profile and (b) enlarge in the lower diagram.

The vertical profiles show the top of the tube on the left (water/tablet interface is at 0.02cm), the bottom on the right and the tablet in the middle (between 0.02 to 0.3cm). The signal intensity declines towards the sides of the profiles as only the central 10mm of the sample resides in the MRI coil. The substantial difference in the signal intensity between the dry tablet (black solid line) and the tablet exposed to water for 17mins (blue solid line) suggested that initially water diffused into the system quite rapidly. The subsequent gentle build up of the signal in the tablet with time as observed from the images in Figure 5-3 was indicated by the rising intensity in the central band. There was a slight increase in width, more evident in the enlarge profile, that suggested the tablet of initial thickness 0.28cm had swelled at most 4%, which was not significant compared to the 20% observed for the standard system.
The $^1$H MRI 2D images of 100% drug compressed tablets were obtained for tablets exposed to different amounts of water ranging from 0.1ml to 2ml. An example is shown in Figure 5-5 where only the top of a 100% drug tablet was exposed to 2ml of water. The tablet was made up of two layers. A 100% drug layer sitting above a 100% Eudragit layer, which provided structural integrity during the experiment.

**Figure 5-5:** $^1$H MRI 2D images of 100% Diltiazem HCl tablet exposed to 2ml of water only from the top surface.

The 2D images showed that water penetrated the system and by the end of the experiment, at 11hrs, the length of the tablet had been reduced compared to the initial time as seen from Figure 5-5-11hrs image. This suggested that water had started slowly to dissolve the material. The vertical profiles extracted from the MRI images are shown in Figure 5-6.

**Figure 5-6:** $^1$H MRI one-dimensional profiles extracted from the images shown in Figure 5-5 for the 100% Diltiazem HCl tablet (a) full profile and (b) profile without the 100% Eudragit layer.

The vertical profiles show the tablet exposed to water only from one side, the left side, which corresponded to the top surface in the MRI image. The water/tablet interface is at -0.02cm. The end of the drug tablet is at 0.22cm and the end of the polymer layer is at 0.3cm. The increase in the intensity signal within the drug layer indicates the water ingress into the system. It was observed that as water invaded into the drug tablet there was an increase in the width of the tablet as seen in Figure 5-6(b) at 24mins (red solid line) and 85mins (green solid line). This suggested...
that the tablet had swelled at most 6% at 85mins. After that the width of the tablet decreased, Figure 5-6(b) 4.2hrs and 11hrs, suggesting that the material was starting to dissolve. Especially in the 11hrs profile where it was clear that the width of the tablet had significantly changed due to the dissolution of the tablet. The decrease in the intensity values of bulk water, taken from the top of the tablet, was probably due to the dissolved drug in water.

Therefore, MRI experiments suggested that virtually nothing happened when a 100% Eudragit tablet was exposed to water and a small percentage of swelling followed by dissolution proceeded for a 100% Diltiazem HCl tablet. On the other hand when a compressed polymer/drug tablet was exposed to water a swelling of the matrix was observed.

5.1.2 Porosity of drug loaded Eudragit and 100% Eudragit tablet

A vital parameter that affects the release of the drug is the porosity of the matrix. Initially, a standard system and a 100% Eudragit tablet were examined under the microscope to observe any pores on the surface. The tablets were examined dry and after they were exposed to water for 1hr for the standard system and 11hrs for the polymer tablet. The polymer and drug powders were also observed to estimate their particle size. An example of the optical micrographs obtained at different magnifications under reflected and transmitted illumination is shown in Figure 5-7.
Figure 5-7: Optical micrograph of (a) polymer loose powder and (b) drug loose powder at different magnification under transmitted illumination, (c)-(d) dry and wet 100% Eudragit tablet and (e)-(f) dry and wet 45% drug loaded tablet under reflected illumination.

Figure 5-7(a)-(b) suggest that the particle size of the polymer and drug loose powders varied from small particles, less than 50\(\mu\)m, to larger ones, greater than 100\(\mu\)m. The surface of the dry tablets was highly compacted. Large polymer particles can be distinguished in both 100% Eudragit and 45% (w/w) drug loaded tablet as shown in Figure 5-7(c)-(e). In the latter the white powder spread between the larger polymer particles, as seen in Figure 5-7(e), can be assumed to be the drug powder. The optical micrographs of the wet samples indicated that the morphology of the tablets had changed. However, at this magnification no clear evidence of the porosity of the system was obtained.

Therefore, the porosity of the sample matrix was estimated gravimetrically based on the density of the two components. The density of the drug was calculated with respect to water. As the polymer is insoluble in water its density was estimated with respect to acetone [Sigma-Aldrich Chemicals]. For each component a known volume of liquid was placed in a glass vial. Then, powder was
added into the vial and dissolved. The difference of mass uptake and liquid volume was used to calculate the density, $\rho$. The results gave

$$\rho_{\text{polymer}} = 1.10 \pm 0.01 \, \text{gr/cc}$$

$$\rho_{\text{drug}} = 1.24 \pm 0.03 \, \text{gr/cc}$$

The porosity of the compact tablet was determined from the volume of system and components and for a 45% (w/w) drug loaded tablet was estimated to be (-2.0 ± 4)% . The percentage error was derived from the measurement of the polymer and drug density. The w/w drug percentage required to yield 0% porosity for the measured parameters was 65% (w/w).

The porosity of the matrix was also estimated from MRI. The $^1$H MRI 2D images of a completely dry 45% (w/w) drug loaded Eudragit and 100% Eudragit tablets were acquired. Then water was added on the top of the tablets and another 2D image was obtained (9mins acquisition time). The 45% (w/w) drug loaded tablet consisted of two layers, a drug loaded Eudragit and a pure Eudragit layer (see Chapter 3, Section 3.2.4.1, Dynamic dissolution section for sample structure).

$$\text{(a) 3 mm}$$

$$\text{dry}$$

$$\text{(b) 3 mm}$$

$$\text{dry}$$

Figure 5-8: Dry and wet $^1$H MRI 2D images of (a) 45% (w/w) drug loaded Eudragit and (b) 100% Eudragit tablets.

An average signal intensity value was taken from the images of the dry and wet tablets. Intensities were extracted from an area within the water, the tablet and from an area below the tablet, where the teflon sleeve supported the tablet (see Chapter 3, Section 3.2.3.1, Figure 3-8 for experimental set up). The intensity values for both the tablets are listed in Table 5-1 and Table 5-2.

<table>
<thead>
<tr>
<th></th>
<th>Avg. Water Intensity(a.u)</th>
<th>Avg. Tablet Intensity(a.u)</th>
<th>Avg. Teflon Intensity(a.u)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dry Tablet</strong></td>
<td>0.0086</td>
<td>0.0078</td>
<td>0.0068</td>
</tr>
<tr>
<td><strong>Just Wet Tablet</strong></td>
<td>0.1028</td>
<td>0.0108</td>
<td>0.0076</td>
</tr>
</tbody>
</table>
Table 5-2: Average signal intensities taken from $^1$H MRI 2D images of a dry and just wet 100% Eudragit tablet.

<table>
<thead>
<tr>
<th></th>
<th>Avg. Water Intensity(a.u)</th>
<th>Avg. Tablet Intensity(a.u)</th>
<th>Avg. Teflon Intensity(a.u)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry Tablet</td>
<td>0.0084</td>
<td>0.0087</td>
<td>0.0092</td>
</tr>
<tr>
<td>Just Wet Tablet</td>
<td>0.1048</td>
<td>0.0129</td>
<td>0.0086</td>
</tr>
</tbody>
</table>

Table 5-1 suggested that the mean signal intensity due to background noise (the data were modulus) was 0.0077 and so the tablet and water signal intensities were 0.0031 and 0.0951, respectively. Hence, the porosity of the 45% (w/w) drug loaded Eudragit tablet was 3.2%.

Similarly the porosity of the 100% Eudragit tablet was 4.4%. This percentage corresponds to the air space between the compressed polymer particles in the tablet. It does not take account of the nano-porosity of the loose polymer grains, which is not measured here. The analysis suggested that the porosity of the drug loaded matrix was much less than that of the pure polymer presumably as the drug powder was soft and filled the pores between the polymer grains under compaction. This was also observed from the optical micrographs in Figure 5-7(e) where the drug was spread between larger polymer particles. The result obtained is comparable to that calculated from the gravimetric analysis.

5.1.3 Analysis of MR images of standard system

5.1.3.1 Initial capillary uptake to porosity

One conclusion that can be drawn from the estimation of the porosity of the standard system was that the initial ingress of water across the whole tablet occurred very fast. That was supported from vertical profiles extracted from the $^1$H 2D MRI images shown in Figure 5-8(a). The profiles are shown in Figure 5-9.
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Figure 5-9: (a) $^1$H MRI one-dimensional profile extracted from a central region of the image data obtained for a dry and wet 45% (w/w) drug loaded tablet and (b) enlarged region of the tablet.

The tablet was exposed to water only from the top surface, which is the left side on the diagram. The water/tablet interface is at 0cm and the tablet is between 0 and 0.3cm. The upper layer (up to 0.2cm) is the drug loaded Eudragit and the lower layer (0.2 to 0.3cm) is 100% Eudragit. The profile of the wet tablet indicated an increase in the intensity values across the whole tablet (Figure 5-9(b)) with more water present in the lower layer of the matrix. This suggested that there was a rapid capillary uptake of water into the porosity of the tablets ahead of the primary dissolution. Rapid uptake was also observed in the profiles for the 100% Eudragit tablet in Figure 5-4(b).

5.1.3.2 Diffusion coefficient of water in the tablet

MRI experiments on water exposed drug loaded Eudragit tablets showed that initially the water rushed in across the whole tablet very quickly. The $^1$H 2D images in Figure 5-1 revealed that water ingressed into the matrix with a sharp diffusion front that advanced in a much slower rate.
Figure 5-10 shows exemplar intensity profiles extracted from the $^1$H 2D MRI images of the standard system at two different time points.

The vertical profiles showed the tablet exposed to water from both surfaces, as labelled on the graph, with the upper water/tablet interface at 0cm. The 90mins profile indicated that water ingressed into the system as there was an increase in intensity in the central band, which is the tablet (red solid line between 0 and 0.3cm). The water ingress proceeded into the system with a sharp diffusion front. There was also an increase in the width of the tablet suggesting the swelling of the system. Measuring the distance of water ingressed as a function of time led to an estimate of the transport diffusion coefficient of water, $D_{f}(H_2O)$. Figure 5-11 shows plots of the distance of water ingress against time and square root of time.

The data revealed that water ingress proceeded linearly with the square root of time, $t^{1/2}$. Hence, it was suggested to characterise the advance of the water sharp front as a “Fickian like” diffusion [Chapter 2, Section 2.4 for Fickian diffusion]. An indicative estimate of the diffusion coefficient,
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$D_{(H_2O)}$, was made by calculating the $[\text{gradient}]^2$ of the fitted line (solid line) in Figure 5-11(b). It was approximately $1.8 \times 10^{-5} \text{cm}^2/\text{s} \pm 3\%$.

- The Boltzmann's Transformation

Figure 5-11(b) suggested that the ingress of the primary dissolution front – as opposed to any initially capillary uptake into the tablet pore space – was governed by Fickian diffusion [Chapter 2, Section 2.4]. The data obtained from the self diffusion measurements (see Chapter 4 Section 4.3) revealed that the self-diffusivities of water and drug were concentration dependant (Chapter 4, Figure 4-18). Fick's second law for one-dimensional diffusion when the diffusion coefficient, $D$, depends on the concentration, $c$, is

$$\frac{dc}{dt} = \frac{d}{dx} \left[ D(c) \frac{dc}{dx} \right]$$

Equation 5-1

It was advantageous to transform the data according to Boltzmann's transformation [Crank, 1975] in order that the curves lie on a master profile. Boltzmann demonstrated that for semi-infinite boundary conditions when the diffusion coefficient, $D$, is a function of concentration, $c$, then the diffusion can be expressed in terms of a new variable

$$\eta = \frac{x}{2t^{1/2}}$$

Equation 5-2

Equation 5-2 can be reduced to an ordinary differential equation in $c$ and $\eta$ as shown below.

$$-2\eta \frac{dc}{d\eta} = \frac{d}{d\eta} \left[ D(c) \frac{dc}{d\eta} \right]$$

Equation 5-3

Integrating equation 5-3 it is possible to estimate the diffusion coefficient as a function of concentration [Crank, 1975]:

$$D_1(c) = \frac{-2 \int_{\eta}^{c} \eta dc}{dc/d\eta}$$

Equation 5-4

The transformation was applied to all the intensity profiles extracted from the $^1\text{H} \text{2D}$ images of the standard system obtained in Section 5.1. The results shown in Figure 5-12 are from profiles taken after 43mins of initial water exposure until it was fully invaded the tablet.
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Figure 5-12: Boltzmann’s transformation of the intensity profiles of 45% (w/w) drug loaded Eudragit tablet.

The water/tablet interface is at $\eta = 0 \text{cm/s}^{1/2}$. The graph shows clearly three distinct regions: region A is the bulk water; region B is the dissolution region (water in the tablet) and region C is the water in the capillaries between the particles in the tablet (the initial capillary uptake of water). From Figure 5-12 the drug fraction was estimated from the intensity values of the three regions according to:

$$\frac{B-C}{A} \times 100 = \text{percentage drug fraction.}$$

If values from the 43mins run were taken then the drug fraction was equal to 46%. This was in good agreement with the expected percentage of drug in the tablet which was 45%. So it was suggested that in region B there was 46% of drug. As solid drug did not give any signal and if the $^1\text{H}$ concentration in drug was similar to water, then it could be assumed that the solution in region B was saturated and that drug was dissolved.

However, the estimation of the drug fraction has some limitations. There is a difference in the intensity values throughout the sample. For instance in regions A and B this difference is due to difference in relaxation times. It can be assumed that the initial signal intensity in region A is proportional to 100% water. However, $T_1$ and $T_2$ relaxation times are different for the bulk water and the adsorbed water in the tablet (region B) resulting in different signal intensity values, which makes calibration difficult. The Boltzmann’s transformation considers semi-infinite boundary conditions. However, here water is also ingresses into the system from the back end of the tablet, as both surfaces were exposed to water, illustrated in Figure 5-12 as the rear front. Finally, it is observed that the intensity values of the bulk water (region A) throughout the run are varying probably due to the presence of dissolved drug in the water with time.
Figure 5-12 showed evidence that dissolution proceeded slowly (>5hrs until the two fronts met) presumably due to water saturation in the tablet by the liquid drug given that up to 29% of drug could be dissolved in water as discussed in Chapter 3 Section 3.2.2.2. The water diffused into the tablet forming a sharp diffusion front, which is suggested to comply with Fickian diffusion. Boltzmann’s transformation analysis was applied to the data with the assumption that the surface was well defined and not moving. So the transform was applied in a frame of reference fixed to the “sample surface”. Hence, the profiles in Figure 5-12 were integrated to yield the diffusivity as a function of concentration based on equations 5-4. This was a more rigorous procedure than the simple position, $x$, against square root of time plot previously used (Figure 5-11(b)).

The concentration of water within the sample was calculated and plotted against the variable $\eta$. Figure 5-13(a) shows the transformed and smoothed data of Figure 5-12 and Figure 5-13(b) the transport diffusion coefficient of water as a function of concentration.

Figure 5-13: (a) % Concentration of water against $\eta$, (b) diffusion coefficient of water in tablet as function of concentration.
Figure 5-13(a) shows that approximately 53% of water had gone into the tablet. It was observed that there was a minor surface resolution problem as the boundary surface (bulk water and tablet) at $\eta = 0 \text{cm/s}^{1/2}$ was not completely well defined. That was partly due to (i) the dissolution and swelling of the tablet, that caused problems to the Boltzmann analysis, (ii) to the actual imaging experiments and (iii) to the roughness of the tablet surface. Finally, Figure 5-13(b) revealed the $D_t(\text{H}_2\text{O})$ to be in the order of $10^6$–$10^7 \text{cm}^2/\text{s}$. Similar to value obtained from Figure 5-11(b).

5.1.4 Air voids in the standard system

MRI experiments were conducted on a standard system exposed to water for longer times. Figure 5-14 shows exemplar $^1\text{H}$ 2D images of a bi-layer constructed tablet (see Chapter 3 Section 3.2.4.1 for sample structure) exposed to water for 4 days. Each image took approximately 34mins to acquire. The last picture is a diagram of the image illustrated the different characteristics of the images after 4 days of water exposure.

![Figure 5-14: $^1\text{H}$ MRI 2D images of 45%(w/w) drug loaded Eudragit tablet exposed to water for 4 days. (Image pixel size 29×188μm²)](image)

The image after one hour of water exposure showed the ingress of water into the system followed by swelling of the sample matrix. As before there was evidence that water was present at the back end of the tablet (above the Eudragit layer) corresponding to the rapid capillary uptake of water into the porosity of the tablet ahead the primary dissolution. The new observation from these experiments was that after water fully invaded into the tablet there was accumulation of air voids in the system with time. The observation of air voids in the system from the MRI experiments led to the microstructural analysis of the matrix using high resolution X-ray μCT.

5.1.4.1 X-ray μCT of drug loaded Eudragit tablets exposed to water

The purpose of the X-ray μCT experiments was twofold: firstly, to obtain 10μm high spatial resolution visualisation of drug loaded Eudragit tablets in order to gain information on the microstructure of the sample; the overall porosity of the system and the drug distribution and secondly, to confirm the MRI results obtained from experiments discussed in Section 5.4.1.
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microstructure of the sample; the overall porosity of the system and the drug distribution and secondly, to confirm the MRI results obtained from experiments discussed in Section 5.4.1.

X-ray \( \mu \text{CT} \) differed from MRI, as a single slice was not acquired independently of the other slices. Instead a large number of X-ray radiograph projections were acquired whilst rotating the sample through 360 degrees. The X-ray projections contained superimposed images of the entire sample which were recovered into three-dimensional data as described in Chapter 3 Section 3.2.5. Figure 5-15 shows exemplar of 2D reconstructed X-ray \( \mu \text{CT} \) images of a dry and wet 25% (w/w) drug loaded Eudragit tablet prepared according to the method in Chapter 3 Section 3.2.5.1 and acquired using a third-generation cone-beam X-ray \( \mu \text{CT} \) scanner with parameters listed in Chapter 3, Section 3.2.5. The process of acquiring projections and mechanically moving the sample was inherently slow and the scan time for each sample was 8hrs. The experiment was conducted under static dissolution conditions where the sample was exposed to water for 2 days prior to imaging as described in Chapter 3, Section 3.2.5.1. The images were central slices extracted from the three-dimensional data set. The vertical slice was taken along the axis of the sample cell and included one diagonal whereas the horizontal slice was orthogonal to that plane.

Figure 5-15(a) shows the sample cell (grey outer circle), the tablet (inside circle) and the air (circle between container and tablet). The reconstructed X-ray \( \mu \text{CT} \) data were essentially a set of consistent but un-calibrated grey-scale values. The dry tablet has clearly two different grey-levels.

![Figure 5-15: X-ray \( \mu \text{CT} \) images of a 25%\%(w/w) drug loaded Eudragit tablet (a) dry, horizontal slice, (b) dry, vertical slice, (c) in water for 2 days, horizontal slice, (d) in water for 2 days, vertical slice. Linear dimension of each voxel was 10\( \mu \text{m} \) over a field-of-view of 5.12 \( \times \) 5.12mm\(^2\).](image-url)
A bright (white) corresponding to drug and a darker (grey) corresponding to the polymer, which has similar grey scale to the teflon container. On the other hand, from the image of the wet system, Figure 5-15(c) and (d), it was really difficult to distinguish the actual tablet. The electron density of the whole matrix had changed radically after leaving the sample in water for two days and it seemed that the entire sample had a single grey scale intensity similar to that of the polymer. The wet images showed evidence that there was accumulation of air voids in the sample after two days exposure to water as seen in MRI experiments (Figure 5-14). There was a faint white circle around the tablet, which was probably a mixture of water and drug.

Histograms of the above data were obtained so as to assign the grey scales of the components in the heterogeneous system. The histograms of the data did not separately resolve each of the components polymer, drug, water and air in the partially swollen system. So, calibration scans of just water, 100% drug and 100% polymer powders compressed at 0.1tons (0.137GPa) were obtained under the same acquisition parameters in order to allow the grey-scales associated with the individual components to be attributed to grey-scales in the heterogeneous system. The histograms of the materials provided information on the component fraction in the sample. The air was calibrated from an area above the tablet. The resulting histograms of the components are shown in Figure 5-16.

![Histograms of Air, Polymer, Water and Drug](image)

**Figure 5-16: Histograms of air, polymer, water and drug.**

It was observed that the histograms of air, polymer and drug were well separated from each other. So in a dry system it would be easy to assign the grey scales of the components. On the other hand, in a wet system, water dramatically complicated the matrix as it had a very similar density and composition to polymer and the grey-scale values in the histogram overlapped. This can be seen in Figure 5-15(c) and (d) where it is difficult to distinguish the polymer and water in the wet samples. There was also the problem of partial filling of voxels by more than one medium (air / drug / polymer / water). The tablet swelled as water ingressed into the system and the voxels were
filled with a mixture of dissolved drug and a fraction of polymer, water and air. The mixture of
drug/water outside the tablet as shown in Figure 5-15(c) was again difficult to define.
Consequently, it was possible to assign the grey scales of each individual component in the
heterogeneous system only for a dry tablet using the values obtained from the calibration data.
Figure 5-17 shows the colour coded images of the dry tablet obtained in Figure 5-15 (a) and (b).

![Image of dry tablet](image)

Figure 5-17: Colour coded images of (a) horizontal slice and (b) vertical slice of the
dry 25%(w/w) drug loaded Eudragit tablets shown in Figure 5-15(a) and (b).

The components in the dry tablet were successfully assigned giving black for air, red for drug and
green for polymer. The colour coded images revealed that \((25 \pm 0.5)\%\) of the system was drug,
which was a reasonable approximation, uniform distributed within the tablet and that the porosity
of the system was very low as not much air was present in the sample.

Another set of static dissolution experiments were conducted according to the method in Chapter
3 Section 3.2.5.1 where the wet sample was exposed to water for 60mins. The excess reservoir of
water was removed and scans were acquired immediately using the same parameters in order to
observe any effect in the morphology of the matrix. Figure 5-18 shows exemplar 2D colour coded
images of dry and wet tablets. The wet sample were left to dry for 2.2 days. During that time the
images were recorded. The acquisition time of each scan was approximately 8hrs and the 2D
images were central slices extracted from a three-dimensional data set during that time. The
images in Figure 5-18 are labelled with the acquisition time of each scan.
Figure 5-18: X-ray µCT images of a 25% (w/w) drug loaded Eudragit tablet. Vertical 2D slices (10µm) of a (a) dry, and wet tablet left to dry for (b) 8hrs, (c) 16hrs, (d) 31hrs, (e) 39hrs and (f) 54hrs. Image area 5.12 x 5.12mm².

The dry colour coded image shows that the drug was uniformly distributed throughout the tablet. The images obtained for the wet tablet left to dry revealed two distinct regions in the sample. One outer region showed where the water had ingressed into the tablet and an inner second region, where it had not and the morphology of the tablet remained unaltered. It can be inferred that the ingress of water into the system proceeded with a sharp diffusion as seen from the separation of the two regions which was well defined. This agrees with the results obtained from the MRI imaging experiments (see Figure 5-1). The colour coded images suggested that water had fully penetrated into the system with undissolved drug left in the tablet, which can be seen from the early drying stages (image (b)) where water (blue) and drug (red) dominated the inner region of the tablet. It can be assumed that water had gone into the system but there was not sufficient time and amount of water, in the whole system, to allow the full dissolution of the drug to take place. This compares well to the observation made in the MRI experiments that initially water rushed in across the whole tablet very quickly followed by slower dissolution of the tablet. The histograms (Figure 5-16) obtained for each component showed that the polymer and water grey scales overlapped and hence at these values it was difficult to identify accurately the specific components. This interfering region corresponded to the light blue colour in the colour coded images that dominated both regions in the beginning of the experiment as seen in image (b).

It can be observed that the morphology of the sample changed completely with time. The outer region became very porous presumably due to evaporation of water. In the inner region there was
accumulation of drug at the edges with time. It can be assumed that initially water dissolved some of the drug. The drug was then carried to the surface by water. However, there was not sufficient time to continue the release of the drug out of the system as by the end of the experiment most water evaporated leaving the drug at the edges. Similar effect was observed at the top surface of the tablet where image(f) showed evidence that the drug had moved at the surface possibly attempting to egress out of the system. The deformation of the top left surface of the wet tablet was caused by the needle used to remove the excess reservoir of water from the top.

5.2 Modify Standard System

The dissolution mechanism of the drug was studied as a function of manufacturing parameters. These parameters included, the drug loading, polymer and drug particle size, the degree of compression of the tablet, and at the last stages, the incorporation of a third highly soluble component in the matrix and the use of a different type of polymer. All the experiments were conducted on tablets compressed at 2tons (0.303 GPa) under static dissolution conditions.

5.2.1 Water ingress into tablets containing different drug loadings

Tablets containing different amounts of drug loading were examined in order to observe the effect on water diffusion in the system. Figure 5-19 shows exemplar $^1$H 2D MRI images of tablets containing 15% (w/w), 35% (w/w), 55% (w/w) and 75% (w/w) drug load prepared according to the method in Chapter 3, Section 3.2.3.2 and acquired with parameter sets listed Section 3.2.3.1. Each image took approximately 9mins to acquire.
Figure 5-19: $^1$H MRI 2D images of Eudragit tablet containing (a) 15% (w/w) soluble drug, (b) 35% (w/w) soluble drug, (c) 55% (w/w) soluble drug and (d) 75% (w/w) soluble drug, compressed at 2 tons.

The images are presented and understood in a manner analogous to that discussed for the standard system in Figure 5-1. The 2D images of all the samples showed that water ingressed into the system with a sharp diffusion front. For the high drug content tablets ($\geq$ 45% (w/w) drug load) the ingress of water appeared to be very fast, sometimes resulting in the destruction of the tablet, that fell to the bottom of the NMR tube. This can be seen in Figure 5-19(c) and (d) where by the end of the run a uniform bright area is observed throughout the sample indicating only the presence of water. On the other hand, the ingress of water in the low drug content tablets ($<$ 45% (w/w) drug load) proceeded in a much slower rate and without any immediate effect on the structure. The images showed evidence that the swelling of the sample matrix was more dominant for tablets with high drug content ($\geq$ 45% (w/w) drug load). These have a dome like shape also observed in the standard system in Figure 5-1. The experimental data suggested that the 55% (w/w) drug loaded tablet swelled approximately 31%, obtained similarly to Figure 5-2, compared to 14% for the 35% (w/w) drug loaded tablet, derived from the intensity profiles.
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The transport diffusion coefficient of water, $D_t(H_2O)$, in each sample was estimated from the plot of the distance of water ingress into the tablet against square root of time, as discussed in Section 5.1.3.2. The results are summarised in Table 5-3 and presented in Figure 5-20.

**Table 5-3: $D_t(H_2O)$ of the different drug loaded Eudragit tablets.**

<table>
<thead>
<tr>
<th>% Drug load (w/w)</th>
<th>$D_t(H_2O) \times 10^{-6} (cm^2/s)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>0.9 ± 2%</td>
</tr>
<tr>
<td>35</td>
<td>1.2 ± 3%</td>
</tr>
<tr>
<td>45</td>
<td>1.8 ± 3%</td>
</tr>
<tr>
<td>55</td>
<td>9.6 ± 3%</td>
</tr>
<tr>
<td>75</td>
<td>23.0 ± 4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(a) Distance of water ingress against $Time^{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(b) $D_t(H_2O)$ vs. % Drug load (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image2.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Figure 5-20: Plot of (a) distance of water ingress against $Time^{1/2}$ for calculating the $D_t(H_2O)$ of the different drug loaded Eudragit tablets and (b) $D_t(H_2O)$ against % Drug load (w/w).

The data revealed that the diffusion of water correlated with the drug loading in the tablet as the higher the drug load the faster it diffused. For the 75% (w/w) drug load the diffusion of water was very fast (as seen from the images) with an estimated $D_t(H_2O)$ value close to that of the bulk water ($2.5 \times 10^{-5} cm^2/s$).

As the front advanced according to “Fickian like” diffusion the Boltzmann’s transformation analysis was applied to all the intensity profiles obtained from the images in Figure 5-19 and an example of a low and a high drug loaded tablets is shown in Figure 5-21.
Figure 5-21: Boltzmann’s transformation analysis for the 35% (w/w) and 55% (w/w) drug loaded tablets; (a) intensity profiles data, (b) % Concentration of water vs. $\eta$ and, (c) diffusion coefficient of water in tablets as function of concentration.

The data were interpreted similarly to the standard system discussed in Section 5.1.3.2. For both examples the estimation of the drug fraction in the tablets was subject to the limitations discussed for the Boltzmann’s transformation (Section 5.1.3.2). For the 35% (w/w) drug loaded tablet the results suggested that the drug fraction was roughly 33% with approximately 40% of water in the tablet and a $D_f(H_2O)$ in the order of $10^{-6}-10^{-7}$ cm$^2$/s. For the high drug content tablet problems in the Boltzmann’s transformation analysis were encountered, as shown from the shape of the data in Figure 5-21(b) due to the fast penetration of water into the system and to the higher degree of the swelling in the tablet. Careful analysis suggested that the drug fraction was 54% and approximately 66% of water had gone into the system. The $D_f(H_2O)$ is in the order of $10^{-5}-10^{-6}$ cm$^2$/s, faster than the lower content tablet.
The experiments showed that changing the amount of drug in the system had an immediate effect to the diffusion of water into the sample. The higher the amount of drug (≥45%) the greater the $D_d(H_2O)$ and also the bigger the swelling of the tablet compared to the low drug content tablets.

5.2.2 Water ingress into drug loaded Eudragit tablets with different particle size components

$^1$H MRI experiments were carried out on drug loaded tablet having different particle size components for both polymer and drug in order to observe the effect of particle size on dissolution. The experimental parameters and samples studied are listed in Chapter 3 Table 3-4. The $^1$H 2D images revealed that in all the samples water ingressed into the system with a sharp diffusion front followed by a swelling of the matrix. The $D_d(H_2O)$ of each sample was again estimated from the plot of the distance of water ingress to the square root of time as shown in Figure 5-22 and the results are summarised in Table 5-4.

![Figure 5-22: $D_d(H_2O)$ of drug loaded Eudragit tablets with different particle size components.](image)

Table 5-4: $D_d(H_2O)$ of tablets with different particle size components.

<table>
<thead>
<tr>
<th>Particle size: Small (&lt;45μm), Medium (45-180μm) and Large (&gt;180μm).</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Polymer</td>
<td>% Drug (w/w)</td>
</tr>
<tr>
<td>Small</td>
<td>Large</td>
<td>45</td>
</tr>
<tr>
<td>Medium</td>
<td>Large</td>
<td>45</td>
</tr>
<tr>
<td>Large</td>
<td>Small</td>
<td>45</td>
</tr>
<tr>
<td>Medium</td>
<td>Medium</td>
<td>25</td>
</tr>
</tbody>
</table>

The data obtained showed that there was an apparent effect of the particle size on dissolution as small drug particles allowed water to ingress diffused faster as indicated by the higher diffusion constant. This was also confirmed from the Boltzmann’s transformation analysis of all the
intensity profiles of the samples. Figure 5-23 shows exemplar data sets of tablets with small and large drug particle size.

Figure 5-23: Boltzmann’s transformation analysis for 45% (w/w) loaded tablets consisting of different particle size components; (a) intensity profiles data, (b) % Concentration of water vs. \( \eta \) and, (c) diffusion coefficient of water in tablets as function of concentration.

Figure 5-23(a) shows that water fully invaded the tablet with smaller drug particles in less than half the time compared to the larger drug particle. The two samples had similar drug fractions but the transformed and smoothed data (Figure 5-23(b)) suggested that in the tablet with the smaller drug particles more water had gone into the system, approximately 47% as opposed to 40% for the larger drug particle size tablet. The estimations were subject to the limitations discussed for the Boltzmann’s Transformation in Section 5.1.3.2. Finally, the \( D(H_2O) \) of the two sample demonstrated that the smaller the drug particles the faster the water diffusion as for small drug
was in the order of \(10^6 - 10^7 \text{cm}^2/\text{s}\) whereas for large drug particles was \(10^7 - 10^8 \text{cm}^2/\text{s}\). This seemed sensible as large particles with less surface area per unit volume takes longer to dissolve.

It was possible to measure the time required for a single drug particle to dissolve and so to determine the dissolution constant of the drug. The dissolution constant of drug particles with size \(>180 \mu\text{m}\) was estimated using optical microscopy. A single drug particle was placed under the microscope. The particle was exposed to water and snapshots of the particles dissolving with time were recorded. The decreasing size of the particle was measured from the snapshots for each time and the change of its size was plotted against that time to estimate the dissolution constant. An example is shown Figure 5-24 with the corresponding graph of size against time.

![Overlay Figure 5-24](image)

**Figure 5-24:** (a) Optical micrograph of drug particle with size over 180 μm, (b) time required for a single drug particle to dissolve in water.

The graph showed that the total time for the particle to dissolve was approximately 2mins. The dissolution constant was estimated from the gradient of the dotted line and found to be equal to \(5 \times 10^3 \text{cm/s} \pm 3\%\). This information was subsequently used for modelling the dissolution mechanism.

### 5.2.3 Water ingress into polymer tablets with different compaction levels

The effect of the pressure in the ingress of water into the system was also examined by conducting experiments on tablets prepared with different compression levels. These experiments were completed on polymer tablets prepared according to the method in Chapter 3 Section 3.2.3.2. Figure 5-25 and Figure 5-26 show exemplar \(^1\text{H} 2\text{D MRI images of} 100\% \text{Eudragit tablets compressed at} 0.1\text{tons (0.015GPa)} \text{and} 3\text{tons (0.455GPa) respectively with the intensity profiles. Data for each sample were acquired for four consecutive days and here images recorded after 17mins and 3days for Eudragit tablet at 0.1tons and after 17mins and 3.8days for Eudragit tablet at 3tons are presented. Each image took 17mins to acquire.}
Figure 5-25: $^1$H MRI 2D images of 100% Eudragit tablet compressed at 0.1tons and exposed to water at 17mins and 3days. Intensity profiles show an enlarge region of the tablet extracted from the 2D images.

Figure 5-26: $^1$H MRI 2D images of 100% Eudragit tablet compressed at 3tons and exposed to water at 17mins and 3.8 days. Intensity profiles show an enlarge region of the tablet extracted from the 2D images.

The images show the tablet (dark band) exposed to water (bright region) from both surfaces. The intensity profiles extracted from the images suggested that after 17mins of exposure the intensity of water in the low compressed tablet was significantly higher compared to the high compressed tablet, which reached that level after more than 3days. The intensity of the water signal of Eudragit tablet at 3tons compares well with that obtained for Eudragit tablet at 2tons in Figure 5-4. Hence, Eudragit tablet at 0.1tons was more permeable to water as there was more air space between the grains to absorb the water due to lower compaction. This adds to the first observation that initially water rushed in across the whole tablet very quickly (Figure 5-9) but the rate and amount is presumably affected by the degree of compaction. In both experiments no significant swelling was observed.
The $T_1$ weighed images of the Eudragit tablets were acquired for an array of saturation delay times according to the method in Chapter 3, Section 3.2.3.2. Intensity profiles were extracted from the resultant magnitude Fourier transformed images at different locations in the image. The intensity of bulk water and polymer were recorded at these specific locations and plotted against the saturation delay time (Chapter 3, Section 3.2.3.2). An example is shown in Figure 5-27.

$$M(t) = C_{\text{offset}} + M_0 \left(1 - \exp\left(-\frac{t}{T_1}\right)\right)$$

Matching the $T_1$ values of the polymer tablet with the values obtained from the spatially equilibrated samples could lead to the estimation of the water fraction in the tablet. However, this estimation was not possible, as there was a noticeable difference between the $T_1$ values of the compressed tablet and the equilibrated samples (Chapter 4, Section 4.1.1.3). The fraction of water in the tablet was determined from the amplitudes of water and tablet obtained from the exponential fit used to extract the $T_1$ of the tablet. The amplitude of the water data fit corresponded to just bulk water. On the other hand the amplitude of the tablet data fit corresponded both to a fraction of water and a fraction of polymer, with the latter showing no signal. So the fraction of water in the tablet was estimated from $\frac{\text{Amplitude}^{\text{Tablet}}}{\text{Amplitude}^{\text{Water}}}$. 

![Figure 5-27: Plot of intensity of water and polymer extracted from specific location in the image (raw 276) for Eudragit 0.1tons and 3tons exposed to water after 2 days.](image-url)
A summary of the water and tablet amplitudes from each fit, the H₂O fraction and the T₁ of the polymer obtained from a location near the centre of the tablet are listed in Table 5-5.

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2.54</td>
<td>0.06</td>
<td>0.02</td>
<td>1750 (@ 17mins)</td>
</tr>
<tr>
<td>2.54</td>
<td>0.08</td>
<td>0.03</td>
<td>880 (@ 1day)</td>
</tr>
<tr>
<td>2.55</td>
<td>0.12</td>
<td>0.04</td>
<td>1020 (@ 2days)</td>
</tr>
<tr>
<td>2.59</td>
<td>0.20</td>
<td>0.07</td>
<td>1460 (@ 3days)</td>
</tr>
<tr>
<td>2.54</td>
<td>0.23</td>
<td>0.09</td>
<td>1498 (@ 4days)</td>
</tr>
</tbody>
</table>

Figure 5-28 shows the plot of T₁ and fraction of water in the polymer, over the whole period of measurements.

Figure 5-28: T₁ of polymer for 100% Eudragit tablet compressed at 3tons vs. H₂O mass fraction.

Figure 5-28 shows similar behaviour with that discussed for the equilibrated sample in Chapter 4 Figure 4-7 but with different T₁ values. The T₁ relaxation time obtained for the equilibrated samples corresponded to an effective T₁ value of polymer and water as discussed in Chapter 4 Section 4.1.1.3. The difference of the T₁ values between the equilibrated samples and the tablet may be due to various reasons. A plausible suggestion would be that the values here were obtained from non-equilibrated compressed tablets where the water was probably spread between the grains of the powder giving average longer T₁ values.

The surface of dry Eudragit tablets compressed at 0.1tons and 3tons were examined under the microscope. An example of the optical micrographs obtained under reflected illumination is shown Figure 5-29.
Figure 5-29: Optical micrograph of the surface of a (a) Eudragit tablet compressed at 0.1tons and (b) Eudragit tablet compressed at 3tons, under reflected illumination.

The surface of the Eudragit 0.1tons tablet appeared to have small cavities whereas the polymer particles on the surface of the Eudragit 3tons tablet seemed to be more close together with a better defined surface due to higher pressure. The surface of both tablets seemed to be rough.

5.2.4 Water ingress into drug loaded Eudragit tablets incorporating a third component in the sample matrix

A highly soluble component was added to the standard system in order to observe the effect on the dissolution of the drug. The third component in the matrix was Sucrose and the Sucrose/Eudragit/Diltiazem HCl tablets prepared according to method in Chapter 3 Section 3.2.3.4 were exposed to water. Figure 5-30 shows exemplar $^1$H 2D MRI images of a tablet containing 10%(w/w) Sucrose / 45% (w/w) Drug / 55% (w/w) Polymer, acquired with the parameter sets listed in the same section, exposed to water. The acquisition time of each image was approximately 9mins. The tablet was made up of two layers according to the method in Chapter 3 Section 3.2.4.1.

Figure 5-30: $^1$H MRI 2D images of 10% (w/w) Sucrose / 45% (w/w) Drug / 55% (w/w) Polymer loaded tablet exposed to water.
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The 2D images show the water ingressed into the system with a sharp diffusion front. Images suggested that there was no apparent effect on the shape of the matrix as observed for the high drug loaded tablet (≥ 45% (w/w) drug load) in Figure 5-1 and Figure 5-19(c) and (d). There was evidence of water signal at the back end of the tablet (above the 100% Eudragit layer) after 9mins of water exposure indicating the rapid capillary uptake of water to the porosity of the matrix. This can also be observed from the 9mins intensity profile in Figure 5-31, where there is an increase in the intensity value in the lower layer of the matrix (the tablet is between 0 and 0.32cm). The dry intensity profile was taken from the 100% Drug tablet intensity profile in Figure 5-6. The swelling of the matrix was estimated from the intensity profile extracted from the images

![Graph showing intensity profile](image)

**Figure 5-31:** $^1$H MRI one-dimensional profiles extracted from the central region of images obtained for the 10%(w/w) Sucrose / 45% (w/w) Drug / 55% (w/w) Polymer tablet in Figure 5-30 exposed to water for 9mins and 18.8hrs.

The vertical profiles showed the tablet exposed to water from both surfaces with the upper water/tablet interface at 0cm and the lower interface at 0.32cm. The 18.8hrs profile indicated that water ingressed into the system as there was an increase in intensity in the central band. The increase in the width of the tablet after 18.8hrs of water exposure was measured suggesting that the tablet swelled at most 6%. Similarly, for a 30% (w/w) sucrose load the tablet swelled about 12% which compares with low drug content (35% (w/w)) results in Section 5.2.1. The water ingressed with a sharp diffusion front which proceeded as a square root of time leading to the estimation of the transport diffusion coefficient of water, $D_\text{(H}_2\text{O)}$ as in Figure 5-11(b). A summary of the values are in Table 5-6 with the corresponding graph in Figure 5-32.
Table 5-6: $D_\text{(H}_2\text{O)}$ of Sucrose / 45% (w/w) Drug / 55% (w/w) Polymer loaded tablets.

<table>
<thead>
<tr>
<th>% Sucrose load (w/w)</th>
<th>$D_\text{(H}_2\text{O)} \times 10^6$ (cm$^2$/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.69 ± 2%</td>
</tr>
<tr>
<td>10</td>
<td>0.7 ± 2%</td>
</tr>
<tr>
<td>20</td>
<td>0.7 ± 4%</td>
</tr>
<tr>
<td>30</td>
<td>1.2 ± 4%</td>
</tr>
</tbody>
</table>

Figure 5-32: $D_\text{(H}_2\text{O)}$ of tablets containing three components: Sucrose-Drug-Polymer.

The diffusion coefficient of water suggested that the higher the percentage of sucrose in the sample matrix, with constant drug/polymer ratio, the faster the ingress of water into the matrix.

5.2.5 Water ingress into drug loaded Eudragit tablets exposed to water using Eudragit RLPO as polymer

MRI experiments, under static conditions, were conducted on tablets containing Eudragit RLPO as a solid polymer matrix instead of Eudragit RSPO. Both polymers are permeable in aqueous media due to the presence of quaternary ammonium groups in their structure as discussed in Chapter 3, Section 3.2.3.5. Eudragit RLPO has a greater proportion of these groups and so is more permeable than Eudragit RSPO. Figure 5-33 shows exemplar $^1$H MRI 2D images of a 55% (w/w) drug loaded Eudragit RLPO tablet prepared according to the method in Chapter 3 Section 3.2.3.5 and acquired with parameters listed in Section 3.2.3.1. Each image took approximately 9mins to acquire. The tablet was exposed to water only from the top surface.
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Figure 5-33: $^1$H MRI 2D images of 55% (w/w) drug loaded Eudragit RLPO above 100% Eudragit layer exposed to water only from the top and compressed at 2tons.

The MR images showed the ingress of water followed by the swelling of the sample matrix. The distance of water ingressed was measured as a function of time ($t^{1/2}$) to estimate the diffusion coefficient of water, $D_{(H_2O)}$. It was found to be approximately $10.2 \times 10^6 \text{cm}^2 \text{s}^{-1} \pm 2\%$. The diffusion coefficient of water obtained for an equivalent drug loaded Eudragit RSPO tablet was $9.6 \times 10^6 \text{cm}^2 \text{s}^{-1} \pm 3\%$ (see Table 5-3), suggesting faster diffusion of water into RLPO systems. Oth and Moes [Oth and Moes, 1989] studied the sustained release of solid dispersions of indomethacin from Eudragit RS and RL in buffer solutions where the release profiles of the drug were fitted to the square root of time. They observed that solid dispersions prepared with Eudragit RS gave slower release rates than those with Eudragit RL. This seemed reasonable due to the structure of the polymer as it was more permeable to water. The total change of tablet height over time was measured and compared with the equivalent drug loaded Eudragit RSPO tablet from Figure 5-19(c). Figure 5-34 shows the resulting graphs where the height in both tablets was determined by taking an average value of the increased height across the length of the tablet at each time point measured from the top surface of the tablet.

Figure 5-34: Increase of tablet size with time for 55% (w/w) drug loaded Eudragit RLPO and RSPO tablets.
The difference in the experimental times was due to Eudragit RSPO tablet being exposed to water from both surfaces as seen in Figure 5-19(c). The data analysis revealed that by the end of the experiment the Eudragit RLPO tablet swelled about 38% compared to the 31% of Eudragit RSPO tablet. This was probably related to the different type of polymer.

In order to validate this assumption the $^1$H MRI 2D images of a 100% Eudragit RLPO tablet exposed to water were obtained as shown in Figure 5-35. Each image took 17mins to acquire.

![Figure 5-35: $^1$H MRI 2D images of 100% Eudragit RLPO tablet exposed to water and compressed at 2tons.](image)

Figure 5-36 shows the vertical profiles at 17mins and 2.6 days extracted from the central region of the MRI images. The dry profile was taken from the 100% Eudragit RSPO tablet in Figure 5-4.

![Figure 5-36: $^1$H MRI one-dimensional profiles extracted from images in Figure 5-35 for 17mins and 2.6 days.](image)

Figure 5-36 suggests that after 17mins of water exposure there is a substantial increase in the signal intensity within the tablet (between 0.01 and 0.31cm) compared to the dry tablet indicating that water diffused into the system quite rapidly. There is a further increase in the intensity until the end of the experiment, which is not significant suggesting that most of the water invaded the matrix in 17mins. The width of the tablet had changed indicating that it had swelled at most 6% compared to the 4% of Eudragit RSPO. So data suggested that there was an increase in the length of the 100% Eudragit RLPO but the percentage was small compared to the drug/polymer matrix.
5.3 Modification to the environment of the standard system

The previous experiments identified the effect on the dissolution mechanism of the drug as a function of the manufacturing parameter of the standard system when the sample was exposed to water. The effect on dissolution mechanism was also examined by changing the environment to which the tablet was exposed to. In the subsequent experiments the samples were made up of a layer of drug loaded Eudragit RSPO above a 100% Eudragit RSPO, which provided structural integrity as the experiment proceeds, and compressed at 2tons (0.303GPa).

5.3.1 Drug loaded Eudragit tablets exposed to water under dynamic dissolution conditions

MRI experiments revealed that the dissolution of the drug from a sample matrix exposed to water under static dissolution conditions was a slow process. In order to initiate the faster drug egress the sample was exposed to a continuous flow of tap water over its surface. The dynamic dissolution experiments enabled the determination of the amount of drug in solution and the rate at which the drug diffused out of the system. Figure 5-37 shows exemplar ¹H 2D MRI of 55% (w/w) drug loaded tablet prepared according to the method in Chapter 3, Section 3.2.4.1 exposed to a slow, but continuous flow, in the order of 4.6ml/min, of tap water. Each image took approximately 10mins to acquire, with parameters listed in Chapter 3, Section 3.2.3.1. The first image was recorded 10mins after the water started flowing over the sample.

Figure 5-37: ¹H MRI 2D images of a 55% (w/w) drug loaded Eudragit tablet exposed to water under dynamic dissolution conditions.

The 2D images show that the ingress of water proceeded with a sharp diffusion front with no evidence of image distortion from the continuous flow of water. After two hours most of the water had penetrated the tablet followed by swelling of the system. The images recorded at 56mins and 2.2hrs indicated two regions in the tablet. One region at the top of the sample shows clearly the water in the tablet. The second in the middle of the tablet just above the Eudragit layer shows the rapid capillary uptake of water to the open porosity of the tablet ahead of the primary dissolution.
The diffusion coefficient of water, $D_{(H_2O)}$, was estimated as in Figure 5-11 and was approximately $2.3 \times 10^{-6}\text{cm}^2\text{s}^{-1} \pm 2\%$. Similarly, the diffusion coefficient of water obtained for an equivalent drug loaded Eudragit tablet under static condition (see Section 5.2.1) was estimated to be $9.6 \times 10^{-6}\text{cm}^2\text{s}^{-1} \pm 3\%$. This difference may be due to the slow flow rate of water above the surface of the tablet. The FID of the water samples collected every hour was recorded but did not show evidence of the drug. Thus, similar dynamic experiments were conducted using a greater water flow rate so as to achieve detecting drug in water. Figure 5-38 shows exemplar $^1\text{H}$ 2D images of such experiment with flow rate of 32ml/min.

Figure 5-38: $^1\text{H}$ MRI 2D images of a 55% (w/w) drug loaded Eudragit tablet exposed to water under dynamic dissolution conditions with high flow rate.

Figure 5-38 shows that the imaging experiments were affected by the high flow rate but still the water region remained visible. There are flow artefacts as flow corrupts the phase encoding of the MR signal. The FID of the collected samples was recorded but again it was not possible to determine the drug content in the solution. Probably the concentration was too small and as the water signal dominated the $^1\text{H}$ spectrum of the drug solution as seen also in Chapter 4 Figure 4-10(b), it was difficult to obtain a signal for the drug. For this purpose, UV spectroscopy was used as an alternative technique.

5.3.1.1 Determination of drug content in solution using UV spectroscopy

The UV absorbance of the samples collected from the MRI dynamic dissolution experiments at different time points was measured in order to estimate the drug concentration in solutions. Calibration measurements were conducted on solutions of known drug concentrations according to the method in Chapter 3 Section 3.2.6 as shown in Figure 5-39.
Figure 5-39: (a) Absorbance of standard drug solution vs. wavenumber, (b) absorbance of standard drug solution vs. standard concentration.

Calibration showed that standards were in a very good agreement. The absorbance values of the standards were used to normalise the data obtained from the collected samples and estimate the drug content in solution. Figure 5-40 shows the results of three distinct experiments of 55% (w/w) drug loaded tablets with different water flow rates.

Figure 5-40: %Drug concentration in the sample solution over time for three different experiments with flow rates of (a) 17.6ml/min, (b) 32ml/min and (c) 8ml/min.

The volume of the drug was estimated by integrating the area under the curve and multiplying by the flow rate. From Figure 5-40 the total volume of drug released was; (a) 0.02cc, (b) 0.08cc and (c) 0.07cc. The actual volume of drug in the 55% (w/w) tablet was 0.08cc. Experimental results compared well with the expected volume apart from the first experiment (Figure 5-40(a)) the run time of the experiment was short compared to the Exp. 2 and Exp. 3 in Figure 5-40. The results
indicated that the drug was released and it was a process that took approximately 24hrs. Figure 5.40 illustrates that the shape of the line demonstrating the drug release is a 'noisy' line, especially in Exp.1 and Exp.2. This might be due to flow rate fluctuations during the experiment. Controlling the flow rate and keeping it completely constant was a difficult process as there was no actual visibility of the sample cell since it was inside the magnet as shown in Chapter 3, Figure 3-10. The water travelled in and out of the system using long rubber tubing, more than a meter in both directions, due to the size of the magnet. Given that the water had to travel such long distances before it was collected it can be assumed that some of the drug particles were released, dissolved and finally diluted by the high amount of water. The experimental results showed that it was feasible to detect the drug in solution. However, it was deemed necessary to improve the experiment setup so that it would be possible to perform the analysis in a more controlled environment. The drug content in the solution surrounding the tablet was also determined by NMR spectroscopy.

5.3.1.2 Determination of drug content in solution using NMR spectroscopy

The UV spectroscopy results were correlated with NMR spectroscopy experiments. A static dissolution experiment was set up according to the method in Chapter 3, Section 3.2.6 by exposing the top surface of a 55% (w/w) drug loaded Eudragit tablet to water. The $^1$H NMR spectrum of the solution above the tablet was recorded periodically, in order to determine the amount of drug released over that period. The proton spectrum of a 29% (w/v) drug solution, as shown in Chapter 4, Figure 4-10(b), was used to normalise the data. The $-\text{CH}_3$ groups of the drug molecule in the spectrum have already been assigned from the CYCLCROP experiments discussed in Chapter 4, Section 4.2. The intensity of each drug peak was determined from the peak areas in the $^1$H spectrum. Figure 5-41 shows the results of two different experiments.

![Figure 5-41: % Drug concentration in the sample solution over time for two different experiments.](image)

For both experiments the final percentage concentration of drug in solution was approximately 1.6%. The volume of the liquid above the tablet was 6mls resulting in the total volume of drug released to be approximately 0.09cc. This was again in reasonable agreement with expectation, which was 0.08cc. Figure 5-41(a) shows that the drug was released giving two distinct gradients
whereas in the second experiment the release was initially slow but then it advanced with a straight line until it finished. For both experiments the area of the water peak remained reasonably constant.

Based on the above analysis it was possible to determine the transport diffusion coefficient of the drug. A standard system was assumed, with the tablet exposed to water from one side. A simple diagram showing the water going into the system is presented in Figure 5-42.

![Simple diagram of sample matrix exposed to water from one side.](image)

The rate of transfer of drug diffusing out of the system is proportional to the concentration gradient and so the flux of drug is

\[ F = D \frac{\partial c}{\partial r} \quad 5-6 \]

where \( c \) corresponds to the maximum concentration of the drug in solution, which was 29% (w/v) already determined in Chapter 3, Section 3.2.2.2, \( r \) is the distance of water front ingress into the system, which evidence showed that advanced as square root of time. So \( r = \alpha t^{1/2} \), where \( \alpha \) is the gradient of the line obtained in Figure 5-11(b). If it is assumed that \( D \) was constant and no air voids were present in the system then the volume of the drug, \( V_{drug} \), was proportional to the integral of the flux in equation 5-6:

\[ V_{drug} = \int F \, dt = \int_0^t D \frac{29}{\alpha t^{1/2}} \, dt \quad 5-7 \]

According to data in Figure 5-41 and by differentiate equation 5-7 the transport diffusion coefficient of drug was estimated to be in the order of \( 10^{-7} \text{cm}^2/\text{s} \).
5.3.2 X-ray μCT dynamic dissolution experiments

The ingress of water into the system was also visualised using X-ray μCT. In the high resolution dynamic dissolution experiments the tablet was exposed to water and images were recorded in real-time. Figure 5-43 shows exemplar of 2D reconstructed X-ray μCT images of a 25% (w/w) drug loaded Eudragit tablet prepared according to the method in Chapter 3 Section 3.2.5.1 and exposed to water. The acquisition parameters are listed in the same section. The scan time of each image was 47mins with total experimental run time of approximately 6hrs. Images presented here were taken during the time of each sample acquisition. The 2D vertical slices were extracted from the middle of a 3D data set.

![Figure 5-43: X-ray μCT images of a 25% (w/w) drug loaded Eudragit tablet under dynamic dissolution](image)

Similarly to Figure 5-15 the bright white areas in the dry image(a) corresponded to drug whereas the darker grey corresponded to polymer. As water was introduced into the system the density of the whole sample changed and it became difficult to distinguish the edges of the tablet due to the overlapping grey scales of polymer and water shown in the histograms (Figure 5-16). However, the penetration of water into the system was still visible as the region of the bright white drug became smaller over time. It was observed that dissolution proceeded slowly with a sharp diffusion front, which was consistent with the MRI experiments. Image(h) suggested that full dissolution of the drug had not occurred as there was still bright white region left in the bottom of the sample by the end of the run.
The important observation of these dynamic dissolution experiments was the high accumulation and growth of air voids in the wet sample with exposure time. The high spatial resolution of the X-ray \( \mu \text{CT} \) system assessed the feasibility for determining the air void size distribution of the samples as it changed with time. As images were extracted from a three-dimensional data set all subsequent analysis was carried out in respect to volume so as to obtain data characteristic for the whole sample. A subset of the three-dimensional data for each sample was extracted using the dry system data set (Figure 5-43(a)) to determine the boundaries over which the analysis was to be conducted. The binary threshold of the data was obtained based on the grey-scale values of air previously determined from Figure 5-16. The data set was then labelled, assigning each discrete volume a unique range of values. The number of voids and their size was determined with a three-dimensional void labelling algorithm written in IDL version 6.0 [Jenneson et al., 2004]. The air void distribution within the samples was determined by the histograms of the above analysis. The resulting graphs of the frequency against the air-void volume size distribution for each exposure time are shown in Figure 5-44. The raw data were plotted on a normal and natural logarithmic scale for the volume axis.

The experimental data showed that the histogram of the air voids distribution plotted on a natural logarithm scale as seen in Figure 5-44 gave a characteristic bell shaped form. It was decided to fit the data to a log-normal size distribution as discussed later in Chapter 6 Section 6.1. The log-normal distribution is a common particle size distribution. A random variance \( x \) has a log-normal distribution if its natural logarithm, \( y = \log(x) \), has a normal distribution (or Gaussian distribution) [O'Grady and Bradbury, 1983]. The experimental data shown in Figure 5-44 for the natural logarithm plots were fitted to a Gaussian function according to:

\[
p(lnV) = \frac{1}{s\sqrt{2\pi}} \exp\left(-\frac{(lnV - \ln V)^2}{2s^2}\right) \tag{5-8}
\]

where \( p(lnV) \) was the probability distribution function of \( ln(V) \), with \( V \) was the air void volume shown in Figure 5-44, \( \ln V \) and \( s \) were the mean and standard deviation of \( \ln(V) \). An example graph of the lognormal distribution of air voids from a single data set is shown in Figure 5-45.
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Figure 5-44: Histograms of air void distribution from data in Figure 5-43. Frequency of air void against the normal and natural logarithm scale of the air void volume.

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Figure 5-45: Lognormal distribution of air voids of a single experimental data (black line) fitted to a Gaussian curve (red line).

It was more convenient to work in terms of just air void volume, $V$, so as to obtain the actual mean and standard deviation of the distribution. The probability distribution function of the lognormal distribution of $V$ is given by

$$ f(V) = \frac{1}{V s \sqrt{2\pi}} \exp\left(\frac{(\ln V - \ln \bar{V})^2}{2s^2}\right) \quad \text{for } V > 0 \quad 5-9 $$

The mean, $\bar{V}$, and standard deviation, $\sigma$, of $V$ distribution given in terms of mean, $\ln \bar{V}$, and standard deviation, $s$, of $\ln(V)$ are shown below.

$$ \bar{V} = \exp\left(\frac{2\ln \bar{V} + s^2}{2}\right) \quad 5-10 $$

$$ \sigma = \sqrt{\exp(2\ln \bar{V} + s^2) - \exp(2\ln \bar{V} + s^2)} \quad 5-11 $$

Subsequently, the mean volume of each air void distribution data set was calculated using equation 5-10 and plotted against time as shown in Figure 5-46.
Figure 5-46: Mean volume of air voids in the sample for the whole experiment against time.

Data showed that the mean volume followed a linear trend with time suggesting that the size of the air voids increased over time which seemed reasonable to occur. Data at early time points could not be obtained due to resolution limitations as shown also in Figure 5-44.

In order to detect if the voids in the wet tablet were moving the distance of several air-voids relative to each other were calculated from their centres of gravity. The distances were measured for each image of the dynamic experiment (see Figure 5-43). Figure 5-47 shows the distance between two different pairs of air-voids in the tablet and an example of an X-ray μCT image labelling the voids used for the calculations.

Figure 5-47: X-ray μCT vertical slice showing the air voids used to estimate the distance between two different pairs of voids over time and the associated graph.

The graph showed that there was only a small, but not zero, motion of voids at the late times in the experiment. The model of the air voids formation is discussed in more detail in Chapter 6 Section 6.1.
5.3.3 Drug loaded Eudragit tablets exposed to phosphate buffer pH 7.4

$^1$H MRI 2D images of drug loaded Eudragit samples exposed to phosphate buffer solution pH 7.4 under static dissolution conditions were conducted according to the method in Chapter 3, Section 3.2.4.2 in order to observe the behaviour of the system in the different dissolution medium. Figure 5-48 shows exemplar 2D images of a 55% (w/w) drug loaded tablet. Each image took approximately 9mins to acquire.

![Figure 5-48: $^1$H MRI 2D images a 55% (w/w) drug loaded Eudragit tablet exposed to phosphate buffer pH 7.4 compressed at 2tons.](image)

The images revealed that the buffer solution ingressed into the system with a sharp diffusion front followed by the swelling of the system. The diffusion coefficient of the phosphate buffer solution, $D_t(\text{Phos})$ was estimated with the similar method used to estimate that of the water in Figure 5-11. The swelling of the tablet was also determined from the change of tablet height over time (as in Figure 5-2).

![Figure 5-49: Plot of (a) distance of phosphate buffer ingress against $\text{Time}^{1/2}$ for calculating the $D_t(\text{Phos})$ and (b) increase of tablet size with time for the 55% (w/w) drug loaded Eudragit tablet exposed to phosphate buffer.](image)

$D_t(\text{Phos})$ was found approximately $9.9 \times 10^{-6} \text{cm}^2\text{s}^{-1} \pm 3\%$ and the tablet swelled at most 29%.

The analysis suggested that the results were not very different from those obtained for a 55%
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(w/w) drug loaded tablet exposed to water, which had $D_{\text{H}_2\text{O}}$ of $9.6 \times 10^{-6}$ cm$^2$/s ± 3% and swelled at most 31%.

MRI experiments on 55% (w/w) drug loaded tablets were conducted on tablets exposed to electrolyte solution. The chosen electrolyte solution in this study was aqueous sodium chloride solution (NaCl). The matrix was exposed to two different concentrations: 0.2M and 2M. The samples were prepared according to method in Chapter 3 Section 3.2.4.2. Figure 5-50 shows exemplar $^1$H MRI 2D images of 55% (w/w) drug loaded tablets exposed to 0.2M and 2M salt solution. The acquisition parameters are listed in Section 3.2.3.1. Each image took approximately 10 mins to acquire.

![Figure 5-50: MRI 2D images of 55% (w/w) drug loaded tablet exposed to (a) 0.2M and (b) 2M NaCl solution.](image)

The images revealed that at low salt concentration the matrix swelled whereas at high salt concentration it did not. This was probably due to the charge-screening effect caused by the presence salt which is discussed in Chapter 6 Section 6.5.

5.3.4 100% Eudragit tablets exposed to concentrated drug solution

Thus far it was observed that the release of the drug from the high loaded Eudragit tablets (≥ 45%) was associated with the swelling of the sample matrix. Experimental evidence in Section 5.1.1 confirmed that the neither of the two components, polymer or drug compacts, significantly swelled when exposed to water. A 100% Eudragit RSPO tablet was exposed to concentrated drug solution prepared in order to rule out the possibility that the swelling was not due to the dissolved drug present in the tablet. Figure 5-51 shows exemplar $^1$H 2D MRI images of a 100% Eudragit tablet exposed to 29% (w/v) drug solution prepared according to the method in Chapter 3, Section
3.2.4.3 under static dissolution conditions. The drug was dissolved in copper sulphate solution in order to reduce the nuclear spin lattice relaxation time of pure water as described in method in Chapter 3 Section 3.2.3.1. Each image took 21 mins to acquire.

Figure 5-51: $^1$H MRI 2D images of 100% Eudragit RSPO tablet (2tons) exposed to 29% (w/v) drug solution under static dissolution conditions.

Figure 5-52 shows the vertical profiles at 21 mins and 2.1 days extracted from the central region of the MRI images. The dry profile was taken from the 100% Eudragit RSPO tablet in Figure 5-4.

Figure 5-52: $^1$H MRI one-dimensional profiles extracted from images in Figure 5-51 for 21 mins and 2.1 days.

The intensity profiles revealed that the tablet had swelled at most 4% after 2 days of exposure to concentrated drug solution. Hence, it can be concluded that the concentrated drug solution had virtually no effect on the sample matrix.
5.4 Discussion

In this chapter, manufacturing parameters affecting the release of Diltiazem HCl from solid Eudragit matrix were determined in order to understand the dissolution mechanism of the sample. It is believed that the total porosity of the highly compressed tablets (2tons) was very low. Evidence showed that the porosity of the compact Eudragit was less than 5% and for the drug loaded Eudragit matrix was even less in the order of 3%, presumably as the drug is soft and fills the pores under compaction. MRI experiments on water exposed drug loaded Eudragit tablets showed the uniform ingress of water into the system. The intensity profiles extracted from the images revealed that initially the water rushed in across the whole tablet very quickly, in the order of less than 10 minutes. This rapid capillary uptake of water into the pore space of the tablets, ahead of the primary dissolution, was affected by the compaction level of the tablet as low compressed 100% polymer systems absorbed greater amount of water compared to higher ones in same exposure times. Subsequently, dissolution process was at a much slower rate accompanied by swelling of the sample matrix. The swelling was observed only for the drug/polymer matrix with a characteristic dome like shape for the higher drug loaded system (≥45% (w/w) drug load) and found to be approximately 20%. Virtually no swelling for the 100% Eudragit tablet (about 4%) and simple dissolution for the 100% drug tablet was observed with a swelling of the matrix in order of 6%.

The dissolution proceeded with a sharp diffusion front, which advanced according to “Fickian like” diffusion. Therefore, the transport diffusion coefficient of water in the tablet was estimated as a function of concentration. This was limited by the dissolution of the drug and saturation of the pore space solution. Experimental evidence showed that the rate of water ingress into the system was directly related to the amount of drug in the tablet and the particle size of the components. The water diffused faster in higher drug loaded tablets (≥ 55% (w/w drug load)) with a transport diffusion coefficient in the order of $10^{-5}$ cm$^2$/s. Similarly, the MRI experiments conducted on tablets prepared with carefully characterized and varied polymer and drug particle sizes revealed that water ingressed faster into tablets with small drug particles. This was consistent with optical microscopy observations. The effect on water diffusion in systems with three components (Sucrose/Eudragit/Diltiazem HCl) was also determined. The amount of the third highly soluble component (Sucrose) in the system changed the rate at which the water ingress. However, in these samples the swelling of the matrix was not visual. Different polymer matrix was used, Eudragit RLPO, to observe any effect on dissolution. This type of Eudragit is more permeable to water due to its molecular structure. It is more porous and thus allows faster ingress of water into the system. Although the imaging experiments suggested higher degree of swelling
of such matrix, the 100% polymer tablet did not show evidence of any significant swelling in water, in the order of 6%.

The egress of drug was followed both by UV and NMR spectroscopy. The UV absorption of samples collected from MRI dynamic dissolution experiments showed that most of the drug was accounted for in approximately 24hrs. The resulting curve demonstrating the drug release suggested that further experimental development was needed to perform more accurate measurements. Thus the data obtained from the static NMR spectroscopy measurements were used to interpret the drug egress, which took approximately 5 days. An estimation of the transport diffusion coefficient of drug was made and found to be in the order of $10^7 \text{cm}^2/\text{s}$.

MRI experiments revealed accumulation of air voids in the matrix exposed to water for five days. Consequently, high spatial resolution X-ray $\mu$CT experiments were conducted to observe the microstructure of the system. The experiments revealed that water ingresses into the system with a sharp diffusion front and air voids started to accumulate and grow in the sample which agreed with findings already seen from MRI experiments. The observation of air-voids ripening within the matrix suggested that the accumulation of air voids is a significant process affecting the dissolution mechanism of the drug. The X-ray $\mu$CT system allowed the air-void size distribution to be quantified as it changes over time. The data showed that the mean volume of the air voids followed a linear trend with time.

Finally, the sample matrix was exposed to different dissolution environments, phosphate buffer pH 7.4 and drug concentrated solution. In the phosphate buffer the system had similar behaviour as in water whereas in the concentrated solution virtually no swelling was observed. This suggested that the swelling of the system was not due to the saturated drug solution present in the sample matrix during dissolution.

A simple schematic diagram of the dissolution model of the sample matrix as discussed above is shown in Figure 5-53.
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Figure 5-53: A simple schematic diagram illustrating the dissolution model of the sample matrix.

All the above observations were used to construct theoretical models able to describe the air voids formation and the swelling and dissolution mechanism as discussed in Chapter 6.

5.5 Conclusion

In this chapter non-destructive imaging techniques were used to observe the dissolution of drug from a solid polymer matrix and the evolving micro-structure of the system during dissolution. Different manufacturing parameters were studied such as different drug loading, levels of compaction, particle size, matrix type and dissolution environments, which will enable to understand the dissolution mechanism of the sample matrix. It is suggested that initially water rushed in across the whole tablet very quickly and then dissolution proceeded in a much slower rate with a sharp diffusion front that advanced according to “Fickian” diffusion. Subsequently, the swelling of the sample matrix was observed only for the drug/polymer matrix since virtually no swelling for the 100% Eudragit tablet and simple dissolution for the 100% drug tablet was observed. The drug egress was followed both by UV and NMR spectroscopy. The imaging techniques of MRI and X-ray \( \mu \)CT have both been used to independently image the ingress of water into the system and observe the formation of air-voids in drug loaded Eudragit matrices exposed to water. The high spatial resolution of the X-ray \( \mu \)CT system allowed the air-void size distribution to be quantified as it changes over time. The mean-volume of the air-voids was observed to increase linearly with time.
Chapter 6

6 Theoretical models of air voids formation and dissolution mechanism

In this chapter models are presented to describe the accumulation and ripening of air voids, swelling and dissolution mechanism of the sample matrix. The models were developed based on the experimental results found in Chapters 4 and 5.

6.1 Model of air voids formation

MRI and X-ray μCT showed evidence that as water ingressed into the tablet there was accumulation of air voids in the system. The high spatial resolution of the X-ray μCT experiments revealed that these small air voids were ripening to form bigger voids with smaller total surface area with time. The results obtained showed three main features; (i) the probability distribution function of air voids was broad and well fitted by a log-normal distribution function, (ii) the mean volume increased linearly with time and (iii) the voids moved only small distances relative to their size at late times.

Attempts to understand the ripening or coarsening of droplets, particles or voids have a long history. Many systems have a final equilibrium that has two separate bulk phases but start out with the two phases mixed on a small or even microscopic scale. This length scale then increases: this process is called Ostwald ripening, it is also referred to as ripening or coarsening. In Ostwald ripening, large molecules or clusters of atoms grow in size at the expense of smaller ones, a process that continually decreases the total interfacial area of the system [Che and Houyt, 1995].

Two main mechanisms have been studied extensively over the years that cause the increase in length scale. These include the diffusion of individual molecules or atoms and coalescence.

The theory for the ripening occurring not via coalescence but via diffusion of molecules is well developed. It was initially introduced by Lifshitz, Slyozov [Lifshitz and Slyozov, 1961] and Wagner [Wagner, 1961] (LSW) and much work has been done since [Voorhees and Glicksman, 1984] [Yao et al., 1993]. The LSW theory describes a model where the growth of particles or voids occurred via continuous diffusion driven by chemical potential gradients. The size
distribution predicted by the LSW theory was a rather narrow distribution with quite sharp decline at large sizes as seen in Figure 6-1. The graph was redrawn from [Lifshitz and Slyozov, 1961].

Figure 6-1: The LSW probability distribution. Redrawn from [Lifshitz and Slyozov, 1961].

Figure 6-1 shows the probability distribution of a particle or void in the sample that would have a reduced volume \( Z \) as a function of \( Z^{1/3} \). The volume was reduced such that particles or voids with \( Z^{1/3} \) of 1 neither grew or shrunk, while diffusion made the larger particles or voids to grow at the expense of the voids with \( Z^{1/3} \) less than 1. The LSW theory also yielded the well known result that the cube of the average particle radius (or the volume) increased linearly with time [Che and Houyt, 1995].

The second mechanism that causes the increase in length scale is coalescence occurring via conventional diffusion of particles or voids into contact by migrating particles or voids in the matrix as observed in emulsions. The droplet size distribution in emulsions has been studied by different groups and has been well described by log-normal size distribution [Lonnqvist et al., 1997, McDonald et al., 1999]. Dickinson et al. [Dickinson et al., 1999] studied the Ostwald ripening kinetics in \( n \)-alkane oil-in-water emulsion stabilised by sodium caseinate to monitor the time-dependent changes in the average droplet diameter and droplet size distribution. They showed the linear increase of droplet size with time stored.

However, coalescence can be considered as an episodic process where the particles or voids are not continuously growing or shrinking by difference in radii but they grow via discrete events, as shown in Figure 6-2.
This episodic process of coalescence can lead to a log-normal size distribution as the log-normal distribution is a generic property and does not necessarily require that particle size distribution is due to diffusion of voids into contact.

According to the experimental observations the data were well fitted to log-normal size distribution and there was a linear growth of the mean volume with time. The linear growth is consistent with the LSW theory. However, the particle size distribution did not have the shape predicted by the LSW theory that of an asymptotic narrow distribution, but more closely matched the much broader log-normal distribution. Moreover, it was shown that there was only small, but not zero, translational motion of voids at the late times in the experiments. This observation ruled out the mechanism of coalescence via migration as seen in emulsions. According to Figure 6-2 it can be suggested that the increase of the void size within the matrix was via coalescence in a sense that pairs of nearby voids were becoming bigger by combining suddenly in discrete events. As the experiments only yielded data on length scales of micrometres and upwards, and the acquisition times were long, it was not feasible to either directly observe coalescence or to follow the diffusion of individual air molecules. Therefore, this combining of the air voids could possibly involve little motion or some local diffusion.
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Discrete time:

<table>
<thead>
<tr>
<th>LSW Diffusion</th>
<th>Continuous diffusion of air voids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emulsion Moving</td>
<td>Coalescence in long distances</td>
</tr>
<tr>
<td>Combining process</td>
<td>combining suddenly in discrete events</td>
</tr>
<tr>
<td>Polymer/Drug Matrix</td>
<td></td>
</tr>
</tbody>
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**Figure 6-3:** Void ripening mechanisms of: LSW theory; Emulsion moving; and predicted theory.

The experimental data in Chapter 5 Section 5.3.2 showed the log-normal distribution of air voids at a given time. It was suggested that the ripening of the air voids in the sample matrix was via a sudden combining, which could lead to a log-normal size distribution. A simple model based on this combining process of the air voids with voids all initially of the same size, \( V_0 \), can be built as follows. It can be assumed that at any time, \( t \), the size of the void \( i \), which was directly related to the volume was \( V(t) \). At \( t=0 \), the volume of the void was \( V_0 \). After one collision with a void of the same volume the volume changed to \( 2V_0 \) and after a second collision per void it changed to \( 4V_0 \) and so on. Therefore, after \( n = \) number of collisions per void the volume became

\[
V_n = 2^n V_0 \Rightarrow \frac{V_n}{V_0} = 2^n
\]

assuming at each step that the combining voids have equal volumes. Alternatively, this could be written as

\[
\ln \frac{V_n}{V_0} = n(\ln 2)
\]

where \( n \) was an independent random variable with its probability distribution, \( p(n) \), a Gaussian distribution. Granqvist and Buhrman [Granqvist and Buhrman, 1976] showed that coalescence naturally leads to a volume that can be expressed according to equation 6-2 which is Gaussian distribution. Hence, at any time \( t \) the volume of a void \( i \), \( V_i \), could be expressed as
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\[ V_t(t) = 2^{n(t)} \]

where \( n(t) \) was the number of combining events for void \( i \) which has occurred at time \( t \).

According to the assumption that the driving mechanism of the growth of the air voids was the sudden combining of the air voids discussed above, a simple differential equation was considered able to describe the rate of change of total number of air voids per unit volume \( \mu(t) \) as function of time \( t \)

\[ \frac{d\mu}{dt} = -k(V)\mu^2 \]

where \( k(V) \) was the rate coefficient for the combining of a pair of air voids with volume \( V \). This simple equation neglected the spread in void volumes at a given time, and also neglected any variation in space, i.e., any heterogeneities. The number of voids per unit volume \( \mu \) and the volume of a void \( V \) must be inversely proportional to one other as the product \( \mu V \) equalled the fraction of air in the sample, which was assumed to be constant. The experimental data yielded a volume per void that increased linearly with time, \( V \propto t \), and so \( \mu \propto t \). If in equation 6-4, the rate coefficient for the combining of the air voids was set constant, \( k(V) = \text{constant} \), then \( \mu \propto t \) is indeed a solution to this equation. Thus if the air voids combined at a rate proportional to the square of the number of air voids per unit volume, then the time dependence of the void volume found in experiment was obtained. This was very reasonable, since if the voids were distributed at random in the sample then the number of pairs of voids close to each other would scale as the square of their number density.

It has been observed that the combining of the air voids can generically lead to a log-normal distribution after times such that each void has combined with many other voids. A simple physically reasonable model of this combining thus agreed with the experimental observations that of the log-normal distribution of air voids at a given time and of the linear relationship of the mean volume with time. Finally, coalescence of voids did not necessarily require large-scale motion within the sample. It can be considered as an episodic process and thus agreed with the final experimental observation that there was a small but not zero motion of voids within the sample at late times.

6.2 Development of a model of dissolution mechanism

In Chapter 5 experimental evidence showed that changing certain parameters in the manufacturing process of the drug/polymer matrix had an effect in the release of the drug from the system. The next step was to get insight into the process of dissolution by developing a mathematical model able to describe all the experimental facts.
Chapter 6: Theoretical models of air voids formulation and dissolution mechanism

The quantitative description of the experimental results developed in this chapter was based on key observations made from the experimental analysis. The observations included the porosity of the drug/polymer matrix, the ingress of water that was characterised by a sharp diffusion front advancing as a square root of time, the swelling of the polymer/drug matrix, the effect particle size and drug loading and the \( D_{air} \) measurements of water and drug.

In Chapter 1, experimental and theoretical work of several different research groups have been discussed that have elucidated the dissolution mechanism of polymeric drug delivery systems. Here, the theoretical description of drug release from the sample matrix was a combination of diffusion and dissolution processes.

Diffusion is the most important mechanism used to control drug release. The transport of water, into a matrix where diffusion is concentration gradient driven can be described by Fick's second law [Crank, 1975]

\[
\frac{\partial c_w}{\partial t} = \frac{\partial}{\partial x} \left[ D(c_w) \frac{\partial c_w}{\partial x} \right]
\]

where \( c_w \) is the concentration of water, \( D(c_w) \) is the concentration dependent diffusion coefficient of water, \( x \) the position, and \( t \) time. The ingress proceeds at a square root of time. However, this simple law does not account for swelling and the back flow of the matrix material if total volume is to be preserved. Nor does it permit the back flow of a third component such as drug. For systems with more than one component the process is more complicated and involves the interdiffusion of components. The general equation that describes the Fick's first law for multicomponent system diffusion is [Wallin et al., 2000] [Bird et al., 2002]

\[
F_i = \sum_{j=1} D_{i,j}^* \frac{\partial c_j}{\partial x}
\]

where \( F_i \) is the flux of component \( i \), \( c_j \) is the concentration of component \( j \), and \( D_{i,j}^* \) is a multicomponent coefficient. Generally, \( D_{i,j}^* \neq D_{j,i}^* \) and not all the \( D_{i,j}^* \) are mutually independent. For example, a ternary system has four independent coefficients. If \( D_{i,j}^* = D_{j,i}^* \) then this reduced to three. Different authors have tried to rewrite this equation in terms of binary mixture diffusion coefficients. For the heterogeneous system studied in this thesis the diffusion model chosen was based on that described by Wallin et al. [Wallin et al., 2000]. These authors studied polymer mobility as a function of depth in cross-linking latex coatings during their film formation. They adopted a model of diffusion that occurred by pairwise exchange of components using an "atomistic" approach on a discretised lattice. So the diffusion coefficient of component \( i \) in component \( j \) can be expressed as \( D_{i,j} \). In such circumstances the flux of component \( i \) with respect to component \( j \) is given by
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\[ D_{ij} \left( c_i \frac{dc_i}{dx} - c_j \frac{dc_j}{dx} \right) \]

where \( D_{ij} = D_{ji} \) so that the effective diffusion equation relating to component \( i \) is

\[ \frac{\partial c_i}{\partial t} = \sum_j D_{ij} \left( c_j \frac{\partial^3 c_i}{\partial x^3} - c_i \frac{\partial^3 c_j}{\partial x^3} \right) \]

For a system of \( n \) components, this expression requires definition of \((1 + 2 + 3 \ldots + (n-1))\) diffusion coefficients.

The second process described in the model was dissolution. The rate at which the solid drug particles dissolve was proportional to the total solid drug particle surface area and the difference in concentration of surrounding solution from equilibrium. According to the Noyes-Whitney equation [Noyes and Whitney, 1897].

\[ \frac{dc_{\text{solid drug}}}{dt} = -A \ k \ (f(\text{eq}) - f(t)) \]

where \( c_{\text{solid drug}} \) was the concentration of solid drug, which was related to the volume of drug per unit volume, (dimensionless), \( dc_{\text{solid drug}}/dt \) was the rate of dissolution, \( A \), was the area of the drug particles per unit volume of tablet (cm\(^3\)), \( k \) was the dissolution constant (cm/s) and \( f(\text{eq}) \) and \( f(t) \) were the fractions that corresponded to the saturation concentration of drug in solution and the concentration of drug at time \( t \), respectively. In particular \( f(\text{eq}) \) was 29% (w/v). One way to increase dissolution rate of a drug was to increase the surface available for dissolution. This can be done by reducing particle size of the component as a few large particles would dissolve at a much slower rate than lots of smaller size. According to Equation 6-9 it was essential to consider how the surface area of the drug particles changed with time. It was assumed that all the drug particles were spherical and had the same initial size. For a uniform drug particle distribution in the solid matrix the surface area was dependent on the size of the particles and was expressed as

\[ A(t) = \frac{3 \left[ c_{\text{solid drug}}(t) \right]^{1/3}}{r_0} \left[ c_{\text{solid drug}}^0 \right]^{1/3} \]

where \( c_{\text{solid drug}}^0 \) was the initial concentration of drug in the matrix, \( c_{\text{solid drug}}(t) \) was the concentration at time \( t \), and \( r_0 \) was the initial drug particle radius.

Noyes-Whitney equation has been used by different groups to describe the drug dissolution. Frenning and Stromme [Frenning and Stromme, 2003] presented a model combining dissolution, diffusion, and immobilization caused by adsorption of the drug to the tablet constituents. They studied the drug release using alternating ionic current method [Frenning et al., 2002]. Their
model was formulated in terms of a pair of coupled nonlinear partial differential equations, based on Fick's law, Noyes-Whitney equation and Langmuir-Freundlich adsorption isotherm, which were solved numerically by using finite differences. Schreiner et al. [Schreiner et al., 2005] measured the wettability, porosity, water uptake, and drug release rates of several ketoprofen-excipient preparations (powder blends, granulations, tablets). The drug release was determined via dissolution measurements. They showed that the time-dependent change of the effective dissolution surface in all preparations followed stochastic models where the dissolution equation was based on the differential Noyes-Whitney equation combined with a distribution function the e.g. the lognormal distribution, and numerically solved using a specialised software system. The model adopted here followed many of these ideas. However, the model constructed in this thesis was based on observation obtained from MRI experiments, which has the ability to provide internal images of the matrix under study in real-time conditions, non-destructively and non invasively with high spatial resolution.

The model equations were solved numerically using standard finite differences techniques by writing codes in IDL version 5.5 (Research Systems Inc., Colorado, USA). The model considered four components: water, polymer, solid drug and liquid drug. The initial concentration of the solid drug was set uniform throughout the sample. Time and space steps, $\Delta t$ and $\Delta x$ were defined and the step-sizes used in the calculations were set small to 0.2sec and 0.014cm respectively. The numbers were kept small so as to achieve small increments. The calculations proceeded in a series of time loops. Within each loop there were basic steps: (i) updated concentrations for dissolution and (ii) updated concentrations for diffusion. The steps were repeated for each loop. It was sensible to suggest that the amount of solid drug decreased at the same rate as the total drug in solution increased in the absence of diffusion.

$$\frac{dc_{\text{liquid\_drug}}}{dt} = -\frac{dc_{\text{solid\_drug}}}{dt}$$

6-11

The model was constructed in a series of steps, which systematically included different processes as shown in Figure 6-4.
Figure 6-4: Model constructed in a series of Diffusion and Dissolution step in loop.

The diffusion step was performed in which the concentration of each component in the sample was updated according to Equation 6-8 in order to reduce any spatial concentration gradient. The dissolution step was performed to calculate the decrease in the concentration of the solid drug and the increase of the concentration of liquid drug.

The model was tested for a non-swelling system and a swelling system as discussed in the following sections.

6.3 Model for a non-swelling system

For the non-swelling system the model was effectively simplified to just two components: water and liquid drug. The diffusion mechanism involved two processes. The water penetrated the drug/polymer matrix and the liquid drug diffused out of the system as shown in Figure 6-5.
Figure 6-5: Water ingress into the system of length, L, and liquid drug diffuse out. The green block denote the polymer particles and the red blocks the drug particles of size $r_0$.

There was an exchange of water and drug within the system with a constant mutual diffusion coefficient for drug in solution in which the flux of drug balanced the flux of water the other way. From equations 6-8

$$\frac{\partial c_w}{\partial t} = D_{w,\text{liquid\_drug}} \left( c_{\text{liquid\_drug}} \frac{\partial^2 c_w}{\partial x^2} - c_w \frac{\partial^2 c_{\text{liquid\_drug}}}{\partial x^2} \right)$$  \hspace{1cm} 6-12

$$\frac{\partial c_{\text{liquid\_drug}}}{\partial t} = D_{\text{liquid\_drug},w} \left( c_w \frac{\partial^2 c_{\text{liquid\_drug}}}{\partial x^2} - c_{\text{liquid\_drug}} \frac{\partial^2 c_w}{\partial x^2} \right)$$  \hspace{1cm} 6-13

In first approximation the diffusion coefficient of polymer ($D_p$, anything) and solid drug ($D_{\text{solid\_drug},\text{anything}}$) were assumed zero.

A system was constructed consisting of a tablet of solid drug and polymer and a small fraction (3%) void filled with water in contact with a reservoir of water at time zero. The initial conditions were obtained from the assumption that all the drug was undissolved in the initial state and for a 45% drug loaded tablet

$x<0 \quad c_w = 1$, $c_{\text{liquid\_drug}} = 0$, $c_{\text{solid\_drug}} = 0$ and $c_p = 0$

$x\geq0 \quad c_w = 0.03$, $c_{\text{liquid\_drug}} = 0$, $c_{\text{solid\_drug}} = 0.45$ and $c_p = 0.55$

where $c_w$ was set to $c_w = 0.03$ for $x\geq0$ to allow the initial capillary uptake of water. No flux boundary conditions were assumed at the lower tablet surface and at the upper water surface.
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The model inherently conserved volume and there was therefore no swelling. It was assumed that locally solid drug dissolved to liquid drug according to equation 6-9 and that water and drug diffused according to equations 6-12 and 6-13. Simulations were conducted to observe what happened. They did predict the sharp diffusion front of water and the drug egress. These simulations were meant to compare to the experiment results in Chapter 5 and the initial parameters were set based on the experimental formulations. Figure 6-7 and Figure 6-8 show a typical result for a 45% drug loaded tablet, 0.3 cm in length, dissolution constant, $k$, of $2.5 \times 10^{-6}$ cm/s, $D_w = 1.82 \times 10^{-6}$ cm$^2$/s and drug particle radius, $r_0 = 0.0045$ cm. The water–tablet interface was at $x = 0$ cm; water to the left ($x<0$) and tablet to the right ($x>0$). The water reservoir extended to $-0.6$ cm. Profiles are shown at selected times.

![Figure 6-6: Initial condition of the model of the two component system.](image)

![Figure 6-7: Water profiles of model data (45% w/w), $k = 2.5 \times 10^{-6}$ cm/s, $D_w = 1.82 \times 10^{-6}$ cm$^2$/s.](image)
Figure 6-8: Liquid drug profiles of model data (45% w/w), $k=2.5 \times 10^{-6} \text{cm/s}$, $D_w=1.82 \times 10^{-6} \text{cm}^2/\text{s}$.

Figure 6-7 shows the water penetrating into the system with a sharp diffusion front until it reaches the end of the tablet, at $x = 0.3 \text{cm}$. Until the water reached the far end of the sample, it was essentially a semi-infinite system to which the Boltzmann transform could be applied. Figure 6-9 shows the Boltzmann transform of the data in Figure 6-7. It is seen that, with the exception of the very early time profiles, all the profiles lie on master curve.

Figure 6-9: Boltzmann’s transform of modelled (45% drug load). Data of Figure 6-7.

The Boltzmann transform of the data (Figure 6-9) is very similar to the curve obtained from the experimental data (Chapter 5, Figure 5-12). The data show the sharp diffusion front which advances according to the square root of time. This was also confirmed from the plot of the distance of water ingress from the initial time until it was fully invaded the tablet against time$^{1/2}$ which gave a straight line.
Figure 6-10: Plot of the distance of water moved into the tablet against $\text{Time}^{1/2}$ for model data of 45% drug load.

Figure 6-11 shows calculated profiles and the corresponding Boltzmann’s transform for a different set of parameters: 45% drug loaded tablet, 0.3 cm in length, $k = 2.5 \times 10^{-8}$ cm/s, $D_w = 1.82 \times 10^{-6}$ cm$^2$/s and drug particle radius, $r_0 = 0.0045$ cm. These parameters were the same as in Figure 6-7 except for the dissolution constant, $k$, which was 100 times smaller than before. It can be observed that the shape of the profiles is completely different and the Boltzmann’s transform did not yield a master curve.
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(a)

Water profile of modelled data (45% drug load)

(b)

Boltzmann's transform of modelled data (45% drug load)

Figure 6-11: (a) Water profile of modelled data (45% (w/w) drug load) \(k=2.5\times10^{-4}\text{cm/s}, D=1.82\times10^{-6}\text{cm}^2\text{s}^{-1}\) and (b) Boltzmann's transform of modelled data (45% (w/w) drug load).

The difference in shape between Figure 6-7 and Figure 6-11(a) is due to the change in balance between diffusion and dissolution between the two parameters set. In the former the process is diffusion limited whereas in the latter is dissolution limited.

The values for the \(D_w\) used for the simulations were similar to the corresponding transport diffusion coefficient of a 45% (w/w) drug loaded Eudragit tablet obtained from the experiments (Chapter 5, Section 5.1.3.2). It was anticipated that the self-diffusion coefficients of the drug and water obtained in Chapter 4 would be helpful. In this event transport diffusion coefficients were used. Although the two are of comparable magnitude, currently no satisfactory link between the two has been identified. Although some authors have tried [Ciampi and McDonald, 2003, Liu and Gao, 2003].
6.3.1 Dimensionless analysis

A dimensionless parameter was introduced to best reflect the competition between dissolution and diffusion. This parameter was defined as the ratio of the time required for water to diffuse across the tablet and the time for the drug to dissolve. The characteristic timescale of diffusion, $\tau_{\text{dif}}$, for water diffusion across the tablet was defined as

$$\text{Timescale of Diffusion, } \tau_{\text{dif}} = \frac{L^2}{D_w}$$

where $L$ was the length (thickness) of the tablet in cm and $D_w$ the diffusion coefficient of water in cm$^2$/s. The corresponding characteristic timescale for dissolution of a drug particle $\tau_{\text{dis}}$ was defined as

$$\text{Timescale of Dissolution, } \tau_{\text{dis}} = \frac{r_0}{k}$$

where $r_0$ was the drug particle radius in cm and $k$ is the dissolution constant in cm/s.

A dimensionless “time” parameter was defined as the ratio of the timescale of diffusion and the timescale of dissolution

$$\tau = \frac{\tau_{\text{dif}}}{\tau_{\text{dis}}} = \frac{L^2 k}{D_w r_0}$$

A relevant model to this study was the one developed by Harland et al. [Harland et al., 1988b] as already discussed in Chapter 1 Section 1.4. They described the drug dissolution and diffusion mechanism by one single equation. In this thesis, two coupled equations are used to describe the diffusion and dissolution mechanisms. Moreover, Harland et al. also introduced a dimensionless parameter to classify different dissolution regime limits. As already discussed in Chapter 1 their parameter was defined as

$$D_i = \frac{kR^2}{D}$$

where $k$ have units of s$^{-1}$, different to the $k$ parameter defined here which has units of cm/s. However, $D_i$ implicitly only included a single length scale $R$, which is equivalent to the tablet size $L$ defined in equation 6-16. It did not include the size of the drug particle $r$, which in this analysis would require the typical dimension of a pore within the microstructure and, due to the different definition of $k$, also the total internal surface area of porous microstructure. Therefore, Harland cannot discuss the time for dissolution as effectively as in the current work.
In this thesis model profiles were calculated for different dimensionless numbers, $\tau$, by varying the dissolution rate, tablet length, drug load and diffusion constant. It was observed that when $\tau \gg 1$ there is a rapid dissolution at the front that saturates the solution and prevents front advancing. It is the subsequent egress by diffusion of drug which limits the progress and we call this drug-diffusion limited. When $\tau \ll 1$, the reverse is true. The water at the front is not saturated so readily and therefore a normal water diffusion front occurs. The egress rate is thus limited by the dissolution rate and we term this drug-dissolution limited. This basic idea is analogous to Harland except of course his $D_l$ involves the single length scale and looses inherent information about microstructure.

The effect of the particle size on the theoretical model data was also investigated. Figure 6-12 and Figure 6-13 show calculated water profiles and their corresponding Boltzmann's transforms for particle sizes of 0.0045cm (dimensionless number: 14) and 0.45 (dimensionless number: 0.14) respectively. The other parameters were: 45% drug load, 0.3cm length, $k = 2.5\times10^{-6}$cm/s and $D_w = 3.5\times10^{-6}$cm$^2$/s.
Figure 6-12: (a) Water profile (b) Boltzmann’s transform (c) Solid drug profile and (d) Liquid drug profile of model data for 45% drug load, $r_d=0.0045\text{cm}$ and Dimensionless number 14.

Figure 6-13: (a) Water profile (b) Boltzmann’s transform (c) Solid drug profile and (d) Liquid drug profile of model data for 45% drug load, $r_d=0.45\text{cm}$ and Dimensionless number 0.14.
It can be observed that for big drug particle size, giving small dimensionless number (0.14), the process was drug-dissolution limited and for small particle sizes, with large dimensionless number (14), was drug-diffusion limited.

The model was tested for similar parameters as the experiments (e.g. dissolution constant, particle size, porosity, drug load) and the resulting profiles were shown to yield release characteristics in good agreement with those observed experimentally (drug-diffusion limited). However, this version of the model did not take into account at all the swelling of the sample matrix and so that led to the second approach of the modelling, the incorporation of the swelling effect.

6.4 Model of a swelling system

Experimental evidence showed that the swelling of the tablet was only observed for a polymer/drug matrix. In this part of the model it was considered that the drug and water diffuse independently so that swelling was possible. At this stage, no mechanism for the independent diffusion is yet discussed. In order to achieve swelling it was allowed that

\[ c_w + c_{\text{liquid, drug}} + c_{\text{solid, drug}} + c_p \neq 1 \]

in a unit length of sample. Thus, to accumulate \( c_w + c_{\text{liquid, drug}} + c_{\text{solid, drug}} + c_p = 1 \), the length scale was renormalised by considering the amount of the components at location \( x \) fixed but \( \delta x \) was changed to allow swelling. Hence, the length of the \( z^\text{th} \) element

\[ \delta x_z = \delta x_w^0 \left( \sum \left( c_w + c_{\text{liquid, drug}} + c_{\text{solid, drug}} + c_p \right) \right) \]

so that the position of the \( z^\text{th} \) element was

\[ x_z = \delta x_w^0 \left( \sum \left( c_w + c_{\text{liquid, drug}} + c_{\text{solid, drug}} + c_p \right) \right) \]

on the assumption that \( c_w + c_{\text{liquid, drug}} + c_{\text{solid, drug}} + c_p = 1 \) at \( t = 0 \).

The results presented are for constant values for the water and drug diffusion coefficient. So for a 45% drug loaded matrix of 0.3cm in length and \( r_0 = 0.0045\text{cm} \) the selection of the water and liquid drug diffusion coefficients were obtained according to experimental findings in Chapter 5. So a 45% drug loaded tablets had a \( D_w \) in the order of \( 1.82 \times 10^{-6}\text{cm}^2/\text{s} \) and the \( D_{\text{liquid, drug}} \) was approximately 10 times smaller in the order of \( 1.82 \times 10^{-7}\text{cm}^2/\text{s} \). The dissolution constant was set at \( k = 2.5 \times 10^{-6}\text{cm/s} \) as previously done. Figure 6-14 shows the resulting profiles at selected times with water–tablet interface set at \( x = 0\text{cm} \); water to the left and tablet to the right. The water reservoir extended to \(-0.6\text{cm}\).
Figure 6-14: (a) Water profile modelled data, (b) liquid profile modelled data and (c) polymer profile modelled data.
From Figure 6-14(a) and (b) it can be seen that as the water was going into the system the boundary of the water and the tablet was shifted to left indicating the swelling. In the water profile, it is observed that the water has reached the end of the tablet whereas from the liquid drug profile it can be seen that there was not sufficient time for the drug to come out with that simulation length. Only a very small amount did. Figure 6-14(c) shows the polymer profile. As the water was going into the tablet the polymer expanded. The polymer stopped expanding after 101.3hrs (solid orange line). After that it started slowly to recover back to its initial position. The black solid line at 176hrs implies that the length of polymer has just started to return back to its initial position. The above profiles showed that swelling of the matrix was observed if independent drug and water diffusivities were assumed. The total change of tablet height over time was measured for the model data and compared with one obtained from experiment. The model data were obtained with similar parameters as for the experimental data for a 55% drug loaded matrix with $D_w = 10^{-5}$ cm$^2$/s, $D_{\text{liquid, drug}} = 10^{-6}$ cm$^2$/s, $k = 2.5 \times 10^{-6}$ cm/s, matrix length 0.3cm and $r_0 = 0.0045$ cm.

Figure 6-15: Increase of tablet size with time for 55% (w/w) drug loaded tablet (a) experimental data and (b) model data.

Thus far simulations did not consider the origin of the swelling. One plausible suggestion was to assume that the swelling of the sample matrix was due to double layer repulsion inherit in the system as discussed in the following section.

### 6.5 Swelling of the sample matrix due to osmotic pressure

It was assumed that the driving force for the swelling of the sample matrix was double layer repulsion. In literature, work can be found on clay swelling systems [Madsen and Muller-Vonmoos, 1989] and polyelectrolyte polymer gel swelling systems [Elliott and Hodson, 1998] in which models were based on electric double layers.
In general when ionised surfaces are in a medium that contains counter-ions, they interact with each other by electrostatic forces. The simple charged interactions are moderated by two effects: the first one is that the counter-ions will tend to weakly interact with opposite charges and the second is that there is a screening of these electrostatic forces by the bulk concentration of ions in solution. So when the two charged surfaces approach each other the ion concentration between the surfaces increases due to the requirement to maintain electrical neutrality and so a greater osmotic pressure is generated that leads to a repulsive force. This can be applied to the system studied here as it contains Eudragit polymer and Diltiazem HCl drug, which were both positively charged molecules (cationic) as shown from their structure in Chapter 3, Figure 3-1 and 3-2 respectively. As water enters the system there is a local increase in the concentration of counter-ions, leading to an increase in the local osmotic pressure, which results in a repulsion between the particles. Therefore, it can be assumed that the osmotic pressure in the system led to repulsive forces that resulted in the swelling of the sample matrix. A schematic diagram of the double layer repulsion is shown in Figure 6-16.

![Figure 6-16: Double layer repulsion within the sample matrix leading to swelling.](image)

Such a process is effectively a pressure acting on the water forcing it to ingress the tablet and cause swelling. Whilst it is likely that it can be dressed mathematically to look like diffusion, it need not strictly be diffusion and hence one should not be surprised if the effective diffusion coefficients for the water and drug are independent.

In a medium that contains free charges such as an electrolyte solution, these interactions become screened [Israelachvili, 1991]. This charge-screening effect occurs as a result of the presence of a large number of free ions in solution that are able to cluster around surface charges. This has the effect of shielding these surface charges from participating in their normal electrostatic interactions and so weakens the repulsive forces that presumably drive the swelling of the matrix. A very common electrolyte solution is aqueous sodium chloride solution (NaCl). Hence when two
surfaces are exposed to NaCl solution the repulsive pressure, which is the force per unit area, between the two surfaces at a constant surface potential, $\psi_0$, is \cite{Israelachvili, 1991}

$$P = \left(1.59 \times 10^8 \right) \left[NaCl\right] \gamma^2 e^{-\kappa D}$$

where $\gamma = \tanh(\varepsilon \psi_0 / 4kT)$, where $\varepsilon$ is the valency, $e$ is the electronic charge, $k$ is the Boltzmann’s constant and $T$ is the absolute temperature, $[NaCl]$ is the concentration of NaCl (mol/dm$^3$) and $e^{-\kappa D}$ is the screening effect with $D$ being the distance between two surfaces (m). So the double-layer interaction between two surfaces decays exponential with distance according to $e^{-\kappa D}$ where the characteristic decay length, $\kappa^{-1}$ (m), is known as the Debye screening length \cite{Israelachvili, 1991}. When $e^{-\kappa D}$ is very small then the pressure is very small as well and so no swelling is occurring. More salt in solution increases the value of $\kappa$ leading to a more dominant screening effect as

$$\frac{1}{\kappa} = \frac{0.304}{\sqrt{[NaCl]}}$$

where $\kappa^{-1}$ is in nm \cite{Israelachvili, 1991}. The chosen electrolyte solution for this study was NaCl solution. The polymer/drug matrix was exposed to two different concentrations of salt solution: 0.2M and 2M. The results presented in Chapter 5 Section 5.3.3 showed that when the tablet was exposed to 0.2M solution the matrix swelled whereas when it was exposed to 2M it did not. As the particles were compressed in a tablet it can be suggested that the distances between them in the compact sample were very small. Hence from the experimental results it can be assumed that small distances of particles can swell in concentration of 0.2M with $\kappa = 1.5\text{nm}^{-1}$. Above this concentration, at 2M NaCl, the particles cannot see each other in the presence of salt due to screening effect as $\kappa$ has higher value, $\kappa = 4.7\text{nm}^{-1}$, and so the matrix did not swell.

Another plausible suggestion for the swelling of the matrix is the solvation of drug particles. As water diffuses into the system it can be assumed that the drug particles attract more water molecules than the polymer particles due to their chemical structure (more polar groups). So as drug particles start to dissolve there is an increase in the area around them because it dissolves which possibly leads to the swelling of the matrix.
6.6 Conclusions

In this chapter models were adopted to explain the accumulation and ripening of air voids in the sample matrix observed during the ingress of water into the sample matrix, and the dissolution and swelling mechanisms.

The predicted model for the air voids distribution enabled to make an educated suggestion about how the ripening proceeded. It seemed likely that the increase of the void size within the matrix was due to a sudden combining of voids in discrete events which possibly involved little motion or some local diffusion. The rate of combining per unit volume was proportional to the square of the number density of voids. The predicted model was compared with existing models in literature which also shown the linear relationship of particle size (or volume) with time. However, it can be suggested that measuring just the mean size as a function of time is not sufficient to distinguish between the two mechanisms of ripening, diffusion and coalescence by migrating particles. An imaging technique, such as the MRI and X-ray μCT, that enables the distribution function to be obtained is required. The techniques and system studied here was actually one of the few systems by which the probability distribution function can be measured in situ and non-destructively.

It was possible to develop a model to describe the release of the drug from the matrix by combining diffusion and dissolution processes based on Fick’s law and Noyes-Whitney equation respectively. The initial stage of the model described a non-swelling matrix where a mutual diffusion coefficient of the water and liquid drug was assumed. The next stage involved a swelling matrix where it was necessary to decouple the mutual diffusion coefficient to separate $D_w$ and $D_{\text{liquid-drug}}$ to achieve swelling. The model was tested for different parameter sets and was able to reproduce the characteristic trends of the experiments reported in Chapter 5. The important outcome of this model was the introduction of a dimensionless parameter able to reflect the
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competition between dissolution and diffusion. The parameter was the ratio of the time of diffusion and the time for dissolution. When the parameter was greater than one the process was drug-diffusion limited. When it was less than one it was drug-dissolution limited.

Finally, it was suggested that the driving force of the swelling of the drug/polymer matrix observed in the experiments was due to osmotic pressure. An assumption based on the double layer repulsion as the two components in the sample matrix were cationic molecules.
Chapter 7

7 Conclusions and Future work

7.1 Conclusions

In this thesis the principal factors affecting the release of a soluble drug from a non-swelling polymer matrix are studied so as to understand better the dissolution mechanism. The release of the drug is examined using a variety of non-destructive and non-invasive imaging methods including MRI, X-ray μCT, UV spectroscopy and optical microscopy. The tablets are prepared with different drug loadings, level of compaction, particle size, matrix type and exposed primarily to water and other dissolution environments. MRI experiments on drug loaded tablets exposed to water suggest that there is a rapid capillary uptake (<10 mins) of water into the initial pore space the tablet ahead the primary dissolution. This porosity is determined to be very small, less than 4% for 100% Eudragit tablet and even less for drug loaded tablet. Slow subsequent dissolution characterised by a sharp diffusion front is observed, which separates the invaded and un-invaded regions. It is shown that water ingresses linear with the square root of time and the transport diffusion coefficient of water in the tablet is estimated as a function of concentration. The rate of water ingress is affected by the drug load and the drug particle size. Swelling of the whole tablet at intermediate drug loading (≥45%) is detected but no comparable swelling for either 100% polymer or 100% drug tablets. NMR and UV spectroscopy were used to assess the amount of drug released. An important observation made in this thesis, is the accumulation and ripening of air voids within the sample matrix as water ingresses into the tablet. This is important as it possibly affects the release rate of the drug. This phenomenon was both observed by MRI and X-ray μCT. The high spatial resolution of the X-ray μCT system allowed the air-void size distribution to be quantified as it changes over time. A simple model is proposed predicting that the ripening of the air-voids occurred via a combining process of air voids, which possibly involves little motion or some local diffusion. A mathematical model is developed able to describe the dissolution mechanism of the sample matrix based on the observations made from the experimental analysis. The theoretical description of drug release from the sample matrix is a combination of diffusion and dissolution processes. A dimensionless time is introduced to best reflect the competition between dissolution and diffusion. This parameter is defined as the ratio of
the time required for water to diffuse across the tablet and the time for the drug to dissolve. This parameter helped describe the effect of particle size on dissolution. Finally, it is assumed that the driving force for the swelling of the drug loaded polymer matrix observed in the experiments is the osmotic pressure. This assumption is based on the double layer repulsion as the two materials in the system were cationic molecules.

7.2 Future work

In this thesis it was possible to understand in great extent the dissolution mechanism of a soluble drug from a non-swelling polymer matrix by varying principal manufacture parameters. However, there is still potential for further work by changing more parameters and observe the effect on the dissolution mechanism.

In Chapter 5, the effect of pressure in the ingress of water into the system was examined by conducting experiments on tablets prepared with different compression levels. These experiments were completed only on 100% Eudragit tablets compressed at 0.1 and 3tons (0.015 and 0.455GPa). The data obtained suggested that tablets with low compression were more permeable to water as there was more air space between the grains to absorb the water due to lower compaction. The drug loaded matrices were only studied on tablets compressed at 2tons (0.303GPa). Therefore, similar experiments could be conducted on drug/polymer matrices prepared with different compression levels, ranging from 0.1 up to 3tons (0.015 and 0.455GPa) to observe the effect of pressure on drug release and diffusion of water. The different compression level could also affect the initial pore space of the dry matrix. This could be determined as discussed in Chapter 5 Section 5.1.2 and observe any changes. All the experiments presented in this thesis were conducted at room temperature. Increasing the temperate, for example to 37ºC, would help observe any effect on the dissolution mechanism.

MRI and X-ray μCT experiments showed evidence that as water ingressed into the polymer/drug matrix there was accumulation of air voids in the system. The X-ray μCT system allowed the air-void size distribution to be quantified as it changes over time. Varying the experimental parameters in the X-ray μCT experiment such as, drug loading, compression level, polymer type (Eudragit RLPO), different dissolution environment (phosphate buffer) could enable to check if there is any affect in the degree of coalescence. One more suggestion would be to try incorporating the air voids formulation into the mathematical model developed to describe the dissolution mechanism.

The theoretical explanation of the swelling of sample matrix observed in the experiments was based on the assumption that there was a built of osmotic pressure within the system. It would be
useful though to demonstrate this experimentally. A possible suggestion could be to take two glass tubes and fill one with concentrated drug solution (29% w/v) and the other with just water. Then connect the two tubes with a membrane that is permeable to water but not to drug. This could be a thin layer of Eudragit compressed tablet. Epoxy adhesive can be used around the Eudragit layer so as to hold the system together. Water should then permeate to the tube containing the drug/water solution and the difference in height would help determine the osmotic pressure.

The egress of drug from the system was followed both by UV and NMR spectroscopy. The UV experiments showed a 'noisy' line representing the drug release. This led to the assumption that it was necessary to perform the experiment in a more controlled environment. The water travelled in and out of the system using long rubber tubing so one suggestion could be to try to use shorter tubing. However, this could be still difficult due to the size of the magnet.
Chapter 8

8 References


Chapter 8: References


