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Mixed Polymer Hydrophilic Matrices Containing HPMC and PEO

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Abstract

The research in this thesis describes investigations of (i) mixed polymer HPMC and PEO hydrophilic matrices and their performance in low and high ionic environments and (ii) understanding the internal behaviour of HPMC and PEO mixed systems. It was postulated that using a blend of these polymers might provide advantages over the use of single polymers.

A series of 'realistic' 30% w/w polymer matrix formulations, containing different weight ratios of HPMC and PEO and a soluble model drug (caffeine), were tested in ionically challenging media, up to 1M sodium chloride (NaCl). Dissolution testing showed how HPMC dominated formulations exhibited accelerated release in high ionic strength media (0.8M NaCl or higher), whereas PEO dominated formulations did not. Power law analyses suggested the release mechanism of matrices in 0.6M NaCl and below were anomalous non-Fickian transport, but case II transport was observed in HPMC dominated matrices at 0.8M NaCl and above. A polymer ratio of 4:6 HPMC:PEO allowed an extended release tablet to be formulated that was resistant to 1M NaCl. In 0.6M NaCl or below, increasing the proportion of HPMC in a mixed HPMC:PEO tablets, increased the duration of extended release.

Confocal laser scanning microscopy was used to investigate the structure of the HPMC:PEO matrix hydrated gel layer. The results provided evidence that HPMC and PEO particles swell independently in the gel layer. They remained substantially unmixed during gel layer formation, and each appeared to contribute independently to gel layer structure.

Magnetic resonance imaging showed how PEO matrices hydrated more rapidly than HPMC matrices, but PEO matrices completely dissolved after 9 hours. In the case of 4:6 HPMC:PEO and HPMC matrices, a hydrated gel remained. This reflected the behaviour of these matrices in the dissolution tests. Unfortunately, MRI could only be applied in zero salt media, as the dielectric properties of NaCl interfered with the results, and other techniques were required to examine matrix behaviour in high salt media.

Texture analysis showed that at low NaCl concentrations, the HPMC gel layer exhibited higher gel strength than PEO, and that by substituting HPMC for PEO increased gel layer

strength was obtained. The later stages of gel layer morphology were also investigated by digital optical macroscopy. Images showed greater gel longevity of HPMC and mixed matrices, with evidence for a higher gel strength and less erosion than PEO matrices.

Swelling of single polymer particles showed how increasing NaCl concentration significantly inhibited HPMC particle swelling but only had a limited effect on PEO particle swelling. The ability of PEO particles to swell in high salt media may explain the resistance of PEO matrices to high NaCl dissolution media.

The miscibility of HPMC and PEO in dilute solution was studied by rheology and phase contrast microscopy. Measurements of storage modulus (G') at 1% w/v showed how most polymer mixtures showed negative deviations from ideal mixing at all oscillatory frequencies studied (0.1Hz, 1Hz, and 10Hz). This is evidence that these polymers are immiscible in solution. Phase contrast microscopy provided direct optical evidence of phase separation in blended HPMC:PEO solutions (4% w/v). The tendency of these polymers to be immiscible, suggests that they may also be phase separated in the more concentrated environment of the gel layer. Gel layer morphology in binary polymer tablets was investigated directly by confocal microscopy (up to 15 min) and by attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) up to 3 hours. The confocal microscopy images showed that HPMC and PEO appeared to swell independently during early gel layer. Each polymer appeared to contribute independently to gel layer structure. ATR-FTIR imaging allowed chemical mapping of the three components (water, PEO and HPMC) in the gel layer, providing evidence that each polymer formed individual domains. PEO appears to be more extensively swollen than HPMC and may form the outer part of the gel layer, protecting HPMC from the effect of high ionic media.

The work in this thesis suggests that mixed polymer HPMC:PEO matrices may have certain advantages over the use of matrices containing only single polymer. PEO confers resistance to highly ionic media, while HPMC provides a longer drug release than PEO alone. Each polymer appears to contribute separately to the gel layer, but the ability of PEO to swell in highly ionic environments, may allow formation of a diffusion barrier that protects the incorporated HPMC from ionic media, and allows it to contribute to gel layer structure.

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Appendix 1

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Abbreviations and symbols

ATR-FTIR	Attenuated total reflection fourier transform infrared
CLSM	Confocal laser scanning microscopy
Cl ⁻	Chloride ion
DR	Delayed release
ER	Extended release
FDA	Food and Drug Administration
FOG	Fixed observational geometry
FTIR	Fourier transform infrared
G	Grams
G'	Storage modulus
G''	Loss modulus
GI	Gastro-intestinal
GIT	Gastro-intestinal Tract
GRAS	Generally regarded as safe
h	Hours
HCl	Hydrochloric acid
HEMC	Hydroxyethyl methylcellulose
HPMC	Hydroxypropyl methylcellulose
HEC	Hydroxyethyl cellulose
HPC	Hydroxypropyl cellulose
Hz	Hertz
IR	Immediate release or mid infrared
<i>k</i>	Rate constant
LVR	Linear viscoelastic region
λ_{max}	Wavelength of maximum absorbance intensity
μm	Micrometres
MC	Methylcellulose
MCR-ALS	Multivariate curve resolution–alternating least squares

mg	Milligram
Mgst	Magnesium stearate
ml	Millilitre
mm	Millimetre
MPa	Megapascal
mPa.s	Millipascal second
MR	Modified release
MRI	Magnetic resonance images
MSPS	Microscope slide positioning system
N	Newton
n	Release exponent
Na ⁺	Sodium ion
NaCl	Sodium chloride
NaCMC	Sodium carboxymethylcellulose
NMR	Nuclear magnetic resonance
ODT	Orally disintegrating tablets
PEG	Polyethylene glycol
PEO	Polyethylene oxide
rpm	Rotations per minute
USP	United States Pharmacopeia
UK	United Kingdom
USA	United States of America
UV	Ultraviolet
WSR	Water soluble resin

Chapter 1

Introduction

1.1 A brief introduction to oral modified release dosage forms

Modified release (MR) dosage forms are defined by the Food and Drug Administration (FDA) as formulations in which the time course or location of drug release has been altered to achieve therapeutic advantage, or better convenience. Whilst the FDA/ United States Pharmacopeia (USP) divides MR dosage forms into delayed release (DR), and extended release (ER) [1]. Other categories can be identified. For example, one textbook divides MR dosage forms into four major types: extended release, delayed release, targeted release, and orally disintegrating tablets (ODT) [2].

Other terms are often used to describe oral MR dosage forms. For example, extended release can be described as controlled release, sustained release, prolonged release or 'long acting'. Delayed release can be more specifically described as gastro-resistant, enteric coated, or GI targeted.

Figure 1.1, illustrates idealised plasma profiles which compare an extended release (ER) dosage form with multiple dosages of an immediate release (IR) dosage form. The ER product should provide at least a twofold reduction in dose frequency in comparison with the corresponding immediate release product [2]. An extended release dosage form can provide many advantages. For example it can keep drug plasma levels within the therapeutic range, minimising side effects and preventing symptom breakthrough due to plasma concentrations falling below the minimum therapeutic level. It is also convenient for the patient, as they can take it once or twice, rather than three or more times a day. As the frequency of administration has been reduced, the potential for irritation of the GI tract is also reduced [3].

Delayed release dosage forms release all their drug content at a later time, rather than immediately after swallowing. Enteric coated (gastro-resistant) dosage forms are the most common examples. For example, in the case of aspirin and other NSAID drugs, the enteric coating can reduce direct stomach irritation from the drug, and in the case of omeprazole, it protects the drug from acid degradation [4].

Targeted dosage forms may combine immediate, delayed and extended drug release characteristics in order to release drug at or near the intended physiological site of action. For example, a colon specific drug delivery system should be capable of ensuring an oral drug is not degraded until it has been delivered to the colon. This drug delivery method is used to treat large bowel diseases such as ulcerative colitis, Crohn's disease, amebiasis, and colonic cancer [5] [6]. The approach may also enable some oral vaccines to avoid enzymes in the upper parts of indigestion tract [7].

In contrast, ODT are dosage forms designed for very rapid release of drug in the mouth. They often disintegrate in seconds when placed on the tongue. This is a relatively new oral modified drug delivery method, which is used when a very rapid action is required in specialist uses: for example in paediatric, geriatric, and psychiatric patients, and those with dysphagia[8].

1.2 Technologies for oral modified release

A wide range of formulation types have been developed for the purpose of achieving oral modified release. The most common approaches utilise polymer coatings, the embedding of drug in an inert, hydrophilic or wax matrix, or an osmotic pump.

1.2.1 Coatings

MR tablet coatings can be generally divided to two groups obtained by polymeric film coating or compression coating [9]. Compression coating involves compressing a

powdered coat onto a tablet core, whilst film coating, which is far more widely used, involves spray coating with a polymeric macromolecule which then dries to a film on the tablet surface. The drug release behaviours of both types depend on the physicochemical properties of the resulting coat, such as its water solubility and thickness. In mixed polymer coats, the ratio of polymers, (e.g. water soluble and water insoluble polymers) can be used to change the water permeability and drug diffusion characteristics of the coat and alter drug release rates [10, 11]. In addition plasticiser levels may have to be varied to avoid stickiness in manufacture or brittleness of the dried coat [12]. Ethyl cellulose, methacrylate copolymers, hydroxypropyl methylcellulose acetate succinate, and cellulose acetate phthalate are common materials used in modified release film coatings that provide DR and ER drug release [7].

1.2.2 Matrices

Matrices contain drug embedded throughout a solid matrix, and drug release occurs through percolation, swelling, drug diffusion and/or erosion mechanisms. The rate of the drug release is controlled both by the rate of fluid penetration into the matrix, and the rate of external or internal erosion of the polymers [13]. Drug release processes can be influenced by the hydrophilicity/hydrophobicity of the polymer, the matrix shape and size, drug solubility, drug loading, and the hydrodynamic conditions of the dissolution environment [14].

Common materials used to create matrix tablets can be grouped into hydrophobic polymers, hydrophilic polymers, biodegradable polymers, minerals, fats and waxes. Matrices can be manufactured by standard tableting processes including direct compression, wet and dry granulation, or in the case of thermoplastics by injection moulding or 3D printing [15].

1.2.2.1 Inert matrices

In inert matrices, the drug is embedded in an insoluble material which does not swell significantly in gastrointestinal fluids and in order to be released, the drug has to diffuse through the polymer, or percolate through the capillary network between the compacted particles [3, 13]. Early types of inert matrices utilised plastics, but minerals such as calcium phosphate have also been used [16].

1.2.2.2 Hydrophilic matrices

Hydrophilic matrices are two basic types. Less common are the 'hydrogel' matrices, which comprise of a block of cross-linked hydrophilic polymer which exhibits limited swelling and is water insoluble. Examples include cross-linked polyvinyl alcohol and cross-linked polyvinyl pyrrolidone.

Far more common as commercial products are hydrophilic matrix tablets based on non-cross-linked polymers. These are popular as an extended release technology for oral administration, but they can also be designed for application to mucosal surfaces such as the buccal mucosa [17], periodontal cavity [18], eye [19], rectum, and cervical canal [20]. When in contact with water or body fluid, this type of hydrophilic matrix tablets hydrates, and the surface polymer swells to form a gel layer around the dry core of the tablet. This retards further ingress of water and thereby acts as a rate-controlling barrier to drug release [21].

Typical polymers utilised in hydrophilic matrix tablets include cellulose ethers (e.g. Hydroxypropyl methylcellulose (HPMC)), natural or semisynthetic polymers (e.g. xanthan gum and modified starches), and synthetic polymers (e.g. Carbopol and Polyethylene oxide (PEO)) [13]. The work in this thesis investigates a two polymer system (HPMC and PEO) in this type of hydrophilic matrix.

1.2.2.3 Fat and wax matrices

These tablets contain drug embedded in a fat or wax matrix. They can be made by direct compression, roller compaction or hot-melt granulation[3]. They release drug primarily by surface erosion and leaching [13]. Example materials include carnauba wax and cetyl alcohol.

1.2.3 Microspheres and Microcapsules

Microcapsules are spherical particles varying in size between 50nm to 2mm. The core can be solid, lipid or even a gas and the coating material can be gelatin, polyvinyl alcohol, ethyl cellulose, cellulose acetate phthalate or styrene maleic anhydride [22]. The coating is usually applied using a fluid bed method. Microcapsules can be internally complex and Figure 1.2 shows the structure of one type of complex microencapsulates. Microcapsules can be delivered in hard or soft gelatine capsules or as a liquid suspension or as a dried powder [23-25].

1.2.4 Osmotic pumps

Osmotic drug delivery systems were first described in 1955 by Rose and Nelson [26], and were developed in the 1970's by the Alza Corporation [27, 28]. There are many different designs, but essentially, an osmotic pump contains an outer semi-permeable membrane, surrounding an inner core which contains an osmotically active excipient and a drug reservoir. Extended release is obtained by drug being squeezed through the pump orifice as a result of osmotic pressure being generated when water penetrates an external membrane, and causes an internal osmotic layer to swell [29]. It has been claimed that osmotic pump drug delivery systems can provide constant drug plasma levels that are independent of GI conditions, through minimising fluctuations in the dissolution kinetics of the formulation [30].

1.2.5 Ion Exchange Resins

Ion exchange resins can be used as controlled release drug carriers in pharmaceutical formulations. They are usually white or yellowish beads with a

diameter of 0.5-2 mm. The resin is an insoluble polymer with acidic or basic functional groups, and which have the ability to exchange drug counter-ions in aqueous liquids [31]. Ion exchange resins can be cationic or anionic, and can be weakly or strongly acidic or basic. The resins are inert and not absorbed by the body because the polymers are high molecular weight and water insoluble. Ion exchange is a reversible process : the resin is loaded with by ion exchange, but when exposed to gastrointestinal fluid, drug is then released from the resin by ion exchange and diffusion out of the bead [32, 33].

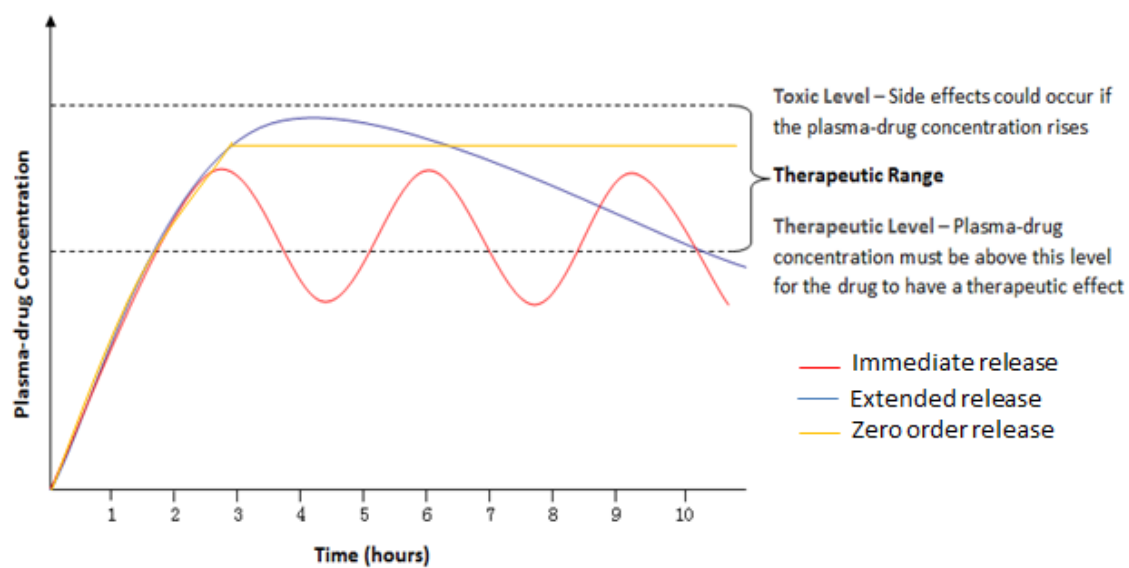


Figure 1.1: Idealised plasma drug concentrations from extended and immediate release dosage forms.

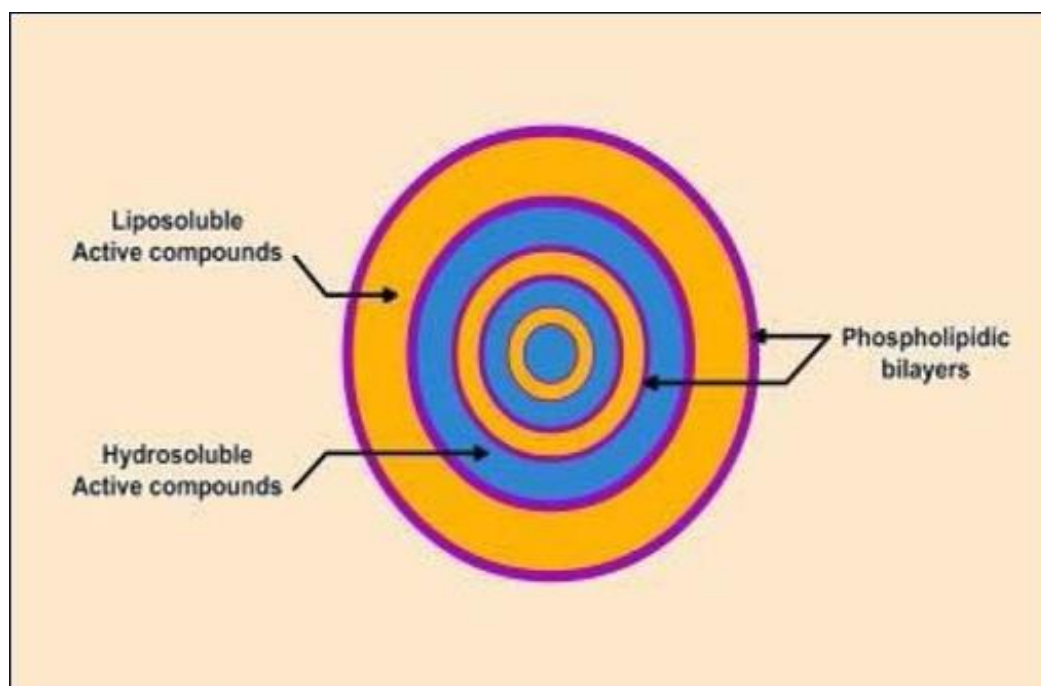


Figure 1.2: The structure of a complex microcapsule [23].

1.3 Cellulose ethers

1.3.1 Cellulose:

Cellulose is a natural organic chemical commercially obtained from wood and cotton. It is a linear polysaccharide with β 1 $\rightarrow$ 4 glycosidic bonds linking repeating units of D-glucose [34] (Figure 1.3). Regular and extensive hydrogen bonding holds the linear cellulose polymer chains in an ordered crystalline structure and as a result, native cellulose is practically insoluble in water. However this regular hydrogen bond sequence can be disrupted by the introduction of side groups, which results in the remaining hydroxyl groups becoming more accessible to water and making the resultant 'cellulose ether' polymers, water-swellable and often water soluble [34-36].

1.3.2 The manufacture of cellulose ethers:

Native cellulose is converted to 'alkali cellulose' by heating with sodium hydroxide to disrupt hydrogen bonding between adjacent chains. Different types of etherifying reagents can then be used to add substituents to the cellulose hydroxyl groups. Example reagents include methyl chloride and propylene oxide, which are used to introduce methoxyl and hydroxypropyl groups in the manufacture of hydroxypropyl methylcellulose [37]. Figure 1.4 shows the backbone of the cellulose and the potential sites available for ether substitution, and Table 1.1 lists some commonly encountered cellulose ether polymers.

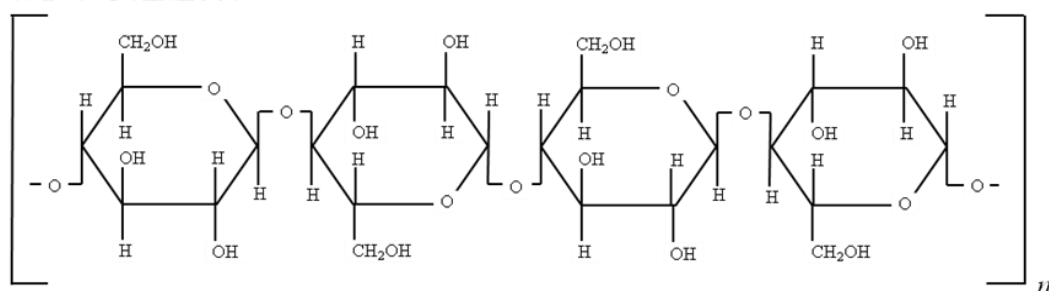
Native Cellulose

Figure 1.3: The chemical structure of native cellulose [38]

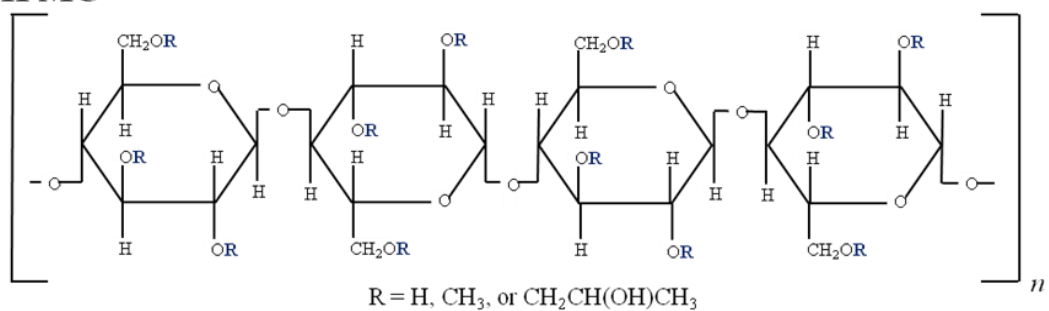
HPMC

Figure 1.4: The chemical structure of HPMC, where the R group is an available substitution site [38].

Cellulose Ether	"R" Substituents	Common Uses
Methylcellulose (MC)	- H, -CH ₃	Foods, pharmaceutical suspensions, adhesives, paints
Hydroxyethyl methylcellulose (HEMC)	- H, -CH ₃ , -CH ₂ CH ₂ OH	Paper manufacture, pharmaceutical tablets, paints, detergents, cosmetics, adhesives
Hydroxypropyl methylcellulose (HPMC)	- H, -CH ₃ , -CH ₂ CH(OH)CH ₃	Pharmaceutical matrix tablets, film coatings and artificial tears, foods, cosmetics, adhesives
Ethylhydroxyethylcellulose (EHEC)	- H, -CH ₂ CH ₂ OH, -CH ₂ CH ₃	Wood finishes, inks, plastics, adhesives
Hydroxyethyl cellulose (HEC)	- H, -CH ₂ CH ₂ OH,	Paints, cosmetics, adhesives
Hydroxypropyl cellulose (HPC)	- H, -CH ₂ CH(OH)CH ₃	Pharmaceutical matrix tablets, printing inks, adhesives, paint removers
Sodium carboxyl methylcellulose (NaCMC)	- H, -CH ₂ COONa	Ceramics, pharmaceutical tablets and suspending agent, paper processing, material coatings

Table 1.1: Common types of cellulose ethers and their substituents [34].

1.3.3 Hydroxypropyl methylcellulose (HPMC) as a hydrophilic matrix polymer

Hydroxypropyl methylcellulose (HPMC) is by far the most widely used cellulose ether used in hydrophilic matrix polymer. It is low cost, has GRAS (generally regarded as safe) status and it is commercially available in a variety of pharmaceutical grades. It has the most extensive literature database of any polymer in this application [39].

As a result of the manufacturing process, methoxy and propoxyl substitution is unevenly spaced along the cellulose polymer chain. This results in methoxyl-rich, propoxyl-rich, mixed and unsubstituted regions as shown in figure 1.5. Additionally, another propoxyl group can attach through the C₂ hydroxyl group, resulting in multi propoxylation. The methoxyl-rich regions are hydrophobic but have a considerable influence on the thermal properties and ion sensitivity of the polymer. Hydroxypropyl and unsubstituted hydroxyl groups are hydrophilic and they allow these polymers to swell rapidly when exposed to aqueous solutions. The progressive plasticisation of an HPMC polymer on the surface of a matrix tablet is shown in figure 1.6. AS hydration proceeds, there is swelling and eventual dissolution of the polymer, as inter- and intramolecular polymer hydrogen bonds are broken by hydrogen bonds formed with the incoming water, causing the polymer chains to uncoil and extend. This molecular disentanglement leads to more locations becoming available for hydrogen bonding and an increase in hydration until the polymer dissolves [35, 40, 41].

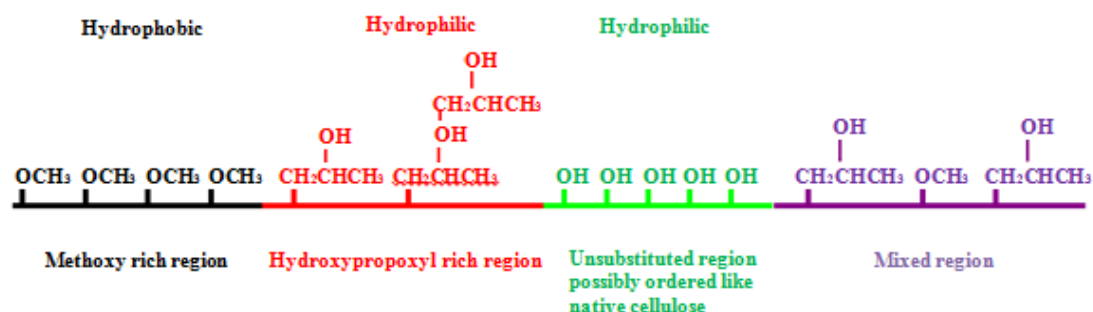


Figure 1.5: An illustration of the regional variation in substitution in the HPMC polymer chain [38].

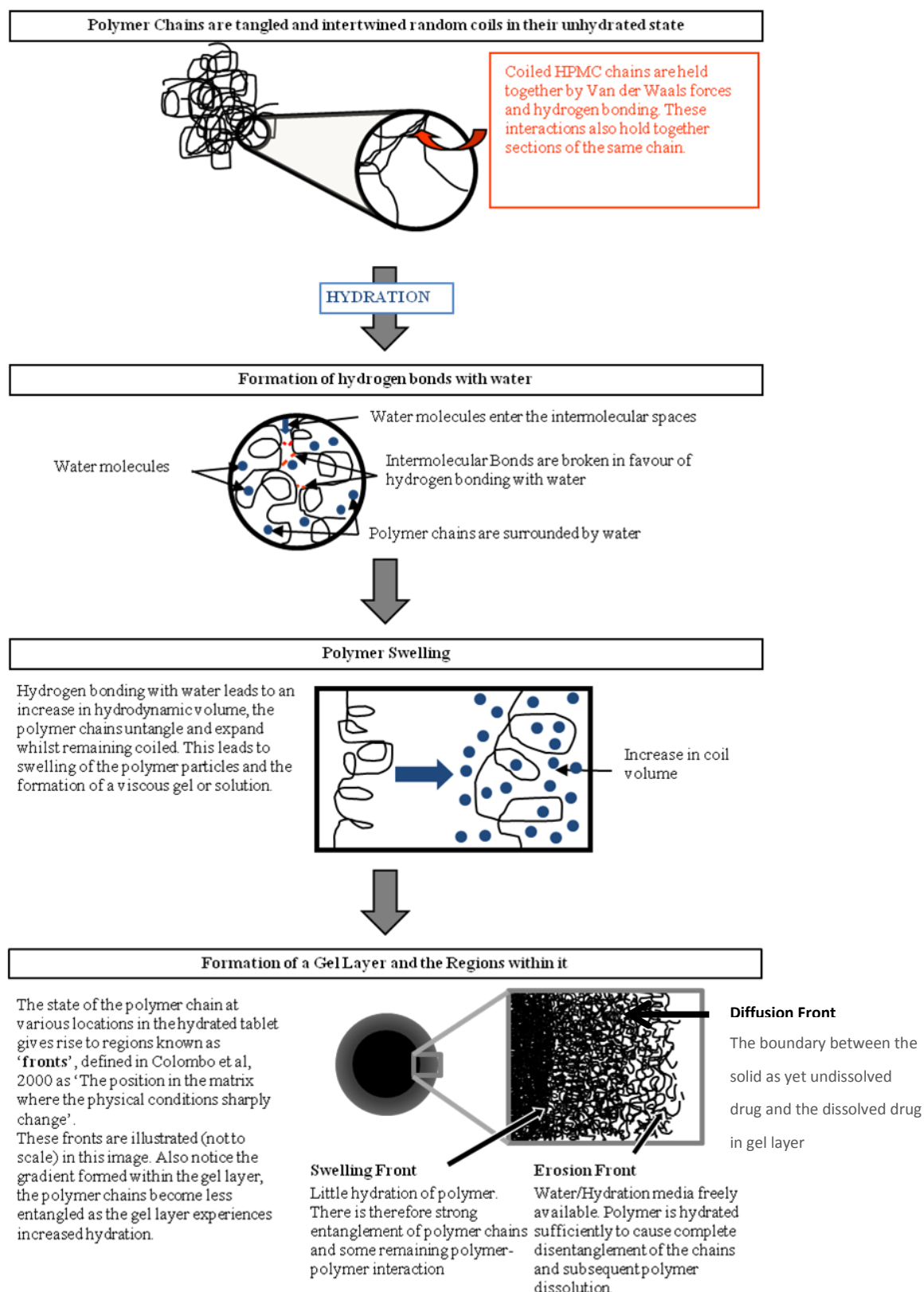


Figure 1.6: The progress of HPMC matrix hydration, swelling and gel layer formation

1.3.4 HPMC substitution types

Commercial HPMC polymer grades vary in their (i) degree of hydroxypropyl and methyl substitution, and (ii) polymer chain length which is a determinant of solution viscosity. Pharmaceutical grades of HPMC are defined by the USP as Hypromellose 1828, 2208, 2906 2910, where the first two digits signify the approximate percentage methoxyl substitution, and the last two, the hydroxypropyl substitution [42].

Commercial HPMC grades are usually identified by a code. The Dow Chemical Company codes their different HPMC polymers as Methocel® E, F, and K grades with each letter being related to the degree of substitution[43]. Figure 1.7 shows different substitution levels in Methocel® products. The K or E grades are used for extended release hydrophilic matrices, because these two grades have a higher ratio of hydroxypropyl substitution than grade F. The F grade is commonly used in the coating industry.

Within each HPMC substitution grade, there are a range of polymer viscosities available, with different polymer chain lengths and average molecular weights. Table 2, lists selected HPMC grades with their molecular weights and viscosity values [44]. The Dow HPMC classification system adds numbers to the substitution grade, such as K4M, K15M and K100M (table 1.2). The number identifies the viscosity measured in millipascal seconds (mPas) for the HPMC at 2% w/v at 20°C. The letter M following the number means it is multiplied 1000 times. LV denotes a low viscosity grade, whilst CR denotes a grade suitable for controlled release.

The work in this thesis uses only K100M grade (hypromellose 2208, and the highest viscosity). This type been reported to form gel barriers most rapidly and provide the greatest prolonged release, because it has a lowest ratio of methoxy (19-24%) to hydroxypropyl substitution (7-12%)

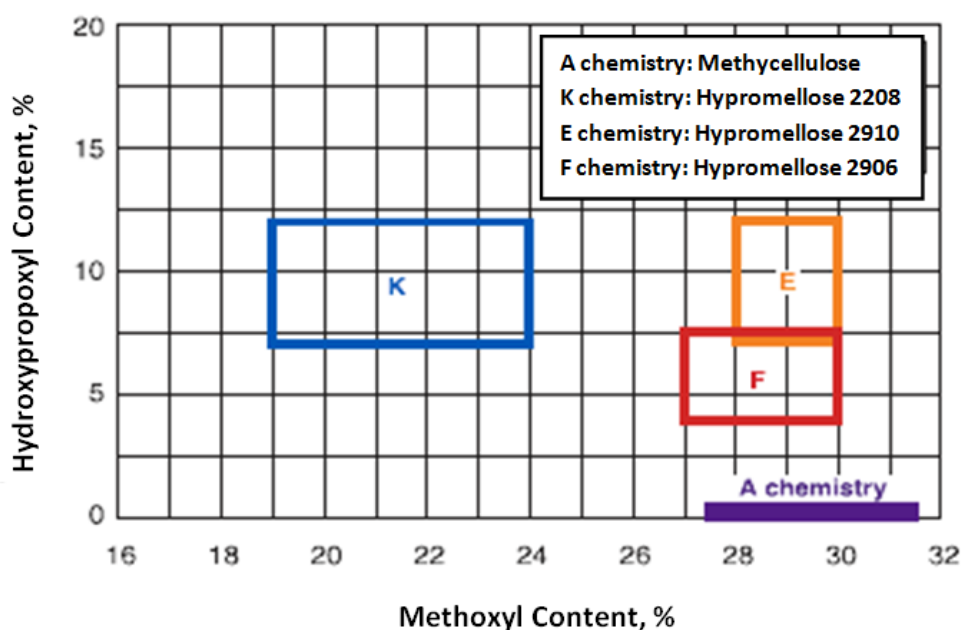


Figure 1.7: The range of substitution levels in Methocel® HPMC products [43].

METHOCEL Premium Product Grade		K4M Premium CR	K15M Premium CR	K100M Premium CR	E4M Premium CR	E10M Premium CR
Methoxyl, %	USP	19-24	19-24	19-24	28-30	28-30
Hydroxypropoxyl, %	USP	7-12	7-12	7-12	7-12	7-12
Substitution type	USP/EP	2208	2208	2208	2910	2910
Chlorides, max., %	EP	0.5	0.5	0.5	0.5	0.5
Apparent viscosity, 2% in water at 20°C, cP	USP	3000- 5600	11250- 21000	80000- 120000	3000- 5600	7500- 14000
Apparent viscosity, 2% in water at 20°C, mPa·s	EP	2308- 3755 [2903 Nom]	6138- 9030 [7382 Nom]	16922- 19267 [18243 Nom]	2308- 3755 [2903 Nom]	4646- 7070 [5673 Nom]

Table 1.2: Typical grades of Dow HPMC polymers used in hydrophilic matrices [44].

1.3.5 The properties of HPMC and its sensitivity to pH and ionic salts

1.3.5.1 The thermal properties of HPMC

Temperature is one of the principal variables that affect the hydration of HPMC. As the temperature of an HPMC solution rises, the viscosity of HPMC solutions is reduced. At a temperature termed the 'gel point' however, the viscosity dramatically rises as a result of increased polymer-polymer interactions between the hydrophobic methoxy substituted regions [45]. This often results in visible precipitation of HPMC, a phenomenon known as a cloud point. The cloud point temperature can be measured: when light transmission reaches 97.5% it is called the incipient precipitation temperature, whilst the term cloud point temperature usually refers to a drop to 50% transmission [46]. It has been noted that cloud point temperatures (measured by light transmission) and thermal gelation temperatures (measured by viscometry) do not always correlate. Generally, at low HPMC concentrations, HPMC gelation occurs after the cloud point, whilst at higher concentrations, HPMC solutions produce a turbid solution after gelation occurs [47]. Figure 1.8 shows typical changes in HPMC viscosity with respect to temperature.

Different HPMC grades exhibit differences in their thermal gelation temperatures. These temperature can be explained through the type and number of the substituents on the cellulose anhydroglucose rings. Figure 1.9 shows the approximate gel temperature of Methocel HPMC grades as 2% aqueous solutions.

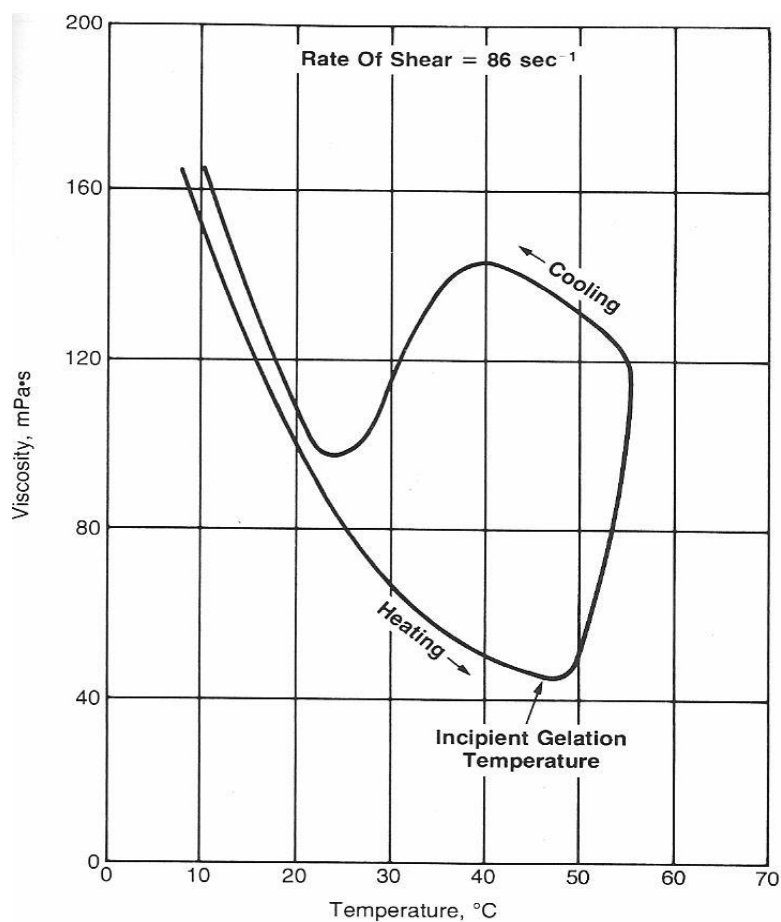


Figure 1.8: The relationship between temperature and viscosity of aqueous hydroxypropyl methylcellulose and methylcellulose solutions [48].

Substitution Type	Gelation Temperature °C
A	48
F	54
E	56
K	70

Figure 1.9: The approximate gel points of Methocel products (2% aqueous solution) [43]

1.3.5.2 The effect of pH:

HPMC has no ionisable groups and so polymer solubility and viscosity are little affected by changes in pH. However, Mitchell et al. have reported that the cloud point of HPMC can be influenced at extremes of low pH. This results from the protonation of ether groups at very low pH. A similar effect has been seen in concentrated sodium hydroxide, possibly a result of the Hofmeister effects of high concentrations of sodium and hydroxyl ions. In both cases there is also the possibility of chain hydrolysis, although reductions in chain length have been reported to have little effect on cloud point[47].

1.3.5.3 The effect of salts and other dissolved solutes

Inorganic salts are a major factor that can affect the cloud point of HPMC solutions. In the case of most ions, cloud point decreases as the molarity of the electrolyte is increased. This is because ions can cause dehydration by removing water of hydration from the polymer hydration sheath, and ions embedded in the sheath can also disrupt the water hydration structure around the methoxyl regions. This has a significant effect on the cloud point temperature [49]. Generally there is a linear relationship between cloud point reduction and the concentration of the salt[47]. The potency of different ions to raise or lower the cloud point follow a Hofmeister series (cations: $\text{Li}^+ > \text{Na}^+ > \text{K}^+$, anions : $\text{CNS}^- < \text{I}^- < \text{Br}^- < \text{NO}_3^- < \text{Cl}^- < \text{tartrate} < \text{SO}_4^{2-} < \text{PO}_4^{3-}$ [47]. Other solutes can exert Hofmeister effects, for example different sugars can affect HPMC thermal properties lowering the cloud point of HPMC solutions in relation to their ability to disrupt water structure [50]. A study of an L-amino acids series also showed Hofmeister effects with some raising and some lowering the cloud point, depending on their molecular structure [51].

1.3.6 Mechanisms of drug release from HPMC matrices:

Once a HPMC matrix contacts an aqueous liquid, liquid penetration into the capillaries of the tablet and into the voids of the polymer causes polymer hydration. Water breaks any polymer-polymer hydrogen bonds, and forms a hydration sheath, causes expansion as polymer chains extend and uncoil. This leads to more sites becoming available to hydrogen bond with water and to a swelling mass of polymer restrained by entanglement. As the water content increases, the polymer becomes increasingly hydrated and swollen. Once the full diffusion barrier characteristics of the gel layer have been formed, water uptake will be retarded [41, 52-54].

confocal microscopy evidence suggests that the initial uptake of water into an HPMC matrix tablet occurs through the capillary pore network of the tablet [55]. Within a minute after water exposure, there is rapid polymer swelling, and a surface gel layer is rapidly formed. During this process, drug on the surface of the matrix and in the new gel layer is often released as a burst. However, once the gel layer has formed, and the swelling polymer has blocked the tablet pores, water uptake and drug release is significantly retarded. At this stage, drug release will occur by diffusion through, and erosion of, the gel layer, the dominant mechanism being dictated by the solubility of the drug [41, 52-54]. In the case of soluble drugs, the rate of the molecular diffusion through the gel layer and barrier layer erosion from the matrix are the key processes controlling drug release, and most of the time, both diffusion and erosion occur simultaneously [56-58]. Highly soluble drugs are released from a hydrated matrix by both diffusion and erosion, but poorly soluble drugs may not significantly dissolve in the gel layer and are released primarily by erosion.

Figure 1.10 shows a simple diagram of the three stages of drug release from a matrix tablet. Firstly, the surface gel layer grows with time, then the gel layer thickness stabilises as surface erosion is balanced by hydration of the dry core. Finally, when all

the core has been hydrated the size of the matrix progressively shrinks, and may completely dissolve [59].

The gel layer formation and hydration processes can be described in more depth in terms of the underlying polymer science. The unhydrated HPMC polymer behaves as glassy polymer when the ambient conditions are lower than the HPMC glass transition temperature ($T_g = 157\text{--}180\text{ }^{\circ}\text{C}$)[60]. When the HPMC matrix is exposed to aqueous fluids, the polymer on the matrix surface is plasticised by water. This reduces the T_g to below ambient, so that the polymer is now in the rubbery state and the resulting swelling is identified as the hydrated 'gel' layer. Figure 1.6 shows the gel layer contains at least three moving fronts which from inner to outer are termed (i) the swelling front (ii) the diffusion front, and (iii) the erosion front. The overall rubbery state 'gel layer' lies between the swelling and erosion fronts whereas the diffusion front represents the point in the gel layer when significant amounts of drug have dissolved. It is the drug concentration gradient in the gel between the diffusion and erosion front which has been reported as the main driver for drug release [61]. The erosion front is marked by the edge of the gel layer and in this region, the polymer is in a highly hydrated state and polymer chains will be disentangling prior to them dissolving in the media. At this stage, the polymer will be in the rubbery-flow state and will be vulnerable to loss from shear exerted by mixing forces in the gastrointestinal environment.

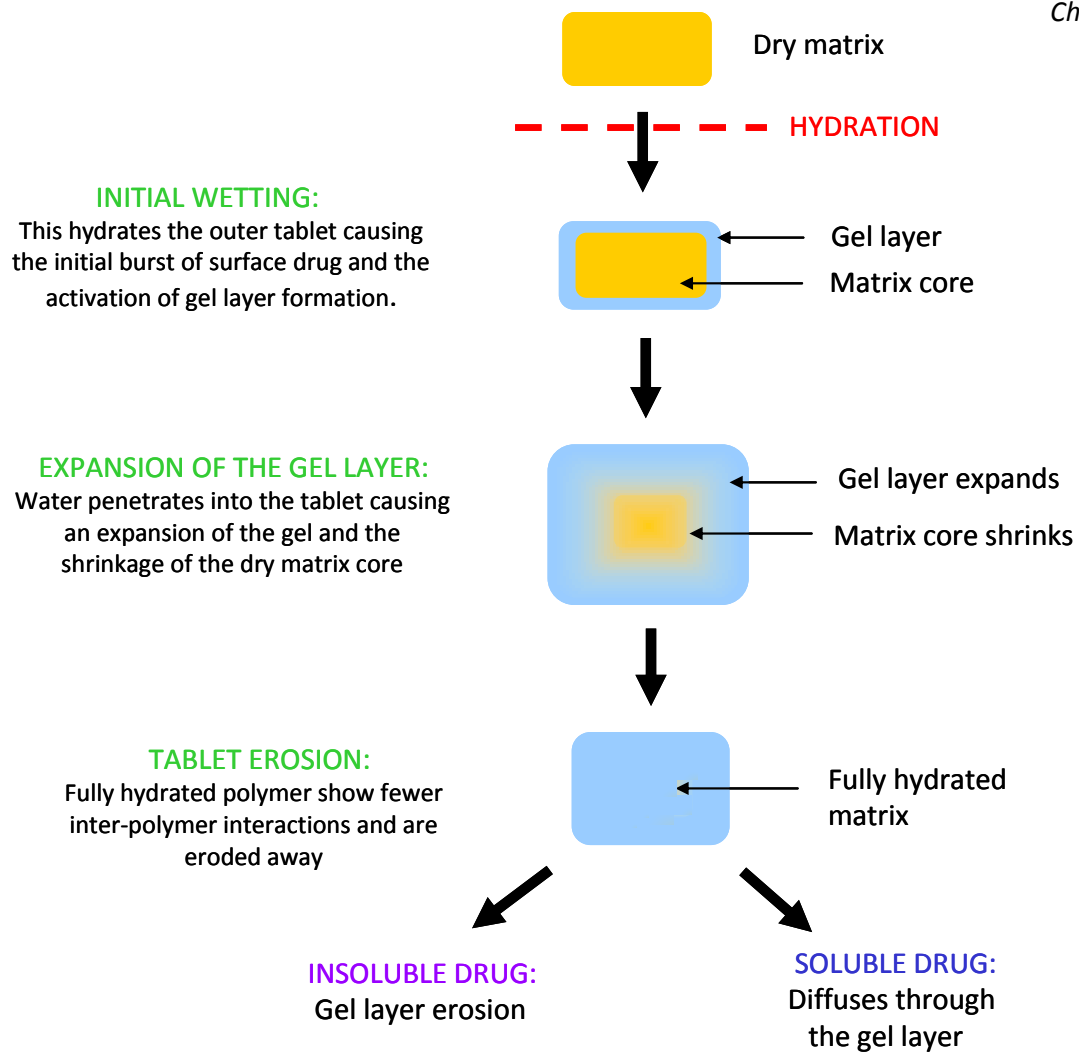


Figure1.10: The progress of drug release from the matrix tablet [43].

1.3.7 Factors affecting drug release from HPMC matrices

1.3.7.1 The HPMC content of the matrix

There needs to be sufficient polymer present within the matrix to form a continuous gel layer rapidly enough, to prevent further significant water penetration. Low polymer matrices do not have sufficient polymer to form a coherent gel layer and therefore a minimum polymer level in the matrix tablet is required to provide extended release. An amount of 30%w/w of a high viscosity K grade HPMC is usually recommended. Below 20%, the gel layer can become weaker and less resistant to diffusion and erosion. Lower levels of polymer can result in erratic release behaviour, even immediate release kinetics ('dose dumping' which is unintended, rapid and premature drug release may be caused by environment factors in modified dosage form) especially if the matrix contains a high content of high solubility drugs or soluble diluents [62]. In general, the drug to polymer ratio will affect the rate of the release and when this is decreased, the drug release kinetics become slower [62].

1.3.7.2 Polymer substitution level

Methoxyl and hydroxypropyl substitution is unevenly spaced along the cellulose polymer chain. The number and the type of substitution on the cellulose chain can influence polymer hydration, swelling, and water transport, and hence affect drug release [63]. Hydroxypropyl groups are more hydrophilic and increase polymer swelling to a greater extent than methoxyl groups. Dahl et al. reported that the degree of hydroxypropyl substitution could be a key factor in controlling naproxen release from HPMC matrices [64, 65]. The level of hydroxypropyl substitution also was an important factor for other low soluble drugs releasing by erosion. [66].

1.3.7.3 Polymer viscosity

In general, higher average molecular weight HPMC polymers provide slower drug release. However, HPMC manufactures do not classify HPMC polymers according to

molecular weight, but instead use dilute solution viscosity values [67]. Matrices formed by low viscosity grades of HPMC show high erosion rates, and thinner gel layers, leading to more rapid drug release. In pharmaceutical manufacture therefore highly soluble drugs are often formulated with high viscosity HPMC, but less soluble drugs are often formulated with low viscosity HPMC matrices, to achieve the optimal controlled drug release [68-70].

1.3.7.4 HPMC particle size

HPMC particle size plays an important role in the rate of drug release. Smaller particle sizes of HPMC (<90 μ m) hydrate rapidly and routinely form stable gel layers. Larger particle sizes require a longer hydration time, and may be erratic in their ability to provide adequate controlled release. Large size HPMC particles (~250 μ m) decrease the stability of the gel structure, because there are fewer of them per unit volume, and there are larger pores between them [71]. High polymer levels can override the effects of particle size [72] but the use of a slower hydrating HPMC can exacerbate the problem. One HPMC polymer manufacturer, Dow Chemicals, has responded to the need for performance consistency by introducing sieved fractioned 'CR' (controlled release) grades of HPMC with a smaller average particle size.

1.3.7.5 Drug Factors

The solubility of the drug is another important factor in HPMC matrix performance. Highly soluble drugs can make the gel structure more porous and weak as they can act as pore formers, increasing drug release rates by making pathways less tortuous within the gel layer [73]. Poorly soluble drugs, released primarily by erosion, can be released too slowly to be clinically useful, and may require faster-releasing matrices, which can be difficult to formulate [74]. Depending on the drug solubility and the polymer to drug ratio, drug particle size can also have an effect on drug release from HPMC matrices. When the drug is freely water soluble, and there is a high level of HPMC in the matrix, changes in drug particle size have little effect. However, drug

particle size can play an important role when the drug has low aqueous solubility because the rate of drug dissolution can depend on surface area [75].

The drug itself can cause HPMC to 'salt in' and 'salt out', and this may influence drug release from an HPMC matrix. Hino et al. have reported that nicotinamide can cause the 'salting in' of HPMC increasing the gelation temperature and solution cloud point temperature. This because the hydrogen bonding of nicotinamide to the hydrophilic groups of HPMC molecules [76]. Rajabi-Siahboomi et al. found that the drug diclofenac sodium decreased HPMC gelation and cloud point temperatures, a 'salting out' effect [77-79].

There is also evidence for specific drug polymer interactions. For example Pygall et al. showed that adding meclofenamate to HPMC solutions increased solution viscosity, reduced the gel point and the self-diffusion coefficient of the drug in water. They hypothesised that the electron density on the carbonyl group of meclofenamate was increased by tautomerism, which was stabilised by hydrogen bonding to the HPMC [80].

Although pH changes within the physiological range do not appear to influence HPMC matrix gel layer formation it can affect the ionisation state of weak base or weak acid drugs when the pH change occurs over the drug pKa. In these cases drug release rate can be altered by changing the pH of the GI tract and to ensure good *in vivo* bioavailability, we may need to incorporate buffers in the matrix tablet [81].

1.3.7.6 Dissolution media

The discussion above shows that polymer hydration can be influenced by the presence of ionic salts and other solutes in the hydrating liquid. These effects depend on temperature, solution concentration and the position of the ions within the Hofmeister series [45]. Highly concentrated ionic solutions are able to inhibit the hydration of HPMC to such an extent that an effective surface gel diffusion barrier fails to form, and drug release from HPMC matrices can be accelerated [82, 83]. This effect is also seen with other soluble species such as sugars and amino acids, and it appears to be related to changes in water structuring and water-polymer binding [82] [84, 85].

Many studies have reported how increasing the ionic strength in the dissolution medium at first reduces the drug release rate. Then, if ionic strength is further increased HPMC matrices can show burst release and at higher levels of ions, complete disintegration and 'dose dumping'. Bajwa et al. have reported that this effect on drug release profile might relate to an effect on early gel layer formation. When the medium contained 0.1 – 0.5M NaCl, they found that HPMC matrix gel layer growth was suppressed, but above this concentration HPMC particles still swelled, but did not appear to coalesce. As a result, gel layer formation was disrupted and there was enhanced liquid penetration and surface disintegration leading to burst drug release behaviour[55, 86].

Sheu et al. have reported how drug ion interactions can also affect release through solubility effects. NaCl was found to reduce the solubility of diclofenac sodium through a common ion effect, resulting in changes to the drug release rate [87].

1.3.7.7 Tablet strength:

Ali R. Rajabi-Siahboomi et al. reported that, once the crushing strength is achieved with a certain applied compression force, there is no significant affect to drug

release [88]. This may be explained as when tablet made as the lowest crushing strength, the matrix goes to an initial burst effect due to partial initial disintegration. Once the gel layer is formed, the drug release becomes similar as the tablets made with a higher crushing strength[89]. Several researches have stated that the compression force is a significant factor for tablet hardness, but it only has very little effect on drug release [90-92].

1.3.7.8 Others:

There are reports of tablet shape and size , lubricants influencing drug release rates in individual hydrophilic matrix tablet formulations [93].

Tablet shape and size affect drug release profiles because of surface area-to-volume ratios. To achieve the similar drug release profiles as a larger tablet, the smaller tablet requires a higher polymer level.

In common with other types of tablet, the type, quantity, method of addition, and blending time of lubricants can affect the tensile strength and friability of HPMC matrix tablets, and their drug release rates[57].

1.4 Polyethylene oxide

1.4.1 PEO: A general introduction

Polyethylene oxide (PEO) is a high molecular weight hydrophilic polymer with the repeating monomer unit $\text{CH}_2\text{CH}_2\text{O}$, and a molecular weight ranging from 100,000 to eight million. PEO and poly (ethylene glycol) (PEG) have the same chemical structure, but the term PEO is reserved for the high molecular weight polymer, synthesized through a ring-opening polymerization of ethylene oxide. The term PEG is used to describe the low molecular weight version which is usually synthesized through a condensation polymerization of ethylene glycol [94]. There is no clear division between PEO and PEG by average molecular weight. A molecular weight of 20,000 has been suggested by Harris and Dhawan [95]. This divides the viscous liquids typical of PEGs, from the waxy solids typical of PEO. Other experts have suggested a molecular weight boundary of 100,000 [96].

PEO is a non-ionic, water soluble and highly hydrophilic polymer. It is a free flowing, crystalline white powder [97].

1.4.2 PEO toxicity

Animal studies show that PEO has very low oral toxicity with no mortality or toxic signs when given at the maximum practical dosage of 2g/kg of body weight. This is because these polymers are poorly absorbed from the GIT and are completely and rapidly excreted because of their high molecular weight. PEO as a dry powder or in aqueous solution, do not appear to cause skin or eye irritation[98].

1.4.3 Applications of PEO

In industry, PEOs are used as flocculating, thickening, lubricants, dispersing, and water-retentive agents [99]. As pharmaceutical excipients they are generally regarded as safe (GRAS) by the Food and Drug Administration (FDA), and they have

found many applications. These include their use in hydrogels, hydrophilic matrices osmotic systems and pulsatile drug delivery. They can be used as vehicles, carriers and coatings in injectable, microparticulate systems (liposomes, nanoparticles, and microparticles), mucoadhesives, ocular drug delivery, PEGylation reactions, and as water-soluble films[99].

1.4.4 Structure and synthesis of PEO:

PEO is a synthetic semi-crystalline linear polymer with the chemical structure $(-\text{O}-\text{CH}_2-\text{CH}_2-)_{\text{n}}\text{OH}$. Ethylene oxide is polymerised in the presence of a catalyst to a linear chain (Figure 1.11) [97] by two main synthetic routes. Anionic polymerization uses sodium or potassium hydroxides as catalysts to provide the lower molecular weight PEO grades, whereas coordination catalysts are used to produce the highest molecular weight PEO. These catalysts include divalent metal compounds (carbonates, sulphates, alkoxides, oxides, and chelates), mixtures of transition metal compounds with compounds of neighbouring metals (Ziegler-Natta systems, e.g. aluminium and zinc alkyls), and metal-porphyrin complexes [100].

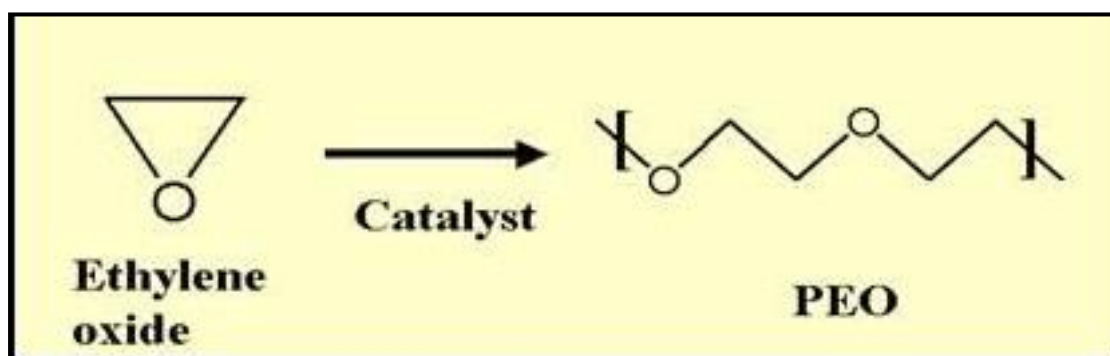


Figure 1.11: The synthesis of PEO[97].

1.4.5 Physical properties of PEO:**1.4.5.1 Solution properties:**

PEO polymers are hydrophilic and completely soluble in water in cold or warm water. Each ethylene oxide unit from PEO is extensively hydrated and bounded by approximately 2 to 3 water molecules in aqueous solution[101, 102]. Additional neighbouring water molecules (each ethylene oxide unites up to 16 water molecules) are also structured [103]. Polymer solubility is disrupted when the temperature approaches boiling point as discussed in the section on thermal properties below. PEOs are also soluble in certain organic solvents such as chlorinated hydrocarbons [104]

1.4.5.2 Viscosity:

PEO forms viscous aqueous solutions but, in common with many other polymers, solution viscosity depends on molecular weight, concentration, and temperature. In addition, because PEO solutions are pseudoplastic, the measured viscosity can depend on the rate of shear applied during viscosity measurement. Table 1.3 shows how viscosity depends on polymer molecular weight for the different Dow POLYOX™ grades of PEO [104].

POLYOX™ Water-Soluble Resin NF Product	Approximate Molecular Weight	Viscosity Range at 25°C, cP		
		5% Solution	2% Solution	1% Solution
WSR N-10	100,000	30 – 50		
WSR N-80	200,000	55 – 90		
WSR N-750	300,000	600 – 1,200		
WSR N-205	600,000	4,500 – 8,800		
WSR N-1105	900,000	8,800 – 17,600		
WSR N-12K	1,000,000		400 – 800	
WSR N-60K	2,000,000		2,000 – 4,000	
WSR-301	4,000,000			1,650 – 5,500
WSR Coagulant	5,000,000			5,500 – 7,500
WSR-303	7,000,000			7,500 – 10,000

Table 1.3: The relationship between molecular weight and viscosity for different Dow POLYOX™ grades of PEO[104].

1.4.5.3 Thermal properties of PEO

PEO exhibits a change in solubility when the water reaches nearly boiling point (98°C). At this temperature the PEO-water system separates into two phases; a polymer-rich phase and a polymer-lean phase, and solutions therefore exhibit a cloud point [105]. This is because at this temperature, there is disruption of the hydrogen-bonded water structure around the ether oxygens of PEO, leading to a reduction of PEO-water interactions and favouring PEO-PEO interactions[106].

Electrolytes typically reduce the cloud point temperature in a concentration dependent manner, as they can further disrupt the hydration shell surrounding PEO chains, allowing phase separation at a lower temperature[105, 106]. The ability of electrolytes to affect cloud point follows a rank order $K^+ > Na^+ > Li^+ > Cs^+$ and $NO_3^- > Cl^- > CNS^-$ [107].

1.4.6 Drug Release from PEO matrices

PEO has been investigated as an alternative to HPMC in oral controlled release formulations [108-113]. However, the numbers of reported studies in the literature are far fewer than for HPMC. Drug release from a PEO matrix does not appear to be influenced by the pH of the dissolution medium[108, 109] and, as PEO is non-ionic, there are no ion-pair interactions between the polymer and drugs [114].

The drug-release mechanism of PEO hydrophilic matrices appears to be very similar to HPMC matrices. Drug release is controlled by swelling and erosion of the polymer, or a combination of both. The thickness of the gel layer has been suggested as one of the most important factors controlling drug release, and the relative magnitude of the rate of polymer swelling at the moving rubbery-glassy front, and the rate of polymer erosion at the swollen polymer-dissolution medium front, influences the release kinetics of drug from the tablet. Gel layer growth has been divided into three stages: (i) polymer swelling and the rapid formation of a gel layer on contact with dissolution medium. Interestingly this occurs with a suppression of the initial drug

release burst seen in some HPMC formulations. (ii) When the rate of polymer erosion at the interface of tablet surface and the rate of polymer swelling at the rubbery-glassy front are similar, drug release can be zero order. (ii) Finally, when the dry polymer in the glassy core has been depleted, drug release occurs by erosion as the gel matrix reduces in size [115, 116].

The molecular weight of the polymer appears to be the key factor which decides which release process (diffusion or erosion) dominates. Increasing PEO polymer molecular weight can decrease matrix drug release. Kim et al. have reported that the lower the PEO molecular weight, the earlier the synchronization of gel layer thickness takes place [109]. High and low molecular weight PEO polymers appear to have similar hydration rates, but a PEO matrix containing a higher molecular weight PEO forms a thicker gel layer because it has a slower polymer dissolution rate at the gel surface [117]. Drug release is related to polymer swelling and drug diffusion in high molecular weight PEO matrices, but is related to polymer swelling and erosion when low molecular weight PEO is used [104, 118].

As occurs with HPMC matrices, the polymer content of the matrix can significantly affect drug release. To ensure matrix robustness and a consistent extended drug release profile, a minimum content of 20% to 30% PEO is recommended [36]. Ensuring the PEO content is higher than the minimum level also ensures better product stability. PEO suffers viscosity loss on storage, and higher levels of polymer help minimise drug release variability [36]. In the case of highly soluble drugs, increasing the PEO polymer content in the matrix generally leads to more extended drug release. However, once the polymer level has reached a threshold (in some studies reported to be 40%) using higher polymer contents may not significantly change the drug release profile. At this level of PEO, gel layer strength and erosion resistance is high, and the dominant drug release mechanism will be drug diffusion through the gel layer [119].

As is the case for HPMC matrices, water-soluble drugs are released by diffusion and gel layer erosion, whereas poorly soluble drugs are released by surface erosion of the PEO matrix gel layer. Drug solubility and loading can influence drug release and depending on drug solubility, can either hinder or facilitate media penetration into the matrix. This affects matrix hydration and swelling and characteristics. For example, a high content of high solubility drug is less likely to reach zero-order release because the drug will facilitate media penetration, and release is dominated by diffusion. Drugs with lower solubility have release kinetics dominated by erosion, and drug release is slower and closer to zero-order release [104, 120, 121]. Drug solubility and drug loading do not appear to significantly affect drug release in low molecular weight PEO matrices because swelling and erosion dominates the release process [109]. Release of drugs with a pH dependent solubility is dependent on the pH of the dissolution medium, but as PEO is non-ionic, the polymer itself does not respond to changes in pH [36].

The type of filler (tablet diluent) can play an important role in determining the drug release profiles because these can modify solvent ingress and gel layer properties and. When the filler is soluble, drug release rates are increased, as the filler dilutes the polymer in the hydrated matrix, lowering the hydrated gel layer viscosity. This promotes drug diffusion through the hydrated gel layer, and increases outer gel layer erosion. A water insoluble filler such as MCC does not increase drug release rate in this way. It has been reported that a partially pregelatinized starch (Starch 1500) provided the slowest drug release in a PEO matrix, because it has partial water solubility, and self-swelling characteristics. This allowed it to slow the penetration of swelling front into the core and further retard drug release [122].

Work by Maggi et al. has shown that a change in compression force from 10 to 30kN does not affect the drug release profile of Diltiazem hydrochloride in both low or high molecular weight PEO matrices [117].

1.5 The use of HPMC and PEO mixtures in hydrophilic matrices for extended release

HPMC and PEO are independently capable of forming good extended drug release hydrophilic matrices but there have been very few studies of HPMC PEO combinations.

Kazarian et al. has reported a tablet-in-tablet formulation containing HPMC and PEG in a Fourier Transform Infrared Spectroscopy (FTIR) imaging investigation, but in this formulation, the researchers manufactured the HPMC polymer as a shell and PEG polymer as a core [123]. Research by Jayan in our group at Nottingham, investigated an HPMC Methocel K4M in combination with a relatively low molecular weight PEO (100,000 -300,000). The mixed polymer matrix provided a delay and then accelerated drug release of a poorly soluble drug, typically after 2-6 hours. This formulation had potential benefits in that an arthritic patient might take the medication at bed time, but receive the maximum symptomatic relief from the burst release in the morning. Jayan investigated matrix hydration and drug release aspects, and whilst no specific HPMC : PEO interaction was found , his work suggested that PEO may influence HPMC hydration within the matrix [94]. Very little of this work was published.

A patent by Gusler et al. has described a mixed HPMC and PEO matrix which claims to provide optimal gastric retention enabling controlled release for both soluble and less soluble drugs. The PEO in the matrix limited the initial release of soluble drugs and provided gastric retention through hydration, while HPMC limited swelling and erosion of the matrix. In the case of less soluble drugs, HPMC in the matrix prevented premature drug release by retarding the erosion rate of the PEO [124].

1.6 Aims of this work and an overview of the thesis

The overall aims of this thesis are:

- (i) To investigate drug release from mixed HPMC: PEO matrices, and their resistance to ionic challenge, with respect to some basic formulation variables.
- (ii) To identify if mixed systems have advantages or disadvantages over matrices containing single polymers.
- (iii) To investigate the internal morphological changes those underpin the drug release process with respect to polymer composition and ionic challenge.

The work has been restricted to the use of a single soluble drug, caffeine (Approximately 16 mg/ml at room temperature), which is a widely accepted model drug in this field. Likewise, the studies of ionic effects used only sodium chloride (NaCl) as a model representative ionic electrolyte.

The chapters of the thesis reflect the stages of the investigation:

Chapter two: Describes the manufacture and formulation design of HPMC and PEO tablets with some basic disintegration and dissolution tests to identify ionic and food effects.

Chapter three: Understanding the internal behaviour of HPMC, PEO and HPMC:PEO hydrophilic matrices in NaCl media

Chapter four: Investigates HPMC and PEO particle swelling and mixed polymer solution properties.

Chapter five: Investigates early and later gel layer morphology in binary HPMC and PEO matrices.

Chapter six: Provides a summary and draws conclusions for the research.

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Chapter 2

Tablet Manufacture and Formulation Design

2.1 Aims

The aim of chapter was the formulation design and manufacture of hydrophilic matrix tablets suitable for the investigations described in this thesis. These were required to contain HPMC, PEO and mixtures of these two polymers in different ratios, suitable filler, and a model drug. This chapter also describes a short initial study using disintegration tests to find a suitable solute challenge for these dosage forms, and dissolution test for the *in vitro* drug release from the matrices.

2.2 Introduction

Hydroxypropyl methylcellulose (HPMC) is widely used as a water swellable rate controlling polymer in hydrophilic matrix formulations as it has GRAS (generally regarded as safe) status, is low cost, has several commercially available grades and has a wealth of previous literature in this application [1]. One weakness of HPMC is that polymer hydration can be influenced by dissolved solutes, with their effects being linked to their ordering within the Hofmeister series [2]. Highly concentrated solutions or multivalent ionic salts can inhibit the hydration of HPMC to such an extent that they lose their extended release properties and exhibit burst release [3, 4]. Over the last two decades several research groups [5-8] have reported how high molecular weight polyethylene oxides (PEO) can provide a good alternative to the use of HPMC in extended release matrices. The work in this thesis will examine if a blend of these polymers can provide improved matrices by utilising the physical and chemical properties of both polymers [9].

2.3 Formulation design

Matrix composition was based on an 8mm flat faced tablet formulation used successfully in previous research projects in our group. This provides both a starting point for obtaining a robust formulation, and facilitates comparisons with previous PhD studies that have used

HPMC or other polymers in hydrophilic matrices. Table 2.1 shows the formulation composition of hydrophilic matrices used in this study.

- The grade of HPMC was Methocel® K100M CR Premium. Methocel K grades are USP2208. They are the most widely used HPMC grades in extended drug release formulation.
- The grade of PEO was POLYOX WSR 303 coagulant because it had the highest polymer molecular weight and the highest viscosity. It is also, according to its suppliers, the most common grade used in extended drug release formulations.
- Caffeine anhydrous was chosen as a model drug because it is a widely accepted model soluble drug in this field, it also has pH independent solubility, good stability, and suitable UV characteristics
- Direct compression was chosen as a method of manufacture because it is simple and facilitates easy manufacture, and it is suitable for moisture and heat sensitive ingredients such as PEO [10].

2.4 Materials

Full information on all materials listed in Appendix 1. The materials used in the matrices were caffeine anhydrous, magnesium stearate, lactose (Fast-flo USP), partially pregelatinized starch (Starch1500TM), microcrystalline cellulose USP (MCC) (Avicel PH102), HPMC K100M, and PEO WSR 303. In the disintegration and dissolution tests media, the water was maxima HPLC grade with a maximum conductance of 18.2 MΩ.cm, NaCl was used to prepare the different ionic strength media (0M, 0.2M, 0.4M, 0.6M, 0.8M and 1.0M), concentrated HCl (≥ 37%) used to adjust pH. The fruit juices and ingredients of the FDA breakfast are described in tables 2.2 and 2.3.

2.5 Tablet manufacturing method

Matrix tablets were prepared from powder blends containing by weight 10% caffeine anhydrous, 30% polymer, 59.5% fillers and 0.5% magnesium stearate. The polymer composition was varied so that matrices contained HPMC and PEO in weight ratios of 10:0, 8:2, 6:4, 4:6, 2:8 and 0:10 (Table 2.1). The properties of the filler were varied : lactose represented a water soluble diluent, Starch1500TM a partially water soluble but swellable diluent that might enhance the gel layer [11], and MCC represented an insoluble but wettable diluent. Formulation compositions are summarised in Table 2.1.

The powder blends were prepared in batches of 99.5g in 500ml bottle, by mixing all ingredients except magnesium stearate for 20 minutes at 47rpm in a shaker-mixer (Turbula, Willy A. Bachofen Maschinenfabrik AG, Basel, Switzerland) then adding 0.5g magnesium stearate, and mixing for a further five minutes.

Matrices were manufactured by dry compression of powder blends on a rotary tablet press (Riva Piccola rotary press, Buenos Aires, Argentina), to form 8mm diameter round flat-faced tablets of weight 250±3mg. The compression force was determined in the next study.

Polymer ratio (HPMC:PEO)						
	10:0	8:2	6:4	4:6	2:8	0:10
HPMC	30	24	18	12	6	0
PEO	0	6	12	18	24	30
Caffeine	10	10	10	10	10	10
Filler	59.5	59.5	59.5	59.5	59.5	59.5
Mg Stearate	0.50	0.5	0.5	0.5	0.5	0.5
Total	100	100	100	100	100	100

Table 2.1: Formulation composition of matrices containing different HPMC:PEO polymer ratios. Composition is given as percentage by weight. The filler was varied between lactose, MCC or Starch1500TM. Tablets were 8mm diameter round flat-faced cylinders with a target weight of 250±3mg.

2.6 Tablet strength profiles

2.6.1 Rationale

Tablet strength provides an indication of tablet resistance to further processing, capping, aberration or breakage during storage, transportation and handling. If the tablet is too soft, it may not be able to undergo subsequent unit processes such as coating, packaging, or shipping. However, if the tablet is too hard, it may not provide the extended drug delivery and fail the dissolution tests. In most cases, the normal strength of an oral tablet is between 4 and 10kgcm⁻². A strength of 4kgcm⁻² is considered as a minimum crushing strength for satisfactory tablets. However, some extended release formulations may require higher strength which is 10 to 20kgcm⁻² [12].

In addition, tablet strength is associated with tablet properties such as density and porosity. Dabbage et al. 1996 have reported that the porosity of a matrix can affect the drug release mechanism in hydrophilic matrices [13]. Results reported in section 1.3.7.8, suggested a similar pattern that, if the matrix was made with too low a compression force, it can release the drug more rapidly. At high porosity, a water could influx into the tablet core more easily, and there would be less drug diffusion control [14-16].

2.6.2 Method

Tabletting was undertaken on the standard formulation, containing different fillers, at different compression forces up to about 400MPa. 20 tablets have been placed on Pharma test PTB 311 hardness tester (Hertfordshire, the UK) for the tablet strength test.

2.6.3 Results

Figures 2.1 and 2.2 show the compression profiles for HPMC and PEO matrices formulated with different fillers (lactose, Starch1500TM, and MCC). The formulations, showed how increasing the compression force increased tablet hardness. Most profiles showed greater increases below 120MPa and above this value, compression force had less effect on tablet hardness.

Fillers in the formulations appeared to play a very important role in influencing matrix hardness, with the rank order being MCC>lactose>Starch1500TM. HPMC matrices showed slightly higher hardness values than PEO matrices containing the same fillers.

In the case of HPMC matrices, the maximum compression force the tablet machine could deliver for lactose formulations was 320MPa, for Starch1500TM it was 400MPa, and with MCC as filler it was 240MPa. If the compression force was set above these values, the tablet machine jammed and stopped automatically. In the case of PEO matrices these values were 200MPa for lactose, 240MPa for Starch1500TM, and 200MPa for MCC.

2.6.4 Conclusion the compression force chosen for future studies

To ensure that the tablet machine would run safely and smoothly and reasonable tablet hardness properties were obtained, the compression force chosen for tableting in this PhD project was about 160MPa.

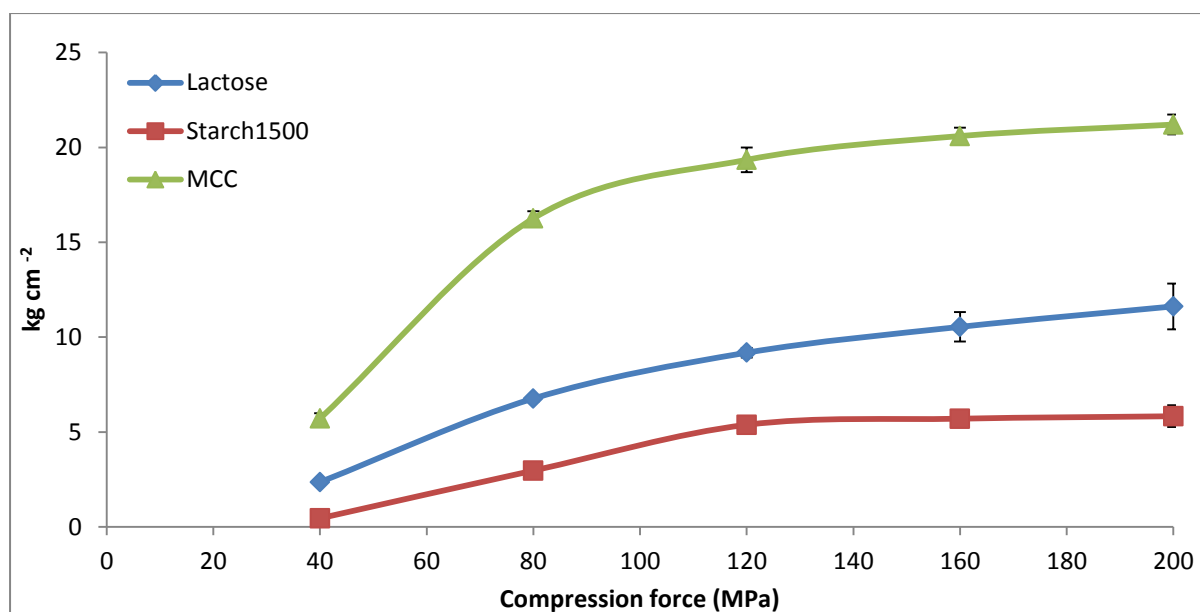


Figure 2.1: The strength and compression force from HPMC matrices. Each matrix contained 30% HPMC, 10% caffeine, 59.5% filler, and 0.5% magnesium stearate. (Mean n=20, $\pm$ SD)

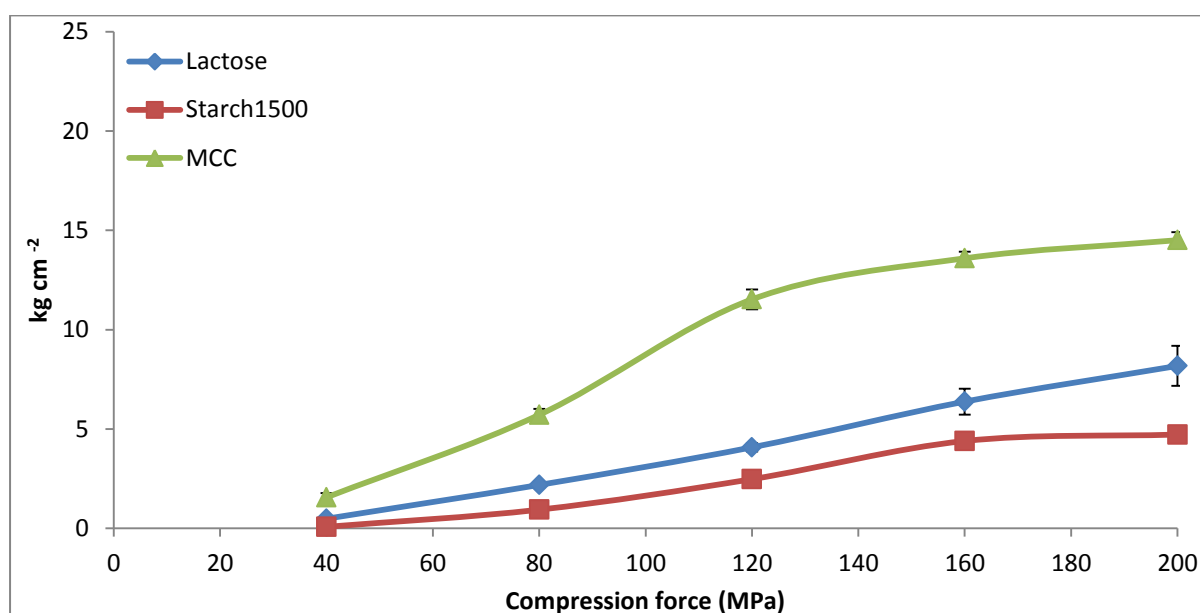


Figure 2.2: The strength and compression force from PEO matrices. Each matrix contained 30% PEO, 10% caffeine, 59.5% filler, and 0.5% magnesium stearate. (Mean n=20, $\pm$ SD)

2.7 Identifying a suitable solute challenge

2.7.1 Rationale

As described previously, HPMC matrices can be sensitive to solutes in the hydration or dissolution medium [17, 18]. Previous work has identified a wide range of solutes that could be used to challenge these matrices, including salts, buffers, sugars, amino acids etc. [19-21]. Each of these provides a challenge because they exert Hofmeister effects on HPMC solubility and may induce changes in the matrix drug release profiles.

Recently, there have been moves towards more 'biorelevant' dissolution media, which better imitate the effects of food [22-24]. This chapter therefore includes a speculative study to examine if certain high sugar juices and the FDA breakfast might be worthwhile considering as challenge media.

2.7.2 Method

Disintegration testing was undertaken in a USP Disintegration apparatus A (Copley ZT 44, Nottingham, UK). 6 tablets were placed in 900 ml medium at 37 ± 0.5 °C, the disintegration media used were (i) sodium chloride solutions (0, 0.2M, 0.4M, 0.6M, 0.8M, and 1.0M), (ii) various easily obtained fruit juices with a high sugar content and (iii) a homogenised FDA standard breakfast. The origin and composition of these are shown in Tables 2.2 and 2.3. To prepare an FDA standard breakfast suitable for disintegration testing, the various food components were homogenised in a blender, made up to 900ml with water, and the pH adjusted to 1.2 with HCl. The time was recorded once all tablets had disintegrated. Disintegration tests were undertaken for 60 minutes and then stopped if disintegration was incomplete.

	Carbohydrate as Sugars (g/100ml)	Concentration calculated as hexose monosaccharides (M)
Sainsbury's 100% Squeezed orange juice Smooth, BN 2024MN BB 12-07-2012	9.1	0.50
Tesco orange juice from concentrate smooth, BN X202 2021 BB 19-03-12	10.5	0.58
Tesco pineapple juice from concentrate, BN X202 2021 BB 19-03-12	12.4	0.69
Tesco apple juice from concentrate BN X205A 2026 BB 24-03-12	11.1	0.61
Tesco high juice orange (fruit 50% juice)	41.8	2.32

Table 2.2: Commercial fruit juices used in these tests with their labelled sugar contents

FDA Breakfast	Salt (g)	Sugar (g) as disaccharide (M)
240ml Iceland fresh pasteurized whole milk BN: D11901LTC010	0.24	11.28
2X Tesco Bacon 10 unsmoked back rashers BN: 12954H	3	0
2X Tesco 15 free range eggs	0.4	0
4X McCain Southern Fries	1.6	6.4
2X Hovis Soft white medium 800g	0.8	2g
Total (g)	6.04	19.68
Concentration in final volume of 900ml (M)	0.11M	0.57M

Table 2.3: Composition of the FDA standard breakfast, their labelled salt and sugar contents, and the final potential concentration in the disintegration test [25]

2.7.3 The effect of sodium chloride concentration on matrix disintegration

The disintegration tests in salt provided a rapid screening of the robustness of each formulation when exposed to different NaCl environments. Table 2.4 shows test results with respect to polymer composition and NaCl concentration for matrices containing the different tablet diluents.

HPMC matrices containing lactose disintegrated within 30 minutes in 0.8M NaCl, and more rapidly (less than 5 minutes) in 1M NaCl. However, matrices containing substituted PEO showed greater robustness to high NaCl concentrations, and at an HPMC:PEO ratio of 6:4 or higher, they resisted 1.0M NaCl for 60 minutes.

HPMC matrices containing the less water soluble fillers (Starch1500TM and MCC) showed higher NaCl resistance than those containing lactose. They resisted 0.8M NaCl for 60 minutes but disintegrated within 60 minutes when NaCl concentration reached 1.0M. Again, it was found that substituting PEO to the matrix increased its resistance to high salt. Although disintegration tests tell us nothing about matrix drug release kinetics, they suggest that inclusion of PEO in the formulation may enhance the resistance of HPMC hydrophilic matrices to ionic challenge.

2.7.4 Matrix disintegration in commercial fruit juices

HPMC matrices are susceptible to high concentrations of sugars [19] and this section investigates a few high sugar juices that might be used as a realistic sugar challenge. Table 2.5 shows the disintegration times for hydrophilic matrices in a range of high sugar juices obtained from UK supermarkets. These juices contain carbohydrate as sugar in the range 9.1 to 41.8 g/100ml. This is equivalent to 0.5M to 2.32M of monosaccharides. We would expect this to be a mixture of fructose, glucose and disaccharides.

The results (Table 2.5) showed HPMC matrices were resistant to disintegration in all juices except the Tesco high juice orange. Again substituting PEO appeared to help HPMC matrices become more resistant to the high juice orange. Unfortunately, Tesco high fruit juice is intended to be diluted before ingestion, and therefore in its concentrated form, it would be

an unrealistic test. Additionally, we do not know its true composition and for these reasons the use of fruit juices in further work was abandoned.

2.7.5 Matrix disintegration in a homogenised FDA breakfast

This study examined a homogenised FDA breakfast as a potentially relevant food challenge. The potential total NaCl and sugar (sucrose) concentration in a homogenised portion of FDA breakfast in the disintegration vessel was calculated from the food labelling to be 0.11M and 0.57M respectively (table 2.3). Table 2.6 shows that all matrices did not disintegrate in 60 minutes in the FDA breakfast.

2.7.6 Conclusions:

The disintegration test is a rapid and simple experiment which provided an indication of the early susceptibility of hydrophilic matrices to the different media tested. Based on the results above, a range of NaCl concentrations (from 0M to 1M) was chosen as the most suitable solute challenge for future work. It is used as a variable in subsequent chapters to examine the resistance of mixed HPMC:PEO matrices, to aid our understanding of gel layer behaviour and drug release mechanisms, and to choose a formulation that shows better resistance to adverse solute environments.

Table 2.4 a						
Disintegration time (min) for matrices containing lactose as a filler						
Polymer composition	NaCl concentration(M)					
	0M	0.2M	0.4M	0.6M	0.8M	1.0M
HPMC	60	60	60	60	32.7	4.5
HPMC:PEO 8:2	60	60	60	60	60	22
HPMC:PEO 6:4	60	60	60	60	60	60
HPMC:PEO 4:6	60	60	60	60	60	60
HPMC:PEO 2:8	60	60	60	60	60	60
PEO	60	60	60	60	60	60

Table 2.4 b						
Disintegration time (min) for matrices containing Starch1500™ as a filler						
Polymer composition	NaCl concentration(M)					
	0M	0.2M	0.4M	0.6M	0.8M	1.0M
HPMC	60	60	60	60	60	38.5
HPMC:PEO 8:2	60	60	60	60	60	60
HPMC:PEO 6:4	60	60	60	60	60	60
HPMC:PEO 4:6	60	60	60	60	60	60
HPMC:PEO 2:8	60	60	60	60	60	60
PEO	60	60	60	60	60	60

Table 2.4 c						
Disintegration time (min) for matrices containing MCC as a filler						
Polymer composition	NaCl concentration(M)					
	0M	0.2M	0.4M	0.6M	0.8M	1.0M
HPMC	60	60	60	60	60	47
HPMC:PEO 8:2	60	60	60	60	60	56
HPMC:PEO 6:4	60	60	60	60	60	60
HPMC:PEO 4:6	60	60	60	60	60	60
HPMC:PEO 2:8	60	60	60	60	60	60
PEO	60	60	60	60	60	60

Table 2.4: Matrix disintegration times as a function of HPMC:PEO composition and sodium chloride concentration. Matrices contained 30%w/w total polymer and (a) lactose (b) Starch 1500™ or (c) MCC as a filler. USP disintegration apparatus A, 900 ml, 37 ± 0.5 °C, in sodium chloride adjusted to pH1.2 with HCl. (n=6) except where a value of 60 is shown: this indicates a disintegration time of 60 minutes or greater.

Table 2.5 a					
Disintegration time (min) for matrices containing lactose as a filler					
Polymer ratio and Juices	Sainsbury's orange juice	Tesco orange juice	Tesco pineapple juice	Tesco apple juice	Tesco high juice orange
HPMC	60	60	60	60	27.6
HPMC:PEO 8:2	60	60	60	60	38
HPMC:PEO 6:4	60	60	60	60	60
HPMC:PEO 4:6	60	60	60	60	60
HPMC:PEO 2:8	60	60	60	60	60
PEO	60	60	60	60	60

Table 2.5 b					
Disintegration time (min) for matrices containing Starch1500TM as a filler					
Polymer ratio and Juices	Sainsbury's orange juice	Tesco orange juice	Tesco pineapple juice	Tesco apple juice	Tesco high juice orange
HPMC	60	60	60	60	35.8
HPMC:PEO 8:2	60	60	60	60	60
HPMC:PEO 6:4	60	60	60	60	60
HPMC:PEO 4:6	60	60	60	60	60
HPMC:PEO 2:8	60	60	60	60	60
PEO	60	60	60	60	60

Table 2.5 c					
Disintegration time (min) for matrices containing MCC as a filler					
Polymer ratio and Juices	Sainsbury's orange juice	Tesco orange juice	Tesco pineapple juice	Tesco apple juice	Tesco high juice orange
HPMC	60	60	60	60	40.5
HPMC:PEO 8:2	60	60	60	60	58
HPMC:PEO 6:4	60	60	60	60	60
HPMC:PEO 4:6	60	60	60	60	60
HPMC:PEO 2:8	60	60	60	60	60
PEO	60	60	60	60	60

Table 2.5: Matrix disintegration times as a function of HPMC:PEO composition in different juices. Matrices contained 30%w/w total polymer and (a) lactose (b) Starch 1500™ or (c) MCC as a filler. USP disintegration apparatus A, 900 ml, 37 ± 0.5 °C, juices adjusted to pH1.2 with HCl. (n=6) except where a value of 60 is shown: this indicates a disintegration time of 60 minutes or greater

Disintegration time (min) for matrices in FDA breakfast			
Polymer ratio and fillers	lactose	Starch1500™	MCC
HPMC	60	60	60
HPMC:PEO 8:2	60	60	60
HPMC:PEO 6:4	60	60	60
HPMC:PEO 4:6	60	60	60
HPMC:PEO 2:8	60	60	60
PEO	60	60	60

Table 2.6: Disintegration times for HPMC: PEO matrices in a homogenised FDA breakfast (pH=1.2). USP apparatus A, 900 ml, 37 ± 0.5 °C, (n=6) except where a value of 60 is shown: this indicates a disintegration time of 60 minutes or greater

2.8 *In vitro* dissolution testing

2.8.1 Methods

Dissolution testing was undertaken in USP dissolution apparatus I (basket) rotated at 100 rpm (Prolabo, Dissolutest, France) in 900ml deaerated media at $37 \pm 0.5^\circ\text{C}$, pH adjusted to 1.2 using concentrated HCl. UV spectrometry at 273 nm was used to determine caffeine concentration with media being transferred into 10mm quartz flow-through cells by a closed-loop Agilent automated dissolution system (Agilent 8453, Agilent Technologies, Stockport, UK). Sink conditions are maintained.

2.8.2 Mathematical modelling of drug release

The Power law [26] was used as an empirical model to evaluate the mechanism of drug release. Data from 10% to 70% drug release was fitted to equation 1. .

Power law:
$$\frac{M_t}{M_\infty} = kt^n$$
 Equation 1

Where M_t/M_∞ is the fraction of drug released at time t , calculated by dividing the mass of drug released at time t by the amount of drug released as t approaches infinity. k is the kinetic or rate constant and n is the exponent for drug release, which can be used to identify the drug release mechanism from a polymeric device.

The time for 80% drug release (T80) was used as a simple measure of the length of extended release.

2.8.3 Results and Discussions

2.8.3.1 Study of formulations with lactose as filler

Figure 2.3 shows drug release profiles for matrix formulations containing different ratios of HPMC and PEO with lactose. The concentration of NaCl in the dissolution medium was varied in order to show the effect of ionic strength. In matrices containing only a single polymer, HPMC matrices exhibited slower drug release than PEO matrices, but only in media containing less than 0.6M NaCl. Above 0.6M, HPMC matrices showed significantly accelerated drug release confirming previous reports [3, 20]. PEO matrices were not significantly affected by NaCl concentration and when mixed HPMC and PEO matrices were used at a ratio of HPMC: PEO 6:4 or higher, the tablets retained their extended release profiles in the presence of 1M NaCl. Most of the mixed polymer matrices produced longer extended drug release than PEO matrices, at all NaCl concentrations.

Table 2.7 provides kinetic parameters (k and n) obtained from fitting the Power law to drug release data between 10%-70% [11]. The exponent k is a release constant and the exponent n can be used to broadly indicate the drug release mechanism. Correlation coefficient values (r^2) were close to 0.999, indicating the model was a good fit to the data. The exceptions occurred when drug release was rapid. In these cases, the matrix exhibited immediate release, rather than extended release characteristics. The exponent n values were used to provide an indication of the release mechanism: Fickian diffusion, anomalous transport, or case II transport. Table 2.7 shows that when the polymer ratio of HPMC: PEO was 6:4 or higher, values of the diffusion exponent value (n) were 0.45 to 0.89 all NaCl media. This suggests that in these matrices, the drug release mechanism was anomalous non-Fickian transport, which means a coupling of drug diffusion with polymer relaxation [27]. However, when the matrices had ratio of HPMC: PEO 8:2 or HPMC was alone, values of n in high NaCl content media (0.8M or above) were >0.89 . This mathematically represents drug release depending on the polymer relaxation rate, which is known as case II transport.

The power law equation shows mathematically how NaCl concentration can significantly affect HPMC matrix drug release, but had very limited effects to PEO or blended HPMC:PEO matrices when the HPMC:PEO ratio was 6:4 or higher.

The time for 80% drug release (T80) was used as a simple measure of the length of extended release and table 2.8 shows T80 values with respect to the polymer composition and the NaCl concentration in the dissolution medium.

In matrices utilising only HPMC, T80 values can be seen to increase with salt concentration up to 0.4M, but at 0.8M and above, the matrices exhibited immediate release characteristics. This initial prolongation, followed by the loss of extended release characteristics at very high salt concentrations, has been reported previously [3]. There is evidence that this results from a failure to develop an effective gel layer diffusion barrier during the early stages of matrix hydration as a result of inhibition of polymer swelling through Hofmeister effects [28] [29].

In sharp contrast, 30% PEO matrices retained their capability to extend drug release in all the salt concentrations studied. It is well documented that PEO is sensitive to salts in solution but the threshold seems to be much higher than HPMC [28] [29] [30] [31]. In this work, there was no dose dumping, and increasing NaCl concentration resulted in increased extended release times, from T80 = 237 minutes (0M NaCl) to T80 = 292 minutes (1.0M NaCl).

Table 2.8 also illustrates the effects of using mixed polymer combinations. The principal effects were two folds. Firstly, by progressively replacing PEO by HPMC, matrices with greater extended release were produced. In low salt concentrations, the effects appeared to be additive rather than synergistic. Secondly, substituting with PEO, helped HPMC matrices became more resistant to NaCl as using a polymer ratio of HPMC: PEO 6:4 or higher, abolished the salt-induced relatively rapid release in 0.8M and 1.0M NaCl.

In table 2.8, matrices with a HPMC:PEO ratio of 4:6 appear to provide a good compromise between maximising the extended release profile and minimising the drug release variability across the salt concentration range. Increasing NaCl in dissolution media to 0.2M, the matrices provided about 30 minutes longer drug release than 0M. 0.2M NaCl was arguably

the most likely salt strength range to be encountered in the stomach, but whether this would give rise to a noticeable effect *in vivo*, would require clinical studies.

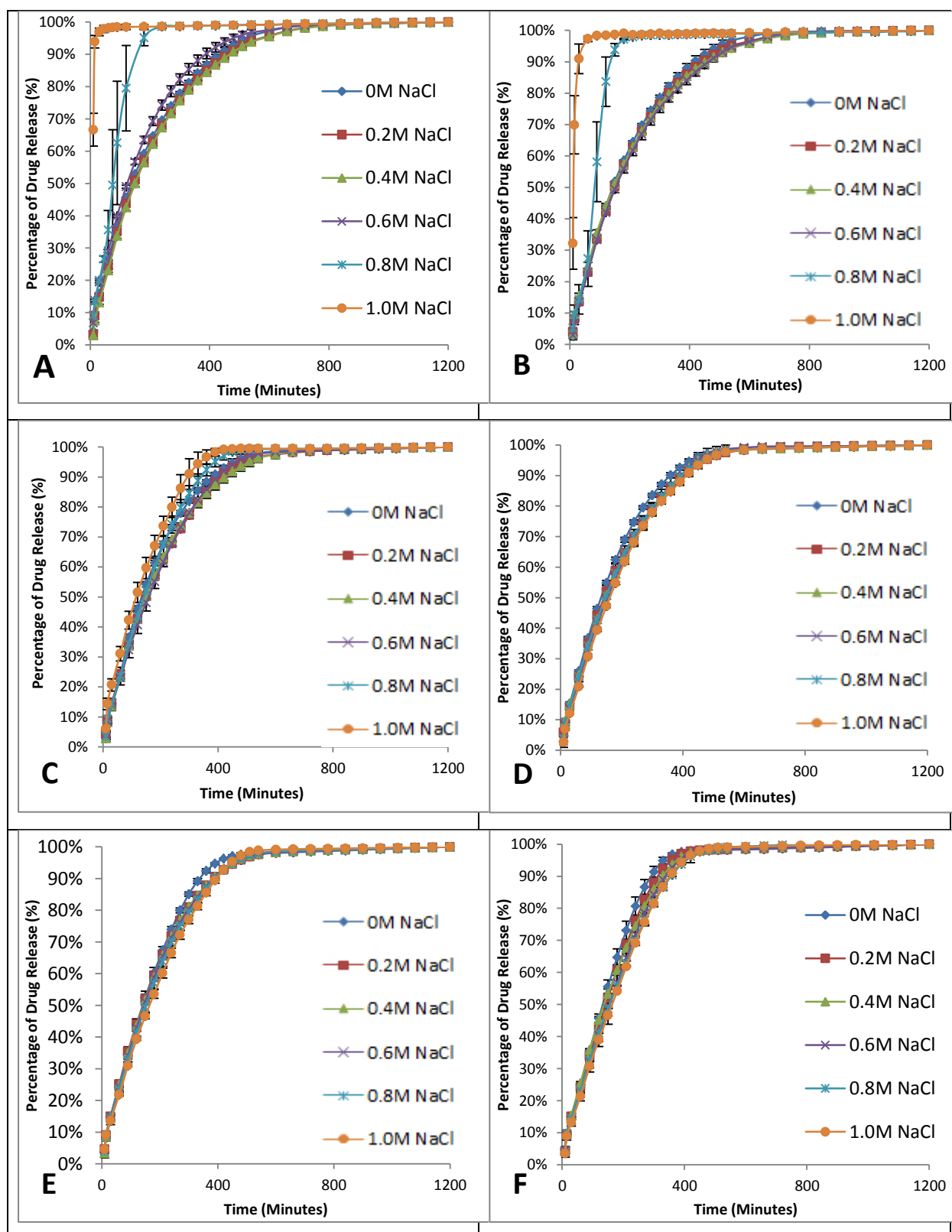


Figure 2.3: Release of caffeine from 30% HPMC:PEO matrix tablets with 59.5% lactose as a function of sodium chloride concentration in the dissolution medium (pH=1.2). USP apparatus 1, 100 rpm, 900 ml, 37 ± 0.5 °C, Mean ($n=3$, $\pm$ SD).

HPMC:PEO polymer ratios A: polymer ratio (10:0), B: polymer ratio (8:2), C: polymer ratio (6:4), D: polymer ratio (4:6), E: polymer ratio (2:8), F: polymer ratio (0:10)

Parameter and correlation coefficients with respect to HPMC:PEO ratios and NaCl Concentration (M)							
		0	0.2	0.4	0.6	0.8	1
HPMC	k	1.634	1.531	1.262	2.105	0.495	N\A
	n	0.689	0.693	0.727	0.655	1.067	N\A
	r^2	0.9969	0.9961	0.9953	0.9980	0.9743	N\A
HPMC:PEO (8:2)	k	1.071	1.245	1.649	1.261	0.122	N\A
	n	0.767	0.731	0.680	0.726	1.363	N\A
	r^2	0.9955	0.9961	0.9969	0.9967	0.9633	N\A
HPMC:PEO (6:4)	k	1.065	1.305	1.085	1.058	0.954	2.200
	n	0.780	0.724	0.761	0.760	0.797	0.658
	r^2	0.9973	0.9983	0.9983	0.9996	0.9990	0.9984
HPMC:PEO (4:6)	k	1.149	1.233	1.254	0.986	1.148	0.741
	n	0.768	0.741	0.736	0.777	0.753	0.807
	r^2	0.9990	0.9974	0.9993	0.9991	0.9992	0.9993
HPMC:PEO (2:8)	k	0.936	1.236	1.172	1.127	1.055	1.005
	n	0.800	0.744	0.753	0.759	0.767	0.765
	r^2	0.9989	0.9992	0.9994	0.9994	0.9995	0.9992
PEO	k	0.854	0.915	1.174	0.884	1.045	0.796
	n	0.802	0.807	0.760	0.801	0.766	0.813
	r^2	0.9991	0.9986	0.9993	0.9990	0.9990	0.9987

Table 2.7: The exponents (n), constants (k) and goodness of fit data (r^2) obtained by fitting Power law equation to drug release data in HPMC and PEO matrices with lactose as a filler respect to NaCl concentration.

T80 (Minutes) of 30% polymers with lactose as a filler						
Polymer ratio and NaCl concentration(M)	0M	0.2M	0.4M	0.6M	0.8M	1.0M
HPMC	320	336	341	282	120	12
HPMC:PEO 8:2	312	330	330	346	116	22
HPMC:PEO 6:4	285	320	317	314	270	240
HPMC:PEO 4:6	270	308	311	308	305	317
HPMC:PEO 2:8	270	293	292	297	306	321
PEO	237	257	267	278	289	292

Table 2.8: T80 values as a function of polymer composition and sodium chloride concentration in the dissolution medium. T80 is the time for 80% caffeine release from 30% HPMC:PEO matrix tablets with 59.5% lactose. Dissolution medium (pH=1.2). USP apparatus 1, 100 rpm, 900 ml, 37 ± 0.5 °C, Mean (n=3, ±SD).

2.8.3.2 Study of formulations with Starch1500TM as filler

Starch1500TM is a partially pregelatinized maize starch containing water soluble amylose and water insoluble amylopectin at an approximate ratio of 1:3. Starch1500TM was used as filler in this study as it's partially water soluble.

Figure 2.4 shows 20 hours drug release profiles from 30% HPMC:PEO matrix tablets with 59.5% Starch1500TM as a function of sodium chloride concentration, at a pH 1.2 to mimic the stomach environment.

Similar to the formulation made with lactose as filler, matrices with the HPMC as a single polymer were significantly affected when the NaCl concentration reached 0.8M. At 0.8M or higher matrices provided accelerated drug release rather than extended drug release. However, substituting PEO for HPMC matrices above a HPMC:PEO ratio of 8:2, resulted in matrices becoming more resistant to NaCl. In 0.8M and 1.0M NaCl, the matrices exhibited a biphasic release profile (Figure 2.4.2 B). They maintained extended release for 400 minutes, before rapidly release all the remaining caffeine within one hour. Increasing the PEO content to an HPMC:PEO ratio of 6:4, the matrices were able to maintain extended release at 0.8M NaCl, but the biphasic release profile was shown in the end stages of drug release at 1.0M NaCl. This suggested that matrices were swelling during the first few hours of hydration, but then the swollen mass quickly disintegrated thereafter. When the polymer ratios reached at HPMC:PEO 4:6, 2:8, 0:10, the matrices were all robust to NaCl up to 1.0M.

Table 2.9 mathematically analyses drug release profiles using the Power Law using drug release data between 10% to 70% from the dissolution tests. The values the goodness of fit to the Power law equation (r^2) was 0.995 or greater.

When the NaCl concentration was 0M, there was a progressive increase in n value from 0.65 to 0.89 as the polymer composition changed. This suggests a movement from a more diffusion controlled to a more erosion controlled release mechanism.

Most n values at NaCl concentrations between 0.2M and 0.6M, were between n=0.65 to 0.8. These values suggest drug release occurred by 'anomalous non-Fickian transport' in which

drug diffusion is coupled with polymer relaxation. When NaCl concentration was over 0.8M, formulations containing HPMC: PEO ratios of 6:4 or higher, they remained as anomalous non-Fickian transport. However, formulations with HPMC or 8:2 HPMC: PEO gave the n values that were either no reading or above 0.89. This indicates drug release from these two formulations in high NaCl content media was dependent on polymer relaxation rate, a mechanism known as case II transport [27].

Table 2.10 shows T₈₀ values. These provide evidence of the duration of extended drug release with respect to NaCl concentration. HPMC matrices showed both positive and negative effects from NaCl, depending on the NaCl concentration. In the lower NaCl concentrations (0-0.4M), NaCl had a positive effect on extended release: as NaCl concentration was increased, the HPMC matrix provided longer drug release. The maximum T₈₀ achieved was 660 minutes at 0.4M. Increasing NaCl above 0.4M, it had the negative effect on T₈₀, which was reduced to 634 minutes at 0.6M, then dropped significantly at 0.8M and 1.0M.

T₈₀ values for PEO matrices increased over the whole range of NaCl concentrations from 355 minutes to 470 minutes.

In the NaCl media (less than 0.6M), increasing HPMC polymer into PEO matrices, T₈₀ was increasing. The mixed polymer matrices showed similar effects to matrices containing lactose, and again combinations of HPMC and PEO helped the matrices maintain extended drug release in high NaCl media, and extended T₈₀ compared with PEO matrices alone.

The best T₈₀ in table 2.10 was the formulation containing HPMC:PEO in the ratio 6:4. This formulation provided the most stable drug release based on a T₈₀ calculation, with values between 400 and 600 minutes. However, as above, this matrix showed a biphasic drug release profile after 80% drug release in 1.0M NaCl. So although this formulation gave the best T₈₀ profile, the burst release in 1.0M NaCl, did not indicate it was the best formulation.

A polymer ratio of 4: 6 may be the best overall, NaCl concentrations had very limited effects to the formulation over the whole range yet provided longer drug release than PEO matrices.

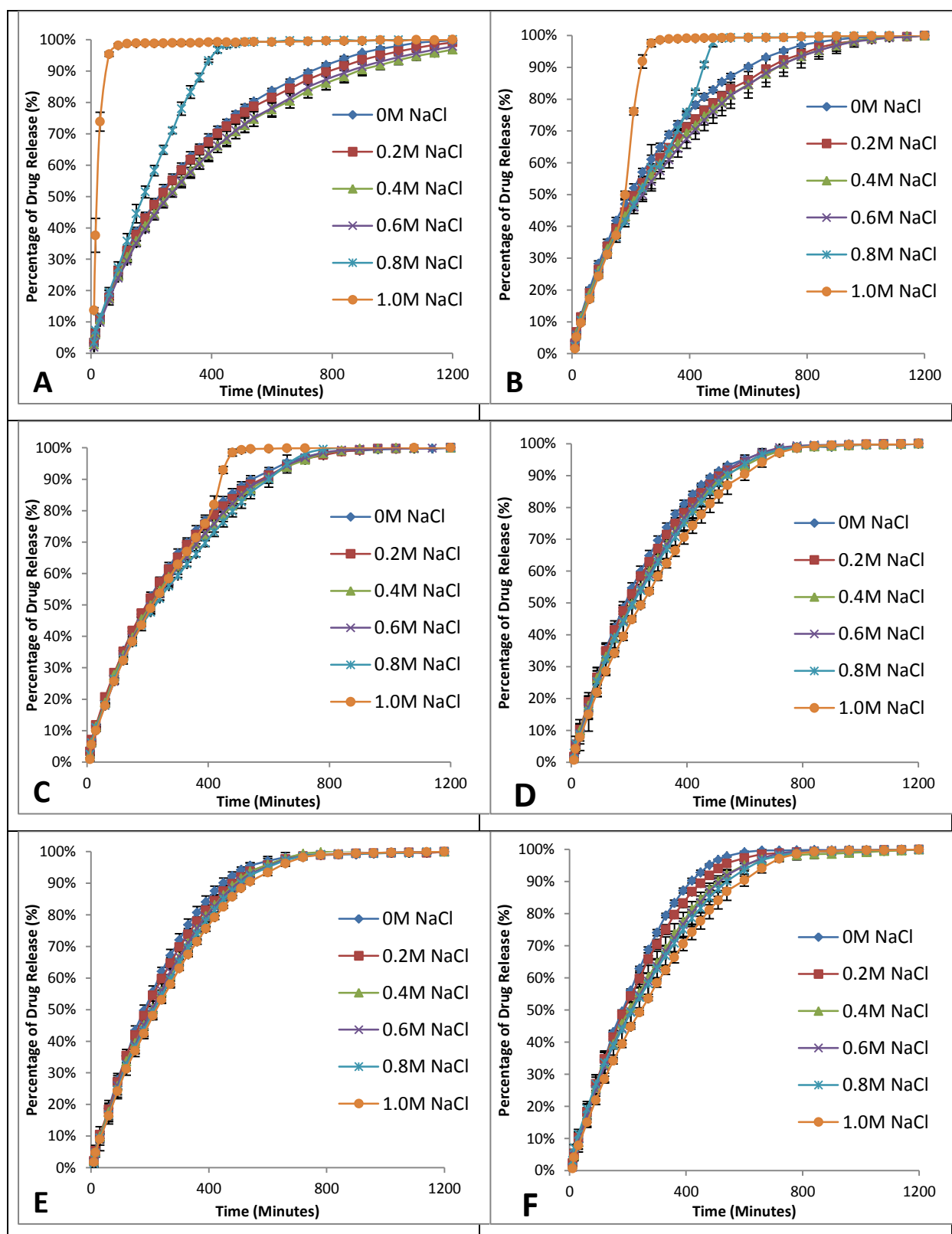


Figure 2.4: Release of caffeine from 30% HPMC:PEO matrix tablets with 59.5% Starch1500™ as a function of sodium chloride concentration in the dissolution medium (pH=1.2). USP apparatus 1, 100 rpm, 900 ml, 37 ± 0.5 °C, Mean ($n=3$, $\pm$ SD).

HPMC:PEO polymer ratios A: polymer ratio (10:0), B: polymer ratio (8:2), C: polymer ratio (6:4), D: polymer ratio (4:6), E: polymer ratio (2:8), F: polymer ratio (0:10)

Parameter and correlation coefficients with respect to HPMC:PEO ratios and NaCl Concentration (M)							
		0	0.2	0.4	0.6	0.8	1
HPMC	k	1.445	1.411	1.513	1.333	0.639	N\A
	n	0.650	0.651	0.627	0.648	0.843	N\A
	r^2	0.9960	0.9952	0.9958	0.9964	0.9990	N\A
HPMC:PEO (8:2)	k	1.295	1.318	1.383	1.210	0.860	0.055
	n	0.687	0.673	0.658	0.676	0.747	1.334
	r^2	0.9973	0.9969	0.9968	0.9974	0.9979	0.9499
HPMC:PEO (6:4)	k	1.079	1.235	1.218	1.075	1.257	0.880
	n	0.723	0.697	0.691	0.711	0.676	0.749
	r^2	0.9975	0.9978	0.9969	0.9968	0.9969	0.9988
HPMC:PEO (4:6)	k	0.745	0.903	0.885	0.801	0.823	0.624
	n	0.800	0.758	0.751	0.768	0.760	0.795
	r^2	0.9968	0.9970	0.9980	0.9975	0.9959	0.9984
HPMC:PEO (2:8)	k	0.701	0.759	0.782	0.672	0.661	0.687
	n	0.816	0.796	0.776	0.807	0.805	0.792
	r^2	0.9973	0.9979	0.9964	0.9983	0.9987	0.9988
PEO	k	0.486	0.698	0.782	0.801	1.103	0.624
	n	0.887	0.812	0.776	0.768	0.709	0.795
	r^2	0.9984	0.9985	0.9964	0.9975	0.9993	0.9984

Table 2.9: The exponents (n), constants (k) and goodness of fit data (r^2) obtained by fitting the Power law equation to drug release data in HPMC and PEO matrices with starch1500TM as a filler respect to NaCl concentration.

T80 (Minutes) of 30% polymers with Starch1500 TM as a filler						
Polymer ratio and NaCl concentration(M)	0M	0.2M	0.4M	0.6M	0.8M	1.0M
HPMC	540	568	660	634	311	39
HPMC:PEO 8:2	442	498	522	526	410	217
HPMC:PEO 6:4	420	436	464	456	480	410
HPMC:PEO 4:6	380	405	420	420	434	470
HPMC:PEO 2:8	354	378	410	400	406	428
PEO	335	360	410	420	434	470

Table 2.10: T80 values as a function of polymer composition and sodium chloride concentration in the dissolution medium. T80 is the time for 80% caffeine release from 30% HPMC:PEO matrix tablets with 59.5% Starch1500TM. Dissolution medium (pH=1.2). USP apparatus 1, 100 rpm, 900 ml, 37 ± 0.5 °C, Mean (n=3, ±SD).

2.8.3.3 Study of formulations with MCC as filler

Figure 2.5 A shows drug release profiles for HPMC matrices after 20 hours with respect NaCl concentration. Increases in NaCl concentration from 0M to 0.4M, had positive effects on extended release and the longest drug release profile was seen in 0.4M. In 0.6M NaCl, HPMC matrices still show extended drug release profile, but slightly quicker than the drug release in 0.2M and 0.4M NaCl. When the NaCl concentration reached 0.8M, drug was released from HPMC matrices in less than 300 minutes, much faster than in the lower NaCl media which takes more than 900 minutes

For matrices containing HPMC: PEO in the ratio 8:2, there was biphasic drug release in 0.8M NaCl, with controlled release for 150 minutes, then burst drug release. HPMC matrices and HPMC: PEO 8:2 matrices could not resist 1M NaCl, and an accelerated drug release profile was seen in figure 2.5 B.

Figure 2.5 C shows how mixed HPMC: PEO 6:4 matrices provided biphasic drug release profiles in 0.8M and 1.0M NaCl, but substituting more PEO into matrix made them more resistant to high NaCl media

Figures 2.5 D, 2.5 E and 2.5 F show that, when PEO was predominant in these matrices, NaCl has limited effect on drug release up to 1M.

Table 2.11 shows the parameters from Power law equation analysis of figure 2.5. The values of $r^2 > 0.997$ show the Power law is the suitable equation used in this mathematical analysis. Results were similar to formulations with lactose and starch1500TM. HPMC matrix with MCC as a filler provided anomalous non-Fickian transport when the NaCl concentration was less than 0.8M. Changing to this insoluble filler did not make the HPMC matrix more resistant into to solutions greater than 0.8M NaCl. Substituting PEO into the matrix (not less than a 6:4 HPMC: PEO ratio) ensured that all formulations provide n values between 0.45 and 0.89 and anomalous non-Fickian transport drug release across the range of NaCl concentrations. .

Table 2.12 provides T80 values for the MCC matrices. HPMC matrices have higher T80 values than mixed and PEO matrices, when the NaCl concentration was no more than 0.6M. Table

2.12 shows the T80 of HPMC matrices are increasing as NaCl concentration increased, and reaching a maximum of 600 minutes at 0.4M. Increasing NaCl concentration from 0.4M to 0.6M, reduced T80 to 540 minutes still extended drug release. However, increasing NaCl to 0.8M, T80 of HPMC dropped to 200 minutes, and burst release in 1.0M NaCl.

Table 2.12 also shows NaCl having positive effects on the T80 of PEO matrices as shown with the other diluents. As NaCl concentration increased from 0M to 1.0M, T80 increased from 355 to 420 minutes. The T80 results show that PEO matrices provide extended drug release in NaCl up to 1.0M. However, in low NaCl media, HPMC matrices provide higher T80 values than PEO matrices.

The advantages of HPMC and PEO polymers have shown previously for mixed HPMC: PEO matrices were also seen in these formulations. Substituting HPMC in PEO matrices provided higher T80 values when the NaCl concentration not more than 0.6M. At HPMC: PEO ratios of 4:6 or above, the matrices provided extended drug release up to 1.0M.

HPMC matrices exhibited burst drug release in 1.0M NaCl and the best overall T80 values were obtained from the mixed HPMC: PEO 4:6 matrices.

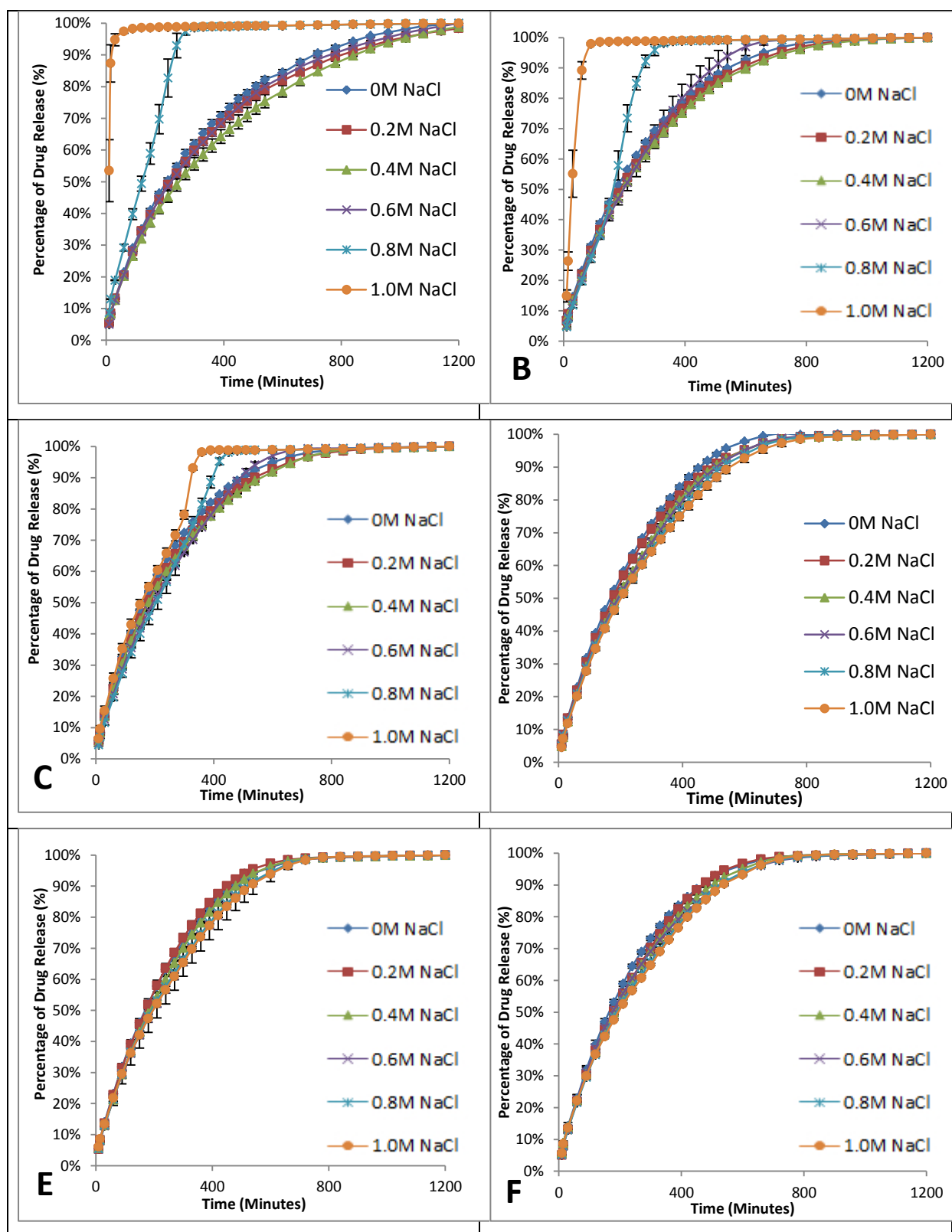


Figure 2.5: Release of caffeine from 30% HPMC:PEO matrix tablets with 59.5% MCC as a function of sodium chloride concentration in the dissolution medium (pH=1.2). USP apparatus 1, 100 rpm, 900 ml, 37 ± 0.5 °C, Mean ($n=3$, $\pm$ SD).

HPMC:PEO polymer ratios A: polymer ratio (10:0), B: polymer ratio (8:2), C: polymer ratio (6:4), D: polymer ratio (4:6), E: polymer ratio (2:8), F: polymer ratio (0:10)

Parameter and correlation coefficients with respect to HPMC:PEO ratios and NaCl Concentration (M)							
		0	0.2	0.4	0.6	0.8	1
HPMC	k	1.794	1.861	1.913	1.807	1.461	N\A
	n	0.620	0.606	0.589	0.611	1.125	N\A
	r^2	0.9972	0.9971	0.9982	0.9972	0.9756	N\A
HPMC:PEO (8:2)	k	1.585	1.516	1.421	1.154	0.206	N\A
	n	0.666	0.665	0.672	0.713	1.088	N\A
	r^2	0.9985	0.9985	0.9989	0.9999	0.9818	N\A
HPMC:PEO (6:4)	k	1.441	1.408	1.517	1.263	0.861	1.697
	n	0.693	0.687	0.668	0.695	0.766	0.669
	r^2	0.9983	0.9982	0.9976	0.9990	0.9995	0.9986
HPMC:PEO (4:6)	k	1.293	1.224	1.398	1.301	1.348	1.593
	n	0.713	0.715	0.686	0.692	0.680	0.651
	r^2	0.9989	0.9991	0.9993	0.9993	0.9990	0.9989
HPMC:PEO (2:8)	k	1.206	1.397	1.129	1.486	1.354	1.478
	n	0.724	0.694	0.725	0.673	0.682	0.665
	r^2	0.9996	0.9989	0.9997	0.9984	0.9991	0.9994
PEO	k	1.319	1.265	1.203	1.422	1.438	1.259
	n	0.706	0.706	0.708	0.685	0.673	0.690
	r^2	0.9984	0.9988	0.9990	0.9977	0.9979	0.9980

Table 2.11: The exponents (n), constants (k) and goodness of fit data (r^2) obtained by fitting Power law equation to drug release data in HPMC and PEO matrices with MCC as a filler respect to NaCl concentration.

T80 (Minutes) of 30% polymers with MCC as a filler						
Polymer ratio and NaCl concentration(M)	0M	0.2M	0.4M	0.6M	0.8M	1.0M
HPMC	510	561	626	540	204	13.9
HPMC:PEO 8:2	403	427	442	391	227	51
HPMC:PEO 6:4	368	398	416	405	353	303
HPMC:PEO 4:6	360	377	390	403	420	436
HPMC:PEO 2:8	350	360	375	390	408	415
PEO	355	370	370	390	400	420

Table 2.12: T80 values as a function of polymer composition and sodium chloride concentration in the dissolution medium. T80 is the time for 80% caffeine release from 30% HPMC:PEO matrix tablets with 59.5% MCC. Dissolution medium (pH=1.2). USP apparatus 1, 100 rpm, 900 ml, 37 ± 0.5 °C, Mean (n=3, ±SD).

2.8.4 Discussion and conclusions from the *in vitro* dissolution testing

This section has described *in vitro* dissolution tests of hydrophilic matrices designed with different ratios of HPMC and PEO and containing different fillers.

Lactose, a water soluble filler, will dissolve in contact with the hydration medium. In the tablet, this means the HPMC particle may need to swell to greater extent to fill the void space left by the dissolved lactose. As a result the gel layer may become more diluted and result in a weaker gel layer compared with the less water soluble fillers. These ideas also have already been reported in previous studies [32-34]. The osmotic effect of dissolving lactose may also result in more water penetration into the matrices, further weakening the gel layer. As a result, formulations with lactose as filler provide the fastest drug release.

MCC, a water insoluble filler, provided more extended drug release probably through a higher gel layer strength. MCC plays no role in gelling, but remains in the gel layer during hydration, and is unlikely to create void spaces. The less void spaces also mean less swelling of HPMC and, less water penetration into the system

Starch1500TM is a partially water soluble filler and provides the longest drug release profile. Starch1500TM is a pregelatinized starch, which exhibits more complex behaviour than lactose and MCC, as it contains both a soluble (amylose) and insoluble (amylopectin) polymer components. Levina et al. have reported how 75% of Starch1500TM is composed of amylopectin, which will behave in a similar manner to a water insoluble filler, providing a tortuosity barrier and limiting polymer swelling. The water soluble amylose can potentially interact with each of the hydrophilic polymers in helical inclusion complexes, and increase the viscosity in the hydrated gel layer [35]. The complex chemical make up of Starch1500TM and the potential interaction with hydrophilic polymers may explain why it provided the longest drug release.

Although, changing the filler can influenced drug release profiles, all HPMC matrices could not resist NaCl 0.8M or more no matter which filler was used. Substituting PEO for HPMC in the matrices did increase matrix resistance to NaCl. The results above showed, changing the

HPMC: PEO polymer ratios in the formulations could be a better solution than changing the filler, when design extended hydrophilic matrices resistant to ionic environment.

2.9 Further investigation

From the results above a matrix with a polymer ratio of HPMC:PEO 4:6 appears to achieve an optimal drug release profile with minimal ionic effects over the range of NaCl concentrations studied. However, there are many more questions that need to be asked in order to understand the phenomena observed in this chapter. These include:

- (i) How does PEO provide the matrix less sensitivity to NaCl than HPMC?
- (ii) How do mixed HPMC and PEO polymer matrices provide optimal drug release?
- (iii) How quickly can water penetrate into the hydrophilic matrix, and does the kinetics of water penetration relate to drug release in HPMC, PEO and mixed matrices?
- (iv) What is the early and later gel layer morphology may behave with respect to HPMC and PEO polymer ratios in the various NaCl concentrations?

Experiments were undertaken in chapter 3 to answer some of these questions above.

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Chapter 3

Understanding the Internal Behaviour of HPMC, PEO and HPMC:PEO Hydrophilic Matrices in NaCl Media

3.1 Aims and introduction

The *in vitro* drug release dissolution testing in chapter 2 has shown the hydrophilic matrices with a HPMC:PEO polymer ratio of 4:6 could provide an optimised drug release profile in all NaCl concentrations. The aim of the current study is to better understand why HPMC:PEO blend formulations provide extended drug release with a minimal sensitivity to ionic challenge. This has been investigated by confocal laser scanning microscopy (CLSM), Magnetic resonance imaging (MRI), macroscopic optical imaging and texture analysis. HPMC and PEO matrices with lactose as a filler were chosen for this study.

3.1.1 Confocal laser scanning microscopy

In the mid-1950s, Marvin Minsky developed the basic concept of confocal microscopy. Compared with conventional wide field optical microscopy, a confocal system has the advantages of controlling the depth of field, so that background information from outside the focal plane can be eliminated or reduced, increasing the image resolution. In addition, serial optical sections from thick specimens can be collected from which 3-dimensional reconstructions can be made [1]. There are several types of confocal microscope, but the confocal laser scanning microscope (CLSM) is the main tool that has been developed in our group to investigate the development and structure of the early gel layer in HPMC matrices [2-4].

Figure 3.1 shows the general working of a confocal laser scanning microscope. A laser at the chosen excitation wavelength passes through the light source pinhole aperture, is reflected by the dichromatic mirror, focused by the objective lens and scanned across the specimen in a defined focal plane. The objective lens collects both the reflected light and emitted fluorescence which, filtered by the beam splitter, is reduced to the emitted fluorescence

wavelengths. These pass back through the dichromatic mirror and pinhole aperture to a photo multiplier detector. Out-of-Focus fluorescence emission that arises from above and below the focal plane is not confocal with the pinhole, and cannot pass through. Because very little out-of-focus fluorescence emission contributes to the final image, the resolution of acquired image is increased [1, 5].

3.1.2 Congo red

Congo red (figure 3.2) is an anionic azo dye with a maximum absorption at 497nm in alkaline conditions. It has been used as a biological stain for axons and for cellulose since the 1880s [6]. Wood et al. 1980 had shown how Congo red has a high binding affinity for β 1 $\rightarrow$ 4 linked D-glucopyranosyl sequences which are native to cellulose [7]. Mirza et al. pointed when the cellulose fibres hydrated, the available binding sites were increased, and hence, the binding is increased [8]. Congo red and cellulose binding occurs through electrostatic, hydrophobic interactions and H-bonds between the azo and amino groups of the dye, and the native cellulose chain[9].

3.1.3 Magnetic resonance imaging

Magnetic resonance images (MRI) are generated from the nuclear magnetic resonance (NMR) signal from certain nuclei (e.g. ^1H , ^{19}F , ^{31}P and ^{13}C). When subjected to a radio-wave irradiation and a strong magnetic field, these nuclei which have a net magnetic moment, align with the applied magnetic field. The NMR signal is a small induced voltage in a surrounding tuned coil when the resulting net magnetization precesses and is disturbed from equilibrium. Intrinsically, an NMR signal is very weak, but the signal strength increases with increasing magnetic field and magnetogyric ratio, in this case, the most popular usage of MRI is applied to samples with ^1H nuclei in high concentrations, such as water. MRI used magnetic field gradients to spatially encode the NMR signal [10].

There are two relaxation times (T_1 and T_2) which characterize the return of nuclear magnetization to equilibrium after application of a radio-frequency pulse. T_1 (the spin-lattice relaxation time) is a return to alignment with the polarizing field. T_2 (the spin-spin relaxation time) which is the decay of the NMR signal as relates to the decay of the precessing component of the magnetisation. Mapping the NMR signal of ^1H in water provides us with

an opportunity to identify regions of matrix hydration, as the relaxation times strongly depend upon the local molecular relaxation. The sequence of radio-frequency pulses, the concentration of the target nuclei within the sample and the T_2 relaxation times all influence the MRI image intensity. For example, the higher the molecular mobility is the longer the T_2 relaxation time, free water decays slower than the water bound within a polymer matrix, which provides the ability to map water penetration during matrix hydration [10].

It is difficult to mathematically model drug release from hydrophilic matrices, due to the many simultaneous dynamic processes (e.g. polymer hydration, swelling and erosion) that contribute to the drug release process. For this reason *in-situ* imaging is becoming increasingly utilised. MRI is one such technique that in recent years has become a tool in the pharmaceutical research community to study the internal morphological evolution of ER formulations, and in particular the hydration, swelling and erosion behaviour of hydrophilic matrices [10-15]. HPMC matrices have been often studied by MRI since the first reporting by Rajabi-siahboomi et al. in 1994, but this technique has seldom been applied to hydrophilic matrices comprising other polymers [12, 13, 16-20]. This work is one of the first times MRI has been used to study a mixed polymer system.

3.1.4 Other techniques used in this chapter

CLSM is a technique used to study only the first 15 minutes of hydration, because of the limited penetration of Congo red and unfortunately it was found that MRI was too sensitive to NaCl in solution to be useful. Therefore texture analysis and macroscopic optical imaging were used in this study to understand the effects of NaCl on matrix properties during the later stages of hydration. Texture analysis has been claimed to be a suitable tool for providing information on gel layer strength as previously demonstrated by Fassihi et al. [21-23].

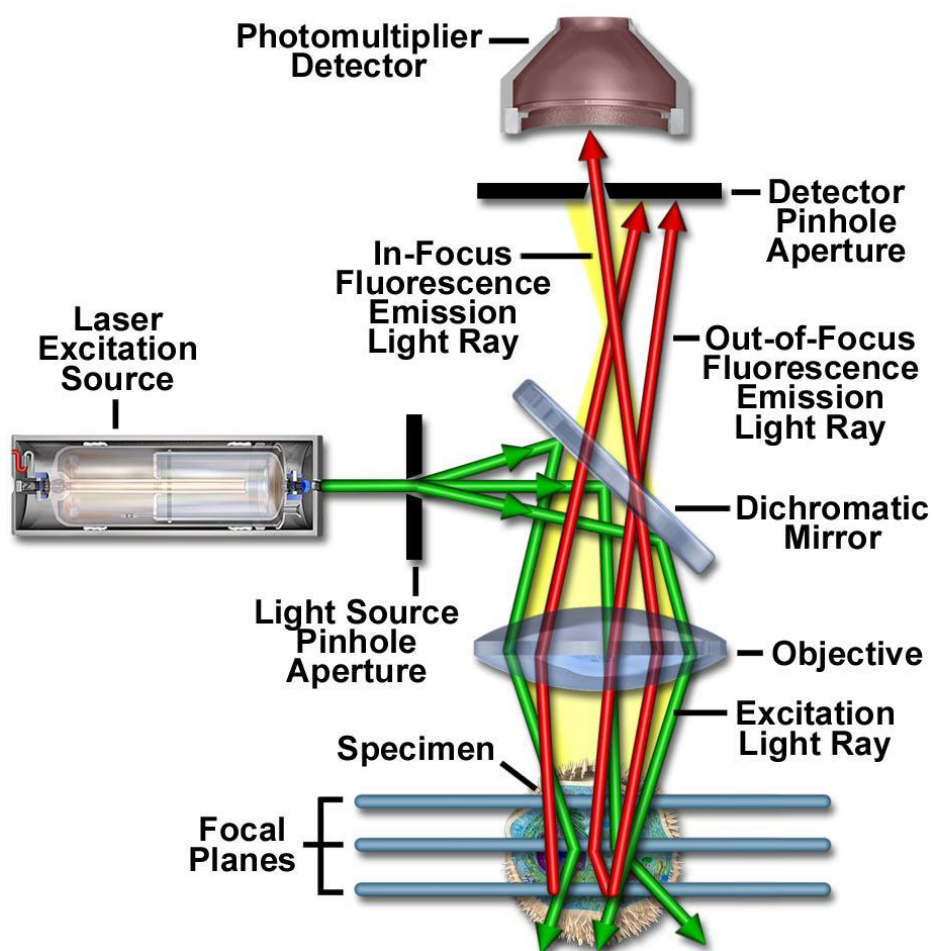


Figure 3.1: Schematic diagram of the light path within a confocal laser scanning microscope[1].

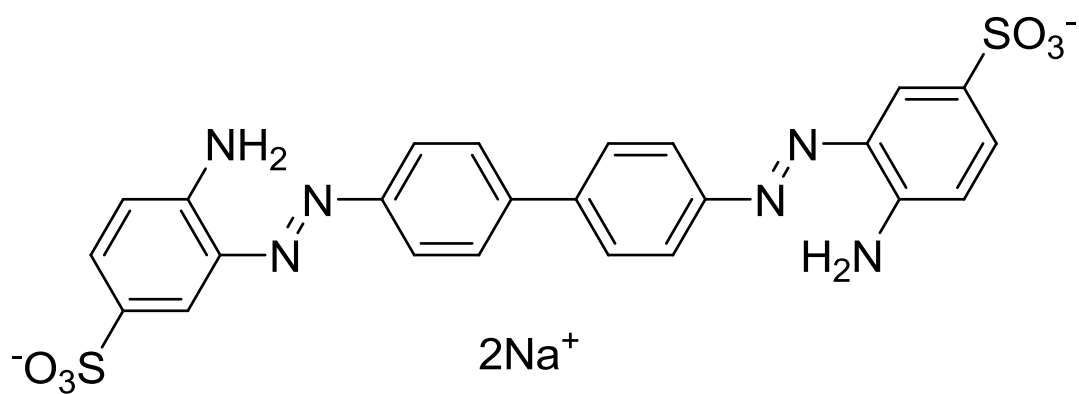


Figure 3.2: The chemical structure of Congo red.

3.2 Materials and methods

3.2.1 Materials

All materials used in this chapter are listed in Appendix 1. The hydrophilic matrices used in this study were the standard formulated tablets described in Chapter 2. They contained HPMC and PEO (total 30%w/w polymer), caffeine anhydrous, lactose and magnesium stearate. Full formulation and tablet manufacturing details are provided in chapter 2 (section 2.5). NaCl solutions were prepared by the method in chapter 2 (section 2.4) and concentrated HCl used to adjust to pH 1.2.

3.2.2 Confocal laser scanning microscopy

Studies of initial gel layer growth at the radial periphery of the tablet matrix were undertaken using a Bio-Rad MRC-600 confocal microscope (Hemel Hempstead, UK) equipped with a 15mW Krypton Argon laser, a Nikon Optiphot upright microscope, and 4x/0.13NA plan air objectives. The experimental geometry is shown in figure 3.3. The tablet was fixed between two Perspex® discs held by three acrylic screws in a Fixed Observational Geometry (FOG) sample cell based on the design of Bettini et al. [24]. The FOG apparatus was placed within a temperature controlled ($37\pm1^{\circ}\text{C}$) vessel and immersed in hydration fluid containing the cellulose active fluorophore (Congo red 0.008% w/v) to identify hydrated regions of HPMC within the gel layer (24). A time series of images were obtained up to 15 minutes, using the Ex488nm line of the Argon ion laser and a BHS filter block with Ex 488/Em >510nm. The fluorescent intensity value of each pixel was coded for fluorescence intensity between 0-255 on a continuous grey-scale. Images were Kalman averaged ($N=3$) to improve the signal-to-noise ratio.

The following microscope settings were found to provide optimum image quality:

- Black level (on a scale of 0-255): 4.9
- Gain (image brightness): 8.9
- Confocal aperture: 2

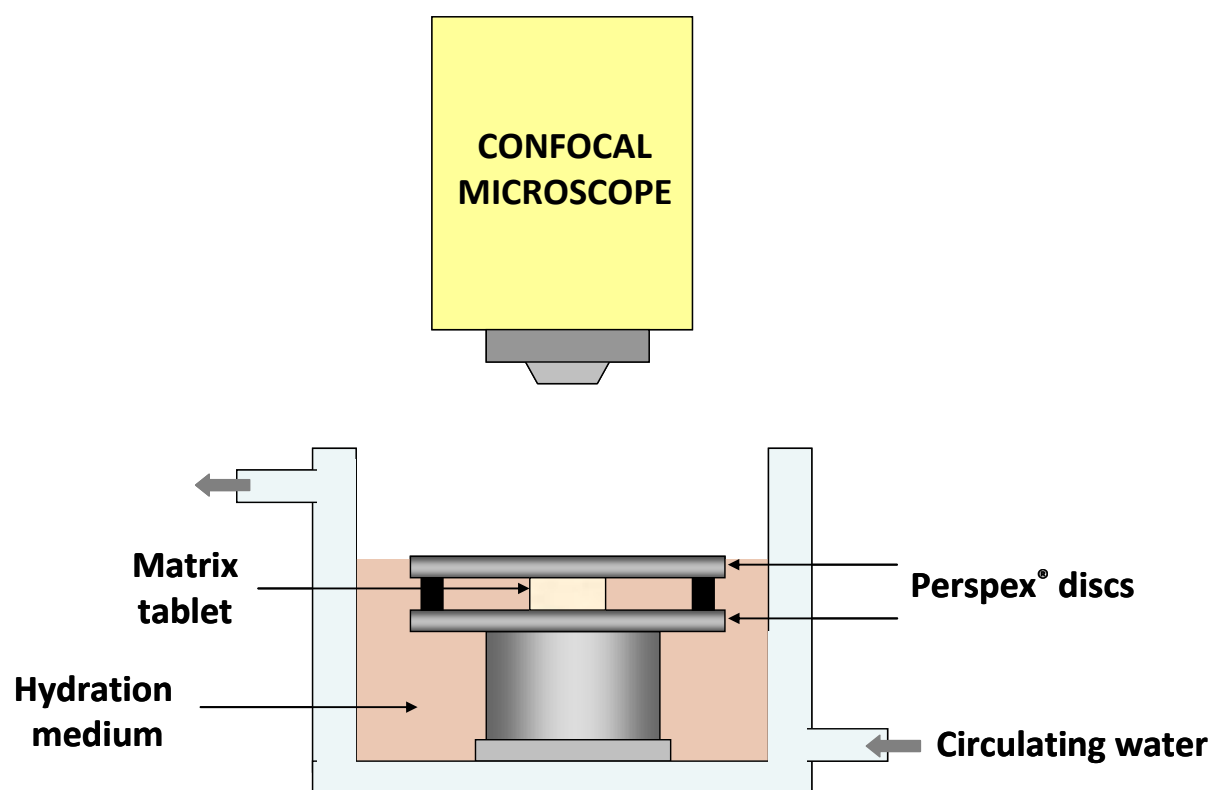


Figure 3.3: Schematic diagram showing the experimental geometry for confocal imaging, $37\pm1^{\circ}\text{C}$.

3.2.3 Magnetic resonance imaging

All experiments were performed on a Bruker AV400 spectrometer with a vertical 9.4 T superconducting magnet and micro imaging facilities. A 25 mm birdcage radio frequency (r.f.) dual resonance coil operating at 400.22 MHz (^1H) was used. The T_2 -pRARE (T_2 -preconditioned Rapid Acquisition with Relaxation Enhancement) pulse sequence was used to acquire quantitative water concentration (C_{wat}) and spin-spin relaxation time (T_2) maps of the dissolving tablet [17, 19, 25]. Water self-diffusivity maps were acquired by applying the standard bipolar gradient stimulated echo diffusion preconditioning sequence prior to the acquisition of the RARE image (D -pRARE) [17, 25].

A schematic diagram of the experimental setup is shown in Figure 3.4. The tablet was placed vertically in the USP-IV dissolution cell, with its cross-section selected as the imaging plane. The dissolution medium used in the experiments was 500 mL adjusted to pH 1.2 using concentrated HCl. Following the method of Zhang et al., a standard USP-IV flow-through dissolution cell (i.d. 22.6 mm) (Sotax, Switzerland) was used for the tablet dissolution study under flowing conditions at 37 °C (32). A peristaltic pump (205S, Watson Marlow, USA) was used in the experiment and the flow rate was set to 8 ml/min. The tablet was placed vertically in the USP-IV dissolution cell, with its cross-section selected as the imaging plane.

The MRI imaging was undertaken by Dr Chen Chen at the Department of Chemical Engineering and Biotechnology, University of Cambridge.

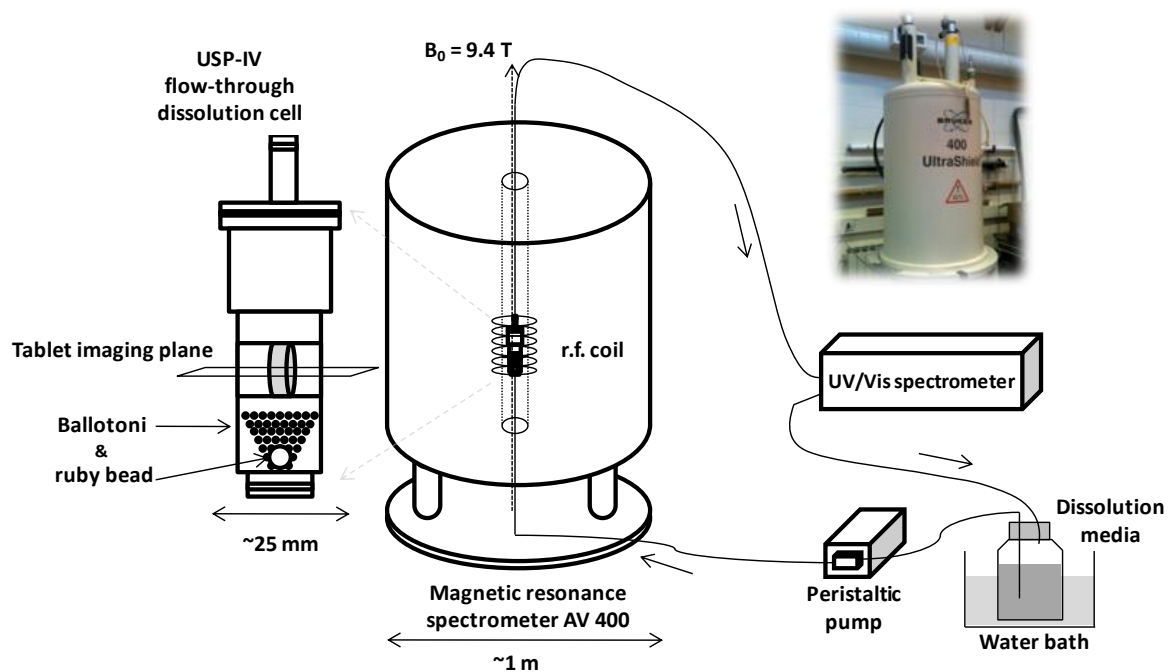


Figure 3.4: Schematic diagram showing the experimental geometry for MRI imaging. The loaded USP-IV flow cell was inserted into spectrometer inside the rf coil. $37 \pm 1^\circ\text{C}$

3.2.4 Texture analysis

Texture analysis was undertaken using a TA. XT. Plus Texture analyser (Texture technologies Corp, Goldalming, The UK) equipped with a 5kg load cell and a 2mm round, flat-tripped steel probe. A tablet was fixed using double sided tape to a 22x22mm glass cover slip, and placed into 900ml media containing NaCl (0M, 0.4M and 1.0M) with a paddle speed of 50rpm to simulate the tablet dissolution process. Tablets were taken from the media and placed under the texture analyser after 0.5, 1, 2, 4, 6 and 8 hours hydration. Data recording was initiated by a trigger force of 0.005N and thereafter the probe penetrated the hydrated gel layer at 0.1mm s^{-1} [22]. Resistance to penetration into gel layer was measured until a maximum force 1N was reached. All measurements were carried out in triplicate. Results were analysed using Texture Expert software (Texture technologies Corp, Goldalming, The UK).

3.2.5 Macroscopic imaging

Tablets that been subject to texture analysis were digitally imaged, images of the hydrated tablets, before and after axial sectioning by cutting with a scalpel, were obtained against a black background, under standardised lighting conditions, using a Cool Snap Pro cf camera (Media CyberneticsTM) fitted with a Nikon AF Micro Nikkor 600 mm macro lens.

3.3 Results and discussions

3.3.1 Confocal microscopy studies of early gel layer growth

A rapidly formed, coherent gel layer is required for effective control of water ingress and ensure extended drug release from a hydrophilic matrix [26]. Studies of early gel layer formation in HPMC, PEO and 4:6 HPMC:PEO matrices were undertaken with respect to NaCl concentration for up to 15 minutes hydration time.

Figures 3.5 shows the results at 15 minutes from an HPMC matrix hydrated in 0M and 0.4M NaCl media containing 0.008% w/v Congo red. These matrices exhibit an uninterrupted high intensity fluorescent boundary at the periphery of the hydrated gel layer. In this region, HPMC is highly hydrated and the polymer is disentangling and dissolving. Congo red can easily access into the gel layer and bind to HPMC, and therefore absorption of the dye is intense [27]. The highly intense fluorescent region only identifies the outer region of the gel layer, but the inner regions of the hydrated gel layer are also identifiable, because the fluorophore has penetrated in the initial phase through capillary channels (24). Bajwa et al. explained the inhomogeneous pattern of Congo red binding as porous channels in the gel layer becoming rapidly blocked by HPMC swelling after the initial capillary of liquid uptake, and the newly formed gel layer then acting as a diffusion barrier [28].

The images show that in 0M and 0.4M NaCl, HPMC matrices formed compact gel layers in this very early stage of hydration. This early gel layer formation morphology reflects the subsequent extended release characteristics in the dissolution test. In 0M and 0.4M of NaCl solution, HPMC matrix can form a coherent gel layer, hence drug release from these formulations in low NaCl solution, is well controlled by polymer swelling, and gel layer formation.

Figure 3.5 also shows the results for an HPMC matrix in 1M NaCl. The extensive penetration of the fluorophore suggests the hydrated layer has little in the way of barrier properties. In very high concentrations of NaCl, HPMC particle swelling is significantly suppressed [28-30], and fluid can therefore penetrate deeply. Without a coherent gel layer diffusion barrier,

these HPMC matrices could not provide extended drug release in the dissolution tests reported in Chapter 2.

Figures 3.6, 3.7, 3.8, and 3.9 show early gel layer formation in the mixed HPMC:PEO matrices. In 0M and 0.4M NaCl, the all matrices had formed a compact gel layer after 15 minutes. However, the gel layer morphology from blended HPMC:PEO matrices appeared to differ in comparison with single HPMC or PEO polymer matrices. HPMC and PEO have different affinities for Congo red, and consequentially can be identified through their different fluorescent intensities. In addition, however, Figure 3.10 shows how PEO also facilitates Congo red transport uniformly into the gel layer.

In the images, HPMC rich regions can be identified by high intensity fluorescence (bright white) and PEO by its less intense fluorescent signal (grey areas). Not surprisingly, the regions of high intensity were not continuous, and it looked like hydrated PEO was filling the intervening areas. The early gel layer in mixed HPMC and PEO matrices is not uniform, possibly because the polymers were immiscible and each formed separate parts of the gel layer.

In the low NaCl media, all the mixed HPMC:PEO matrices formed a compact gel layer formation (and all exhibited extended drug release in the Chapter 2 dissolution tests). In 1M NaCl, the HPMC:PEO (8:2) behaved like an HPMC matrix, figure 3.6 showed with extensive NaCl in the media, the lack control of release seen in dissolution tests is taken as evidence.

Figures 3.7, 3.8, and 3.9 show the confocal images of matrices with a higher PEO content in 1M NaCl. In the 6:4 HPMC:PEO the early gel layer is significantly swollen but the layer gets increasingly more compact with increasing PEO content. In this way the addition of PEO appears to stabilise the gel layer and this could help explain how mixed polymers matrices become more robust to high NaCl in the dissolution tests.

Figure 3.10 shows a PEO matrix hydrated in 0M, 0.4M and 1.0M NaCl after 15 minutes. Unlike the image of the HPMC matrix, there was less fluorescence intensity and no preferential staining of the surface of the PEO hydrated gel layer. This can be explained by

Congo red having a lower binding affinity for PEO. The PEO gel layer was uniformly stained between the periphery and the inner gel layer, which suggests that Congo red can penetrate the PEO gel layer in comparison with an HPMC gel layer. PEO images at different NaCl concentrations did not look significantly different. The gel layer was a continuous and uniform and might be expected to be an effective diffusion barrier.

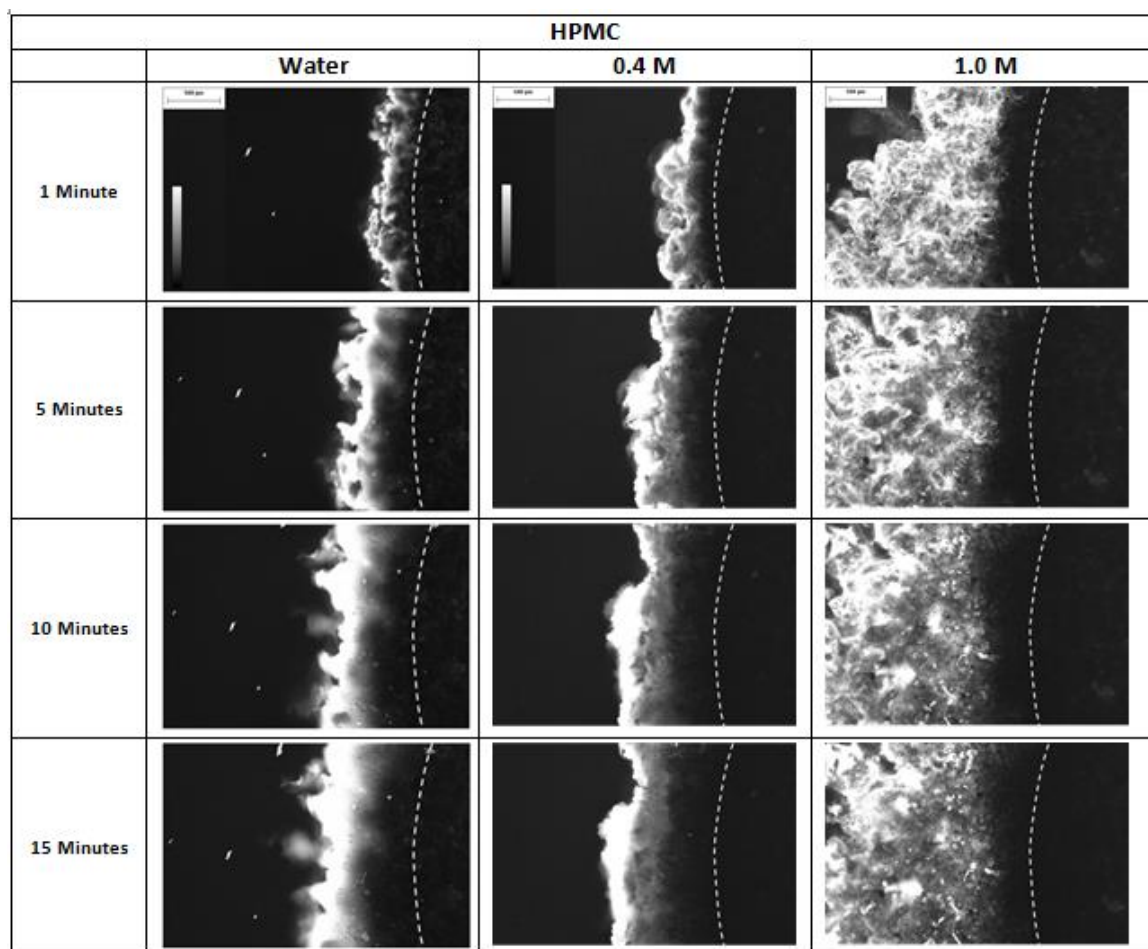


Figure 3.5: HPMC matrices: early gel layer formation. Confocal fluorescence imaging at Ex 488/EmN510 nm. Experiments conducted at 37 ± 1 °C using NaCl media containing 0.008% w/v Congo red as a visualisation aid. Images coded for fluorescence intensity using a continuous grayscale (White highest, black lowest). Scale bar 500 μ m.

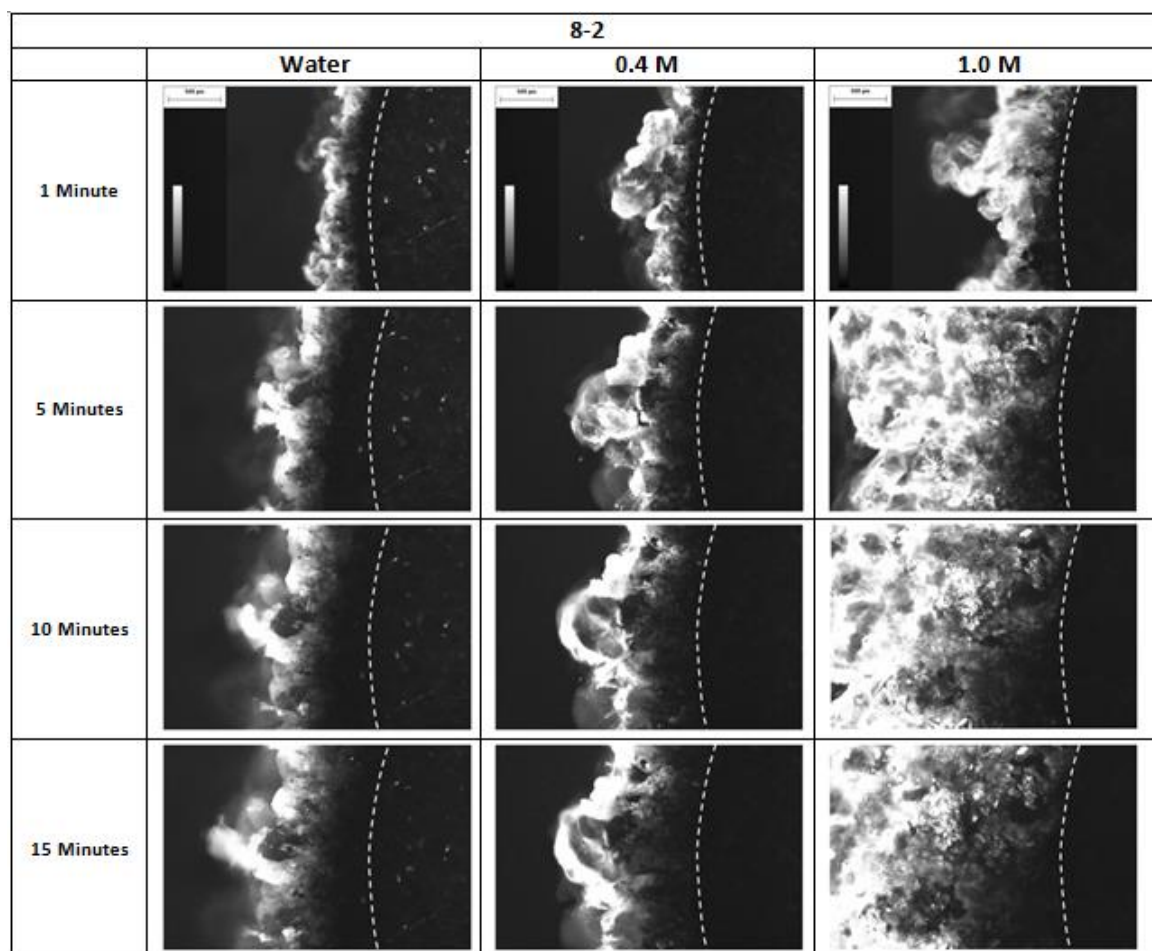


Figure 3.6: HPMC:PEO 8:2 matrices: early gel layer formation. Confocal fluorescence imaging at Ex 488/EmN510 nm. Experiments conducted at 37 ± 1 °C using NaCl media containing 0.008% w/v Congo red as a visualisation aid. Images coded for fluorescence intensity using a continuous grayscale (White highest, black lowest). Scale bar 500 μ m.

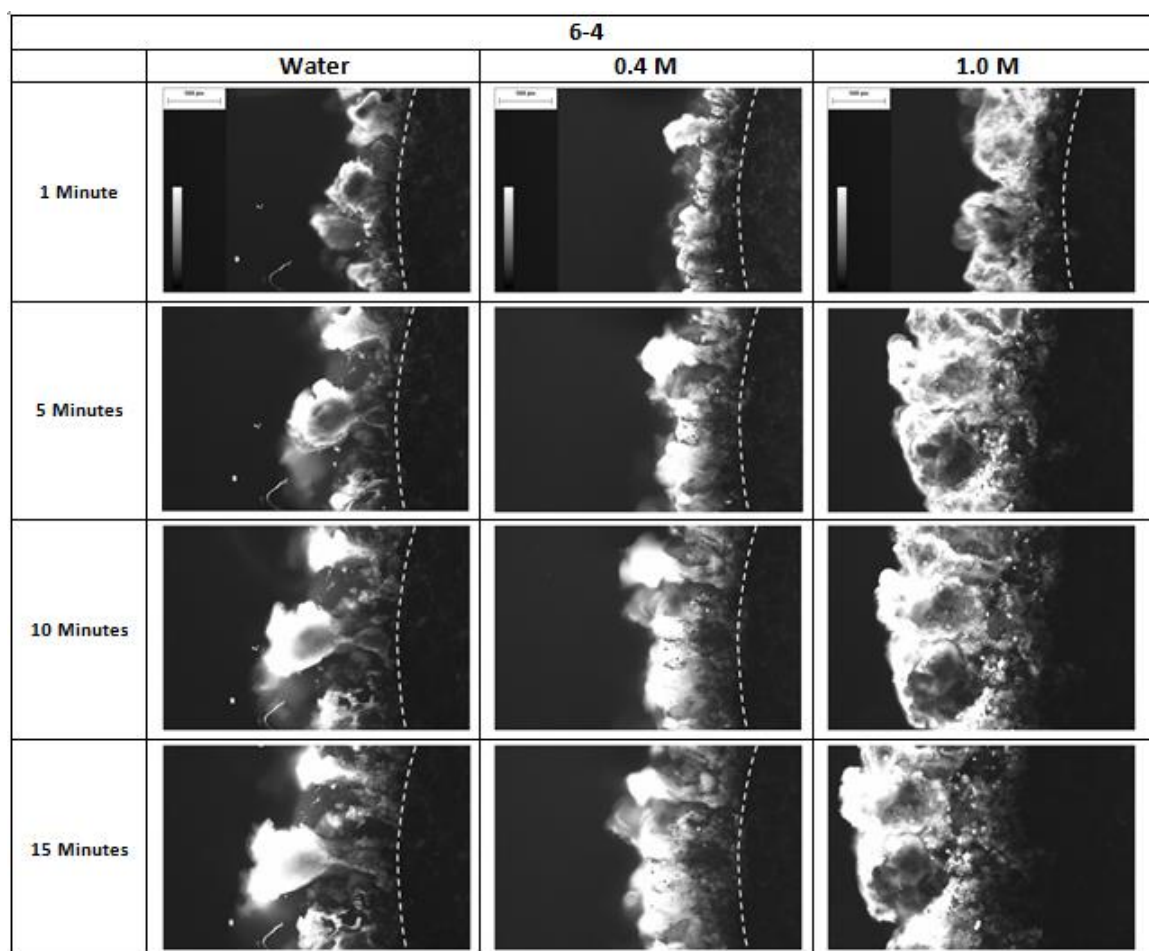


Figure 3.7: HPMC:PEO 6:4 matrices: early gel layer formation. Confocal fluorescence imaging at Ex 488/EmN510 nm. Experiments conducted at 37 ± 1 °C using NaCl media containing 0.008% w/v Congo red as a visualisation aid. Images coded for fluorescence intensity using a continuous grayscale (White highest, black lowest). Scale bar 500 μm .

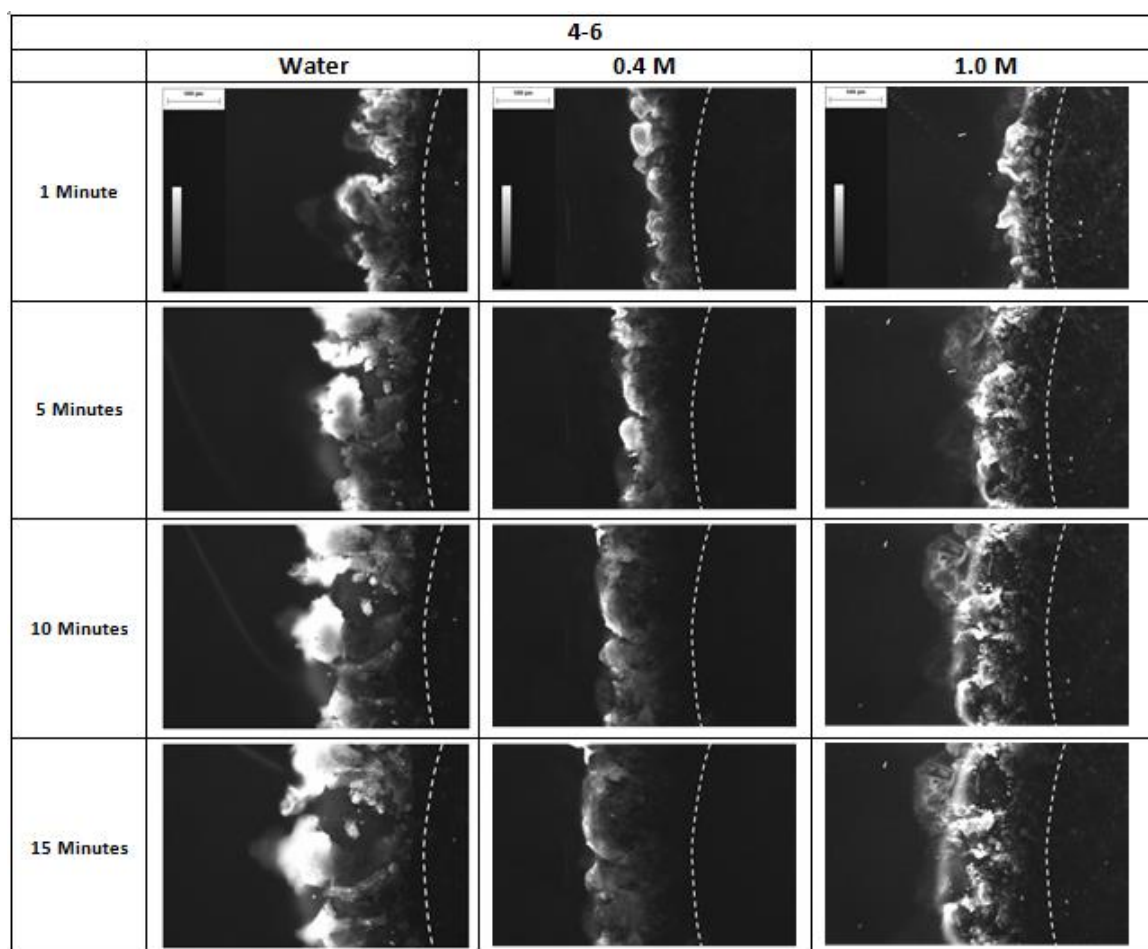


Figure 3.8: HPMC:PEO 4:6 matrices: early gel layer formation. Confocal fluorescence imaging at Ex 488/EmN510 nm. Experiments conducted at 37 ± 1 °C using NaCl media containing 0.008% w/v Congo red as a visualisation aid. Images coded for fluorescence intensity using a continuous grayscale (White highest, black lowest). Scale bar 500 μ m.

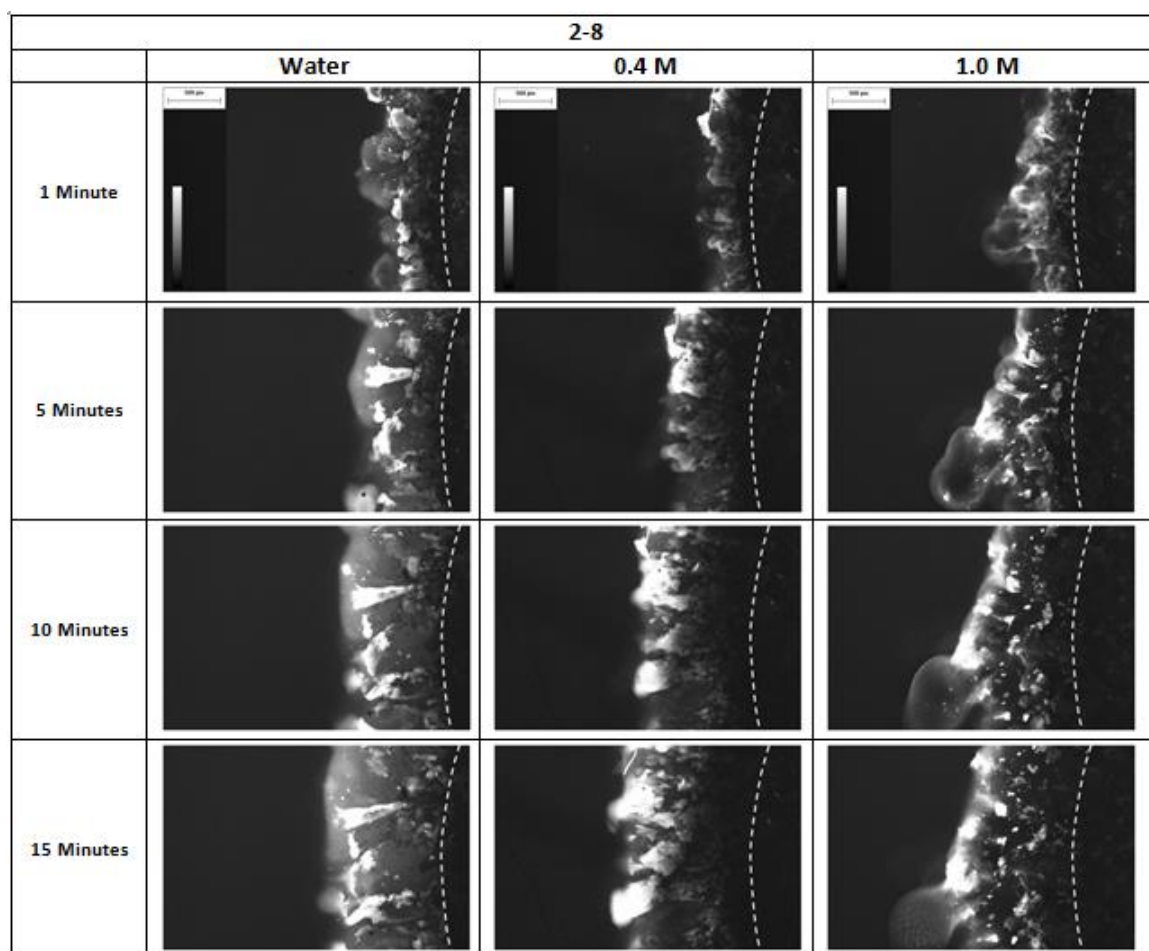


Figure 3.9: HPMC:PEO 2:8 matrices: early gel layer formation. Confocal fluorescence imaging at Ex 488/EmN510 nm. Experiments conducted at 37 ± 1 °C using NaCl media containing 0.008% w/v Congo red as a visualisation aid. Images coded for fluorescence intensity using a continuous grayscale (White highest, black lowest). Scale bar 500 μ m.

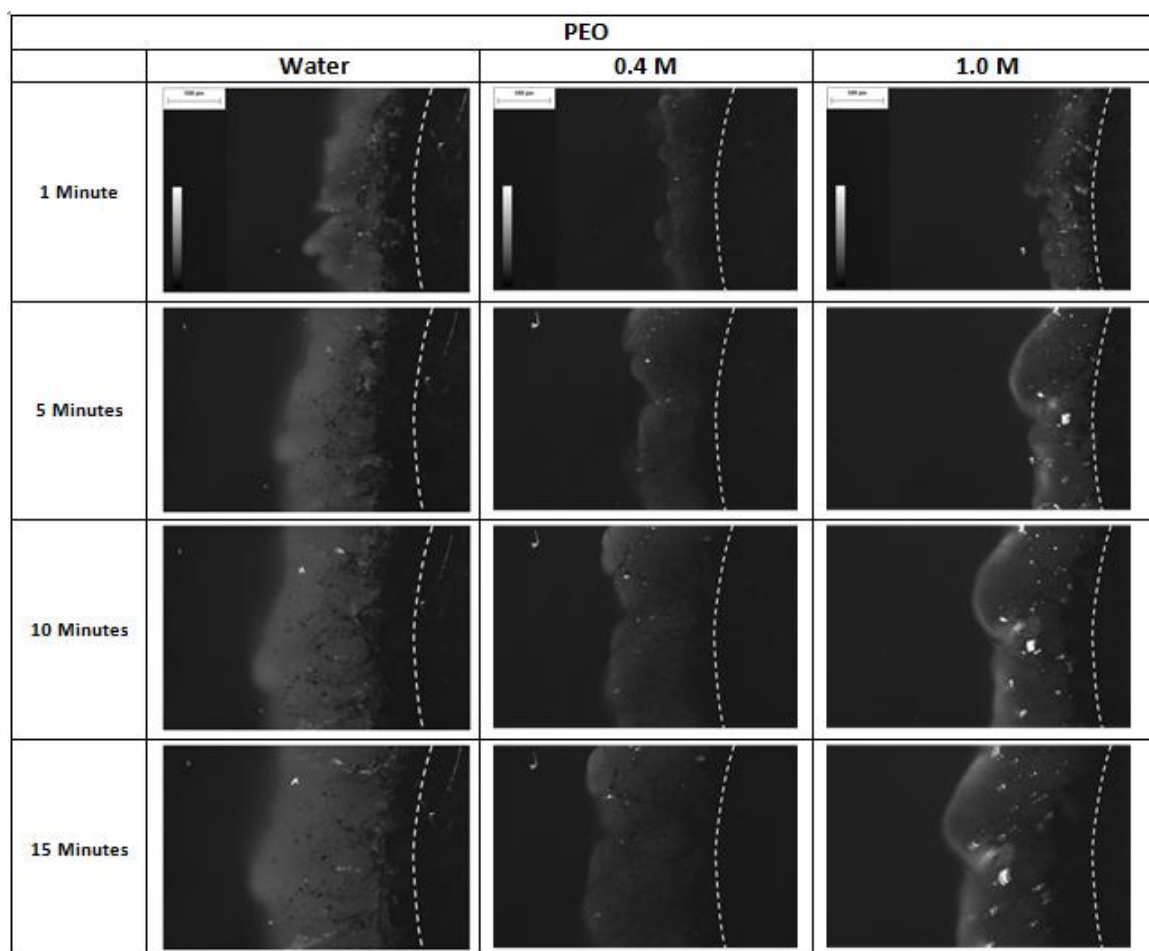


Figure 3.10: PEO matrices: early gel layer formation of time. Confocal fluorescence imaging at Ex 488/EmN510 nm. Experiments conducted at 37 ± 1 °C using NaCl media containing 0.008% w/v Congo red as a visualisation aid. Images coded for fluorescence intensity using a continuous grayscale (White highest, black lowest). Scale bar 500 μm .

3.3.2 MRI studies of internal matrix hydration at later hydration times

T_2 relaxation time maps were used to compare the swelling and internal hydration behaviour of single and mixed polymer matrices, up to 9 hours. Figure 3.11 shows axial cross-sectional images obtained for HPMC, HPMC:PEO 4:6, and PEO matrices, spatially resolved and colour-coded for T_2 . These provide a series of semi-quantitative visual maps which show the progression of hydration within each matrix type. It is reasonable to assume that the regions coded black (where the T_2 relaxation is short) relates to the driest region: the unhydrated dry core.

The images show that the rate and extent of water ingress appears to be substantially different in matrices containing HPMC and PEO. The top row of images in figure 3.11 shows that the HPMC matrix:

- (i) Adopted a swollen dumb-bell shape in the early stages of hydration.
- (ii) Showed early-stage axial swelling (the horizontal direction).
- (iii) Showed a relatively slow progression of internal hydration.
- (iv) Retained its shape after 9 hours, leaving a substantial hydrated mass of gelled polymer at the end of the experiment.

This is typical behaviour of HPMC-based matrices [17]. The early dumb-bell shape and axial swelling are thought to result from uniaxial relaxation of stored elastic compression forces [10].

The bottom row of images in Figure 3.11 shows the behaviour of a PEO matrix. This showed:

- (i) Less dimensional change during the first hour of hydration.
- (ii) That swelling occurring isotopically (in both axial and radial directions).
- (iii) A more rapid ingress of water into the matrix.
- (iv) Complete matrix dissolution at 9 hours.

The PEO grade used in this study has a higher average molecular weight (7×10^6 Da) than the HPMC. However, any molecular weight enhancement of gel layer viscosity and gel strength appears to be offset by differences in polymer water affinity. In HPMC we might expect slower hydration in relation to PEO, arises from the partially hydrophobic nature of

polymer substitution: Methocel K100M HPMC (USP type 2208) has 22% methoxy substitution whereas PEO has none. This aspect is sometimes ignored when comparing the performance of chemically different polymers in HPMC matrices [31]. The high water affinity of PEO is well known, and is exploited in its use as an osmotic agent in osmotic pump dosage forms [32].

MRI images of the mixed polymer matrix (Figure 3.11, middle row) show hydration behaviour which is intermediate between HPMC and PEO:

- (i) Reduced axial swelling in comparison to the HPMC matrix
- (ii) A reduced rate of water ingress with respect to the PEO matrix
- (iii) Matrix integrity is retained at 9 hrs.

Although HPMC is the minority polymer, over the whole timescale the hydration development of the 4:6 polymer matrices appears visually more similar to the HPMC matrix rather than the PEO matrix.

These characteristics could be useful when formulating new hydrophilic matrices. For example, the MRI images show that substitution HPMC for PEO matrices slow water penetration, and improve matrix integrity at later hydration times. At 9 hours, the PEO matrix has eroded completely, whereas the mixed polymer formulation retains some shape. This may give the matrix a greater longevity.

0M NaCl media was used in the MRI experiments because the 25 mm birdcage r.f. coil used cannot be properly tuned to a working frequency, as a result of the dielectric influence from the NaCl. Therefore additional techniques were required to investigate the longer term HPMC and PEO matrix behaviour in different NaCl media. These are described below.

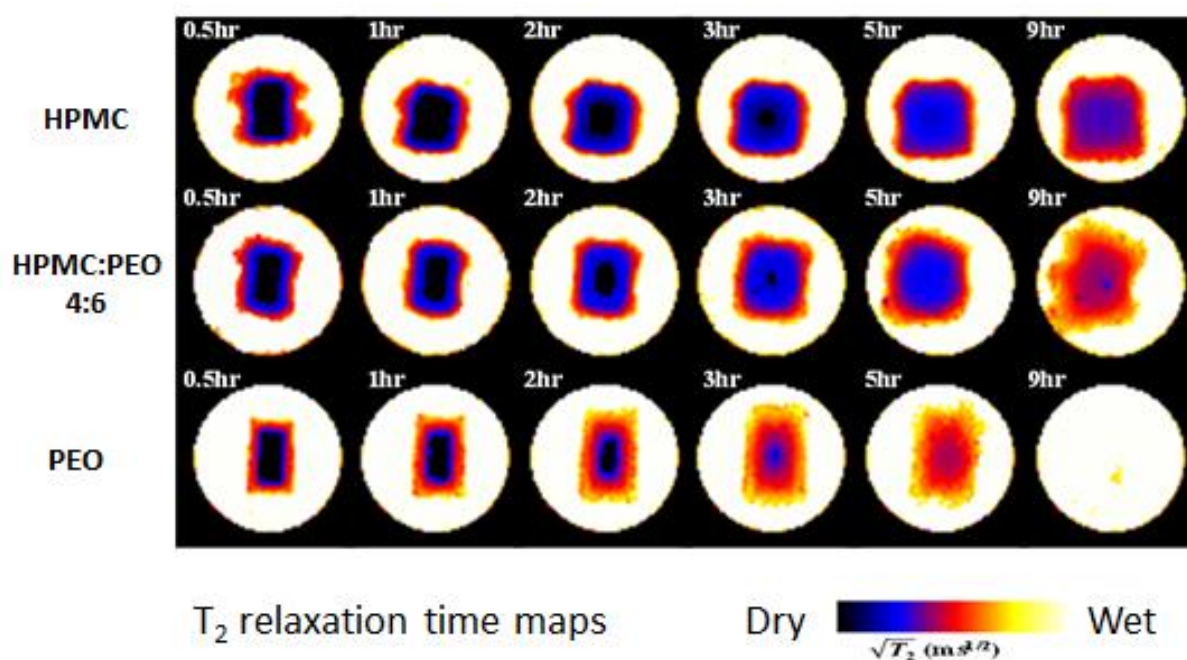


Figure 3.11 MRI images of matrix hydration over 9 hours. T_2 relaxation time maps of HPMC, HPMC:PEO 4:6 and PEO hydrophilic matrices in USP-IV dissolution cell in 500 ml water (pH 1.2). Each image is 25mm. Colour coding for T_2 is shown in the colour bar. Matrices are standard formulated tablets as described in Chapter 2.

3.3.3 Texture analysis and macroscopic optical imaging of matrix hydration

3.3.3.1 Matrices hydrating in 0M and 0.4M NaCl.

Figures 3.12A and 3.13A show representative force-displacement profiles from the texture analysis penetrometry studies in 0M and 0.4M NaCl. The graph shows the matrices hydrating in water for up to 8 hours. To confirm our interpretation of the texture analysis profiles, digital images of the whole matrix ('macroscopic optical imaging') were then taken. These are shown in figures 3.12B and 3.13B.

Fassihi etc. has defined the force-displacement textural profile with respect to force transition regions in a swollen matrix gel layer [21-23]. The penetrometry profiles in figures 3.12A and 3.13A start at the point that the probe detects gel strength (0.005 N) and the resistance to penetration is then measured by the probe as a function of the depth of probe penetration. The profile can be used to identify the strength of the hydrated matrix swollen gel layer.

In the early stages, after 1 hour hydration, all three matrices showed high resistance to penetration, as seen by the small distance travelled by probe and the dramatic gradient increase thereafter. This is consistent with a limited penetration of the water front into the tablet and formation of a thin gel layer. Profiles at later hydration times demonstrate a thicker gel layer and a weaker core resulting from (i) deeper penetration of the water front and (ii) the core weakening under the influence of water vapour penetration and elastic stress release. Penetrometry profiles at 4 and 8 hours suggest that the matrix has lost much of its strength, probably becoming a low strength gel mass with little core.

PEO matrices exhibited the fastest gel layer growth, but the least gradient. This suggests weaker gel layer strength under texture analysis, and identifies PEO matrices as having the greatest polymer chain disentanglement, and thickest gel layer formation in these media.

HPMC and the blended HPMC:PEO matrices showed less gel layer formation and higher gradients in the first hour of hydration. Profiles for the mixed polymer matrix show that

substituting HPMC for PEO in the matrix appeared to result in less water penetration and a stronger gel.

The swelling rate at the water penetration front and the erosion rate at the outer surface of the gel layer are the two factors in the growth of the gel layer. Figures 3.12A and 3.13A show how HPMC matrices swelling rate is greater than the erosional rate up to 8 hours hydration, as the hydrated gel layer is seen to increase in thickness and reach a maximum at 8 hours. However, maximum gel layer thickness for the PEO and HPMC:PEO matrices occurred at 4 hours. This suggests that, at about 4 hours' hydration, in the PEO and the mixed HPMC:PEO matrices the polymer concentration has reached a threshold value and the erosion rate becomes dominant.

Figures 3.12B and 3.13B provide the optical images to support the results from figures 3.12A and 3.13A. In 0M and 0.4M NaCl, all three matrices show a hydrated outer gel layer and a dry (or less hydrated) inner core in the first hydration hour. This supports the conclusion that the texture analysis probe only penetrated a short distance into the gel layer before contacting the dry core.

After 4 hours, all the matrices show a greater hydrated gel layer and less dry core, corresponding with the texture analysis probe penetrating further into the gel layer. At this stage all matrices have a well-established gel layer of similar thickness and the predominant drug release mechanism would be diffusion through the gel layer.

After 8 hours hydration time, the dominant mechanism at this stage is probably gel layer erosion because the remaining matrices were different in size (The rank order was HPMC > HPMC: PEO (4:6) > PEO) and the PEO matrix had either eroded or dissolved in the media. It suggests different formulations suffer different degrees of erosion because of their hydrated polymer properties. Figures 3.12B and 3.13B show a substantial matrix shaped gel, and therefore drug still needs to diffuse through the HPMC matrix gel layer to be released into the medium. However, the most of drug released from PEO may be through erosion between 4 to 8 hours hydration as the PEO matrix is small and weak as in the images it has collapsed. The HPMC: PEO (4:6) matrix retained a stronger gel than the PEO matrix at 8

hours. This suggested that, in substituting HPMC for PEO, erosion of the fully hydrated matrix can be reduced, this may explain why blended HPMC:PEO matrices provided longer drug release than a PEO matrix in the 0M NaCl.

3.3.3.2 Matrices hydrating in 1.0M NaCl.

Figures 3.14A and 3.14B show the texture analysis results and digital images of the three formulations. As shown in the confocal study, HPMC cannot form a coherent gel layer diffusion barrier in 1.0M NaCl, in the first 15 minutes, and hence it was not surprising that in figure 3.14A and 3.14B, the matrix had fully eroded by 1 hour. The PEO and blended HPMC: PEO 4:6 matrices however showed similar results to those seen at lower NaCl concentrations. As PEO is less sensitive to NaCl than HPMC, the presence of PEO in the matrix made it physically resistant in to 1.0M NaCl media. In the dissolution tests these provided matrices provided extended release, and the HPMC:PEO matrix gave longer drug release than the PEO matrix.

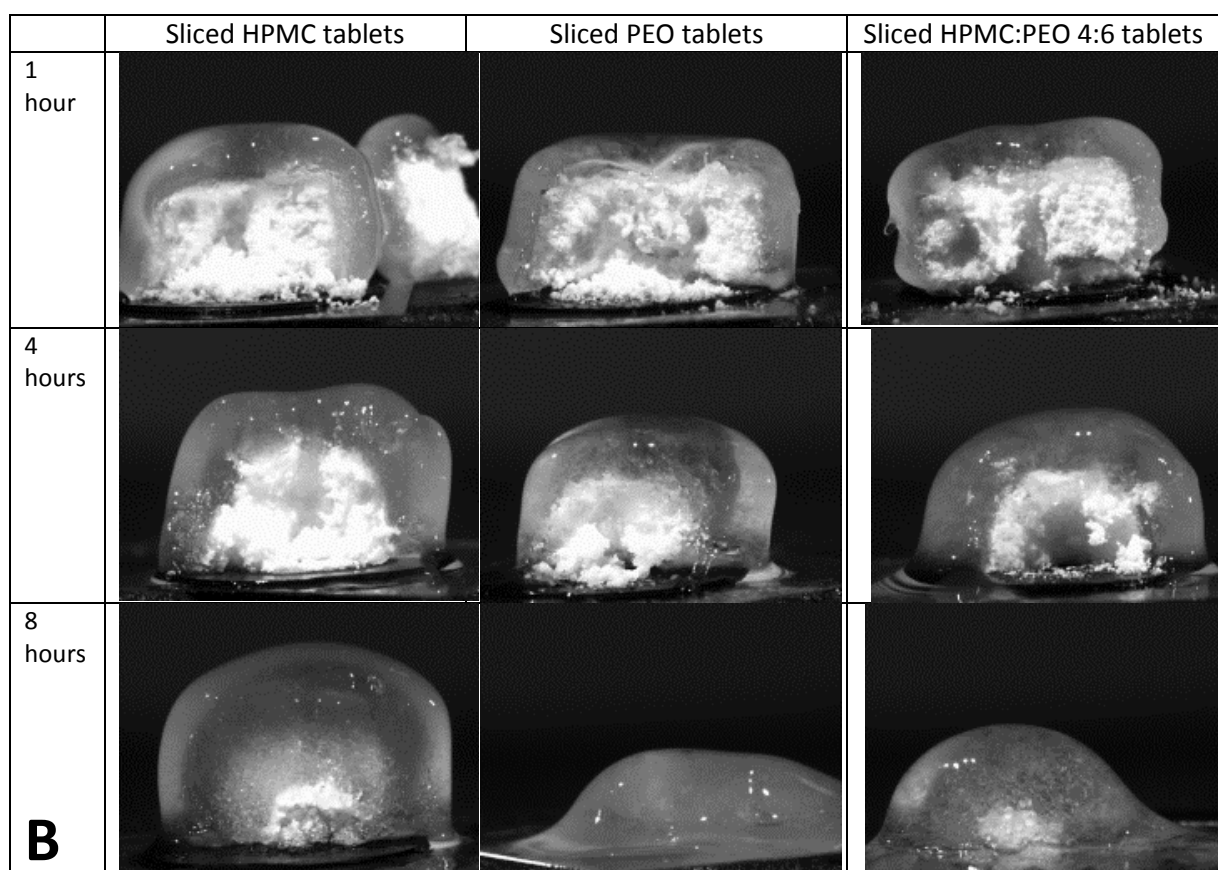
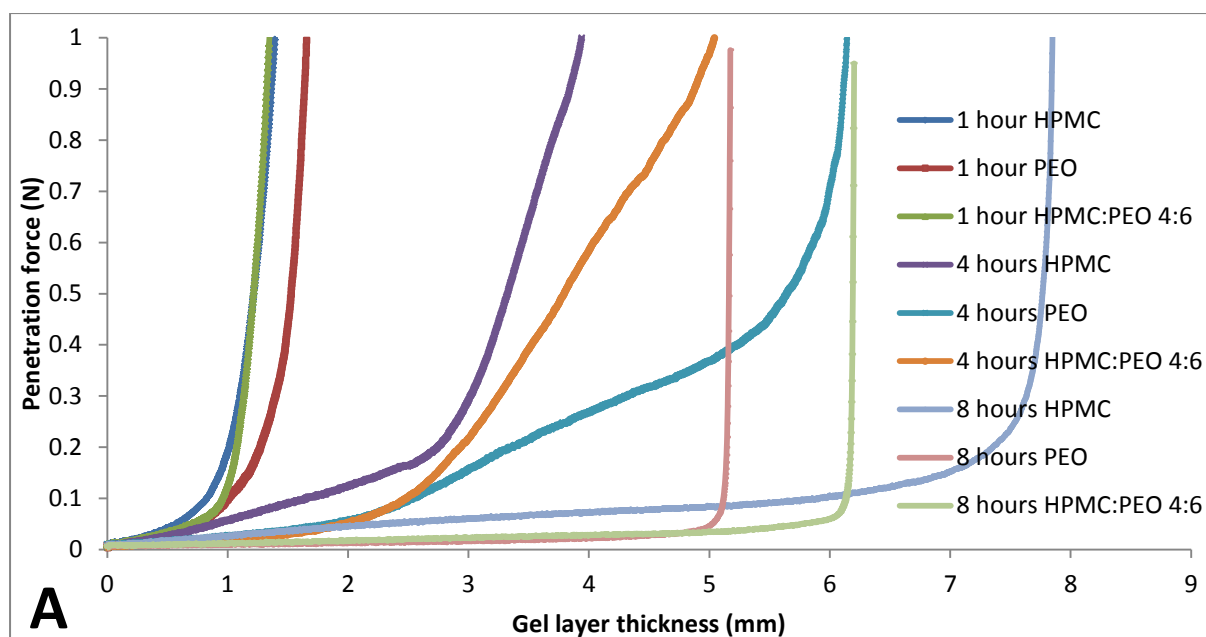


Figure 3.12: Gel layer behaviour in HPMC and PEO matrices in 0M NaCl after 8 hours. Experiments conducted at 37 ± 1 °C, pH 1.2.

A: Representative force-displacement and gel layer growth profiles for hydrophilic matrices in 0M with respect to time.

B: Macro images of 8 hours hydrated sliced HPMC and PEO matrices images in 0M NaCl

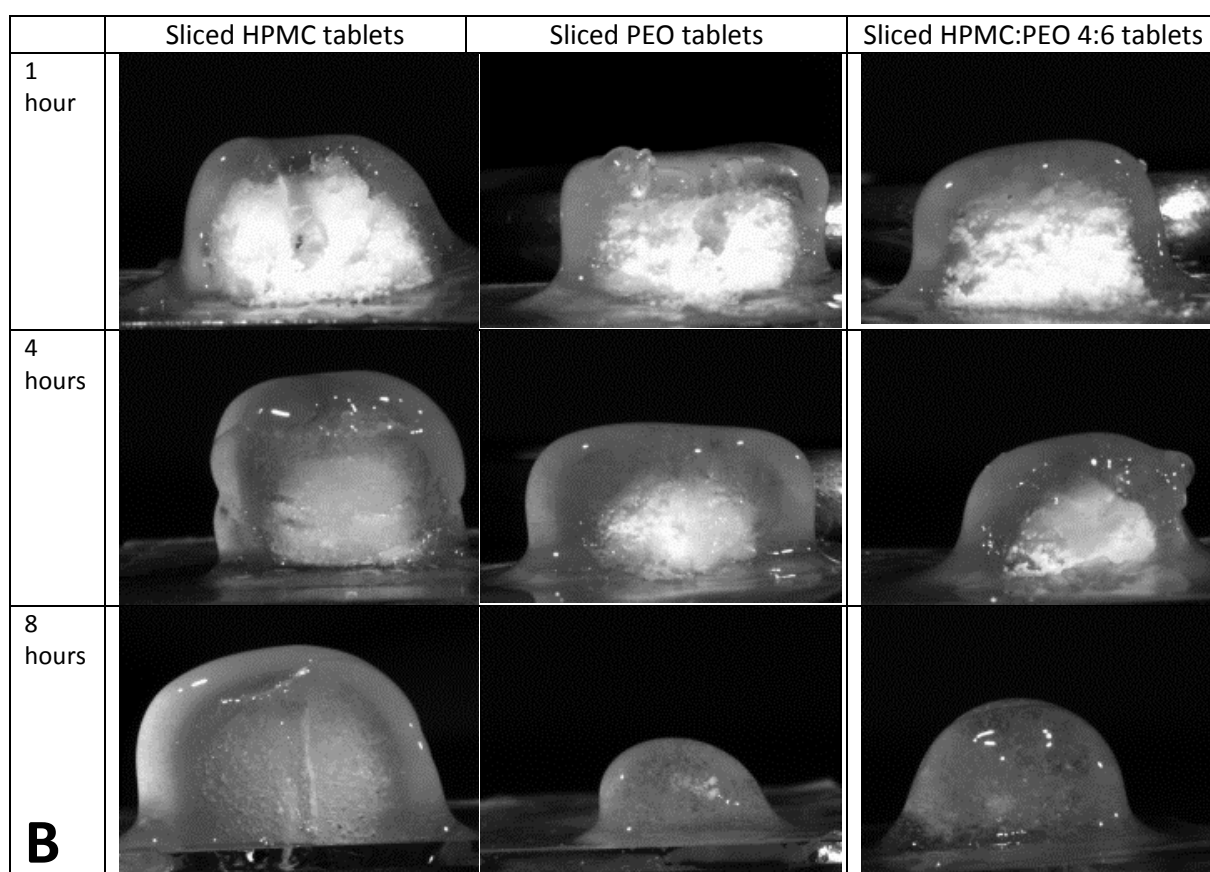
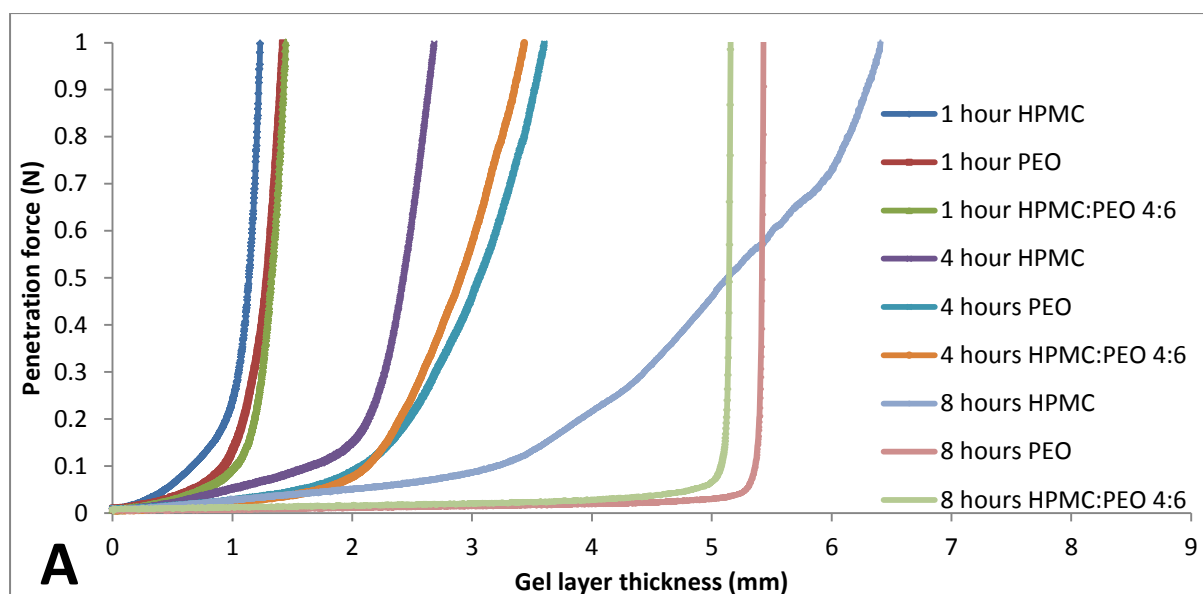


Figure 3.13: Gel layer behaviour in HPMC and PEO matrices in 0.4M NaCl after 8 hours. Experiments conducted at 37 ± 1 °C, pH 1.2.

A: Representative force-displacement and gel layer growth profiles for hydrophilic matrices in 0.4M with respect to time.

B: Macro images of 8 hours hydrated sliced HPMC and PEO matrices images in 0.4M NaCl

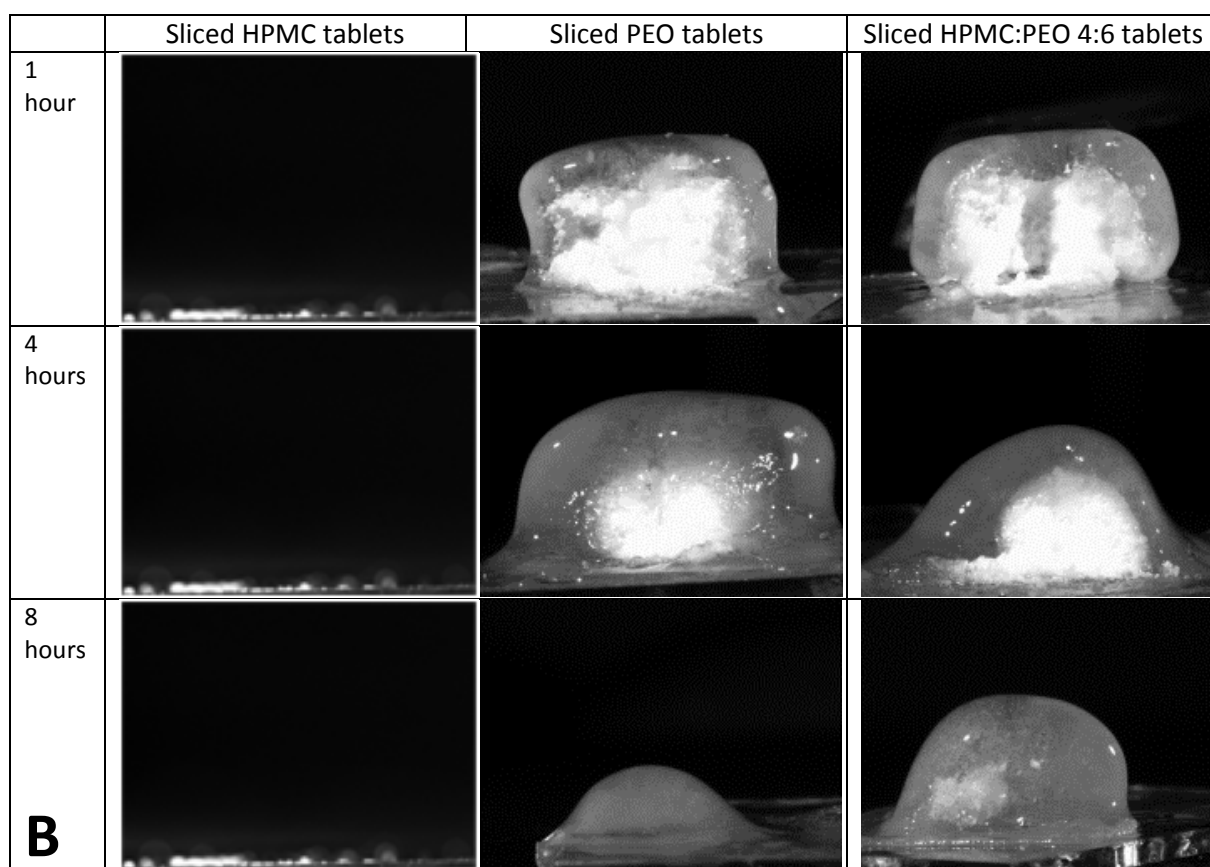
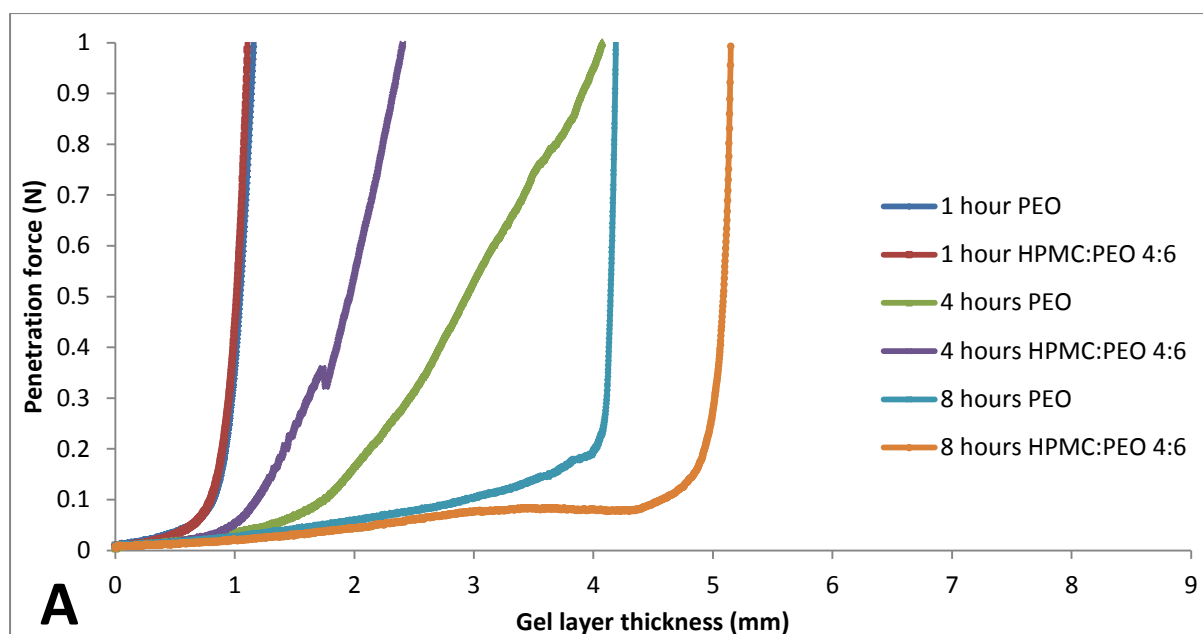


Figure 3.14: Gel layer behaviour in HPMC and PEO matrices in 1.0M NaCl after 8 hours. Experiments conducted at 37 ± 1 °C, pH 1.2.

A: Representative force-displacement and gel layer growth profiles for hydrophilic matrices in 1.0M with respect to time.

B: Macro images of 8 hours hydrated sliced HPMC and PEO matrices images in 1.0M NaCl

3.4 Conclusions

Confocal microscopy provided evidence that HPMC based matrices are significantly affected by high concentrations of NaCl but gel layer formation in mixed polymer matrices with HPMC:PEO 6:4, 4:6, 2:8 were not significantly affected by NaCl concentration. Confocal microscopy images also suggested early gel layer formation may be one of the key factors in establishing extended drug release in hydrophilic matrices. If the hydrated matrices can form a compact gel layer in the early stage, the diffusion barrier will be able to retard water penetration and drug release from the matrices. This confirms previous work with HPMC matrices [28-30].

In low concentrations of NaCl, MRI images, texture analysis, and the macroscopic optical imaging demonstrate that HPMC matrices may possess stronger gel layers, and have a slower rate of water penetration, than into PEO matrices. This would explain why HPMC matrices provided the longest extended drug release in Chapter 2. However, PEO is not sensitive to the ionic strength in the solution and the hydration and swelling behaviour of the matrix are similar in all NaCl media. The mixed HPMC:PEO matrix (4:6) was immune to an ionic challenge up to 1.0M as well and represents a compromise between the best properties of both polymers. It provided a stronger gel layer and a longer release profile, without being significantly affected by the concentration of NaCl.

The extent that NaCl concentration can affect HPMC and PEO swelling and how this relates gel layer behaviours and morphology in mixed matrices are not fully understood. In the next two chapters (chapters 4 and 5), there will be investigation of (i) HPMC and PEO particles swelling, (ii) the polymer solution miscibility, and (iii) binary matrices in their early and later gel layer morphology. In this way the study hopes to provide more evidences why mixed polymer HPMC and PEO matrices, can bring the advantages of both polymers together to provide the optimal drug release with less ionic sensitivity.

3.5 References

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CHAPTER 4

Particle Swelling and Dilute Solution Behaviour of Single and Mixed HPMC:PEO Systems

4.1 Aims and Rationale

This chapter aims to provide insights into the results of Chapter 3 and provide a background for Chapter 5. Chapter 3 showed that the HPMC:PEO polymer ratio was a key factor influencing matrix release profile in ionic environments and that whilst single polymer HPMC matrices had limitations, the blended HPMC and PEO matrices could provide extended drug release over the full concentration range of NaCl studied in the dissolution tests. In order to understand how polymer behaviour might influence the gel layer, a two-pronged approach was adopted. To understand the hydration behaviour of mixed HPMC and PEO matrices in the presence of NaCl, the swelling behaviour of individual polymer particles was studied. Then, the phase behaviour of mixed solutions was studied by rheological methods and phase contrast microscopy to examine if the two polymers were miscible in solution, and therefore potentially within a hydrated the gel layer.

4.2 Introduction

4.2.1 HPMC and PEO particle swelling

In the previous study, HPMC matrices failed to form a compact and coherent gel layer, which showed burst drug release in 0.8M NaCl and above. This has been previously reported as resulting from the formation of a gel layer with a high porosity to water, possibly due to the inhibition of polymer particle swelling [1-3].

The importance of rapid polymer particle swelling during gel layer formation can be understood as follows. When exposed to an aqueous environment, water is adsorbed by the macromolecular chains leading to a swelling of the hydrated network until a quasi-

equilibrium state of hydration and network structure is reached. This three-dimensional network structure is stabilised by physical chain entanglements, hydrogen bonds, tie junctions, or tie points [4, 5]. Sodium chloride in the hydrating medium may result in the slowing of HPMC particle swelling reducing the ability of the hydrophilic polymer chains to hydrate [3]. There is a threshold concentration of inorganic ions where this allows sufficient water ingress to disrupt the formation of the gel layer, and there is also evidence to suggest that the coalescence (sticking together) of hydrated particles may be also inhibited [3]. If this protective gel layer fails to form, there is continued water ingress into the matrix core, and a failure of the matrices to provide extended release. Particle swelling experiments will therefore support our understanding of how NaCl concentration affects the early development of the gel layer diffusion barrier. Individual particle swelling experiments can be conveniently carried out using the Microscope Slide Positioning System (MSPS) described by Wong [6].

4.2.2 Phase behaviour of HPMC: PEO binary solutions

Chapter 3 has shown how the use of mixed polymers can provide more desirable matrix drug release profiles. The blending of polymers is common, and is often undertaken to reduce costs, improve processing and maximize important polymer properties [7-9]. However, mixing polymers in solution can result in miscible or immiscible systems that show phase separation. This can take the form of a polymer-polymer precipitate in a polymer depleted environment, or the formation of two distinct phases with different polymer being enriched in each of the two phases. The microstructure of such two-phase aqueous mixtures often resembles that of a classical emulsion: a dispersion of droplets in a continuum [10].

In this section the phase behaviour of HPMC:PEO mixtures is examined. The miscibility of binary mixtures of low viscosity HPMC and PEO has been studied by others [7, 11, 12], and it has been reported when HPMC is predominant in the mixture, the two polymers are miscible in dilute solution. However, there appears to be little evidence in the published literature for the miscibility of high viscosity HPMC and PEO grades used in extended drug release.

Whether two polymers in solution are miscible or immiscible is governed by the Gibbs Free Energy of mixing (ΔG) as given by equation 4.1:

$$\Delta G = \Delta H_m - T\Delta S_m$$

Equation 4.1

ΔS_m is the entropy factor and is a measurement of disorder or randomness. ΔH_m is the heat that is either consumed (endothermic) or generated (exothermic) during mixing.

Hydrogen bonding, dipole-dipole, and ionic interactions are the most common specific interaction found in polymer blends and in the presence of strong specific interactions between polymers, mixing is exothermic and a homogeneous one phase system results, i.e., the polymers are miscible. In the case of high molecular weight polymers however, the combinatorial entropy of the two polymers is quite small. Thus, the usual source of free energy as a driving force for mixing is virtually absent. For this reason, two high molecular weight polymers will rarely be miscible [13].

To establish the phase behaviour, microscopy is often the first approach. However, direct microscopic observation by standard light microscopy often proves to be challenging because of the limited optical contrast of the two phases and because of the small scale of the microstructure to be discriminated. Another classical method to evaluate presence or absence of phase separation is to centrifuge the mixtures at high speed and observe the formation of a precipitate phase or two liquid phases but this method is not applicable if the density differences are small. Some preliminary centrifugation trials using dilute HPMC:PEO mixtures in this study provided no clear conclusions with respect to phase separation. Thus, a rheological approach was chosen to study the phase behaviour of HPMC:PEO mixtures in combination with phase contrast microscopy which was applied to more concentrated mixtures.

4.2.3 Rheological assessment of the aqueous phase behaviour of HPMC:PEO solutions at 1% w/v total polymer

Dynamic oscillatory rheology was undertaken to determine the viscoelastic properties of HPMC:PEO mixtures in dilute solution. This has been used previously in studies of polymer miscibility in binary polymer solutions [8, 14-16]. The measurement of dynamic viscoelastic properties depends on separating sample behaviour into elastic and viscous components. For an ideal elastic solid, a force applied will result in a deformation in which energy is stored, and which is then released on sample relaxation. The same force applied to an ideal viscous liquid, which results in loss of energy through heat or sound as the liquid flows. Most polymer materials exhibit both elastic and viscous properties and these are called viscoelastic or Maxwell materials [17]. In terms of polymer solution properties, the more inter-chain interactions (entanglement or cross-linking) within the polymer network, the greater the elastic character in response to an applied stress in comparison with a less entangled polymer [18].

The phase shifts that can be seen when dynamic oscillatory rheology applies an oscillating force to an elastic or viscous material are illustrated in figure 4.1. When a force is applied to an ideal solid, elastic behaviour is observed and strain and stress are seen to be in phase ($\delta=0^\circ$). This in-phase component can be described by the storage modulus G' . In the case of an ideal liquid, viscous behaviour is observed in which energy loss due to flow, leads to the strain and stress being out of phase ($\delta=90^\circ$). This is described by the loss modulus G'' . Realistic viscoelastic materials show both elastic and viscous properties and exhibit phase shifts between 0° and 90° [17, 19]. These changes can be expressed mathematically by equation 4.2.

$$\sigma = G''\gamma \sin(\omega t) + G'\gamma \cos(\omega t) \quad \text{Equation 4.2}$$

G' is the storage modulus which corresponds to the amount of energy stored, G'' is the loss modulus and represents the amount of energy dissipated during deformation. σ is the sample stress, γ is the strain, ω the frequency of oscillation and t is the time.

The ratio of G'' and G' which is the tangent of phase angle δ , is a parameter that describes the ratio of applied energy lost to energy stored within a sample also known as damping factor. When a sample shows a predominantly liquid character ($G'' > G'$), damping factor is greater than 1, but for a sample showing a predominantly gel-like character ($G'' < G'$), damping factor is less than 1.

Measurements of elasticity and viscosity are only accurate within the “linear viscoelastic region” (LVR), when the deformation is small enough for stress to be proportional to strain [20].

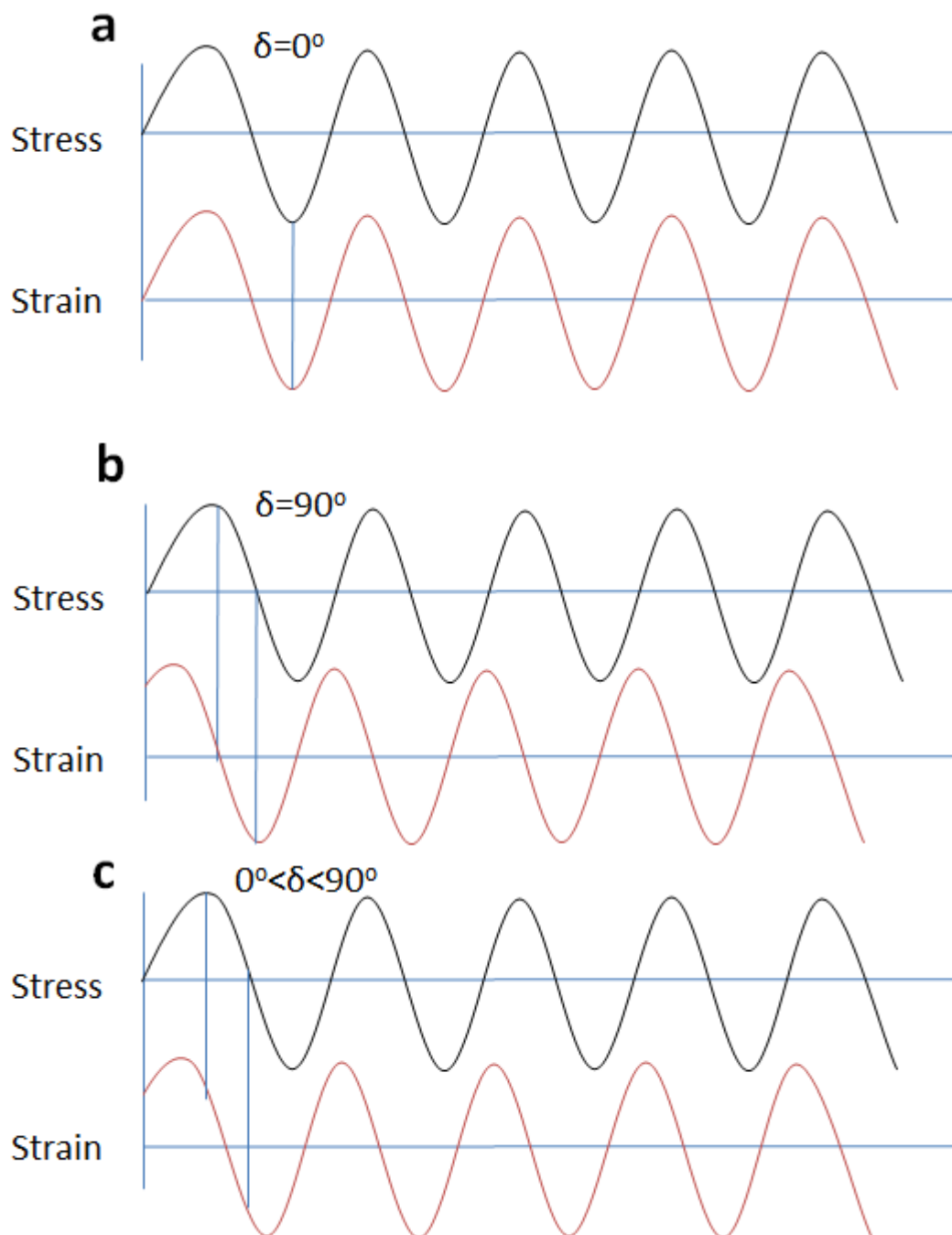


Figure 4.1: The relationship between stress and strain of different materials during dynamic oscillatory rheology. Material (a) ideal solid; (b) ideal liquid and (c) a viscoelastic material. Adapted from Rao [19]

4.2.4 Phase contrast microscopy

In 1934, the Dutch physicist Frits Zernike described how high contrast images can be produced by converting the invisible phase shift of light passing through a transparent specimen to variations in visible brightness [21, 22]. Compared with the ordinary light microscope, a phase contrast microscope contains an extra condenser annulus with an opaque flat-black plate and has a transparent annular placed between the light source and condenser to provide defocused, parallel light wavefronts emanating from the ring. When light passes through the sample, the phase differences cannot be detected by the human eye, but when converted by the phase plate in front of image plane to an amplitude difference, they can be seen variations in visible brightness under the phase contrast microscope.

Phase contrast microscopy, plays an important role in microscopic biology, including observations of living cells, microorganisms, thin tissue slices and subcellular particles [23-26]. It has been widely used to study phase behaviour in mixed polymer systems [27-29].

4.3 Materials and methods

4.3.1 Materials

All materials used in this chapter are described in Appendix 1. HPMC, PEO and NaCl were the same batches as used previously. Congo red 0.008% w/v solutions and 0.4M and 1.0M NaCl solutions were prepared before the experiment by the methods described in Sections 3.2.2 and 2.4

4.3.2 Confocal microscopy method for the assessment of single particle polymer swelling

A Bio-Rad MRC-600 confocal microscope (Hemel Hempstead, UK) (as described in Chapter 3.2.2) equipped with a 4x/0.13NA air objective was used to observe the 2D swelling behaviour of individual polymer particles of HPMC and PEO. 0.008%w/v Congo red solution was used as a fluorophore to visualise the hydration of both HPMC and PEO particles.

Particle swelling was observed using a specialised cell, the Microscope Slide Positioning System (MSPS), built by Dr Emma Wong in our group. This is designed to restrict swelling in the axial (upward) direction and show a 2D area of defined thickness when viewed from Figure 4.2 [6]. Particles of HPMC and PEO were selected from a 63 to 90 μm sieve fraction, placed on the lower microscope slide and then covered by the upper microscope slide. Both slides were secured in place by the MSPS and the gap between the slides adjusted by the vernier knobs. The MSPS lacks temperature control, and thus experiments were undertaken at room temperature ($20\pm1^\circ\text{C}$). The loaded MSPS was positioned on the stage of the confocal laser scanning microscope, and hydration medium was introduced into the gap between the two microscope slides to hydrate the HPMC or PEO particles. Images of hydrating particles were captured every 10 seconds for 120 seconds and particle areas were quantified using Image Pro Plus V6.2 image analysis software. Figure 4.3 provides a sample screen shot. To account for the variability in dry particle morphology and size, the results are presented as normalised swollen area as defined by equation 4.3.

$$\text{Normalised Swollen Area} = \frac{\text{Area (Hydrated particle)} - \text{Area (unhydrated particle)}}{\text{Area (unhydrated particle)}} \quad \text{Equation 4.3}$$

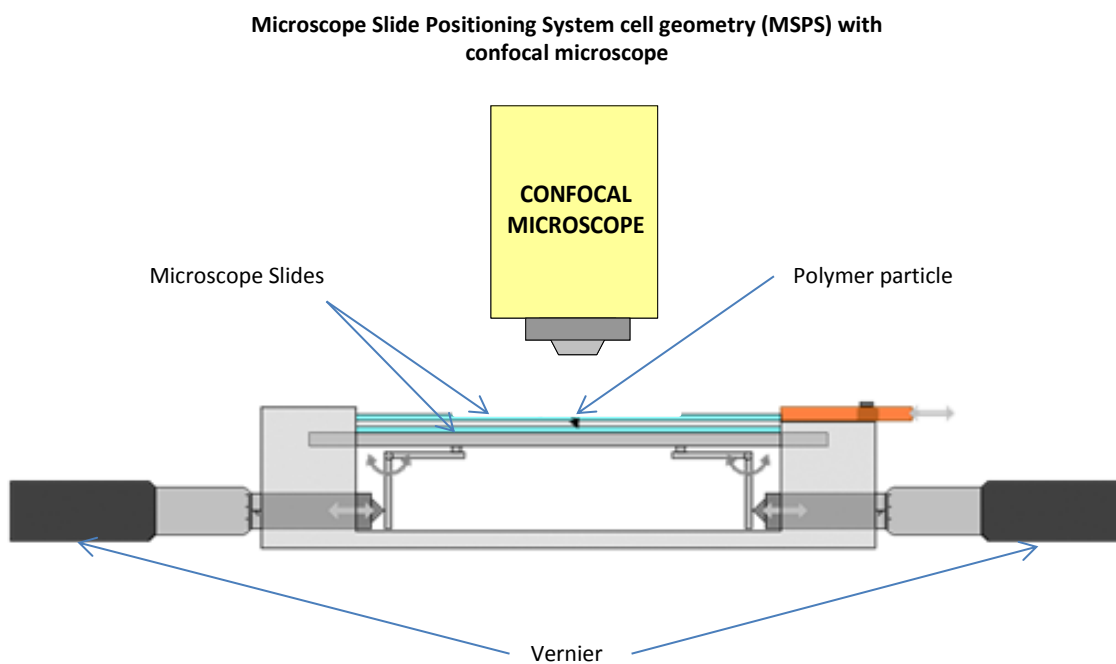


Figure 4.2: Schematic diagram showing the experimental geometry used for 2D confocal imaging of single particle swelling.

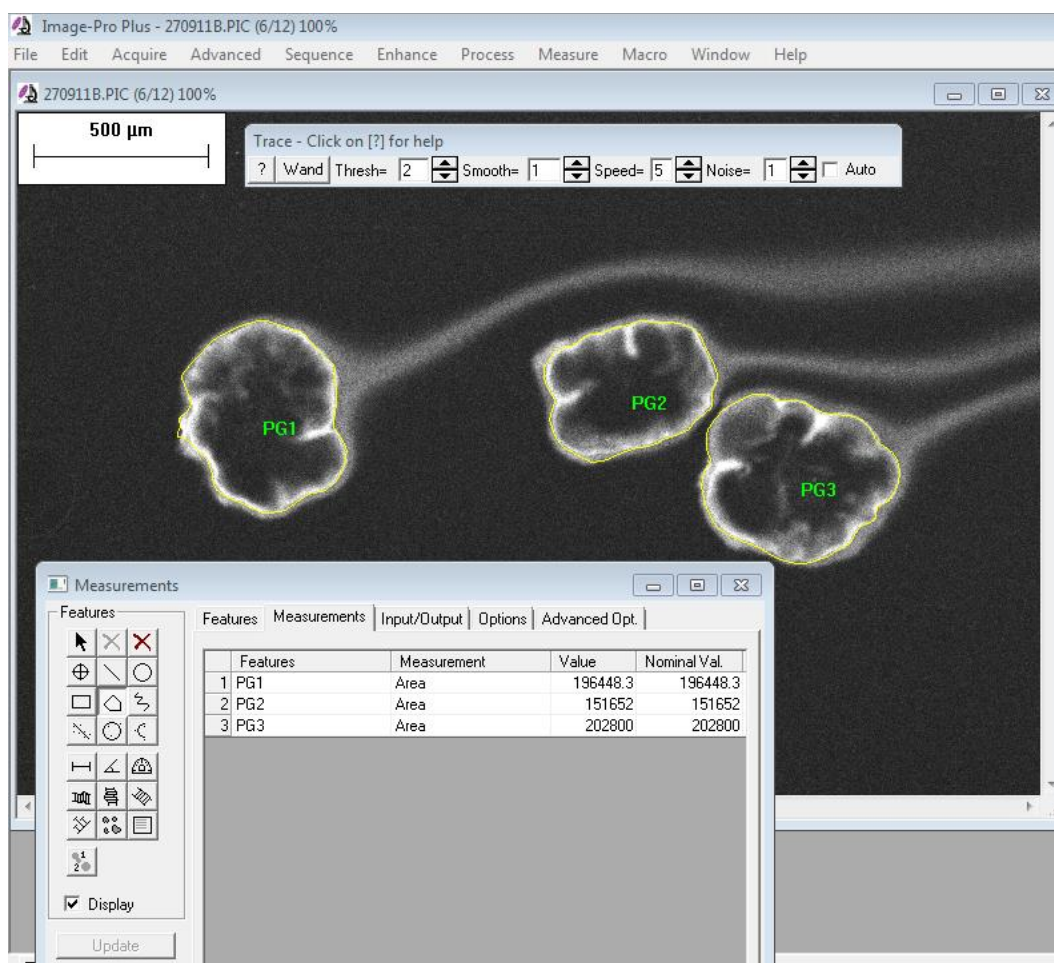


Figure 4.3: Screen shot of swelling particles showing the application of image analysis to measure the 2D swelling area of HPMC particles. These pictures show HPMC particles after 60 seconds. The area calculated is outlined in yellow.

4.3.3 Preparation of mono and binary component polymer solutions

Polymers solutions of 1%, 2% and 4% w/v total polymer content were prepared as follows. 100ml water was heat at $\sim 80^{\circ}\text{C}$ in a beaker and mixed using the mixer (EURO-ST D S2, IKA-WERKE, Germany) at a medium-high setting to enable the production of a vortex, and then 1g, 2g or 4g dry polymer was slowly added into the vortex to produce the solution in the concentration of 1%, 2% or 4% w/v. Solutions containing HPMC:PEO at weight ratios of 10:0, 8:2, 6:4, 4:6, 2:8 and 0:10 were produced in this way. After 30 to 60 minutes of mixing, the solutions were then stored in a fridge at $2-8^{\circ}\text{C}$ for at least 24 hours to minimise air bubbles in the solution prior to use.

4.3.4 Dynamic oscillatory rheology of HPMC:PEO mixtures at 1% w/v total polymer concentration

A dynamic shear rheometer (MCR-301, Anton Paar, Graz, Austria) fitted with a Peltier temperature control element, and with a cone-and-plate geometry (2° cone angle, 50mm diameter cone and plate) was used in the rheology study. Samples were loaded onto the bottom plate and the cone was lowered into the measurement position. The circumference of the sample exposed to the environment was coated with a low-viscosity mineral oil (Fisher Scientific, Leicestershire, UK) to prevent evaporation during the test. The measurement temperature was $25^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

4.3.5 Phase contrast microscopy

A microscope (Olympus CHBS Microscope, Tokyo, Japan) equipped with phase contrast optics, x10 objective and an Olympus DP-20 digital camera was used. Experiments were conducted at room temperature ($20 \pm 1^{\circ}\text{C}$). One drop of 1%w/v, 2%w/v and 4%w/v polymer solution was placed on a glass slide, and a cover slip was added carefully ensuring no entrapment of air bubbles before the sample examined under the microscope.

4.4 Results and Discussion

4.4.1 HPMC and PEO particle swelling

Figure 4.4 shows examples of confocal laser scanning micrographs from the particle swelling experiments. Figure 4.4A shows dry HPMC particles before addition of solvent. The particles appear to have weak auto fluorescence at Ex 488/Em>510 nm. Figure 4.4B shows the same particles hydrated 120 seconds after the addition of Congo red solution. The hydrated particles exhibit an uninterrupted boundary of high intensity fluorescent around each particle, indicating Congo red has bound to HPMC and emitted fluorescence [30]. The bright periphery arises because the particle is swollen, allowing access of the dye. However there is little fluorescence from inside the hydrating particles, revealing that Congo red penetration is limited. This is perhaps because the majority of the dye has bound to the particle surface. It is also possible that over this short timescale the swollen HPMC layer formed a diffusion barrier, hindering Congo red ingress [31] and that in these very early stages of hydration, particles are forming their own individual micro-matrices [32].

Figures 4.5 and 4.6 show the swelling behaviour of HPMC and PEO particles in aqueous media containing 0M, 0.4M and 1M NaCl. It is clearly visible that both types of particles swell at all three NaCl concentrations. To compare the effect of NaCl concentration on swelling behaviour, a normalised swollen area of the particles was calculated (equation 4.2) and results are plotted in Figure 4.7. The slope of the curves indicates that both HPMC and PEO particles exhibit rapid swelling over the first 10 seconds, but thereafter the speed of the swelling is reduced. PEO particles swelled more rapidly than HPMC, and after 120 seconds the mean normalised swollen area of PEO particles was around 45, about twice the values recorded for HPMC in 0M NaCl.

In the case of HPMC particles, particle swelling was significantly inhibited by the presence of NaCl. This can be related to the results in chapter 3 where it was shown that NaCl concentration can significantly affect HPMC matrix drug release. At 0.4M or lower, although the HPMC swelling was inhibited by increasing the NaCl, but the HPMC matrices in chapter 3 still formed an effective gel layer diffusion barrier. However, when the NaCl concentration was increased to 1.0M, and HPMC particle swelling was further inhibited, the HPMC

matrices in chapter 3 could not form a compact and coherent gel layer in the early stage of matrix hydration and water quickly be penetrates causing an accelerated drug release profile.

Swelling of PEO particles, on the other hand, were not significantly affected by the presence of NaCl (Figure 4.7). This may explain why PEO matrices in the dissolution tests (Chapter 2) appear to be resistant to high NaCl media. If particle swelling is unimpeded they can rapidly form a gel layer diffusion barrier.

To Summaries the HPMC and PEO particle swelling results

- I. Over this short timescale (120 seconds), PEO particles swelled more rapidly, and to a greater extent than HPMC particles.
- II. The swelling of HPMC particles was significantly affected by NaCl concentration.
- III. The swelling of PEO particles showed little dependency on NaCl concentration up to 1.0 M.
- IV. These results may help us to understand the results of the dissolution testing in Chapter 3.

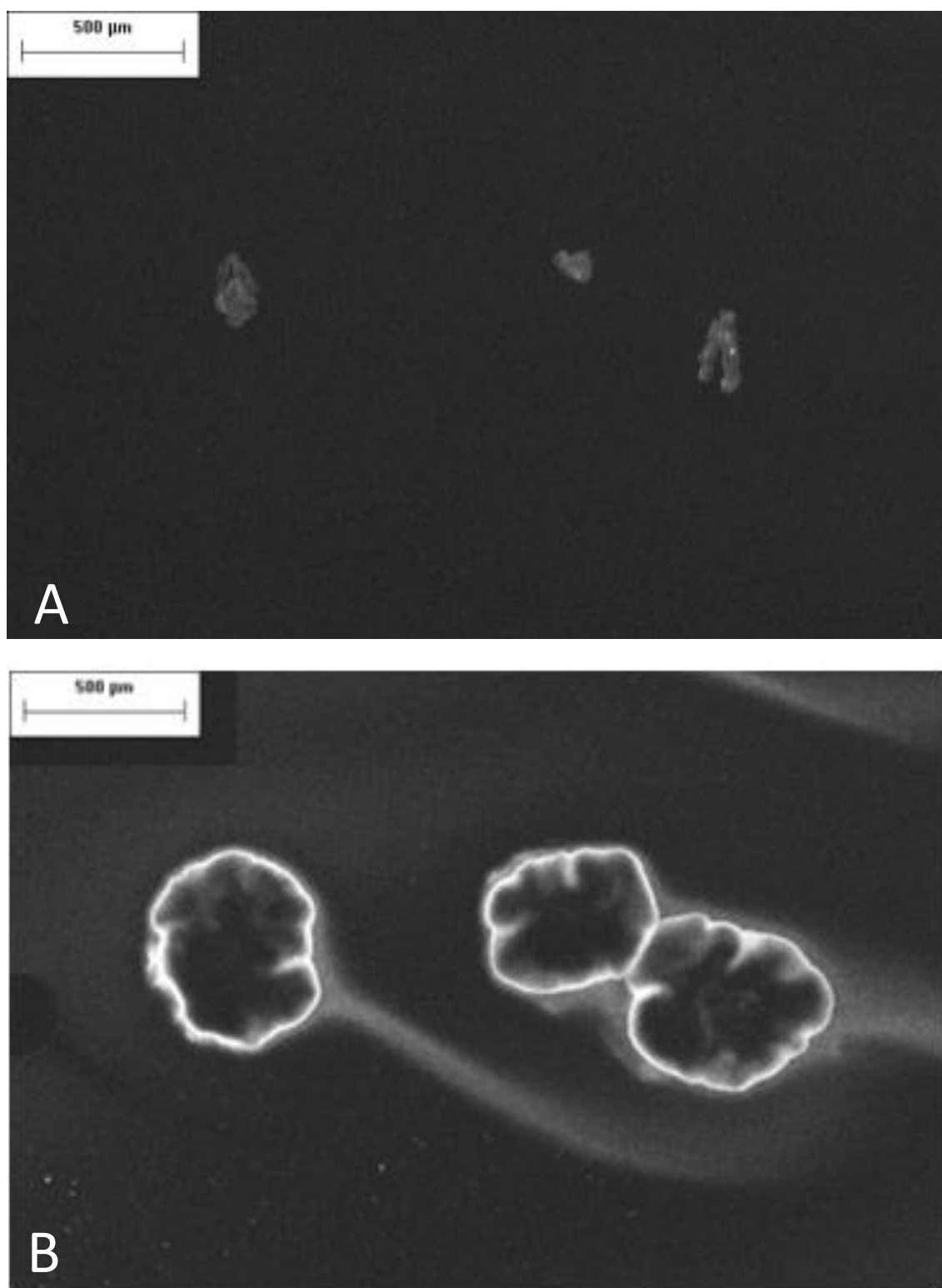


Figure 4.4: Confocal laser scanning micrographs of HPMC particles undergoing hydration in 0M NaCl

A. Dry particles at t=0 min, B. Images taken 120 seconds after addition of 0.008% w/v Congo red solution. Confocal fluorescence imaging at Ex 488/Em>510 nm. Experiments conducted at room temperature ($20\pm1^{\circ}\text{C}$). Scale bar 500 μm .

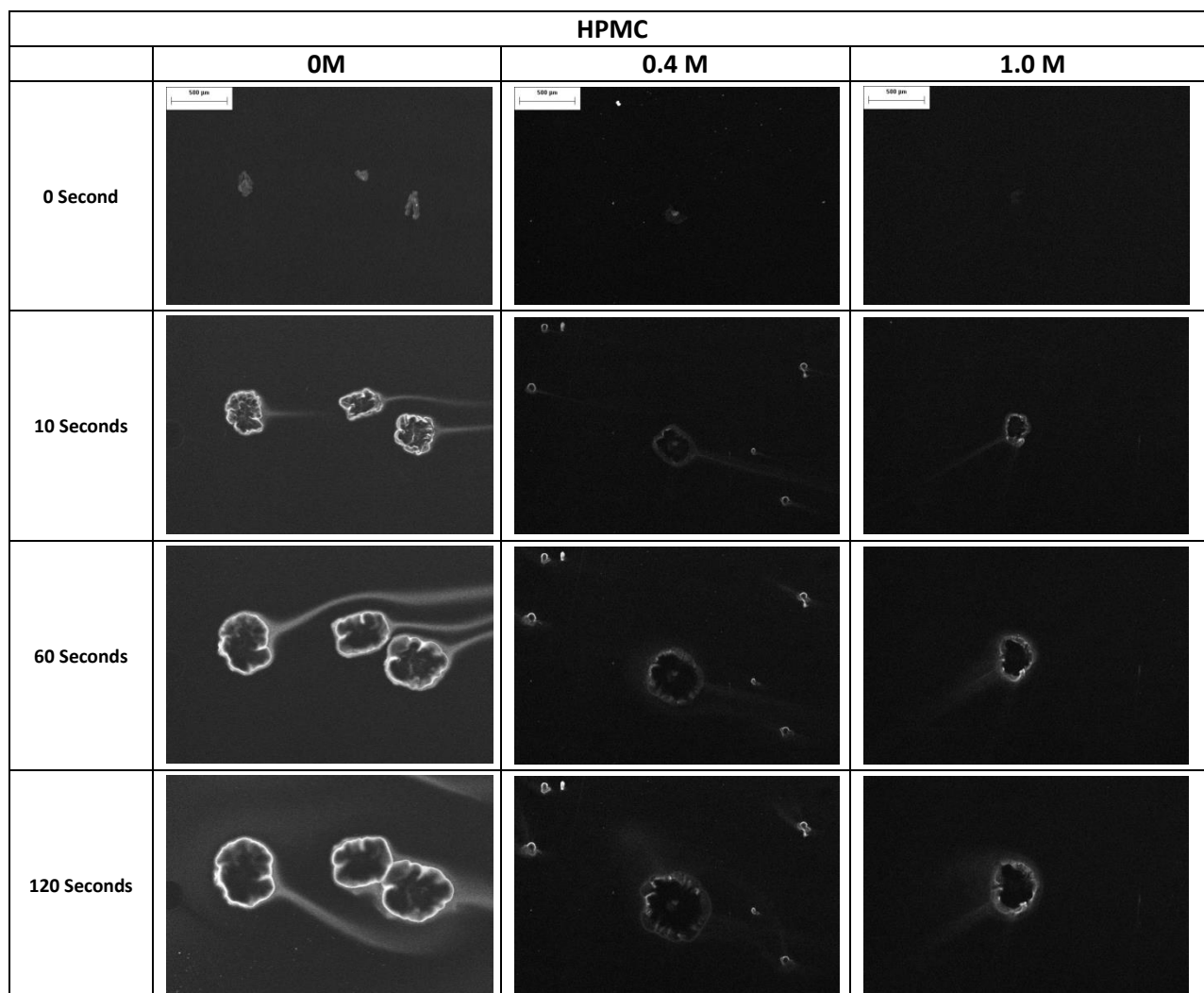


Figure 4.5: HPMC particles after 120 seconds hydration. Confocal fluorescence imaging at Ex 488/Em>510 nm. Experiments conducted at room temperature ($20\pm1^{\circ}\text{C}$), using various NaCl media containing 0.008% w/v Congo red as a visualisation aid. Scale bar 500 μm .

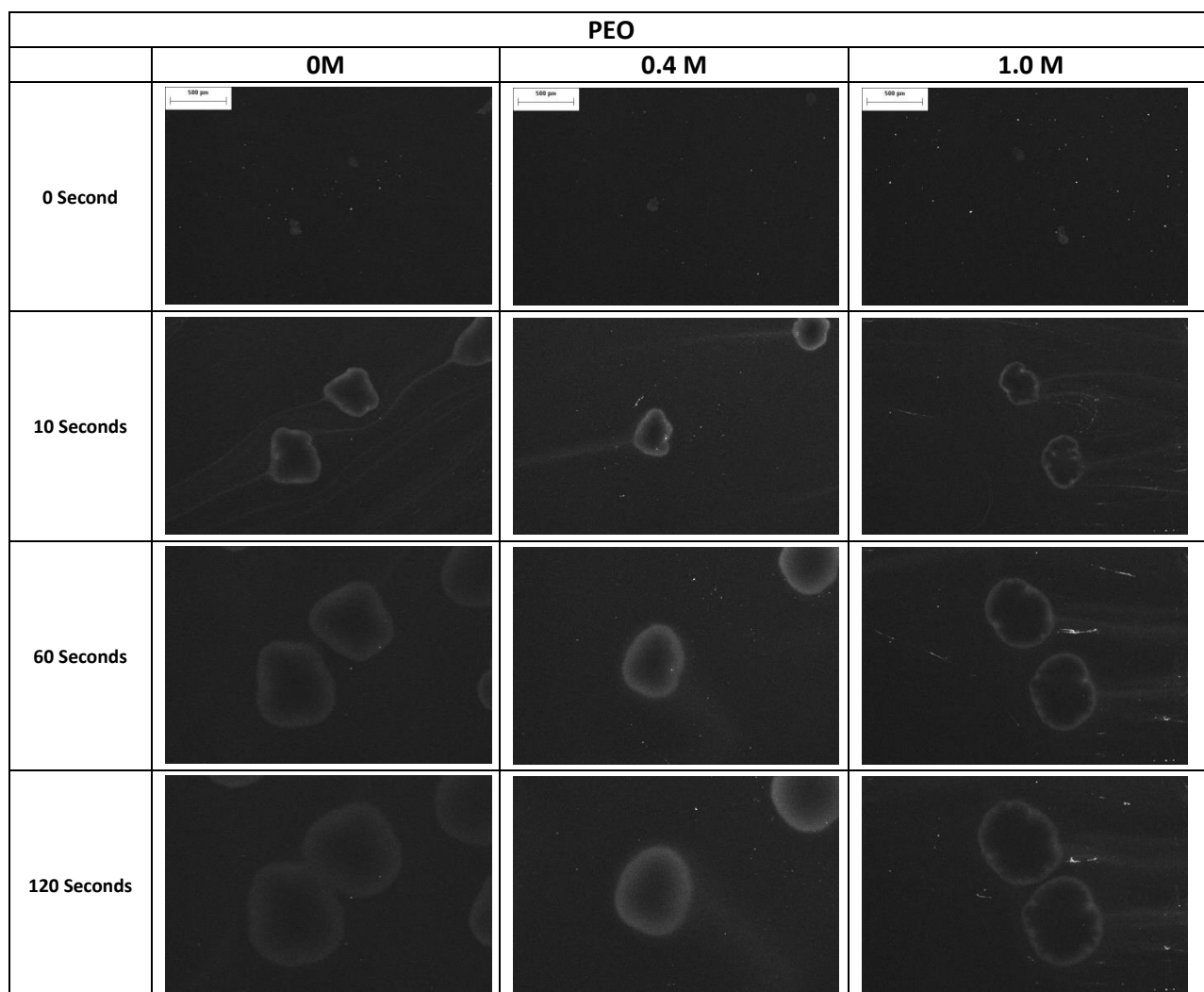


Figure 4.6: PEO particles after 120 seconds hydration. Confocal fluorescence imaging at Ex 488/Em>510 nm. Experiments conducted at room temperature ($20\pm1^{\circ}\text{C}$), using various NaCl media containing 0.008% w/v Congo red as a visualisation aid. Scale bar 500 μm .

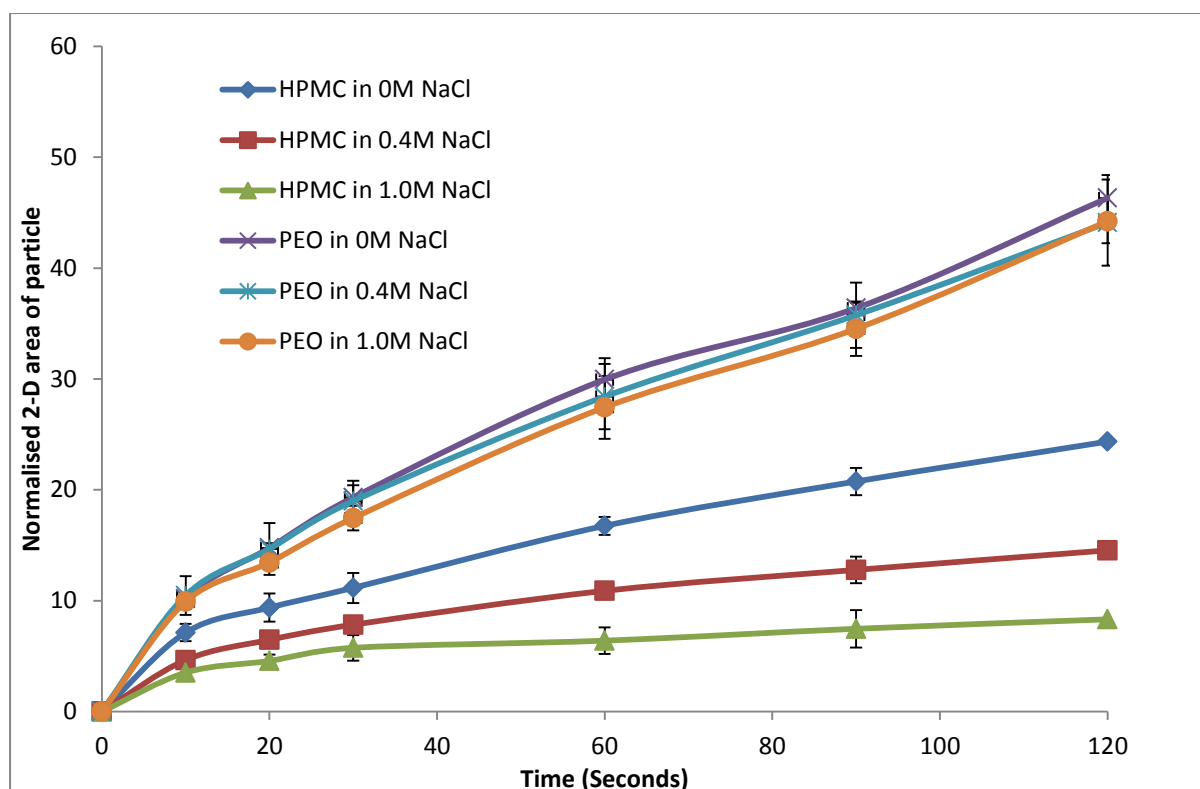


Figure 4.7: Effect of NaCl concentration on the swelling of HPMC and PEO particles. Normalised 2D areas were calculated by image analysis software from the confocal images time series. Mean ($n=10$, $\pm$ SD)

4.4.2 Studies of the dilute solution miscibility of HPMC:PEO mixtures at 1% w/v total polymer concentration

4.4.2.1 Rheological studies of phase behaviour in HPMC:PEO mixtures

The viscoelastic material properties of single polymer solutions and four HPMC:PEO mixtures at 1% w/v total polymer concentration were evaluated in small amplitude oscillatory shear experiments. Initially, the linear viscoelastic region was established and the results of the corresponding strain sweeps are shown as storage modulus (G') and loss modulus (G'') plots in Figure 4.8 and Figure 4.9. Within the strain range analysed, the data show little dependency of G' or G'' with strain. The inconsistency in the data at low strains is almost certainly due to the limited sensitivity of the measurement head under the chosen measurement conditions. Based on these results, 1% was selected as strain amplitude for the frequency sweep experiments.

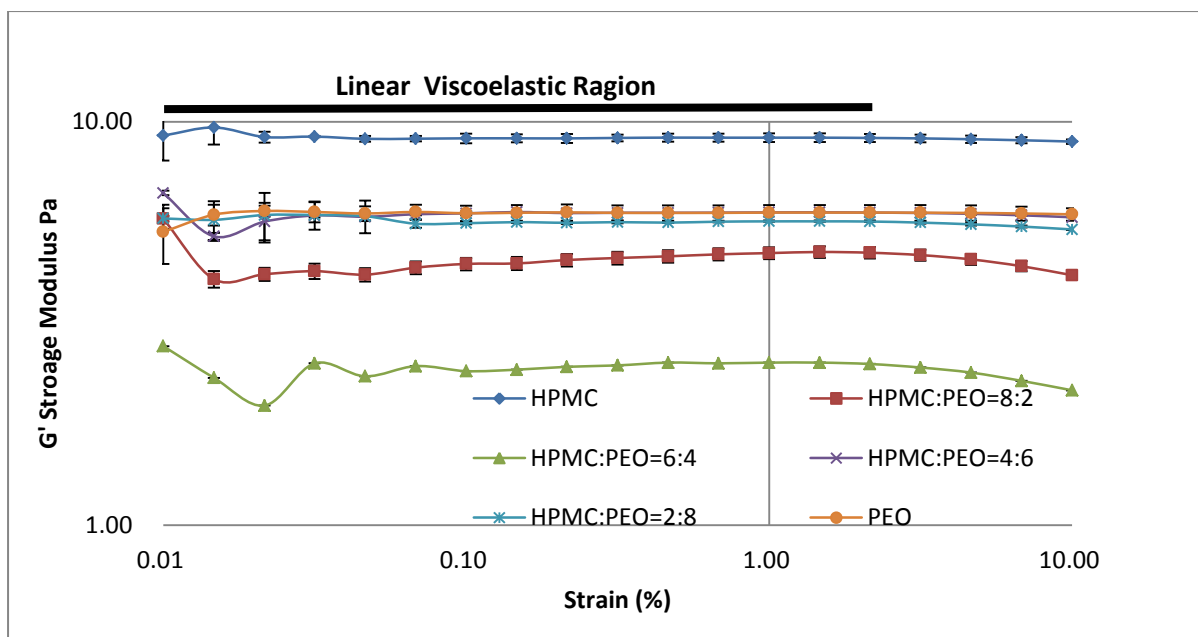


Figure 4.8: The variation in storage modulus (G') during a dynamic amplitude sweep on mixed HPMC:PEO solutions. The linear viscoelastic region (LVR) is identified. Total polymer concentration 1% w/v. Frequency 1 Hz. Temperature $25 \pm 0.1^\circ\text{C}$. Geometry = PP 2°/50mm. Mean ($n=3$, $\pm\text{SD}$)

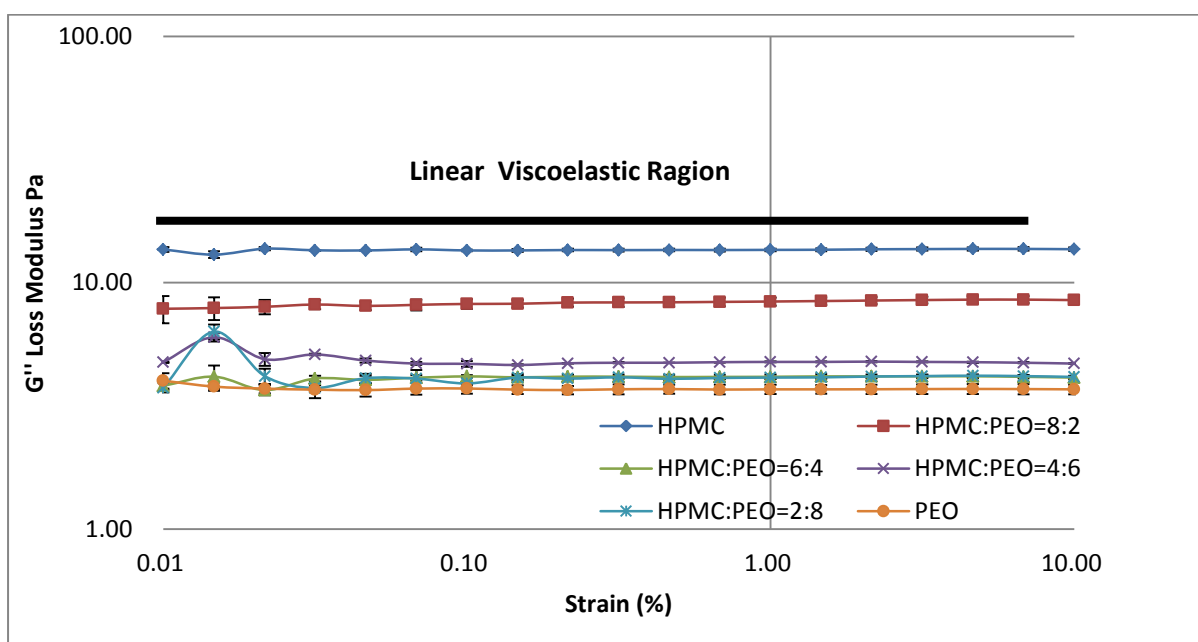


Figure 4.9: The variation in loss modulus (G'') during a dynamic amplitude sweep on mixed HPMC:PEO solutions. The linear viscoelastic region (LVR) is identified. Total polymer concentration 1% w/v. Frequency 1 Hz. Temperature $25 \pm 0.1^\circ\text{C}$. Geometry = PP 2°/50mm. Mean ($n=3$, $\pm\text{SD}$)

The results of the frequency sweeps are shown in Figures 4.10 and 4.11. It becomes apparent from both the G' and G'' graphs that samples cluster into two groups: HPMC dominant samples and PEO dominant samples. While the frequency dependent G' and G'' values for PEO dominant solutions nearly coincide, there is a clear dependency on mixing ratio in the HPMC dominant samples. Increasing the amount of PEO leads to a decreased frequency dependence of G' and G'' . The G' and G'' values acquired for the HPMC dominated samples show a greater slope than those acquired for PEO dominated samples.

The higher slopes from HPMC dominated samples are indicative of a more liquid-like behaviour, and suggests that HPMC solutions show greater polymer-polymer deformation with respect to frequency, whilst PEO solutions show less polymer-polymer deformation.

The different viscoelastic behaviour observed in these samples may be a result of differences in molecular weight, number of chain contacts, polymer lifetimes, and topography [33].

The damping factors (figure 4.12) are dependent on the proportion of HPMC and PEO in solution and were reduced as the PEO content was increased. In HPMC dominated mixtures, the damping factor was greater than 1, as these solutions showed more liquid like behaviour, whilst in PEO dominated mixtures, damping values were less than 1, suggesting that solutions were more solid-like. The more solid like behaviour of PEO dominated solutions suggests greater entanglement coupling involving neighbouring molecules, which can be thought of as a “hooks” that impede the translational motion of the polymer [34].

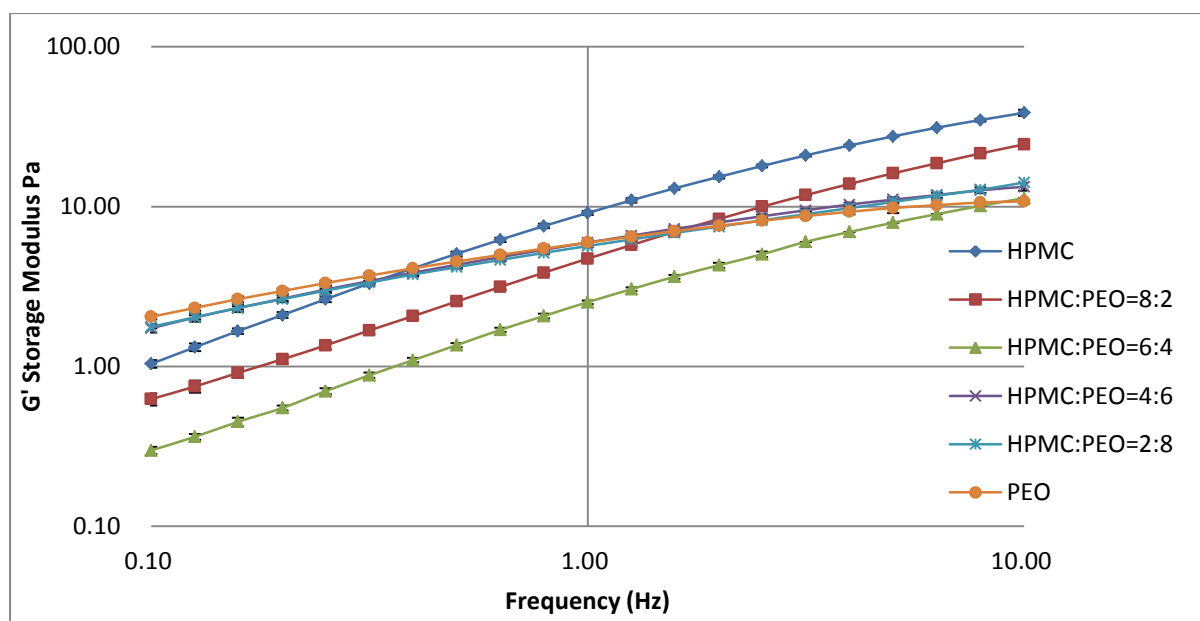


Figure 4.10: The variation in storage modulus (G') with respect to oscillation frequency for mixed polymer solutions. Total polymer concentration 1% w/v. Temperature $25 \pm 0.1^\circ\text{C}$. Applied strain 1% was within the linear viscoelastic region of the samples. Geometry = PP $2^\circ/50\text{mm}$. Mean ($n=3$, $\pm\text{SD}$)

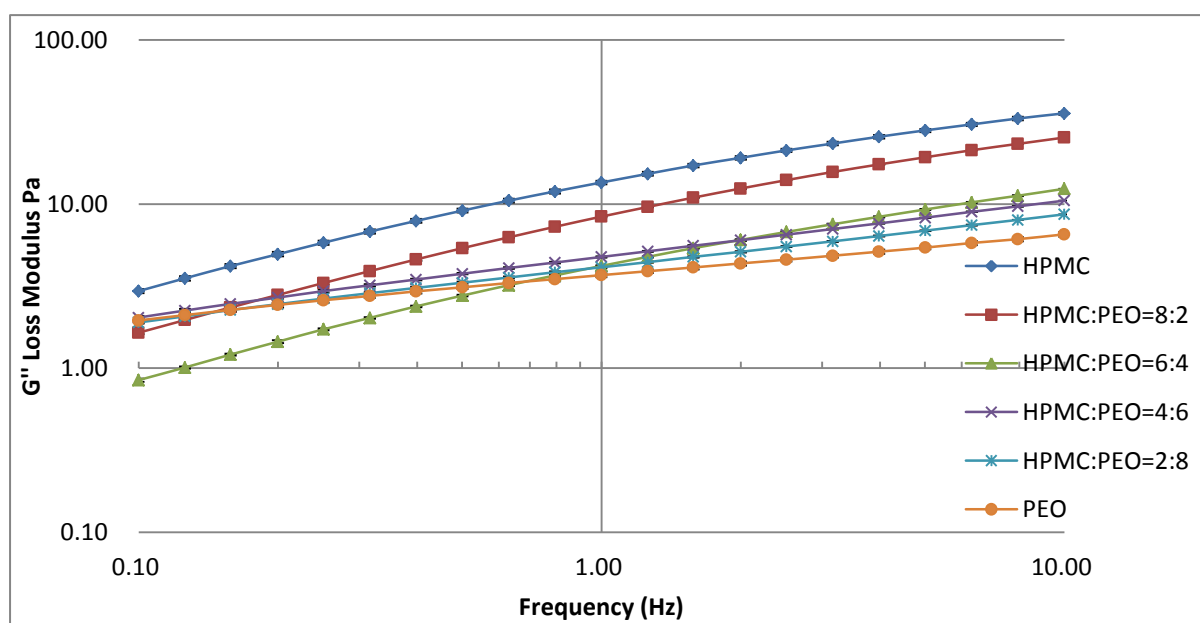


Figure 4.11: The variation in loss modulus (G'') with respect to oscillation frequency for mixed polymer solutions. Total polymer concentration 1% w/v. Temperature $25 \pm 0.1^\circ\text{C}$. Applied strain 1% was within the linear viscoelastic region of the samples. Geometry = PP $2^\circ/50\text{mm}$. Mean ($n=3$, $\pm\text{SD}$)

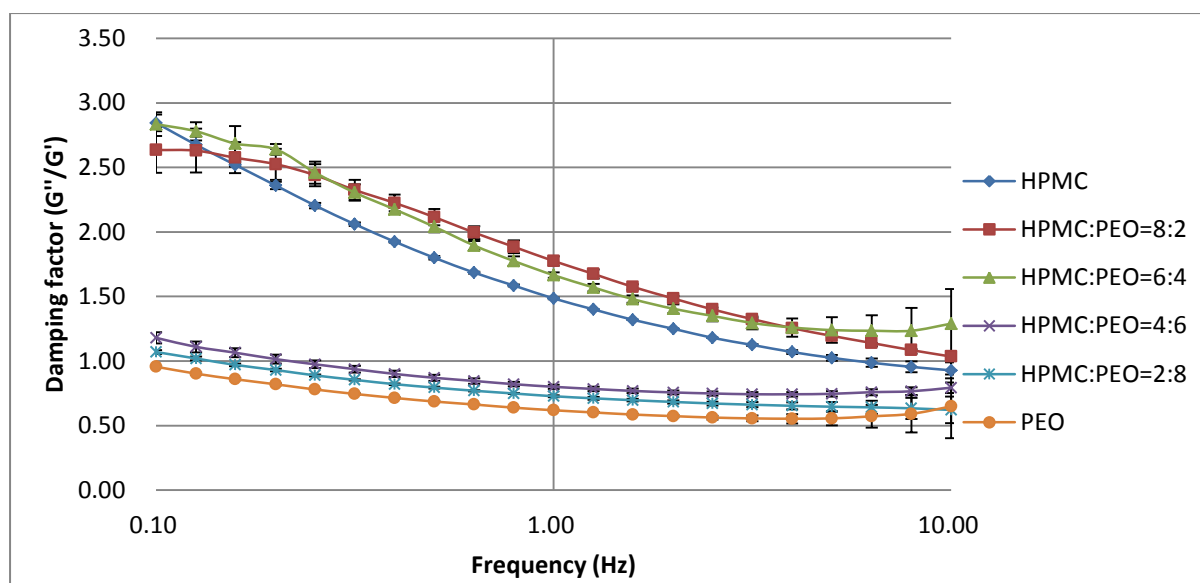


Figure 4.12: The damping factor (G''/G') with respect to oscillation frequency for mixed polymer solutions. Total polymer concentration 1% w/v. Temperature $25 \pm 0.1^\circ\text{C}$. Applied strain 1% was within the linear viscoelastic region of the samples. Geometry = PP $2^\circ/50\text{mm}$. Mean ($n=3$, $\pm\text{SD}$)

4.4.2.2 HPMC and PEO miscibility

Figure 4.13 shows the storage moduli (G') obtained from figure 4.10 at frequencies of 0.1, 1, and 10Hz. The unbroken line shows the actual results whilst the broken lines show the relationship that would be expected if the polymers followed ideal mixing rules and were completely miscible in solution. At a HPMC:PEO ratio of 2:8, these results overlap the ideal miscible line suggesting that these compositions were miscible, but at lower ratios there were pronounced negative deviations from ideal mixing, strongly suggesting the polymers were immiscible. In other mixed polymer systems it is common to find that polymers blends are immiscible and multiphase morphology is seen as a small combinatorial entropy and positive enthalpy of mixing [8, 10, 35, 36].

4.4.2.3 Summary of the dilute solution miscibility studies

- I. Solutions of both polymers exhibited viscoelastic properties in the frequency range studied (0.1Hz to 10Hz).
- II. HPMC dominated solutions (HPMC: PEO 10:0, 8:2 and 6:4) exhibit more liquid-like behaviour, whereas PEO dominated solutions (HPMC: PEO 4:6, 2:8 and 0:10) were more solid-like and less frequency dependent.
- III. There was evidence for phase separation (as a negative deviation from the ideal mixing rule) in solutions containing HPMC and PEO at ratios of 8:2, 6:4 and 4:6.
- IV. There was evidence for miscibility only at a HPMC: PEO ratio of 2:8.

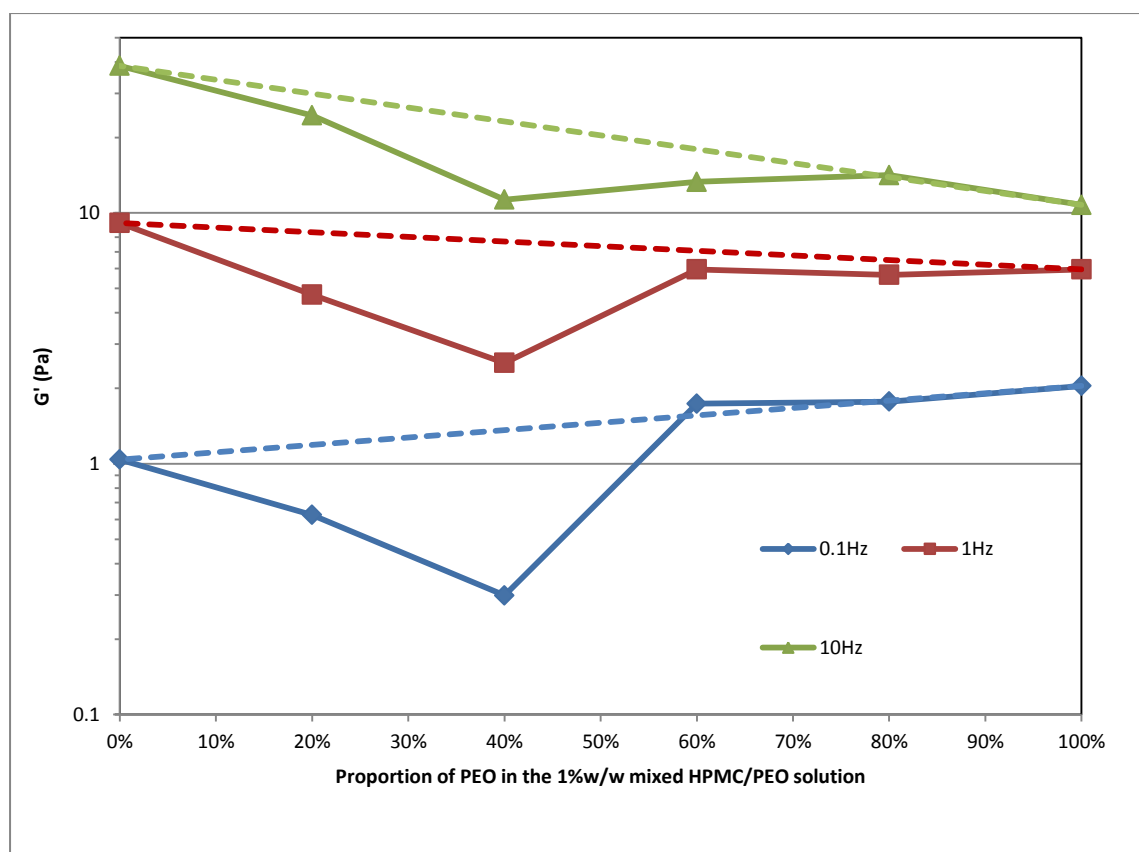


Figure 4.13: The effect of HPMC: PEO ratio on the storage modulus (G') at three different frequencies. The graphs exhibit negative deviations from linear mixing typical of phase separation. Ideal mixing is shown as dotted lines. Total polymer concentration 1% w/v. Temperature $25 \pm 0.1^\circ\text{C}$. Geometry = PP 2°/50mm. Mean ($n=3, \pm\text{SD}$)

4.4.3 Phase contrast microscopy of 4% w/v HPMC : PEO binary solutions

Preliminary studies of 1% and 2% mixed polymer solutions showed very small changes under the phase contrast microscope. Only when the polymer concentration was raised to 4%, were significant features seen.

Figure 4.14 shows images of 4% w/v binary HPMC:PEO mixed solutions under phase contrast microscopy. Single polymer solutions showed no significant variations in brightness across the field of view, at this magnification except for a few isolated dots which could be undissolved HPMC or PEO particles.

In contrast, phase contrast images of binary solutions showed evidence of structure across the whole polymer ratio range studied (at HPMC:PEO ratios 8:2, 6:4, 4:6 and 2:8). Bicontinuous and interconnected tube like structures were observed, similar patterns to those seen in previous studies of polymer miscibility [27, 28, 37]. The patterns of darkness and light arise from the two phases having different refractive indexes (which phase contrast detects) and it strongly suggests that phase separation occurs in all HPMC and PEO mixed solutions at this concentration.

Other studies have reported how other polymers can be excluded by PEO in aqueous environments, and report that phase separation often occurs when PEO is mixed with other water soluble polymers above a critical concentration [38]. Our phase contrast microscopy studies show that a 4% w/v mixture of PEO and HPMC appears to be above the critical concentration. The rheology however, appears to be a more sensitive measure, and suggests phase separation at 1% w/v.

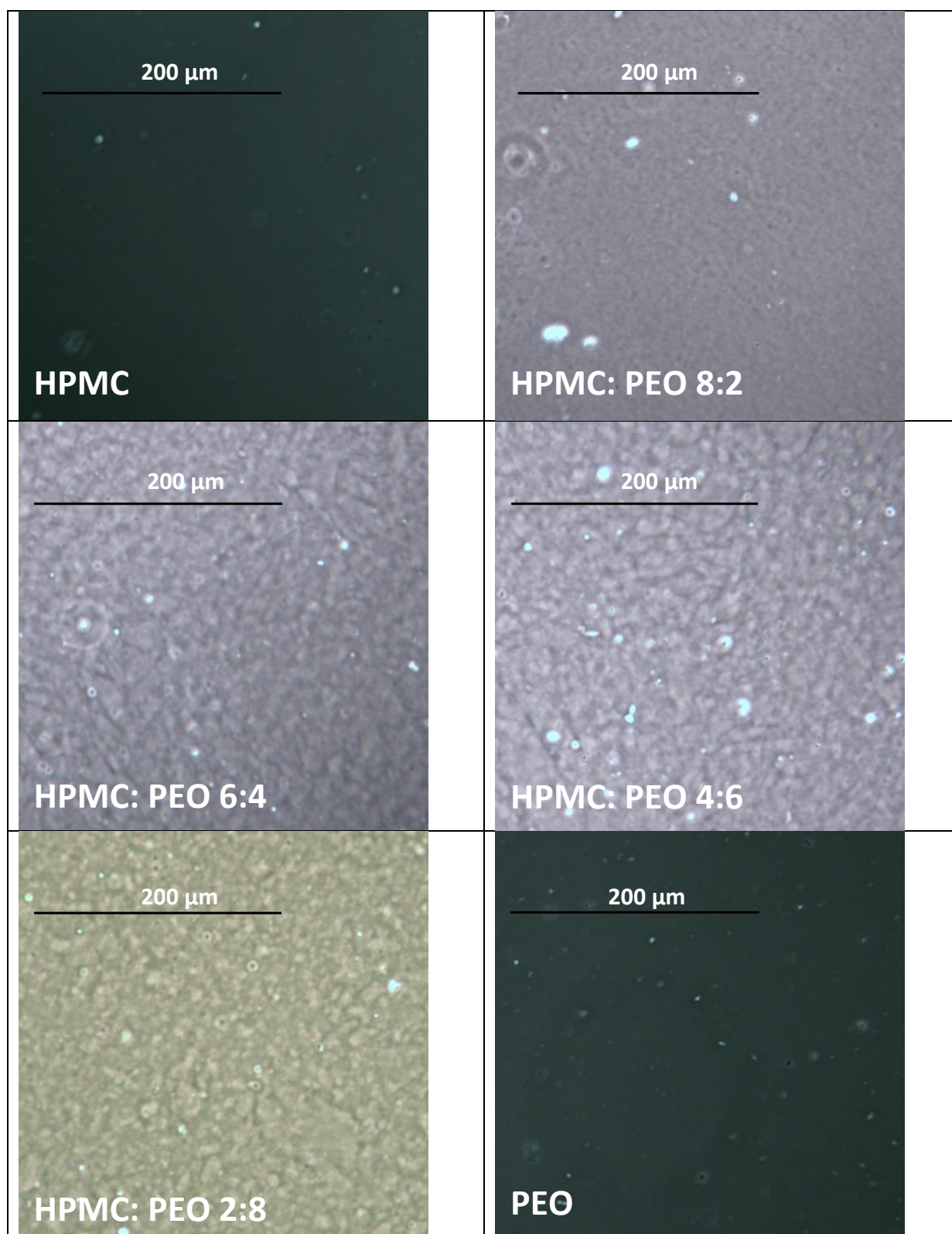


Figure 4.14: Phase contrast microscopy images of 4% w/v polymer(s) solutions. Magnification x10 in room temperature. $20^{\circ}\text{C} \pm 1^{\circ}\text{C}$

4.5 Conclusions

The swelling of HPMC and PEO particles and the miscibility of binary HPMC:PEO solutions have been investigated in this chapter. These experiments were undertaken to better understand how these two polymers might contribute to the gel layer of a matrix tablet.

It was found that HPMC particle swelling can be inhibited by increasing NaCl concentration. This helps us to understand the early gel layer confocal microscopy results in chapter 3, in which high concentrations of NaCl were seen to disrupt gel layer formation. At extreme concentrations (1.0M) HPMC particles swelling were highly inhibited and confocal microscopy results in chapter 3, showed there was little coherent gel layer formation and burst drug release occurred. PEO particles were seen to swell about twice as rapidly as HPMC particles but were unaffected by NaCl concentration. This could explain why in chapter 3, matrix drug release profiles remained relatively unaffected by NaCl in the dissolution medium.

The rheological results in this chapter suggested that 1% HPMC:PEO solutions were phase separated at polymer ratios of HPMC:PEO 6:4, 4:6, and 2:8 but were miscible at an HPMC:PEO ratio of 8:2. Phase contrast microscopy revealed evidence of phase separation in mixed 4% w/v HPMC:PEO solutions, but at all the polymer mixture ratios examined (HPMC: PEO 8:2, 6:4, 4:6 and 2:8). Whilst this suggests the polymers are immiscible when blended in solution the nature of this separation was not further investigated.

The results above provide a hypothesis for the behaviour of mixed HPMC:PEO matrices particularly with respect to the formation and structure of the gel layer. As PEO particle swelling occurs twice as fast as HPMC swelling, and these two polymers are immiscible, the PEO particles would swell faster when forming the matrix gel layer. We can hypothesize that a gel layer of PEO may be formed before the HPMC hydrates. This would result in a gel layer structure comprising of an outer gel high in PEO content and an inner gel region enriched in HPMC. The improvement in salt tolerance of HPMC matrices by substitution of PEO, may arise from PEO particle swelling being unaffected by NaCl. This means the outer PEO gel layer might form a protective barrier for HPMC, enabling mixed polymer matrices to resist high concentrations of NaCl.

This hypothesis cannot be substantiated by the experiments in this chapter and will be taken forward into studies of the early and later gel layer in the next chapter.

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Chapter 5

Exploring the Gel Layer Morphology of mixed HPMC:PEO Hydrophilic Matrices

5.1 Rationale and Aims

Chapter 4 showed, (i) how PEO particle swelling was faster than HPMC. (ii) how swelling rate was affected by NaCl and (iii) how HPMC and PEO were immiscible in dilute solution. A hypothesis was advanced in chapter 4, that PEO would swell more rapidly than HPMC at the surface of the matrix, and perhaps forms an outer gel layer to protect HPMC from high concentrations of NaCl. This might explain how a matrix containing a ratio of 4:6 HPMC:PEO was able to provide extended drug release in 1M NaCl.

This chapter aims to study the morphology of the early and later gel layer to provide further understanding of the drug release profiles observed in chapter 2, and provide further evidence to support or refute this hypothesis.

Confocal microscopy imaging was used to examine the early gel layer morphology in the first 15 minutes, and Attenuated Total Reflection Fourier Transform Infrared Spectroscopy (ATR-FTIR) imaging used to examine the gel layer up to 180 minutes hydration.

5.2 Introduction

In the early stages of gel formation it is polymer swelling and the motion of the internal water front that characterize the hydration process [1, 2]. Of particular interest is the interface between the glassy polymer in the core and the swollen rubbery gel layer termed the swelling front [3, 4]. Within the gel layer, the polymer hydrates, swells and the swollen particles coalesce to form the gel layer. This swollen barrier retards further water penetration into the core, and provides the rate control required for the extended release of drugs.

HPMC and PEO can both form hydrophilic matrices but due to the different types and number of hydrophilic groups on the polymer chain, they exhibit significant differences in water affinity. Chapter 4, showed how each polymer exhibited different rates of particle swelling. To understand how these polymers behave in the mixed polymer gel layer of a binary matrix, imaging techniques are required.

5.2.1 Studying early gel layer morphology with confocal microscopy

Early gel layer morphology has been studied by confocal microscopy in chapter 3 in which the background and theory have been described. Chapter 3 showed how each polymer exhibited a different fluorescent intensity when exposed to the fluorophore (Congo red). However, these matrices were complex formulations containing drug (caffeine) and excipients, as well as HPMC and PEO. To minimize image obscuration from these other ingredients, the matrices used in this chapter contained only HPMC and PEO. Bajwa et al. reported that, single HPMC matrices rapidly hydrate as HPMC particles swell in a columnar manner to form the nascent gel barrier [5]. As HPMC and PEO particles have different fluorescent intensities, this provides the opportunity to observe how individual HPMC and PEO particles will behave in mixed matrices.

5.2.2 Studying the later gel layer morphology with ATR-FTIR

Several other imaging methods have been used to understand gel layer morphology, including optical microscopy and NMR microscopy [6-11] but only ATR-FTIR can provide the spatial and chemical resolution to resolve different polymers within the gel. This is the method chosen in this study, which we would hope will provide evidence of polymer distribution, miscibility and particle swelling information of HPMC and PEO in the hydrated gel layer.

5.2.2.1 Infrared theory

Molecular total energy contains electronic, vibrational, rotational, and translational energy levels. The different energy levels require different amounts of energy absorbed from light (electronic > vibrational > rotational > translational). Electron transition requires energy to achieve raise electrons to a higher electron energy level. Vibrational transition requires absorption of quantized energy. Rotational transition requires absorption of radiation to

achieve a higher rotational energy level. Different as the energy levels above, translational is small amounts of energy store as kinetic energy, which is unquantized and hence not relevant to spectroscopy [12].

The infrared (IR) region of the electromagnetic spectrum encompasses several recognized sub-regions. The near-infrared (NIR) region (wavenumbers 14000 to 4000 cm^{-1}) excites overtone or harmonic vibrations. The mid infrared (MIR) region (wavenumbers 4000 to 400 cm^{-1}) includes molecular vibrations and can be used to study the fundamental and associated rational vibrational structure. The far-infrared (400 to 4 cm^{-1}) has lower energy than NIR and MIR, and can be used for rotational spectroscopy [13].

In this study, the term 'IR' will be used to indicate the mid-IR region, where fundamental vibrations of polyatomic molecules occur and the spectra can be used to identify specific chemical moieties [14].

When IR radiation is directed at a sample, specific wavelengths are absorbed which can cause a change in the molecule's net dipole moment, inducing transitions between quantized vibrational energy which are dependent on the molecular vibrations of the substance. This is called 'the selection rule'.

The atoms in the molecule are fluctuating continuously rather than being stationary because of various types of vibrations and rotations from the bond of a molecule. Modes of vibrational movement include stretching (symmetric stretches, asymmetric stretches) and bending (twisting, wagging, scissoring and rocking). Diatomic or triatomic molecules can be easily defined by these movements (except for some molecules such as O_2 and N_2 which do not show a change in their dipole moment during the stretch vibration, and these molecules cannot absorb IR radiation) [12, 15].

Infrared spectroscopy based on the infrared absorbance of sample, can provide both chemical and structural information [16]. The earliest method of spectroscopy was transmission, in which infrared light was passed through a sample between two IR transparent windows. However, IR spectroscopy in this mode requires short path lengths of

less than 6-10 μm through the absorbing sample. This would be impractical because our polymers will be studied in water, which is a strong absorber of IR light and so little of the IR radiation would reach the detector. This problem can be addressed by using the ATR-FTIR mode of spectrometry described below.

5.2.2.2 Attenuated Total Reflection Fourier Transform Infrared Spectroscopy (ATR-FTIR)

FTIR instruments are based on a Michelson interferometer, an optical device which can split radiation into two paths and then recombine them. The function of path difference can be detected from the exit beam with intensity variations [17, 18]. Fourier transform converts the interferogram received from the Michelson interferometer from a time domain response, to a frequency domain spectrum.

FTIR has a throughput (Jaquinot) advantage, as there is no restricting wavenumber range slit, and the increased light energy passing through the sample provides a better signal-to-noise ratio. There is also a multiplex (Fellgett) advantage. Dispersive systems can only measure a limited range of wavenumbers at a time, but FTIR can detect all frequencies at the same time. In addition, by using a superimposed laser beam (normally at a wavelength of 632.8 nm), a better frequency accuracy can be obtained which can be then used to compare and correct the spectra. This is called the Connes advantage [19].

In ATR-FTIR spectrometry, infrared radiation is directed at an interface between an internal reflection element and a sample located on its surface. The internal reflection element is a material with a high refractive index, and in this study was diamond. The infrared light penetrates into the sample as an evanescent wave with a defined depth of penetration [14, 16]. ATR-FTIR has the advantages of simple sample preparation (no dye or labelling is required) and is much more amenable to study of aqueous systems in particular.

ATR-FTIR spectroscopy can be combined with imaging (by coupling an FTIR spectrometer with a focal plane array detector) in order to obtain spatially resolved chemical images of the sample. A large number of spatially resolved ATR spectra are collected, and the imaging of spatial distribution of different components is detected through the absorbance of specific absorption bands, corresponding to different chemical groups.

ATR-FTIR imaging has been used in studies of pharmaceutical systems, such as those by Kazarian et al. [14, 20, 21] who demonstrated the ability to image the spatial distribution of drugs and polymers, and quantify drug release as a function of time in various formulations. Li et al. have reported how ATR-FTIR can be used to determine drug concentration profiles and the extent of water penetration in HPMC extended drug release matrices [22].

5.3: materials and methods:

5.3.1 Materials:

All materials used in this chapter are described in Appendix 1. HPMC and PEO were the same batches used throughout this thesis.

5.3.2: Methods:

5.3.2.1 Manufacture of matrix tablets:

The matrix tablets used in these studies contained HPMC, PEO or were binary combinations of HPMC: PEO in the weight ratios of 8:2, 6:4, 4:6 and 2:8. Batches of 100g were mixed for 20 minutes in a Turbula mixer at 47rpm (Willy A. Bachofen AG Maschinenfabrik, Basel, Switzerland). Magnesium stearate (0.5% w/w) was added and the blend was mixed for another five minutes. Compression into 8mm diameter round flat tablets (250 ± 3 mg) was undertaken at 160MPa on a Riva Piccola rotary press (Riva, Buenos Aires, Argentina). (The same batch size as chapter 2)

5.3.2.2 Confocal laser scanning microscopy

A Bio-Rad MRC-600 confocal microscope (Hemel Hempstead, UK) equipped with a 15mW Krypton Argon laser, a Nikon Optiphot upright microscope, 4x/0.13NA air objective was used in the experiment. Bajwa et al. have reported that Congo red solutions of 0.008% w/v were a suitable fluorophore for this type of study [5]. Experiments were undertaken at 37°C hydrating the matrices with aqueous 0.008% w/v Congo red solution, using the method described in Chapter 3. Images were taken at intervals up to t=15 minutes and processed using Image Pro Plus image analysis software (Media Cybernetics) as described in Chapter 3.

A dry tablet image was taken before putting the media into the hydration cell, and obtaining images of early gel development at intervals over a period of 15 minutes. The thickness of the early hydrated gel layer was determined by overlaying a grid of 10 radiating lines, and measuring the distance between the original dry tablet boundary and the outer edge of the gel layer for each line. This method is illustrated in figure 5.1. Gel layer thickness was expressed as the mean of the 10 measurements.

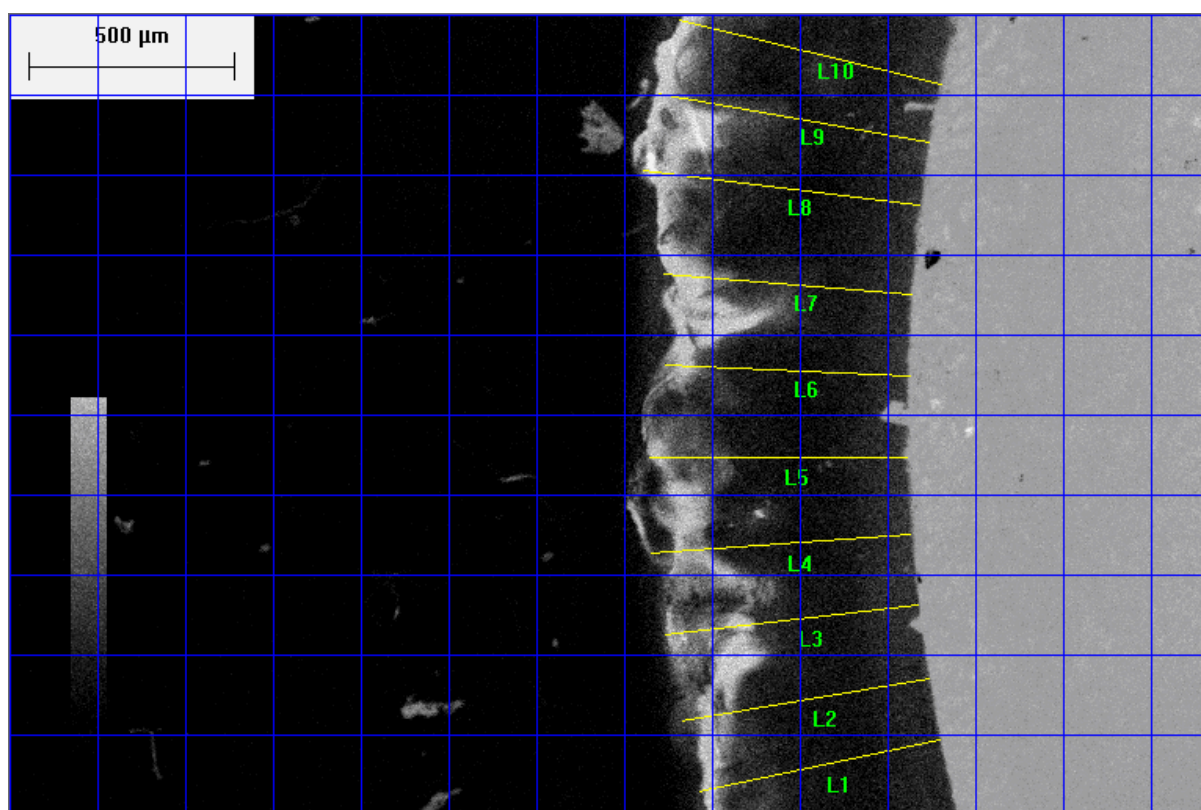


Figure 5.1: The measurement of hydrated hydrophilic matrix gel layer growth after 15 minutes. The grey circle is the image of the original dry tablet perimeter, which was superimposed on each confocal image. The yellow lines (L1 to L10) are the grid used to calculate the average mean thickness of the gel layer.

5.3.2.3 ATR-FTIR imaging

An Agilent 680-IR FT-IR spectrometer was used to collect infrared images in real time. An image of 64 x 64 pixels (4096 spectra) were collected from an image area of 640 μm x 640 μm using the Golden Gate™ Imaging Single Reflection ATR Accessory (Specac Ltd), coupled with a mercury cadmium telluride focal plane array detector MCT-FPA cooled by liquid nitrogen. In the image, therefore, each of the pixels represented a 10 μm x 10 μm square, and one spectrum. Images were recorded in rapid scan mode with overall image collection time of around 3 minutes.

The experimented geometry is shown in figure 5.2. A matrix tablet was carefully placed to cover 1/3 of the area of ATR crystal, and sufficient pressure applied to obtain good surface contact. Once a satisfactory dry image had been collected, the aqueous hydrating fluid was introduced and images collected at intervals. Experimental temperature was controlled at 37 ± 1 °C.

The raw IR images were collected using the Agilent Technologies' Resolutions Pro FTIR Spectroscopy software version 5.2.0(CD846) and pre-processed using MATLAB Version 7.10 (R2010a). The pre-processing steps were; (i) cropping the spectra between 1800 and 900 cm^{-1} (this region includes the characteristic bands associated with HPMC, PEO and also the water $\delta(\text{OH})$ peak ~ 1640 cm^{-1}), (ii) applying a second derivative with a polynomial order of 3 and filter length of 13 in order to remove pixel to pixel baseline variations. In order to remove systematic discrepancies such as variations in detector and contact non-uniformity, all raw IR images were then vector normalised to minimise absorbance variance. Vector normalisation works such that each spectrum is divided by the vector length which is square root of the sum of all absorbance values squared.

Following pre-processing, Multivariate Curve Resolution–Alternating Least Squares (MCR-ALS), an iterative resolution method applicable to Hyperspectral data sets [23]. It was used to separate component spectra and corresponding spatial distribution as multivariate image analysis, which provide better spatial resolution and quantitative information inherited from the ability of deconvolution compared to peak height image analysis [23].

Water, HPMC and PEO images were generated using ALS2004 software [24] . This runs in MATLAB 7.10 (R2010a) as a toolbox to deconvolute individual component spectra from the multicomponent spectra using the MCR-ALS algorithm. It also plots the spatial distribution of each estimated component based on its calculated score. The detail of the algorithm is given elsewhere [25] and the parameters used were; non-negativity, unimodality, the number of components (2 or 3) and initial estimates of the single component spectra.

This data analysis was undertaken by Dr Hakan Keles at the Materials Engineering Research Institute at Sheffield Hallam University.

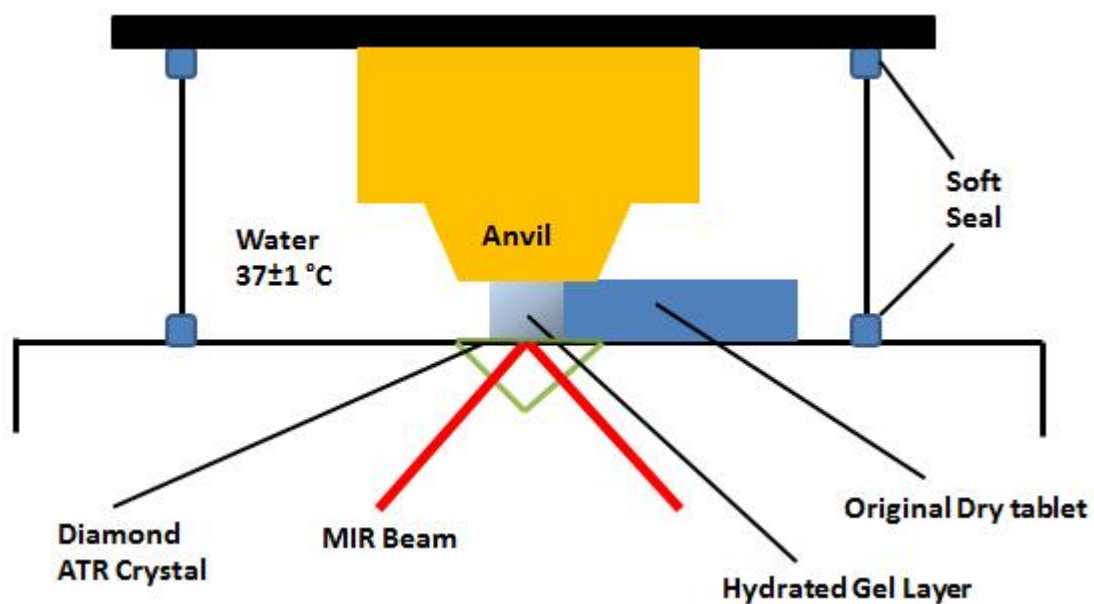


Figure 5.2: Schematic diagram of the experimented geometry for the ATR-FTIR imaging. The dry tablet was placed under the anvil, to cover 1/3 of the ATR crystal area, and pressure was applied. Hydration fluid was then added and imaging undertaken using the MIR beam. Temperature 37 ± 1 °C

5.4 Results and Discussion

5.4.1 Studies of early gel layer formation

5.4.1.1 Early gel layer morphology in binary matrices

The confocal microscopy studies in chapter 3 and chapter 4, have confirmed that 0.008% w/v Congo red can stain HPMC and PEO gel layers but with different fluorescent intensities. HPMC appears bright in the images, especially at the matrix periphery, whereas PEO exhibited a uniform and low-level fluorescence.

Figure 5.3 shows the very early gel layer formation (1 minute) in HPMC, PEO and mixed polymer matrices. All the matrices formed a gel layer within the first minutes of hydration. All images showed four major regions: (i) the hydration media with minimal fluorescence, (ii) Congo red binding at the periphery of matrices containing HPMC, with good detail in the high fluorescent region, (iii) an inner hydrated gel layer with less fluorescence from Congo red binding, and (iv) a dry core with a very low fluorescence. There were observable differences in gel layer morphology within the gelled region.

In the single HPMC matrices, polymer particles were swelling in a columnar manner and there was highlighting of hydrated areas where Congo red had bound. This was not observed in the PEO matrix, the hydrated layer appeared thicker and more uniform and of much lower fluorescent intensity. The former suggests that PEO swells more rapidly, and the latter that Congo red spreads uniformly through the PEO gel, reducing the features we might see. In the binary matrices it appeared that the two polymers hydrated separately. As both types of staining are seen, giving the appearance of irregular swelling within the gel.

Figure 5.4 shows the images of gel layer 15 minutes hydration. At this time point in the HPMC matrix, only the outer gel was highly fluorescent, a similar result to that seen in Chapter 3, for the formulated matrix. We believe this occurs because Congo red can only gain access rapidly through pore channels or by slow diffusion through the gel. As rapid swelling had blocked the porous channels, further penetration fluorophore was retarded

and highly fluorescent area was dye binding to the outer layer of swollen HPMC [5]. In contrast, the PEO hydrated gel layer showed a uniform fluorescence, although at a lower signal intensity to HPMC. This suggests that Congo red did not bind strongly to PEO and was free to diffuse throughout the gel layer. In binary matrices therefore, there may be deeper penetration of Congo red as it can penetrate through hydrated PEO regions.

The binary matrices exhibited a discontinuous and non-uniform gel layer. After 15 minutes hydration, HPMC rich regions of high fluorescent intensity and PEO rich regions of low fluorescent intensity could be easily identified. The images confirmed that during early gel layer formation, HPMC and PEO particles were swelling separately, and that HPMC appeared to be embedded within a PEO hydrated gel layer. The two polymers however, can form a coherent diffusion barrier, which shows that there may be interparticulate bonding between swollen particles of HPMC and PEO. This can happen because there highly hydrated polymer can deform and flow to fill the space between each other's surface. There is significant opportunity for molecular interaction and interpenetration at these surfaces.

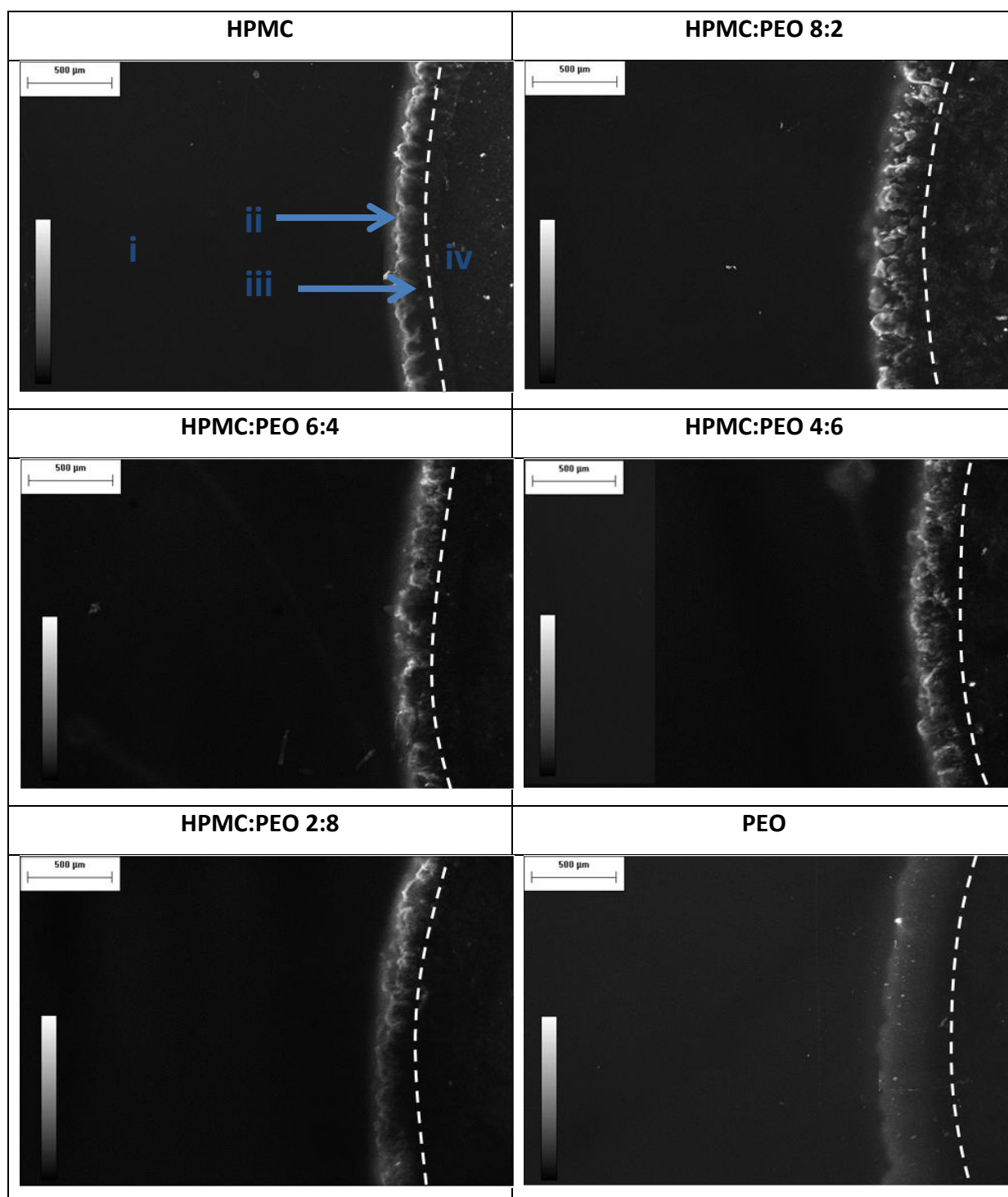


Figure 5.3: Confocal images of gel layer growth at 1 minute with respect to polymer composition of the matrix. (i) Medium, (ii) outer hydrated gel layer, (iii) inner hydrated gel layer, (iv) dry core. Confocal fluorescence imaging at Ex 488/EmN510 nm. Experiments conducted at 37 ± 1 °C using 0.008% w/v Congo red. Images coded for fluorescence intensity using a continuous grayscale (White highest, black lowest). Scale bar 500 μm

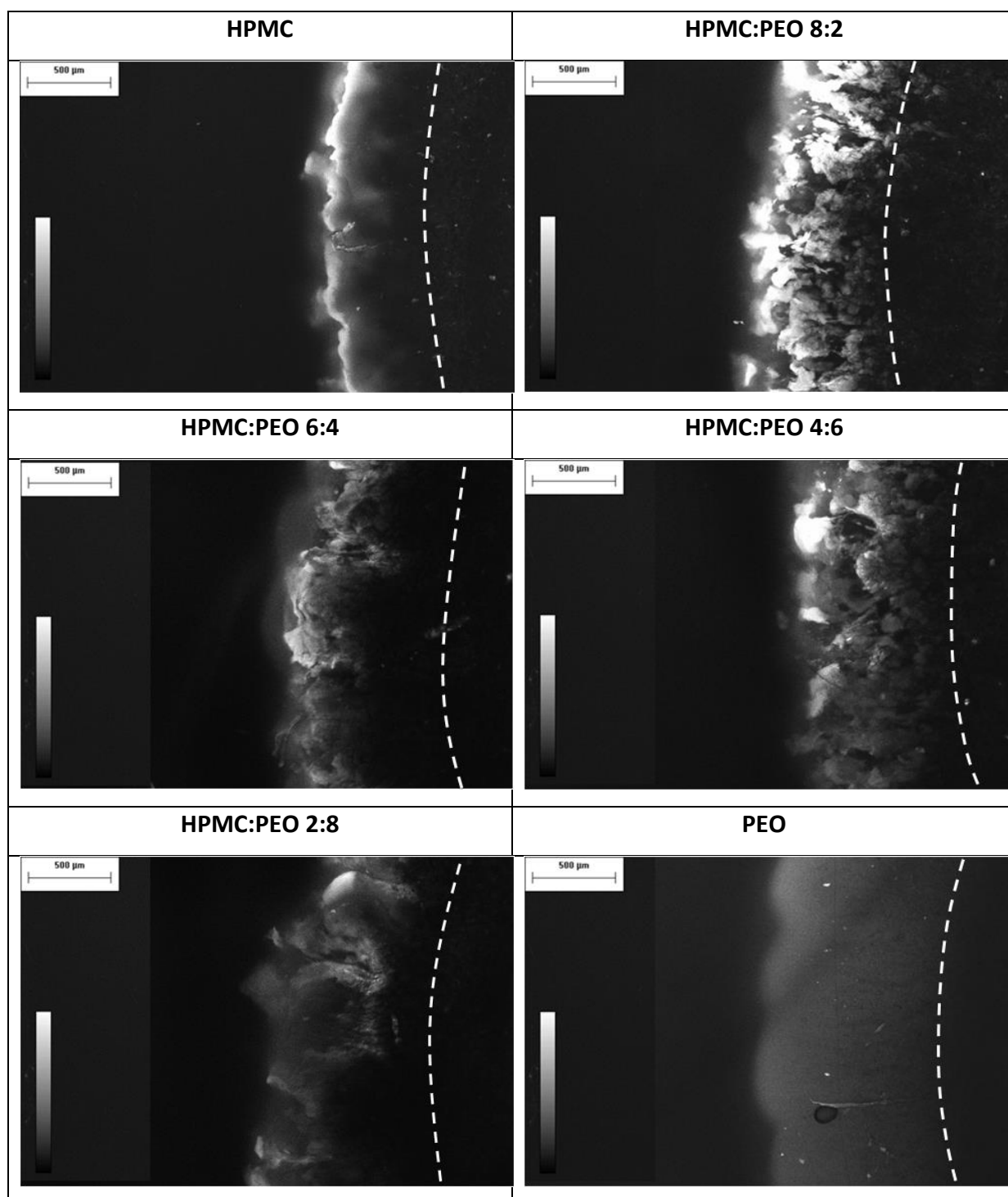


Figure 5.4: Confocal images of gel layer growth at 15 minute with respect to polymer composition of the matrix. Confocal fluorescence imaging at Ex 488/EmN510 nm. Experiments conducted at 37 ± 1 °C using 0.008% w/v Congo red. Images coded for fluorescence intensity using a continuous grayscale (White highest, black lowest). Scale bar 500 μm

5.4.1.2 Effect of NaCl on early gel layer formation

The results in chapter 4 showed that NaCl concentration can significantly affect HPMC particle swelling, [26-29]. It had only a limited effect on PEO particle swelling.

Figure 5.5 shows early gel layer growth with respect to HPMC and PEO polymer ratio and NaCl concentration. In 0M NaCl, gel layer growth after 15 minutes was less than 600 μm in the HPMC matrix, but 1000 μm in PEO matrices. This is a similar swelling result reported in previous research using different techniques [30], and the HPMC and PEO single particle swelling work in chapter 4, also supports this. When the PEO polymer ratio was increased gel layer thickness also increased, and at a HPMC and PEO polymer ratio of 4:6 or above, the matrices formed gel layers that were not significantly different to a single PEO matrix. This suggests that when a certain amount of PEO is present in the binary matrices, the early gel layer is mainly contributed by PEO particle swelling.

Figure 5.5 also showed that at increased NaCl concentrations, the HPMC gel layer reduced from slightly less than 600 μm to about 400 μm . In contrast, there was little effect on PEO gel layer growth at NaCl concentrations up to 1M. These results help us to understand how drug release from HPMC matrices can be significantly affected by NaCl concentration, whereas PEO matrices drug release was much less affected.

In binary HPMC:PEO matrices at ratios of 8:2, 6:4 and 4:6, early gel layer growth was inhibited by increasing NaCl concentration. These results suggest that in these binary matrices, HPMC particle swelling had a significant effect on matrices gel layer growth. At an HPMC: PEO polymer ratio of 2:8, however, NaCl had only a limited effect on the matrix. This suggests that at this ratio, the majority of gel layer growth is contributed by PEO swelling.

NaCl and other ionic species have been reported to inhibit HPMC particle swelling, with the result that HPMC particles do not coalesce rapidly enough to form a gel layer that retards water penetration. However, in this study, the single HPMC matrix was seen to form a compact gel layer in 1M NaCl media, a different outcome to previous studies [5, 31, 32]. The reasons for this could be (i), in Bajwa's study, a more hydrophobic HPMC (Methocel E4M CR Premium EP/USP) was used. Methocel E4M has a higher methoxyl substitution and a lower

molecular weight than HPMC K100M [4]. HPMC K100M may have a faster water uptake than the HPMC E4M, and the particles may swell quickly enough to coalesce and form a gel layer [30, 33]. Alternatively, the formulation used by Williams contained only 30% of HPMC polymer in the matrix. The soluble component (caffeine) and the lactose filler may dissolve and may also influence HPMC swelling [31, 32].

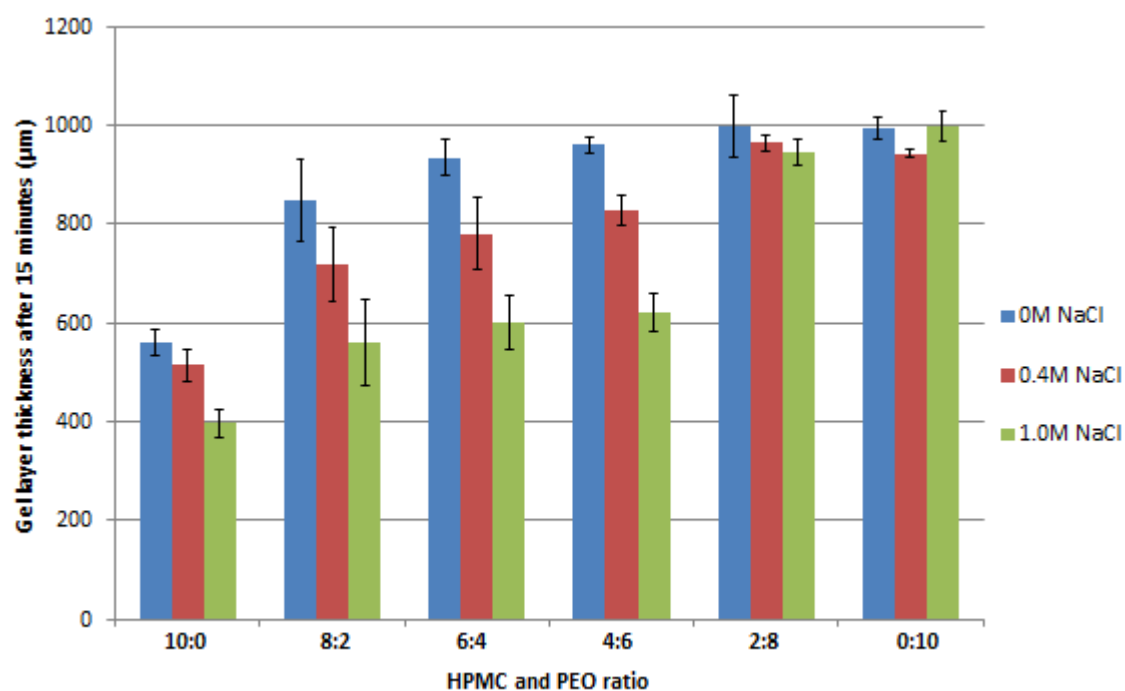


Figure 5.5: Gel layer thickness at 15 minutes with respect to polymer composition of the matrix and NaCl concentration. Data obtained from the confocal microscopy images using the method from figure 5.1. (n=10, $\pm$ SD)

5.4.2 Studies of later gel layer morphology up to 3 hours

5.4.2.1 FTIR-ATR imaging of a hydrating HPMC matrix

Before water was added into the system, a dry HPMC matrix was imaged as a reference, and to determine the exact position of the matrix edge. Figure 5.6 shows an FTIR spectrum obtained from the unhydrated HPMC matrix. It is similar to those obtained by other researchers. The HPMC showed a complex band between 1200 and 1000 cm^{-1} , comprised of numerous C-O vibrations which include those from glycosidic C-O-C, C-OH, C-OCH₃, and C-OCH₂CH₂OH groups [21, 22, 34, 35]. Using the method of MCR-ALS described in section 5.3.2.3, an image was generated and is shown in figure 5.7. This image was $640 \times 640\text{ }\mu\text{m}$ and based on the calculations was colour-coded for the presence of HPMC, red for high intensity and blue for low intensity. On the right side of the figure 5.7, about 1/3 of the pixels are red, which showed that the dry HPMC matrix covered 1/3 of the ATR crystal, and was in the position required.

Figure 5.8 shows the image of water penetration after 5 minutes into the HPMC matrix whilst figure 5.9 provides the image of HPMC concentration, based on the same spectral row data. In figure 5.8, the color change from red to blue suggests water concentration is reduced from left to right, typical of the water diffusion gradient that would be expected across the gel layer. Figure 5.9 shows the HPMC with an opposite concentration gradient to water. These results show how different components can be resolved with respect to their spectral intensity in each pixel. The images could clearly distinguish HPMC and water in the same system. Figure 5.10 shows a time series of images up to 180 minutes. These illustrate how water progressively penetrates the HPMC matrix and dilutes the HPMC.

It took around 60 minutes of gel layer growth to cover the whole image area ($640 \times 640\text{ }\mu\text{m}$) and the edge of the gel layer could not be seen after 180 minutes hydration.

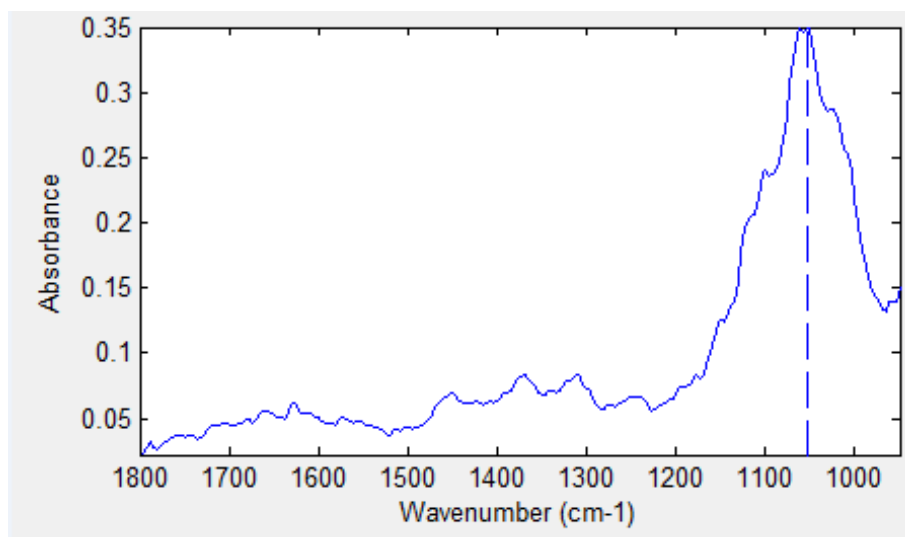


Figure 5.6: ATR-FTIR spectrum of an unhydrated HPMC matrix. Experiments conducted at 37 ± 1 °C

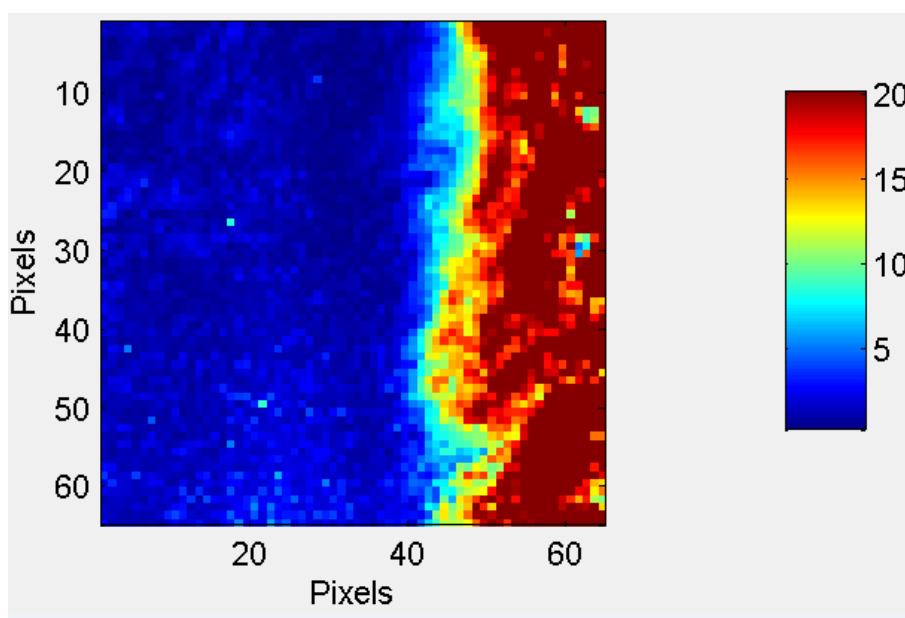


Figure 5.7: ATR-FTIR image of an unhydrated HPMC matrix. Experiments conducted at 37 ± 1 °C, 640×640 μm . Red colour denotes a high HPMC intensity, and blue colour denotes a low HPMC intensity

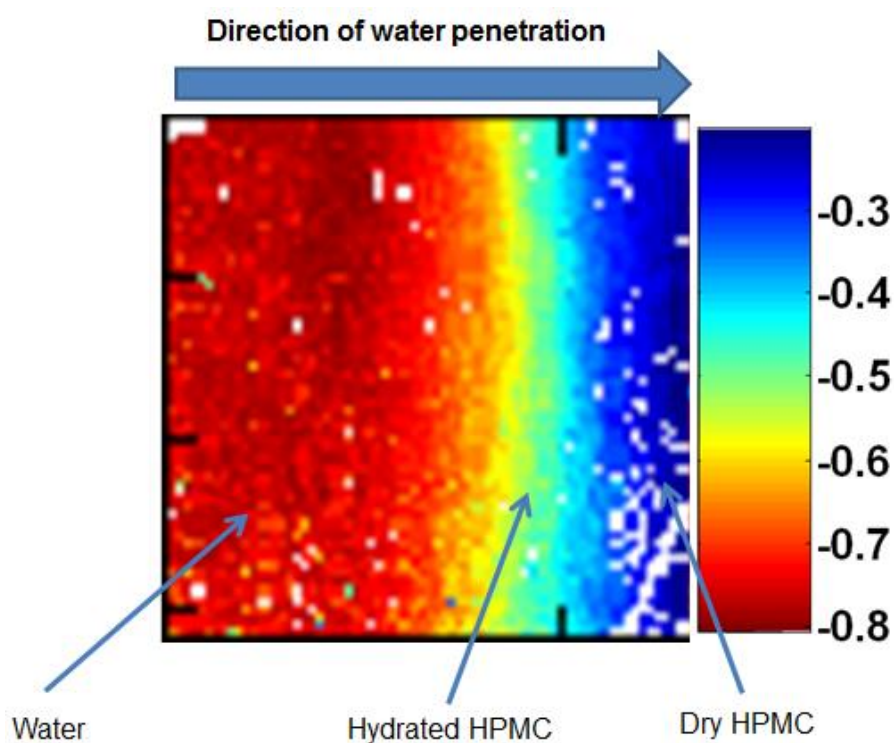


Figure 5.8: ATR-FTIR image of water in an HPMC matrix hydrated system for 5 minutes, mapping based on water signal extracted from the ATR-FTIR spectra. Experiments conducted at 37 ± 1 °C, 640×640 μm . Red colour denotes high water intensity, and blue colour denotes low water intensity

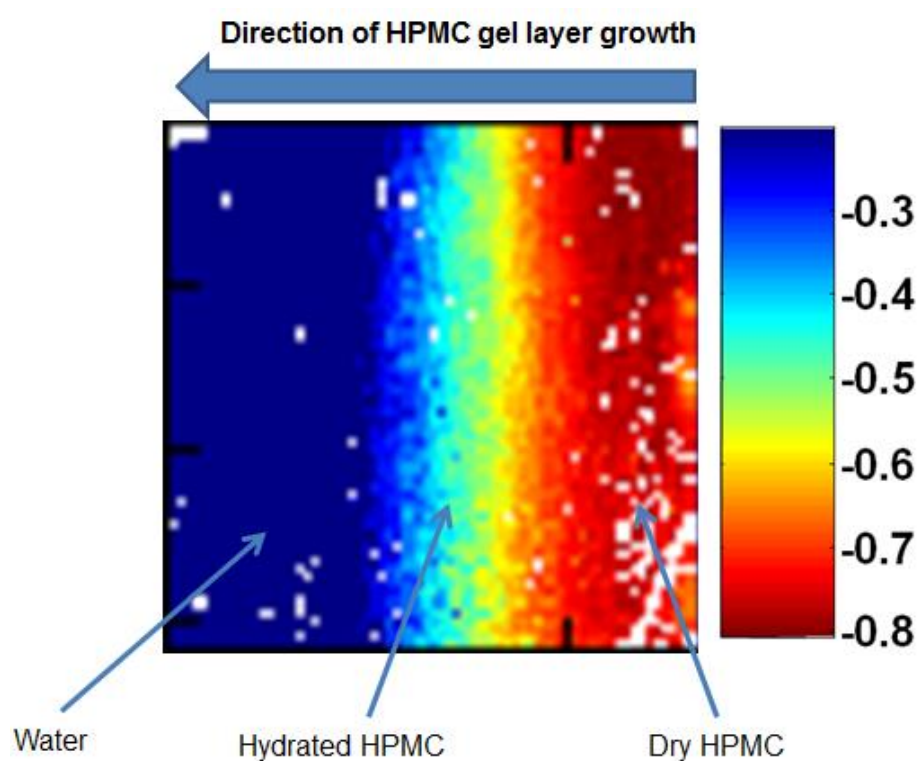


Figure 5.9: ATR-FTIR image of HPMC in an HPMC matrix hydrated for 5 minutes. Mapping based on HPMC signal extracted from the ATR-FTIR spectra. Experiments conducted at 37 ± 1 °C, 640×640 μm . Red colour denotes high HPMC intensity, and blue colour denotes low HPMC intensity

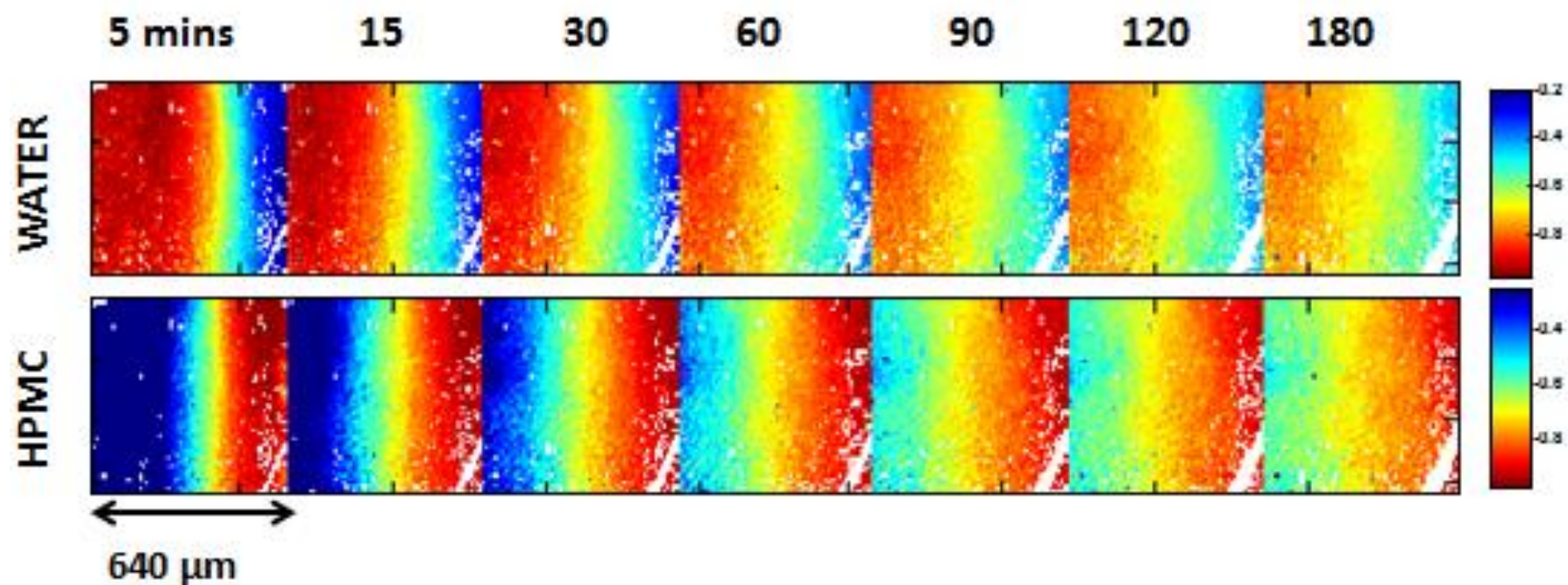


Figure 5.10: A time sequence of FTIR images showing water penetration and a HPMC matrix during hydration up to 180 minutes. Upper row mapping based on water signal extracted from the ATR-FTIR spectra, and lower row based on HPMC signal extracted from the ATR-FTIR spectra. Experiments conducted at 37 ± 1 °C, 640×640 μm. Red colour denotes high component intensity, and blue colour denotes low component intensity.

5.4.2.2 FTIR-ATR imaging of a hydrating PEO matrix

Figure 5.11 shows the FTIR spectrum from an unhydrated PEO matrix and the functional groups also identified by previous researchers: 1469 cm^{-1} (CH_2 stretching), 1342 cm^{-1} (CH_2 wagging), 1280 cm^{-1} and 1242 cm^{-1} (CH_2 twisting), 1148 cm^{-1} and 1113 cm^{-1} (CO stretching), 1062 cm^{-1} (CO stretching, CH_2 rocking, CC stretching), 963 cm^{-1} (CH_2 rocking, CH_2 stretching), and 843 cm^{-1} (CH_2 rocking, CO stretching) [36-39]. These peaks provided information for further analysis by MCR-ALS (section 5.3.2.3) using the method originally developed by Dr Keles [23].

Figures 5.11 and 5.15 show images from PEO matrix hydration corresponding to those obtained for HPMC. (ATR-FTIR mapping of PEO under hydration has been undertaken by previous researchers using other spectrum mapping analysis methods such as peak high integration [14, 21, 36].

A comparison of figures 5.9 and 5.14 provides clear evidence that gel layer growth in the PEO matrix occurred more quickly than in the HPMC matrix, even in the very early stages of hydration. This correlates with the results observed in the HPMC and PEO particle swelling and confocal microscopy studies.

Figure 5.15 shows changes in water and PEO concentrations up to 180 minutes. Water took 30 minutes to penetrate the whole image area, and PEO gel layer growth took 30 minutes to cover the image. After one hour, the edge of the gel layer had moved out of the image area. There was little change in the water and PEO maps after 60 minutes.

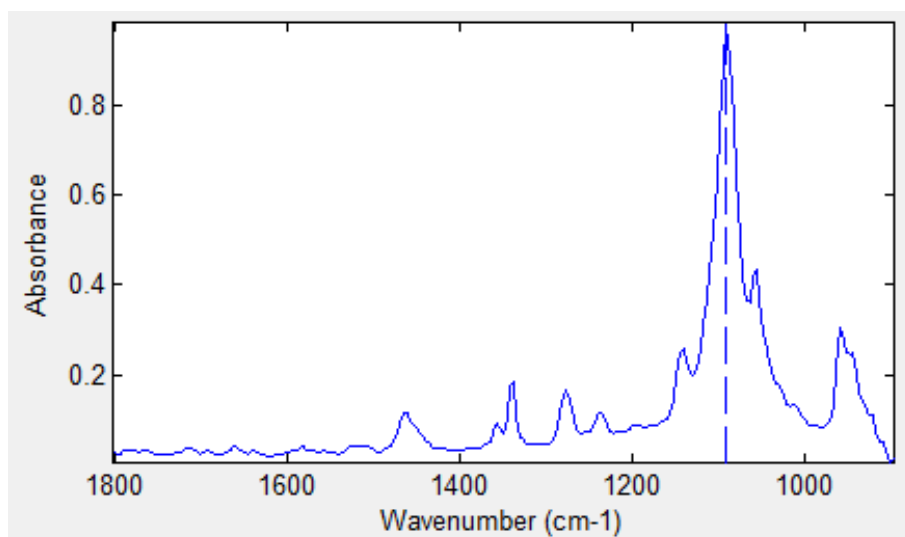


Figure 5.11: ATR-FTIR spectrum of an unhydrated PEO matrix. Experiments conducted at 37 ± 1 °C

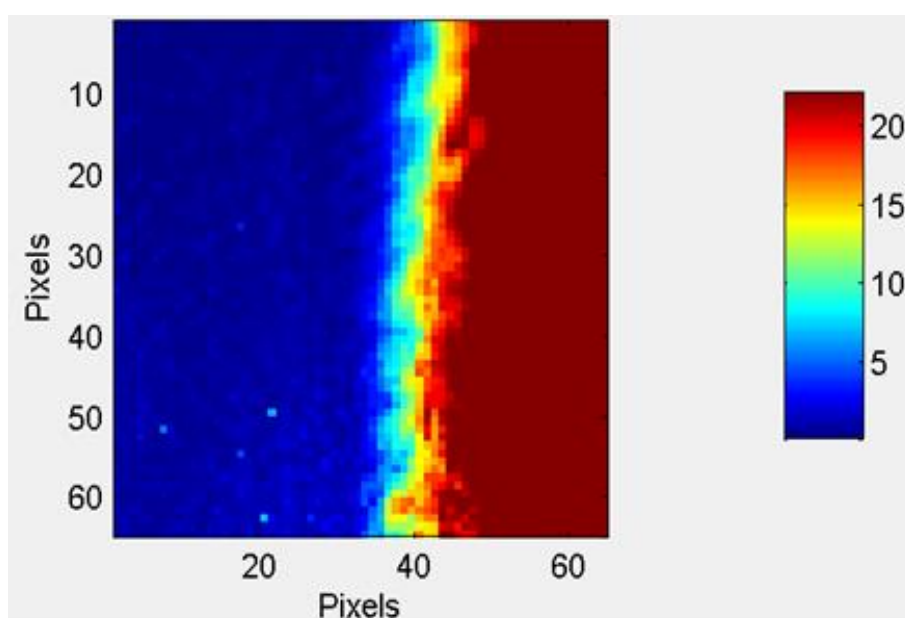


Figure 5.12: ATR-FTIR image of an unhydrated PEO matrix. Experiments conducted at 37 ± 1 °C, 640×640 μm . Red colour denotes a high PEO intensity, and blue colour denotes a low PEO intensity

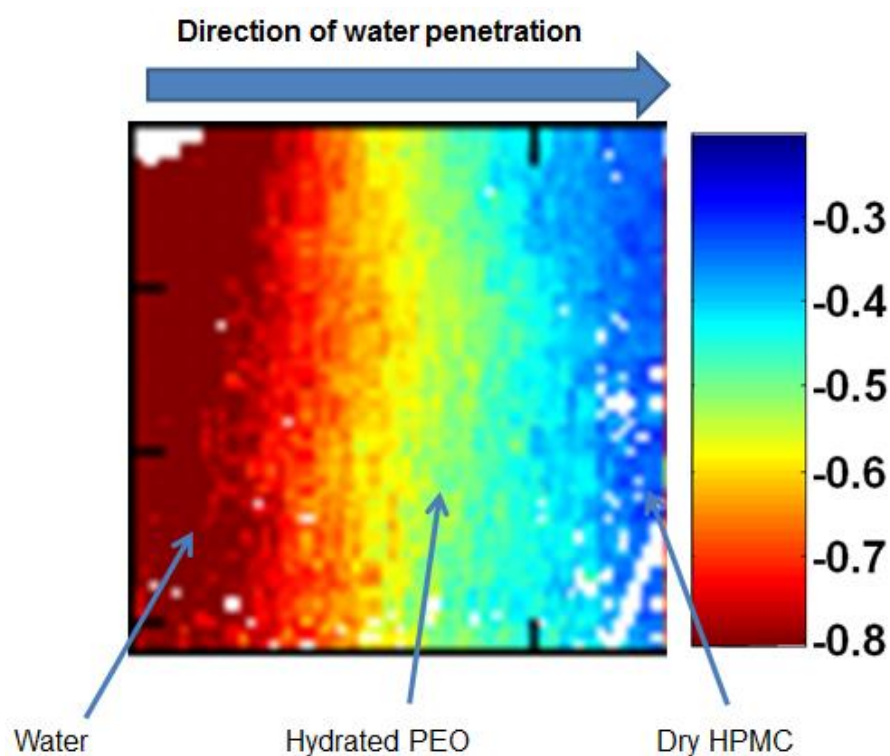


Figure 5.13: ATR-FTIR image of water in a PEO matrix hydrated system for 5 minutes. Mapping based on water signal extracted from the ATR-FTIR spectra. Experiments conducted at 37 ± 1 °C, 640×640 μm . Red colour denotes high water intensity, and blue colour denotes low water intensity

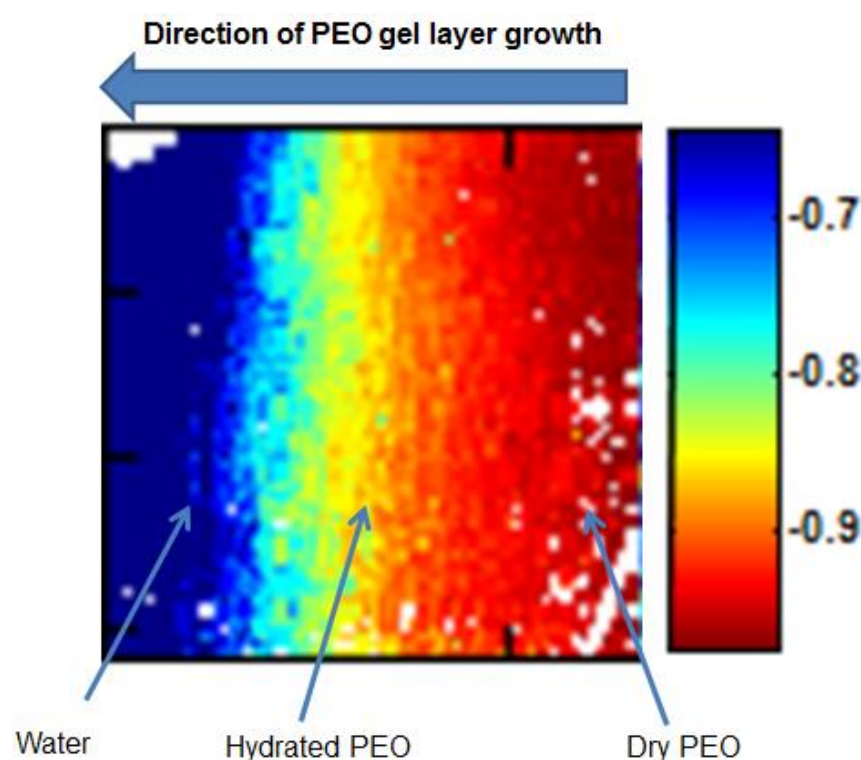


Figure 5.14: ATR-FTIR image of PEO in a PEO matrix hydrated for 5 minutes, mapping based on HPMC signal extracted from the ATR-FTIR spectra. Experiments conducted at 37 ± 1 °C, 640×640 μm . Red colour denotes high PEO intensity, and blue colour denotes low PEO intensity

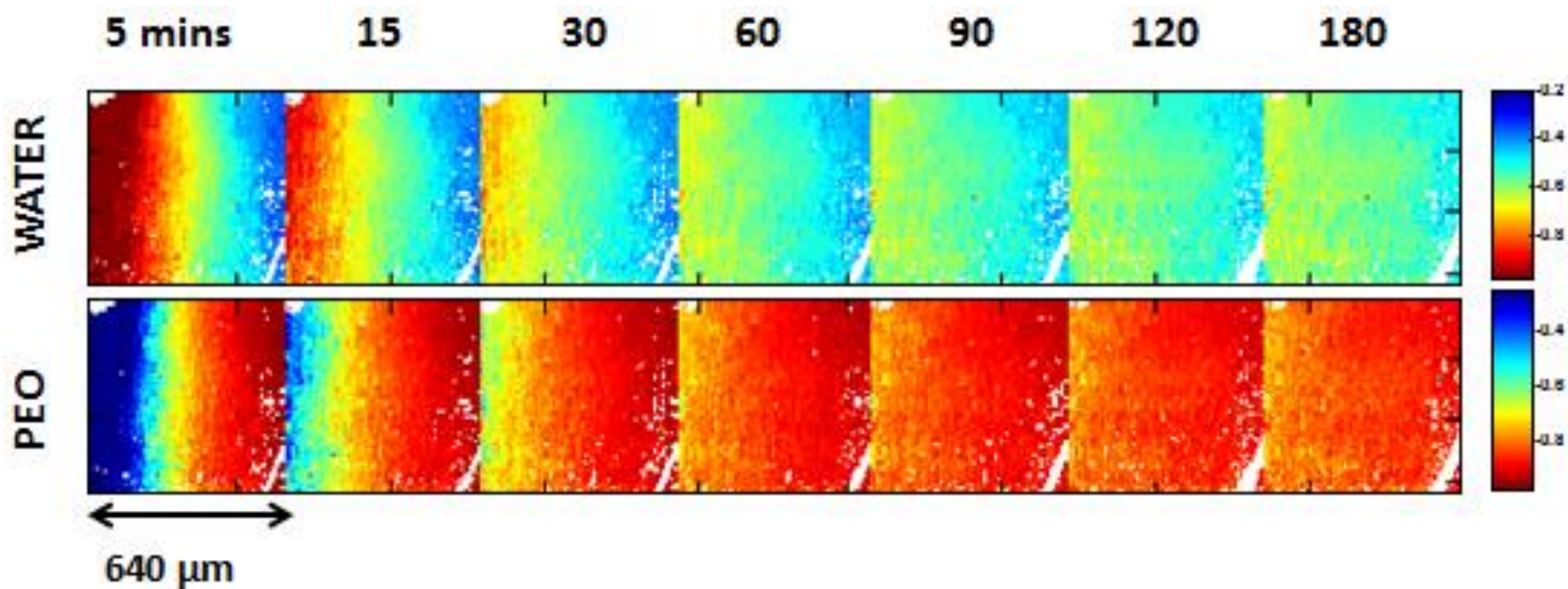


Figure 5.15: A time sequence of FTIR images showing water penetration and a PEO matrix during hydration up to 180 minutes. Upper row mapping based on water signal extracted from the ATR-FTIR spectra, and lower row based on PEO signal extracted from the ATR-FTIR spectra. Experiments conducted at 37 ± 1 °C, 640×640 μm. Red colour denotes high component intensity, and blue colour denotes low component intensity.

5.4.2.3 FTIR-ATR imaging of a hydrating binary HPMC: PEO (4:6) matrix

The previous two sections (5.4.2.1 and 5.4.2.2) show how dry and hydrated single HPMC and PEO matrices can be successfully mapped under ATR-FTIR. However, the key aim of this chapter was to investigate the gel layer morphology of a mixed HPMC:PEO tablet. A matrix with a HPMC:PEO ratio of 4:6 was chosen for this study.

The unhydrated binary matrix is shown in figure 5.16, which shows the overall matrix position without any resolution of the two different polymers. Figure 5.17 shows a map based on PEO spectral intensity, with areas of high PEO concentration showing as red or yellow. In the observed area, the PEO occupies the inner side of the image, with a few PEO particles also embedded in HPMC.

Figures 5.18 and 5.19 show the images of HPMC and PEO after 5 minutes hydration. The separate regions of high HPMC and PEO concentration provide evidence that, in this early stage of gel layer growth, the two polymers hydrate independently as was observed in confocal microscopy study (5.4.1.1). Figures 5.18 and 5.19 also show that HPMC was located in the inner part of the hydrated gel layer whereas PEO occupied the outermost region of the hydrated layer. This was even though most of PEO polymer was observed to be located inside the HPMC in the unhydrated matrix (figure 5.17). The position of PEO in the hydrated gel layer probably arises from the more rapid swelling of PEO, as previously seen in sections 4.4.1 and 5.4.1.2, which together illustrated how PEO particle swelling was much faster than HPMC particles in single particles, in single polymer matrices, and in the binary matrices.

Figure 5.20 shows the changing distribution of the three components (water, HPMC, PEO) in a time series of images up to 180 minutes hydration. There is progressive penetration of water, and PEO exhibits further expansion but the HPMC regions within the hydrated gel remained a similar shape and size. This suggests PEO particles may swell preferentially either due to a higher water affinity than HPMC or because PEO may be inhibiting HPMC particle swelling as reported by Jayan et al [40]. In these series of images, PEO in the hydrated gel layer was constantly in front of the HPMC hydrated gel layer, which suggests that, when a binary HPMC and PEO matrix hydrates, PEO may form an outer gel layer with the HPMC gel layer (embedded in swollen PEO) appearing to form an inner gel layer.

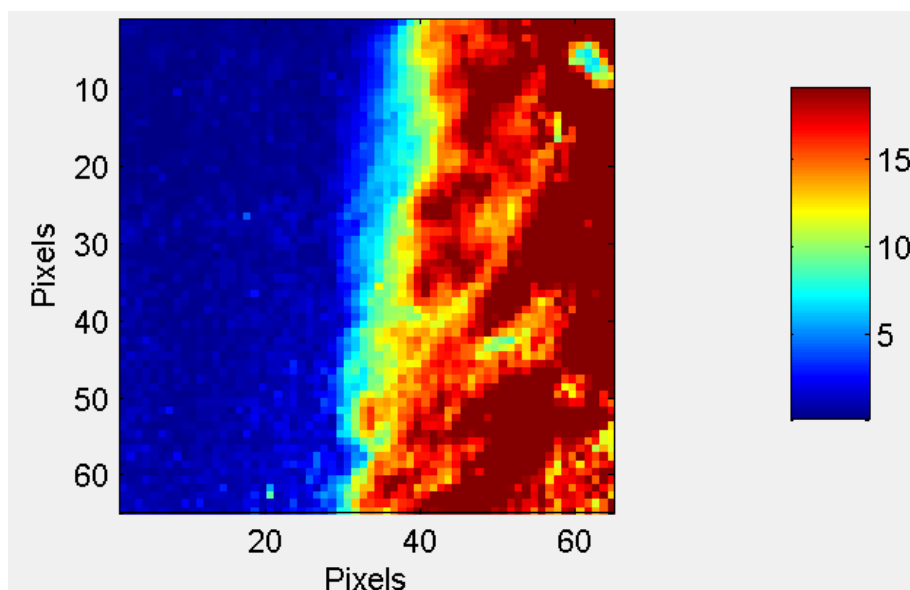


Figure 5.16: ATR-FTIR image of an unhydrated binary matrix (HPMC: PEO 4:6). Experiments conducted at 37 ± 1 °C, 640×640 μm . Red colour denotes high unspecified polymer intensity, and blue colour denotes a low unspecified polymer intensity

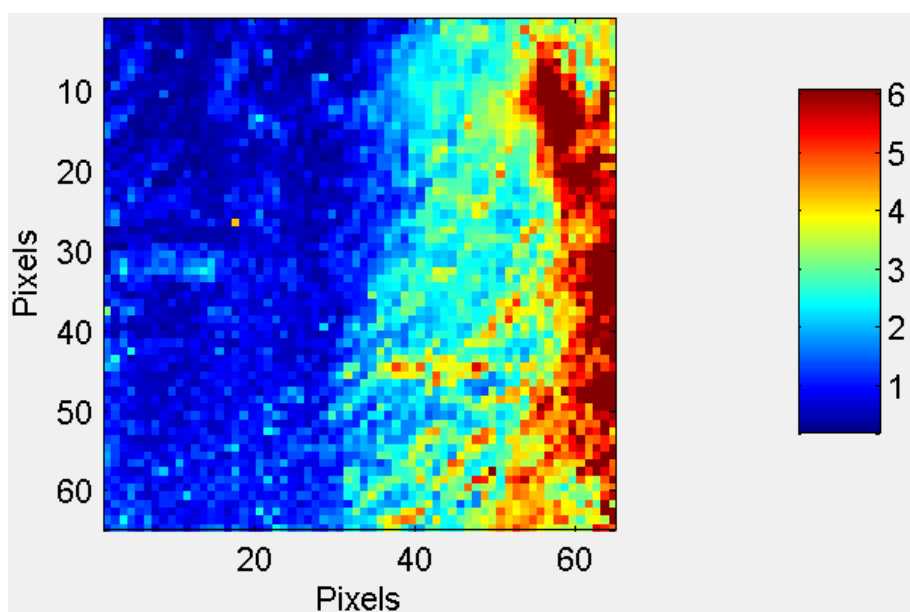


Figure 5.17: ATR-FTIR image of an unhydrated binary matrix (HPMC: PEO 4:6). Experiments conducted at 37 ± 1 °C, 640×640 μm . Red colour denotes a high PEO intensity, and blue colour denotes a low PEO intensity.

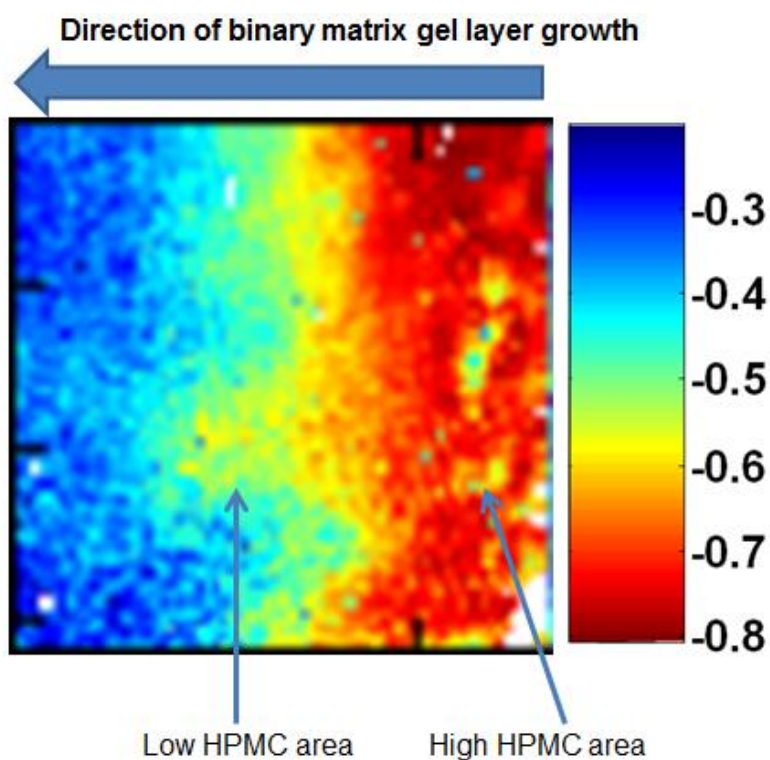


Figure 5.18: ATR-FTIR image of HPMC in a binary matrix (HPMC: PEO 4:6) hydrated for 5 minutes. Mapping based on HPMC signal extracted from the ATR-FTIR spectra. Experiments conducted at 37 ± 1 °C, 640×640 μm . Red colour denotes high HPMC intensity, and blue colour denotes low HPMC intensity

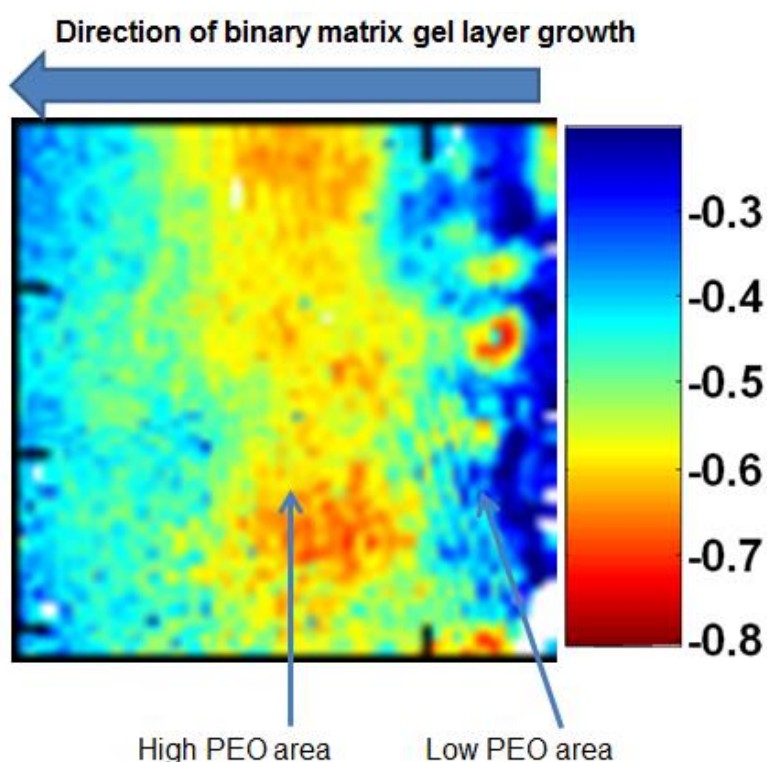


Figure 5.19: ATR-FTIR image of PEO in a binary matrix (HPMC: PEO 4:6) hydrated for 5 minutes. Mapping based on PEO signal extracted from the ATR-FTIR spectra. Experiments conducted at 37 ± 1 °C, 640×640 μm . Red colour denotes high PEO intensity, and blue colour denotes low PEO intensity.

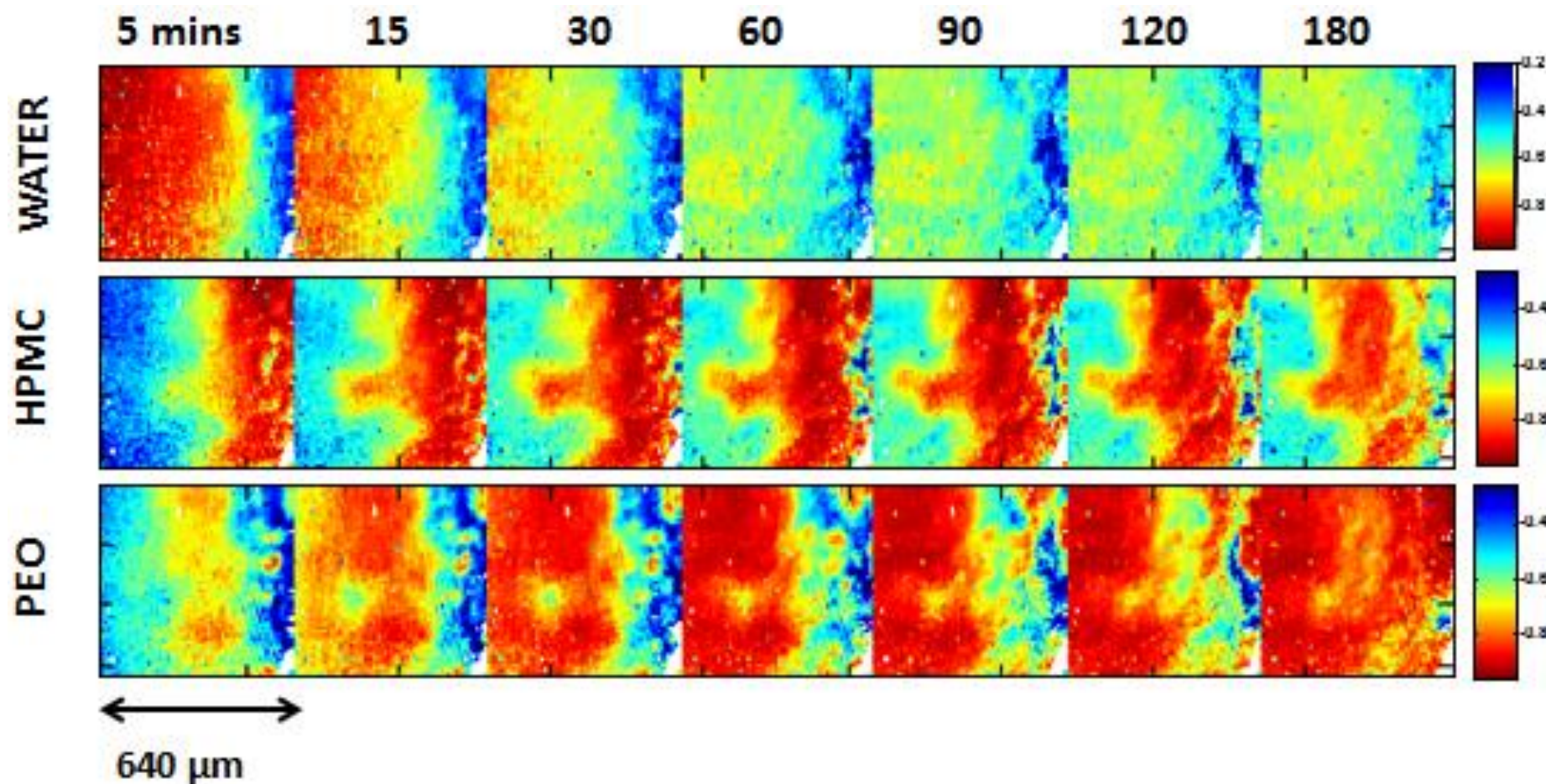


Figure 5.20: A time sequence of FTIR images showing water penetration and a binary matrix (HPMC: PEO 4:6) during hydration up to 180 minutes. Upper row mapping based on water signal extracted from the ATR-FTIR spectra, middle row based on HPMC signal extracted from the ATR-FTIR spectra, and lower row based on PEO signal extracted from ATR-FTIR spectra. Experiments conducted at 37 ± 1 °C, 640×640 μm. Red colour denotes high component intensity, and blue colour denotes low component intensity.

5.5 Conclusions

The works in this chapter have used confocal microscopy to investigate early gel layer growth with respect to the polymer composition of single and binary polymer HPMC:PEO matrices and NaCl concentration in the hydrating medium. The results show how early gel layer growth in HPMC matrices can be significantly inhibited at high NaCl concentrations. In single PEO matrices and binary matrices containing at least 80% of PEO, NaCl concentration had a very limited effect on gel layer growth.

The confocal microscopy studies suggested that the HPMC and PEO might be phase separated in the early matrix gel layer, and ATR-FTIR studies over a longer hydration period (180 minutes) indicated that the two polymers hydrated and swelled independently. The ATR-FTIR images also suggest that PEO swells in preference to HPMC particles in the gel layer, resulting in a gel layer structure which consists of PEO forming an outer gel layer, and HPMC rich regions comprising the inner gel layer.

Previous studies had shown how both polymers had advantages and disadvantages: PEO matrices have less ionic sensitivity than HPMC matrices, but less gel layer strength. Figure 21 shows the results obtained in this chapter, provide more evidence to support the hypothesis in chapter 4: that the binary HPMC and PEO matrix could automatically form a gel layer, with the less NaCl sensitive PEO swelling faster to form an outer gel layer, which then protects HPMC particles from ionic influence. In return, the HPMC provides a higher strength gel layer in the inner part of the matrix to maintain matrix gel layer integrity at later dissolution times. As this mixed polymers gel layer brings the two polymer advantages together, this provides better opportunities to control drug release, in that the mixed polymer matrices provided longer drug release than a PEO matrix, and higher ionic resistance than a HPMC matrix.

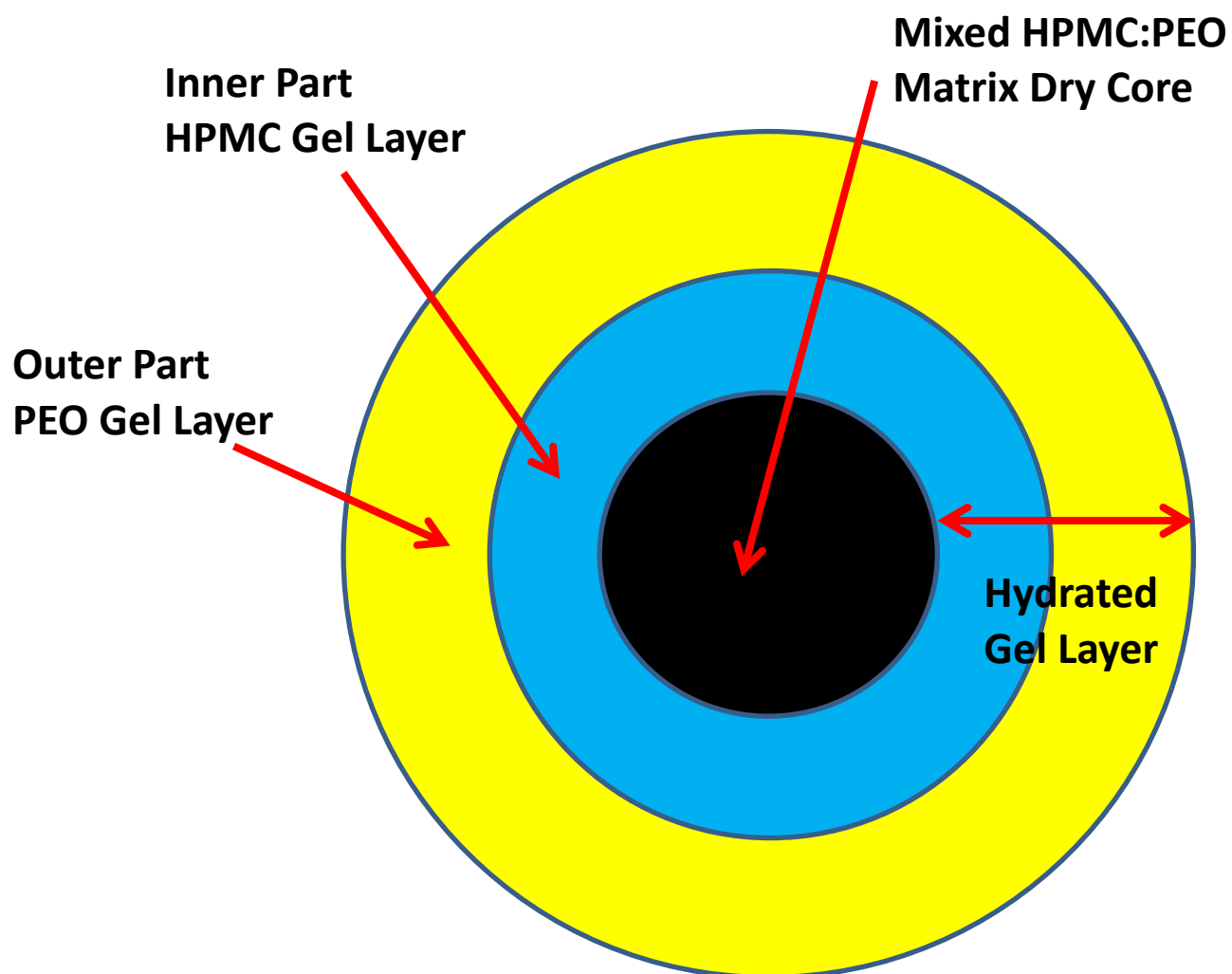


Figure 5.21: Hydrated mixed polymer HPMC:PEO matrix gel layer morphology.

5.6 Reference

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Chapter 6

Summary, Discussions and Future Work

6.1 Summary

The principal aims of this thesis were to explore if hydrophilic matrices containing mixtures two polymers HPMC and PEO, could possess advantages over the use of single polymers. A further aim was to understand the behaviour of the mixed HPMC:PEO matrix system. In this chapter, the key findings of this thesis will be summarised and discussed.

Chapter 2 developed and designed matrices based on HPMC, PEO and blends of these polymers in different ratios. The recommended polymer content of 30% was used in all formulations and caffeine was chosen as a model drug for the study as it has pH independent solubility, good stability, and suitable UV characteristics.

The results of chapter 2 showed that:

- I. Matrices could be easily manufactured by direct compression, to give tablets of acceptable hardness, at all the polymer ratios studied.
- II. HPMC and PEO matrices were resistant to fruit juices and a homogenised FDA breakfast although it was found that HPMC matrices disintegrated into a concentrated juice intended for dilution. These media were rejected in favour of NaCl as a solute challenge.
- III. NaCl solutions over the range 0 to 1.0M affected the disintegration times and drug release profiles of HPMC based matrices. These were used as an ionic challenge to mimic low to extremely high ionic environments.
- IV. Disintegration and dissolution tests showed that HPMC (but not PEO) matrices were affected by high NaCl concentration. Above 0.8M NaCl, HPMC matrices disintegrated rapidly and exhibited burst drug release, whilst PEO matrices did not.

- V. A range of fillers (tablet diluents) were examined. Changing from a more water soluble to a less water soluble filler prolonged drug release but did not significantly increase the robustness of HPMC matrices to high concentrations of NaCl.
- VI. Substituting HPMC for PEO extended drug release profiles in low NaCl media up to 0.6M and conversely, the substitution of PEO for HPMC produced matrices that were better resistant to ionic environments. When the HPMC:PEO ratio was 4:6 or 2:8, the matrices provided extended drug release profiles unaffected by 1.0M NaCl.
- VII. The best overall combination of drug release profile and ionic robustness appeared to be matrices containing 4:6 HPMC:PEO.

Chapter 3 used techniques to help us understand the drug release behaviour of matrices with different polymer compositions. Water penetration was examined by MRI, early gel layer formation by confocal fluorescence imaging, gel layer strength by texture analysis and the later stages of gel layer development and matrix hydration by sectioning and macroscopic optical imaging.

The results from this chapter suggested that:

- I. In low NaCl concentration media (<0.4M), all matrices formed compact and coherent early gel layers. However, in 1.0M NaCl, HPMC matrices failed to form a hydrated barrier and liquid penetrated into the matrices rapidly. This lack of diffusion barrier explained the burst drug release seen in dissolution tests.
- II. Substituting PEO for HPMC (at polymer ratios of HPMC:PEO 6:4, 4:6 and 2:8) resulted in matrices formed a gel layer in the early stage of matrices hydration. This matched the dissolution test results from chapter 2, and suggested that, the early gel layer formation could be one of the conditions for whether hydrophilic matrices were able to provide extended drug release in ionic media.
- III. Water penetration is one of the principal factors controlling drug release kinetics from hydrophilic matrices. MRI studies showed how water penetration into PEO matrices occurred much more rapidly than in HPMC matrices. HPMC:PEO 4:6 matrices exhibits were intermediate, showing that by substituting HPMC for PEO retarded water penetration. This explains how (in low NaCl concentration media)

the HPMC and mixed polymer matrices could provide longer drug release than PEO matrices in the dissolution tests in chapter 2.

- IV. Unfortunately whilst MRI provided clear evidence of faster water penetration into PEO matrices, the sensitivity of MRI to ionic salts meant that media with added NaCl could not be used. Therefore to understand matrices in the later stages of hydration, in the presence of salt, optical imaging of sectioned matrices was undertaken.
- V. Texture analysis has been used previously to understand the gel layer strength, as this can also influence drug release profile from hydrated matrices. Substituting HPMC for PEO appeared to result in an increase in gel layer strength, which again supported the dissolution test results, where substituting HPMC provided longer drug release than matrices containing PEO alone.
- VI. Digital imaging of sectioned matrices showed how, in low NaCl media (<0.4M), substituting HPMC for PEO improved matrix longevity whilst the presence of PEO in HPMC matrices (at HPMC:PEO 4:6), provided resistance to 1.0M NaCl media,.

In Chapters 2 and 3, the behaviour of fully formulated, commercially realistic, matrices containing 30% polymer, an active ingredient, a diluent and a lubricant, were studied. In chapters 4 and 5 studies were undertaken on isolated polymer particles, or 'binary' tablets containing only the two polymers, with respect to polymer ratio and NaCl concentration. This was in order to understand the behaviour of these polymers within the gel layer of a hydrated matrix,

In chapter 4, the swelling of individual HPMC and PEO particles with respect to NaCl concentration was investigated by imaging, and miscibility studies of HPMC and PEO solution were undertaken to see if these polymers might form a single solution or be phase separated when hydrated.

- I. HPMC and PEO individual particle swelling rates have been reported by others [1, 2], but there appear to be no comparative studies of how ionic environments can affect particle swelling until this thesis. Confocal fluorescence microscopy showed that without added NaCl, PEO particles swelled twice as rapidly as HPMC in the initial 120 seconds. HPMC swelling was inhibited by increasing NaCl concentrations, but NaCl

had only a limited effect on PEO particle swelling. These results provided evidence for the different drug release profiles and how PEO gel layer formation progresses normally, and remains unaffected by salt concentration. In the dissolution tests, these matrices retained their extended release properties. However, extreme concentrations of NaCl disrupt HPMC particle swelling and also particle coalescence in the gel layer. This explains the failure of the gel to form a diffusion barrier to block water penetration.

- II. Investigations of solution miscibility may play an important role in understanding gel layer formation in mixed matrices. Dilute polymer solutions (1% w/v) were studied by rheology. Miscibility depended on the HPMC and PEO polymer ratio. At a ratio of 8:2 HPMC:PEO, the two polymers were miscible, however, at other ratios (HPMC:PEO 6:4, 4:6, and 2:8) the two polymers appeared to be phase separated.
- III. Phase contrast microscopy showed that, at a concentration of 4% w/v, HPMC and PEO were immiscible at all polymer ratios.

However, the results above cannot fully explain HPMC and PEO gel layer morphology and behaviour. And so in chapter 5, mixed polymer matrices were studied. These were either pure or binary mixtures of HPMC and PEO, and were studied in order to minimize potential influences from other ingredients.

- I. Confocal microscopy studies over 15 minutes suggested that HPMC and PEO particles swelled separately, forming separate domains during early gel layer formation.
- II. Although all binary polymer tablets formed good gel layers at all NaCl concentrations there was evidence of inhibition up to a ratio of 4:6 HPMC:PEO. Only in PEO matrices and HPMC:PEO 2:8 matrices was gel layer growth not significantly affected by NaCl concentration.
- III. ATR-FTIR imaging was used to chemically map the growing gel layer up to 180 minutes. Results suggested that PEO swelled faster than HPMC. There was evidence that this hydration behaviour resulted in (i) a PEO-rich region forming the outermost gel layer to protect swelling HPMC in the matrix from the inhibitory effects of a high ionic environment and (ii) an HPMC-rich inner part of the gel which may provide an

increase in gel layer strength. In this way, the polymer combination of HPMC and PEO may confer advantageous properties on the matrix, with each polymer making a different contribution to the properties of the gel layer.

6.2 Overall discussions and conclusions

There have been several studies in the literature that report how the use of polymer mixtures in a matrix can potentially achieve desired drug release profiles in different drug delivery applications. These include achieving better extended, delayed or zero order release, mitigating the effects of external environments, improving tablets or film coating properties.

There is very little published literature on HPMC:PEO combinations with which to compare the work in this thesis. Jayan [2] reported no specific interactions between HPMC 2208 Methocel K4M and a relatively low molecular weight PEO (100,000 - 300,000) in mixed matrices, but he did conclude that PEO in solution appeared to inhibit HPMC polymer hydration. The confocal microscopy findings in the present thesis suggest however, that for the grades studied, that both polymers swell and that PEO becomes sufficiently hydrated within the gel layer to undergo intense staining by Congo Red. HPMC however, hydrates only half as fast as PEO. Jayan's hydrophilic matrix achieved delayed release followed by accelerated drug release for a poorly soluble drug. This would potentially benefit an arthritic patient who might take the medication at bed time, but receive maximum symptomatic relief from the burst release in the morning. This pattern was not seen in our studies. Jayan also suggested that PEO accelerated water ingress into the matrix, and we also have evidence of this.

The work of Gusler et al. [3] also used mixtures of HPMC and PEO in a hydrophilic matrix . The aim in this case was to provide optimal gastric retention, enabling controlled release for both soluble and less soluble drugs through increased residence times in the stomach. However, there was no investigation to gain a fundamental understanding of how the two polymers worked together to provide the desired drug release characteristics.

Combinations of ionic and non-ionic polymers have been used previously to achieve near-zero order *in vitro* drug release in different pH environments. For example HPMC and sodium carboxymethylcellulose have been used to provide pH independent drug release of the basic drug centperazine when the test media pH was switched from pH 3.0 hydrochloric acid to pH 7.0 phosphate buffers. The ionic polymer exhibited faster erosion which mitigated the effect of changing the medium pH on drug release rate [4, 5]. Another example has been the use of a mixed sodium alginate and HPMC matrix [6]. In the work in this thesis, both polymers are non-ionic so we would not anticipate changes due pH, but PEO has been used to mitigate the effects of high ionic environments. This may have potential to mitigate high valency ions such as buffers (eg. trisodium citrate). These can cause problems with HPMC matrices [7].

When these mixed polymers above are used, they may or may not interact chemically, and one of three things can happen: nothing, phase separation due to thermodynamic incompatibility, or the polymers can interact non-covalently or covalently in either a reversible or non-reversible manner, resulting in association of the polymer chains [8]. Xanthan gum with locust bean gum or guar has been used in hydrophilic matrices to enhance extended release properties. This polymer combination undergoes a specific 'synergistic' interaction that increases gel strength and therefore protects against matrix erosion [9, 10]. HPMC and sodium carboxymethylcellulose have also been reported to undergo hydrogen bonding, resulting in an enhanced gel [11]. The investigations of polymers miscibility either in solution or hydrated gel layer have been reported in this thesis, suggests there was no evidence of a specific interaction between HPMC and PEO.

The results in this thesis not just show how by using two common hydrophilic polymers (HPMC and PEO) we can achieve good extended drug release and better resistance to ionic challenges. It is also a systematic study of early and late gel layer formation, taking in aspects of individual particle swelling, and polymer miscibility which could be important factors in describing how mixed polymer hydrophilic matrices extend drug release.

Polymer swelling must be rapid enough to allow hydrated particles to coalesce and form a gel layer in the early stage of hydration. The results shown in this thesis support the work of

previous workers using single polymers that show this is a key factor in hydrophilic matrices providing extended drug release[12-14]. This work has also shown that two polymers together, even though they are probably immiscible, can achieve a coherent gel layer

Like earlier studies, this work has shown that HPMC matrices exhibit early gel layer formation and extended drug release in low NaCl media (<0.6M but as NaCl concentration increases, HPMC particle and matrix swelling is significantly inhibited and the burst drug release results. PEO particles and matrices however, do not show significant effects from NaCl concentration, in fact PEO matrices exhibit slightly longer drug release profiles.

The very different effects of salt on matrix drug release profiles can probably be related to the different chemical structure of the two polymers. HPMC has methoxy and propoxyl groups unevenly substituted along the cellulose backbone, which results in HPMC having both hydrophobic (methoxy rich) and hydrophilic regions. Adding a salt such as NaCl to the medium disrupts water structure especially around the hydrophobic regions on the HPMC polymer, and the HPMC polymer becomes more difficult uncoil and extend as it swells. This effect can also be seen when the polymer is fully hydrated in solution: NaCl decreases the cloud point of HPMC solutions because it causes a reduction in water bonding with the polymer effectively, HPMC dehydration. Hydration and swelling of polymer particles is inhibited by these ionic 'salting out' effects of the dissolution medium and therefore HPMC matrices cannot provide extended drug release in high salt solutions [15-19].

PEO however does not contain areas of hydrophobic substitution. It is a uniformly hydrophilic polymer with the repeating monomer unit $\text{CH}_2\text{CH}_2\text{O}$, and each ethylene oxide unit from PEO is extensively hydrated and bounded by approximately 2 to 3 water molecules in aqueous solution[20, 21]. Additional neighbouring water molecules are also structured and each ethylene oxide unites up to 16 water molecules [22]. As it is highly water binding, chemically completely hydrophilic and is soluble in water, the swelling of PEO particles and matrices are much less influenced by NaCl concentration and exhibit extended drug release over the whole range of NaCl concentrations studied.

Both polymers contribute advantages when mixed together and despite its sensitivity to salt, HPMC plays a very important role in the mixed gel layer. Under investigation from MRI, single polymer and mixed matrices containing HPMC showed slower water penetration, and less polymer erosion in the later stages of hydration. Digital macroscopy images provided clear evidence that HPMC matrices showed greater gel longevity and less erosion than PEO matrices in the media. Moreover, texture analysis provided direct evidence that the HPMC hydrated gel layer exhibited higher gel strength than that observed in PEO matrices. PEO particles show much more rapid hydration than HPMC particles in water, and the rapidly formed diffusion barrier in high salt solutions, will protect the mixed matrix from the disintegration that happens in purely HPMC matrices.

HPMC and PEO were immiscible in dilute solution (the polymers exhibit miscibility only in the ratio HPMC:PEO 8:2 in 1% w/v solution). The phase contrast microscopy suggested two distinct phases with different polymers being enriched in each of the two phases. The early and later gel layer studies also confirmed the mixed hydrated matrices formed the gel layer separately when mixed matrices are hydrated. This may be a result of both polymers being high molecular weight, and the combinatorial entropy of the two polymers being quite small. Mitchell et al. [23] have described how the usual source of free energy as a driving force for mixing is virtually absent and two high molecular weight polymers will rarely be miscible.

These investigations and results above, provide evidence for the hypothesis that PEO may form an outer gel layer which helps maintain matrix resistance to extremely high ionic environments, whilst hydrated HPMC forms an inner region of the gel layer to increase the gel layer strength, longevity and retard water penetration. Consequently, both polymers contribute advantages to help mixed polymer matrices provide optimal drug release profiles in highly ionic media.

6.3 Potential future work

The following future work would extend the current research, and support the use of mixed polymer HPMC:PEO in pharmaceutical hydrophilic matrices. It would also progress our understanding of the fundamental nature of properties of hydrated matrices from mixtures of HPMC and PEO.

- I. The work could be extended to study the effect of drug solubility, a major factor that influences drug release kinetics in hydrophilic matrices. The current work has shown how HPMC and PEO ratio can be used to influence matrix hydration rates, gel strength and potentially gel erosion rates (important for poorly solubility drugs) especially towards the end of the dissolution. It may be that adjusting the ratio of HPMC and PEO in the matrices allows optimization of drug release profiles for drugs with differing solubility.
- II. The important finding of an apparent polymer separation within the gel layer could be further supported by examining a wider range of matrix compositions in the ATR-FTIR studies, or using fluorescently labelled polymers with fluorescence imaging as in the work of Oni [24].
- III. In order to better understand how HPMC in the mixed polymer matrix is protected from high salt concentrations, the ATR-FTIR work should be extended to include a wider range of matrix compositions and different salt concentrations
- IV. The type of phase separation behaviour in concentrated mixed solutions could be investigated by further rheological studies
- V. Studies could be undertaken to examine if HPMC, once hydrated, is susceptible the effects of high salts concentrations, and if the presence of PEO inhibits the swelling of HPMC, as reported by Jayan [2].

6.4 References

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Appendix 1

Materials

Material	Brand name/grade	Manufacturer	Batch No
Caffeine anhydrous	Analytical grade	Sigma-Aldrich, Dorset, UK	101089419
Hydroxypropyl methylcellulose (HPMC 2208 USP)	Methocel TM CR Premium K100M Methoxyl 22.7% Hydroxypropoxyl 10.4%	Colorcon Ltd, Dartford, Kent, UK	Y1090212N01
Polyethylene oxide (PEO)	Polyox WSR 303 coagulant LEO NF	Colorcon Ltd, Dartford, Kent, UK	2F1755S5C3
Lactose	Fast-flo USP	Foremost Farms, Baraboo, USA	DL00008709
Partially pregelatinized starch	Starch1500 TM	Colorcon Ltd, Dartford, Kent, UK	IN506125
Microcrystalline cellulose	Avicel PH102	FMC Inc, Philadelphia, USA	DL00008701
Magnesium stearate	Technical grade	Sigma-Aldrich, Dorset, UK	S03492-325
Sodium chloride	Analytical grade	Fisher scientific, Leicestershire, UK	0797716
Congo red	General purpose grade	Fisher, Leicestershire, UK	1137790
Hydrochloric acid ≥ 37%	Analytical grade	Sigma-Aldrich, Dorset, UK	30721
Water	Maxima HPLC grade with a maximum conductance of 18.2 MΩ.cm	USF, Elga, Buckinghamshire, UK	-

Orange juice	Sainsbury's 100% Squeezed orange juice Smooth	Sainsbury's Beeston, UK	BN 2024MN
Orange Juice	Tesco orange juice from concentrate smooth	Tesco, Beeston, UK	BN X202 2021
Pineapple juice	Tesco pineapple juice from concentrate	Tesco, Beeston, UK	BN X202 2021
Apple juice	Tesco apple juice from concentrate	Tesco, Beeston, UK	BN X205A 2026
High juice	Tesco high juice orange (fruit 50% juice)	Tesco, Beeston, UK	-
Milk	Iceland fresh pasteurized whole milk	Iceland, Beeston, UK	BN: D11901LTC010
Bacon	Tesco Bacon 10 unsmoked back rashers	Tesco, Beeston, UK	BN: 12954H
Egg	Tesco 15 free range eggs	Tesco, Beeston, UK	-
Fries	McCain Southern Fries	Tesco, Beeston, UK	-
Bread	Hovis Soft white medium 800g	Tesco, Beeston, UK	-

Table A1: List of materials used in the thesis

Appendix 2

The UV absorbance at wavelengths used for quantification of caffeine

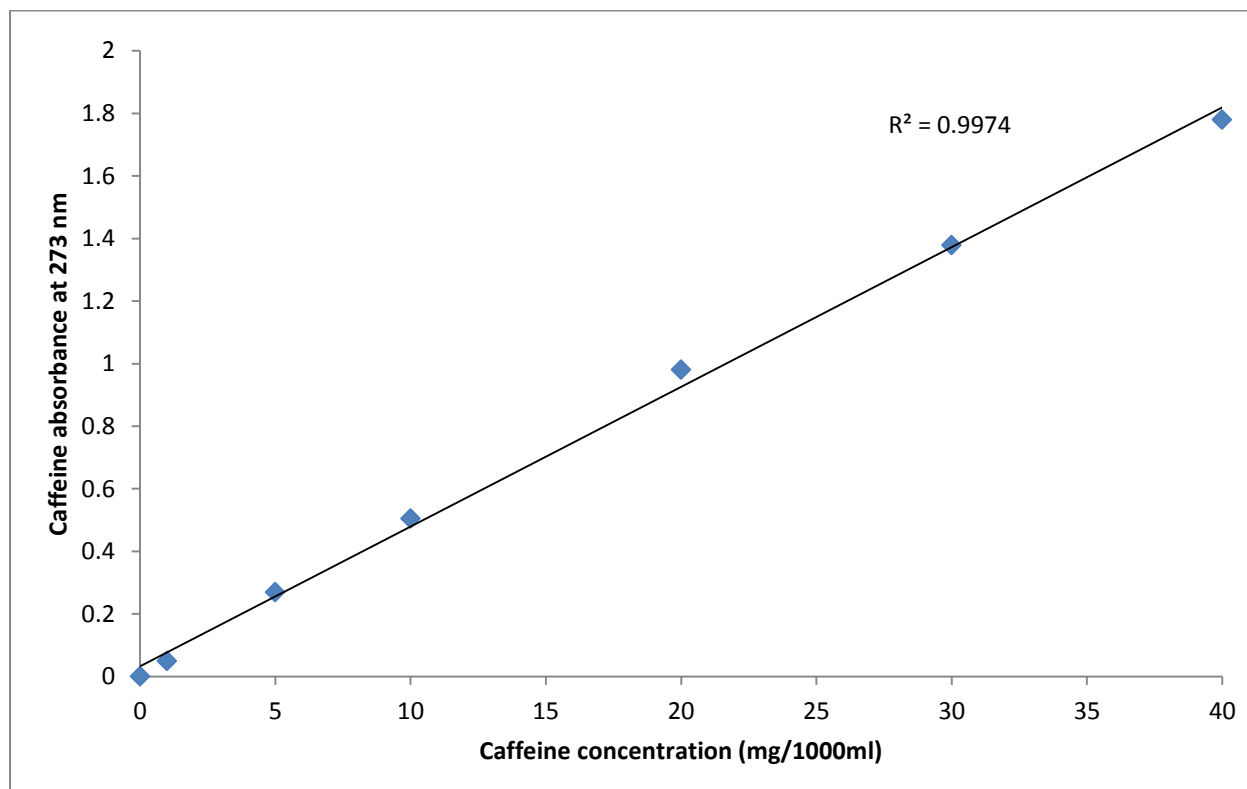


Figure A1: Standard curve for caffeine in water. Values determined at 37 °C in 10mm quartz cells at 273nm

Appendix 3

Publications (In preparation)

Anran Hu, Chen Chen, Laura M Mason, Cameron Alexander, Bettina Wolf, Lynn Gladden, Michael Mantle, Ali Rajabi-Siahboomi, Colin D. Melia, The design of extended release HPMC: PEO hydrophilic matrices with improved robustness to NaCl environments

Anran Hu, Hakan Keles, Bettina Wolf, Kerstin T. Mader, Chris Sammon, Ali Rajabi-Siahboomi, Colin D. Melia, HPMC:PEO Mixed Systems : Solution Behaviour and Gel Layer Morphology in Hydrated Hydrophilic Matrix Tablets

Presentations

Investigating the robustness of hydroxypropyl methylcellulose (HPMC) and polyethylene oxide (PEO) tablet blend as hydrophilic matrices, UK chapter of the Controlled Release Society, Aston, UK, May 2012, Poster presentation

The Behaviour of Mixed Polymer HPMC/PEO Hydrophilic Matrices in Ionic Environments, Controlled Release Society Conference, Hawaii, USA, July 2012, Poster presentation

Can combinations of hydroxypropyl methylcellulose (HPMC) with polyethylene oxide (PEO) improve the extended release profiles of hydrophilic matrices in ionic environments? Biopharmaceutics and Drug Delivery Meeting – Merck Sharp & Dohme Limited, London, UK, November 2012, Poster presentation

Gel layer formation of HPMC/PEO hydrophilic matrices and miscibility of solutions, School of Pharmacy University of Nottingham, Nottingham, UK, March 2013, Oral presentation

Mixed HPMC/PEO study for extended drug release, 1st Hydrocolloid Conference, Huddersfield, UK, September 2013, Oral presentation

Formulation of HPMC/PEO hydrophilic matrices to improve extended release profiles in NaCl environments, INTERREG Training School: UoG-AAPS Student Chapter Conference, Greenwich, UK, July 2014, Oral presentation.

The design of extended release HPMC/ PEO hydrophilic matrices with improved robustness to salty environments, UK chapter of the Controlled Release Society, Nottingham, UK, April 2015, Poster presentation

Phase separated hydration in the gel layer of mixed HPMC/PEO hydrophilic matrices, Controlled Release Society Conference, Edinburgh, UK, July 2015, Poster presentation

The potential of HPMC/PEO mixed polymer hydrophilic matrices, Colorcon Science Meeting, Edinburgh, UK, July 2015, Oral presentation