The University of
Nottingham

Formulation Insights Group
School of Pharmacy
University of Nottingham

Critical processes in drug release from HPMC controlled release matrices

Samuel R Pygall

MPharm, MRPharmS

Thesis submitted to the University of Nottingham
for the degree of Doctor of Philosophy

October 2008

Abstract

This study has investigated the drug release mechanisms from hydroxypropyl methylcellulose (HPMC) hydrophilic matrices. A hypothesis was developed from interpretation of a previous study that drug surface activity has an influence on drug liberation. The validity of the hypothesis was tested by studying the interactions between HPMC and the two non-steroidal anti-inflammatory drugs diclofenac Na and meclofenamate Na, using tensiometry, rheology, NMR, neutron scattering and turbimetry. Meclofenamate Na was found to interact with HPMC, resulting in detectable changes in drug diffusion coefficients and polymer structure in solution. There were increases in HPMC solution solubility and changes in viscoelasticity, which suggested drug solubilisation of the methoxyl-rich regions of the polymer chains. Diclofenac Na did not show evidence of an interaction and exhibited changes consistent with a 'salting out' of the polymer.

A confocal microscopy technique was used to image the drug effects on early gel layer development. The presence of drugs affected gel layer development, depending on the level of drug in the matrix and the concentration of sodium chloride in the hydration medium. Diclofenac Na matrices became increasingly susceptible to disintegration, while meclofenamate Na matrices exhibited resistance to the effects of sodium chloride. The influence of incorporated diluents on the gel layer was also investigated and it was found that lactose had a disruptive effect, whereas microcrystalline cellulose was relatively benign. When co-formulating

drugs and diluents in the matrix, lactose acted to antagonise the effect of meclofenamate, but acted synergistically with diclofenac to reduce gel layer integrity and accelerate matrix disintegration. In contrast, MCC was found to have a relatively neutral effect on drug-mediated effects.

HPMC particle swelling and coalescence are critical processes in gel layer formation extending drug release. Drug surface activity and capability of interacting with HPMC appears to influence particle swelling processes, affecting gel layer formation and provides a mechanistic explanation for the differing release profiles of diclofenac and meclofenamate Na.

Acknowledgements

Within the School of Pharmacy, I thank Mrs Christine Grainger-Boultby for technical assistance. I acknowledge Formulation Insight Group members Hywel Williams, Bow and Barry Crean for being great support during laboratory work. I would like to extend my gratitude to former Formulation Insights Group members Dr Craig Richardson, Dr Matthew Boyd and Dr Gurjit Bajwa for inspiring me to aspire to doctoral studies during my time as a project student in the Formulation Insights Group.

Thanks go to friends at Nottingham who provided a welcome distraction from studies in a variety of forms: Jeff, Gerard, David, Kate, Rachael, Carl, Matthew and Lucy. There were some great nights during my time at Nottingham.

I acknowledge and thank my parents, brother and sister for moral support during my extended period of education.

Lastly but most importantly, I wish to thank Claire for always being there and always supporting me. Her vibrant personality has provided a shining light during the darkest days.

Table of contents

Chapter 1 Introduction

Chapter 2 Interpretation of a previous drug release study from HPMC matrices

Chapter 3 Materials and methods

Chapter 4 Interactions between non-steroidal anti-inflammatory drugs and HPMC

Chapter 5 The effect of drugs and ionic media on the morphology and functionality of the gel layer in HPMC hydrophilic matrices

Chapter 6 The effect of diluents on the early gel layer formation and disintegration of HPMC matrices

Chapter 7 The combined effects of drugs and diluents on early gel layer formation in HPMC hydrophilic matrices

Chapter 8 Conclusions and future work

References

Appendices

List of Figures

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6

Chapter 7

Appendices

List of Tables

Chapter 7

Abbreviations and symbols

2D	Two-dimensional
3D	Three-dimensional
AGU	Anhydroglucose Unit
API	Active Pharmaceutical Ingredient
ATR-FTIR	Attenuated Total Reflection Fourier Transform Infrared
BPP	Buflomendil pyridoxalphosphate
CAC	Critical Aggregation Concentration
CD	Cyclodextrin
CLSM	Confocal Laser Scanning Microscopy
CMC	Critical Micelle Concentration
Cos	Cosine
CP	Cone and Plate
CPT	Cloud Point Temperature
CSEM	Cryogenic Scanning Electron Microscopy
DCP	Dibasic calcium phosphate dihydrate
DSC	Differential Scanning Calorimetry
DTAB	Dodecyltrimethylammonium bromide
EC	Ethylcellulose
EHEC	Ethyl Hydroxyethylcellulose
ESR	Electron Spin Resonance
g	Gram
G'	Storage modulus
G"	Loss modulus
GRAS	Generally regarded as safe

H	Hydrogen
HEC	Hydroxyethylcellulose
HEMC	Hydroxyethylmethylcellulose
HLB	Hydrophilic-lipophilic balance
HM-EHEC	Hydrophobically Modified ethyl hydroxyethylcellulose
HPC	Hydroxypropylcellulose
HPLC	High Performance Liquid Chromatography
HPMC	Hydroxypropyl methycellulose
Hz	Hertz
IGC	Inverse Gas Chromatography
ITC	Isothermal Titration Calorimetry
K_2SO_4	Potassium sulphate
KCl	Potassium Chloride
KDS	Potassium Dodecyl Sulphate
$KHPO_4$	Potassium phosphate
LCST	Lower Critical Solution Temperature
LiDS	Lithium Dodecyl Sulphate
LVR	Linear Viscoelastic Region
μm	Micrometers
MALS	Multi-angle Light Scattering
MC	Methylcellulose
MCC	Microcrystalline Cellulose
m-DSC	Micro-Differential Scanning Calorimetry
mg	Milligram
min	Minute
ml	Millilitre
mm	Millimetre
mM	Millimolar
mPa.s	Millipascal second
MRI	Magnetic Resonance Imaging
Mw	Molecular weight

N	Newton
Na_2CO_3	Sodium Carbonate
Na_2SO_4	Sodium Sulphate
NaBr	Sodium bromide
NaCl	Sodium Chloride
NaCMC	Sodium Carboxymethylcellulose
$NaHCO_3$	Sodium Carbonate
NaI	Sodium Iodide
NaOH	Sodium Hydroxide
NIPA	Poly (N-isopropylacrylamide)
NIR	Near Infrared
nm	Nanometre
NMR	Nuclear Magnetic Resonance
NSAID	Non-Steroidal Anti-Inflammatory Drugs
^{o}C	Degree centigrade
Pa	Pascal
Pa.s	Pascal second
PC	Personal Computer
PEG	Polyethylene Glycol
PEO	Poly(ethylene oxide)
PGSE-NMR	Pulsed gradient Spin Echo Nuclear Magnetic Resonance
PP	Parallel Plate
ppm	Parts per million
PSP	Polymer Saturation Point
PVP	Polyvinyl pyrrolidone
Q	Scattering vector
QMC	Queens Medical Centre
QSPR	Quantitative Structure Property Relationship
RI	Refractometric Index
rpm	Revolutions per minute
s	Second
SANS	Small-Angle Neutron Scattering

S_b	Bulk surfactant concentration
SD	Standard deviation
SDS	Sodium Dodecyl Sulphate
SEC	Size Exclusion Chromatography
SEM	Scanning electron microscopy
Sin	Sine
SLS	Sodium Lauryl Sulphate
T	Absolute temperature (Kelvin)
Tan	Tangent
TMA	Thermomechanical Analysis
UK	United Kingdom
USA	United States of America
USP	United States Pharmacopoeia
UV	Ultraviolet
η	Viscosity (apparent)
γ	Strain
σ	Shear stress
δ	Phase angle (delta)
%	Percentage

Chapter 1

Introduction

1.1 The principle of hydrophilic matrices

In recent years, significant interest has arisen in achieving extended release of drugs from dosage forms. The aims of controlled drug release include: (i) drug liberation at an appropriate time, at a specific rate and site, (ii) maximising therapeutic effectiveness and (iii) reducing the frequency and severity of side-effects. One method used to extend drug release is the hydrophilic matrix, a technology that has been in use since the first patents were filed in the 1960s (Alderman 1984, Melia 1991, Colombo 1993, Li *et al.* 2005).

Hydrophilic matrices are mixtures of drugs and excipients typically manufactured into tablets by compression (Melia 1991). There are a wide range of polysaccharides and synthetic and semi-synthetic water-soluble polymers used in such devices and include: (i) xanthan gum (Cox *et al.* 1999), (ii) sodium alginate (Sriamornsak *et al.* 2007), (iii) chitosan (Phaechamud and Ritthidej, 2007), (iv) polyethylene oxide (PEO) (Wu *et al.* 2005) and (v) the ether derivatives of cellulose, including

hydroxypropyl methylcellulose (HPMC) and methylcellulose (MC) (Alderman 1984, Li *et al.* 2005, Nair *et al.* 2007).

There are many reasons for the continued popularity of hydrophilic matrices despite advances in other extended release technologies. These include formulation simplicity, the ability to be manufactured using conventional tabletting machinery, the ability to accommodate high drug loadings and the relatively low cost and toxicity of the polymers used which are generally regarded as safe (GRAS) excipients (Alderman 1984, Melia 1991, Li *et al.* 2005).

HPMC and other cellulose ethers are the most common polymer carriers used in hydrophilic matrices. HPMC hydrates rapidly to form a gelatinous layer on contact with aqueous fluids, is stable over a wide pH range (3.0 - 11.0) and is enzyme resistant (Alderman 1984, Dow Company Methocel Information, Li *et al.* 2005). A significant amount of work has been carried out in order to characterise HPMC with respect to its performance as a hydrophilic carrier material. This introduction will first consider the chemical nature of HPMC and its properties in solution, before detailing its use in extended release dosage forms. A particular focus will be on the critical factors that affect drug release and a consideration of the interactions between ions, molecules and HPMC. The aims of the experimental programme will subsequently be outlined and discussed.

1.2 The structure and chemistry of cellulose

HPMC is a chemical derivative from the structural plant cell polymer cellulose. Cellulose is the most abundant polymer in the biomass, functioning as the key structural component of green plants (Klemm *et al.* 2005). It represents approximately 1.5 x10^{12} tonnes of the annual biomass production and, as consumer demand increases for

biocompatible products, is considered an almost inexhaustible source of raw material (Klemm *et al.* 2005). Chemically, cellulose is a linear carbohydrate composed of 1:4 linked glucose units (figure 1.1). These constituent glucose units have the empirical formula $C_6H_{12}O_6$, and adopt a cyclic structure, designated as β-D-glucopyranose. The monomer units are covalently linked through acetal functions between the equatorial OH group of C_4 and the C_1 carbon atom (β-1, 4-glucan).
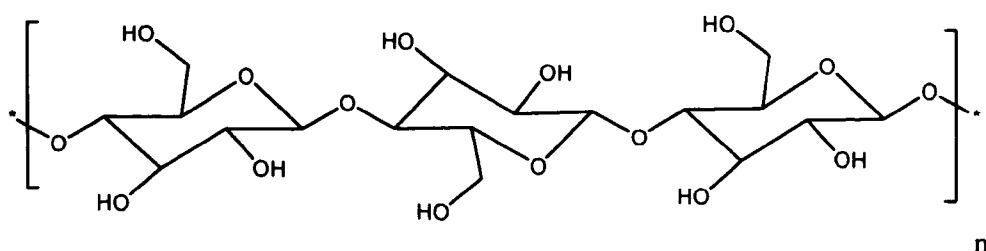
Figure 1.1 - The molecular structure of cellulose

Resultantly, cellulose is an extensive, linear chained polymer with three hydroxyl groups per anhydroglucose unit (AGU) present in the thermodynamically preferred $^4C_1$ conformation. This material is insoluble, with chemical substitutions conducted under heterogenous conditions required to produce polymers, including the cellulose ethers, that possess suitable water soluble functionality (Klemm *et al.* 2005).

1.2.1 Types and uses of cellulose ethers

The cellulose ethers possess a range of properties with respect to solubility, viscosity and surface activity depending on the various alkoxy species used in their manufacture. These properties are exploited in a number of different applications in industry and are summarised in table 1.1.

Table 1.1 Industrial Applications of Cellulose ethers (adapted from Donges 1990)

Abbreviations: methylcellulose (MC), ethylcellulose (EC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), carboxymethylcellulose (CMC), hydroxypropylmethylcellulose (HPMC), hydroxyethylmethyl cellulose (HEMC), sodium carboxymethylcellulose (NaCMC)

Application	Cellulose derivative	Function
Construction materials (plasters, filler, pastes) Paints	MC, HEMC, HPMC, CMC, HEMCMC CMC, HEC, HEMC, HPMC, HEMCMC	Water retention capacity, stability under load, adhesive strength Stability of suspension, thickening, film formation, wetting
Paper manufacture	CMC, HEC, HEMC, HPMC	Agents for binding and suspending, sizing aids and stabilisers
Textile industry (sizes, textile printing dyes)	CMC, MC, HPMC, CMSEC	Adhesive and film-forming properties, thickening and soil release
Polymerisation	HEC, HPMC, HPMC	Protective colloid, surface activity
Drilling industry, mining (drilling fluids)	CMC, CMSEC, HEC, HPC, HPMC	Water retention, flow characteristics, surface activity
Detergents	CMC, HEMC, HPMC	Anti-redeposition power, wetting ability, suspending and emulsifying agents
Engineering (extrusion, electrode construction, ceramic sintering)	MC, HPC, HPMC	Friction reduction, water retention, enhanced ignition processes
Cosmetics (creams, lotions, shampoos)	CMC, MC, HEC, HEMC, HPMC	Thickeners, binding, emulsifying and stabilising agents
Pharmaceuticals (ointments, gels, tablets, coated tablets)	CMC, MC, HEC, HEMC, HPMC	Thickeners, binding, emulsifying and stabilising agents, film formation, tablet disintegrants
Foodstuffs (sauces, milkshakes, bakery products)	CMC, HPMC, MC	Thickeners, binding agents, stabilisers and emulsifiers

1.3 The solution properties of HPMC

The principal solution properties of cellulose ethers will now be discussed.

1.3.1. Solubility

The solubility of cellulose ethers occurs as a result of the introduction of substituent groups along the polymeric backbone. The resulting steric hindrance reduces hydrogen bonding between the native cellulose chains causing reduced crystallinity, exposed hydroxyl groups and consequently an increase in water solubility (Donges 1990). In general, an increase in the degree of substitution, through greater etherification of the anhydroglucose units, is accompanied by a progressive increase in solubility in comparison with insoluble cellulose. The larger the substituent group used in etherification, the lower the degree of substitution necessary to impart aqueous solubility (Greminger 1980).

1.3.2 Surface activity

Amongst the many cellulose ethers, HPMC possesses surface activity. This manifests itself as the ability to reduce the interfacial tension of aqueous systems (Grover 1993, Sarkar 1984, Yasueda *et al.* 2004). The surface activity of cellulose ethers has been ascribed to non-homogenous substitution of the cellulose backbone during manufacture, leading to the simultaneous presence of hydrophobic (alkyl) and hydrophilic (hydroxyl) groups (Doelker 1987). The degree of surface activity is dependent on the distribution of these groups along the cellulose backbone (Sarkar 1984). For example, HPMC USP 2910 and 2906 have surface tensions of 44-50

mN/m, whereas HPMC USP 2208 with a different substitution ratio has a surface tension of 50-56 mN/m (Doelker 1987).

Further insights into the surface activity of HPMC have been recently provided by Perez *et al.* (2006). Surface pressure isotherms and structural and surface dilatational properties at the air-water interface of three grades of HPMC (Methocel E4M, E50LV, and F4M) were determined. The three grades formed very elastic films at the air-water interface, even at low surface pressures. E4M showed the highest surface activity, mainly at low bulk concentrations. The differences observed in surface activity may be attributed both to differential hydroxypropyl molar substitution and molecular weight of different HPMCs. All grades formed films of similar viscoelasticity and elastic dilatational modulus, which the authors suggested was a result of their similar degree of methyl substitution.

1.3.3 Viscosity

Cellulose ether solution viscosity, in common with other polymer solutions, is dependent primarily on molecular weight. This is controlled by cleavage of the glycosidic bonds of polymer chains during manufacture, which is achieved through control of exposure to air during processing.

Thuresson and Lindman (1999) have suggested that the viscosity of cellulose ether solutions may be attributable to short term to polymer entanglements and, in the longer term, strong associations between unsubstituted regions of the native cellulose. These interactions are thought to arise from strong hydrogen bonds between unsubstituted hydroxyl groups in a manner similar to that which makes native cellulose insoluble.

1.4 Thermogelation and the sol:gel transition

Alkyl substituted cellulose ethers, including HPMC undergo the phenomenon of thermo-reversible gelation. This occurs on heating of a solution above a critical temperature (so-called "reversible thermal gelation") and the influence of this transition on solution viscosity is shown in figure 1.2. Initially, an increase in temperature results in a decrease in the solution viscosity. However, as the solution temperature continues to increase, polymer solution viscosity undergoes a marked increase at reaching the incipient gelation temperature. Above this temperature polymer chains associate through hydrophobic interactions between regions highly substituted with methoxyl groups (Grover 1993). This is thought to be as a result of dehydration of the hydration sheath around the hydrophobic, methoxyl-rich regions of the cellulose backbone, in comparison with regions relatively low methoxyl substitution (Haque *et al.* 1993). These sites of intermolecular hydrophobic bonding form "junction zones" resulting in the formation of a three dimensional gel network of polymer chains (Sarkar 1979; Carlsson 1990).

This gelation phenomenon often results in phase separation, which is thermo-reversible on cooling. Repeating the heating and cooling cycle has no significant effect on gel or solution properties (Haque and Morris 1993; Haque *et al.* 1993). Each grade of cellulose ether has a characteristic thermal gelation temperature range as a result of the relative balance of hydrophobic and hydrophilic substituents. Cellulose ethers with a high content of hydroxyalkyl groups tend to have higher gel temperatures whereas higher methoxyl substitution levels result in lower gel temperatures (Sarkar 1979).
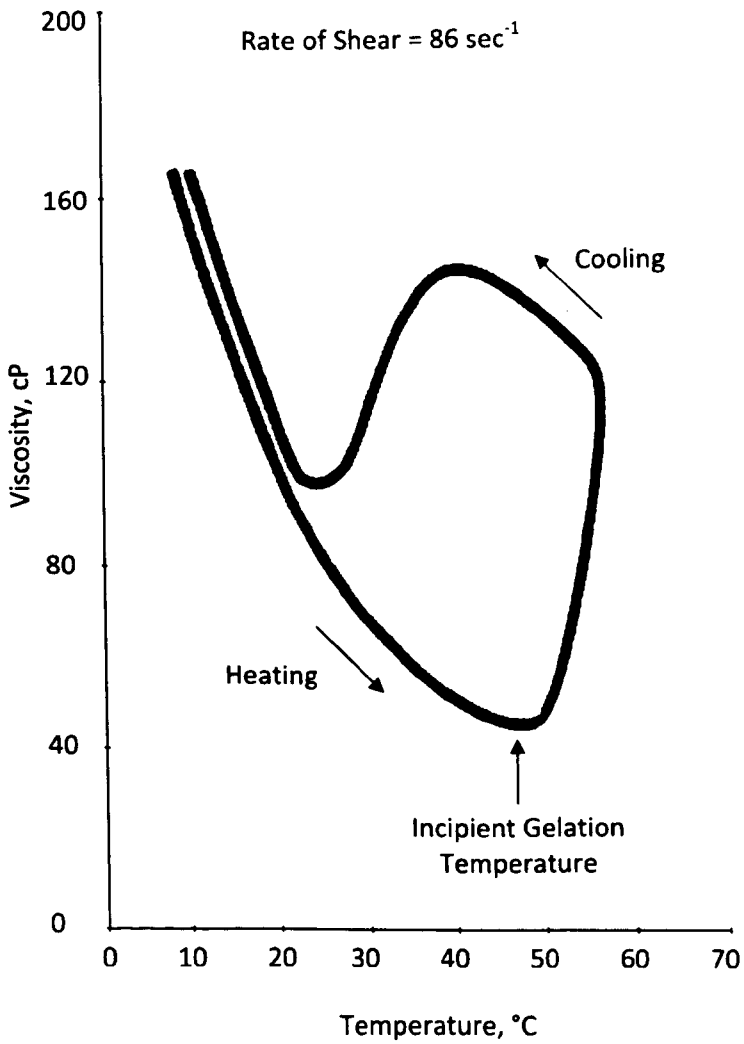
Figure 1.2 Gelation behaviour of a 2%w/w aqueous solution of HPMC on heating and cooling (Methocel E4M)

Adapted from Sarkar 1979.

Recent spectroscopy advances have permitted further insights into the gelation process. Banks *et al.* (2005) have used attenuated total reflection Fourier transform infrared (ATR-FTIR) spectroscopy to probe the behaviour of aqueous solutions of HPMC during the thermal gelation transition. The relative intensities of bands associated with the methoxyl groups and hydrogen-bond-forming secondary alcohol groups were found to change during the gelation process, indicating the involvement of hydrophobic polymer chain interactions. The dominance of inter-molecular H bonding over intra-molecular H bonding within the cellulose ether in solution was also observed.

1.4.1 Factors that affect the thermal gelation phenomenon

1.4.1.1 Molecular weight

There appears to be no relationship between the molecular weight of HPMC and the thermal gelation temperature (Sarkar 1979). It has been suggested (Sarkar 1979) that this may be a consequence of the purity of HPMC samples with regard to their molecular weight. Variations in molecular weight of HPMC samples are usually high and so a definitive pattern of gelation temperatures may be difficult to detect.

1.4.1.2 Substitution

The degree and type of substitution has a significant role in thermal gelation. In hydroxyethyl methylcellulose (HEMC), a high degree of methoxyl substitution is necessary for gel formation to occur (Sarkar 1979). It is believed that methoxyl groups are responsible for gel formation in HPMC with hydroxypropyl substitution significantly modifying gel properties (Sarkar 1979). Increasing the degree of HPMC

substitution leads to a decrease in gelation temperature, owing to an increase in hydrophobic interactions at any given temperature (Sarkar 1995, Sarkar 1979). Increasing molar substitution of HPMC with hydroxypropyl groups is thought to increase the gelation temperature as a result of stabilising the interaction with water and making polymer chain dehydration less favourable. Consequently, a greater heat input is required to dehydrate the polymer and so bring about gelation (Haque *et al.* 1993).

1.4.1.3 Electrolytes and Sugars

When in solution, HPMC is a hydrated colloid and as such is susceptible to "salting out" from solution above certain limits of electrolyte and sugar concentrations (Heyman 1935; Sarkar 1979; Harsh 1991; Nakano *et al.* 1999). The process of "salting out" occurs as a result of competition for water between the polymer and the other solutes present (Sarkar 1979). The propensity of various ions to "salt out" cellulose ethers follows the Hofmeister or lyotrophic series (Touitou and Donbrow 1982), although for anions the trend is more complex (Mitchell *et al.* 1990; Melia 1991; Nakano *et al.* 1999). More detailed consideration of the incompatibilities between electrolytes and HPMC is provided in section 1.9.

1.4.1.4 Surfactants

There is considerable evidence that surfactants interact with cellulose ethers such as HPMC. The addition of sodium dodecyl sulphate (SDS) has been shown to increase the cloud point of HPMC solutions, an effect that equates to an increase in solubility of the polymer (Nilsson 1995). The mechanism for this is thought to result from the solubilisation of the methoxy rich "junction zones" that occur upon gel formation and precede precipitation of the polymer on heating.

Evertsson and Nilsson (1998) have studied the microviscosity of solutions containing mixed micelles of SDS and cellulose ethers. A microviscosity maximum generally corresponded to a low SDS adsorption and resultantly high polymer content mixed micelles. The hydrophobicity of the cellulose derivatives (EHEC, MC, HEC and HPMC) was found to correlate with the amplitude of the overall microviscosity pattern for the mixed micelles. This is evidence that an increased polymer hydrophobicity produced polymer-surfactant aggregates with increased rigidity. All polymer/surfactant combinations investigated gave aggregates with a higher rigidity than the micelles formed from SDS alone, attributed to closer packing of the aggregate structures.

The nature of the counter-ion on the interaction between anionic surfactants and cellulose ethers has been studied by Ridell *et al.* (2002). They used fluorescence probes, microcalorimetry and dye solubilisation to study the interaction between hydroxypropyl methyl cellulose (HPMC) or ethyl hydroxyethyl cellulose (EHEC) and potassium, sodium, and lithium dodecyl sulphates (KDS, NaDS, LiDS). It was found that the counter-ion influenced the concentration at which the interaction began as well as the nature of the mixed aggregates formed. The rank order was found to be KDS < NaDS < LiDS for both HPMC and EHEC. Microcalorimetry measurements confirmed surfactant adsorption onto the polymer is initially endothermic and entropy driven and at a critical level of cluster formation on the polymer chains the process converts to an exothermic reaction, driven by both enthalpy and entropy.

1.5 The application of HPMC in extended release drug delivery

To provide a context for this research, HPMC application in extending drug delivery will now be discussed.

1.5.1 Hydration of HPMC matrices and the mechanism of controlling drug release

When exposed to an aqueous medium, HPMC hydrophilic matrices undergo rapid hydration and chain relaxation (Colombo 1993) to form a viscous gelatinous layer at the matrix surface. This is commonly termed the 'gel layer'. This layer acts as a diffusion barrier, slowing water penetration into the dry core of the matrix and thus preventing disintegration (figure 1.3). Drug present on the surface of the tablet is released as a burst as the gel layer is forming (Ford *et al.* 1985a) but it is the physical characteristics of this 'gel layer' that control the subsequent water uptake and drug release kinetics. If a properly functioning gel layer is formed, drug release is reduced and the rate of release is dependent either on the rate of diffusion through the gel (if the drug is freely soluble) or the rate of mechanical removal and disentanglement of the external surface of the gel layer if drug solubility is low.

Such is the crucial role that it has in understanding the mechanism of controlled release from HPMC hydrophilic matrices, many studies have investigated the formation and nature of the gel layer. It has been suggested by several workers (Melia *et al.* 1992. Ju *et al.* 1995) that three distinct regions exist within the HPMC gel layer. These are: (i) a uniformly hydrated gel/core interface, (ii) a non-uniformly hydrated region in the

centre of the gel layer and finally (iii) the outer most edge of the gel layer that consists of highly hydrated polymer. These theories on the gel layer composition are supported by earlier studies by Melia *et al.* (1990) which studied internal structure and relative levels of polymer hydration within the gel layer using cryogenic scanning electron microscopy coupled with energy dispersive x-ray microanalysis.

Dry
Tablet

Ingestion
of tablet

Initial Wetting of the Tablet
This begins hydration and
formation of the gel layer. Drug
on the surface is released as an
initial burst.

Expansion of the Gel Layer
Water penetrates the tablet
causing expansion of the gel layer
and the soluble drug diffuses
through the layer.

Tablet Erosion
As the gel layer becomes
fully hydrated the intra-
polymer bonds become so
weak they dissolve away,
leading to erosion. The fluid
is able to penetrate further
into the matrix.

Soluble drug is
released primarily
through diffusion of
the hydrated gel layer.

Insoluble drug is
released primarily
through erosion.

**Figure 1.3 The sequence of matrix hydration and drug release from HPMC matrix
tablets**

(Adapted from Colorcon UK Methocel literature)

1.6 Imaging the behaviour and gel layer of hydrophilic matrix tablets

The formation and growth of the gel layer plays a significant role in the overall process of prolonging drug release in hydrophilic matrix tablets. Hence, an understanding achieved through imaging the formation of the gel layer and dosage form swelling kinetics is of crucial importance in producing an insight into the mechanisms underlying dosage form performance. To achieve this, several different methods have been employed to observe the behaviour of hydrophilic matrices during the process of gel layer formation, erosion and dissolution.

Some of the earliest work in this area was carried out by Melia *et al.* (1990). Using a combination of cryogenic SEM and energy dispersive X-ray microanalysis, observation of a hydrated alginate-based hydrophilic matrix tablet elucidated structural details and drug distribution within the dosage form. Cryogenic SEM was used to image the hydrated region of a tablet section, while energy dispersive X-ray microanalysis was used to locate the distribution of the model drug diclofenac within the gel layer. The presence of undissolved particles and the observation of a drug concentration gradient through the gel layer suggest a combined drug release mechanism of diffusion and polymer relaxation (erosion).

In a different investigation (Mitchell *et al.* 1993a), two methods were used to measure the expansion of hydrating HPMC tablets: (a) a thermomechanical probe and (b) the position of a projected laser beam either side of the matrix. Despite no difference in the release of the model drug propranolol from matrices composed of different HPMC grades, it was observed that the amount of axial swelling was dependent on the HPMC grade and that axial swelling was greater than radial swelling.

Other workers have used penetrometers. The first work in this area was carried out by Conte and Maggi (1996), who used a penetrometer attached to a texture analyser and video microscope to analyse the gel layer thickness of hydrating Geomatrix tablets. It was found that results obtained using each technique were similar and that the effect of a rate controlling barrier on one or two surfaces of the tablet could be demonstrated. A disadvantage of the technique was a destructive sectioning procedure that was required prior to data acquistion, preventing an *in situ* gel layer analysis.

A penetrometer has been used alongside backscattered ultrasound by Konrad *et al.* (1998) to measure the position of the gel layer/hydrating media interface, the so-called 'erosion front'. Although both methods produced similar results, the non-destructive nature of the ultrasound technique makes it preferable. There were a number of limitations with this method. The swelling of the tablet could only occur in one plane owing to the special cylinder the tablets were held in and it was not possible to measure the glassy core/rubbery gel interface.

Colombo *et al.* (1993) have calculated releasing surface areas of hydrating matrices by taking photographs at various time points during dissolution. By modifying the swelling behaviour and drug release by coating the tablet surfaces with an impermeable polymer it was shown that drug release was directly dependent on the available surface area. Further work in this area was carried out by Bettini *et al.* (1994) who imaged HPMC tablets held in position between two Plexiglas discs in order to analyse drug release and surface area with respect to time. Investigation into the movement of internal fronts was carried out within the same group using the apparatus (Colombo *et al.* 1995; 1996; 1999a, b). This involved the use of a model drug, buflomendil pyridoxalphosphate (BPP), which is a yellow solid and produces an orange solution. The use of this model drug allowed the observation of three distinct fronts during the

swelling process. These were interpreted by Colombo as: (i) the swelling front, which is the boundary between the glassy polymer and the rubbery gel state, (ii) the diffusion front, which is the interface between the solid drug in the core and the dissolved drug in the gel layer and finally (iii) the erosion front, which is the outermost radial front and forms the boundary between the gel layer and the outside hydrating medium. Figure 1.4 shows a series of images of the matrices containing different percentages of BPP (w/w). They were taken after 120 minutes of swelling.
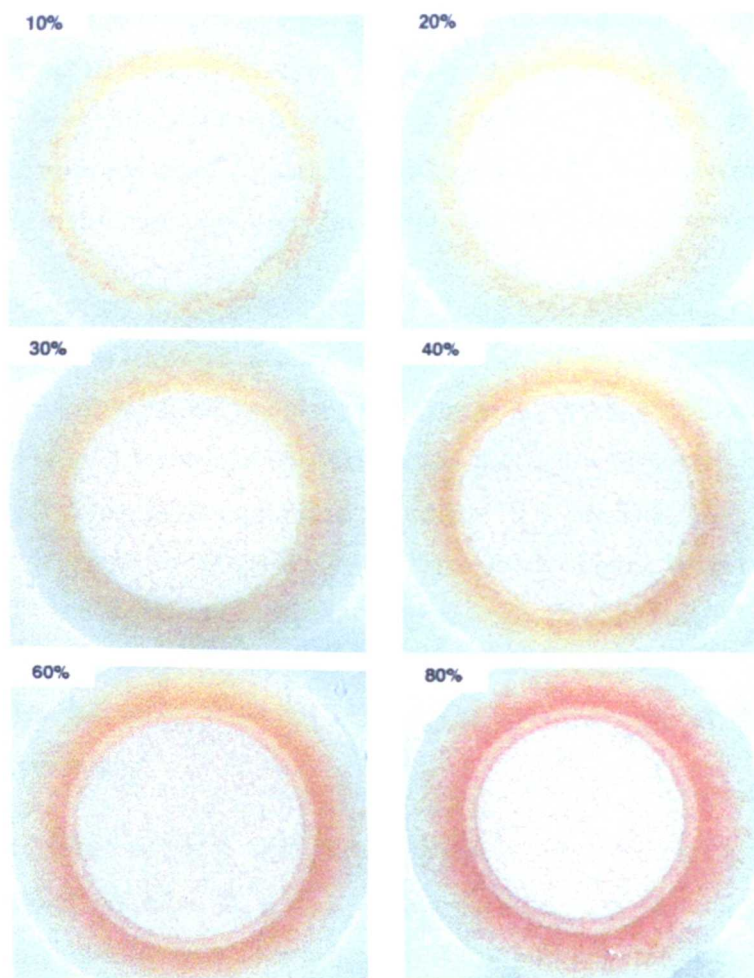
Figure 1.4 Images of HPMC matrices containing different percentages of buflomendil pyridoxalphosphate BPP (w/w) taken after 120 minutes of swelling (from Colombo *et al.* 1999)

Gel layer growth in hydrating HPMC tablets has been examined by nuclear magnetic resonance (NMR) microscopy by Rajabi-Siahboomi *et al.* (1994). NMR microscopy does not require physical sectioning of the tablet, so is non-destructive like some other imaging techniques. One of the key findings from this work was the observation that gel layer growth is similar in both the axial and radial directions and the greater overall tablet growth is in the axial direction, caused by axial expansion of the dry core.

NMR microscopy has also been used to image the disruption of the gel layer caused by incompatibilities with the model drug diclofenac and the observation of insoluble excipient particles in the gel layer (Bowtell *et al.* 1994). Figure 1.5 shows a vertical section through a hydrating Methocel K4M hydroxypropylmethylcellulose matrix that reveals the unusual concave development of gel growth in the axial direction. Water mobility has also been measured using NMR microscopy (Rajabi-Siahboomi *et al.* 1996). It has been shown that a water concentration gradient exists across the gel layer, with the highest level of hydration at the outer regions of the gel.

Another paper by Fyfe and Blazek-Welsh (2000) has exploited one dimensional 19F NMR imaging to follow the release of two model drugs containing fluorine: triflupromazine and 5-fluorouracil. It was shown that the two compounds diffused through the gel layer at different rates and that this was the reason for variation in the dissolution rates.

Matrix tablets were physically sectioned using a two blade knife by Moussa and Cartilier (1996). This destructive technique was able to elucidate the causes of observed differences in drug-release rates from cross-linked amylase matrices by demonstrating that rate of water penetration was dependent on the degree of cross-linking.
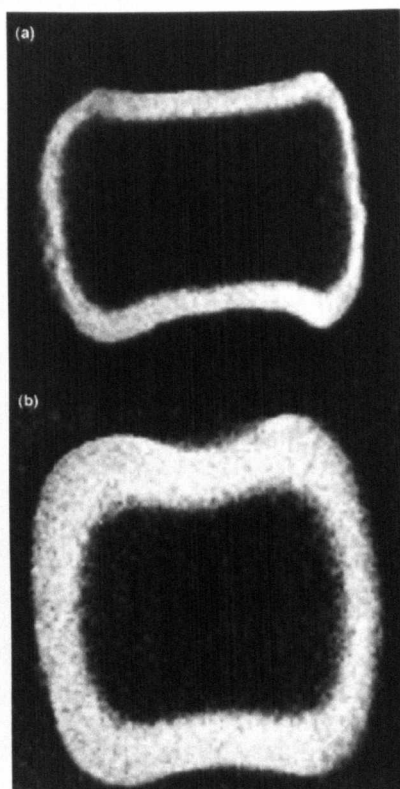
Figure 1.5 Vertical section through a hydrating Methocel K4M hydroxypropyl methylcellulose matrix

The image reveals the unusual concave development of gel growth in the axial direction. (a) 10 min, (b) 30min exposure to distilled water. From Bowtell *et al.* 1994.

Confocal laser scanning microscopy (CLSM) has also been utilised in the study of gel layer formation and growth. Adler *et al.* (1999) produced a tablet hydration cell that held either an intact tablet flat to enable imaging of radial swelling or a halved tablet to image axial and radial swelling. By using fluorescent microspheres as non-diffusing makers and tracking their movement through a time series of CLSM images, it was possible to quantitatively map the pattern of internal swelling within the gel layer. Melia *et al.* (1997) in an early study showed how CLSM along with a fluorescent marker Congo red could be used to observe the expansion of the gel layer in tablet formulations containing HPMC. Only radial swelling was observed through the limitations of the cell geometry.

These studies have been advanced by the development of a real-time confocal fluorescence imaging method which allows the critical early stages of gel layer formation in HPMC matrices to be examined (Bajwa *et al.* 2006). Congo Red, a fluorophore whose fluorescence is selectively intensified when bound to beta-D-glucopyranosyl sequences, allows mapping of hydrated polymer regions within the emerging gel layer, and revealed, the microstructural sequence of polymer hydration during development of the early gel layer. The earliest images revealed an initial phase of liquid ingress into the matrix pore network, followed by the progressive formation of a coherent gel layer by outward columnar swelling and coalescence of hydrated HPMC particles (figure 1.6). Gel layer growth in 0.1-0.5 M NaCl was progressively suppressed until at 0.75 M, particles clearly failed to coalesce into a gel layer, although with considerable polymer swelling. The failure to form a limiting diffusion barrier resulted in enhanced liquid penetration of the core, and the swelling of particles that did not coalesce culminated in surface disintegration.
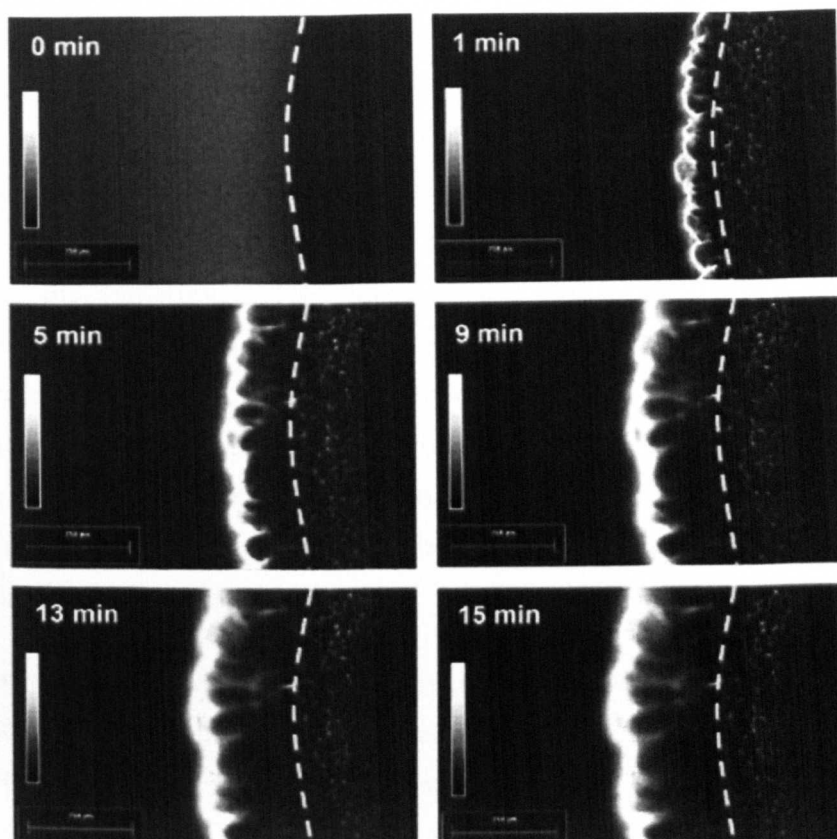
Figure 1.6 Time series of fluorescence images *in situ* of a hydrating HPMC matrix in aqueous 0.008% w/v Congo Red.

The images are coded for fluorescence intensity from white (highest) to black (lowest) as indicated by the wedge. The bright regions indicate areas of high fluorescence, highlighting regions of polymer hydration where the fluorophore has penetrated. Hydration medium maintained at 37°C. Ex 488/E >510 nm. Scale bar =750 μm. (from Bajwa *et al*. "Microstructural imaging of early gel layer formation in HPMC matrices." (2006)

Studies of the front movement have been undertaken by Vlachou *et al.* (2005) using an optical analysis technique. The measurements made of tablets comprising of HPMC alone and with the addition of two model drugs, furosemide and diclofenac, allowed investigation of the progress of the swelling/release processes. It was observed that diclofenac, with twice the solubility of furosemide, caused twice the increase in the dimension of the gel layer and twice the percentage of drug release. Furthermore, with the drug of lower solubility the diffusion front converges with the erosion front, increasing the dimension of the diffusion layer. It was suggested by the authors that diclofenac was released by a combination of diffusion and matrix erosion, whereas furosemide was released by erosion alone.

Kowalczuk *et al.* (2004) have used magnetic resonance imaging (MRI) to study the behaviour of the gel layer thickness in HPMC matrices with different loadings of a soluble drug tetracycline hydrochloride. The swelling properties were described in terms of the solvent penetration front. It appeared that tetracycline hydrochloride decreases the resistance to movement of solvent molecules through the gel network structure and that swelling of the matrix increased with the amount of drug present.

Baumgartner *et al.* (2005) have used MRI in combination with NMR spectroscopy to investigate the *in situ* swelling behaviour of cellulose ether matrix tablets and to quantify the polymer concentration across the gel layer. Combining the proton NMR relaxation parameters of the polymer solutions with the MRI data facilitated a quantitative description of the swelling process on the basis of the concentrations and mobility of water and polymer as functions of time and distance. The different concentration profiles observed after determined swelling times were found to be the consequence of the different polymer characteristics.

Using a similar rationale of combining spectroscopy and imaging, Dahlberg *et al.* (2007) have investigated the swelling characteristics of an HPMC matrix containing the hydrophilic drug antipyrine. MRI revealed the swelling behaviour of matrices when exposed to water whilst NMR spectroscopy provided the concentration of the drug released into the aqueous phase. In agreement with other studies, the authors concluded both swelling and drug release are diffusion controlled.

1.7 Physicochemical factors affecting drug release

The principal factors that have been proposed to affect the release of drugs from HPMC hydrophilic matrices will now be discussed.

1.7.1 Polymer factors affecting drug release

1.7.1.1 Polymer hydration rate

It has been suggested that gel layer formation must occur more rapidly than the dissolution rate of both the drug and other excipients in order for sustained release to be achieved (Alderman 1984). Investigating the effect of substitution type on drug release, Alderman also found that in tablets containing 85% spray dried lactose, 10% HPMC polymer and 5% Riboflavin, only the "fastest-hydrating" polymers such as HPMC 2208 (Methocel™ type K) provided sustained release. The relative rate of hydration of HPMC polymers was thought to be related to the amount of hydrophilic hydroxyl (and hydroxypropoxy) substituents on the cellulose backbone (Alderman 1984). Alderman's matrices however, contained an unusually low content of HPMC and this may have exaggerated the observed effects.

At higher HPMC levels, Mitchell *et al.* (1993a) found no relationship between proposed hydration rates of HPMC grades, and the release rate of drugs from matrix tablets. The authors attributed the different release rates described by Alderman to the differing tablet formulations. Rajabi-Siahboomi *et al.* (1993) investigated the swelling and hydration rate of different HPMC grades using ^{1}H-NMR microscopy and like Mitchell *et al.* (1993) found no relationship between Methocel™ grade and hydration rate.

1.7.1.2 Polymer substitution levels

The release rate of a drug from a matrix tablet has been shown to increase with increasing hydroypropyl content (Dahl *et al.* 1990). The authors attributed this to HPMC particle domains becoming more amorphous. Polymers possessing greater amorphous than crystalline regions are likely to exhibit enhanced dissolution rates (Dahl *et al.* 1990). Haque and Morris (1993*b*) reported that as the hydroxypropyl content of HPMC was increased, a weaker gel was formed and as a result, the gel layer may become more susceptible to erosion leading to faster drug release kinetics.

1.7.1.3 Polymer concentration

Many reports have shown that as the concentration of polymer in a matrix increases, a reduction in drug release rate is observed (Alderman 1984, Dabbagh *et al.* 1999, Gao *et al.* 1996) and some have proposed that the drug:polymer ratio is the most influential variable controlling drug release (Ford *et al.* 1985, Ford *et al.* 1987). This reduction in drug release rate has been attributed to reduced erosion of the gel layer and an increase in the drug diffusion path length and the tortuosity of the molecular environment (Alderman 1984, Mitchell *et al.* 1993b, Velasco *et al.* 1999). However, Gao *et al.* (1995a, b) have attributed the reduction in drug release to an exponential reduction in the diffusion coefficient of drugs as the concentration of HPMC increased, measured by ^{1}H-NMR spectroscopy. It is probable that the reduction in drug release rate is the result of a combination of these factors.

In contrast to these findings, Campos-Aldrete and Villafuerte-Robles (1997) found that the relationship between viscosity grade of HPMC and drug release rate only occurred in matrices containing 10% HPMC. At

HPMC contents of 20 and 30% no significant relationship was found. Wan *et al.* (1993) reported that as the HPMC content of matrices was increased from 5% to 10%, ibuprofen release changed from zero order drug release kinetics to a Higuchi release mechanism. Increasing the polymer content further lead to a reduction in the release rate, however the release mechanism did not change.

1.7.1.4 Polymer viscosity

The molecular weight of the HPMC polymer, and therefore the apparent polymer viscosity, is an important factor in determining drug-release properties (Alderman 1984, Li *et al.* 2005). It is generally accepted that drug dissolution is slower from matrices comprising of a higher molecular weight HPMC, which would produce a gel layer with greater viscosity, resultantly more tortuous and with greater resistance to the forces of erosion (Alderman 1984, Sung *et al.* 1996 and Velasco *et al.* 1999).

Mitchell and Balawinski (2008) have investigated the drug release rate variability from typical controlled release formulations over several HPMC viscosity ranges. Using pentoxifylline, theophylline, and hydrochlorothiazide as model drugs they predicted that drug release variability over the viscosity ranges would be greatest for the lower viscosity grades, such as E50 and K100 LV. It was proposed that drug release variability due to viscosity variations would be expected to be larger when there is substantial erosion contribution to drug release, and smaller for formulations with a predominantly diffusion controlled drug release mechanism.

1.7.1.5 Polymer particle size

HPMC particle size has been found to have a considerable influence on extended release rates. It has been demonstrated (Campos-Aldrete and Villafuere-Robles 1997) that, at low polymer content (<30%), drug release rate increased when HPMC particle size increased. The HPMC content at which particle size is less important varies between 30% and 45% in the literature.

Heng *et al.* (2001) have studied the effects of different HPMC particle size ranges on the release behaviour of aspirin from a matrix tablet. A critical threshold was identified at a mean HPMC particle size of 113 μm as the release mechanism deviated from first order kinetics above this mean particle size. Polymer fractions with similar mean particle size but differing size distribution were also observed to influence drug release rate but not release mechanism. The first order release constant K_1 was found to be related to the reciprocal of the cube root of both mean polymer particle size and number of matrix polymer particles.

Mitchell and Balwinski (2007) have investigated the influence of particle size by selecting combinations of six model drugs and four HPMC (USP 2208) viscosity grades. HPMC samples with different particle size distributions (coarse, fine, narrow, bimodal) were generated by sieving. For some formulations, the impact of HPMC particle size changes was characterized by faster drug release and an apparent shift in drug release mechanism when less than 50% of the HPMC passed through a 230 mesh (63 μm) screen. Within the ranges studied, drug release from other formulations appeared to be unaffected by HPMC particle size changes.

The effect of particle size ratios of HPMC and API has been investigated with respect to percolation thresholds (Fuertes *et al.* 2006, Miranda *et al.*

2006, Miranda *et al.* 2006). In one study (Fuertes *et al.* 2006) matrices were prepared using acyclovir and HPMC Methocel K4M using five different excipient/drug ratios. According to percolation theory, the critical points observed in dissolution and water uptake studies can be attributed to the percolation threshold of the excipients. It was found that this threshold was between 20.76% and 26.41% v/v of excipient plus initial porosity. This conclusion was supported by investigations of different matrix systems containing potassium chloride (Miranda *et al.* 2006a) and lobenzarit disodium (Miranda *et al.* 2006b) respectively.

1.7.1.6 Polymer surface properties

Sasa *et al.* (2006) have investigated the correlation between the surface properties of cellulose ethers and the mechanisms of water-soluble drug release from hydrophilic matrices. Using inverse gas chromatography (IGC), it was found that the differences in the surface free energy of HPC, HEC or HPMC were relatively small. However, there were significant differences in relative polarity in the order HEC > HPMC > HPC. This correlated with water sorption and the degree of polymer matrix swelling. It was concluded that the surface properties of the cellulose ethers may influence their interaction with water and subsequently the release mechanisms of the drug from matrix devices.

1.7.2 Non-polymer factors affecting drug release

1.7.2.1 Drug factors

Drug release from HPMC hydrophilic matrices may also be influenced by the physical properties of the drugs included in the formulations. Several reports have investigated the effect of drug particle size on release rates. Ford and co-workers (Ford *et al.* 1985a,b,c) have found that the effect of particle size of water-soluble drugs (promethazine hydrochloride, propranolol hydrochloride and aminophylline) on the release rate from HPMC tablets was only evident at low HPMC contents and when the particle size was large. However, for a poorly soluble drug such as indomethacin, a particle size increase resulted in a decrease in the release rate. It was proposed that the reduced release rate was simply the result of slower dissolution of large particles as the drug surface area to volume ratio decreased.

In contrast, Velasco *et al.* (1999) found that the particle size of diclofenac Na had no effect on the drug release rate at low HPMC contents, whereas at higher HPMC content an increase in the release rate was noted as the particle size was increased. No rationale for these findings was offered.

Drug solubility is an important factor affecting drug release from HPMC matrices. The mechanism by which soluble drugs are released from HPMC matrices is considered to be Fickian diffusion, whereas poorly soluble drugs are released mainly by gel layer erosion. Using the optical method first described by Colombo *et al.* (1995), Bettini *et al.* (2001) studied the effect of drug solubility on release rates using drugs with a range of aqueous solubility. The rate and amount of drug released from K100M was found to be dependant on drug solubility. A shift of undissolved drug particles from the swelling front of the matrices to the eroding front of the

gel layer was observed and the process was termed "drug particle translocation". It was proposed that drug particle translocation occurred as a result of the spring-like action of macromolecular chains upon transition from the glassy to the rubbery state. Similar observations were reported by Adler *et al.* (1999) for insoluble beads in swellable polymers.

The rate of poorly soluble drug release has been shown to increase on complete hydration of the matrix core (Bettini *et al.* 2001). This was thought to be the result of drug particles reducing the entanglement of the polymer chains, increasing gel layer erosion rate. This was manifested in dissolution profiles as an inflection and was more pronounced as drug solubility decreased. Jayan *et al.* (1999) noted an increase in release rate of hydrochlorothiazide from mixed HPMC: PEO matrices upon complete hydration of the core.

Gafourian *et al.* (2007) have characterised the effect of chemical structure on the release of drugs from HPMC 2910 and 2208 matrices using a quantitative-structure-property relationship (QSPR) technique. Structural descriptors including molecular mechanical, quantum mechanical and graph-theoretical parameters, as well as the partition coefficient and the aqueous solubility of the drugs were used to establish relationships with release parameters. The aqueous solubility and molecular size of the drugs were found to be the most important factors for both HPMC 2208 and 2910 matrices.

1.7.2.2 Lubricants

Magnesium stearate is commonly used as a lubricant for formulations. The hydrophobic nature of magnesium stearate may have implications for tablet wetting and tensile strength and as a result may affect drug release.

Investigations by Rekhi *et al.* (1999) found that magnesium stearate content up to 2% w/w had no effect on drug release rates.

Sheskey *et al.* (1995) also found that the effect of magnesium stearate content between 0.2 and 2% had no effect on drug release. It is probable that at higher concentrations, magnesium stearate would cause a reduction in tablet tensile strength and drug release may be increased.

1.7.2.3 Drug-release modifiers

1.7.2.3.a pH modifying excipients

Drug solubility is a key determinant of release in these dosage forms and, when drug solubility is pH-dependent, the changing pH environment along the gastro-intestinal tract may give rise to poor drug solubility and a change in release mechanism (Badawy and Hussain, 2007). The most common examples are weakly basic drugs, which have high solubility in the stomach but are poorly soluble at the neutral pH of the duodenum. A common approach is to maintain the drug in its soluble form by incorporating pH-modifying excipients in the matrix with the release of weakly basic drugs commonly improved by the inclusion of weak acids or acidic polymers (Gabr, 1992, Thoma and Ziegler, 1992, Streubel *et al,* 2000, Espinoza *et al,* 2000, Varma *et al.* 2005, Kranz *et al.* 2005, Siepe *et al.* 2006).

Streubel *et al.* (2000) have investigated the release of verapamil hydrochloride from HPMC matrix tablets. They evaluated the effect of incorporating various acids into the matrix system. All three acids tested (fumaric, sorbic and adipic) resulted in significant increases in drug release in pH 6.8 and 7.4 phosphate buffers. Fumaric acid was more effective than the other acids in enhancing drug release and exhibited a

release profile that almost overlapped those in pH 1.2. The lower pK_a of fumaric acid was proposed to provide a lower pH within the matrix. Release profiles were also shown to be independent of the amount of fumaric acid in the formulation.

Citric acid has been used to modify the release of pelanserin, a weakly basic drug with a short half-life, from an HPMC formulation (Espinoza *et al.* 2000). Dissolution studies were carried out in pH 1.2 for the first 3 h, and phosphate buffer pH 7.4, h 3–8. Increasing concentrations of citric acid produced increasing values of the kinetic constants, in a cubic relationship. Higher HPMC proportions produced slower dissolution rates but with a citric acid compensating more clearly a decreased solubility of pelanserin at pH 7.4.

1.7.2.3.b. Other polymers

A number of workers have investigated tailoring release profiles from HPMC matrices by incorporating other polymers into the hydrophilic matrix. Examples have included anionic polymers, other natural based polymers and synthetic polymers.

Anionic polymers such as Eudragit S, Eudragit L 100-55 and sodium carboxymethylcellulose have been incorporated into HPMC K100M matrices to modify the drug release (Takka *et al.* 2001). The effects of changing the ratio of HPMC to the anionic polymers were examined in water and different pH media. The interaction between propranolol hydrochloride and anionic polymers was confirmed by UV spectral subtraction. Drug release was controlled with the type of anionic polymer and the interaction between propranolol hydrochloride and anionic polymers. The HPMC–anionic polymer ratio was also found to influence the drug release.

Hardy *et al.* (2007) have investigated the effect of the binder polyvinyl pyrrolidone (PVP) incorporation on the release of the water soluble drug caffeine from HPMC matrices. Mechanistic studies using gel rheology, excipient dissolution and near-infrared (NIR) microscopy were used to investigate the underlying drug release mechanism. It was shown that drug release was modulated by a HPMC viscosity reduction which occurred at a critical concentration of PVP. This resulted in a break-up of the extended release tablet.

Feely and Davis (1988) investigated the effects of the ionic polymers diethylaminoethyl dextran (cationic) and sodium carboxymethylcellulose (NaCMC) (anionic), and the non-ionic polymer polyethylene glycol (PEG) 6000 and the hydrophobic polymer ethylcellulose, on HPMC matrices. They reported that non-ionic polymers were no more effective than HPMC itself, whilst ionic polymers had a slight effect in retarding the release of oppositely charged drugs.

Conti *et al.* (2007) have used HPMC and NaCMC in combination as polymeric carriers. *In vitro* release studies demonstrated how the mixture enabled a better control of the drug release profiles at pH 4.5 and at 6.8 both in term of rate and mechanism. The results suggested that the two cellulose ethers used in combination form a gel, which is less susceptible to erosion and chain disentanglement and the drug release mechanism is mainly governed by diffusion.

1.7.2.3.c Cyclodextrins

The effect of cyclodextrin (CD) incorporation into HPMC dosage forms has been investigated by a number of authors.

A study by Savolainen *et al.* (1998) investigated the effect of various CDs on the bioavailability of glibenclamide when formulated with HPMC in

solution. It was found that the incorporation of HPMC in the solution enhanced the solubilising effects of the CDs, reducing the levels required. No mechanism for this effect was offered.

Koester *et al.* (2004) have evaluated the effect of β-cyclodextrin incorporation by mixing or complexation in a hydrophilic matrix containing carbamazepine and HPMC. It was found that the rate of drug release was increased when the drug was complexed with the CD rather than simply mixed. The methods of drying the complex; spray drying and freeze drying, had no effect when 30% HPMC was used in the formulation but there was significant impairment of gelling and matrix formation at 15% HPMC when complexes were spray dried.

Pose-Vilarnovo *et al.* (2004) have explored the effects of β-cyclodextrin and hydroxypropyl-β-cyclodextrin on the diffusion and release behaviour of diclofenac sodium and sulphamethizole from HPMC gels and matrix tablets. Gels of concentration 0.5-2.0% polymer containing different drug/CD mole ratios showed no effect on cloud point while diffusivity from the gels appeared to be increased, owing to a reduction in polymer/drug hydrophobic interactions.

1.8 Interactions between non-ionic cellulose ethers and pharmaceutical and other additives

During the development of a successful hydrophilic matrix extended release formulation, interactions between individual formulation components and those in dissolution media need to be determined, and where they cause a problem, overcome. This section considers literature pertaining to the interactions and incompatibilities of cellulose ethers with drugs, electrolytes, surface active materials and other excipients. Often, a precise mechanism by which these interactions occur is poorly understood and in the absence of conclusive experimental evidence the theories are speculative.

1.8.1 Incompatibilities with electrolytes

Originally, it was thought that electrolytes depress the solubility of cellulose ether solutions due to their greater affinity for water, and the order of potency follows that of the Hofmeister lyotropic series. Touitou and Donbrow (1982) proposed that the mechanism by which ions reduce the sol:gel phase transition temperature is by removing water from the hydration sheath surrounding the hydrophobic groups of the polymer and hence lowering the temperature by which hydrophobic interactions of the gel state become favourable. However, recent advances in our understanding of Hofmeister effects and how these relate to the interactions between ions and macromolecules have suggested that ions do not affect bulk water properties but may directly interact with the hydration sheath macromolecule (Zhang and Cremer 2006). This is based on the experimental observations that (i) anions have no effect on hydrogen bonding network outside their immediate vicinity (Omta *et al.* 2003), (ii) no thermodynamic changes in bulk water surrounding species

were observed using pressure perturbation calorimetry (Batchelor *et al.* 2004) and (iii) physical behaviour in Langmuir monolayers is only disrupted by direct penetration of ions rather than changes in the properties of the bulk water (Gurau *et al.* 2003).

It is well established that certain phenolic preservatives including chlorocresol, *p*-hydroxybenzoic acid, *p*-aminobenzoic acid and chlorophenol are incompatible with MC (Martindale 1996). This incompatibility was investigated by Tillman and Kuramoto (1957) who reported that the phenolic compounds formed an insoluble complex with methylcellulose and that their effect was associated with a decrease in solution viscosity. It was proposed that the complex was formed by hydrogen bonding between the hydroxyl groups of phenol and MC. However, it was noted that the viscosity of MC solution was not affected by the presence of other preservatives such as sodium phenoate, sodium benzoate, benzoic acid, pyridine or aniline hydrochloride.

Mitchell *et al.* (1990) found that the ability of salts to lower the cloud point of HPMC gels followed their order in the lyotropic series, i.e. chloride < tartrate < phosphates and potassium < sodium. They also found that anions had greater influence than cations in lowering the cloud point. Phosphate and chloride salts were found to influence the dissolution of propranolol hydrochloride from HPMC matrices with an increase in ionic strength decreasing dissolution rates to a minimum before the occurrence of a 'burst' (immediate) release. Disintegration times of HPMC matrices without API also varied with respect to the ionic strength of the disintegration medium.

Kajiyama *et al.* (2008) have studied the effects of inorganic salts on disintegration of HPMC matrices. The disintegration time was reduced by the addition of $NaHCO_3$, $KHPO_4$, K_2SO_4, KCl, or NaCl. Conversely, the

addition of Na_2CO_3 or Na_2SO_4 had no effect on disintegration. It was found that there was a reduction in disintegration time when the heat of dissolution of inorganic salts was endothermic whereas no effect was observed when it was exothermic. These results suggested that the thermal environment and ionic strength inside the tablet might affect the disintegration of HPMC matrix tablets.

Liu et al. (2008) have used micro-differential scanning calorimetry (m-DSC) and rheological measurements to study the effects of inorganic salts on the thermal gelation behaviour of HPMC. The salts included monovalent (NaCl, KCl, NaBr, and NaI), divalent (Na_2HPO_4, K_2HPO_4, and Na_2SO_4), and trivalent (Na_3PO_4) species. It was found that the effectiveness of anionic species in changing the maximum heat capacity (T) of the HPMC solutions followed the Hofmeister series.

Organic ions such as amino acids have been found to influence HPMC gelation temperatures. Richardson and co-workers (2006) have studied the effect of an L-amino acid series on the phase transition temperature of 1% w/w HPMC solutions. The ability to raise or lower the transition temperature was critically related to amino acid hydrophobicity. Smaller and more hydrophilic amino acids reduced the phase transition temperature, whereas large hydrophobic aromatic amino acids increased it. It was proposed that the effects of amino acids are a balance between the ability of their hydrophilic regions to dehydrate and disrupt the polymer hydration sheath, and the ability of their hydrophobic regions to associate with and solubilise methoxyl-dominated regions of the polymer in a manner analogous to that of surfactant systems.

1.8.2 Interactions with surfactants

Interactions between surface active agents and various polymeric materials have been the focus of a wide-range of research within many

different industries, including the cosmetic, oil recovery, food and pharmaceutical areas. This is a result of the possibility of interactions significantly affecting the properties of polymer in solutions.

The addition of a surfactant to an aqueous solution of a hydrophobically modified polymer usually leads to a viscosification of the solution at a moderate level of surfactant addition. In a pharmaceutical context, this may have significant impact on the behaviour of dosage forms containing hydrophobically modified polymers such as HPMC

Nilsson (1995) studied the interactions between HPMC and SDS in water using viscometry, equilibrium dialysis, cloud point determinations, dye solubilization, and fluorescence spectroscopy. He proposed that SDS adsorbs in a cooperative manner as molecular clusters, forming small micelles which solublise the hydrophobic regions of the HPMC polymer chain. This increases the polymer solubility and raises the cloud point temperature. Important rheological effects such as high viscosity are observed over a fairly limited composition range beginning at the onset of adsorption and ending long before adsorption saturation is reached. The maximum capacity of adsorption in HPMC was found to be of the order of one adsorbed amphiphile molecule per polymer monomer unit.

Kulicke *et al.* (1998) have investigated the behaviour of aqueous solutions of three highly substituted, hydrophobic HPMC in mixtures containing the anionic surfactant sodium lauryl sulfate (SLS). In the absence of anionic surfactant, the aqueous HPMC solutions showed predictable polymer solutions flow behaviour. The most hydrophobic HPMC displayed clearly the effects of an SLS-dependent viscosity increase and the appearance of dilatant flow. At constant HPMC concentration (0.5% w/w), a fifteen-fold increase in viscosity was observed in the critical micelle concentration range for SLS.

Wittgren *et al.* (2005) have used size exclusion chromatography (SEC) with online multi-angle light scattering (MALS) and refractometric index (RI) detection to characterise the surfactant-polymer interaction between various cellulose derivatives including HPC, HPMC and HEC and the surfactant sodium dodecyl sulphate (SDS). The more hydrophobic HPC and HPMC adsorbed surfactant to a significantly greater extent than HEC. The inter-chain interactions at compositions close to the critical aggregation concentration (CAC) were clearly seen for HPC and HPMC as an almost two-fold average increase in the apparent molecular mass of the complex.

Sovilk and Petrovic (2006) have used conductivity, viscosity and rheological measurements to study the interaction of HPMC with the anionic surfactant SDS in aqueous solutions. The concentration of SDS at which interaction starts (the critical aggregation concentration (CAC)) and at which it ends (polymer saturation point (PSP)), were determined, and an interaction mechanism was proposed. The linear relationship was found between the PSP and HPMC concentrations, while CAC remained constant. In addition, it was found that stability of the emulsions was influenced by the HPMC–SDS interaction.

1.8.3 Interactions with drugs

There have been several reports of drugs influencing the physiochemical properties of non-ionic cellulose ether solutions. Generally, the studies have lacked a detailed mechanistic explanation.

The effects of nicotinamide on the properties of aqueous HPMC solutions were studied by Hino and Ford (2001). Nicotinamide exhibited a 'salting in' effect on the HPMC solutions resulting in an increase in gelation temperature and cloud point temperature (CPT). Hino and Ford (2001)

proposed that these effects were due to the hydrogen-bonding of nicotinamide to the HPMC, which was suggested by a shift to a longer wavelength of the UV spectra of nicotinamide solutions on the addition of HPMC.

The aqueous interaction of ibuprofen sodium with the cellulose ethers ethyl hydroxyethyl cellulose (EHEC) and HPMC, has been investigated by cloud point, capillary viscometry, equilibrium dialysis, and fluorescence probe techniques (Ridell *et al.* 1999). Fluorescence and microviscosity measurements showed that ibuprofen is an amphiphilic drug which formed micelles in pure water. At the critical micelle concentration (CMC) of the drug, a marked increase in the CPT of the cellulose ethers was reported. It was postulated, that above the CMC, micelles of ibuprofen solubilise the hydrophobic parts of the polymer, and therefore increase the polymer hydration and the CPT (Ridell *et al.* 1999).

Mitchell and co-workers (Mitchell *et al.* 1990, Mitchell *et al.* 1991) have examined the effect of drugs on the thermal properties of HPMC solutions. Propranolol hydrochloride and promethazine hydrochloride increased the CPT of HPMC with this effect more prominent at higher drug concentrations. Promethazine is amphiphilic and forms micelles at concentrations greater than 0.5% w/v. Propranolol hydrochloride is weakly surface active, therefore the response of HPMC in the presence of these drugs may be associated with the surface activity of this drug. Aminophylline and tetracycline gave straight line relationships between their concentration in solution and the observed CPT. Quinine bisulphate and theophylline did not affect the CPT. It was suggested that the hydrating effect of the quinine molecule was counteracted by the dehydrating effect of the sulphate ions.

Touitou and Donbrow (1982) utilised the viscosity-temperature curve to examine the effect of drugs on the sol:gel transition temperature of MC.

Potassium phenoxypenicillin and chlorpheniramine maleate raised the sol:gel transition temperature and this effect was explained on the basis that the drugs are adsorbed onto the macromolecule, carrying with them water molecules and raising the degree of hydration of the polymer. The failure of compressed matrices of MC containing these drugs to undergo attrition or disintegration, unlike the matrices from which these agents were absent, suggests that these drugs stabilised the gel layer of these matrices. Reduction of the gel point by salicylic acid may be as a result of formation of a low solubility complex with the macromolecule (Touitou and Donbrow 1982).

Katzhendler *et al.* (1998 and 2000) have investigated the interactions of HPMC with naproxen sodium and carbamazepine. Using differential scanning calorimetry (DSC), it was found that addition of naproxen sodium increased the fraction of bound water in HPMC 2208 solutions from 1.5 water hydration layers to 2.2. This was explained by water ordering as a result of naproxen sodium adsorbing onto the polymer backbone. In the same study, the viscosity of HPMC 2208 solutions containing naproxen sodium was found to be lower than solutions containing the free acid or no drug.

McCrystal and co-workers (McCrystal *et al.* 1999a, McCrystal *et al.* 1999b) have also used DSC to investigate the effect of propranolol hydrochloride and diclofenac sodium on the distribution of water in HPMC gels. The moles of bound water per polymer repeating unit increased with diclofenac sodium, whereas propranolol hydrochloride had no effect. They suggested that diclofenac sodium 'salted-out' the polymer, reducing its solubility.

1.9 Aims and objectives of this PhD thesis

As has been presented and discussed in this introduction, there is considerable evidence in the literature that the physicochemical properties of HPMC and its performance in extended release hydrophilic matrices can be modified by additives, including salts, surfactants and commercial drugs. To facilitate formulation development, it is essential to achieve a level of understanding of the fundamental interactions between polymer, drugs and incorporated diluents and the macroscopic manifestation of these effects with regard to the morphology, structure and functionality of hydrophilic matrix gel layer.

1.9.1 Principal Aim

The purpose of this thesis is to identify and probe critical processes in drug release from HPMC hydrophilic matrices, primarily by studying the interactions of drugs with HPMC in the context of colloidal science and the macroscopic pharmaceutical consequences of these interactions using a suite of experimental and imaging techniques. Subsequent efforts will attempt to reconcile effects of the former to changes in the latter.

1.9.2 Approach

To accomplish the above principal aim, the work will be divided into the following key areas:

Chapter 2: A critical analysis of a previous study into the release of drugs from hydrophilic matrices with an interpretation with respect to possible molecular interactions.

Chapter 4: An investigation into the effect of non-steroidal anti-inflammatory drugs on HPMC solution properties and probing of the molecular basis of the interactions.

Chapter 5: The effect of drugs on early gel layer formation and the subsequent properties of a hydrophilic matrix comprising of HPMC.

Chapter 6: The effect of soluble and insoluble diluents on the early gel microstructure and the subsequent properties of hydrophilic matrices

Chapter 7: The interactive effects of incorporated drugs and diluents on the morphology and functionality of the nascent HPMC gel layer.

The specific aims and objectives in each of these chapters may facilitate insight into some of the critical processes that are involved in drug release from HPMC hydrophilic matrices.

1.9.3 Thesis organisation

The following diagram shows the organisation of the experimental chapters with respect to achieving the principal aim.

Developing a hypothesis

Chapter 2
Interpretation of a previous drug release study from HPMC matrices

Investigating interactions

Chapter 4
Interactions between non-steroidal anti-inflammatory drugs and HPMC

Pharmaceutical consequences

Chapter 5
The effect of drugs and ionic media on the morphology and functionality of the gel layer in HPMC matrices

Chapter 6
Effects of diluents on the nascent HPMC gel layer functionality, swelling and morphology

Chapter 7
The combined effects of drugs and diluents on early gel layer formation in HPMC hydrophilic matrices

Conclusions and future work

Chapter 8
Conclusions and future work

Chapter 2

Interpretation of a previous drug release study from HPMC matrices

2.1 Aims of this chapter

Several studies in the literature have reported how the performance of HPMC as an extended release carrier may be affected by incompatibilities with drugs, electrolytes and other small molecules. Some of these effects alter the drug release kinetics, whilst others may lead in extreme cases to failure of gel layer formation and immediate drug release (Mitchell *et al.* 1990, Ford 1999, Li *et al.* 2005, Bajwa *et al.* 2006).

To date there have been no studies that directly relate the molecular interactions between drugs and HPMC to the drug release performance of hydrophilic matrices. This opening chapter is an interpretation and rationalisation of the work carried out in a previous PhD study by Simon Banks (Banks 2003) who investigated the release profiles of two non-steroidal anti-inflammatory drugs (NSAIDs) containing similar chemical moieties (diclofenac sodium and meclofenamate sodium) (figure 3.1). These drugs have also been used as the model drugs in the current thesis.
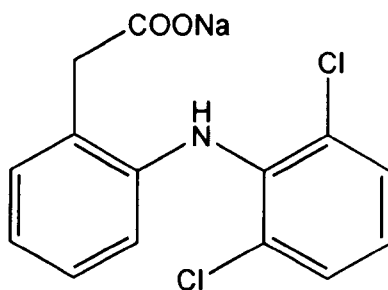
Diclofenac sodium (pK$_a$ 4.0, Log P 4.5)
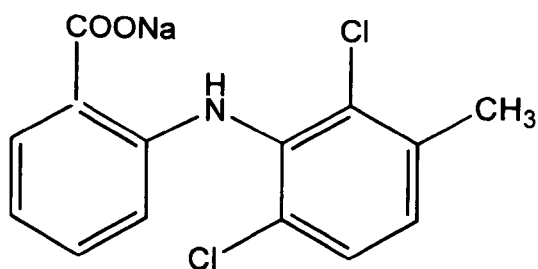
Meclofenamate sodium (pK$_a$ 3.7, Log P 6.0)

Figure 2.1 The molecular structure of NSAIDs used by Banks (2003) and subsequently used as model drugs in this thesis

2.2 Introduction

In this chapter, the release studies performed by Banks of diclofenac Na and meclofenamate Na from HPMC hydrophilic matrices are presented with an interpretation of the potential molecular mechanisms underlying the release process. The aim of Banks' study was to investigate the two drugs as examples of chemical species containing substituted aromatic moieties which may possess incompatibility with HPMC. However, as will become apparent as the data is presented, there was evidence of other phenomena occurring within the dosage forms. The investigation of these is the basis of the experimental work carried out in this thesis.

2.2.1 Identifying a series of model drugs

The original aim of Bank's investigation (Banks 2003) was to identify key chemical moieties within drug structures that were responsible for incompatibilities with HPMC. The incompatibility of HPMC with phenols is well known (Martindale 2005) and Banks (2003) showed that many aromatic molecules including substituted phenol and aniline derivatives can reduce the cloud point temperature (CPT) of aqueous HPMC solutions. Banks' hypothesis was that drug molecules containing these structures may also alter the CPT of HPMC solutions and subsequently influence the drug release characteristics. A range of potential model drug candidates containing phenol or aniline molecules were subsequently identified by searching the Merck Index 1999 (Merck & Co Inc, NJ, USA).

NSAIDs possess a simple molecular structure with the absence of complex side chains and incompatibilities between NSAIDS with cellulose ethers have been reported in the literature (Rajabi-Siahboomi 1993, Ridell *et al.* 1999, Touitou and Donbrow 1982). For this reason Banks explored their effect on release from HPMC matrices.

2.3 Summary of Banks' results

2.3.1 Banks' formulations and matrix preparations

Banks prepared hydrophilic matrices from a 63-90 μm sieve cut of a single batch E4M HPMC (HPMC USP 2910), anhydrous direct compression lactose and the model drugs. The tablets weighed 300 ± 5 mg and had a diameter of 9.35 mm. The drug content was varied from 10% w/w to 50%, and HPMC content varied from 20% to 60% w/w using lactose (qs) to complete the formulation as required. All formulations contained 2.5% magnesium stearate as lubricant and 0.5% silicon dioxide.

2.3.2. The release of diclofenac Na and meclofenamate Na from HPMC hydrophilic matrices

Figure 2.2 shows the release profiles of matrices containing 10%, 25% and 50% w/w diclofenac Na. In the formulations containing 10% w/w diclofenac Na, only matrices containing 60% w/w HPMC afforded extended release and below this HPMC content drug release was immediate. When the drug content was increased to 25% w/w and 50% w/w, all matrices exhibited immediate release profiles.

Figure 2.3 show the drug release profiles for meclofenamate Na matrices with different levels of HPMC content. In contrast with diclofenac Na formulations, drug release rates became increasingly extended as the drug content was increased. Formulations containing 50% w/w meclofenamate Na released drug over 10 hours, whereas at lower drug contents, all drug was released within 60 minutes.
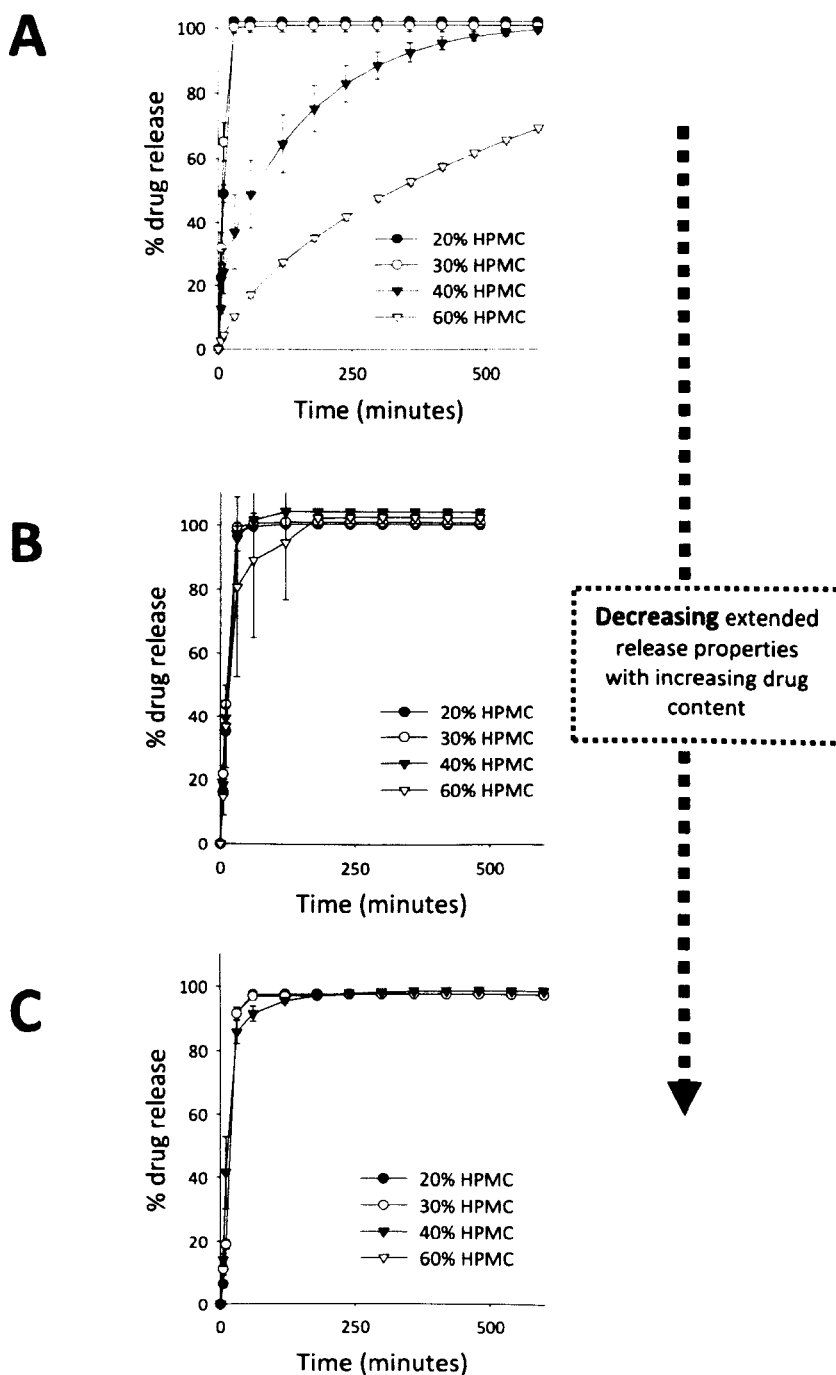
Figure 2.2 Drug release from matrices containing (A) 10% (B) 25% and (C) 50% w/w diclofenac Na at different HPMC levels

Matrices weighed 300 ± 5 mg, Dissolution tests carried out in 0.9% NaCl using the USP I apparatus at 100 rpm, 37 ± 0.5 °C. Mean (n=3) ± 1
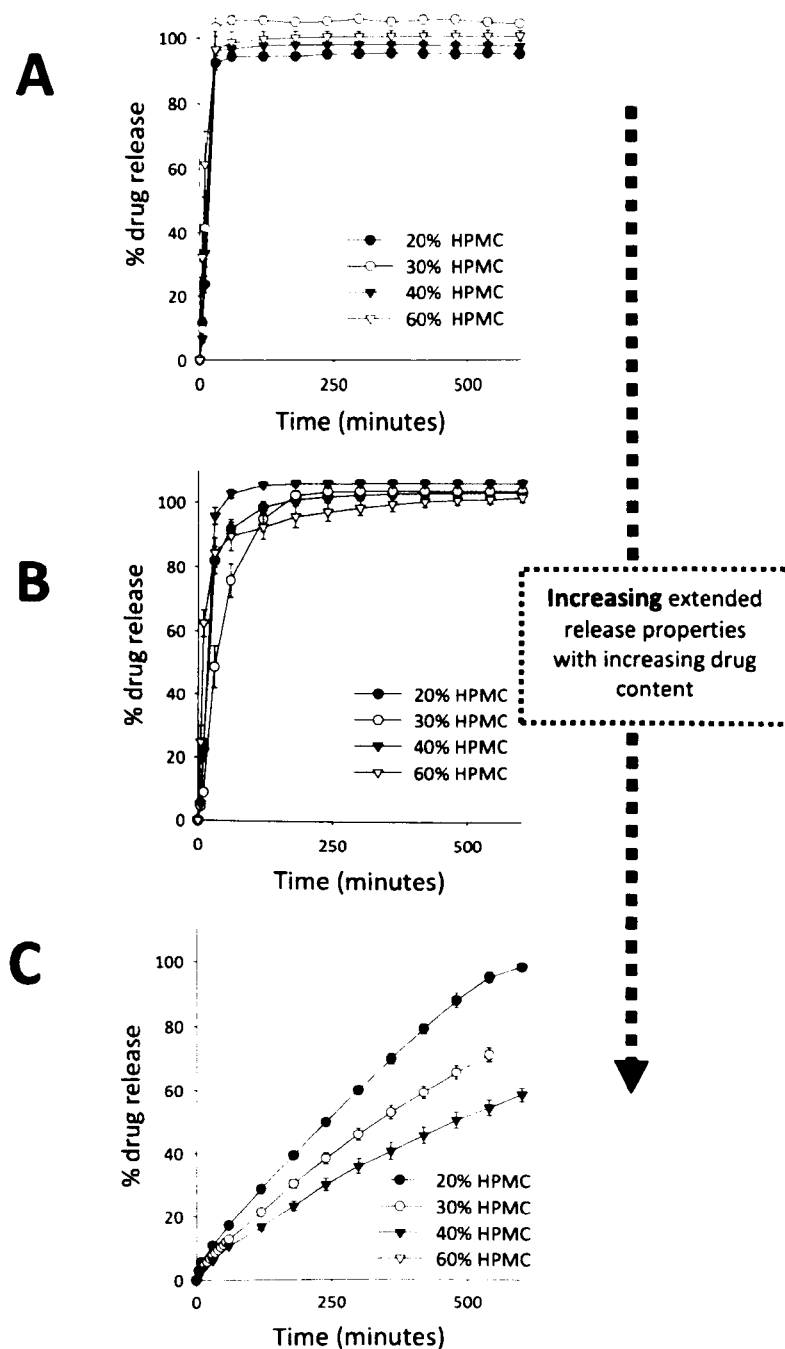
Figure 2.3 Drug release from matrices containing (A) 10% (B) 25% and (C) 50% w/w meclofenamate Na at different HPMC levels.

Matrices weighed 300 ± 5 mg. Dissolution tests were carried out 0.9% NaCl using the USP I apparatus at 100 rpm, 37 ± 0.5 °C. Mean (n=3) ± 1

2.3.3 Banks' disintegration study of diclofenac Na and meclofenamate Na matrices

Table 2.1 shows the disintegration times obtained by Banks (2003) for HPMC matrices containing diclofenac Na and meclofenamate sodium Na. Critical differences were apparent between the two drugs. Both increasing the drug content and decreasing the HPMC content resulted in more rapid disintegration of diclofenac Na matrices. In contrast meclofenamate Na matrices disintegrated more slowly with decreasing HPMC content and increasing drug content. At the highest levels of meclofenamate Na, the matrices did not disintegrate during the experimental period.

Drug Content (%)	HPMC Content (%)	Disintegration Times (minutes)	
		Diclofenac Na	Meclofenamate Na
10	20	15	14
	30	15	19
	40	20	10
	60	20	8
25	20	9	120‡
	30	10	45
	40	10	20
	60	10	8
50	20	15‡	>120
	30	12‡	>120
	40	8	>120

Table 2.1 Disintegration times for HPMC matrices containing the model drugs included in the investigation

Disintegration data obtained in 900ml 0.9% saline at 37 ± 1 °C, observations made from 4 tablets and taken to the nearest minute. ‡ indicates that matrices stuck to the Perspex disc.

2.4 Interpretation of the work of Banks

2.4.1 The role of drug properties

Banks discovered that there were fundamental differences in the manner in which diclofenac Na and meclofenamate Na were released from HPMC hydrophilic matrices despite possessing similar solubility and almost identical chemical structures (figure 3.1). In the case of diclofenac Na, increasing the level drug led to matrix failure and loss of extended release properties whereas in meclofenamate Na- matrices increases in drug levels improved the extended release properties of the formulations. A review of literature describing studies of the interactions between drugs and HPMC has been presented in section 1.9.

Many factors affect the drug release mechanism from HPMC hydrophilic matrices with several drug-related factors being cited as having a critical influence. Particle size has an effect (Ford *et al.* 1985 a, b, c) but only in the case of poorly water soluble drugs when there is a low HPMC content in the matrix. Drug solubility has been highlighted as a key influence on drug release (e.g. Bettini *et al.* 2001, Gafourian *et al.* 2007) but the solubility difference between the two model drugs examined in Banks' work (10 vs 50 mg/ml for diclofenac Na and meclofenamate Na respectively at 25°C) would not explain the disparity in drug release profiles.

An overlooked physico-chemical factor may be the potential surface activity of these drug molecules and their potential to interact with HPMC in the hydrated state. Surface activity is not unique to soap and detergent solutions: many drugs are also surface active and can self-aggregate to form micelles or micelle-like structures above a critical concentration (Attwood 1995, Schreier *et al.* 2000). These include antihistamines,

antidepressants, anticholinergics and tranquillisers as well as NSAIDs (Fini *et al.* 1995). Fini *et al.* analysed the surface active properties of ten NSAIDs of the acetic and propionic classes with respect to their solubilisation of a lipid probe, the azo-orange dye Orange OT. It was found that solubilisation was related to the self-aggregation of the drug anion above a critical concentration, which differed for each drug. Although in this case, the solubilisation capacity of meclofenamate Na and diclofenac Na was not compared, the surface activity of these two drugs will differ as they have different structures, pK_a and solubility.

Polymer association with complementary additives can strengthen or induce connections between polymeric chains and can result in considerable increases in the viscosity of polymer dispersions. In several studies, surfactants have been used to induce changes in the conformation of polysaccharides, and to promote the formation of aggregates. This has been proposed as a way to obtain homogenous aqueous dispersions and to modulate rheological behaviour. For example, in Carbopol 1342 gels, the beta-blocker alprenolol has been found to form micelle-like aggregates with polymer lipophilic residues, increasing the elastic and viscous moduli of Carbopol hydrogels (Paulsson and Edsman, 2002). However, as the drug concentration was increased, the gel collapsed and, when alprenolol amino groups fully neutralised the carboxylic acid groups of the acrylic polymer, precipitation occurred. The changes then observed in alprenolol diffusion rate were concluded to be a consequence of both the interactions with the polymer and the changes induced in the viscosity of the systems.

In another study, the interaction of various phenothiazines (chlorpromazine, trifluoromazine, promazine and promethazine) with hyaluronate caused the gels made of this anionic polymer to shrink with the minimum drug concentration required being proportional to the CMC (Yomota and Okada, 2003). The potential for periodontal drug delivery of non-ionic cellulose ethers with surface active anaesthetic drugs was

highlighted by Scherlund *et al.* (2000). Lidocaine and prilocaine did not interact with EHEC or hydrophobically modified EHEC but strongly affected polymer interactions with sodium dodecyl sulphate and myristoylcholine bromide. As a consequence, the drug loaded systems differed notably from polymer-surfactant dispersions in their viscoelastic behaviour

The addition of surfactants to hydrophilic matrices has also been noted in the literature. An HPMC matrix including sodium dodecyl sulphate (SDS) was shown to release chlorpheniramine maleate more slowly than without surfactant probably as a result of surfactant/drug ionic interactions (Feely and Davis 1988). Surfactants have also been found to induce modifications in the degree of swelling of the gel layer, by establishing interactions with the polymer, which may also alter the drug-release process. Nokhodchi *et al.* (2002) have evaluated the influence of nature and concentration of several surfactants or their mixtures on the release of propranolol from HPMC-Eudragit matrices. Matrices were prepared by direct compression of drug/HPMC/Eudragit exhibited a progressive decrease in drug release rate in both pH 1.2 and pH 6.8 when the SDS proportion was increased up to 20 mg. These results were explained by both drug/surfactant interactions, which decrease drug solubility, and polymer/surfactant interactions, which increase the viscosity of the gel layer.

Hence, a mechanism by which these surface active drugs interact with HPMC and cause viscosification in the case of meclofenamate Na or a drug-mediated 'salting out' with diclofenac Na may be proposed. This would provide an explanation for the differing drug release profiles observed for diclofenac Na and meclofenamate Na.

2.4.2 The influence of lactose content

The choice of diluent and its influence on drug release should also be considered when interpreting Banks' drug release profiles. Lactose is a soluble sugar and its level of incorporation within the matrices in Banks' work was varied to allow alteration of the drug: HPMC ratio. However, the effects of lactose on drug release processes can not be readily discounted.

Lactose has been implicated in the literature as affecting the mechanism and release kinetics of drugs from HPMC hydrophilic matrices. For example, Rekhi *et al.* (1999) have investigated the effect of lactose incorporation on the release of metoprolol tartrate. It was found that increasing the lactose content of matrices from 25 to 61% w/w led to an increase in the drug release rate. When the soluble excipient content exceeded 50% of the matrix weight, rapid dissolution of the excipients led to a fragile and highly porous gel and as a result, there is an increase in both drug diffusion and the rate of gel layer erosion.

An additional factor when considering the potential influence of lactose on hydrophilic matrix performance is the propensity of saccharides to influence the phase transitions of thermally sensitive polymers (Kawasaki *et al.* 1996, Kim *et al.* 1995, Kato *et al.* 2001, Williams *et al.* 2008). These effects may also apply to the modulation of HPMC sol:gel glass transition temperature by simple sugars. Several examples are highlighted in the literature. For example, Kim *et al.* (1995) showed how maltose and glucose reduced the lower critical solution temperature (LCST) of thermo-sensitive polymers such as Pluronics, poly(*N*-isopropylacrylamide), and *N*-isopropylacrylamide copolymers. As the polymer concentration was increased, the saccharide effects became more pronounced. It was found that glucose was more effective than the disaccharide maltose in lowering the LCST, especially in Pluronic solutions. Kawasaki *et al.* (1996) have

investigated saccharide-induced volume phase transition of poly(*N*-isopropylacrylamide) (NIPA) gels. The temperature-induced volume phase transition was decreased by glucose, galactose, and sucrose. The effect of the diluent is therefore investigated in a concentration dependent manner in this thesis.

2.4.3 The choice of dissolution medium

The influence of media chosen for Banks dissolution experiments was not trivial. The swelling of HPMC, in common with other macromolecules, is sensitive to the presence of electrolytes in solution (Bajwa *et al.* 2006 Liu *et al.* 2008). Rajabi-Siahboomi (1993) found that when phosphate buffer was used as a test medium, matrices containing diclofenac Na failed and rapid drug release resulted. Similar observations were made by Fagan *et al* (1989) and Mitchell *et al* (1990) when investigating the effect of electrolytes on the disintegration of HPC and HPMC Methocel K15M matrices respectively. Mitchell *et al* (1990) employed a dissolution medium of distilled water to eliminate the effect of an ionic dissolution medium. However the rapid swelling of HPMC in the absence of an ionic environment is unrealistic, hence the studies of drug release presented in the work of Banks were performed in 0.9% w/w NaCl. This in itself presents problems, since it is not representative of the conditions with the gastro-intestinal tract. In addition, it may affect the proposed interactions between drugs and HPMC, since solubility and self-aggregation behaviour will be strongly dependent on the ionic environment. Therefore the influence of sodium chloride on drug-HPMC interactions will also be investigated in this thesis.

2.5 Conclusions

Banks' work shows considerable disparities in the drug release profiles between diclofenac Na and meclofenamate Na from HPMC hydrophilic matrices. Despite the structural similarities between the two drugs, meclofenamate Na showed progressively extended release as drug content increased and only when the level of drug incorporation was above 50% w/w. In contrast, extended release of diclofenac Na was only achieved at low drug levels with corresponding high levels of HPMC within the matrix.

2.5.1 Interaction hypothesis

A hypothesis has been developed that proposes that below certain ratios with HPMC, meclofenamate Na acts to dehydrate HPMC and compromise the formation of the gel layer. This is rationalised by the immediate release observed in Banks' matrices containing less than 50% w/w drug. Above this threshold, the drug promotes gel layer formation and increases its viscosity, resulting in the extended drug release. Diclofenac Na may not possess this capability and correspondingly extended drug release is not achieved as drug content was increased. The mechanism may be related to drug surface activity, and interactions with the HPMC, modifying the solution properties, externalising as changes to the gel layer.

The validity of this hypothesis will be determined in this thesis by investigating drug-polymer interactions and their effect on the gel layer. These drug effects may also be influenced by the diluent within the matrix, particularly the effect of lactose. Hence, the influence of incorporated diluents and drugs will also be investigated.

Chapter 3

Materials and methods

3.1 Materials

Details of the materials used in this study are included in appendix 1.

3.2 Methods

This chapter contains the general experimental methods used throughout this thesis. Techniques used in individual investigations are described in the appropriate chapters, along with any method development.

3.2.1 Manufacture of 1% w/w HPMC solutions

100 ml solutions of 1% w/w HPMC were prepared by the addition of accurately weighed polymer powder to the water in a glass flask sufficient to make one tenth of the final weight. The dispersion was agitated vigorously using a bench top magnetic stirrer until the powder aggregates were visually dispersed. They were then stored in a refrigerator at 2-8°C for 48 hours to allow complete hydration of the polymer (Ford and Mitchell 1995) and for air bubbles to dissipate. The remaining 90% of

water required to make the solution was then added and stirred in a closed container for a further 24 hours at room temperature prior to use.

HPMC solutions containing drugs, diluents and/or other additives were prepared in a similar manner with the additive dissolved in the additional 90% of water prior to mixing. This incorporation method limited the maximum concentration of additive to 90% w/w of the saturated solubility but minimised interactions between additive and polymer prior to dissolution.

3.2.2 Turbimetric determination of HPMC cloud point temperature (CPT)

Turbimetric measurements were undertaken on 1% w/w HPMC solutions (prepared by the method detailed in section 3.2.1) using a white-light temperature ramped Cloud Point Apparatus (Medical Physics, QMC, Nottingham) (figure 3.1). The solutions were placed in 10 mm path-length quartz cuvettes (Optiglass, Essex) with a magnetic cuvette flea. The cuvettes were placed in the cuvette holder in the heating block, which also contained a magnetic stirrer. The sample was heated at a rate of 2 °C.min^{-1}.

A Tungsten light source was passed through the HPMC solution and detected by a photodiode positioned behind the sample. The diode signal was converted to an absorbance reading by software within the PC. The temperature was monitored by a TC-08 channel silicone coated thermocouple (Pico Technology Ltd, Cambridge, UK) which was inserted into the cuvette to record the sample temperature. The probe was placed in the sample so that it did not interfere with light transmission or come into contact with the side of the cuvette.
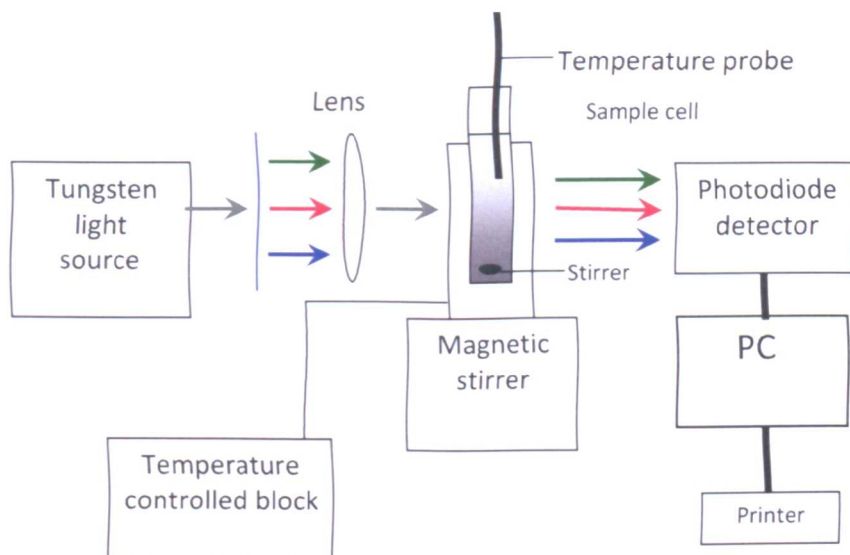
Figure 3.1 Schematic diagram of the cloud point temperature apparatus

HPMC solutions undergo a sol:gel phase transition upon increasing temperature which induces cloudiness in the sample. The temperature at which light transmittance falls to 50% of the original is known as the cloud point temperature (Sarkar 1979, Sarkar and Walker 1995). Absorbance is related to light transmission by the following equation:

$$A = \log T_o/T \qquad \qquad \text{Equation 3.1}$$

Where A is absorbance, T_o is the initial percentage light transmission and T is the percentage light transmission at any given time. Thus the absorbance at the cloud point temperature (CPT) is log 100/50= 0.301.

The solutions were visually observed to confirm gelation since a turbid solution can be achieved before polymer precipitation, which can make the determination of a cloud point subjective (Mitchell *et al.* 1990, Ford, 1999).

3.2.3 Continuous shear viscosity measurements

Continuous shear viscosity measurements were undertaken on 1% w/w HPMC solutions containing additives using a Physica MCR 301 rheometer (Anton Paar, Germany). All samples were studied at 20°C using a stainless steel 2°/50 mm cone and plate geometry. A new sample which had not been subject to any other testing was used for each experiment.

The sample was placed onto the Peltier temperature-controlled plate at 20 $\pm$ 0.1°C. To minimise shear effects before testing, the sample was loaded carefully using a plastic spoon. The cone was lowered into the sample to a predetermined point to provide a gap of 49 μm. Excess sample was removed from the edges of the plate prior to testing. The viscosity profiles of each sample were determined at shear rate values between 0.01 and 100 s^{-1}, increased incrementally on a log scale with an equilibrium period at each shear rate of 30 seconds. This facilitated reproducibility by allowing the sample to reach steady state prior to measurement. Sample testing was performed in triplicate.

3.2.4 The theory of dynamic oscillatory rheology

Viscoelasticity measurements are based on the mechanical properties of materials exhibiting both the viscous flow properties of liquids and the elastic properties of solids. An ideal fluid flows when stressed and ceases upon stress removal. In contrast, an ideal solid recovers its original state as soon as the stress is removed. Some materials exhibit viscoelastic characteristics and show both solid and liquid features.

The viscoelastic characteristics of HPMC solutions were determined using a small amplitude oscillatory shear experiment. A brief synopsis of the mathematical principles behind the technique is now provided.

During an oscillatory shear experiment, the sample is exposed to a continuously changing sinousoidal stress, at a given frequency (Rao 1999). The sample strain will also follow a sinusoidal pattern, provided the stress is within the linear viscoelastic region (LVR) of the material. A controlled stress apparatus is used to achieve a response in the LVR.

For an ideal solid, shear stress is proportional to shear strain, and the amplitude of the strain will follow exactly the amplitude of the stress, as shown in Figure 3.2 (a). For an ideal liquid, shear stress is proportional to the strain rate and the resultant strain will be 90° out of phase with the applied stress as shown in Figure 3.2 (b). It is likely that the samples in this study be viscoelastic showing an intermediate response and a phase angle greater than 0°, but less than 90°, as illustrated in Figure 3.2 (c).

The rheological behaviour was characterised as the dynamic moduli G' and G'' as a function of frequency, where G' is the storage (elastic) modulus and G'' the loss (viscous) modulus. The storage modulus (a measure of the energy stored and recovered per cycle of deformation) reflects solid-like component of viscoelastic behaviour of the material, while the loss modulus (a measure of the energy lost per cycle) reflects the liquid-like component. In addition to the dynamic moduli, the viscoelastic nature of the test sample was further evaluated using the loss tangent, tan δ. Tan δ is an indicator of the overall viscoelasticity of the sample being a measure of the energy loss to the energy stored per cycle (G''/G'). Tan δ < 1 indicates a solid (gel)-like response, whereas tan δ > 1 reflects a liquid like response. Thus, as tan δ becomes smaller, the elasticity of the material increases, whilst the viscous behaviour is reduced.
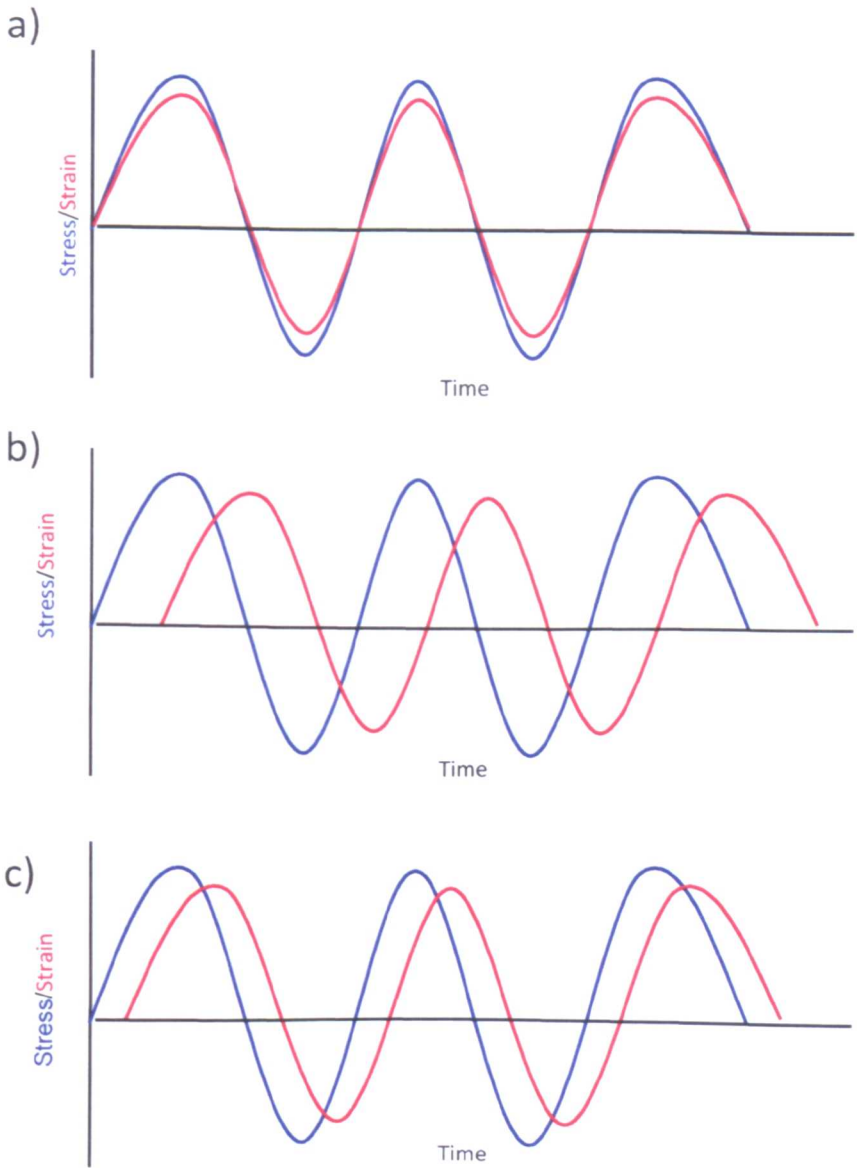
Figure 3.2 Idealised stress and strain response, of (a) an ideal solid, (b) an ideal liquid, and (c) a viscoelastic material

Adapted from Rao (1999).

3.2.5 Dynamic oscillatory rheology - Methods

Dynamic oscillatory rheology was undertaken on a Physica MCR 301 rheometer (Anton Paar, Germany) using a stainless steel 2°/50 mm parallel plate geometry. Plate temperature was controlled at 20°C by the use of a circulating water bath. The sample was carefully loaded onto the plate using a spoon spatula and any trapped air bubbles were removed using a plastic pipette. The parallel plate was lowered to a predetermined point to provide a gap of 1000 μm between the plates. Excess sample was removed from the edges of the plate. To minimise water loss, a thin layer of low viscosity silicone oil (Sigma-Aldrich, Dorset, UK) was placed on the sample periphery.

3.2.5.1 Dynamic oscillatory rheology - amplitude sweep

Oscillatory rheological studies are performed within the linear viscoelastic region (LVR) of the sample in order for measurements to be independent of stress and strain (Ross-Murphy 1988). Viscoelastic changes outside the LVR may result from the destruction of the sample by the rheometer (e.g. shear thinning), and this will significantly affect data accuracy.

An amplitude sweep was performed to establish the LVR. A typical amplitude sweep is shown in figure 3.3. Experiments were performed at strain values ranging from 0.005 to 10 Pa, at a constant frequency of 0.5 Hz. Amplitude sweeps were performed for all the samples studied at the experimental temperature of 20°C.
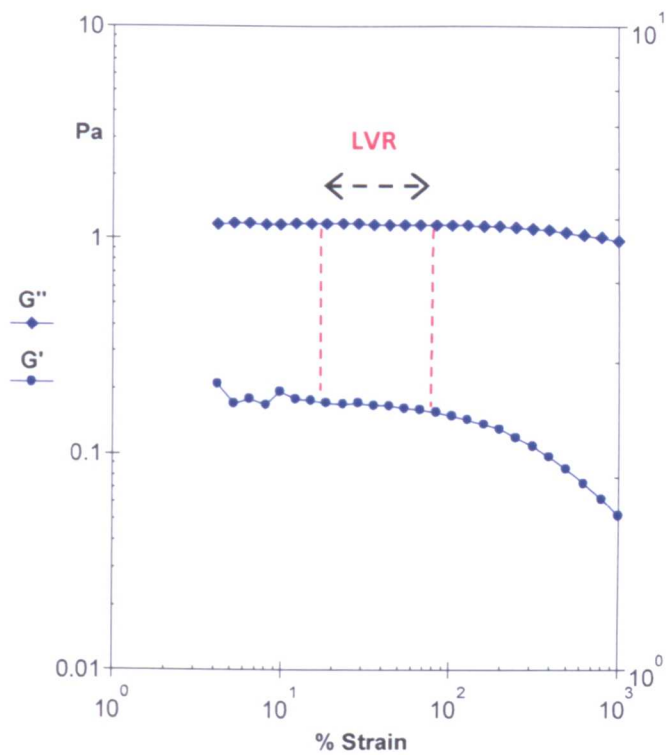
Figure 3.3 A representation of a typical amplitude sweep

Shear strain is compared against both storage (G′) and loss (G″) moduli. The linear viscoelastic region (LVR) is the region where deformation is considered not to damage internal structure. The graph shows a typical amplitude sweep for 1% w/w HPMC (20 °C).

3.2.6 HPMC hydrophilic matrix manufacture

3.2.6.1 Sieving of HPMC powder

Several studies have shown how HPMC particle size has an important influence on the drug release kinetics of hydrophilic matrices (Alderman 1984, Campos-Aldrete and Villafuerte-Robles 1997). To reduce this influence, matrices were prepared using a sieve fraction of 63-90 µm.

The fractionation of HPMC was undertaken as follows: 20 cm diameter, stainless steel sieves (Endecotts Laboratory Test Sieves Ltd., London, UK) were arranged in descending order from 125 µm to 63 µm mesh size with a collecting tray on the bottom. Approximately 40 g of powder was placed onto the top sieve in accordance with the manufacturers guidelines. The sieves were mounted onto an automated sieve shaker (Copley Scientific, Nottingham, UK) and agitated for 30 minutes. Each sieve was weighed and sieved for a further 10 minutes. Sieving was stopped when sieve weight differences between agitations were less than 5%.

3.2.6.2 Formulation preparation

All formulations were prepared in 50 g quantities to allow for manual tablet compression. Sieved HPMC and other tablet excipients, in appropriate quantities for each formulation, were mixed using a Turbula 2TF mixer (Glen Creston Ltd, Middlesex, UK) in a glass container for 15 min. Where a lubricant (magnesium stearate) was included in the formulation this was added afterward and mixed for a further 3 minutes. After mixing, the blends were stored in air tight amber bottles prior to tabletting.

3.2.6.3 Matrix tablet manufacture

Matrix tablets weighing 200 ± 5 mg were prepared on a Manesty F3 single punch tablet press (Manesty, Liverpool, UK) at a compression pressure of 180 MPa, using 8 mm flat-faced punches (I Holland, Nottingham, UK)..
Powder blends were placed in the filling shoe and the tabletting machine was manually taken through the compression cycle. The press was instrumented with a tablet compression monitor TCM1 (Copley Instruments Ltd, Nottingham, UK) to allow measurement of the upper punch compression pressure applied during matrix preparation.

Matrix tablets were periodically sampled and tested for weight uniformity (Mettler Toledo balance) and crushing strength using a CT40 hardness tester (Engineering Systems, Nottingham, UK).

3.2.6.4 Matrix tablet storage

All batches of matrix tablets were assigned a date of manufacture and a batch number for reference and stored in amber glass, air-tight jars. A minimum storage time of 24 hours was allowed prior to further testing, to allow any post-compression relaxation to occur.

3.2.7 Disintegration testing of matrix tablets

The disintegration time of HPMC matrix tablets was measured using a four station Erweka disintegration testing apparatus (Copley Scientific, Nottingham, UK) conforming to the official USP monograph for disintegration testing. Tests were conducted at 37 ± 1°C in 900 ml of test medium, degassed by helium sparging. Perspex discs were used to prevent the matrices floating. Matrices were monitored at 1 minute

intervals for the first 10 minutes and every 5 minutes thereafter up to 120 minutes. After 120 minutes the tests were terminated.

3.2.8 Routine monitoring of HPMC powder moisture content

It is well known that powdered HPMC absorbs moisture and can contain an equilibrium moisture content that varies between 2-10% w/w (Doelker 1993). The moisture content of the HPMC batch used throughout the study was monitored periodically at 3 month intervals using a MB45 Moisture Analyser (Ohaus Corporation, Leicester, UK). Samples (~500 mg) were heated on disposable aluminium pans from ambient to 105°C using a linear temperature ramp over 3 minutes and held at this temperature until there was less than 1 mg change over 2 minutes. The endpoint was automatically determined by the apparatus. The moisture content was found to be maintained in the range 3.5-4.5% w/w throughout the study (see appendix 2).

Chapter 4

Interactions between non-steroidal anti-inflammatory drugs and HPMC

4.1 Introduction

In chapter 2, the release profiles of diclofenac Na and meclofenamate Na from HPMC matrices were presented and interpreted with respect to the HPMC hydrophilic matrix literature. It was proposed that the drug release was a consequence of drug surface activity and different modes of interaction with HPMC in aqueous solution. The aim of this chapter was to investigate the interactions between these drugs and HPMC in solution, to confirm or disprove this hypothesis.

Previously, it has been reported that incompatibilities between drugs and HPMC may have critical effects on the performance of extended release hydrophilic matrix dosage forms (Li *et al.* 2005) and examples from the literature suggest that certain drugs have the potential to interact with HPMC. These include: (i) ibuprofen (Ridell *et al.* 1999), (ii) nicotinamide (Hino and Ford 2001), (iii) propranolol (Mitchell *et al.* 1993), and (iv) aminophylline (Ford *et al.* 1985). Although the relatively simple concepts of 'salting-out' and 'salting-in' have been proposed as the principal

underlying mechanism for the drug-polymer interaction (Mitchell *et al.* 1993, Hino and Ford 2001), there has been little attention paid to the potential for drug interaction with HPMC through the drug molecule surface activity and the consequences for polymer solution properties and drug release performance in HPMC matrices.

4.1.1 Surface activity of drugs

In many pharmaceutical dosage forms, polymers are concomitantly formulated with amphiphilic drugs and excipients (Florence and Attwood 1998). Interaction between these components has the potential to influence the physicochemical properties of the dosage form, for example by altering chemical stability or affecting the drug release kinetics (Puttipipatkhachorn *et al.* 2001, De la Torre 2003, Tang and Singh 2008).

Pharmaceutical excipients such as emulsifiers, solubilising agents and wetting agents are surface active. In addition, a significant number of drugs possess an amphiphilic molecular structure. Resultantly, these drugs are surface active and are capable of forming self-assembled structures such as micelles when in aqueous solution at a concentration higher than their critical micelle concentration (CMC) and at temperatures exceeding their Krafft temperature (Attwood 1995). Examples of surface active, micelle forming drugs can be found in the phenothiazines (Barbosa *et al.* 2008, Cheema *et al.* 2008), tricyclic and tetracyclic antidepressants (Kumar *et al.* 2006), antihistamines (Attwood and Udeala 1975), local anaesthetics (Strugala *et al.* 2000), anticholinergics (Wu *et al.* 1998) and non-steroidal anti-inflammatory drugs (Fini *et al.* 1995). As with more well-known surfactants, surface activity is dependent on the chemical nature and position of the hydrophobic and hydrophilic portions of the drug molecule (Attwood 1995).

4.1.1.1 The surface activity of NSAIDs

The surface activity of several non-steroidal anti-inflammatory drugs (NSAIDs) has been described in the literature by Fini *et al.* (1995). Surface activity was investigated with respect to drug self-aggregation and the subsequent solubilisation of a lipid probe, the azo-dye Orange OT. It was found that the sodium salts of indomethacin and fenclofenac exhibited dye solubilisation activity in pure water at concentrations of 30 and 40 mM respectively, with these values decreasing with increasing ionic strength as sodium chloride was added. Diclofenac sodium was found to possess insufficient solubility to solubilise the dye and a higher solubility salt prepared with an organic base counterion was necessary. Naproxen, sulindac, ketoprofen, indoprofen sodium salts had to be dissolved at high concentrations (100-160 mM) in order to solubilise the dye in the presence of a high total ionic strength.

4.1.2 Interactions between NSAIDs and polymers

Rades and Mueller-Goymann (1998) have investigated the interaction between fenoprofen sodium and high molecular weight poly (ethylene oxide) (PEO). A wide variety of techniques were used including: surface tension measurements, viscometry, cloud point temperature measurements, proton NMR, polarised light microscopy, transmission electron microscopy, and differential scanning calorimetry. These investigations suggested that polymer: drug interaction began below the CMC of the drug as evidenced by: (i) an upheld shift of the PEO proton signal for fenoprofen sodium concentrations below the CMC of the drug, (ii) the absence of a critical association concentration in the surface tension measurements and (iii) cloud point temperature determinations. The surfactant did not appear to bind quantitatively to the PEO, as a higher fenoprofen concentration was needed to cause the same upheld

shift of the PEO proton signal than for more lipophilic surfactants, and no plateau phase in the surface tension reduction isotherm could be determined. Interactions were found to be independent of the PEO chain length.

The interaction of ibuprofen Na with EHEC and HPMC has been investigated (Ridell *et al.* 1999). Fluorescence and microviscosity measurements showed that ibuprofen was an amphiphilic drug which formed micelles in water. At the CMC of the drug, a marked increase in cloud point was reported. It was postulated that above the CMC micelles of ibuprofen may solubilise the hydrophobic methoxyl-rich regions of the polymer, and thereby increase polymer hydration.

4.1.3 Methods for investigating surfactant-polymer interactions

In this chapter, we propose to study the potential interaction of diclofenac Na and meclofenamate Na with HPMC. Therefore, it presents a logical starting point to first assess the surface activity of the drugs before progressing to an investigation of their potential interactions with the polymeric carrier material. A brief review of common methodologies used to investigate surfactant-polymer interactions is necessary and this is provided below.

4.1.3.1 Surface tension

Surface active molecules, including drugs, either adsorb at the surface or form complexes in the bulk, leading to variations in the surface tension (Florence and Attwood 1998). Figure 4.1 depicts a well-established schematic representation of the current understanding of how surface tension (γ) varies with respect to bulk surfactant concentration (S_b).

At low surfactant concentrations, there is preferential adsorption of surfactant molecules at the surface which disrupts the hydrogen bonding between water molecules and as a result, lowers the surface tension progressively as the surfactant concentration is increased. However, at a certain concentration of surfactant (known as the critical micelle concentration or CMC) the surface becomes saturated with amphiphile and it becomes energetically more favourable for the surfactant to form micelles in solution. As a result there is little change in surface tension as the surfactant concentration is further increased.

The use of surface tension measurements to explore the interactions between surfactants and non-ionic polymers was first described by Jones (Jones 1967), who investigated the interaction between sodium dodecyl sulphate and poly(ethylene oxide). Jones first proposed the concept of transition points to describe the interactions and these critical concepts have been further developed by Bell *et al.* (Bell *et al.* 2007). A schematic diagram showing the key concepts is shown in figure 4.2.

Two regions illustrate the clear differences between the surfactant (figure 4.1) and surfactant/polymer systems (figure 4.2). These are: (i) the concentration of the CMC and (ii) a point of lower surfactant concentration known as the critical aggregation concentration (CAC). The CAC represents the point at which the polymer and the surfactant begin to interact in the bulk solution (Bell *et al.* 2007). At concentrations below the CAC there is a monotonic decrease in surface tension. The surface tension is lower in the polymer/surfactant system than in the surfactant-only system at the same bulk surfactant concentration as there is some cooperative disruption by polymer and surfactant. At concentrations above the CAC, there is no significant change in the surface tension with increasing surfactant concentration. Once a certain concentration of surfactant is reached, the surface tension begins to reduce again. This is

the point at which surfactant micellar aggregates have saturated the polymer. The reduction in surface tension then continues until the CMC is reached and once again micelles form in the bulk. As in the surfactant-only system, there is little change in surfactant adsorption at the surface beyond the CMC. It has been found that the length of this 'plateau' in surface tension isotherm from CAC to CMC is dependent upon the concentration of polymer added to the system (Purcell *et al.* 1998).

There are numerous examples in the literature in which measurement of surface tension has been used to characterise the interactions between surfactants and polymers (Nilsson *et al.* 1995, Onesippe and Lagerge 2002, Ridell *et al.* 2002, Peron *et al.* 2007). A recent example is Claro *et al.* (2008) who used surface tension measurements to determine the formation of a complex between hydroxypropyl cellulose-methyl methacrylate and a polyoxyethylene nonylphenyl ether non-ionic surfactant with a high hydrophilic-lipophilic balance (HLB).
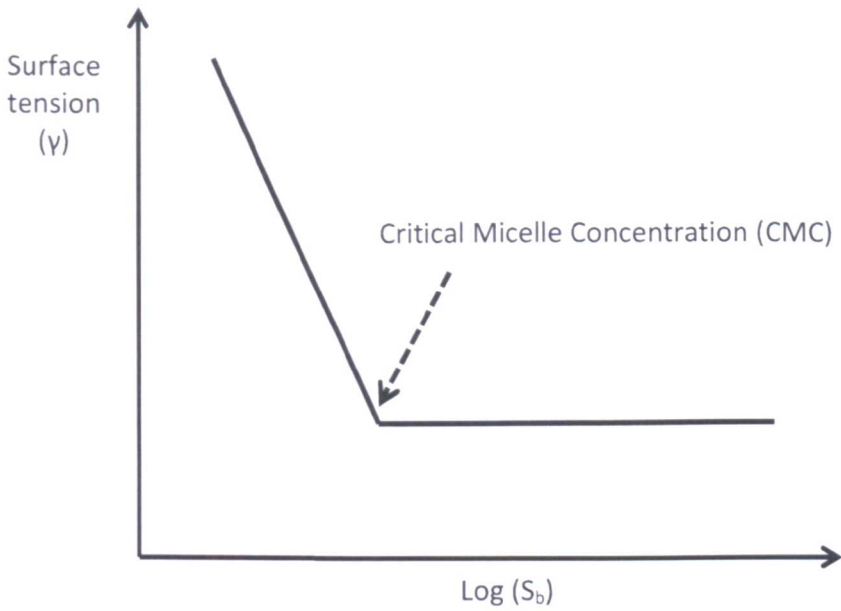
Figure 4.1 Schematic diagram showing how surface tension varies with log(bulk surfactant concentration) (S_b) for an aqueous solution containing an ionic surfactant

(Adapted from Bell *et al.* 2007).
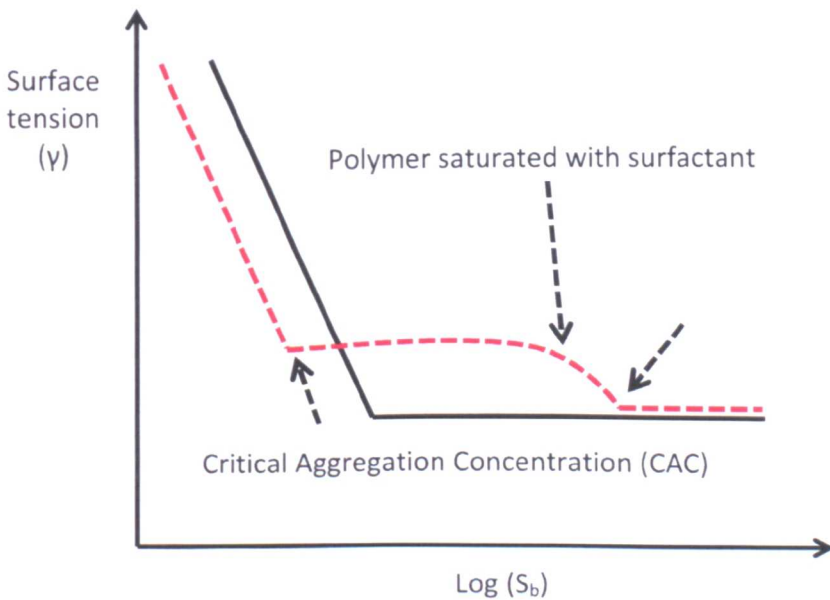
Figure 4.2 Schematic diagram showing how surface tension varies in a surfactant-polymer system in the presence (dashed line) and absence (solid line) of complexation

(Adapted from Bell *et al.* 2007).

4.1.3.2 Rheological techniques

Rheological techniques are commonly used to characterise the association between surface active agents and polymers since these interactions strongly influence polymer conformation and as a result the phase behaviour in solution (Thuresson and Lindman 1997). Rheological behaviour of surfactant-polymer solutions can be described in terms of change in the dynamic moduli G' and G" as a function of frequency, where G' is the storage (elastic) modulus and G" the loss (viscous) modulus.

Rheological analysis can provide insights into the gelation properties of polymer solutions by characterizing swelling and connectivity between polymer chains and the influence of surfactant addition. For example, Zhao and Chen (2007) have investigated the effect of nonionic surfactant addition on the rheology of aqueous solutions of hydrophobically modified hydroxyethyl cellulose and found that surfactant addition altered the rheology of aqueous solutions of the polymer. In addition, the rheology of aqueous solutions of hydrophobically modified polyacrylamides and surfactants has been investigated by Penott-Chang *et al.* (2007).

4.1.3.3 Small–angle neutron scattering (SANS)

Small-angle neutron scattering (SANS) is a useful tool with which to investigate molecular structures ranging in size from 5 Å to several hundred angstroms and often polymeric materials, surfactants and their complexes fall into this range. An advantage of using neutrons to study these systems is the ability to suppress selectively the scattering of either component by adjusting their scattering length densities relative to the solvent (Bu *et al.* 2005). Several papers have described the use of SANS to

study the structure of polymer-surfactant complexes (Griffiths *et al.* 2004, Griffiths *et al.* 2007, Bu *et al.* 2007).

4.1.3.4 Turbidimetry

The determination of solution turbidity is a bulk method that detects the effect of surfactant-polymer interactions on the macroscopic behaviour of the polymer in a solution.   Recent examples in which turbimetric measurements has been applied to characterize surfactant polymer interactions include (i) chitosan and SDS (Lundin *et al.* 2008, Onesippe and Lagerge 2008), (ii) casein and dodecyltrimethylammonium bromide (DTAB) (Liu and Guo, 2007) and (iii) various surfactants with hydrophobically modified alginate (Bu *et al.* 2007).

4.1.3.5 Isothermal Titration Calorimetry (ITC)

The thermodynamics of surfactant-polymer interactions can be characterised using isothermal titration calorimetry (ITC). Such data can provide detailed information about the binding process of surfactants in the absence and presence of a polymer (Wang *et al.* 1997).   The measurement principle of ITC is based on both titration and power compensation techniques. Titration calorimetry measures the enthalpy change of a chemically reacting system as a function of the amount of added reactant (Tam and Wyn-Jones 2006).   Recent applications of calorimetry in the study of surfactant-polymer interactions include the interactions between (i) sodium alginate and SDS (Yang *et al.* 2008), (ii) chitosan and SDS (Onesippe and Lagerge, 2008), and (iii) hydrophobically modified cationic polysaccharides with surfactants (Bai *et al.* 2007).

4.1.3.6 Pulse-gradient spin echo nuclear magnetic resonance (PGSE-NMR)

Owing to its non-invasive nature and wide applicability, pulsed gradient spin-echo (PGSE) NMR has become the method of choice for measuring self-diffusion coefficients of species in the solution state. PGSE-NMR has been used to quantify surfactant-polymer interactions as an association between the two species (Griffiths *et al.* 2002, Davies and Griffiths 2003). Polymers have far lower self-diffusion values compared to low molecular weight species such as drugs, and as such, changes in the self-diffusion behaviour of small molecular weight species can be attributed to interactions between the species and the polymer (Davies and Griffiths 2003).

4.1.3.7 Other techniques

Other significant recent techniques used in the characterisation of surfactant-polymer systems include (i) fluorescence correlation spectroscopy (Bosco *et al.* 2006), (ii) neutron relectometry (Taylor *et al.* 2007) and (iii) x-ray reflectivity (Stubenrauch *et al.* 2000).

4.1.3.8 Choice of techniques to study drug-polymer interactions

The choice of technique to study drug-polymer interactions is dependent on the type and level of experimental evidence required to develop a theory and the availability of equipment. Ideally, complementary techniques should be used to provide a detailed insight that encompasses both the microscopic and macroscopic aspects of potential interactions between drugs and HPMC. Tensiometry, rheological and turbimetric analytical facilities were available within the Schools of Pharmacy and Biosciences at University of Nottingham. Collaboration with Dr P C

Griffiths at the School of Chemistry (Cardiff) allowed access to PGSE-NMR and SANS methodologies. ITC was considered as an experimental methodology but was not used as a result of time constraints.

4.2 Aims and objectives

The overall aim of this chapter was to test the hypothesis that the underlying mechanism for the different drug release profiles is a result of differing interaction modalities between diclofenac Na or meclofenamate Na with HPMC. Specifically, the objectives of this chapter are:

- To investigate the potential for diclofenac Na and meclofenamate Na to influence HPMC solution properties, using cloud point, rheology and surface tension measurements.

- To interpret the experimental findings with respect to the literature pertaining to the interactions of surfactants with macromolecules, and to confirm or disprove the hypothesis that surface activity is significant in drug-HPMC interactions and subsequent drug release.

4.3 Materials and Methods

4.3.1 Materials

4.3.1.1 HPMC

HPMC (Methocel E4M CR Premium) was used a supplied. Full details are listed in appendix 1.

4.3.1.2 Drugs

Diclofenac Na and meclofenamate Na were of analytical grade and used as supplied. Full details are listed in appendix 1.

4.3.1.3 Water

Solutions were prepared using Maxima HPLC grade water except in the case of the pulsed-gradient spin-echo NMR (PGSE-NMR) and small-angle neutron scattering (SANS) experiments where deuterium oxide (Fluorochem, Derbyshire) was used for all solution preparation. Full details are listed in appendix 1.

4.3.2 Manufacture of HPMC solutions

0.1% and 1% w/w solutions of HPMC were prepared by the method described in section 3.2.1.

4.3.3 Turbimetric determination of the sol:gel phase transition

temperature

Turbimetric determinations of the sol:gel transition temperature of HPMC solutions were undertaken using the method described in section 3.2.2.

4.3.4 Density Measurements

Density measurements of 0.1 % w/w HPMC solutions containing the model drugs were made using a DMA 5000 oscillating U-tube Density Meter (Anton Paar, Graz, Austria). The density determination is based on measuring the period of oscillation of a vibrating U-shaped tube that is filled with sample and using the relationship between the period of oscillation and the density. This relation holds as long as the sample is not too viscous. The density was obtained at 20°C and mean values (n=3) were used subsequently in the surface tension measurements.

4.3.5 Interfacial tension measurements of NSAID and HPMC solutions

Surface tension measurements were carried out at 20 ± 1 °C using a Profile Analysis Tensiometer (Sinterface tensiometer PAT1, Berlin, Germany) using the pendant drop method. Solutions of 0.1 % w/w HPMC containing the model drugs were prepared by mixing appropriate quantities of drug and HPMC in solutions and allowing equilibration for 24 hours prior to measurement. Samples were prepared in triplicate. Replicate measurements were automatically determined 100 times. The relative standard deviations of the 100 measurements were smaller than 0.05%.

4.3.6 Pulsed-gradient spin-echo NMR

As an experimental technique, PGSE-NMR permits probing of self-diffusion coefficients within complex colloidal systems since the characteristic structural dimensions in such systems (10 nm-10 μm) are comparable to the displacements on the NMR time-scale (10 ms-10 s) (Griffiths *et al.* 2002).

The strength of the association between drugs and HPMC was quantified using a pulsed-gradient spin-echo NMR (PGSE-NMR) method described previously (Davies and Griffiths 2003). The self-diffusion measurements on 0.1% w/w HPMC solutions containing a range of concentrations of diclofenac Na or meclofenamate Na and the corresponding drug solutions in the absence of polymer were performed on a Bruker AMX360 high-resolution NMR spectrometer (Bruker, Coventry, UK) employing a stimulated echo sequence (figure 4.3).
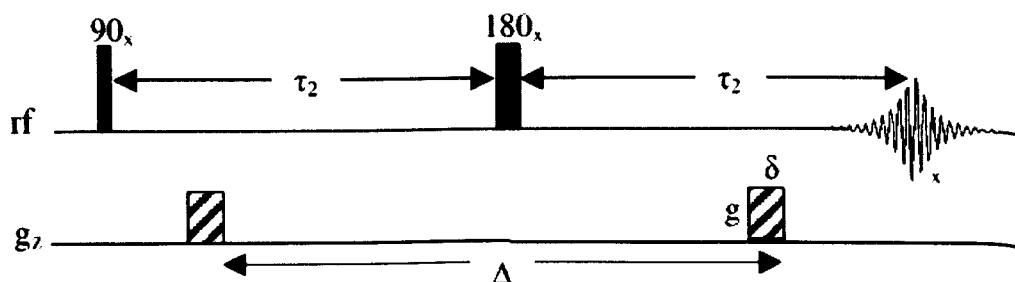
Figure 4.3 Timing diagram for the PGSE-NMR pulse sequence for determining self-diffusion coefficients

(taken from Antalak 2007)

Briefly, a constant current gradient amplifier (Bruker) delivers pairs of read and write gradients matched to better than 10 ppm. These gradients were ramped up to the maximum value and down again over a time σ, typically 250 μs, which in conjunction with three pre-pulses before every scan minimizes distortions due to coil heating and eddy currents.

The self-diffusion coefficient, Ds, was extracted by fitting the data to equation 4.1 the measured peak integral, $A(G, \delta)$, as a function of field gradient duration δ ramp time σ intensity G, and separation Δ:

$$A(\delta,G,\Delta) = A_0 \exp\left[-\gamma^2 G^2 \left(\frac{30\Delta(\delta+\sigma)^2 - (10\delta^3 + 30\sigma\delta^2 + 35\sigma^2\delta + 14\sigma^3)}{30} \right) D_s \right]$$

Equation 4.1

and where γ is the magnetogyric ratio of the nucleus under observation, in this case protons. The A_0 term is determined by the number of protons in the sample. All experiments were performed at $20 \pm 1°C$.

4.3.7 Small-Angle Neutron Scattering (SANS)

SANS is used for studying the structures of a material on a length scale of 10-1000 Å. In particular, it is used to study the size of particles (including macromolecules) in a homogenous medium. SANS is a diffraction based technique which involves the scattering of a monochromatic neutron beam from a sample and measurement of the scattered neutron intensity as a function of scattering angle (figure 4.4). The wave vector transfer $Q(=4\pi\sin\theta/\lambda$, where λ is the incident neutron wavelength and 2θ is the scattering angle in these experiments is small, typically in the range of 10^{-3} to 1.0 Å^{-1}, the wavelength of neutrons used for these experiments usually being 4-10 Å. Since the smallest Q values occur at small scattering and angles ($\sim 1°$) the technique is known as small angle neutron scattering.
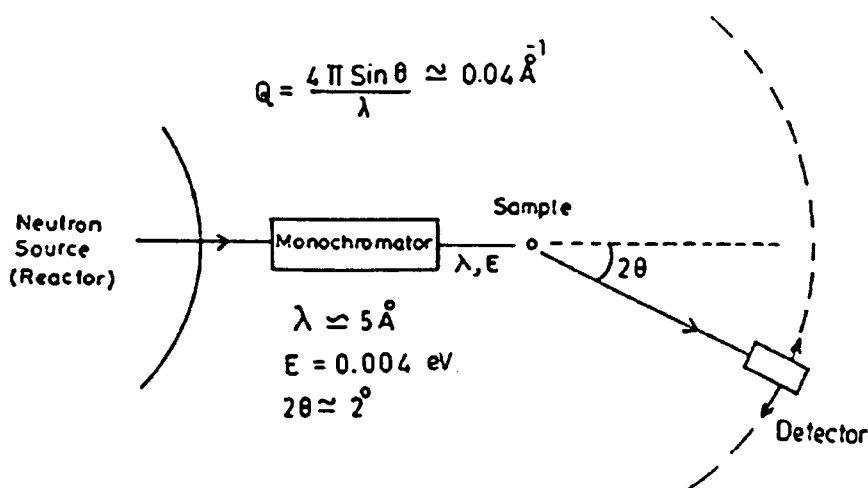
Figure 4.4 Schematic diagram of experimental set-up in SANS experiments (taken from Goyal and Aswal 2001)

Small-angle neutron scattering (SANS) measurements were performed on 60 mM drug solutions in the presence and absence of 0.1% HPMC using a fixed-geometry, time-of-flight LOQ diffractometer (ISIS Spallation Neutron Source, Oxfordshire, UK). This concentration was chosen to maximise the possibility of interaction between the species. By using neutron wavelengths spanning 2.2–10 Å, a $Q = 4\pi \sin(\theta/2)/\lambda$ range of approximately 0.008–0.25 Å^{-1} (25 Hz) is accessible, with a fixed sample–detector distance of 4.1 m. The samples were contained in 2 mm path length, UV-spectrophotometer grade, quartz cuvettes (Hellma, Essex, UK) and mounted in aluminium holders on top of an enclosed, computer-controlled, sample chamber. Sample volumes were approximately 0.4 cm^3. Temperature control was achieved through the use of a thermostatted circulating bath pumping fluid through the base of the sample chamber. Under these conditions, a temperature stability of better than ±0.5 °C can be achieved. Experimental measuring times were approximately 40 min.

All scattering data were (a) normalized for the sample transmission, (b) background corrected using a quartz cell filled with D_2O (this also removed the inherent instrumental background arising from vacuum windows, etc.), and (c) corrected for the linearity and efficiency of the detector response using the instrument-specific software package. The data were put onto an absolute scale by reference to the scattering from a partially deuterated polystyrene blend.

4.3.8 Continuous shear viscosity measurements

Continuous shear viscosity measurements on 1% w/w HPMC solutions containing diclofenac Na and meclofenamate were carried out in triplicate on a Physica MCR 301 rheometer (Anton Paar, Germany) using the method described in section 3.2.3.

4.3.9 Dynamic viscoelastic rheology

Viscoelastic moduli were determined in triplicate on a Physica MCR 301 rheometer (Anton Paar, Germany) with a stainless steel 2°/50 mm parallel plate geometry using the methods described in section 3.2.5.

4.4 Results

4.4.1 Interactions between meclofenamate sodium or diclofenac sodium with HPMC in solution

4.4.1.1 Surface tension measurements

Figures 4.5 and 4.6 show the surface tension concentration behaviours of diclofenac Na and meclofenamate Na, with and without the addition of 0.1% w/w HPMC and these resemble partly the generalised case given in figure 4.2. Both drugs were found to be surface active; i.e. when added to aqueous solution there was a decrease in the surface tension. A critical concentration at which drug addition led to no further reduction in surface tension was identifiable for meclofenamate Na($\sim$ 45 mM) but not for diclofenac Na. In the case of both drugs, the slope of the isotherm in the presence of polymer was very different to the drug solution alone. The lower initial values for these curves are indicative of the surface activity of HPMC. The phenomenon of HPMC surface activity has been given considerable attention in the literature (Perez *et al.* 2006, Martinez *et al.* 2007) and it has been suggested that it is a result of unequal distribution of hydrophobic and hydrophilic substituents along the polymer chain.
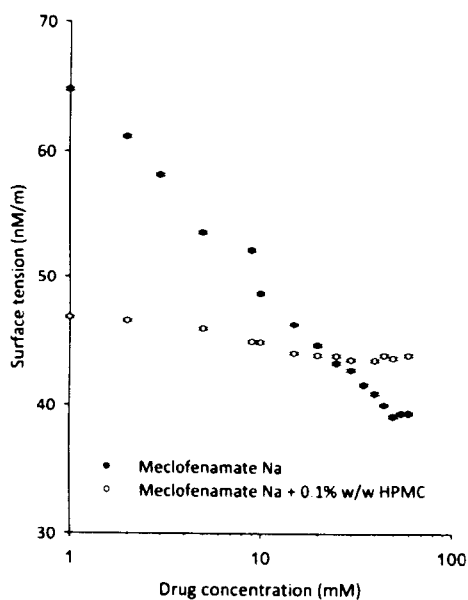
Figure 4.5 The effect of increasing meclofenamate Na addition on the surface tension of water and 0.1% w/v HPMC solution at 20°C. Surface tension measurements were made using the pendant drop method. Mean (n=5) ± SD
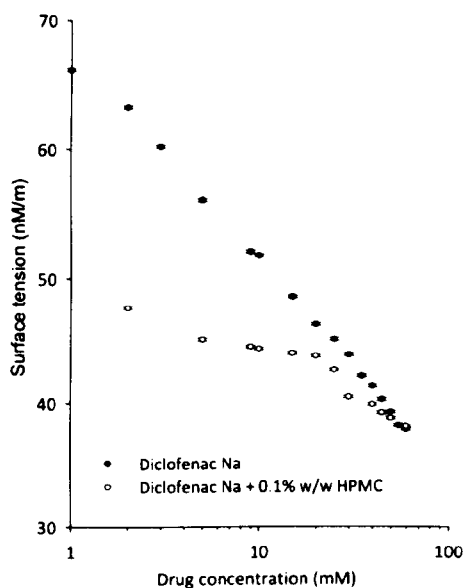
Figure 4.6 The effect of increasing diclofenac Na addition on the surface tension of water and 0.1% w/v HPMC solution at 20°C. Surface tension measurements were made using the pendant drop method. Mean (n=5) ± SD

These results provide evidence for an interaction occurring between the drugs and HPMC. However, the nature of this interaction differs for each drug. In figure 4.5 there is evidence that meclofenamate Na is associated with the polymer even at low concentrations but the onset of drug association with the polymer was not detectable. Evidence for binding is shown by the absence of a surface tension decrease with respect to drug addition (the so-called 'plateau' phase described in the model proposed by Bell *et al.* 2007) as the drug is unable to lower surface tension as it may be associated with the polymer in the bulk solution. A key feature is that above 25 mM drug, the surface tension for the drug/polymer solution was higher than the drug-alone solution, indicating that the surface was either less heavily populated by surface active complex or that the complex is less surface active. Both of these interpretations are consistent with a drug/polymer interaction leading to the formation of complexes within the bulk solution.

As shown in figure 4.6, diclofenac Na was also found to be surface active in aqueous solution. In contrast with meclofenamate Na, it did not demonstrate a critical concentration in aqueous solution, which may be related to its solubility (~10 mg/ml at 20°C) and/or pK_a (4.5). Unlike meclofenamate Na, a possible onset of binding was identified between 3 and 5 mM. This was followed by a plateau phase between 5 and 25 mM and at concentrations above this point, the isotherm decreased in surface tension in a manner analogous to the free drug. This plateau phase suggested diclofenac Na associated with the HPMC. This was followed by saturation of the potential association sites on the polymer and the lowering of the surface tension above a critical concentration as free drug becomes available once again. This is where the drug is free to exert a 'salting out' effect.

4.4.1.2 Pulsed-gradient Spin Echo NMR investigations

PGSE-NMR was used to determine the self-diffusion coefficients of the two drugs in the presence and absence of 0.1% w/w HPMC. PGSE-NMR has been used in previous work to investigate surfactant-polymer interactions and determine the association between the two species (Griffiths *et al.* 2002, Davies and Griffiths 2003). Polymers have significantly lower self-diffusion values than low molecular weight drugs, and as such, changes in the self diffusion behaviour of the drugs can be attributed to interactions between the drug and the polymer (Davies and Griffiths 2003).

Figures 4.7 and 4.8 show self-diffusion coefficient values determined for diclofenac Na and meclofenamate Na in the presence and absence of HPMC. It can be seen that there was a pronounced reduction in the diffusion coefficient of meclofenamate Na in the presence of 0.1% w/w HPMC compared to meclofenamate Na alone. In the case of diclofenac Na, there was little change in the diffusion coefficients of either free drug or drug in the presence of polymer.

Clearly, the presence of polymer affected the self-diffusivity of meclofenamate Na. This is suggestive of association between the drug and polymer in the case of meclofenamate Na, with an increasing association with the polymer with respect to increasing concentration. The onset of this association appeared at around 20 mM, since at concentrations above this the self-diffusion coefficients were seen to reduce dramatically.
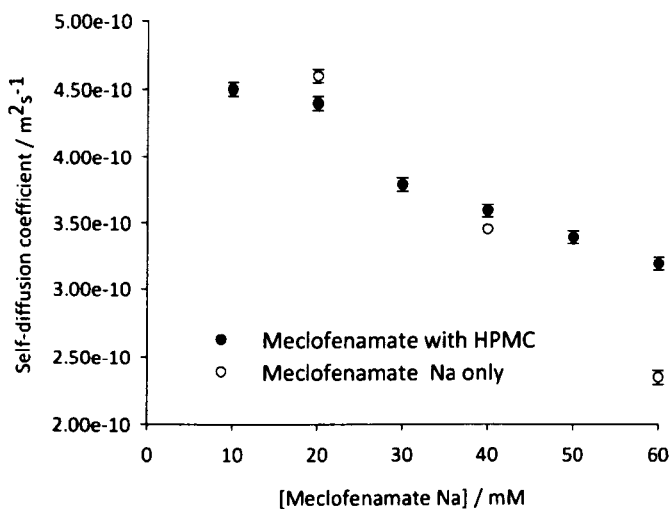
Figure 4.7 The effect of HPMC on the meclofenamate Na self-diffusion coefficient in solution as a function of drug concentration. Determined using PGSE-NMR at 20°C
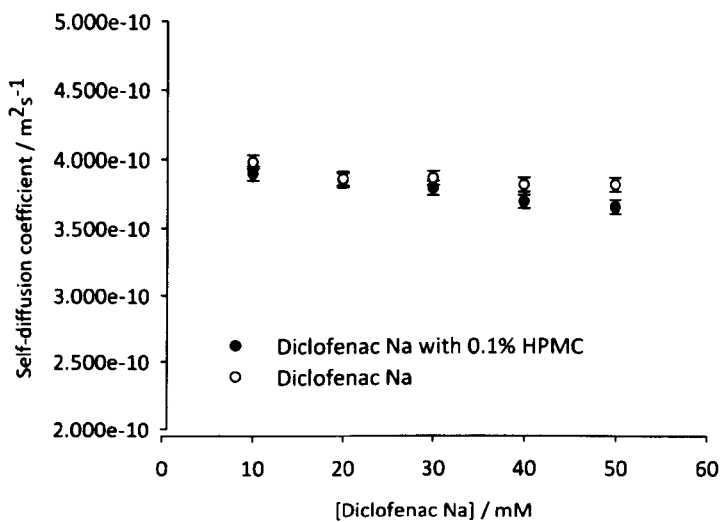
Figure 4.8 The effect of HPMC of the diclofenac Na self-diffusion coefficient in solution as a function of drug concentration. Determined using PGSE-NMR at 20°C.

4.4.1.3 Small-angle Neutron Scattering (SANS)

Neutron scattering curves result from interferences between neutrons scattered by different nuclei in the sample. The interferences are determined by the scalar product Q r, where Q is the scattering vector and r is the vector separating points. For isotropic samples, only the magnitude Q of the scattering vector matters. Then the scattering pattern may be reduced to a scattering curve $I(Q)$. From this scattering curve, geometrical parameters characterising the distribution of scattering length in the sample may be determined (Goyal and Answel 2001).

The results of SANS analysis of 60 mM drug solutions in the presence and absence of 0.1% w/w polymer are presented in figures 4.9 and 4.10. Diclofenac Na clearly showed no measurable scattering (figure 4.9) suggesting the absence of self-associated structures were present, whereas the scattering from meclofenamate Na was also very weak, but perhaps discernible, consistent with the apparent blue tinge of these samples. Clearly aggregates are present, but their concentration is too low to give a measureable signal.

The HPMC scattering was also weak and unaffected by the presence of diclofenac Na, indicating no measurable change in polymer conformation. The situation with meclofenamate Na was quite different however. It can be seen that there was an increase in intensity and above the polymer alone in the presence of meclofenamate Na but not diclofenac Na. There was some evidence of a structure peak (figure 4.10) in meclofenamate Na-containing polymer solutions located at approximately 0.04 Å^{-1}, which is absent in the diclofenac Na solutions. This supports the findings of association between meclofenamate Na and HPMC determined by surface tension and PGSE-NMR studies.
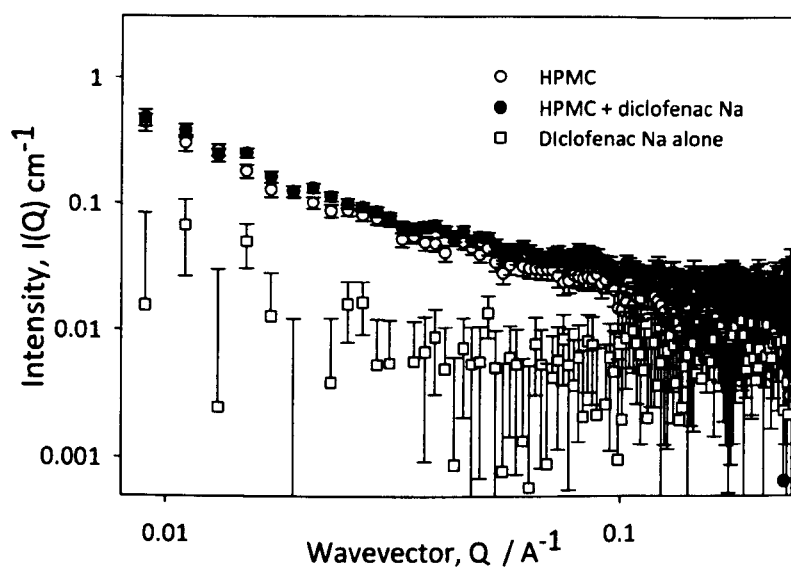
Figure 4.9 SANS scattering curves at 20°C from 60 mM diclofenac Na and 0.1% w/w HPMC solutions
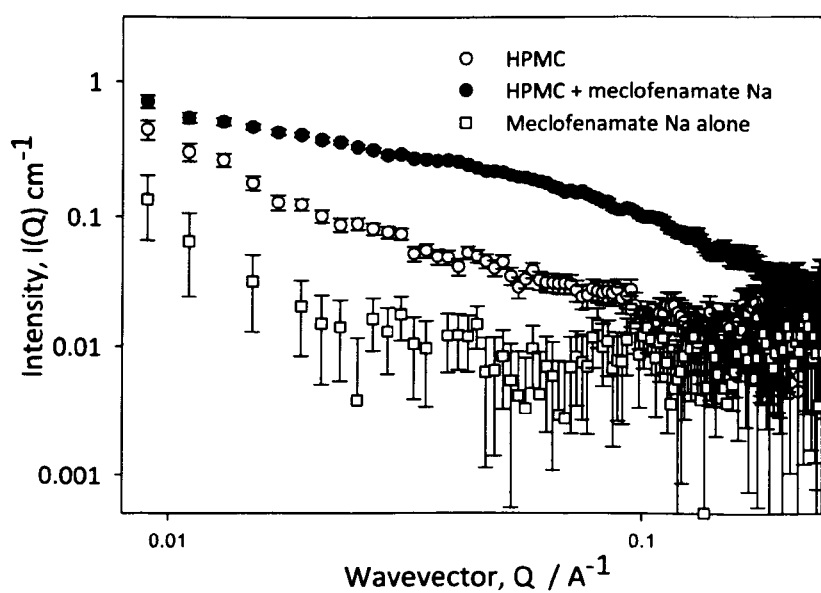
Figure 4.10 SANS scattering curves at 20°C from 60 mM meclofenamate Na and 0.1 % w/w HPMC solutions

4.4.2 The effect of drugs on HPMC solution cloud point (CPT)

Figure 4.11 shows the effect of diclofenac Na and meclofenamate Na on the CPT value up to the limit of aqueous drug solubility. The CPT of 1% w/w HPMC solution in the absence of drugs was found to be 57.1 ±0.2 °C (n=3). Cloud point temperature (CPT) was reduced in a progressive manner as diclofenac Na concentration was increased. A maximum reduction of approximately 12 °C was achieved at 60 mM. In contrast, meclofenamate Na was more potent than diclofenac Na at reducing the CPT values at low concentrations but beyond a maximum reduction in CPT of around 15°C (~33°C), the CPT increased markedly with increasing drug concentration. This minimum CPT for HPMC solutions containing meclofenamate Na occurred at a concentration of 40 mM which approximated to the concentration at which apparent association of drug with the polymer began in the tensiometry studies. At concentrations approximating to the saturated solubility (~60 mM), meclofenamate Na had increased the CPT from this minimum value to 49.7 ±0.45 (n=3).
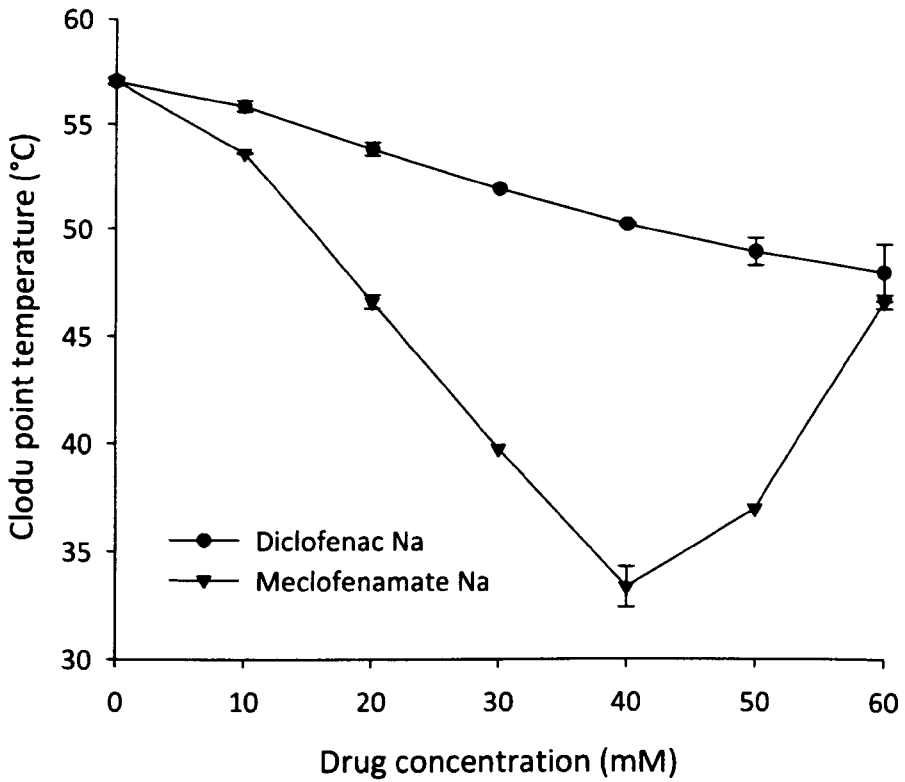
Figure 4.11 The effect of diclofenac Na and meclofenamate Na on the cloud point temperature of 1% w/w HPMC solutions

Cloud point temperature (CPT) measured turbimetrically as a reduction 50% in light transmission (Sarkar 1979). Mean (n=3) ± SD

4.4.3 The effect of drugs on the continuous shear viscosity of

HPMC solutions

The continuous shear viscosity of 1% w/w HPMC solutions at 20°C was measured as a function of shear rate over the range 0.01-100 ^{1}/s at drug concentrations ranging from 0 to 60 mM.

Figure 4.12 shows the viscosity profiles of 1% HPMC solutions containing increasing concentrations of diclofenac Na and meclofenamate Na. The shear viscosity as a function of meclofenamate Na and diclofenac Na concentration are shown in figures 4.13 and 4.14 respectively. The viscosity profile of 1% HPMC without drugs showed a clear Newtonian plateau at low shear rates, and a tendency to shear thin at high shear rates. This solution can therefore be described as non-Newtonian. The corresponding viscosity profiles for HPMC solutions containing increasing concentrations of meclofenamate Na are shown in figure 4.12a. Meclofenamate Na addition increased the solution viscosity and there were dramatic increases at drug concentrations of 40 mM and above. These solutions also exhibited a profound shear thinning at the higher shear rates. The 40 mM threshold corresponded to the earlier inflexion point seen in the cloud point studies (figure 4.11) and approximated to the concentration at which self-association of drug molecules appeared in the surface tension studies(figures 4.5 and 4.6). This point is illustrated more clearly in figure 4.12, where a clear increase in continuous shear viscosity occurs above 20 mM at both low and high shear.

In contrast to the behaviour of HPMC solutions containing meclofenamate the progressive addition of diclofenac Na to the solution increased the solution viscosity only slightly and the shape of the viscosity profile remained the same (figure 4.12b).
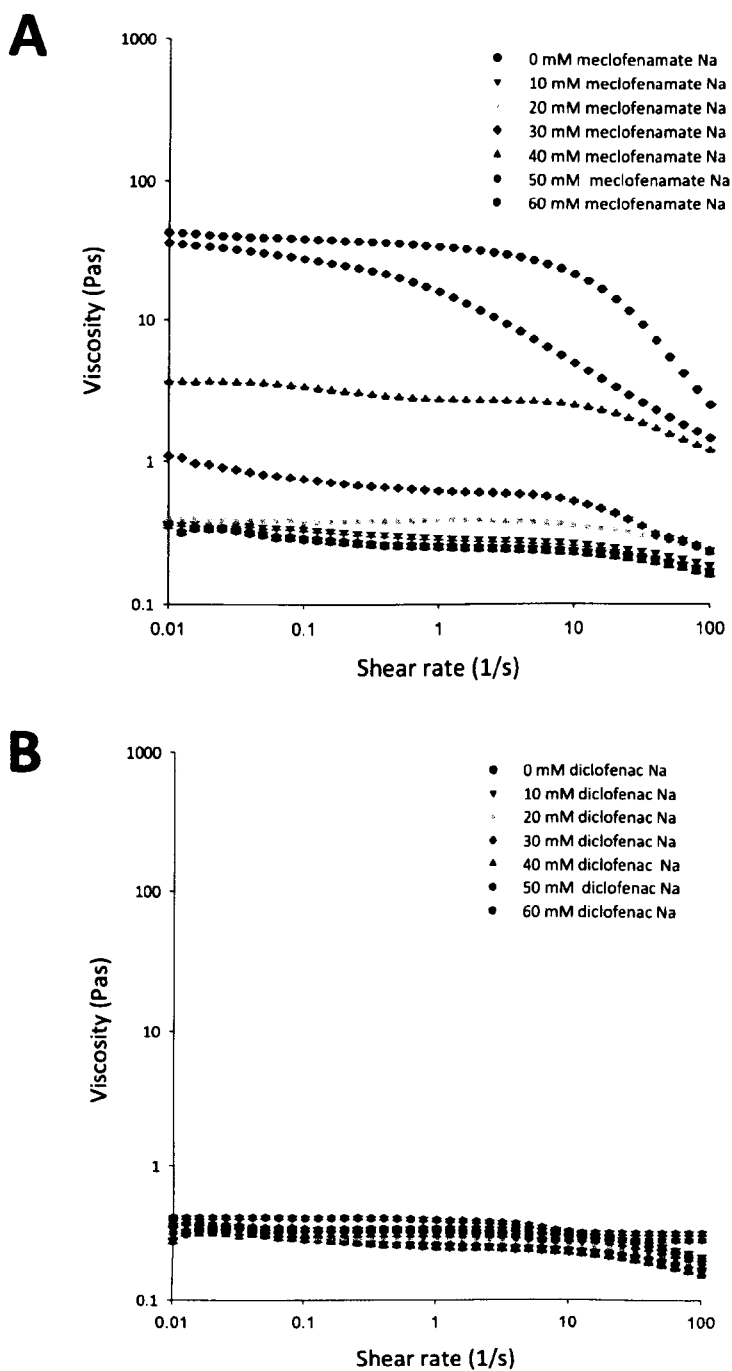
Figure 4.12 The effect of (A) meclofenamate Na and (B) diclofenac Na on continuous shear viscosity of 1% w/w HPMC solution

Geometry = CP 2°/50 mm. Temperature = 20 ± 0.1°C. Mean (n =3) ± 1SD
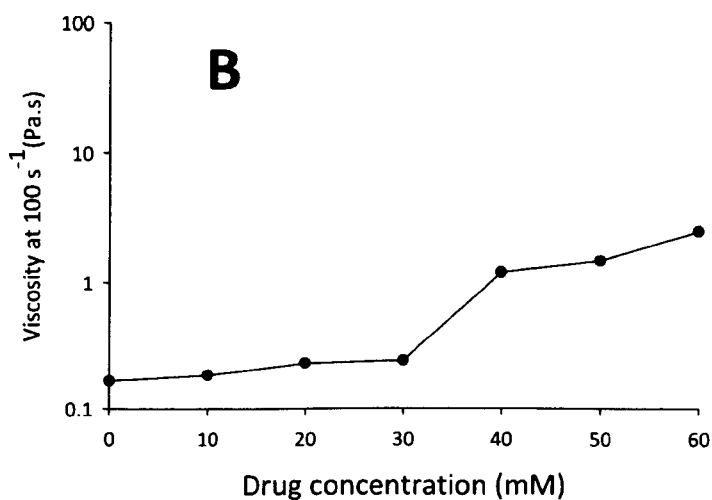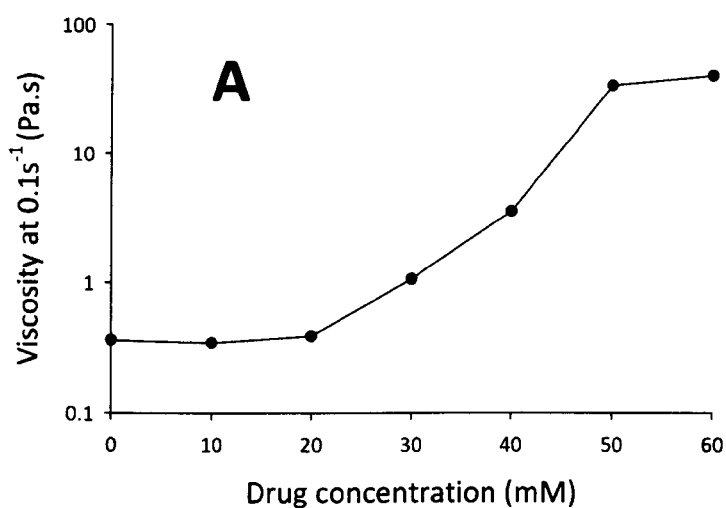
Figure 4.13 The continuous shear viscosity of 1% w/w HPMC and containing various concentrations of meclofenamate Na at (A) low (0.1 s^{-1} and (B) high (100 s^{-1}) shear rates

Geometry = CP 2°/50 mm. Temperature = 20 ± 0.1°C. Mean (n =3) ± 1SD
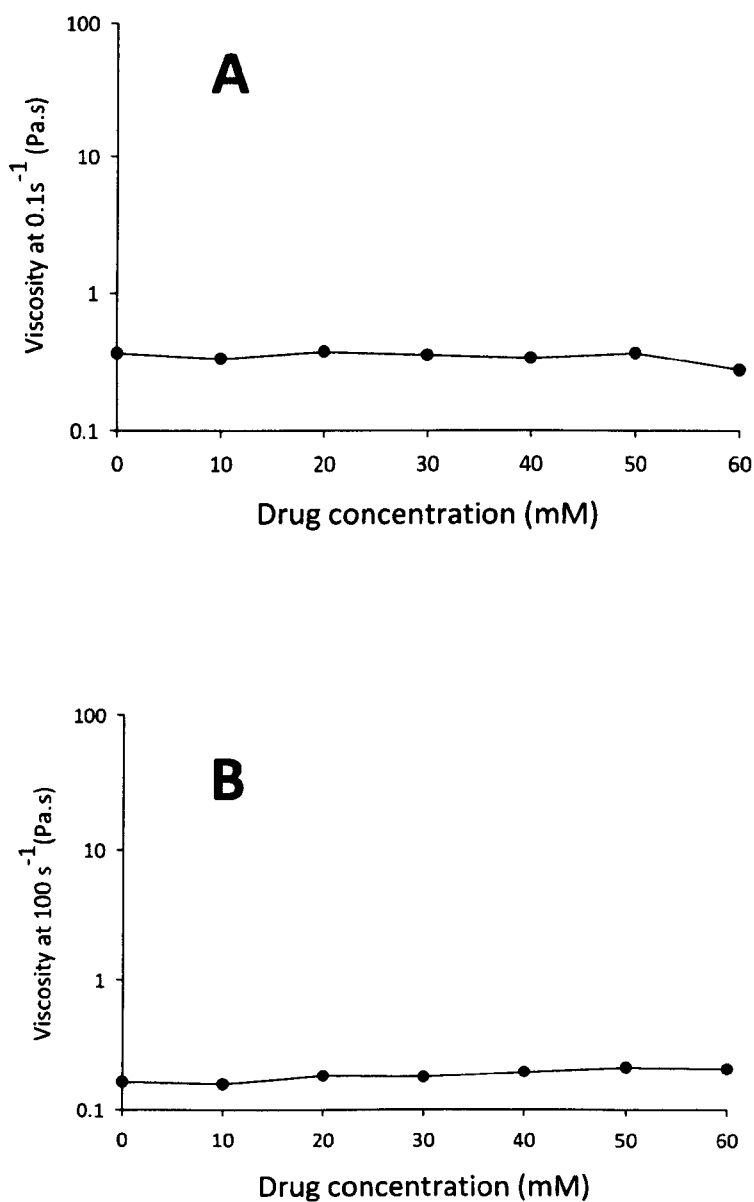
Figure 4.14 The continuous shear viscosity of 1% w/w HPMC solutions containing various concentrations of diclofenac Na at (A) low (0.1 s^{-1} and (B) high (100 s^{-1}) shear rate

Geometry = CP 2°/50 mm. Temperature = 20 ± 0.1°C. Mean (n =3) ± 1SD

4.4.4 The effect of drugs on the oscillatory rheology of HPMC solutions

Dynamic oscillatory shear rheology can provide information about how energy from small oscillations applied to a sample is recovered or dissipated, and hence provide information on the internal structure of samples.

In order to carry out satisfactory oscillatory rheology, the linear viscoelastic region (LVR) was first determined. This was determined at the temperature at which subsequent frequency sweeps were undertaken to determine the effect of drugs on the storage and loss moduli of the HPMC solutions.

4.4.4.1 The effect of incorporated drugs on the complex viscosity of HPMC solutions

Initially, the frequency dependence of the complex viscosity was investigated to gain an insight into the viscoelastic response of the drug-polymer mixtures. It is generally found that this behaviour can be described in terms of a power law where m assumes values of 0 and 1 for a liquid and a solid, respectively (Larson 2005). Figure 4.15 shows the frequency dependencies of complex viscosity, as measured in small-amplitude oscillatory shear experiments, for 1% w/w solutions of HPMC containing meclofenamate Na and diclofenac Na. HPMC solutions containing diclofenac exhibited a liquid-like behaviour at all concentrations of drug. This is shown by gradients close to 0 which is indicative of only weak polymer-surfactant interactions. In contrast, for HPMC solutions containing meclofenamate Na, the elastic (solid-like) response becomes more pronounced with increasing meclofenamate Na concentration and the highest values of m are observed for the system (60

mM meclofenamate Na) that exhibited the most marked viscosity enhancement. This strong elastic response is typical for systems with well-developed association networks (Larson 2005).
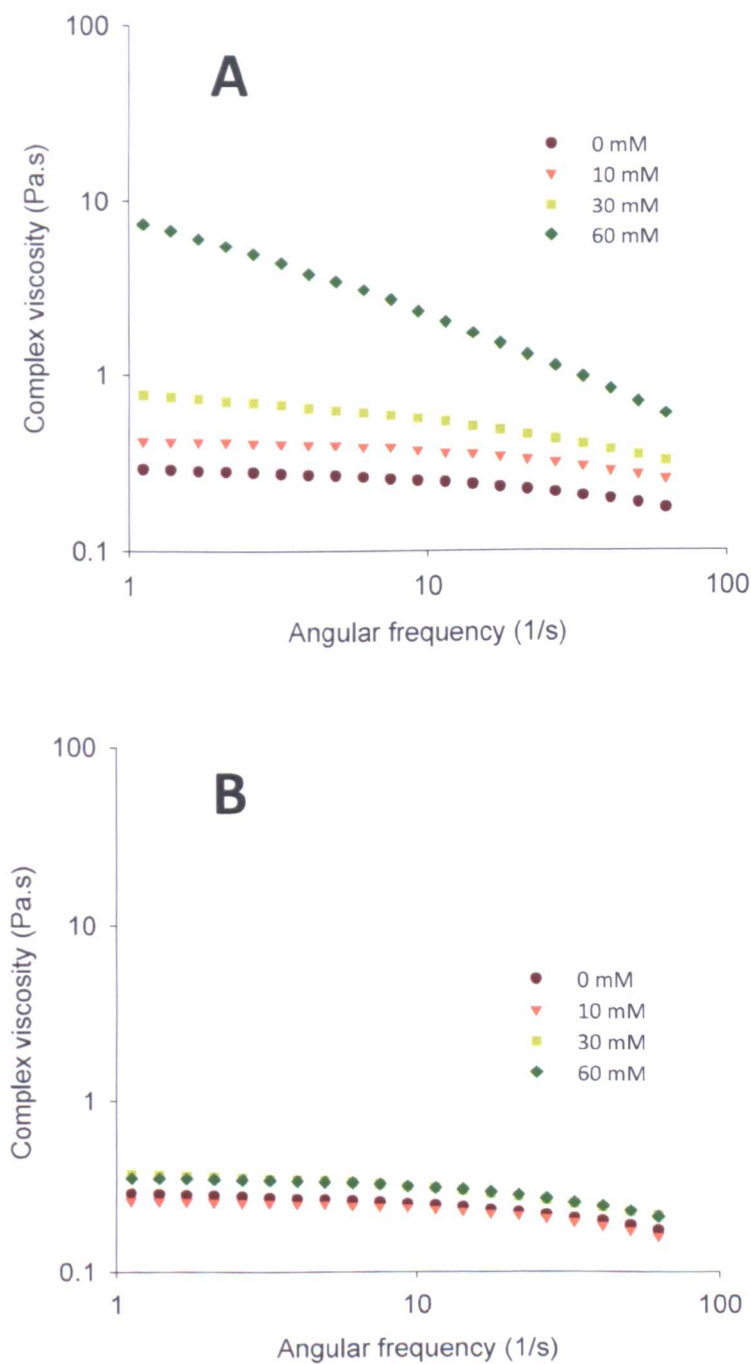
Figure 4.15 Frequency dependence of complex viscosity for 1% w/w HPMC solution containing various concentrations of (A) meclofenamate Na and (B) diclofenac Na at the drug concentrations indicated.

Geometry = PP 2°/50 mm. Temperature = 20 ± 0.1°C. Mean (n =3) ± 1SD

4.4.4.2 The effect of drugs on the storage and loss moduli of HPMC solutions

Figures 4.16 and 4.17 show the mechanical spectra obtained for HPMC solutions containing various concentrations of diclofenac Na and meclofenamate Na. For clarity, the loss and storage moduli with respect to drug concentration are shown separately in figures 4.18 and 4.19. Little or no change was seen in the mechanical moduli of HPMC solutions in the presence of diclofenac Na (figures 4.16 and 17). However, with meclofenamate Na, there were pronounced increases in mechanical moduli as a result of mixing this drug with HPMC, with large increases in both G' (figure 4.16) and G" (figure 4.17), suggesting that both the elastic and viscous properties of the HPMC are enhanced by the addition of the drug.

The magnitude of G' is directly related to the gel strength of the sample. In a strongly cross-linked gel, G' would be much larger than G" and not influenced by the oscillation frequency, while a physically entangled gel network would have a G" exceeding G' at some point in the frequency range with a substantial decline in G' and to a less extent G" at low frequencies. In a physically entangled system, polymer chains entangle and move past each other at low frequencies so that the material behaves more like a viscous liquid. At higher frequencies there is insufficient time for network rearrangements to occur within one oscillation, and as a result the response of the sample is a predominately elastic deformation.

Figure 4.19 shows that diclofenac Na had little effect on the storage and loss moduli of 1% HPMC solutions. The slopes of the G' and G" frequency relationship showed a small concentration dependent increase with respect to 1% HPMC alone. In contrast, meclofenamate Na increased the elastic modulus of 1% HPMC solutions significantly with a corresponding lesser effect on G".
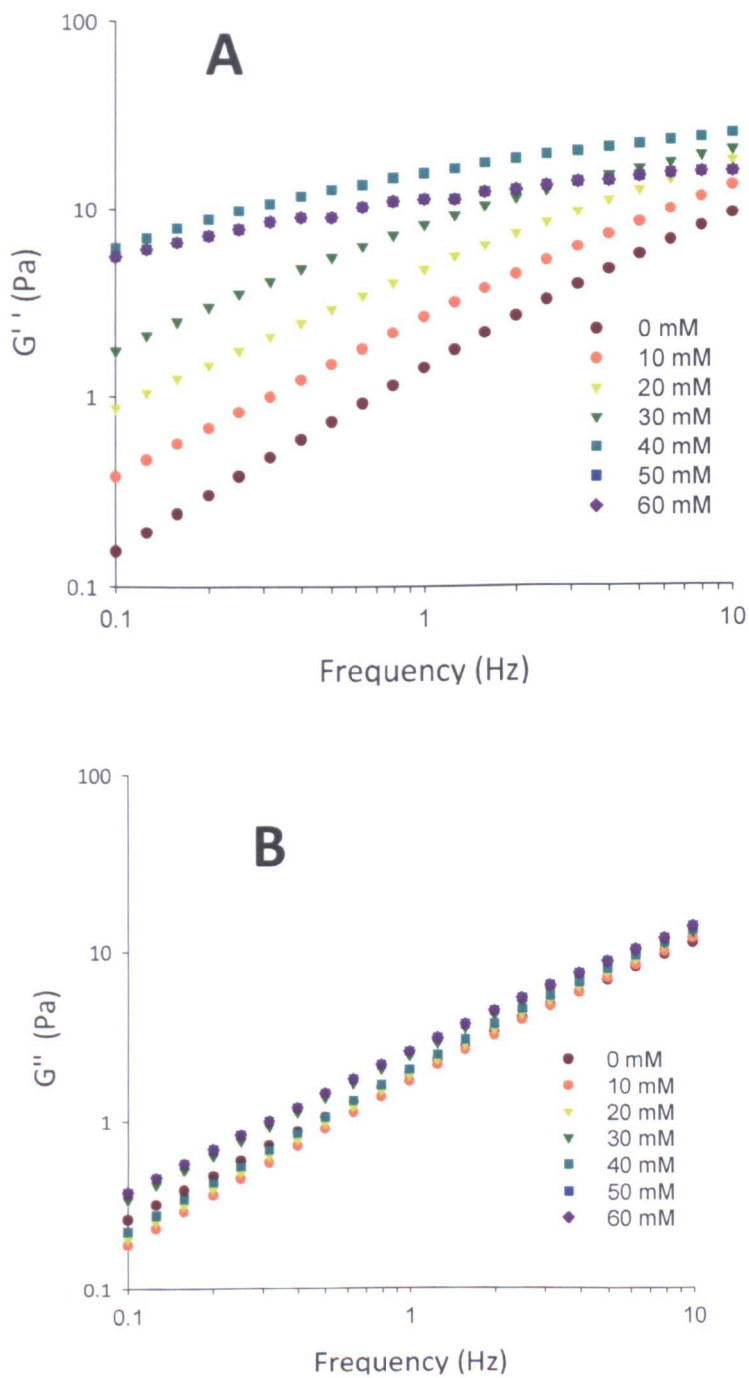
Figure 4.16 The loss modulus (G'') of mixtures containing 1% w/w HPMC and varying concentrations of (A) meclofenamate Na and (B) diclofenac Na

Geometry = PP 2°/50 mm. Temperature = 20 ± 0.1°C. Mean (n =3) ± 1SD
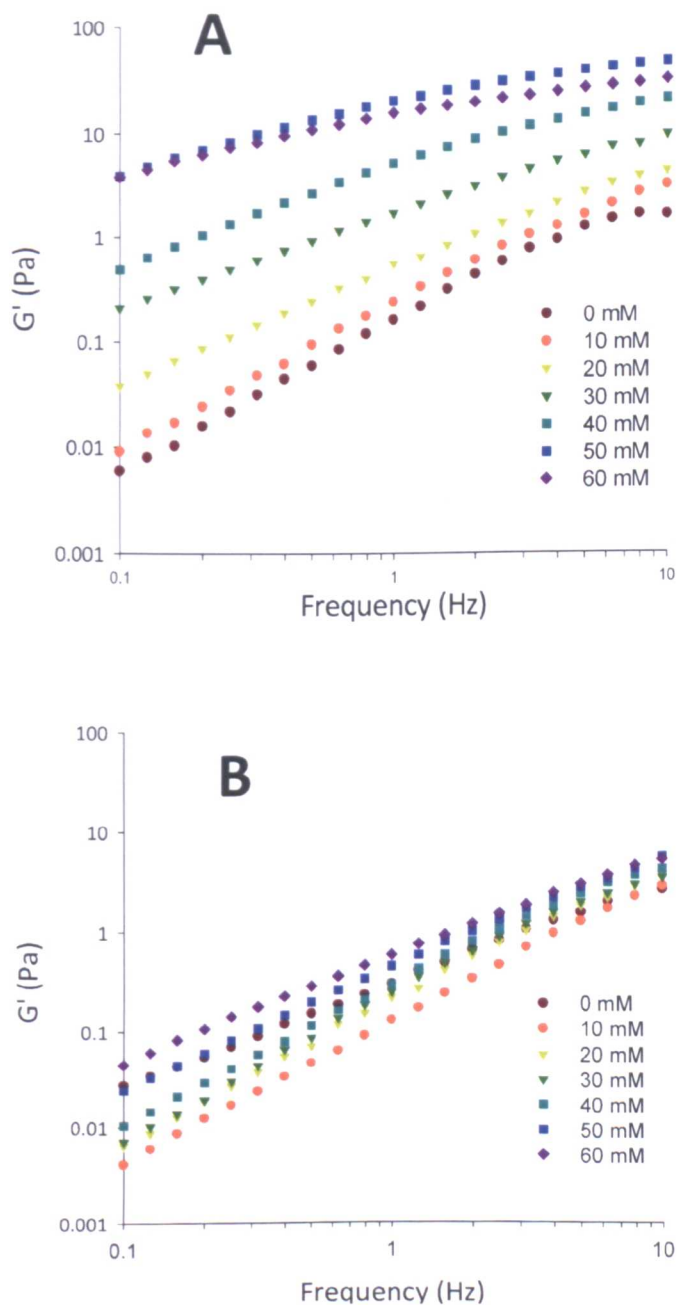
Figure 4.17 The storage modulus (G') of mixtures containing 1 % w/w HPMC and varying concentrations of (A) meclofenamate Na and (B) diclofenac Na

Geometry = PP 2°/50 mm. Temperature = 20 ± 0.1°C. Mean (n = 3) ± 1SD
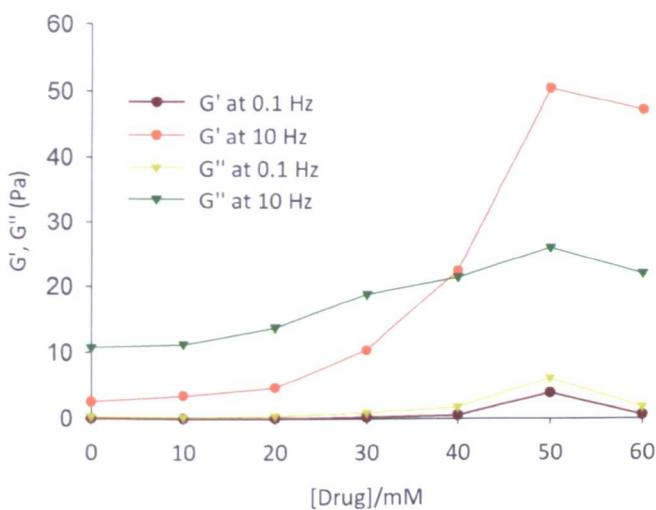
Figure 4.18 The loss (G") and storage (G') moduli of mixtures containing 1% w/w HPMC and varying amounts of meclofenamate Na at 0.1 and 10 Hz

Measurements taken in the linear viscoelastic region (LVR). Geometry = PP 2°/50 mm. Temperature = 20 ± 0.1°C. Mean (n =3) ± 1SD
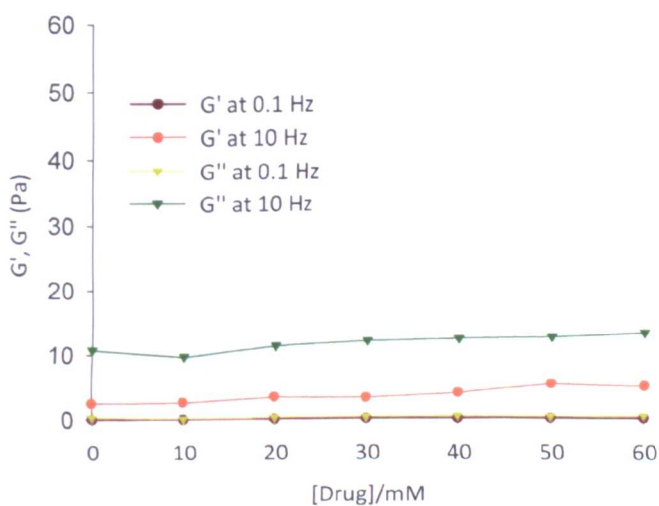
Figure 4.19 The loss (G") and storage (G') moduli of mixtures containing 1% w/w HPMC and varying amounts of diclofenac Na at 0.1 and 10 Hz

Measurements taken in the linear viscoelastic region (LVR). Geometry = PP 2°/50 mm. Temperature = 20 ± 0.1°C. Mean (n =3) ± 1SD

4.4.4.3 The effect of drugs on the tan δ values of HPMC solutions

Tan δ values provide further evidence of the changes in viscoelascity. The tan δ is the ratio of G″ to G′ and indicates the potential of the sample to move towards a gel-like behaviour from liquid characteristics. The point at which tan δ is equal to 1 (G′=G″) was used as a parameter for the interaction of a range of drug concentrations with HPMC.

Figure 4.20 shows the effect of drugs on the tan δ of 1% w/w HPMC solutions. It can be seen that when converting the dynamic moduli to a tan δ an order of magnitude shift in viscoelastic profiles caused by meclofenamate Na in comparison with diclofenac Na became readily apparent. The extent to which the dynamic moduli (and tan δ) is changed is dependent on the interaction between the drug and polymer, where a shift in viscoelastic properties to a much more pronounced elastic behaviour (tan δ <1) indicates a high degree of interaction between the drug and the polymer.
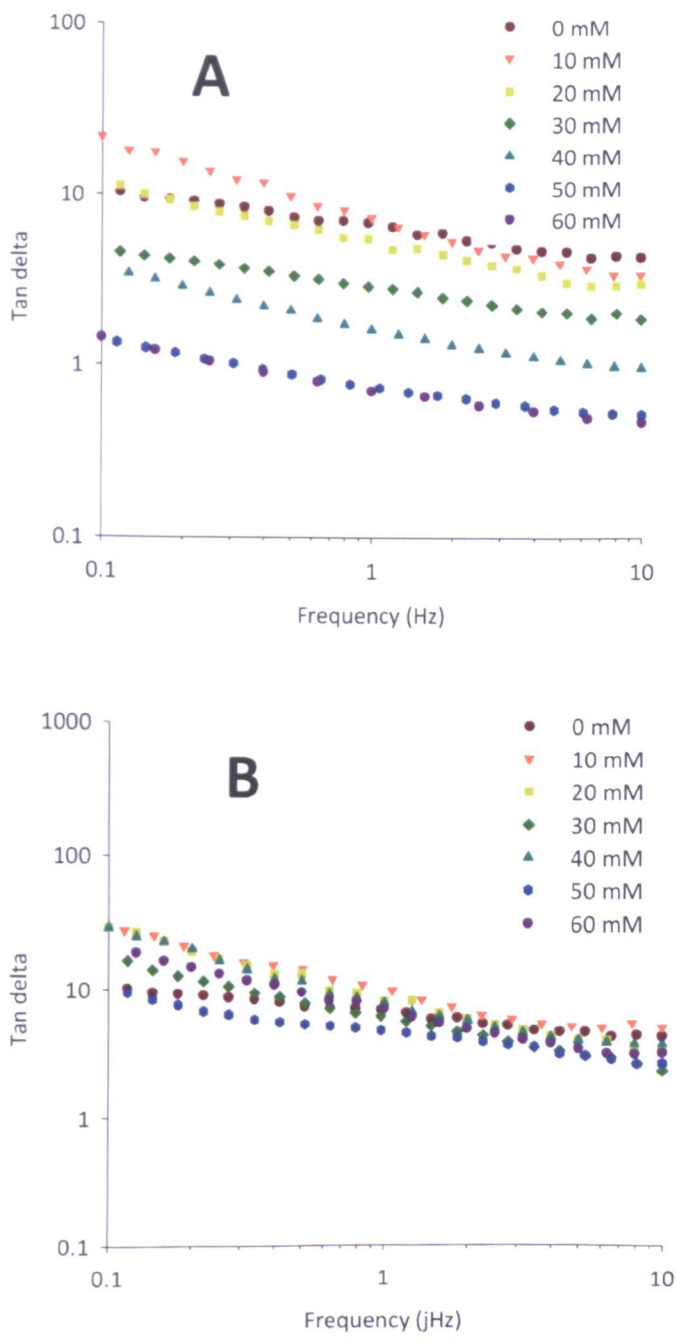
Figure 4. 20 The effect of (A) meclofenamate Na and (B) diclofenac Na on the tan δ of 1% w/w HPMC solutions

Measurements taken in the LVR. Geometry = CP 2°/50 mm. Temperature = 20 ± 0.1°C. Mean (n =3) ± 1SD

4.4.5 The effect of sodium chloride on the interaction between drugs and HPMC

The influence of ionic species on surfactant-polymer interactions has been studied in the literature (e.g. Masuda *et al.* 2002, Thongngam and McClements 2005). As highlighted in the interpretation of the studies in chapter 2 dissolution tests were carried out in 0.9% w/v (0.154 M) NaCl to represent a more realistic swelling medium for the HPMC hydrophilic matrices, hence the effect of NaCl on the drug-HPMC interactions was worthy of investigation.

4.4.5.1 The influence of sodium chloride on drug effects on HPMC solution cloud point temperature (CPT)

Figure 4.21 shows the effect of 0.154 M sodium chloride (NaCl) addition to 1% w/w HPMC solutions containing the model drugs. The effect of drugs without the addition of sodium chloride is included within the figure for reference. In the case of diclofenac Na, the addition of NaCl to HPMC solutions led to a decrease in the CPT at all concentrations of diclofenac Na when compared with drug addition alone. The propensity of NaCl to decrease the thermogelation temperature of HPMC has been noted in the literature (Bajwa *et al.* 2006, Liu *et al.* 2008). Therefore, NaCl and diclofenac Na addition appeared to synergistically 'salt-out' HPMC in solution.

In the case of meclofenamate Na, the influence of NaCl manifested as two key changes. At lower concentrations of drug, the CPT of HPMC solutions was lowered to a greater extent by the combination of drug and sodium chloride, in a manner analogous to diclofenac Na and NaCl. In addition, the meclofenamate Na concentration at which the HPMC solutions became 'salted in' as opposed to 'salted out' was shifted to between 20 mM and 30

mM compared with between 30 to 40 mM in the absence of NaCl. Beyond this concentration, the CPT values increased in a similar manner irrespective of the presence or absence of NaCl.

4.4.5.2 The influence of sodium chloride on the effect of drugs on HPMC solution viscoelastic properties

Figures 4.22 and 4.23 show the changes in loss and storage modulus in 1% w/w HPMC solutions containing 0.154 M NaCl at 0.1 and 10 Hz with respect to increasing drug concentrations of meclofenamate Na and diclofenac Na.

It can be seen that the most profound effect is the shifting of the concentration of meclofenamate Na that resulted in the large increase in the storage modulus. This occurred at around 30 mM in the case of drug alone (figure 4.18) and is shifted to between 10 and 20 mM when NaCl is present in the system (figure 4.22). There is also evidence of a plateau in the storage modulus with respect to drug concentration. In contrast, there was little change in the loss or storage modulus in solutions containing diclofenac Na (figure 4.23) which is comparable to the effects of drug in the absence of NaCl (4.19).

These results are in agreement with findings in the literature with respect to ionic influences on surfactant-polymer interactions. For example, Evertsson and Holmberg (1997) have shown using steady-state fluorescence measurements that the presence of NaCl led to SDS interacting with EHEC at lower concentrations. Also, Wangsakan *et al.* (2006) have shown that NaCl influenced the interaction between SDS and maltodextrin by reducing the onset of interactions concentration of SDS.
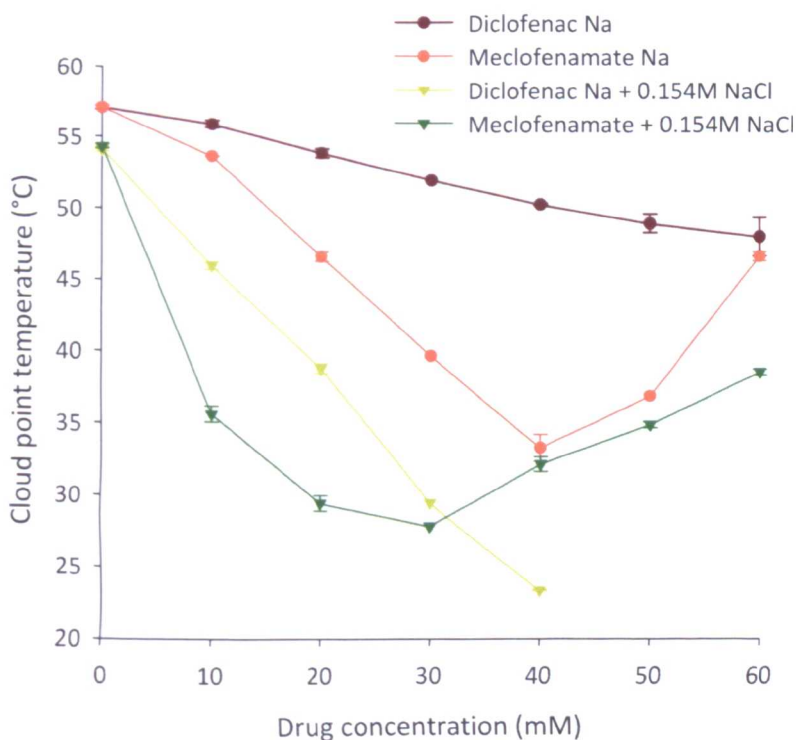
Figure 4.21 Modulation of the effect of diclofenac Na and meclofenamate Na on the cloud point temperature of 1% w/w HPMC solutions by 0.154 M NaCl

Cloud point temperature (CPT) measured turbimetrically as reduction of 50% in light transmission (Sarker 1979). Mean (n=3) ± 1SD
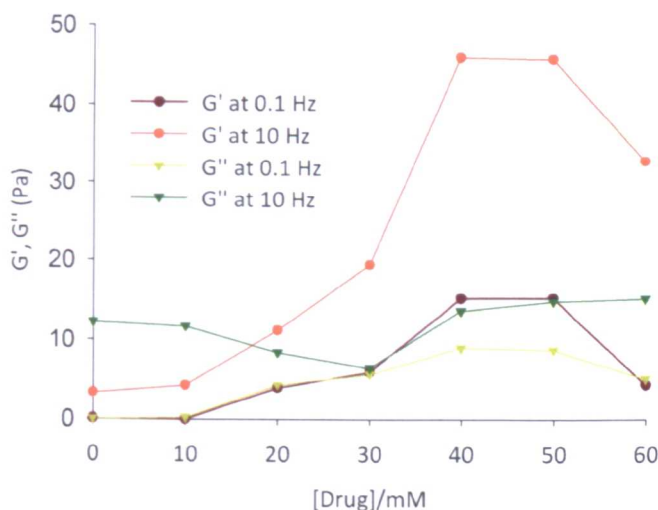
Figure 4.22 The loss (G″) and storage (G′) moduli of mixtures containing 1% w/w HPMC and varying amounts of meclofenamate Na and 0.154 M NaCl at 0.1 and 10 Hz

Measurements taken in the LVR. Geometry = PP 2°/50 mm. Temperature = 20 ± 0.1°C. Mean (n =3) ± 1SD
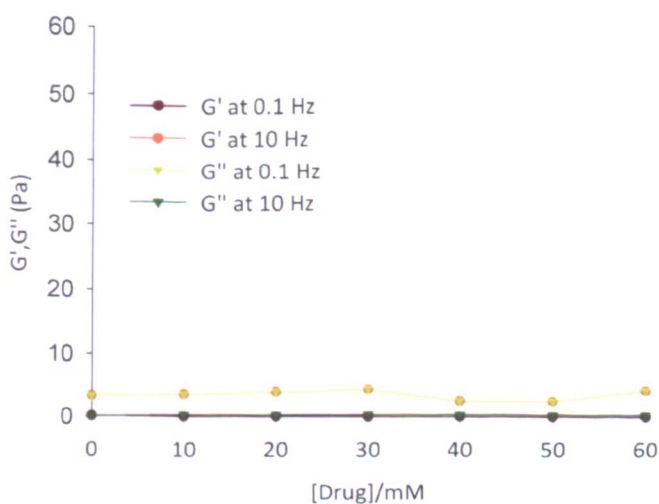
Figure 4.23 The loss (G″) and storage (G′) moduli of mixtures containing 1% w/w HPMC and varying amounts of diclofenac Na with 0.154 M NaCl at 0.1 and 10 Hz

Measurements taken in the LVR. Geometry = PP 2°/50 mm. Temperature = 20 ± 0.1°C. Mean (n =3) ± 1SD

4.5 Discussion

4.5.1 The mechanism of interaction between the model drugs and HPMC

Figure 4.24 depicts a hypothetical scheme describing how diclofenac Na and meclofenamate Na molecules might interact with HPMC. Evidence from the cloud point studies suggested that both drugs exert a 'salting-out' effect. This may be a result of substituted aromatic moieties within the chemical structure (Banks 2003). The propensity to 'salt-out' the polymer is evidenced by the suppression of HPMC solution cloud point on addition of low drug concentrations (<30 mM). Tensiometry and PGSE-NMR results suggested a limited association between drug and polymer at these low concentrations and the rheological investigations confirmed there was little change in polymer chain mobility and connectivity (figure 4.24a). However, it was seen that the different drugs exerted divergent effects on HPMC solution properties as their concentration was increased.

In the case of diclofenac Na (figure 4.24b), the surface tension studies show that the drug was able to associate with the HPMC. However, the results from tensiometry also suggested saturation of binding sites, no formation of a drug-polymer complex as determined by SANS and rheological analysis suggesting insufficient associated drug in order to change polymer conformation in solution. Free drug effects predominated and the polymer was increasingly dehydrated with respect to drug concentration as demonstrated by the turbimetric studies.
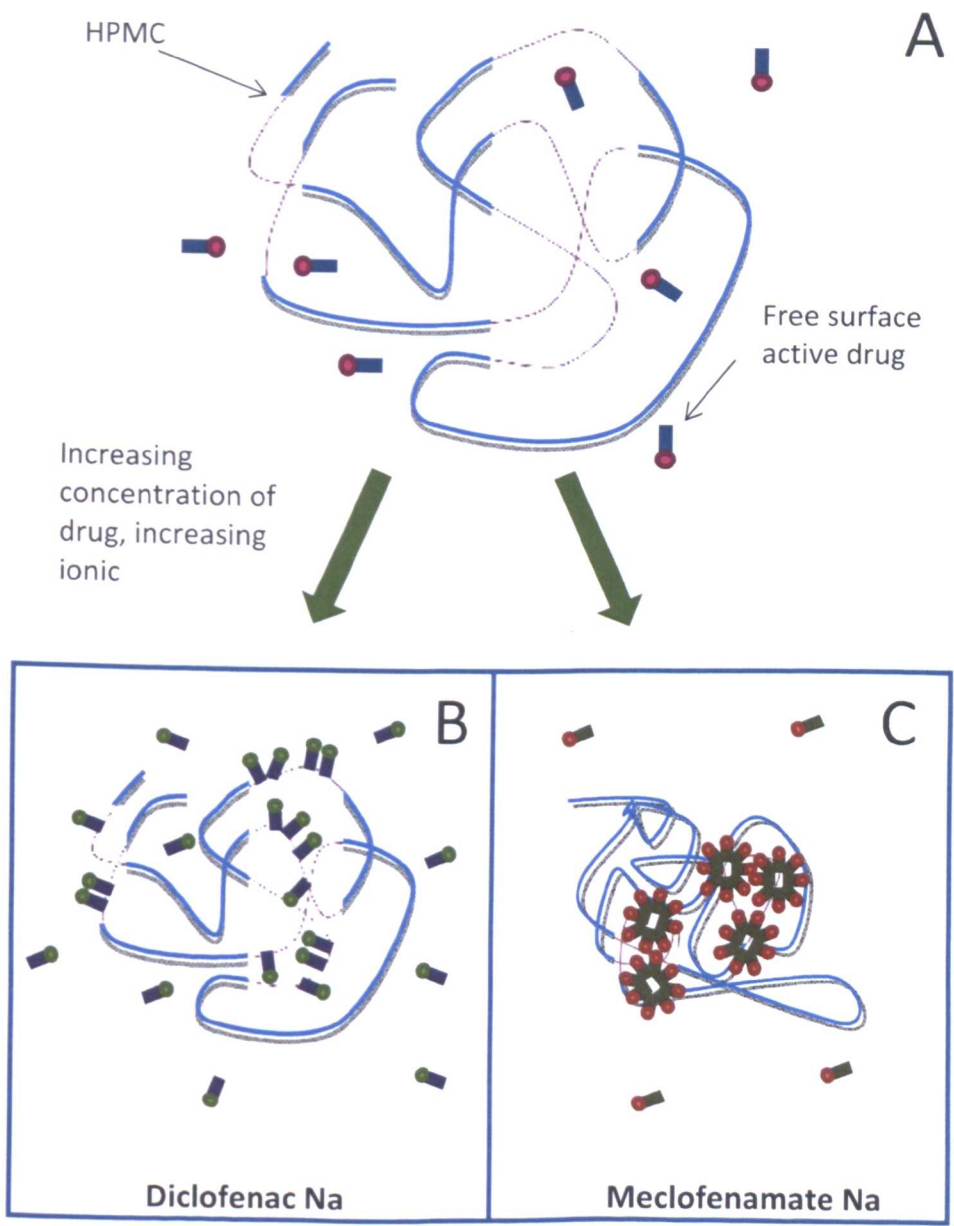
Figure 4.24 Proposed theory for the interaction between NSAIDs and HPMC

(A) Low polymer and drug concentration, (B) Low polymer and high diclofenac Na concentrations and (C) low polymer and high meclofenamate Na concentrations

The influence of meclofenamate Na contrasted with diclofenac Na (figure 4.24c). Tensiometry showed evidence of drug binding, but failed to demonstrate a saturation concentration. This suggested that the drug forms associative structures and co-operatively bound to HPMC, resulting in the formation of drug-polymer aggregates detectable by SANS. These complexes were more soluble than 'salted out' polymer, demonstrated by an increase in cloud point temperature with respect to meclofenamate Ma concentrations above 30 mM. Rheological analysis showed increases in shear and complex viscosity resulting from the increased chain-chain interactions as determined by profound changes in the mechanical moduli of the solutions.

It is proposed that there is a dynamic balance between the associative and the free drug effects on the properties of HPMC in solution. One effect, mediated by free drug in solution, reduces polymer solubility and had little or no effect on polymer viscoelastic properties. The other effect, resulting from association of drug with polymer, led to the formation of a drug-polymer complex with significant increases in chain-chain interactions, resulting in large viscosity increases. In the presence of low drug concentrations, the 'salting-out' mechanism predominates. Above a critical concentration for meclofenamate Na but not diclofenac Na, the drug-polymer complex predominated over free drug effects. This drug-polymer complex possesses poly(electrolyte) characteristics of increased viscoelastic properties, greater solubility and strong susceptibility to modulation by ionic species.

4.5.2 Pharmaceutical Consequences

The potential pharmaceutical consequences of these interactions can be conjectured. In other pharmaceutical systems, the interactions between surface active drugs and polymers have been noted as being potentially

useful in order to achieve an efficient control of release processes from aqueous dispersions (Paulsson and Edsman, 2001, Jimenez-Kairuz *et al.* 2002) or chemically cross-linked hydrogels (Gonzalez-Rodriguez *et al.* 2002, Rodriguez *et al.* 2003a). In our systems, polymer association with complementary additives might be used to rapidly strengthen or induce connections between polymeric chains and may be a useful way to obtain considerable increases in the viscosity of dispersions.

In the case of hydrophilic matrix dosage forms, the establishment of an adequate surface gel diffusion barrier has been proposed as being a critical process in achieving extended release (Alderman 1984, Melia *et al.* 1991, Li *et al.* 2005). From the work in this chapter, we can speculate that the association of drug with the polymer would affect the viscosity and gel strength within the gel layer. This may manifest as changes in the morphology and functionality of the gel layer and result in improved extended release characteristics of meclofenamate Na matrices over diclofenac Na matrices by providing a more efficient barrier to drug release. The dissolution data presented in chapter 3 suggests that this is the case. Subsequent investigations will consider the effects of these drugs on early gel layer development and the potential role of incorporated diluents using a recently developed confocal microscopy methodology.

4.6 Conclusions

In the literature, there is strong evidence that many NSAIDs are surface active (Attwood 1995, Fini *et al.* 1995) and as a consequence, surface tension experiments were performed on aqueous solutions of diclofenac Na and meclofenamate Na in the presence and absence of polymer. These studies demonstrated surface activity and drug association with the polymer. It was found that diclofenac Na saturated the HPMC whereas meclofenamate Na did not show a saturation concentration up to the limit of its aqueous solubility.

Evidence of association between meclofenamate Na and HPMC (but not diclofenac Na and HPMC) was provided by PGSE-NMR and SANS data which suggested that this phenomenon may be responsible for the changes in polymer solution properties containing these two drugs. Turbidimetric studies showed that the effect of these drugs was complex, and that the increased solubility of HPMC seen with higher concentrations of meclofenamate Na (but not diclofenac Na) may be the result of binding of drug molecules in sufficient numbers to form polar drug-polymer poly(electrolyte) complexes that could overcome the inherent 'salting-out' of the free drug molecules.

Rheological investigations showed that at whilst low concentrations, the drugs caused only small increases in HPMC solution viscosity. At higher concentrations, meclofenamate Na caused a dramatic increase in solution viscosity to a value two orders of magnitude greater than that of 1% HPMC alone. This would suggest that a fundamental change in microstructure has taken place as a result of drug association with meclofenamate Na and suggests that this drug induces considerable inter-chain bonding.

Chapter 5

The effect of drugs and ionic media on the

morphology and functionality of the gel layer

in HPMC hydrophilic matrices

5.1 Introduction

In the preceding chapter, a theory describing the interaction between HPMC with diclofenac Na and meclofenamate Na was developed from evidence of drug effects on HPMC solution solubility and viscoelasticity. This interaction and its influence on HPMC particle swelling and early gel layer formation may provide an insight into the drug release mechanism and an explanation for the release profiles presented in chapter 2. The next stage is to obtain experimental evidence to confirm or disprove the hypothesis that interactions between the drugs and HPMC influence the formation and functionality of the early gel layer in hydrophilic matrices.

5.1.1 The importance of particle swelling in HPMC hydrophilic matrix dosage forms

Essentially the HPMC hydrophilic matrix is a compressed particle bed of an active pharmaceutical ingredient (API), HPMC and other tabletting excipients (Hogan 1989, Melia 1991). It can be anticipated that HPMC particle swelling and coalescence during gel layer development will greatly impact on the capability to form an adequate diffusion barrier. This rationale is supported by the recognition that a major influence on the extended release properties of many polymers is the ability to hydrate, swell and coalesce (Alderman 1984, Melia 1991, Ford 1999).

5.1.2 Selection of a technique to characterise the swelling properties of HPMC particles

Several techniques are described in the literature to investigate the effect of dissolved material on polymer swelling. These have included:

(i)   gravimetric measurements (Mortazavi and Smart 1993, Pini *et al.* 2008),

(ii)   volumetric measurements (Bencherif *et al.* 2008),

(iii) direct visualisation (Wan and Prasad, 1990, Degim and Kellaway 1998),

(iv)   ion beam analysis (Riggs *et al.* 1999),

(v)   nuclear magnetic resonance (NMR) microscopy (Katzhendler *et al.* 2000, Marshall *et al.* 2001),

(vi)   electron spin resonance (ESR) (Katzhendler *et al.* 2000)

(vii) thermomechanical analysis (TMA) (Nakamura *et al.* 2000).

The method chosen for this thesis was originally described by Wan and Prasad (1990) who used video microscopy to study the swelling characteristics of individual tablet disintegrant particles in water (figure 5.1). The swelling of excipients was measured by placing a particle on a microscope slide and covering it with a cover slip. The particle was hydrated by water, introduced using a micro-syringe. The swelling was recorded using video microscopy and the change in area of the swelling particle measured using image analysis. This method was selected for use in this chapter as it is high-throughput and simple with respect to the experimental procedure and equipment.

5.1.3 Selection of a technique to characterise the gel layer development in HPMC hydrophilic matrices

The formation and growth of the gel layer plays a significant role in extending drug release (Alderman 1984, Melia 1991, Ford 1999, Li et al. 2005). Several methods have been employed to observe hydrophilic matrices during the processes of gel layer formation, erosion and dissolution. These include (i) photography and video imaging (Gao and Meury 1996, Colombo 1999), (ii) ultrasound (Konrad et al. 1998), (iii) cryogenic SEM (Melia et al. 1993), (iv) thermomechanical or texture analysis probes (Pillay and Fassihi 2000), (v) laser positioning (Mitchell et al. 1993), (vi) NMR microscopy (Bowtell et al. 1994) and (vii) confocal microscopy (Bajwa et al. 2006). A review of the use of these different techniques has been provided in section 1.7.

Each of these techniques possesses their own advantages and disadvantages but few are capable of the spatial and temporal resolution required to follow the processes of early gel layer development. Fluorescence imaging offers good spatial resolution, sensitivity and time resolution (Gumbleton and Stephens 2005, White and Errington 2005)

and confocal microscopy provides fluorescent images that are free from out-of-focus flare.

5.2 Confocal Laser Scanning Microscopy (CLSM)

CLSM has become increasingly used in the characterisation of pharmaceutical systems (Pygall *et al.* 2007) including topical dosage forms, pellets and hydrophilic matrices. The use of CLSM to explore the early development of the HPMC gel layer microstructure has been described by Bajwa (Bajwa *et al* 2006). The technique exploits the temporal and spatial capabilities of CLSM to provide imaging of the rapid structural developments within the emerging gel layer of hydrophilic matrix tablets on hydration in liquids. The following sections provide the reader with brief details of the theory of confocal microscopy.

5.2.1 Theory of Confocal Laser Scanning Microscopy

CLSM offers several advantages over conventional optical microscopy. The most important is that out-of-focus blur is essentially absent from the image, giving the capability for direct non-invasive serial optical sectioning of intact and living specimens (Sheppard and Shotton 1997).

The confocal microscope was first conceived by Minsky in 1955 (Minsky 1988) who determined that in order to observe individual nerve cells within a packed central nervous system, a microscopic technique was required to prevent interference of scattered light from cells adjacent to the cell of interest. To achieve this, he designed a simple instrument in which a pinhole was placed in front of an objective and condensing lens. The pinholes (now termed confocal apertures) discriminated out-of-focus light contributions from the specimen. In 1961 Minsky patented designs

in two geometries: the first used transmitted illumination, with a separate objective lens and condensing lens on either side of the specimen, whilst the second used epi-illumination, where the same lens was used as both an objective and a condenser. This simple concept formed the basis for all future confocal microscopes (Sheppard and Shotton 1997).

Figure 5.1 shows a schematic illustration of the principal components and light paths in a confocal microscope. Excitatory laser light from the illuminating aperture passes through an excitation filter (not shown) and is reflected by the dichroic mirror. It is then focused by the microscope objective lens to a diffraction limited spot at the focal plane within the fluorescent specimen. The emitted fluorescent light is captured by the same objective lens and is focused onto a photomultiplier. Only 'in focus' signals are aligned with the aperture and so pass through to the detector Any signal emanating from above or below the focal plane is stopped by the confocal aperture and so not collected, therefore 'blurring' of the image is avoided as the 'out-of-focus' signal does not contribute to the image. The system shown in figure 5.1 is an epi-illumination system as the same lens is used as both objective and condenser. The signal detected by the photomultiplier is converted to a digital signal and displayed on a computer monitor, with the intensity of the fluorescent emission corresponding to the relative intensity of the pixel in the image. To build a complete image, the beam is scanned over the sample using controlled galvanometer driven mirrors. A more detailed review of confocal microscopy is given elsewhere (Sheppard and Shotton 1997).
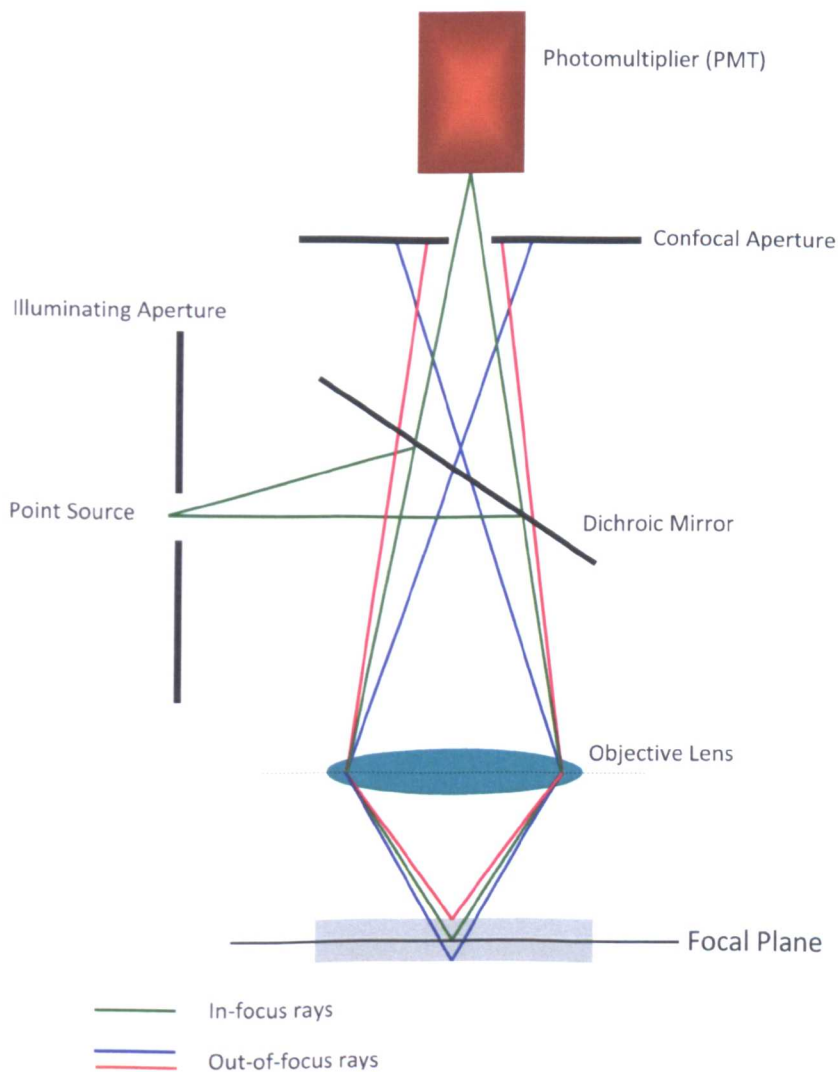
Figure 5.1 Schematic illustration showing the principal components and light paths in a confocal laser scanning microscope

Adapted from Sheppard and Shotton (1997).

5.2.2 Characterisation of the fluorophore Congo red

Congo red (figure 5.2) is used as a histo-pathological and botanical stain for cellulose and in textile dyeing (Horobin 2002). It has been shown to have a high binding affinity with (1-4)-β-linked D-glucopyranosyl native cellulose sequences (Wood 1980).
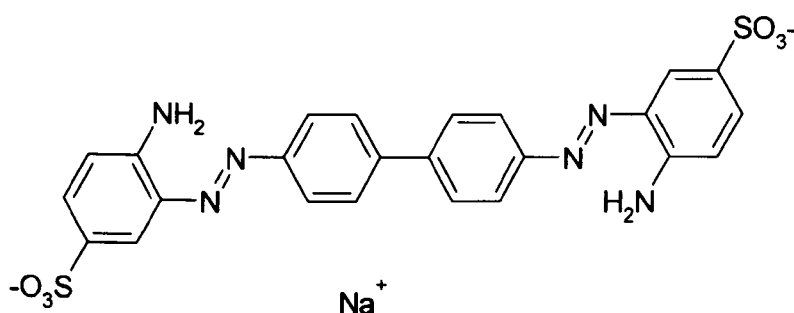
Figure 5.2 Chemical structure of Congo red

Yamaki *et al.* (2005) have shown that Congo red appears to interact with cellulose through a combination of electrostatic and hydrophobic interactions and hydrogen bonding between its azo and amino groups with the native cellulose fibres. There is an increase in the dye sorption when cellulose fibres are hydrated and molecular access of the dye is enhanced (Mirza *et al.* 1996). In the first paper to describe the use of confocal microscopy to investigate early gel layer formation, Bajwa *et al.* (2006) have shown how the use of Congo red at a concentration of 0.008% w/v allowed determination of various regions within a swelling matrix tablet of HPMC, without being at a high enough concentration to affect gel formation and matrix swelling.

5.3 Aims and Objectives

Chapter 4 investigated the interaction between HPMC and the model drugs diclofenac Na and meclofenamate Na. This chapter presents investigations to determine the pharmaceutical consequences of these interactions with respect to HPMC particle swelling and early gel layer formation.

Specifically, the aims of this chapter are:

- To investigate the effect of increasing diclofenac Na and meclofenamate Na matrix content on HPMC particle swelling and early gel layer development

- To relate the influence of drugs on HPMC solution properties to particle swelling and gel layer formation.

- To investigate the influence of sodium chloride on drug effects on early gel layer formation.

5.4 Materials and Methods

5.4.1 Materials

5.4.1.1 HPMC

A sieve fraction of 63-90 μm HPMC (Methocel E4M CR Premium) was used in matrix manufacture. Details of the source and batch number are presented in appendix 1.

5.4.1.2 Drugs

Diclofenac Na and meclofenamate Na were used as supplied. Details of the source and batch number are presented in appendix 1.

5.4.1.3 Silicon dioxide

Silicon dioxide was used as supplied. Details of the source and batch number are presented in appendix 1.

5.4.1.4 Water

Solutions were prepared using Maxima HPLC grade water (source details in appendix 1).

5.4.2 Measurement of single HPMC particle swelling

The method described by Wan and Prasad has been developed within the Formulation Insights Group (Richardson 2002). In the developed method, a haemocytometer counting chamber is used instead of a microscope slide as the distance between the cover slip and chamber surface is precision engineered to 75 μm and an HPMC particle from the sieve fraction 63-90

μm placed in the chamber would be trapped by the weighted cover slip. Trapping the particle in this manner restricts axial swelling and ensures a fixed volume of swelling (figure 5.3). As a consequence, only radial swelling occurs and the extent of swelling can be calculated from a 2D image using image analysis.
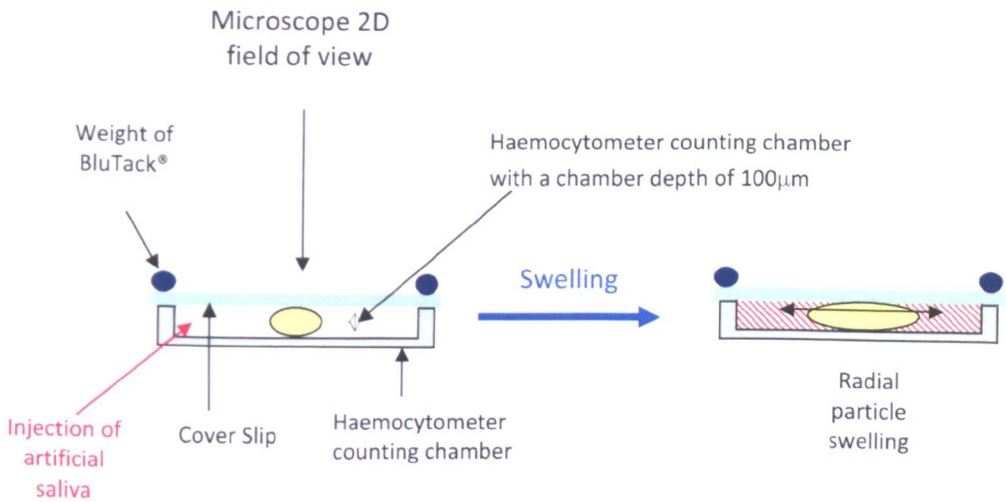
Figure 5.3 The experimental geometry used to visualise single particle swelling (adapted from Richardson 2002)

5.4.3 Method used for the visualisation of single particle swelling

A single HPMC particle was randomly selected from the 63-90 μm HPMC sieve fraction used for matrix manufacture and placed onto the centre of a haemocytometer counting chamber (Thoma, Hawksley, UK). The particle was covered by a cover slip and the cover slip weighted on either side by Blu-Tack® (Bostick Ltd, Leicester, UK). 15 μL of hydration fluid (either water or additive solution) was injected at the front of the chamber, close to the cover slip, using a micropipette. Capillary forces between the chamber surface and cover slip sucked fluid between the interface and immersed the single particle. Using an optical microscope (Nikon Labophot, x2 objective (Nikon UK Ltd Surrey, England), COHU High Performance CCD Camera (Brian Reece Scientific Ltd, Berkshire, UK) it was possible to visualise the radial swelling of individual particles in two dimensions. Image analysis software (Image Pro Plus v.6.2, Media Cybernetics, USA) captured a time sequence of 2D images of the swollen particle at pre-determined time periods (t). The extent of radial particle swelling was calculated by software measurements of the swollen area and used to determine the normalised swollen area as follows:

$$\text{Normalised area of particle at time } (t) = \frac{\text{(Particle area at time t (pixels) – Particle area at t=0 (pixels)}}{\text{Particle area at t=0 (pixels}}$$

Equation 5.1

5.4.4 Preparation of drug solutions

Solutions of diclofenac Na and meclofenamate Na (30 and 60 mM) were prepared in water in 100 ml volumetric flasks. 15 ml of the drug solution was added using a pipette to a scintillation vial containing the appropriate amount of Coomassie Blue dye. The vials were covered with aluminium

foil to avoid exposure to light and minimise photochemical reactions (e.g. photolytic oxidation). The solutions were stirred overnight to ensure an even distribution of the dye.

In the imaging experiments, the Coomassie blue dye allowed the differentiation of HPMC particles in the surrounding drug solution. The dye provides a dark background, enabling easier image acquisition and analysis and does not interact with HPMC particles at this concentration (Wong 2008).

5.4.5 Manufacture of hydrophilic matrix tablets

5.4.5.1 Sieving of HPMC

Fractionation of HPMC by sieving was carried out using the method described in section 3.2.6.1.

5.4.5.2 Formulation preparation

Formulation preparation was undertaken as described in section 3.2.6.2. The formulations of binary drug and HPMC matrices are shown in table 5.1

5.4.5.3 Manufacture of HPMC matrices

Manufacture of HPMC matrices was undertaken using the detailed method described in section 3.2.6.3 using a compression pressure of 180 MPa and 8 mm tablet punches (I Holland, Nottingham, UK).

	Matrix composition	
Percentage of drug (%)	Drug (mg)	HPMC (mg)
0	0	200
10	20	180
30	60	140
50	100	100
70	140	60
80	160	40

Table 5.1 The composition of the binary matrix tablets used in this study

Matrices weighed 200± 5mg, compressed to 180 MPa. Details of matrix manufacture are described in 3.2.6.3

5.4.5.3 Matrix storage

Matrices were stored under the conditions described in section 3.2.6.4.

5.4.5.4 Sample cell geometry for confocal and video microscopy imaging

As a hydrophilic matrix hydrates, a gel layer is formed around the dry core which expands as the level of polymer hydration increases. During this expansion, a fixed imaging position is difficult to achieve as the movement of the matrix may take the emerging gel layer out of the focal plane. To overcome this limitation, the matrices were held in place using the "Fixed

Optical Geometry" (FOG) Apparatus. Figure 5.4 is a schematic diagram of the experimental geometry. It is designed to hold a matrix tablet in a stationary position for imaging, in a similar manner to devices used in other imaging studies (Colombo *et al.* 1999, Bettini *et al.* 2001).

To reduce the effect of the apparatus on water ingress during the initial period of hydration, the Perspex discs were coated with Sigmacote (Sigma, Poole, UK), a chlorinated organopolysiloxane. This made the Perspex discs highly water repellent and prevented hydration media seeping between the surface of the tablet and the Perspex disc. The apparatus and the hydration media were maintained at 37 ±1ºC throughout the experiment by means of a water-jacketed beaker.

5.4.6 Experimental method for confocal imaging of matrix tablets

All confocal imaging was performed using a BioRad MRC-600 confocal microscope (Biorad, Hemel Hempstead, UK) equipped with a 15 mW Krypton Argo laser attached to a Nikon Optiphot upright microscope. The excitatory laser line 488 nm (15 mW) was used for all experiments and fluorescence emission was captured at 510 nm using a BHS filter block.

The setting of the confocal microscope to standardise the background was optimised during preliminary experiments at a pixel intensity of 5 (on a scale of 0-255) and the gain was set to provide the brightest possible image without excessive saturation. The confocal aperture was set at 2 as optimised in the Bajwa (2006) work to produce sufficient fluorescent detail. Capture of the single wavelength images was as a 512 x 768 pixel array, with each pixel coded 0-255 for fluorescent intensity using a continuous grey-scale false look-up table (LUT). To improve the signal to noise ratio, images were the average of three scans (Kalman averaging). The lens used was an x4/0.13NA air lens (Nikon, UK).
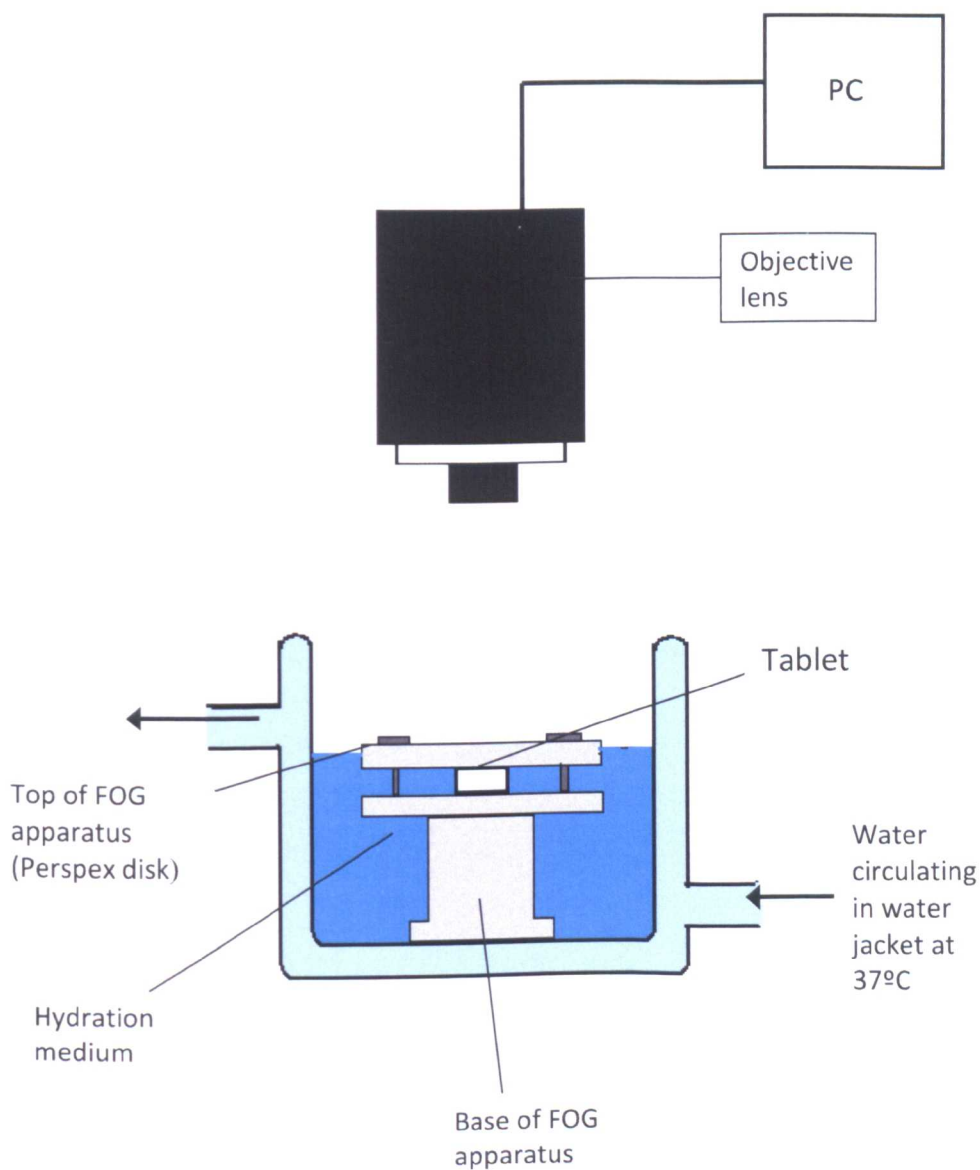
Figure 5.4 Schematic diagram of the experimental geometry used during confocal imaging (adapted from Bajwa *et al.* 2006)

Matrices were hydrated in either degassed water or 0.9% w/v NaCl solution maintained at 37°C using a geometry which allowed the tablets to be observed from above while undergoing hydration at the radial surface.

5.4.7 Image analysis

Measurements of gel layer thickness from the confocal images were carried out using Image Pro Plus, version 6.2 (Media Cybernetics, Maryland, USA). A grid of 10 evenly spaced horizontal lines was superimposed over the images in the same position and measurements were taken along the grid lines between the defined boundaries and averaged (n = 10) for each time interval. Experiments were performed in triplicate.

5.4.8 Matrix tablet disintegration testing

Disintegration testing of HPMC matrix tablets was undertaken using a four station Erweka USP disintegration testing apparatus (Copley Scientific, Nottingham, UK) using the method detailed in section 3.2.7.

5.5 Results

The effect of dissolved diclofenac Na and meclofenamate Na on HPMC particle swelling was investigated upon hydration in water and 0.9% w/v NaCl. The underlying rationale for exploring swelling in both media was the observation that the drug/HPMC interaction was influenced by NaCl in solution (section 4.5.6).

5.5.1 The effect of drugs on HPMC particle swelling and coalescence

Figure 5.5 shows the swelling of an individual particle of HPMC and figure 5.6 shows the coalescence of HPMC particles in water. Distinctive features can be seen in both experiments. In the case of individual particle swelling, there was rapid expansion of the particle swollen area in the first 15 seconds of hydration. The swollen area of the particles was seen to increase with time, with the exterior boundary of the swollen particle becomingly progressively less distinct from the swelling medium.

In the polymer particle coalescence experiments (figure 5.6), the swelling behaviour of individual particles was replicated but as the boundaries between particles met, there was a gradual loss of a distinct interface as hydration proceeded. Eventually, a continuous phase of swollen particles was seen to form. Measurements were made in 30 mM and 60 mM drug solutions (figure 5.7). It can be seen that the swelling was increased in a concentration-dependent manner in meclofenamate Na solutions but was suppressed in a in diclofenac Na solutions.

Unhydrated HPMC particle

Periphery of swollen HPMC particle
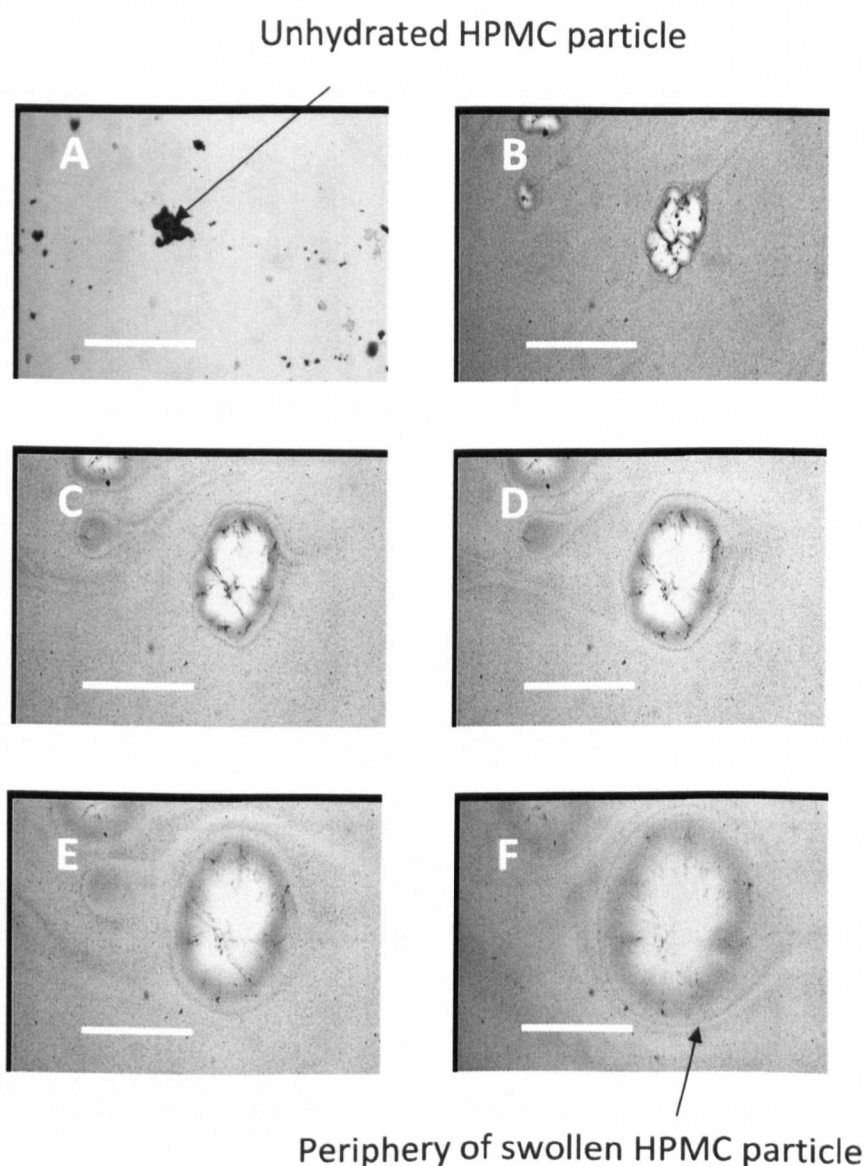
Figure 5.5 Real-time observation of single HPMC particle swelling using 0.003M Coomassie blue as a visualisation aid

(A) 0 minutes (B) 15 seconds post-hydration (C) 30 seconds post-hydration (D) 60 seconds post-hydration, (E) 3 minutes post-hydration, (F) 5minutes.

Scale bar 200 μm
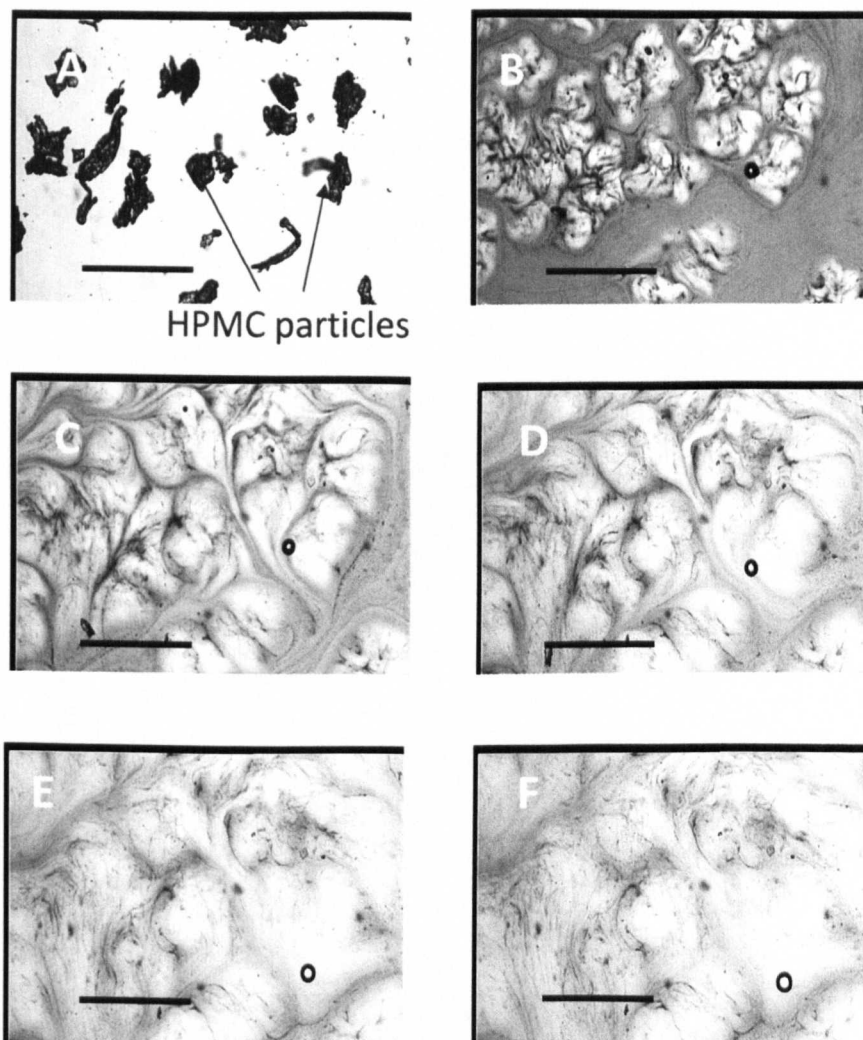
HPMC particles

Figure 5.6 Real-time observation of HPMC particle coalescence using 0.003M Coomassie blue as a visualisation aid

(A) 0 minutes (B) 15 seconds post-hydration (C) 30 seconds post-hydration (D) 60 seconds post-hydration, (E) 3 minutes post-hydration, (F) 5minutes post-hydration.

Scale bar 200 μm
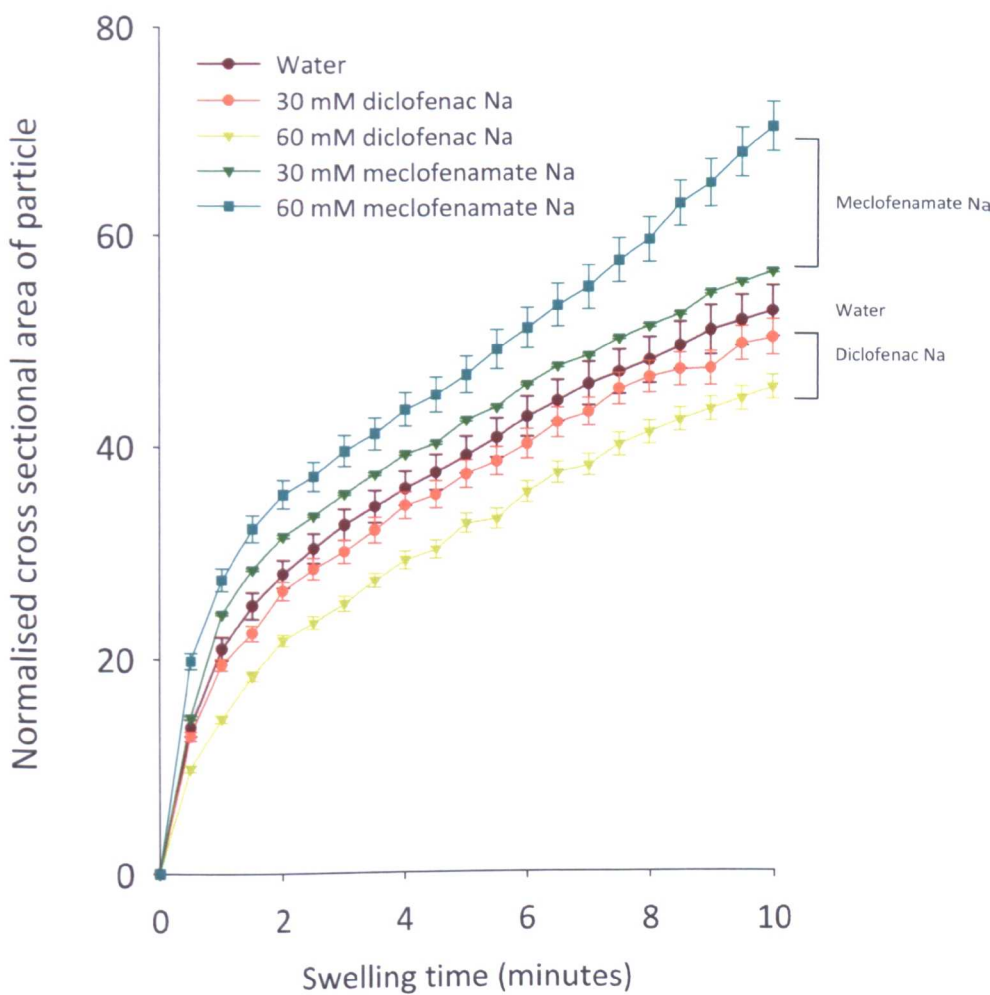
Figure 5.7 The swelling of individual HPMC particles in 0.003M Coomassie blue solution as a function of drug concentration

Swelling at 20±1°C, mean (n=10) ± 1SEM. Definition of normalised cross-sectional area in section 5.4.3.

5.5.2 Early gel layer formation and growth in HPMC hydrophilic matrices

Figure 5.8 shows a time series of fluorescent images of gel layer development in water. The images obtained show the development of three distinct regions as described by Bajwa *et al.* (2006): **B1**- the intense fluorescent boundary at the periphery of the matrix, **B2**- an intermediate region which comprised of domains exhibiting little fluorescence, and **B3**- a network of penetrating towards the dry core of the matrix (figure 5.9). For a detailed interpretation of polymer hydration and behaviour in each of the regions, the reader is directed to this paper. For the purposes of this thesis, only the salient points will be considered.

In our experiments, the innermost network region **(B3)** was visible immediately on contact of the matrix with the hydration medium. Bajwa *et al.* (2006) have suggested that this region may highlight the rapid uptake of the hydration medium by capillary action into the pores of the matrix. It also provided a measure of fluorophore penetration into the tablet core. The highly fluorescent boundary at the periphery of the matrix **(B1)** was a consistent feature throughout the time series. This region is an area of intense fluorescence as a result of the molecular access provided by high polymer hydration and where the polymer is disentangling and dissolving. The outer edge of B1 provides a boundary which, by superimposing the boundary of the dry tablet, can be utilised to measure the radial gel layer swelling kinetics in the early stages of matrix hydration.
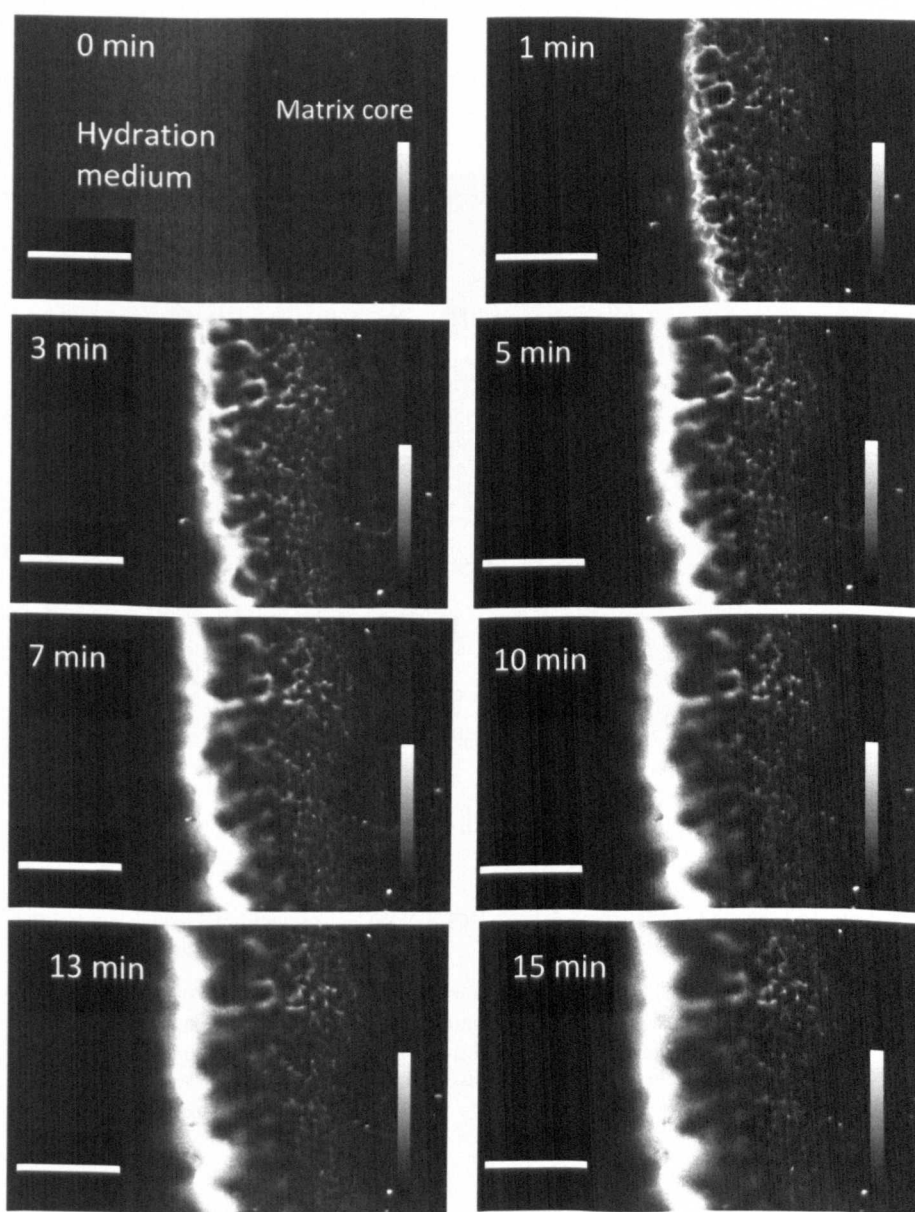
Figure 5.8 Fluorescence images of 100% w/w HPMC matrices hydrating in water

The images are coded for fluorescence intensity from white (highest) to black (lowest) as indicated by the wedge. The bright regions indicate areas of high fluorescence, highlighting regions of polymer hydration where the fluorophore has penetrated and interacted with the cellulose backbone. Matrices were hydrated for 15 minutes in 0.008% w/v Congo red maintained at 37 °C ± 1ºC. Ex488/Em>510 nm. Scale bar = 500 µm.
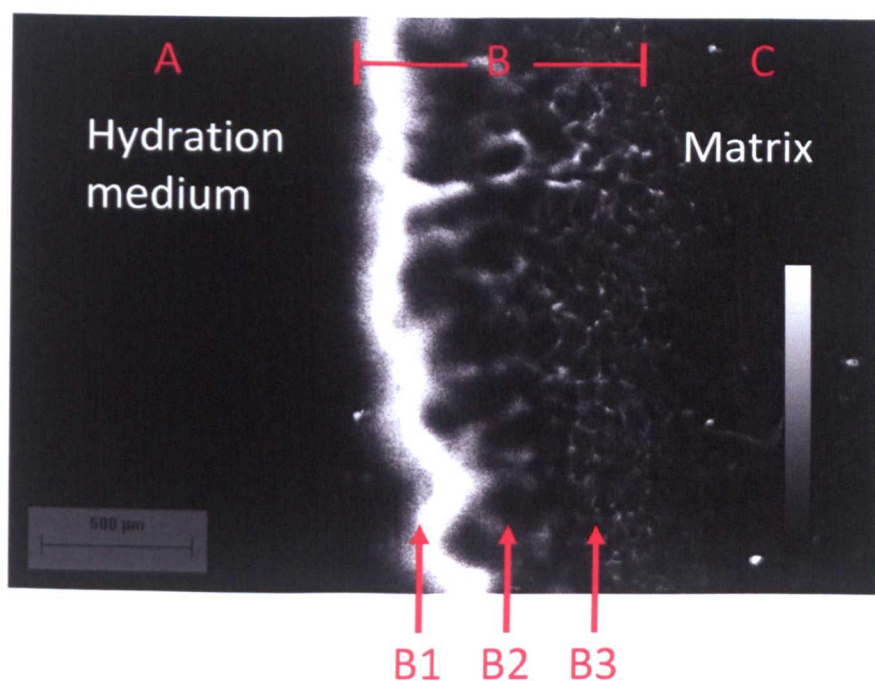
Figure 5.9 A confocal image of 100% HPMC tablet hydrating in water annotated with the key regions

Region A is the hydration medium, region B is the fluorescent areas within the matrix and region C is the core of the tablet. Regions B1, B2 and B3 are sub-sections within the fluorescent region (refer to text for explanation of the different regions).

Image taken after 5 minutes, hydrated in 0.008% Congo red at 37°C. Ex488/Em>510 nm. Scale bar = 500 μm.

The intermediate fluorescent region **B2** contributes significantly to the matrix swelling. From the earliest time points, the B2 region is characterised by non-fluorescent domains interconnected with strands of fluorescence. The pattern is indicative of that observed in region B3, with the fluorescent strands possibly outlining individual particles or groups of HPMC particles. If this rapidly swelling region is compared to the position of the original dry matrix then it can be seen that (i) swelling is originating from very near to the matrix surface and (ii) behind the boundary, the pattern of fluorescence changes very little. This suggests that the surface particles contribute disproportionately to matrix swelling in the early formation of the gel layer. This finding reflects previous work from bead tracking, which showed the outermost layer of a xanthan hydrophilic matrix also contributed disproportionately to gel layer formation (Adler *et al.* 1999).

5.5.2.1 The effect of polymer dilution on early gel layer formation and growth in HPMC hydrophilic matrices

As a control for assessing the possible effects of the drugs, the influence of reducing the level of HPMC in the hydrophilic matrices on the gel layer formation was determined (figure 5.10). The level of polymer was reduced by the addition of silicon dioxide (SiO_2), a compound with very low solubility (0.012g in 100 ml) and which was found to have limited water uptake (<1% over 4 weeks). It can be seen up to the very highest SiO_2 content (80%w/w), the gel layer appeared to form normally, suggesting that a polymer content of at least 30% w/w forms a functional gel layer, with the 'classical features' described above for a 100% HPMC matrix tablet.

Figure 5.10 The effect of incorporating silicon dioxide in the matrix on the evolution of the HPMC gel layer microstructure after 1, 5 and 15 minutes.
The images are coded for fluorescence intensity from white (highest) to black (lowest). Dotted line depicts the dry tablet boundary. Hydration medium maintained contained 0.008% w/v Congo red at 37°C. Ex488>510 nm. Scale bar = 500 µm

5.5.2.2 The effect of drugs on the swelling and gel layer formation in water

Figure 5.11 shows the effect of increasing the diclofenac Na content and decreasing the HPMC content on the developing microstructure of the gel layer. Figure 5.12 and figure 5.13 shows a focus on 50% and 80% w/w diclofenac Na matrices and are annotated with the key features to provide clearer illustration of the effect of the drug. Although there appeared to be gel layer formation at all diclofenac Na contents, there was an overall reduction in gel layer swelling and expansion with respect to dry core as the level of diclofenac Na was increased within the matrix (figure 5.14). The region B2 appeared to be most affected (figure 5.12 and figure 5.13) in comparison with the matrices containing the same level of HPMC with silicon dioxide. This is the region where columnar swelling and growth occurs, and the changes observed suggest that diclofenac Na was having a reductive effect on particle swelling and growth. This assertion is supported by the single particle work in section 5.5 which shows how single particle swelling was suppressed by increasing concentration of this drug.

Figure 5.11 The effect of incorporating diclofenac Na in the matrix on the evolution of the HPMC gel layer microstructure after 1, 5 and 15 minutes.
The images are coded for fluorescence intensity from white (highest) to black (lowest). Dotted line depicts the dry tablet boundary. Hydration medium maintained contained 0.008% w/v Congo red at 37°C. Ex488>510 nm. Scale bar = 500 μm

Reduction in fluorescence at the matrix periphery compared to same content HPMC with SiO_2

Less clarity in the intermediate swelling region with notable absence of clear columnar swelling and growth

Overall reduction in gel layer growth with respect of the dry matrix boundary

Figure 5.12 The effect of incorporating 50% w/w diclofenac Na in the matrix on the evolution of the HPMC gel layer microstructure after (A) 1, (B) 5 and (C) 15 minutes

The images are coded for fluorescence intensity from white (highest) to black (lowest). Dotted line depicts the dry tablet boundary. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Ex488>510 nm. Scale bar = 500 μm

Reduction in fluorescence at the matrix periphery

Loss of a clear intermediate swelling region with notable absence of clear columnar swelling and growth

Overall reduction in gel layer growth with respect of the dry matrix boundary

Figure 5.13 The effect of incorporating 80% w/w diclofenac Na in the matrix on the evolution of the HPMC gel layer microstructure after (A) 1, (B) 5 and (C) 15 minutes
The images are coded for fluorescence intensity from white (highest) to black (lowest). Dotted line depicts the dry tablet boundary. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Ex488>510 nm. Scale bar = 500 μm
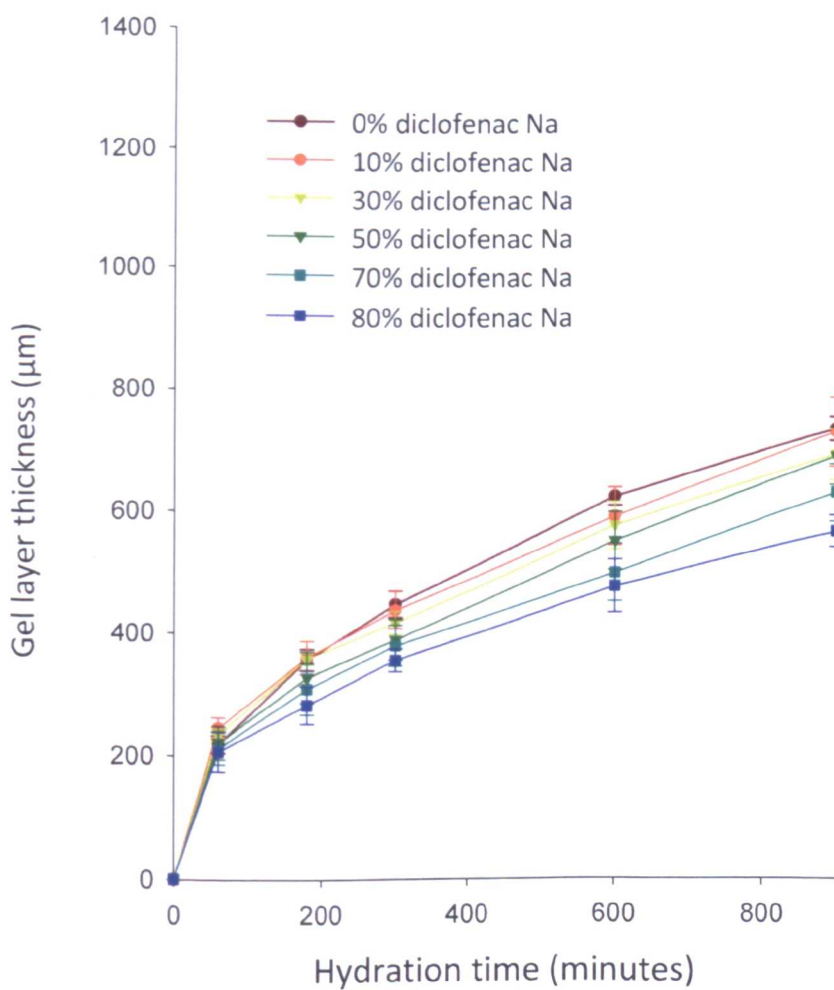
Figure 5.14 The effect of drug loading on the radial gel layer growth in HPMC matrices containing diclofenac Na
Hydration in 0.008% w/v Congo red at 37°C. Gel layer thickness measured from dry tablet boundary to the edge of region B1. Mean (n=3) ±1 SD

Figure 5.15 shows the effect of increasing meclofenamate Na content on the morphology of the HPMC gel layer when hydrated in water. As the meclofenamate Na content was increased within the matrix, there was a progressive change in the gel layer microstructure. This begins to occur with 50% w/w meclofenamate content in the matrix (figure 5.16) and is most clearly shown in the series of images of 80% w/w meclofenamate Na matrices in figure 5.17. The gel layer appeared increasingly more diffuse, with less controlled swelling of individual HPMC particles. The highly fluorescent region lost its contrast with the remainder of the gel layer with the higher meclofenamate Na content. In addition, there was extensive expansion with respect to the dry matrix boundary. The overall matrix gel layer growth with respect to the dry matrix is shown in figure 5.18. In contrast with diclofenac Na matrices, it showed an increase in the gel layer growth with increasing meclofenamate Na content. This increased gel layer growth with less HPMC content suggests a more expansive gel layer but with less HPMC concentration within the gel layer and consequently less barrier function. This hypothesis was supported by images of the receding matrix core behind the dry boundary line with higher meclofenamate Na content, suggesting enhanced erosion of the matrix core.
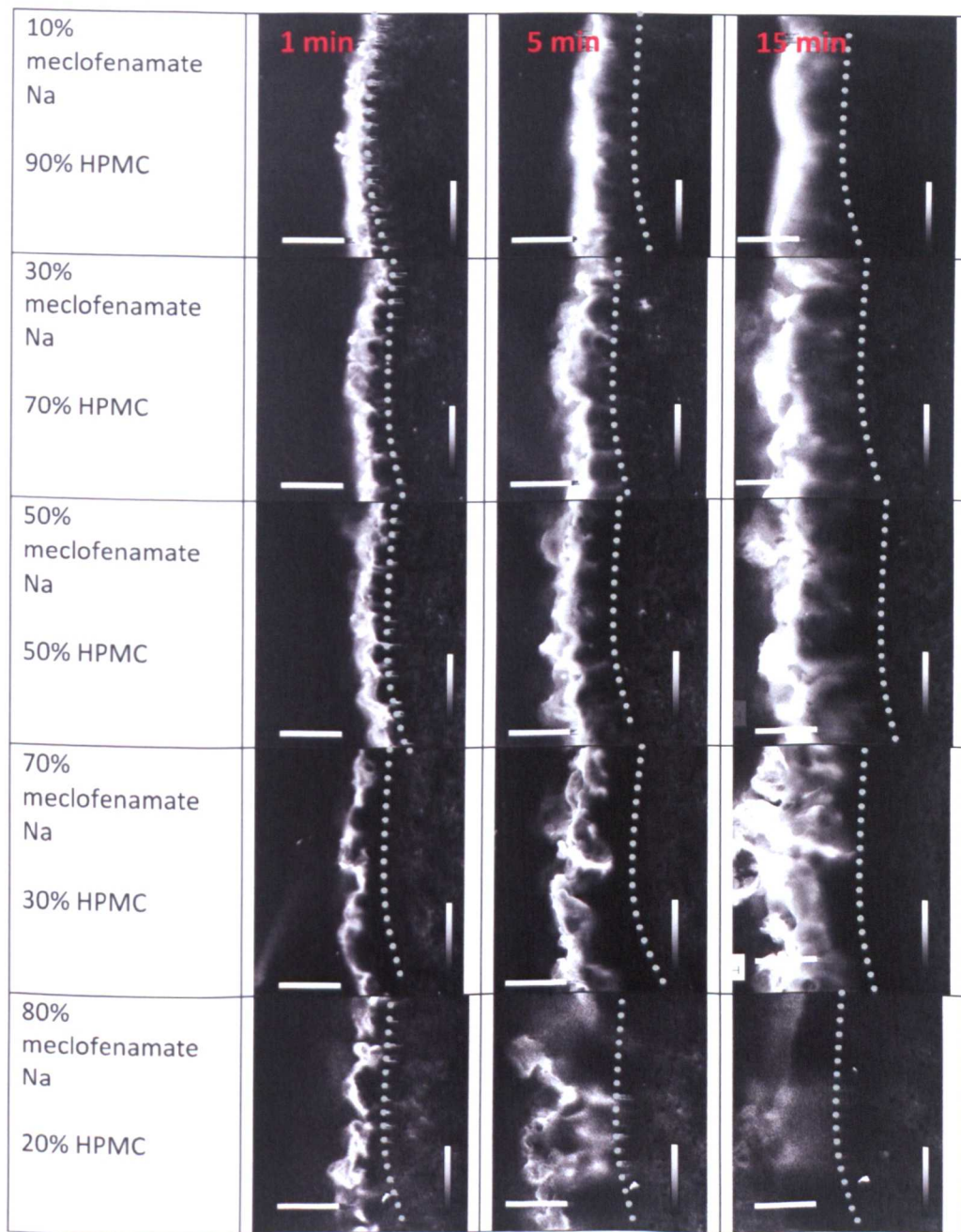
Figure 5.15 The effect of incorporating meclofenamate Na in the matrix on the evolution of the HPMC gel layer microstructure after 1, 5 and 15 minutes
The images are coded for fluorescence intensity from white (highest) to black (lowest). Dotted line depicts the dry tablet boundary. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Ex488>510 nm. Scale bar = 500 μm

Reduction in fluorescence at the matrix periphery compared to control matrices with apparent lack of coherent barrier

Greater expansion in the intermediate swelling region. Large growth and expansion in comparison to the control matrices.

Increase in gel layer growth with respect of the dry matrix boundary with a more diffuse gel layer

Figure 5.16 The effect of incorporating 50% w/w meclofenamate Na in the matrix on the evolution of the HPMC gel layer microstructure after (A) 1, (B) 5 and (C) 15 minutes.
The images are coded for fluorescence intensity from white (highest) to black (lowest). Dotted line depicts the dry tablet boundary. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Ex488>510 nm. Scale bar = 500 μm

Reduction in fluorescence at the matrix periphery compared to control matrices with apparent lack of coherent barrier

Loss of control within the intermediate swelling region. Large growth and expansion.

Apparent erosion of the dry matrix core.

Increase in gel layer growth with respect of the dry matrix boundary with a clearly more diffuse gel layer
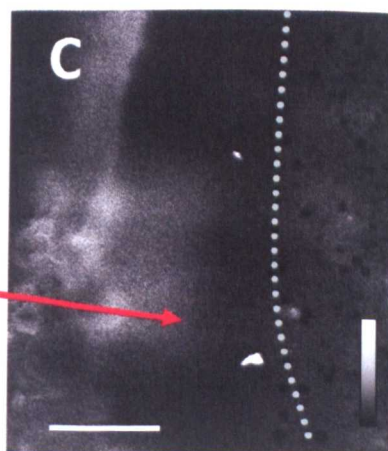
Figure 5.17 The effect of incorporating 80% w/w meclofenamate Na in the matrix on the evolution of the HPMC gel layer microstructure after (A) 1, (B) 5 and (C) 15 minutes.
The images are coded for fluorescence intensity from white (highest) to black (lowest). Dotted line depicts the dry tablet boundary. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Ex488>510 nm. Scale bar = 500 μm
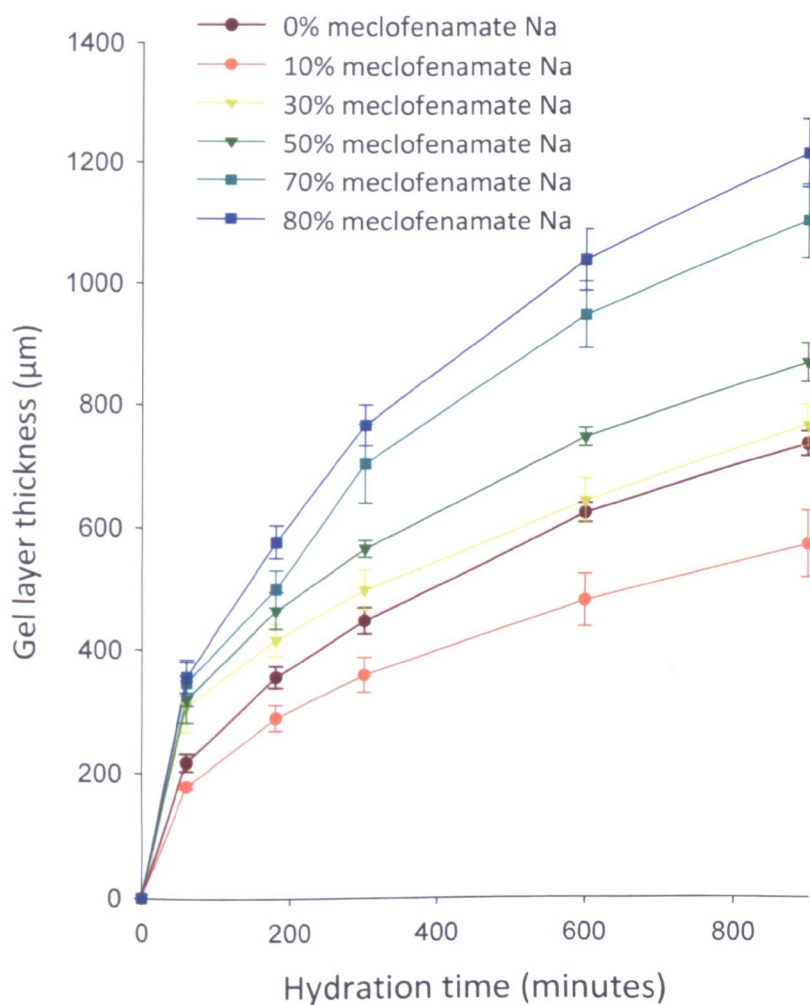
Figure 5.18 The effect of drug loading on the radial gel layer growth in HPMC matrices containing the indicated meclofenamate Na content
Hydration in 0.008% w/v Congo red at 37°C. Gel layer thickness measured from dry tablet boundary to the edge of region B1. Mean (n=3) ±1 SD

5.5.2.2 The effect of drugs on the swelling and gel layer formation in 0.9% w/v NaCl

Figures 5.19 to 5.24 show the same experiments conducted in section 5.5.2.2 but with the matrices hydrating in 0.9% w/v NaCl. This allowed direct correlation with the medium used in the dissolution studies of Banks presented in chapter 2.

In figure 5.19, it can be seen that as the level of diclofenac Na was increased within the matrix, there were changes apparent in early gel layer microstructure. The 'classic' gel layer morphology (i.e. a clear B1, B2 and B3 region) appeared to form in matrices containing up to 30% w/w diclofenac Na. The matrices of 50% diclofenac Na content and above showed disruption of gel layer formation. At 50% w/w diclofenac Na (figure 5.20), this disruption occurred at the earliest time points, with impaired hydration of HPMC particles at the surface of the matrix that are initially exposed to the hydration medium. As time proceeded, swelling eventually recovered as time proceeded, although the region at the boundary between the expanding matrix and the swelling medium was far greater. This has been postulated as the region where the polymer is highly plasticised by the hydration medium and begins to dissolve, facilitating fluorophore access (Bajwa *et al.* 2006).

Matrices containing over 70% w/w diclofenac Na exhibited a mass of discrete hydrated but non-swelling HPMC particles at the matrix periphery. The focus on 80% w/w diclofenac Na shows this more clearly in figure 5.21. The outward expansion of the matrix is clear evidence of polymer swelling, as this would provide the driving force for matrix growth. The images show little particle coalescence and formation of a functional diffusion barrier. The measurements of radial gel layer growth (figure 5.22) shows a loss of controlled radial swelling in 70% and 80% w/w diclofenac Na matrices.
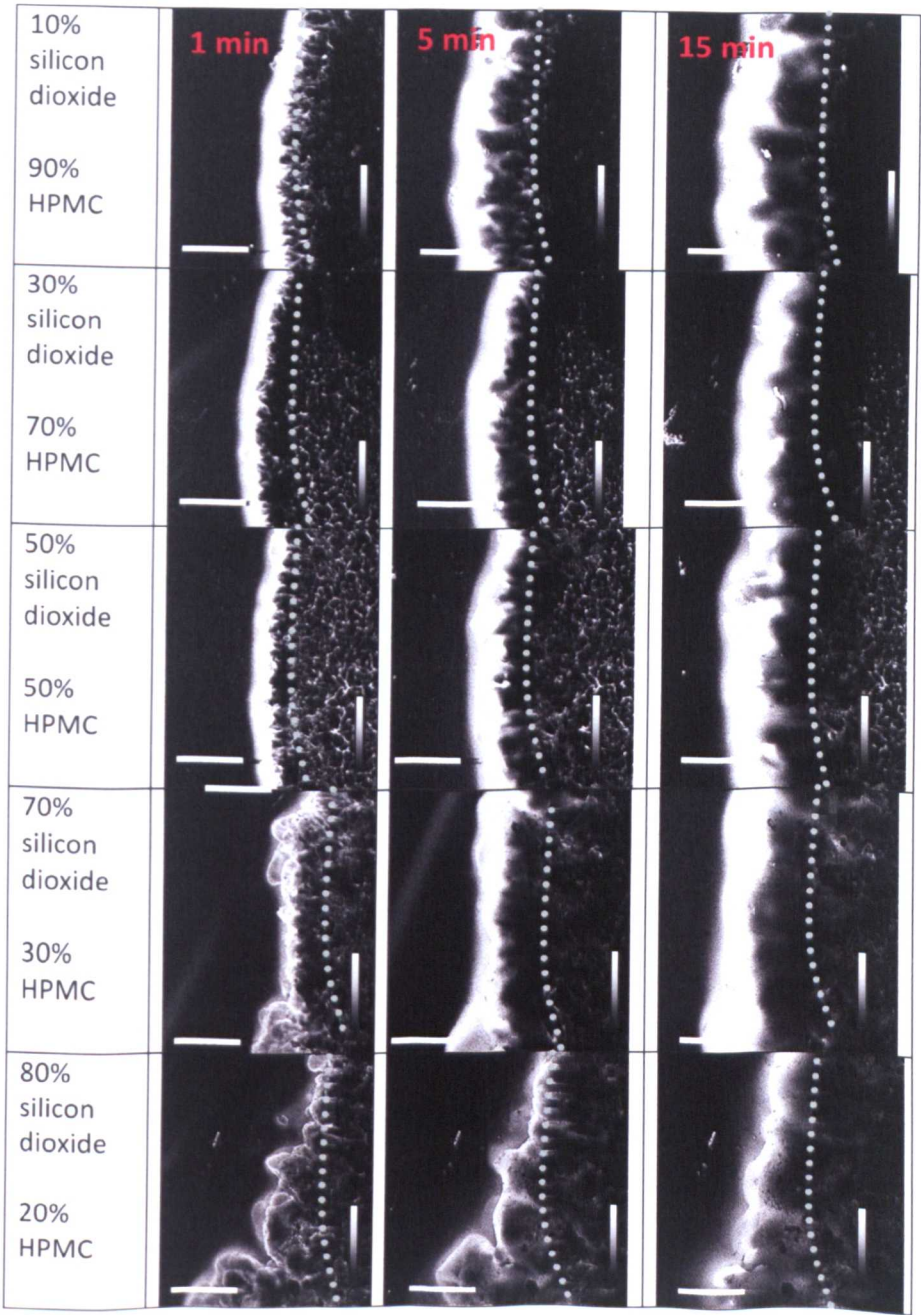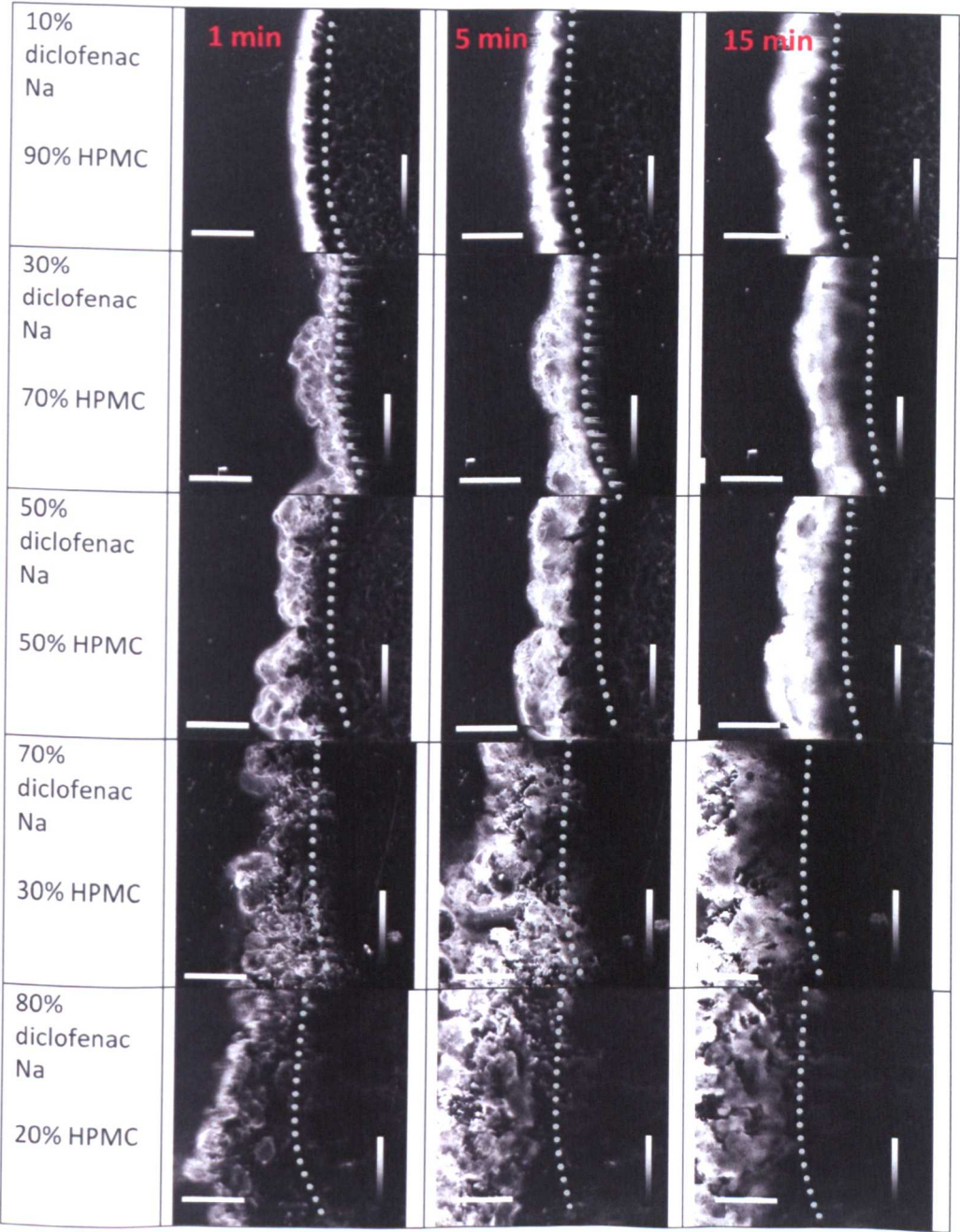
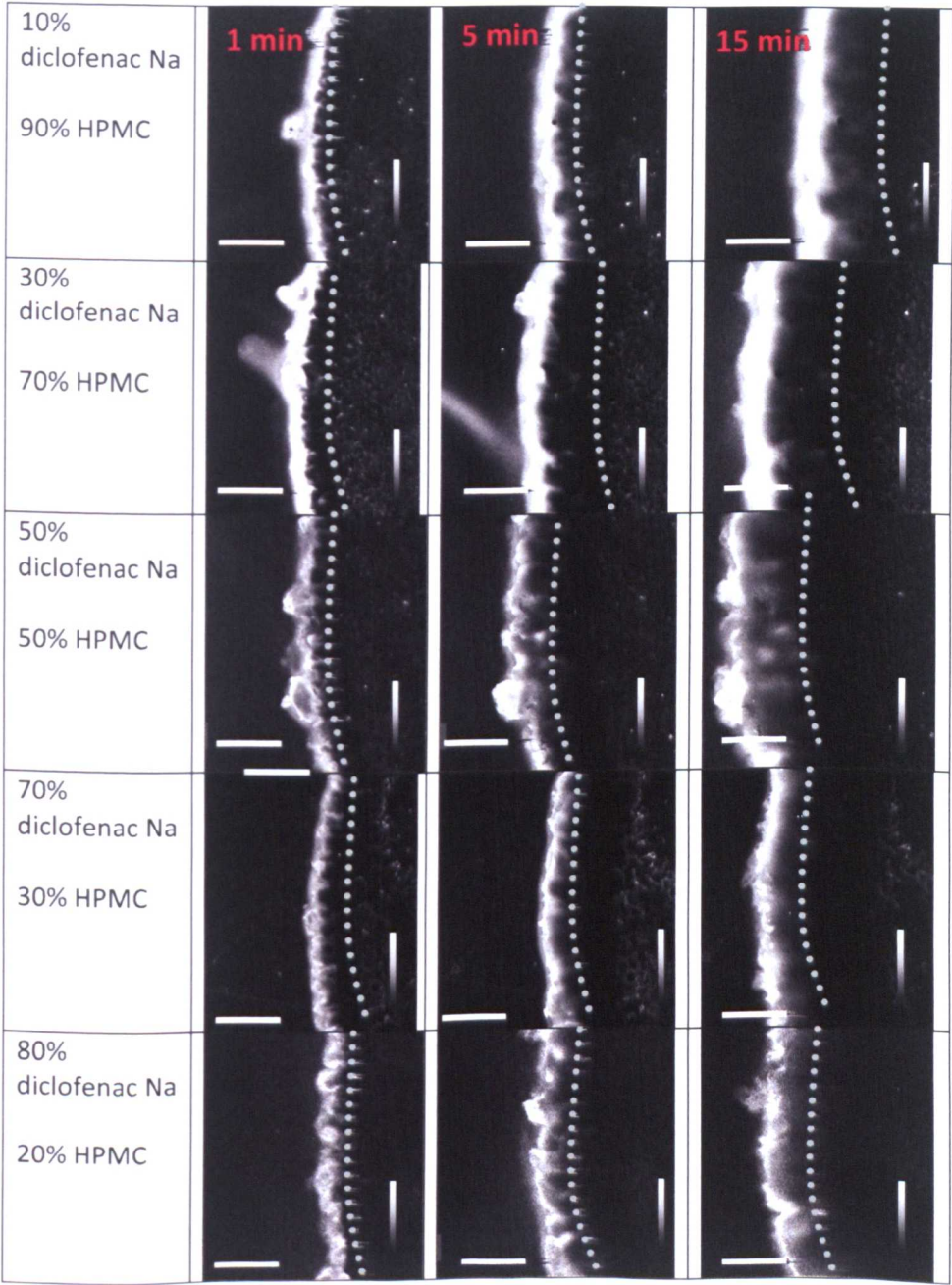**Figure 5.19 The effect of incorporating diclofenac Na in the matrix on the evolution of the HPMC gel layer microstructure after 1, 5 and 15 minutes hydration in 0.9% w/v NaCl**
The images are coded for fluorescence intensity from white (highest) to black (lowest). Dotted line depicts the dry tablet boundary. Hydration medium containing 0.9% w/v Congo red maintained at 37°C. Ex488>510 nm. Scale bar = 500 μm

Large swelling of the matrix in the first minute of hydration with respect to the dry tablet boundary compared with control matrices
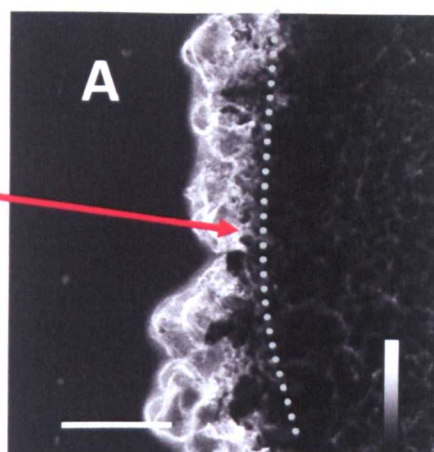
Some loss of a clear intermediate swelling region with absence of clear columnar swelling and growth
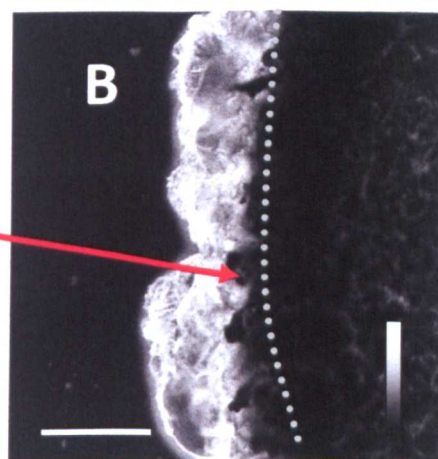
Some degree of recovery towards the end of the hydration period, although some reduction in individual particle coalescence
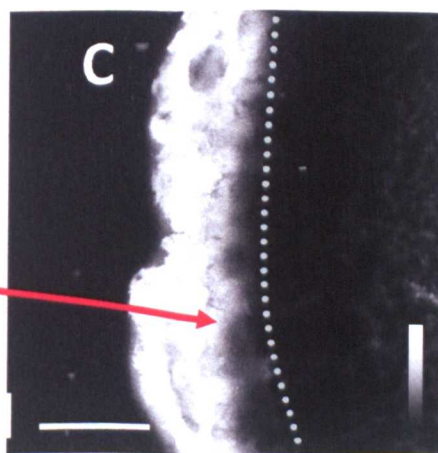
Figure 5.20 The effect of incorporating 50% w/w diclofenac Na in the matrix on the evolution of the HPMC gel layer microstructure after (A) 1, (B) 5 and (C) 15 minutes hydration in 0.9% w/v NaCl
The images are coded for fluorescence intensity from white (highest) to black (lowest). Dotted line depicts the dry tablet boundary. Hydration medium containined 0.008% w/v Congo red maintained at 37°C. Ex488>510 nm. Scale bar = 500 µm

Large swelling of the matrix in the first minute of hydration with respect to the dry tablet boundary

Loss of a clear intermediate swelling region with absence of clear columnar swelling and growth
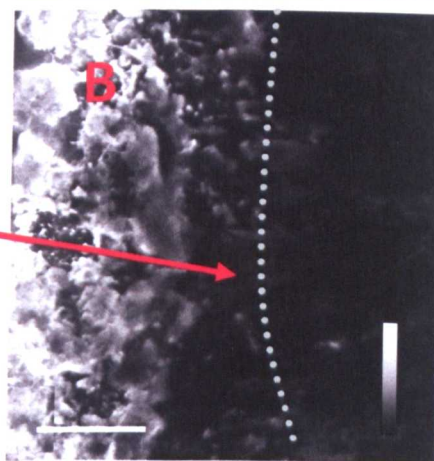
Mass of hydrated but non-swelling HPMC particles at the matrix periphery.
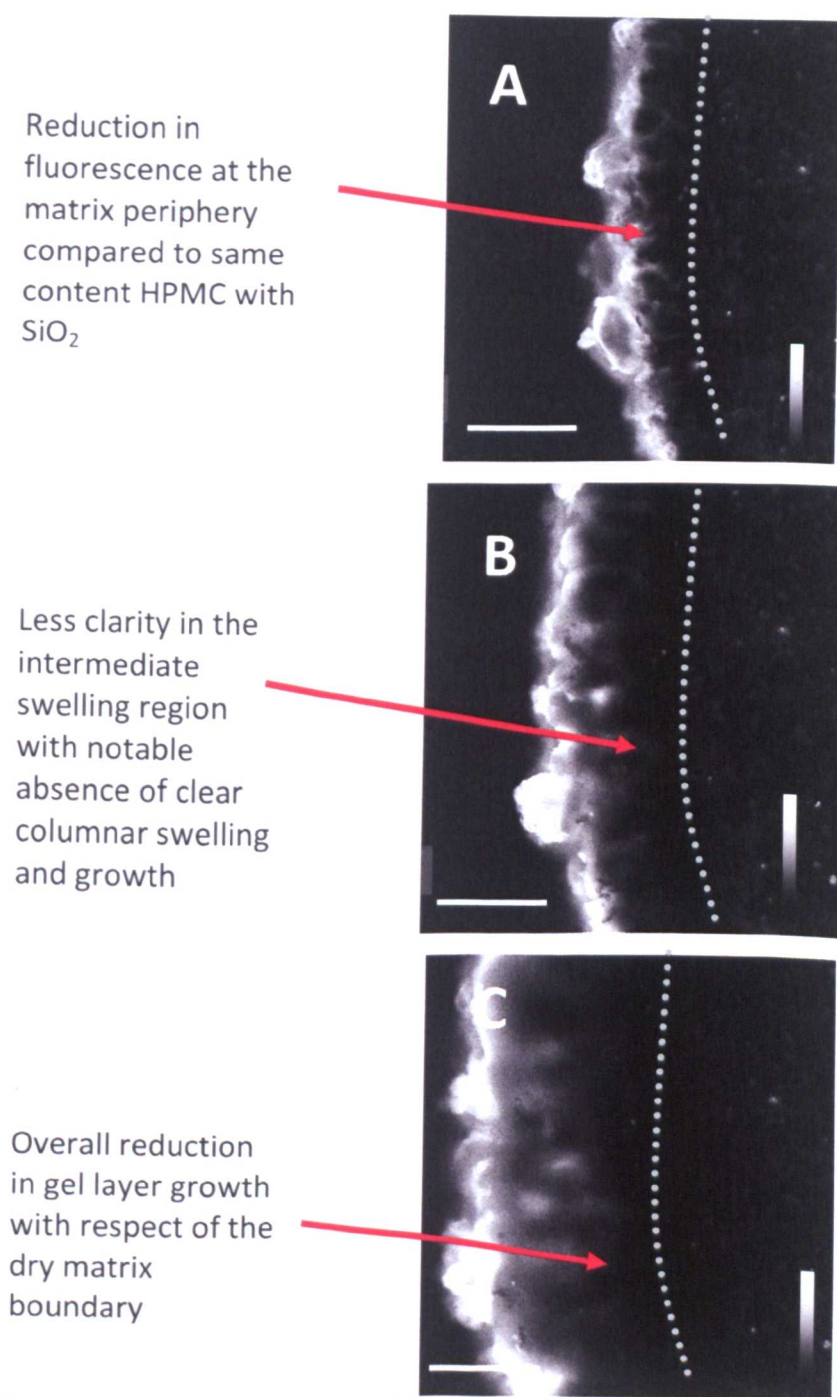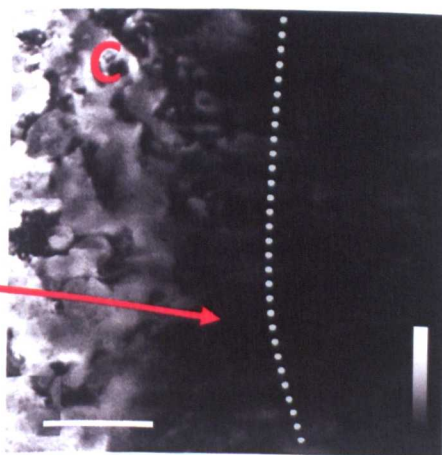
Little evidence of particle coalescence

Figure 5.21 The effect of incorporating 80% w/w diclofenac Na in the matrix on the evolution of the HPMC gel layer microstructure after (A) 1, (B) 5 and (C) 15 minutes hydration in 0.9% w/v NaCl
The images are coded for fluorescence intensity from white (highest) to black (lowest). Dotted line depicts the dry tablet boundary. Hydration medium contained 0.008% w/v Congo red maintained at 37°C. Ex488>510 nm. Scale bar = 500 μm
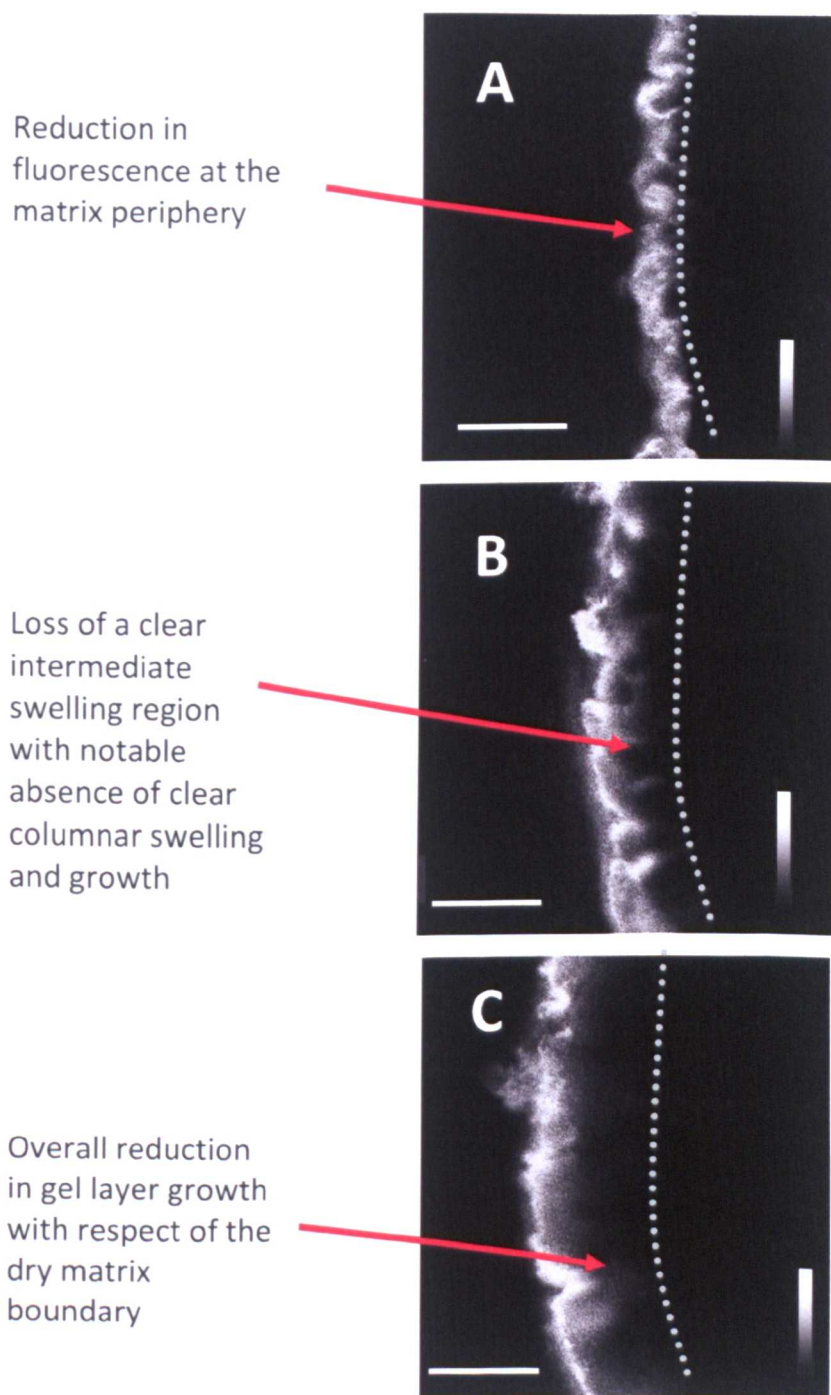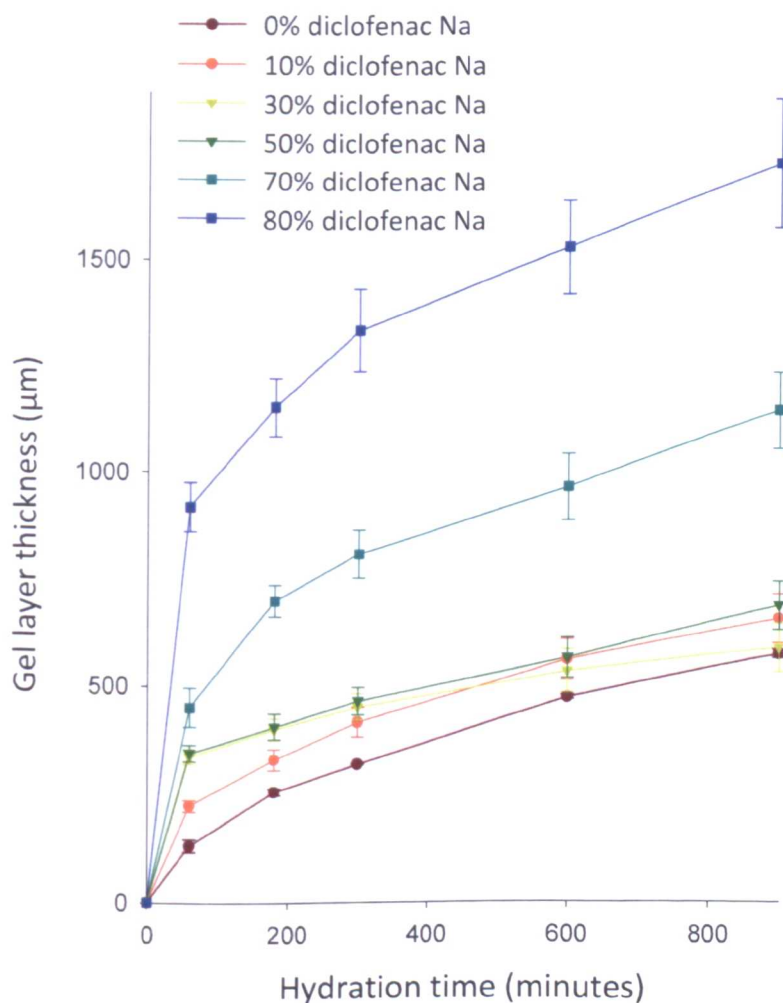
Figure 5.22 The effect of drug loading on the radial gel layer growth of HPMC matrices containing the indicated percentages of diclofenac Na in 0.9% w/v NaCl
Hydration in 0.008% w/v Congo red and 0.9% NaCl at 37°C. Gel layer swelling measured from dry tablet boundary to the edge of region B1. . Mean (n=3) ±1 SD

Figure 5.23 shows the effect of increasing meclofenamate Na content on the morphology and swelling of HPMC matrices hydration in 0.9 % w/v NaCl. As with the matrices hydrated in water, there appeared to be increased hydration of the HPMC particles within the gel layer with increasing meclofenamate Na content. In figure 5.24, it can be seen in that the morphology has changed clearly from matrices containing silicon dioxide and the same formulation hydrating in water. This may be a consequence of the surface activity of meclofenamate Na acting as a wetting agent for individual agent HPMC particles. However, when hydrated in NaCl, there was a distinct, highly hydrated region at the matrix periphery, overall matrix gel layer swelling was suppressed and there was a reduction in recession of the matrix core. This was most clearly shown when comparing the 80% w/w formulation shown in figure 5.25 with the same formulation hydrated in water depicted in figure 5.17. Although swelling and expansion was greater than diclofenac matrices, the general coherence of the gel layer appeared to improve with NaCl present in the hydration medium. The measurements of gel layer growth in figure 5.26 show that swelling was largely unaffected by increasing meclofenamate Na when swelling in 0.9% NaCl, in contrast with the same formulations swelling in water (figure 5.17) although clearly there are profound changes in the gel layer morphology.
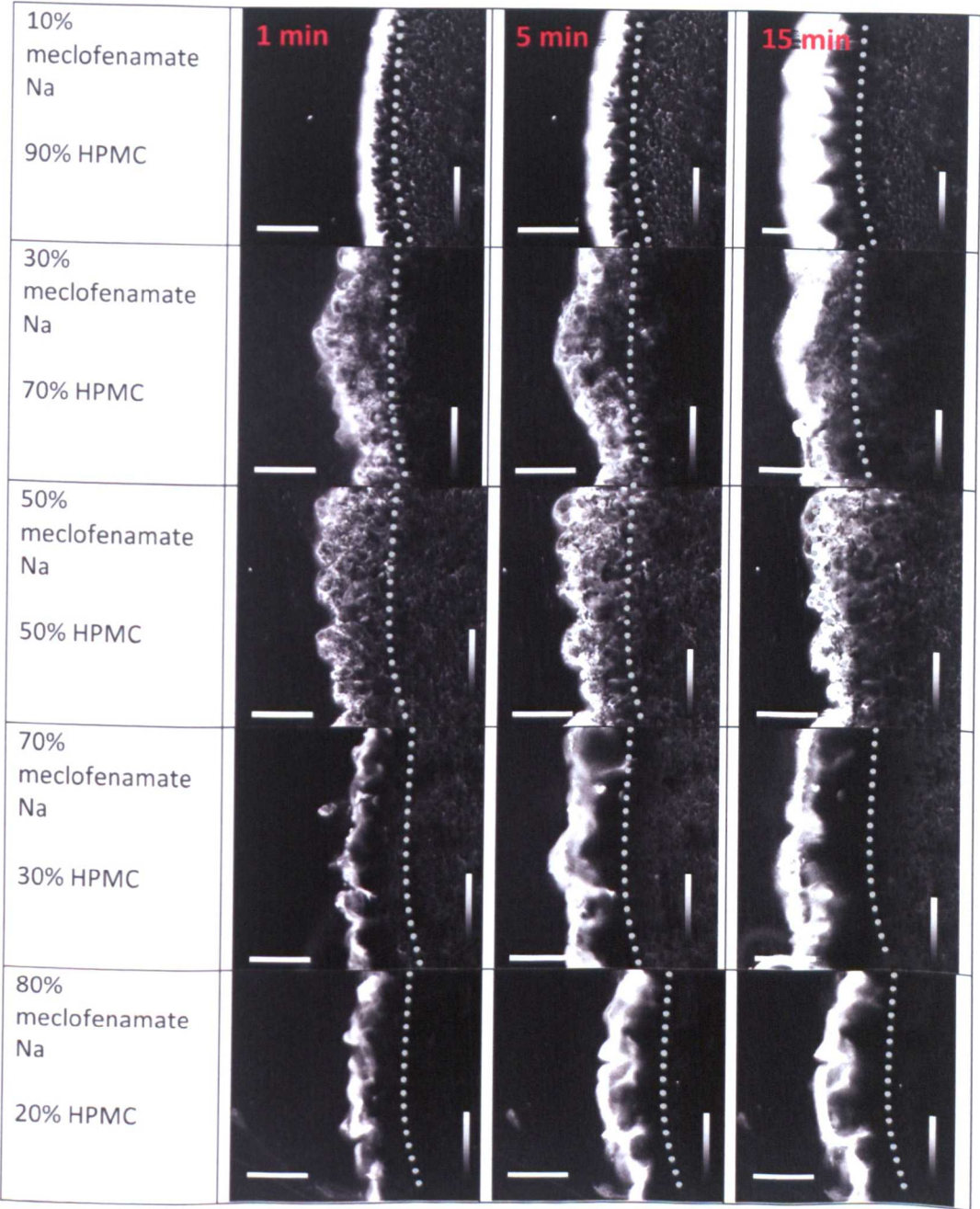
Figure 5.23 The effect of incorporating meclofenamate Na in the matrix on the evolution of the HPMC gel layer microstructure after 1, 5 and 15 minutes hydration in 0.9% w/v NaCl

The images are coded for fluorescence intensity from white (highest) to black (lowest). Dotted line depicts the dry tablet boundary. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Ex488>510 nm. Scale bar = 500 μm

Greater coherence than the same formulations hydrating in water
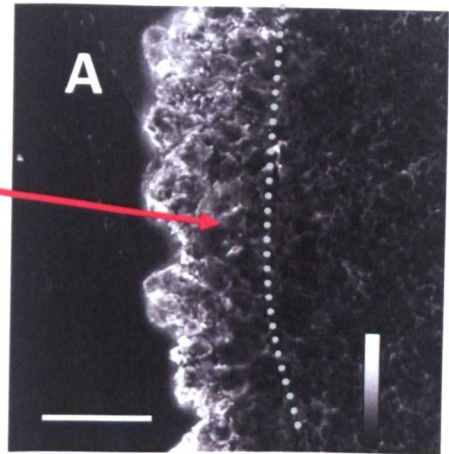
Greater control of swelling within the intermediate region than when swelling in water
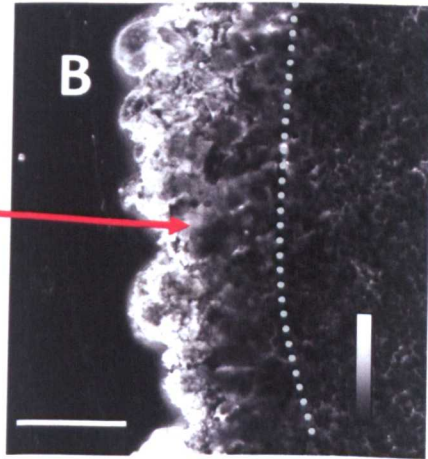
Gel layer appears thicker than control formulations and diclofenac Na matrices
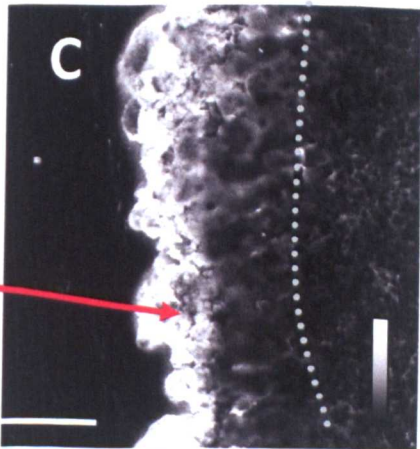
Figure 5.24 The effect of incorporating 50% w/w meclofenamate Na in the matrix on the evolution of the HPMC gel layer microstructure after (A) 1, (B) 5 and (C) 15 minutes hydration in 0.9% w/v NaCl
The images are coded for fluorescence intensity from white (highest) to black (lowest). Dotted line depicts the dry tablet boundary. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Ex488>510 nm. Scale bar = 500 μm

High level of fluorescence at the matrix periphery with greater coherence than the same formulations hydrating in water
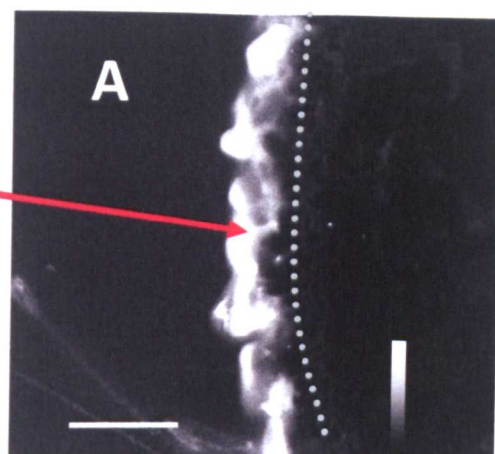
Greater control of swelling within the intermediate region than when swelling in water
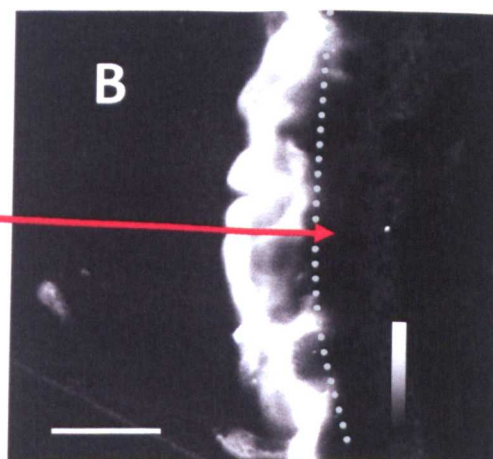
Apparent erosion of the dry matrix core but less than when hydrated in
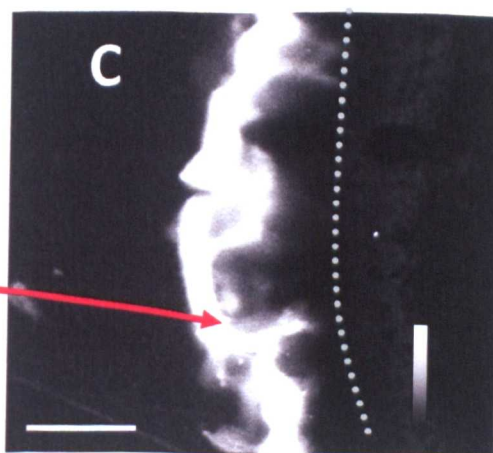
Decrease in gel layer growth with respect of the dry matrix boundary compared to water. However, clearly more diffuse gel layer than diclofenac
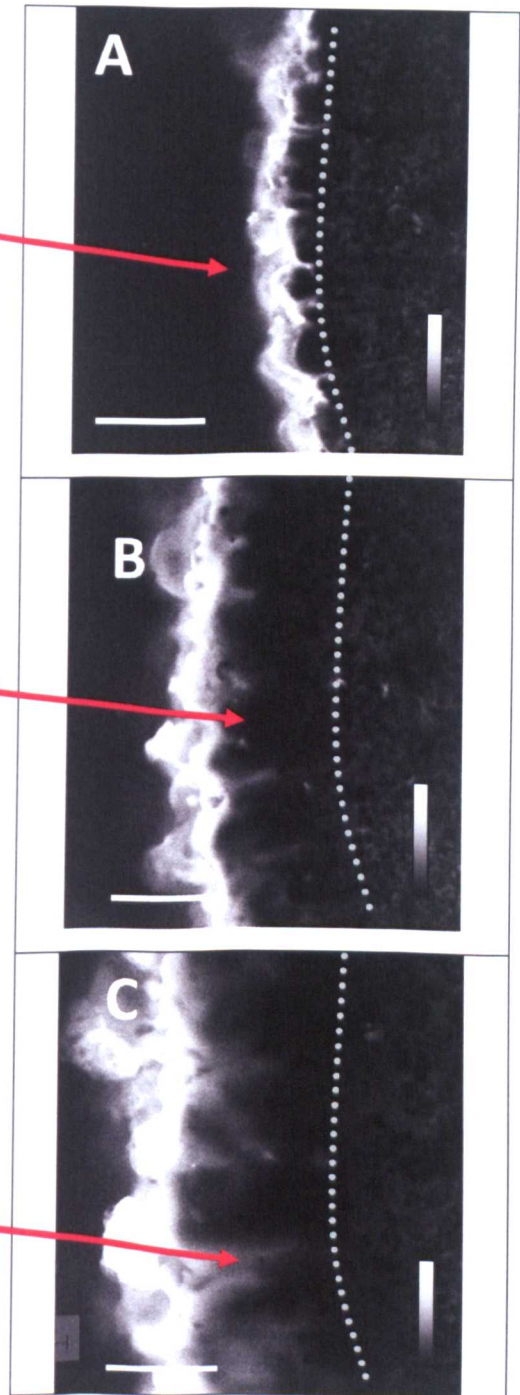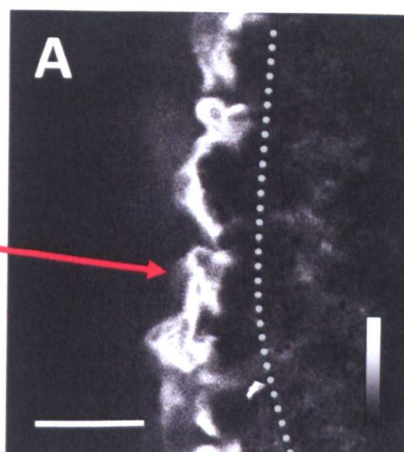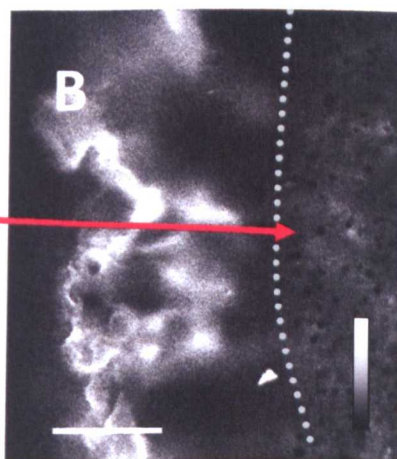
Figure 5.25 The effect of incorporating 80% w/w meclofenamate Na in the matrix on the evolution of the HPMC gel layer microstructure after (A) 1, (B) 5 and (C) 15 minutes hydration in 0.9% w/v NaCl
The images are coded for fluorescence intensity from white (highest) to black (lowest). Dotted line depicts the dry tablet boundary. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Ex488>510 nm. Scale bar = 500 μm
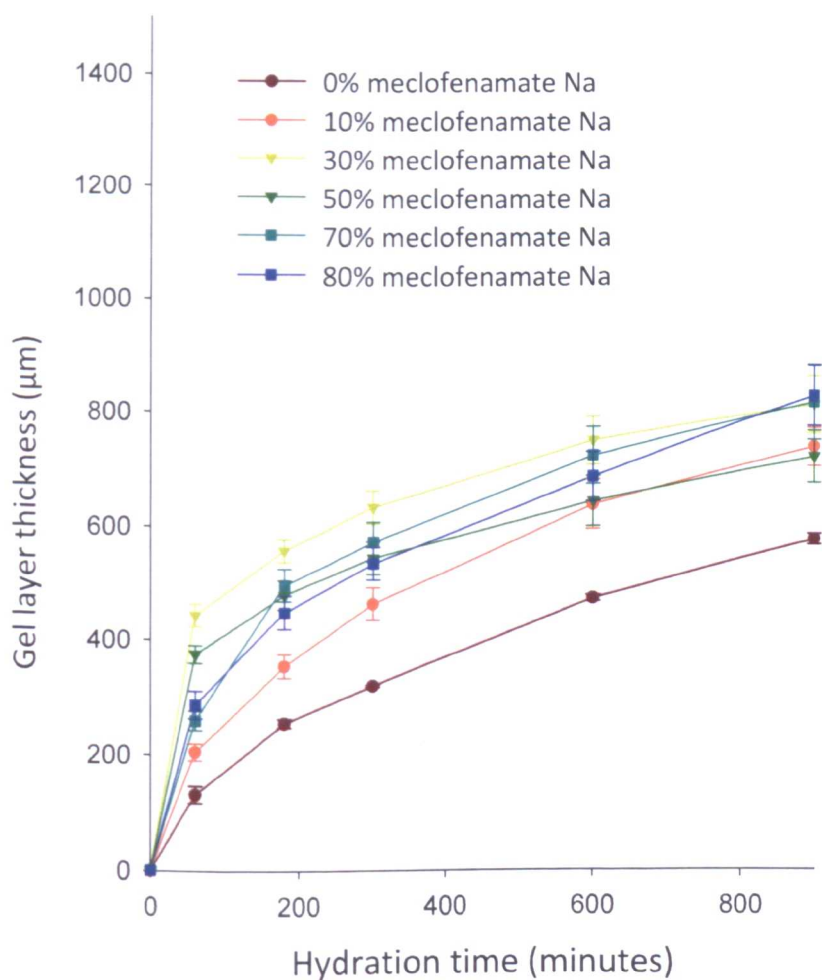
Figure 5.26 The effect of drug loading on the radial gel layer growth of HPMC matrices containing the indicated percentages of meclofenamate Na in 0.9% w/v NaCl
Hydration in 0.008% w/v Congo red and 0.9% NaCl at 37°C. Swelling measured from dry tablet boundary to the edge of region B1. Mean (n=3) ±1 SD

5.5.3 The effect of diclofenac Na and meclofenamate Na incorporation on the disintegration of HPMC matrices

Table 5.2 shows the effect of diclofenac Na and meclofenamate Na content on matrix disintegration when hydrated in water and in 0.9% w/v NaCl. Up to 50% w/w drug content, all the matrices resisted disintegration for the duration of the experimental period, irrespective of drug or type of hydration medium. For these matrices, there appeared to be sufficient HPMC content to overcome the burdens of internal drug and the external electrolyte in the hydration medium. However, different behaviour was seen at higher levels of drug content. At 70% w/w, matrices containing diclofenac Na remained intact in water but disintegrated in 0.9% NaCl after 60 minutes. This trend was reversed for meclofenamate Na matrices, with disintegration in water after 45 minutes but survival in 0.9% NaCl for the duration of the experimental period.

This difference in disintegration behaviour was even more apparent at 80% w/w drug loading. At this level, diclofenac Na matrices failed in both water (75 minutes) and saline (15 minutes). In contrast, meclofenamate Na matrices failed in both media but with increased durability with respect to NaCl concentration (15 minutes and 75 minutes in water and 0.9% NaCl respectively).

Tablet content (% w/w)		Disintegration times of matrices containing diclofenac Na (min)		Disintegration times of matrices containing meclofenamate Na (min)	
Drug	HPMC	Water	0.9% NaCl	Water	0.9% NaCl
0	100	>120	>120	>120	>120
10	90	>120	>120	>120	>120
30	70	>120	>120	>120	>120
50	50	>120	>120	>120	>120
70	30	>120	60	95	>120
80	20	75	20	15	75

Table 5.2 The disintegration times for HPMC containing diclofenac Na and meclofenamate Na in 0.9% NaCl and water
Disintegration data obtained in 900 ml at 37°C, observations made from 4 tablets and taken to the nearest minute

5.5.3.1 The effect of increasing electrolyte challenge on the disintegration of meclofenamate Na and diclofenac Na matrices

The earlier confocal images together with the results in table 5.1 suggested either synergistic or antagonistic effects between internal drugs with external electrolytes in the hydration medium. This was further explored by increasing the concentration of NaCl in the hydration medium and determining the effect on the disintegration times.

Figures 5.27-5.29 show the effect of increasing NaCl challenge on the disintegration of formulations containing 10% w/w, 50% w/w and 80% w/w meclofenamate Na and diclofenac Na. At 10% w/w incorporation (figure 5.27), there was little difference between the matrices, although both disintegrated at a lower threshold concentrations in comparison with a 100% HPMC matrix at 0.7 M NaCl.

At drug loadings of 50% w/w, clearer differences were seen between the drugs (figure 5.28). In the case of meclofenamate Na matrices, the disintegration threshold was not reached until 0.4M NaCl. Above this concentration, matrices disintegrated rapidly. In diclofenac Na matrices, the disintegration threshold was found to be between 0.256 M and 0.3 M NaCl.

At the highest level of drug loading (80% w/w) even clearer differences were apparent between the drugs (figure 5.29). Meclofenamate Na-matrices failed in water but as NaCl was introduced into the swelling medium, matrix integrity was maintained for the duration of the experimental period. The matrices exceeded the disintegration threshold of pure HPMC matrices (0.7 M). This suggests that meclofenamate Na afforded a protective effect to NaCl challenge. In contrast, diclofenac Na-containing matrices were found to disintegrate in all the swelling media, irrespective of the concentration of NaCl.
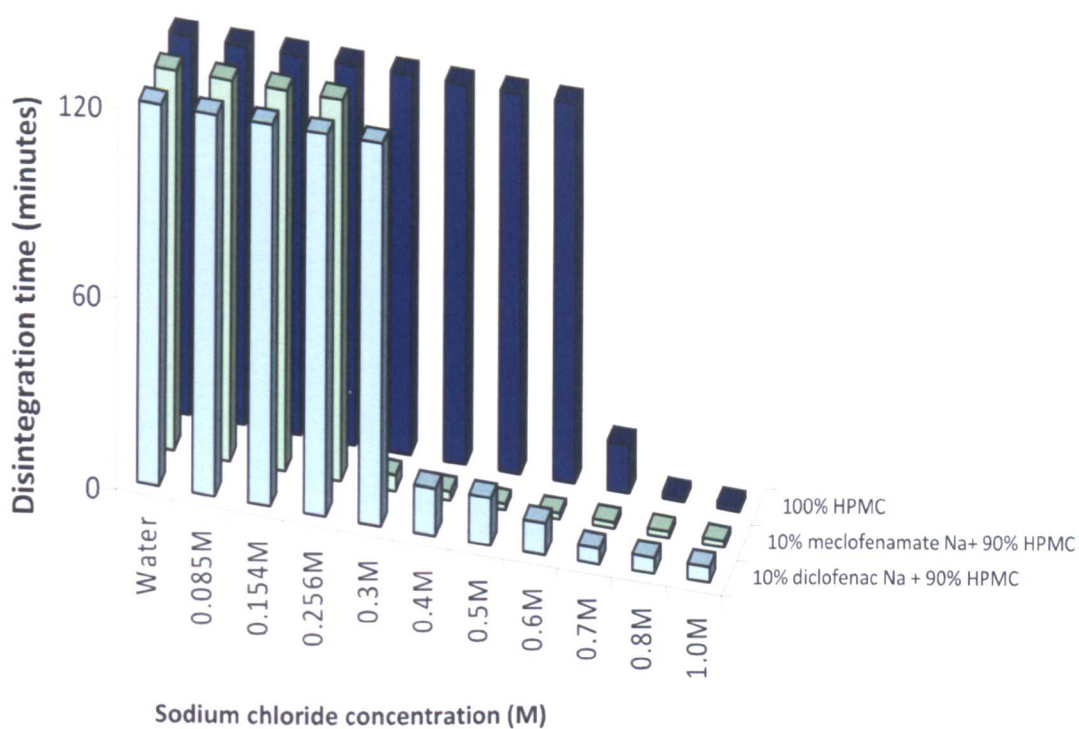
Figure 5.27 The effect of sodium chloride challenge on the disintegration times of 10% w/w meclofenamate Na and diclofenac Na HPMC matrices
Disintegration determined using USP methodology at 37°C. Tested conducted maximally for 120 minutes. Mean (n=4)
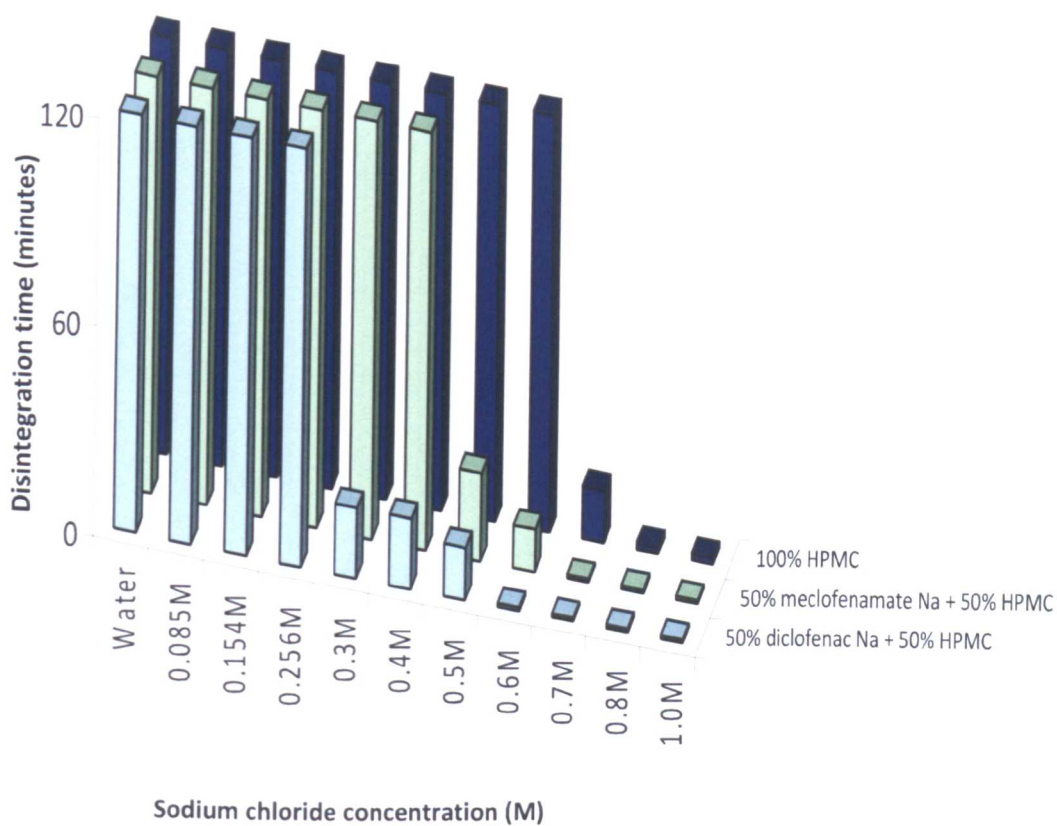
Figure 5.28 The effect of sodium chloride challenge on the disintegration times of 50% w/w meclofenamate Na and diclofenac Na HPMC matrices
Disintegration determined using USP methodology at 37°C. Tested conducted maximally for 120 minutes. Mean (n=4)
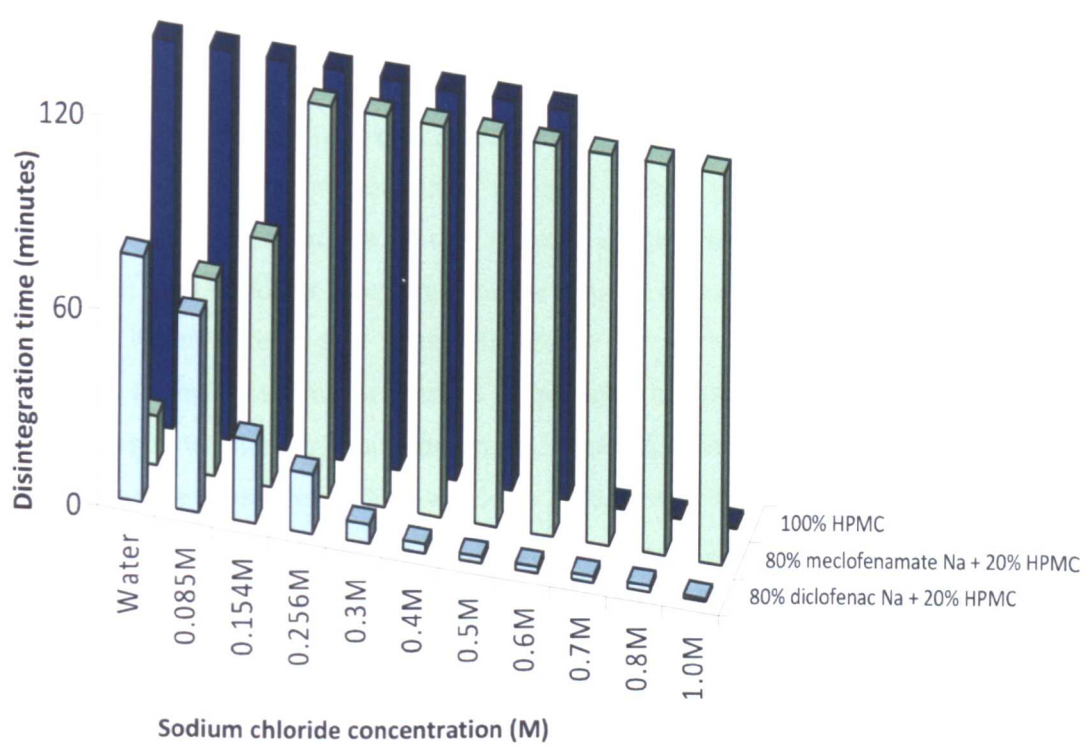
Figure 5.29 The effect of sodium chloride challenge on the disintegration times of 80% w/w meclofenamate Na and diclofenac Na HPMC matrices
Disintegration determined using USP methodology at 37°C. Tested conducted maximally for 120 minutes. Mean (n=4)

5.6 Discussion

5.6.1 The effect of diclofenac Na on HPMC gel layer formation

In Chapter 4, it was shown that diclofenac Na progressively "salted-out" HPMC from solution in a concentration dependent manner, making the polymer less soluble but with minimal effect on the viscoelastic properties. Investigations in this chapter suggest that these effects in solution may manifest as changes in the structure and function of the gel layer. When hydrated in water, diclofenac Na matrices exhibited little change in their swelling properties or gel layer morphology, irrespective of changes to the drug: polymer ratio. The rapid swelling of HPMC in water appeared sufficient for as little as 20% w/w HPMC to overcome the 'salting out' effect of the drug, and patterns of disintegration and gel layer formation were not significantly different from pure HPMC matrices.

However, when the hydration medium was changed to 0.9% w/v NaCl there were clear differences between the different formulations. Matrices containing over 50% w/w drug exhibited a synergistic 'salting-out' of the polymer, with the combined effects of drug in the matrix and NaCl in the hydration medium resulting in matrix failure and disintegration. Confocal images showed that the HPMC content in formulations containing high drug content and hydrated in saline was insufficient to produce a coherent gel layer. There was clear erosion of the gel layer, comprising of partially swollen polymer particles. The polymer appeared to be excessively 'salted out' and failed to form a coherent gel layer. As in water, a 50% polymer level was sufficient to overcome the 'salting-out' effects of the drug in the matrix and the 'salting-out' effect of the NaCl in solution.

This synergy was analogous to the 'salting out' effects of diclofenac Na and NaCl on the cloud point of HPMC solutions in which the combined effect of

was greater when they were present in solution alone (chapter 4). Ford (1999) has stated that a reduction in cloud point temperature is an indication of decreased polymer solubility and a reduced capacity of the polymer to imbibe water. Subsequently, this damages the ability of HPMC to hydrate and form a protective gel layer at the matrix surface. The evidence in this chapter supports this assertion. Rajabi-Siahboomi (1993) also found that if a drug (diclofenac Na) and dissolution medium (phosphate) both salt out HPMC matrix, rapid disintegration occurred. Therefore, it appears that diclofenac Na can act synergistically with other 'salting-out' ions.

5.6.2 The effect of meclofenamate Na on HPMC gel layer formation

In chapter 4 it was shown that meclofenamate Na possessed the propensity to "salt in" the polymer above a threshold concentration of 40 mM. It was proposed that this resulted from drug association with the polymer resulting in the formation of a pseudo poly(electrolyte) complex in solution. In addition, this interaction appeared to be influenced by the presence or absence of NaCl in solution.

The interaction between meclofenamate Na and HPMC resulted in a matrix that gels and swells rapidly in water. However, disintegration studies suggested that HPMC swelling and gelation with high meclofenamate Na and low HPMC content was excessive for the purpose of extending drug release. The matrices failed to form a sufficiently robust gel layer and disintegration occurred rapidly.

It can postulated that in the presence of NaCl, the polymer became dehydrated as the electrolyte competes with the polymer for water of hydration (Bajwa *et al.* 2006, Liu *et al.* 2008). This appears to counteract

swelling and gelation promoted by drug within the matrix, while concurrently reducing the solubility of the drug through a common ion effect. It was evident from the confocal images and measurements of gel layer growth that swelling was sufficiently restricted in 0.9% w/v NaCl to allow a more coherent gel layer to form and increased the resistance to disintegration extended beyond the time seen for the same formulation in water.

These results can be rationalised with reference to the interaction mechanism proposed in chapter 4. It may be suggested that the gel layer swelling is the result of a disparity in the phase behaviour of polymer mixtures arising from the interactions between meclofenamate Na and HPMC within the gel layer.

In simple terms, we can envisage that the gel layer can be viewed as a ternary polymer/polymer/solvent mixture in which the polymers are (i) HPMC, and (ii) HPMC associated with meclofenamate Na (the 'pseudo-polyelectrolyte HPMC-MEC) with the solvent being either (i) water or (ii) 0.9% w/v NaCl. The low entropy of mixing high molecular weight polymers can, depending on the balance between the various monomer-monomer solvent pair interactions, result in liquid-liquid phase separation phenomena which may be understood in the context of the Flory-Huggins theory of polymer mixtures (Flory 1953, Bergfeldt *et al.* 1996). In the case of swelling and gel layer formation in water, there are good interactions between the HPMC and solvent and there is no entropic drive for phase separation. The greater solubility of the pseudo poly(electrolyte) results in a highly swollen but inadequate diffusion barrier. When NaCl is added to the hydration medium, there are poorer interactions between solvent and the two polymers within the gel layer becoming phase concentrated in both HPMC and HPMC-MEC separated from a solvent only phase. This phenomenon is referred to as 'complex coacervation' (Flory 1953, Tostoguzov 2003). The coacervate of the

HPMC and HPMC-MEC will have greater viscosity than a gel layer formed from predominately HPMC alone since it is rich in polymer and deficient in solvent.

The tendency of ternary polymer/polymer/solvent system to phase separate is strongly dependent on the ionic environment (Albertsson 1995). In mixtures of polyelectrolyte/uncharged polymer, the addition of salt reduces the problems with electro-neutrality and encourages separation (Picullel *et al.* 1995). This may explain the apparent meclofenamate Na-mediated resistance to NaCl challenge in the disintegration studies. The increases in NaCl in the swelling medium provided the entropy drive for phase separation since this is a poorer solvent for both HPMC and HPMC-MEC and leads to the formation of a 'coacervate gel layer' which provides an efficient diffusion barrier.

5.7 Conclusions

This chapter has shown how the initial period of gel layer development appears critical for achievement of a functional diffusion barrier and prevention of matrix disintegration. There was a direct correlation between a compromised gel layer, as a consequence of drug and electrolyte effects on the solubility of HPMC, and the onset of matrix disintegration.

This provides further evidence of the validity of the original hypothesis developed in chapter 4 which attempted to explain the contrasting drug release from hydrophilic matrices of diclofenac Na and meclofenamate Na presented in chapter 2. The observed effects of drug addition in HPMC solutions appear to manifest as changes in the gel layer structure and functionality. The drug effects appear to be influenced by the presence or absence of NaCl in the hydration medium, an effect that can be explained

through the changes NaCl afforded to the drug/HPMC interactions in solution.

The next chapter will investigate another experimental avenue arising from analysis of the dissolution data; the role of incorporated diluents on the early gel layer formation and functionality.

Chapter 6

The effect of diluents on the early gel layer formation and disintegration of HPMC matrices

6.1 Introduction

Previously, the effect of diclofenac Na and meclofenamate Na on HPMC solution properties (chapter 4) and gel layer formation (chapter 5) have been investigated. However, drugs are rarely formulated with HPMC as simple binary mixtures, and excipients are routinely included in matrix tablets. Diluents or fillers are used to provide tablet bulk but their effects on gel layer formation and drug release are often discounted as insignificant in comparison with polymer, drug and formulation factors (chapter 1). In the interpretation of the drug release results in chapter 2, it was suggested that lactose may have a significant role in modulating drug-polymer interactions and subsequent drug release from HPMC matrices. The aim of the current chapter is to explore the effect of diluents on the behaviour of the HPMC gel layer in binary matrices in the absence of drug.

6.1.1 The effect of diluents on drug release from HPMC matrices

Several studies in the literature have considered the effects of diluents on drug release. Rekhi *et al* (1999) have investigated the effect of formulation variables on metoprolol tartrate release from HPMC matrices. Increasing the lactose content from 25 to 61% w/w resulted in increased drug release rate. These findings supported the earlier studies of Lapidus and Lordi (1968) and Ford *et al* (1987). It is believed that when the soluble excipient content exceeded 50% w/w, the rapid dissolution of the excipients led to the formation of a fragile and porous gel. As a result, the drug diffusion and gel layer erosion increased.

Sako *et al* (2002) have found that HPMC matrices containing lactose (a moderately soluble filler) and poly(ethyleneglycol) 6000 (PEG 6000) (a highly soluble filler) exhibited similar release rates to matrices that contained an insoluble filler. The soluble component of the matrices was 50% w/w, hence conflicting with the findings of Ford *et al* (1987) who stated that this level of filler should result in a more rapid drug release.

Levina and Rajabi-Siahboomi (2004) have examined the effects of lactose, microcrystalline cellulose (MCC) and partially pre-gelatinised starch on drug release from HPMC matrices. It was found that the incorporation of starch produced a significant reduction in the release of a freely and slightly water soluble drugs in comparison with the other two diluents. It was suggested that this may be the result of a synergistic interaction between starch and HPMC resulting in the formation of a stronger gel structure. No direct evidence for this effect was offered.

Williams *et al.* (2002) have investigated the effect of diluent type and content on the release of alprazolam from HPMC matrices. They investigated the effect of a wide variety of soluble excipients (lactose,

sucrose and dextrose) and insoluble excipients (dibasic calcium phosphate dihydrate (DCP), dicalcium phosphate anhydrous and calcium sulphate dehydrate) on the drug release profiles of matrices containing 40% w/w HPMC. Insoluble excipients reduced in the rate of drug release in comparison with the soluble excipients, with a mixture of lactose and DCP produced an intermediate drug release profile.

Lotfipour *et al.* (2004) have investigated the effects of lactose and DCP on atenolol release from HPMC matrices. An increase in filler concentration resulted in an increase in drug release rate, irrespective of the filler type. Release profiles showed that a decrease in the ratio of HPMC/filler from 3:1 to 1:3 resulted in increased in drug release rates. Low concentrations of DCP had little effect on the release rate. It was proposed that changing the polymer/filler ratio increases the release rate by altering the diffusivity of atenolol through the gel layer.

Huang *et al.* (2004) have optimised an extended release matrix of propranolol for once daily administration, using a constrained mixture experimental design with variable content of HPMC, lactose and MCC. Both MCC and lactose increased drug release but the enhancement by lactose was greater than MCC. The influence of lactose was more significant in the later rather than the early stages of drug release.

Jamzad *et al.* (2005) have investigated the influence of water-soluble and insoluble excipients on front movement, erosion and release of tetracycline hydrochloride from HPMC matrices using texture analysis. Matrices containing 30% w/w drug and lactose had a more pronounced swelling front movement and drug release in comparison with the matrices containing DCP, with lactose formulations having greater water penetration but subsequently a weaker gel structure. For DCP formulations, the gel strength was greater, suggesting less hydration.

6.1.2 The choice of diluents for investigation

The rationale for the choice of diluents investigated in this chapter was as follows. Lactose monohydrate was used in the formulation detailed in chapter 2 and represents the 'classic' soluble filler material used in many tablet formulations (Riepma *et al.* 1992, Lerk 1993, Jelcic *et al.* 2007). Its influence on drug release has been highlighted in the literature with little evidence from imaging techniques.

The other diluents offered contrasting physicochemical properties. DCP is used in tablet formulations both as an excipient and as a source of calcium and phosphorus in nutritional supplements (Bryan and McAllister 1992, Schmidt and Herzog 1993). DCP is insoluble and non-swelling and offers a counterpoint to the behaviour of lactose.

The final diluent was MCC which, although sharing its insoluble nature with DCP, offered an additional water-imbibing and wicking property. MCC is purified, partially depolymerised cellulose that exists as white, odourless, tasteless, crystalline powder composed of porous particles. It is used in pharmaceuticals as a binder/diluent in oral tablet and capsule formulations, in both wet granulation and direct compression applications (Lerk *et al.* 1979, Li and Mei 2006).

Based on the above, the diluents selected for investigation in this chapter were: (i) α-lactose monohydrate, (ii) dibasic calcium phosphate dihydrate and (iii) microcrystalline cellulose. The chemical structures of the diluents are illustrated in table 6.1.

A

.H$_2$O

B

Ca^{2+}

.2H$_2$O

C

n
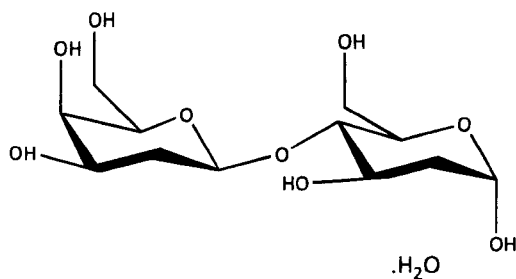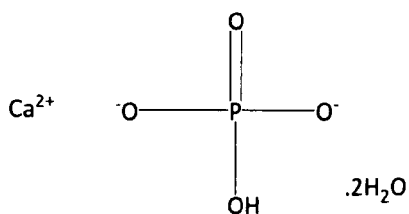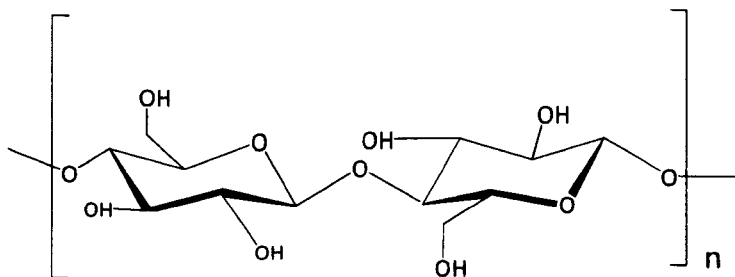
Table 6.1 The chemical structures of diluents used in this chapter

The excipients listed above are: (A) α-lactose monohydrate, (B) Dibasic calcium phosphate dihydrate (DCP) and (C) Microcrystalline cellulose (MCC)

6.2 Chapter Aims

The aims of this chapter are to:

> - To determine the effects of lactose monohydrate on HPMC
> solution properties, including cloud point, viscosity and
> viscoelasticity

> - To assess the affect of varying diluent content and type on
> early gel layer formation and functionality using confocal
> microscopy and disintegration testing

Achievement of these aims will provide insights into the drug release behaviour presented in chapter 2, where it was proposed that lactose played a key role in influencing drug release.

6.3 Materials and Methods

6.3.1 Materials

6.3.1.1 HPMC

A sieve fraction of 63-90 µm HPMC (Methocel E4M CR Premium) was used in matrix manufacture. Details of the source and batch number are detailed in appendix 1.

6.3.1.2 Diluents

Lactose monohydrate, microcrystalline cellulose (Avicel PH102) and dibasic calcium phosphate dihydrate were used as received. Details of the source and batch number are detailed in appendix 1.

6.3.1.3 Water

Solutions were prepared using Maxima HPLC grade water (USF Elga, Buckinghamshire, UK) with a maximum conductance of 18.2 MΩ.cm.

6.3.2 Manufacture of 1% w/w HPMC solutions containing lactose

Manufacture of 1% w/w HPMC solutions containing lactose was undertaken using the method described in section 3.2.1.

6.3.3 Turbimetric determination of the sol:gel phase transition temperature of lactose-containing HPMC solutions

Turbimetric determination of the sol:gel transition temperature of 1% w/w HPMC solutions containing lactose was undertaken by the method described in section 3.2.2.

6.3.4 Continous shear viscosity measurements

Continuous shear viscosity measurements of 1% w/w HPMC solutions containing lactose were undertaken using the method described in section 3.2.3.

6.3.5 Oscillatory rheology

Oscillatory rheology of 1% w/w HPMC solutions containing lactose were undertaken using the method described in section 3.2.5.

6.3.6 Measurement of single HPMC particle swelling

Visualisation and measurement of single particle swelling in the presence of lactose solutions was undertaken using the method described in section 5.4.3.

6.3.6.1 Preparation of lactose solutions containing Coomassie blue

Lactose solutions were prepared in 100 ml volumetric flasks using distilled water. A 15 ml volume of Coomassie Blue 0.003M solution was then made using each of the lactose solutions. The vials were covered with aluminium foil to avoid any exposure to light, in order to minimise

any photochemical reactions (e.g photolytic oxidation). The solutions were left stirring overnight to ensure an even distribution of the dye in the solutions and to reduce the amount of precipitation occurring.

6.3.7 Matrix preparation

6.3.7.1 Preparation of HPMC sieve fractions

Fractionation of HPMC for matrix manufacture was undertaken using the sieving method described in section 3.2.6.1. The diluent powders were used as received.

6.3.7.2 Formulation preparation

Mixtures were prepared in appropriate quantities for 50 g batches of each formulation by mixing as described in section 3.2.6.2.

6.3.7.2 Matrix manufacture

Manufacture of HPMC matrices was undertaken using the method described in section 3.2.6.3 on a Manesty F3 single punch tablet press (Manesty, Liverpool, UK) using a compression pressure of 180 MPa and 8 mm flat-faced tablet punches (I Holland, Nottingham, UK). The matrix compositions are shown in table 6.2.

Percentage of diluent (%)	Matrix composition	
	Diluent (mg)	HPMC (mg)
0	0	200
15	30	170
30	60	140
50	100	100
70	140	60
85	170	30

Table 6.2 The quantity of the diluents in each tablet formulation

Matrices weighed 200± 5mg, compressed to 180 MPa. Details of matrix manufacture are described in 3.2.6.3

6.3.8 Confocal laser scanning microscopy (CLSM) imaging

Confocal imaging was undertaken by the method described in section 5.4.6. Image analysis of confocal images was undertaken using the method described in section 5.4.7.

6.3.9 Tablet disintegration studies

Disintegration studies of matrix formulations containing diluents were undertaken using the method described in section 3.2.7.

6.4 Results

6.4.1 The effect of lactose on the cloud point temperature (CPT) of HPMC solutions

Figure 6.1 shows the effect of lactose on the CPT of a 1% w/w HPMC solution. The addition of lactose lowered the CPT of HPMC solutions, in a manner that appears analogous to the 'salting out' behaviour of commonly formulated soluble excipients such as NaCl with other thermo-sensitive polymers (Eeckman *et al.* 2001, Mori *et al.* 2004). There was a concentration dependent reduction in cloud point, with a 10.1°C reduction at the highest concentration of lactose tested (500 mM).

Incompatibilities between sugars and polymers have been reported elsewhere in the literature (Levy and Schwartz, 1958, Kim *et al.* 1995, Kawasaki *et al.* 1996 and Lee *et al.* 2003). It is known that low molecular weight saccharides are strong water structure makers ("kosmotropes") at high concentrations (Almond 2005, Giangiacomo 2006). The stabilisation of water structure by addition of saccharides may lead to a decrease in interactions between water and polymer chain in solution, enhancing the potential for hydrophobic interactions between methoxyl-rich regions on the HPMC chains. Therefore, it is reasonable that the cloud point of the present polymer solutions decreased with increasing saccharide concentration.
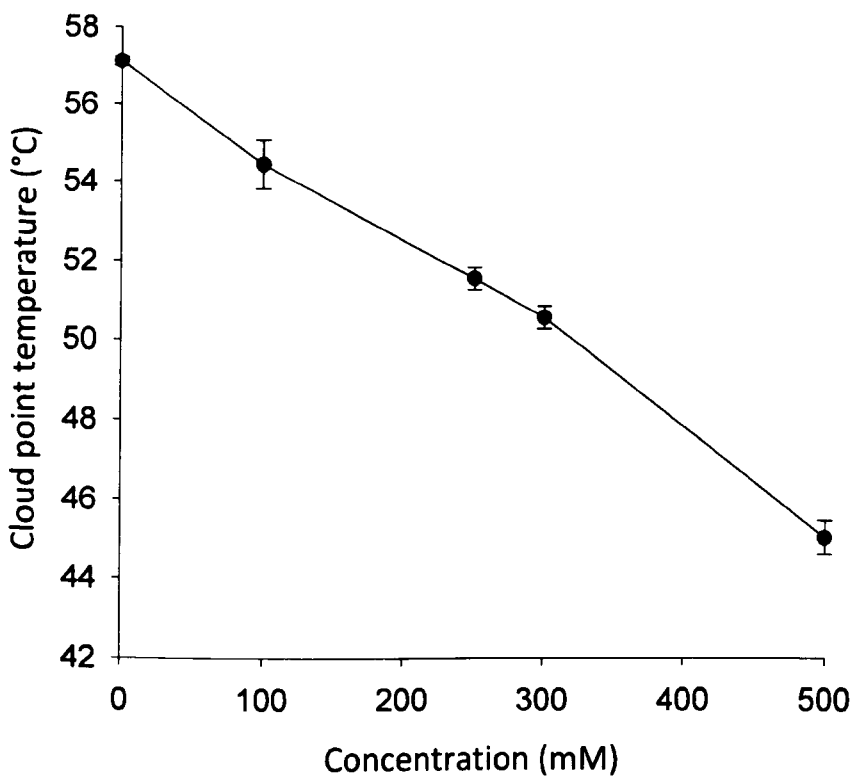
Figure 6.1 The effect of lactose on the cloud point temperature of 1% w/w HPMC solutions

CPT measured turbimetrically as a reduction of 50% in light transmission (Sarker 1979). Mean (n=3) ± 1SD.

6.4.2 The effect of lactose on the solution continuous shear viscosity of HPMC solutions

Figure 6.2 shows the effect of lactose on solution viscosity. Lactose increased the viscosity of a 1% w/w HPMC solution but not to the same order of magnitude as observed with the addition of meclofenamate Na (where viscosity was increased by two orders of magnitude) (chapter 4). This increase in viscosity may be a result of the 'salting out 'by the lactose-mediated effects on the sol:gel phase transition temperature. This assertion is supported by literature findings that electrolytes can slightly increase the viscosity of HPMC solutions (Zatloukal and Sklubalova 2007).

6.4.3 The effect of lactose on the viscoelastic properties of HPMC solutions

Figures 6.3 and 6.4 show the effect of lactose addition on the storage and loss moduli of 1% w/w HPMC solutions. There was a slight increase in both moduli of the polymer solutions. This may be related to the water-structuring effect of the saccharide and resulting increases in hydrophobic interactions between polymer chains as the HPMC are brought closer to their thermogelation temperature.
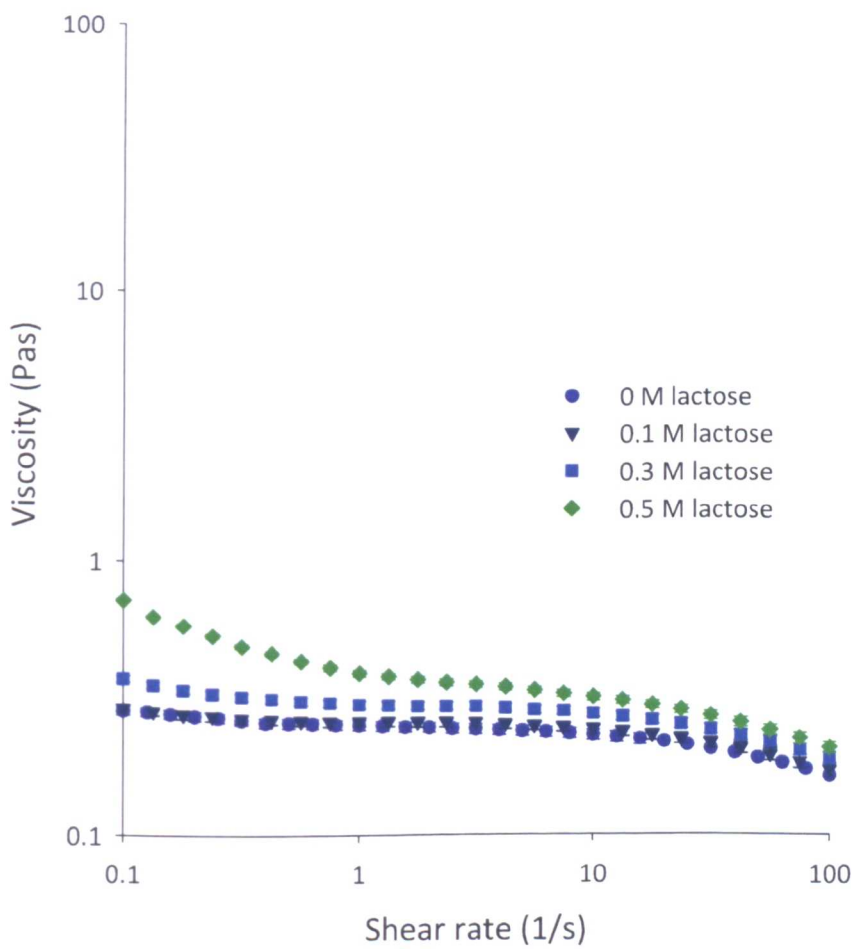
Figure 6.2 The effect of lactose concentration on 1% w/w HPMC solution continuous shear viscosity

Geometry = CP 2°/50mm. Temperature = 20 ± 0.1°C. Mean (n =3) ± 1SD
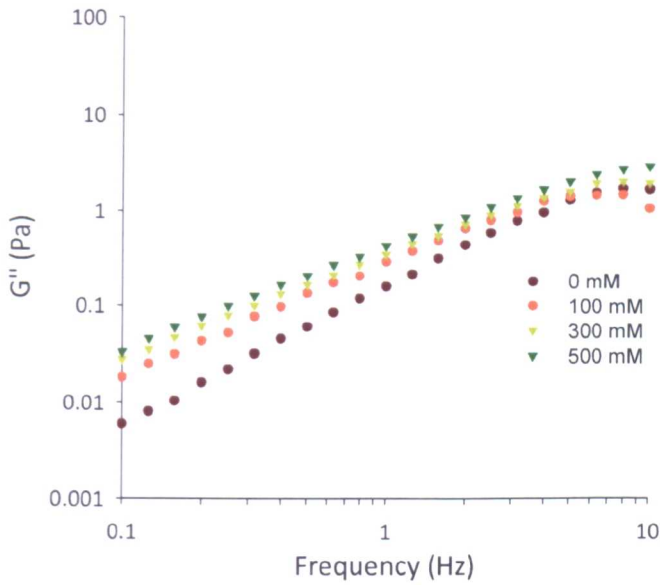
Figure 6.3 The loss modulus (G") of mixtures containing 1% w/w HPMC with respect to lactose concentration

Geometry = PP 2°/50 mm. Temperature = 20 ± 0.1ºC. Mean (n =3) ± 1SD
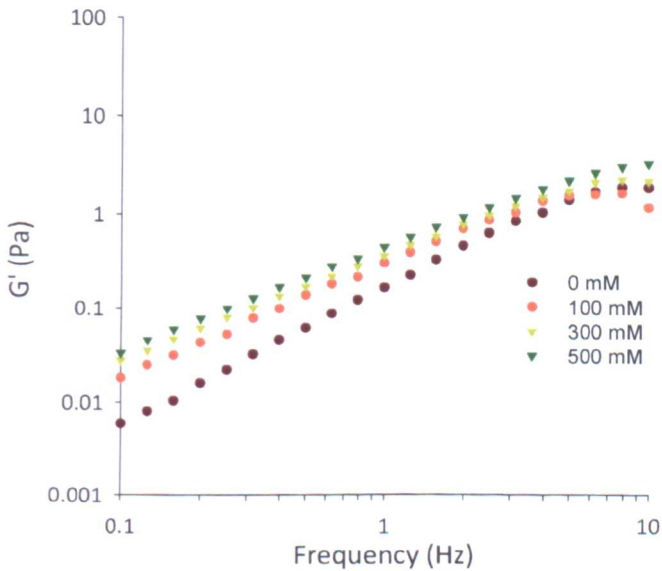
Figure 6.4 The storage modulus (G') of mixtures containing 1% w/w HPMC with respect to lactose concentration.

Geometry = PP 2°/50 mm. Temperature = 20 ± 0.1ºC. Mean (n =3) ± 1SD

6.4.4 The effect of lactose on the swelling of HPMC particles

Figure 6.5 shows a comparison between the swelling of HPMC particles in water and in a 0.5 M lactose solution. Qualitatively, it appeared that the presence of lactose in the swelling medium suppressed the swelling and coalescence of HPMC particles compared with behaviour of the polymer particles in water. In the lactose solution, there were distinct gaps in the swollen particle bed, whereas in water a continuous phase of swollen HPMC particles coalesced by the end of the experiment. The measurement of individual particle swelling shown in figure 6.6 suggested that lactose suppressed particle swelling in a concentration dependent manner

This suppression of polymer particle swelling may be related to the capability of lactose to lower HPMC cloud point which in turn would affect gel layer functionality. Ford (1999) has stated that a reduction in cloud point temperature is an indication of decreased polymer solubility and capacity to imbibe water reducing particle swelling.

6.4.5 The effect of incorporated diluents on HPMC gel layer morphology

The effect of diluent content in the matrix tablet from 15% to 85% w/w on the microstructure of the HPMC gel layer was determined.

Unhydrated HPMC particle

Time	Water	0.5 M lactose solution
0 s		
15 s		
30 s		
180 s		
300 s		
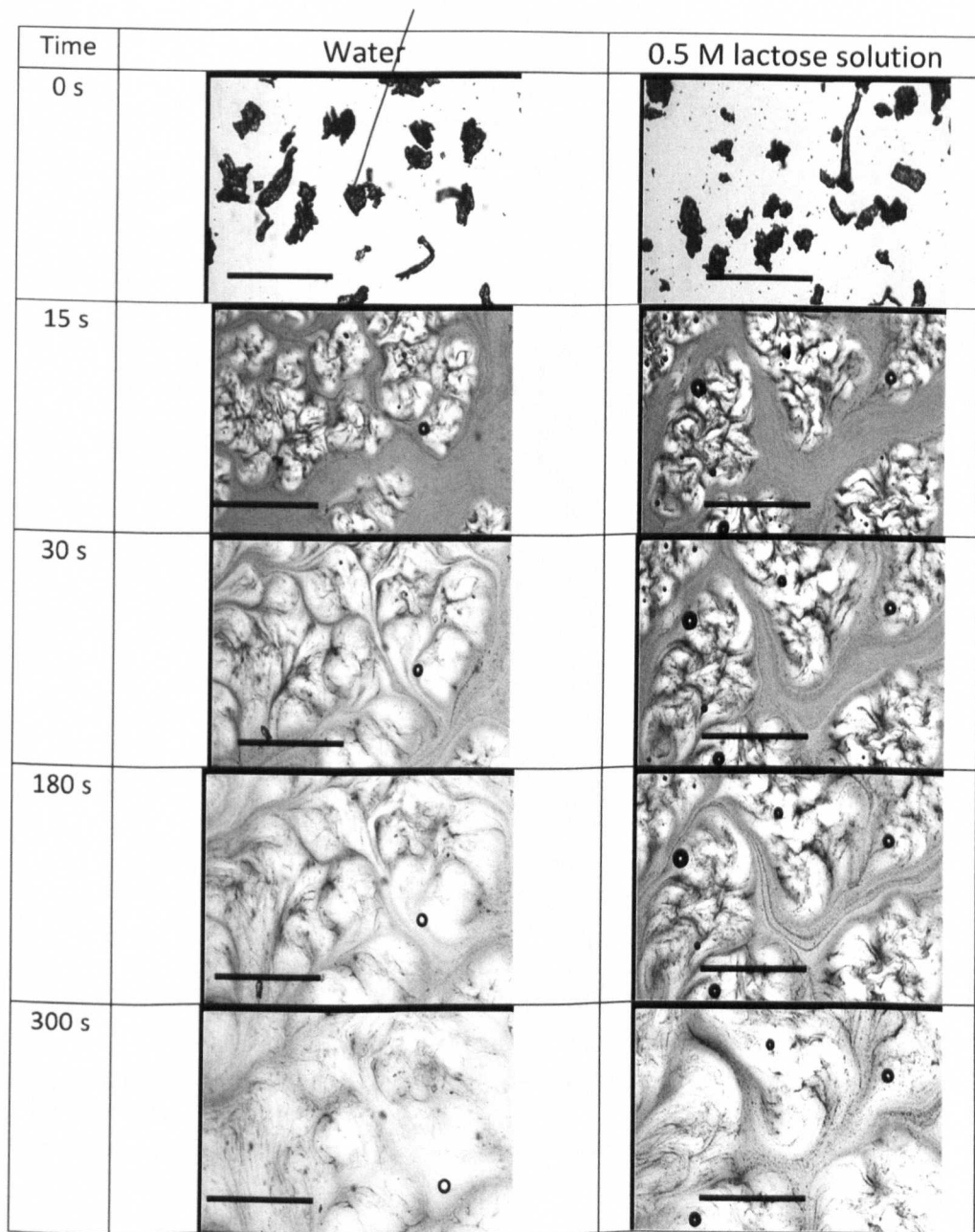
Figure 6.5 Real-time observation of HPMC particle swelling in water and 0.5M lactose solution

Hydrated times indicated in the left hand column. 0.003M Coomassie blue as a visualisation aid. Scale bar: 200 μm
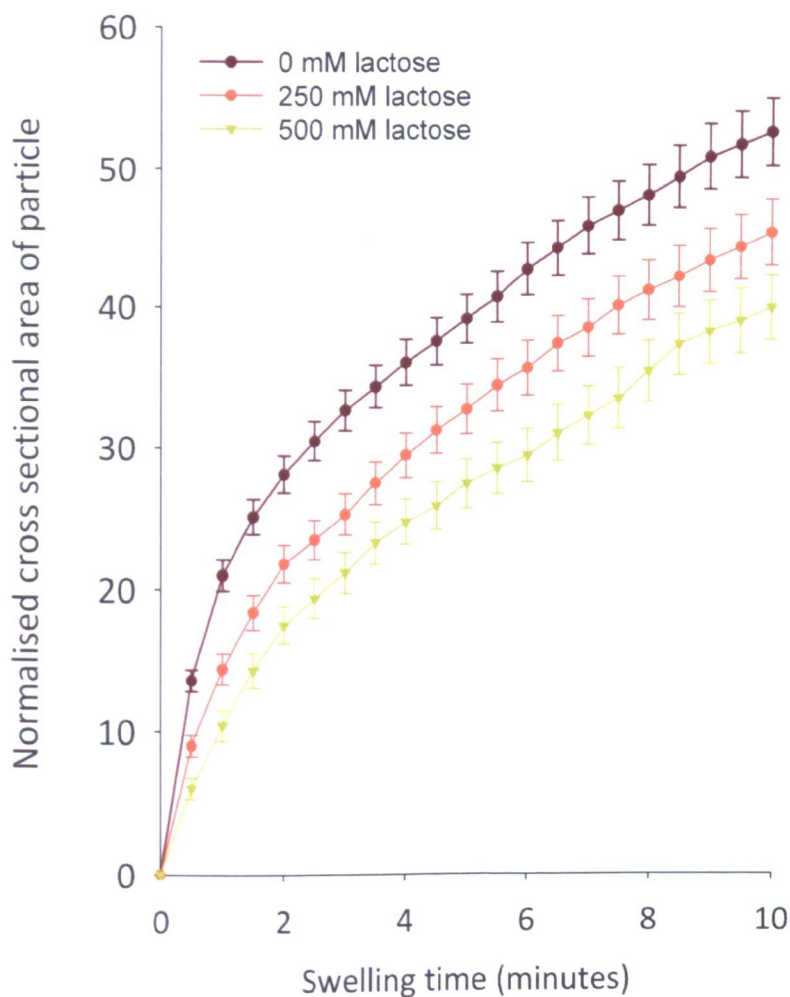
Figure 6.6 The swelling of individual HPMC particles as a function of lactose concentration

0.003M Coomasie Blue solution used as a visualisation aid. Swelling carried out at 20±1°C, mean (n=10) ±1SEM

6.4.5.1 The effect of lactose content on gel layer morphology and swelling

Figure 6.7 shows the effect of increasing lactose content in the matrix on the gel layer development in HPMC matrices. It can be seen that low lactose content (15-30% w/w) had negligible effect on swelling behaviour and gel formation and microstructure were not distinguishable from that of a 100% HPMC matrix.

At high lactose contents (>50% w/w), gel layer swelling was increased markedly and gel layer formation appeared to be disrupted. This first appeared at 50% w/w lactose content (figure 6.8). The disruption occurred during the first minute of hydration, with an initial burst of particulate matter leaving the surface of the matrix, after which the gel layer was seen to recover and form normally.

At the higher lactose loadings (70 and 85% w/w), it appeared that gel layer disruption was significant in the early stages but beyond five minutes a structure began to form, albeit highly swollen and apparently diluted (figure 6.9). This may be a result of lactose diffusing out of the gel layer at a faster rate in comparison with HPMC dissolution at the gel layer periphery, resulting in sufficiently increased polymer concentration in the gel layer to form a dilute structure. Figure 6.10 depicts the expansion of the gel layer within these matrices with respect to the original matrix dimensions and confirms that loss of controlled swelling occurs at the lactose loadings of 70% and 85%. The high variability in measurements is a consequence of material debris falling out of the confocal plane.

The finding that disruption of gel layer development only occurs at the highest lactose content is in agreement with the findings of Ford *et al.* (1987) who suggested that diluent effects only become apparent at levels of incorporation above (>50% w/w).
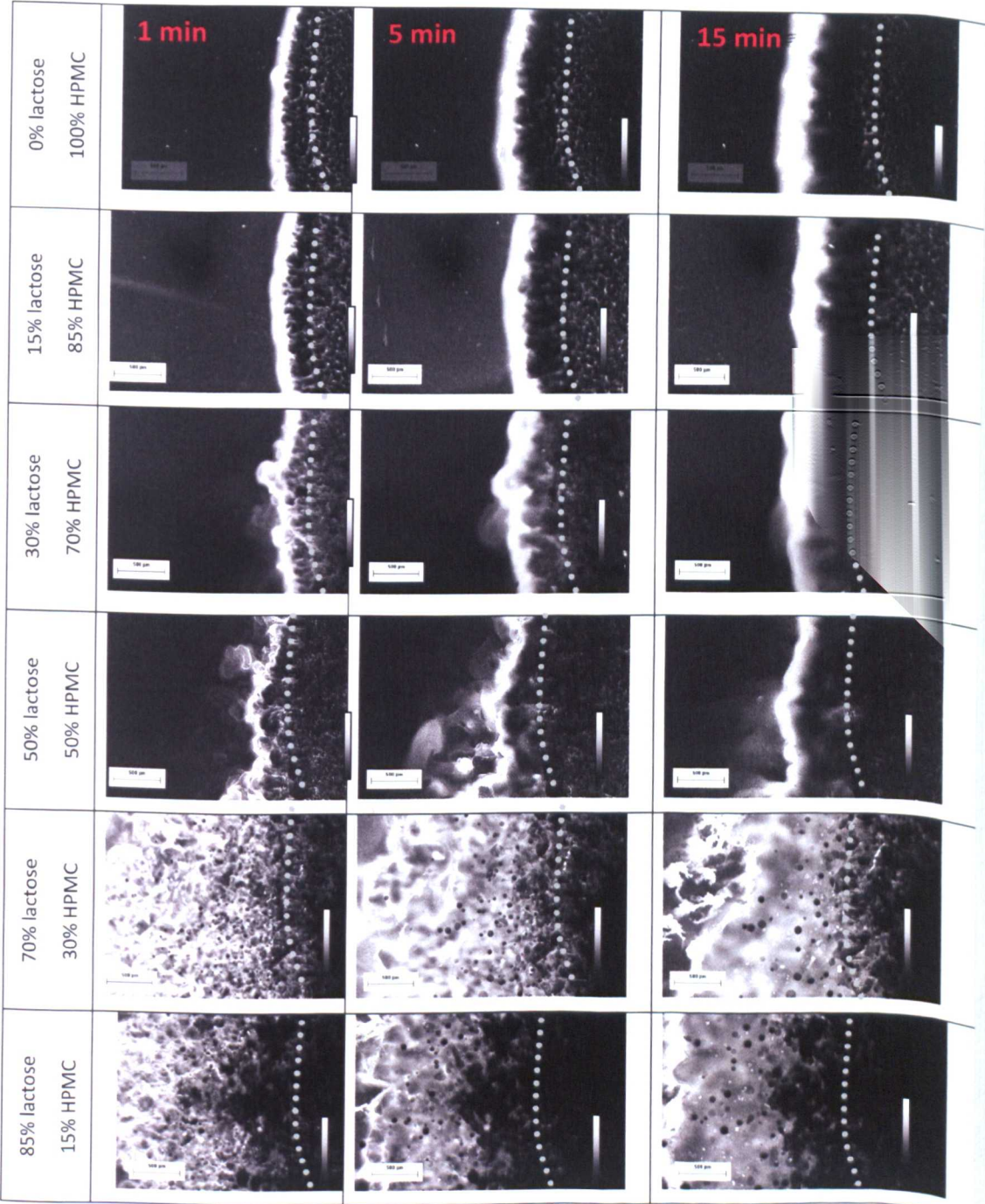
Figure 6.7 The effect of incorporating lactose in the matrix on the evolution of the HPMC gel layer after 1, 5 and 15 minutes hydration in water

Formulations contained the indicated percentages of diluent and HPMC. The images are coded for fluorescence intensity from white (highest) to black (lowest) as indicated by the wedge. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Ex488>510 nm. Scale bar= 500 μm.

Burst of particulate matter leaving the matrix surface
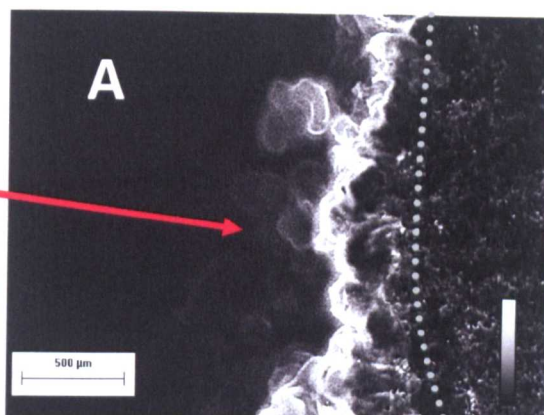
Gradual recovery of gel layer after five minutes of hydration
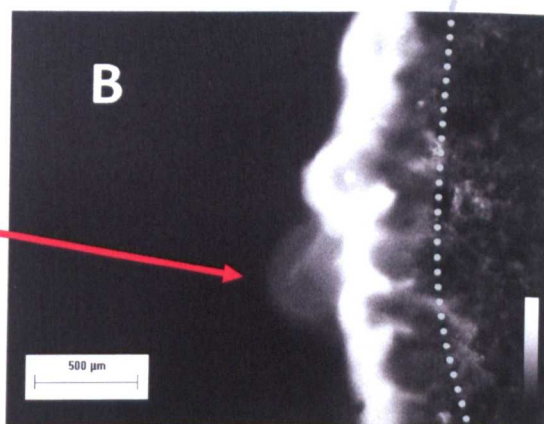
Gel layer formation has fully recovered and morphology is similar to that seen in 100% HPMC matrices
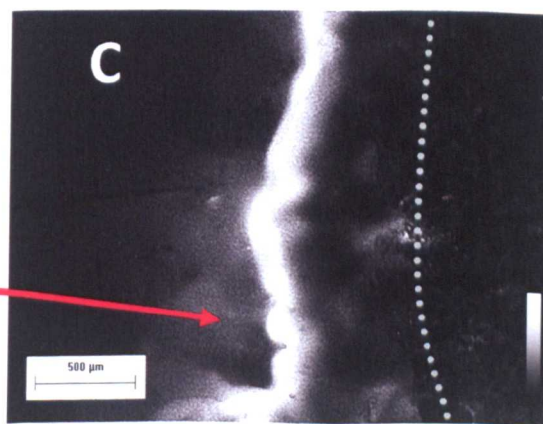
Figure 6.8 The effect of incorporating 50% w/w lactose in the matrix on the evolution of the HPMC gel layer microstructure after (A) 1, (B) 5 and (C) 15 minutes

The images are coded for fluorescence intensity from white (highest) to black (lowest). Dotted line depicts the dry tablet boundary. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Ex488>510 nm. Scale bar = 500 μm

Massive disruption of the gel layer in the first minute of hydration
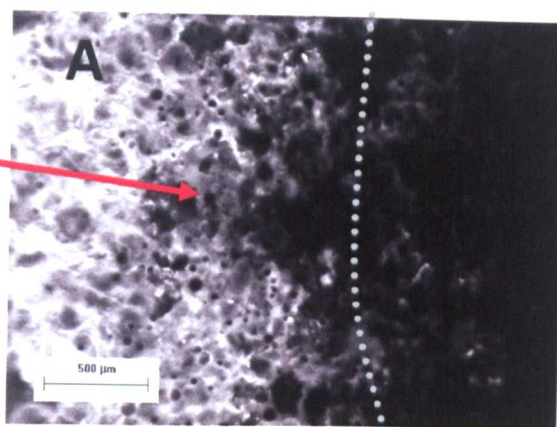
Particles appear to coalesce to form a partial structure
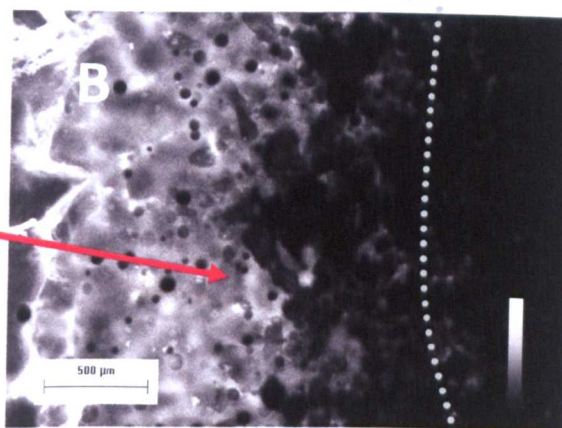
Formation of a highly swollen gel layer with erosion of the dry core
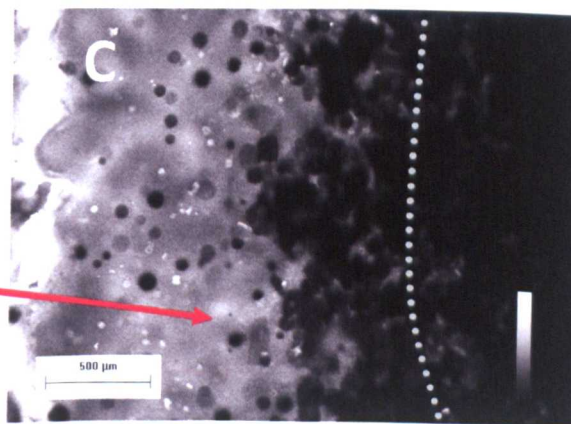
Figure 6.9 The effect of incorporating 85% w/w lactose in the matrix on the evolution of the HPMC gel layer microstructure after (A) 1, (B) 5 and (C) 15 minutes

The images are coded for fluorescence intensity from white (highest) to black (lowest). Dotted line depicts the dry tablet boundary. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Ex488>510 nm. Scale bar = 500 µm
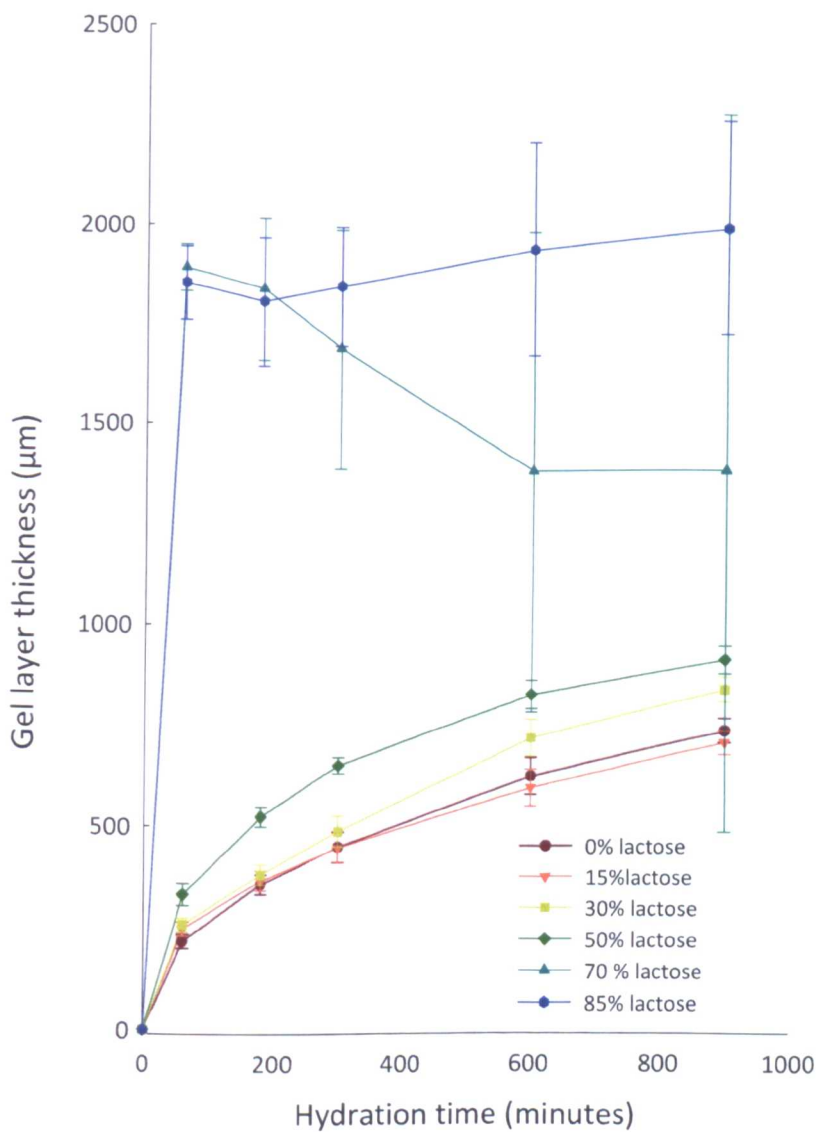
Figure 6.10 The effect of diluent content on the radial gel layer growth of HPMC matrices containing lactose

Formulations contained the indicated percentages of lactose and HPMC to 100%. Hydration in 0.008% w/v Congo red at 37°C. Swelling measured from dry tablet boundary to the edge of region B1. Mean (n=3) ±1 SD

6.4.5.2 The effect of DCP content on gel layer morphology and swelling

Figure 6.11 shows the effect of DCP content on gel layer morphology and growth. At low DCP content, there was minimal effect on the gel layer formation. However, when DCP content was increased to 85% w/w, a major disruptive effect was observed with the matrices apparently becoming incapable of forming a coherent gel layer.

DCP is an insoluble, non-swelling excipient and on a microscopic scale the images show how HPMC particles had to swell around insoluble areas of DCP. This supports the findings of Bettini *et al.* (2001) who suggested the presence of solid particles in the gel layer reduced the swelling and the entanglement of polymer chains and as a result, the matrix became more erodible. There is visual evidence of this occurring in the confocal images of figure 6.12, with clear hydration of HPMC particles around DCP in the 85% w/w DCP matrices. However, with increasing DCP content, the particles were too physically separated to coalesce and form a continuous gel layer. At lower DCP contents, the physical separation afforded by DCP did not prevent gel layer formation. The measurements of gel layer swelling shown in figure 6.13 show a controlled swelling up to 70% w/w, after which the gel layer was shown to grow in an uncontrolled manner.

These results may explain why similar release profiles have been noted in the literature for DCP and lactose despite the differences in their solubility (Ford *et al.* 1987, Williams *et al.* 2002). Gel layer porosity is increased with increased incorporation of both these diluents by different mechanisms; by movement of soluble particles increasing water penetration in the case of lactose and physical separation of hydrated HPMC particles in the case of DCP, up to the point where catastrophic disintegration occurs.
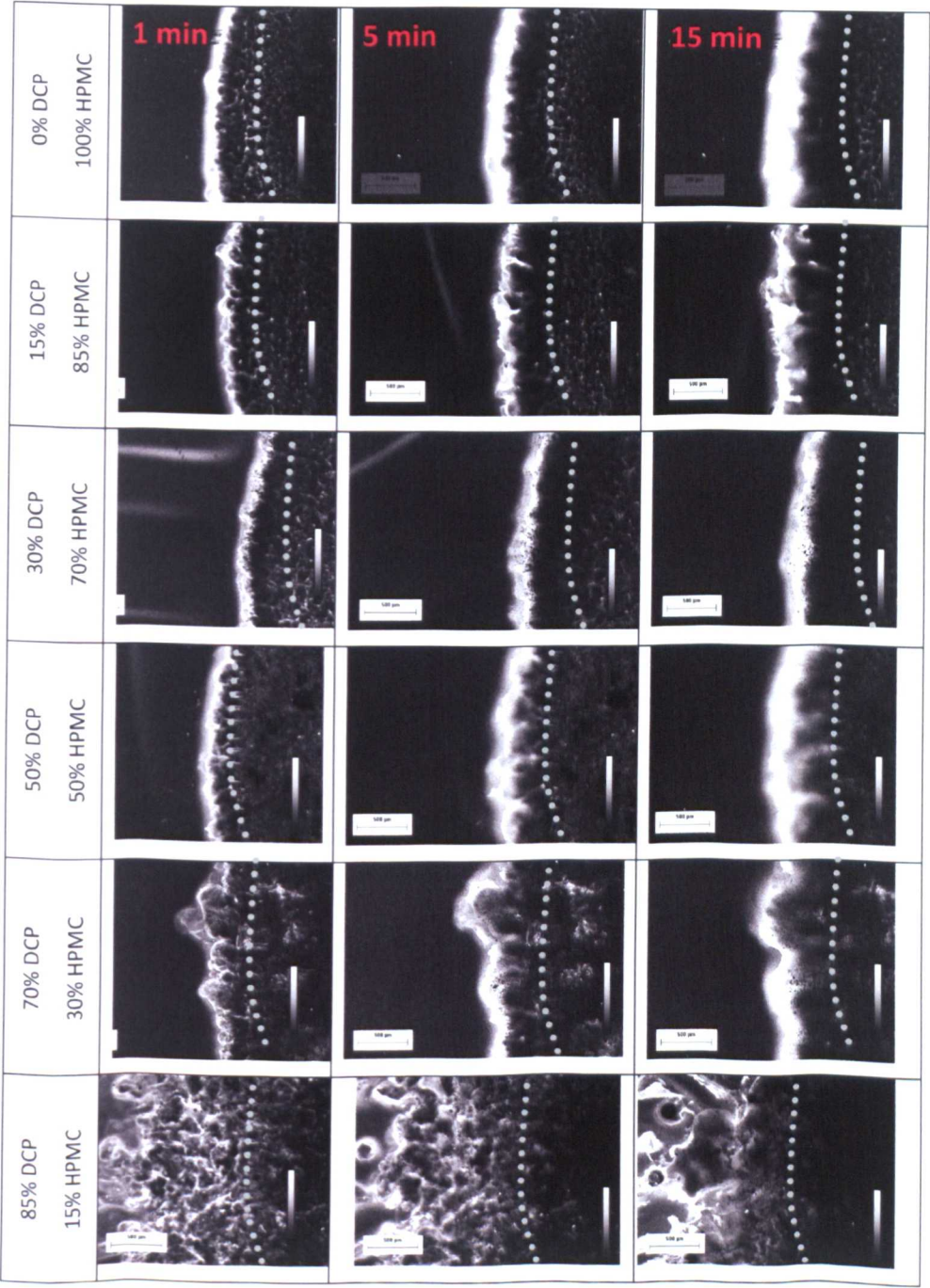
Figure 6.11 The effect of incorporating dicalcium diphosphate dihydrate in the matrix on the evolution of the HPMC gel layer after 1, 5 and 15 minutes

Formulations contained the indicated percentages of diluent and HPMC. The images are coded for fluorescence intensity from white (highest) to black (lowest) as indicated by the wedge. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Ex488>510 nm. Scale bar= 500 μm.

Massive disruption of the gel layer in the first minute of hydration
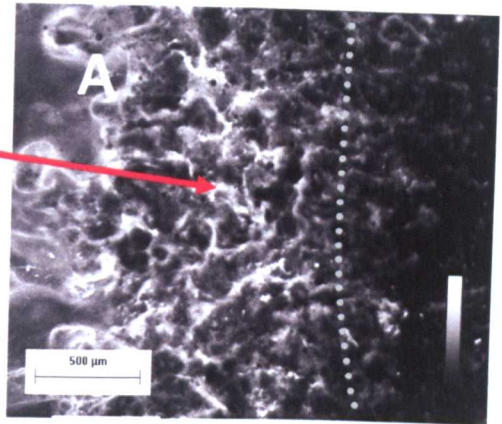
HPMC particles clearly hydrated and swelling but unable to form a coherent barrier owing to presence of high levels of insoluble material
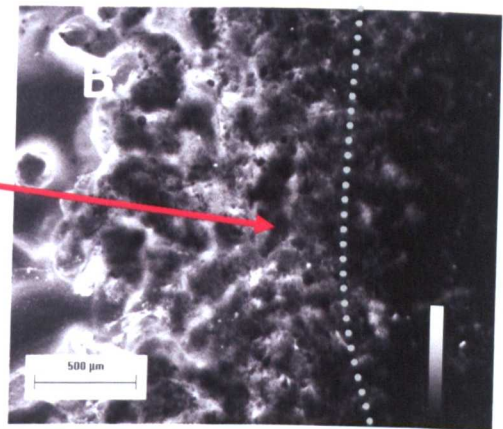
Formation of a swollen gel layer towards the end of the experiment including particles of DCP
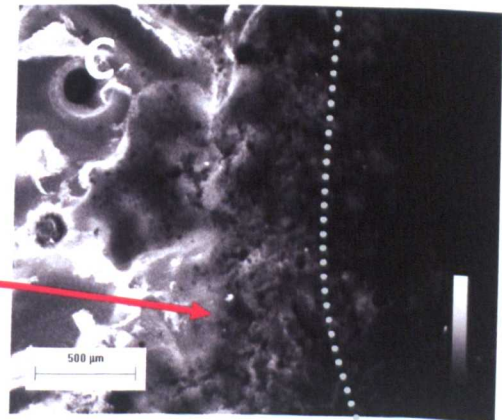
Figure 6.12 The effect of incorporating 85% w/w dibasic calcium diphosphate in the matrix on the evolution of the HPMC gel layer microstructure after (A) 1, (B) 5 and (C) 15 minutes
The images are coded for fluorescence intensity from white (highest) to black (lowest). Dotted line depicts the dry tablet boundary. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Ex488>510 nm. Scale bar = 500 μm
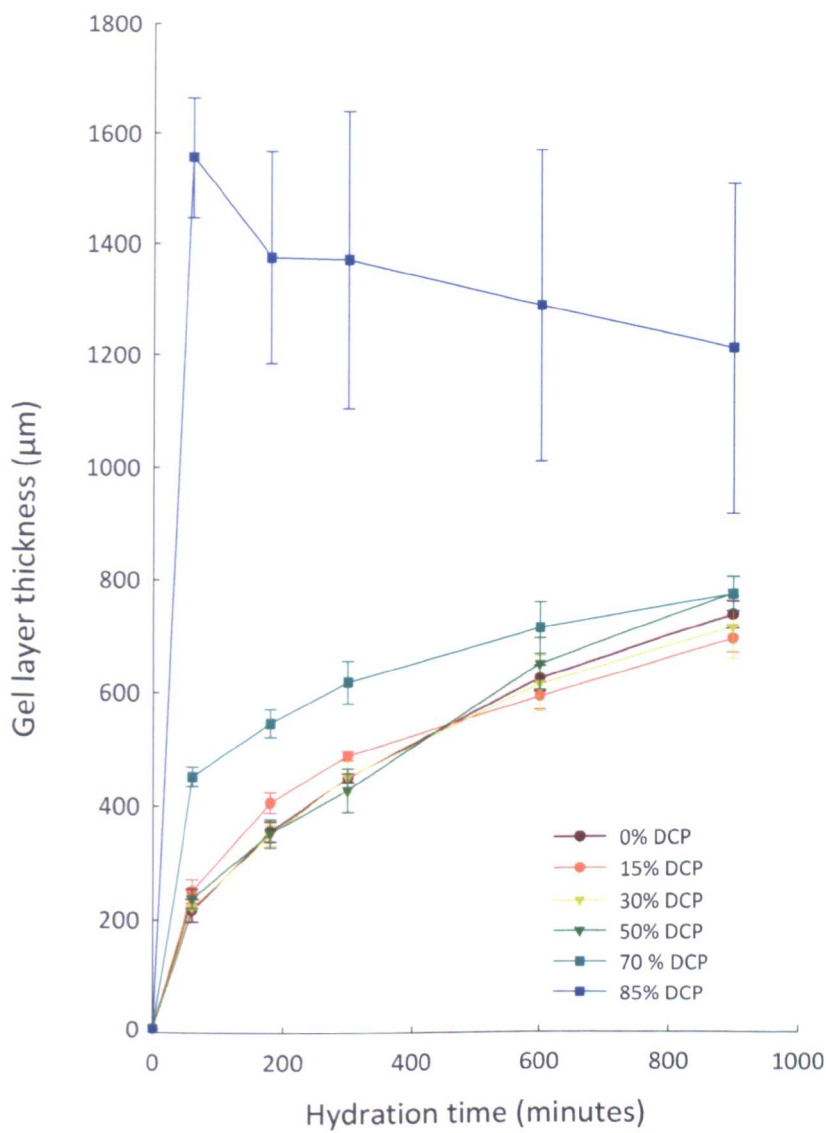
Figure 6.13 The effect of diluent content on the radial gel layer growth of HPMC matrices containing dicalcium phosphate dihydrate

Formulations contained the indicated percentages of DCP and HPMC to 100%. Hydration in 0.008% w/v Congo red at 37°C. Swelling measured from dry tablet boundary to the edge of region B1. Mean (n=3) ±1 SD

6.4.5.3 The effect of MCC content on gel layer morphology and swelling

Figure 6.14 shows the effect of increasing MCC content on HPMC gel layer development. In common with DCP and lactose, at low contents of MCC (15-30% w/w) there was little effect on the microstructure or the swelling of the gel layer. At higher contents (>30% w/w), MCC had a profound effect on the swelling and gelation of the HPMC matrix. A 'classical' gel layer was not formed, and disintegration of the underlying matrix was observed as hydration proceeded, with highly hydrated MCC particles 'crumbling' away from the matrix. This is most clearly shown in the matrices containing 85% w/w MCC in figure 6.15. Gel layer swelling kinetics (figure 6.16) showed that the thickness of the gel layer was proportional to the MCC content in the matrix with some variability in measurements as consequence of material debris falling out of the confocal plane

The disintegration of the matrix at high MCC content, through the wicking and imbibing of water of this diluent, would reduce the controlled release functionality and would result in premature drug release.
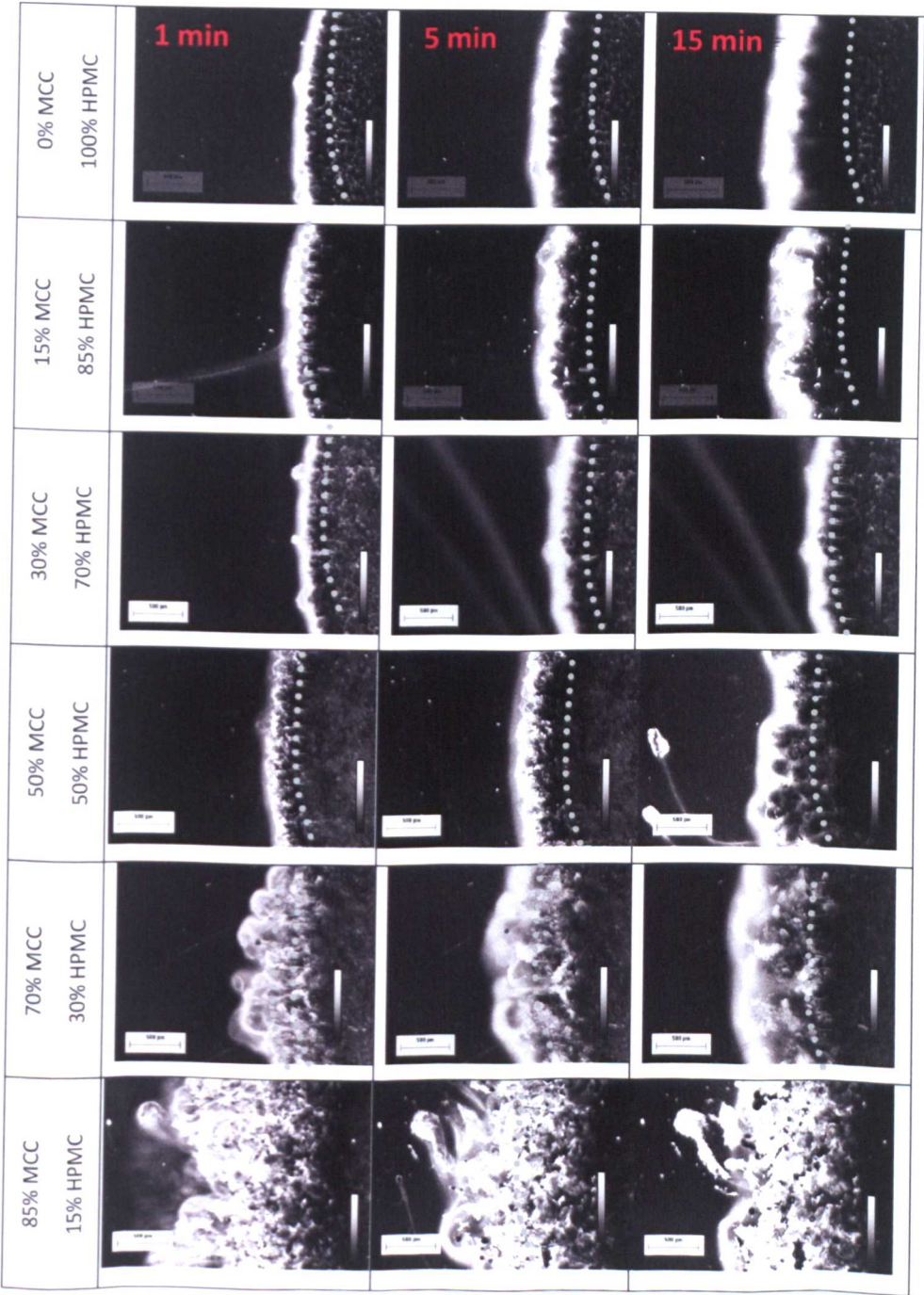
Figure 6.14 The effect of incorporating microcrystalline cellulose in the matrix of the HPMC gel layer after 1, 5 and15 minutes hydration in water

Formulations contained the indicated percentages of diluent and HPMC. The images are coded for fluorescence intensity from white (highest) to black (lowest) as indicated by the wedge. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Ex488>510 nm. Scale bar= 500 μm.

Massive disruption of the gel layer in the first minute of hydration

Matrix fails to form a coherent gel layer around the highly hydrated MCC particles

High levels of fluorescence for hydrated MCC and HPMC particles that undergoes disintegration during hydration
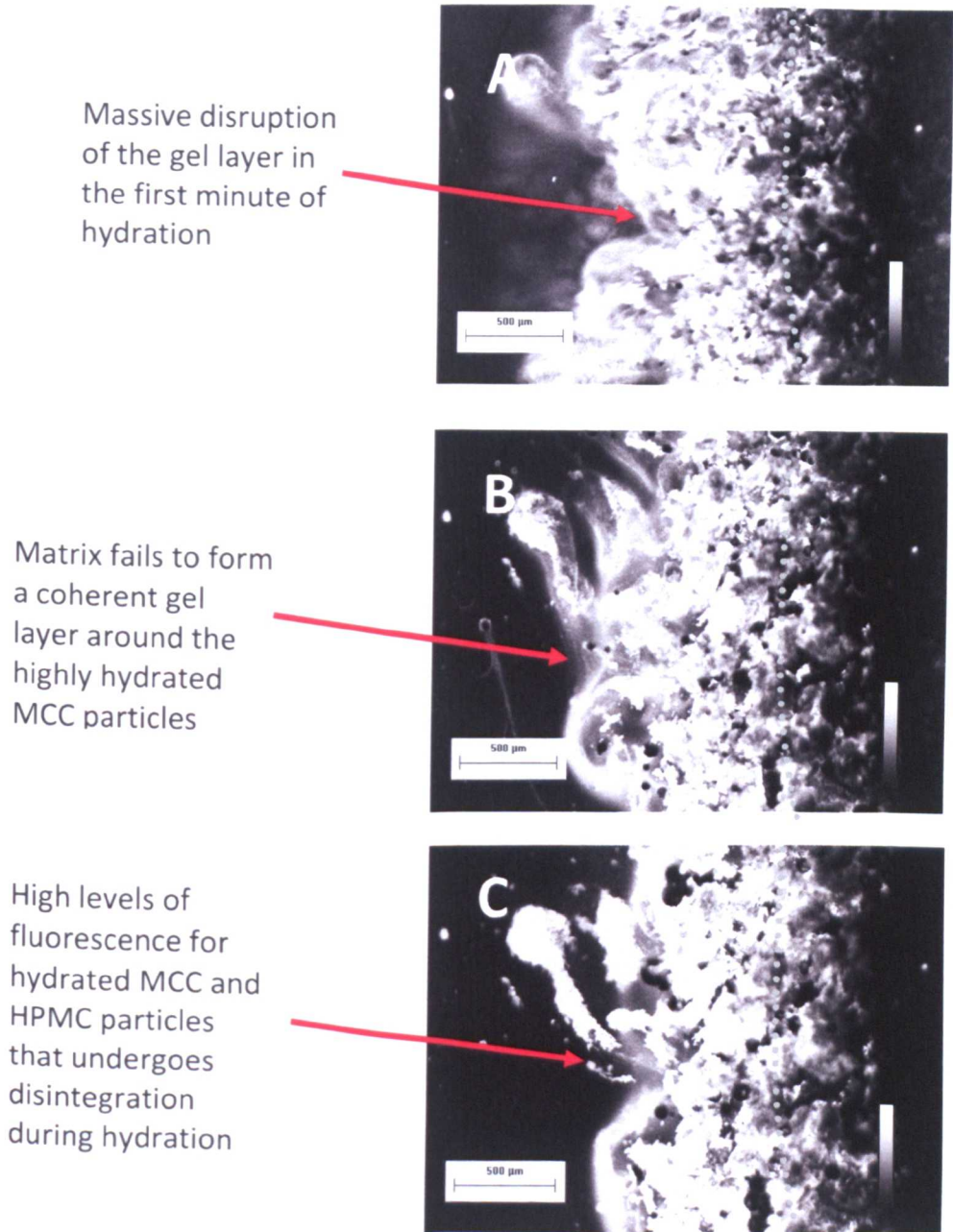
Figure 6.15 The effect of incorporating 85% w/w microcrystalline cellulose in the matrix on the evolution of the HPMC gel layer microstructure after (A) 1, (B) 5 and (C) 15 minutes
The images are coded for fluorescence intensity from white (highest) to black (lowest). Dotted line depicts the dry tablet boundary. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Ex488>510 nm. Scale bar = 500 µm
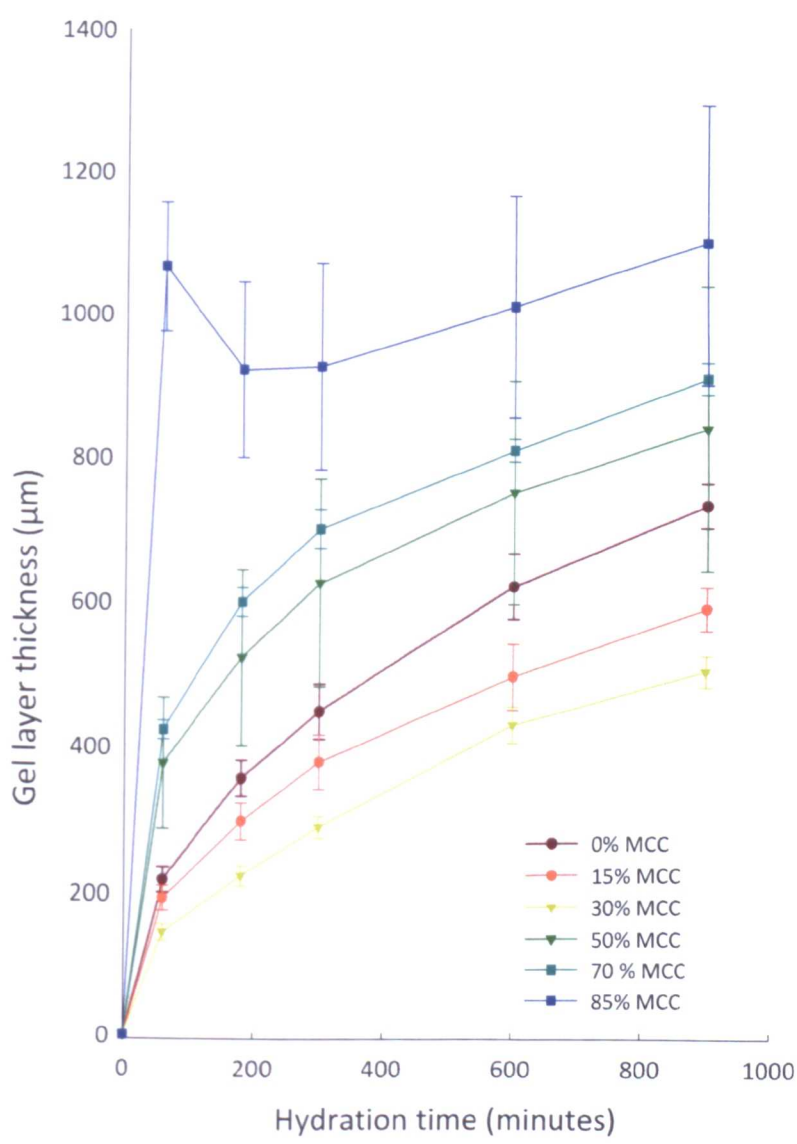
Figure 6.16 The effect of diluent content on the radial gel layer growth of HPMC matrices containing MCC

Formulations contained the indicated percentages of MCC and HPMC to 100%. Hydration in 0.008% w/v Congo red at 37°C. Swelling measured from dry tablet boundary to the edge of region B1. Mean (n=3) ±1 SD

6.4.6 The effect of diluent content on matrix disintegration

Disintegration times of HPMC matrices containing various levels of diluent content are shown in table 6.3. In water, 100% w/w HPMC matrices remained intact throughout the experimental period. Matrices with 15% w/w diluent content did not disintegrate, irrespective of the diluent employed. This was also the case for matrices containing 30% and 50% w/w diluent and supports the confocal images that show little evidence of gel layer disruption at these diluent contents. However, at 70% and 85% w/w diluent content, matrices disintegrated faster in 0.9% NaCl w/v than in water. In all cases, matrices, containing 85% w/w diluent, disintegrated more rapidly than those containing 70% w/w.

6.4.8.1 The effect of diluent content on matrix disintegration in sodium chloride solution

The influence of increasing NaCl concentration in the swelling medium on the disintegration of DCP, MCC and lactose matrices is shown in figures 6.17, 6.18 and 6.19 respectively. The incorporation of diluent in the matrix reduced the disintegration thresholds of the matrices when compared to 100% HPMC matrices. This supported the confocal work suggesting that all diluents disrupted gel layer formation at the higher content.

MCC matrices afforded the greatest resistance to electrolyte challenge, whereas lactose matrices appeared to be the most susceptible. This suggested a combined burden upon HPMC particle swelling and coalescence provided by NaCl in the swelling medium and the 'salting out' soluble diluent in the matrices.

Tablet content (% w/w)		Disintegration times of matrices containing MCC (min)		Disintegration times of matrices containing DCP (min)		Disintegration times of matrices containing lactose (min)	
Diluent	HPMC	Water	0.9% NaCl	Water	0.9% NaCl	Water	0.9% NaCl
0	100	>120	>120	>120	>120	>120	>120
15	85	>120	>120	>120	>120	>120	>120
30	70	>120	>120	>120	>120	>120	>120
50	50	>120	>120	>120	>120	>120	>120
70	30	>120	35	>120	>120	30	4
85	15	10	6	5	1	1	1

Table 6.3 Disintegration times of HPMC matrices containing different diluents in 0.9% w/v NaCl and water
USP Standard methodology, 37°C, carried out maximally for 120 minutes. Mean (n=4) ± 1 SD.
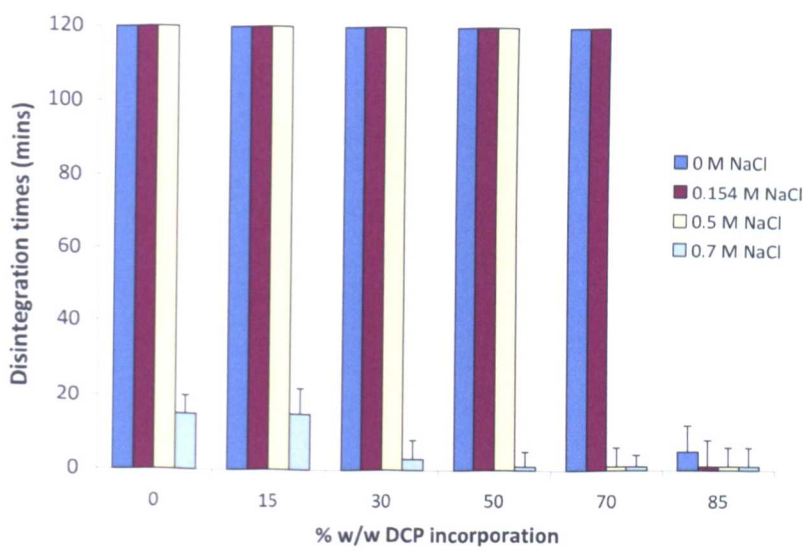
Figure 6.17 The effect of DCP incorporation on HPMC matrix disintegration time with respect to increasing sodium chloride concentration
USP Standard methodology, 37°C, carried out maximally for 120 minutes. Mean (n=4) ± 1 SD. (0.154 M = 0.9% NaCl)
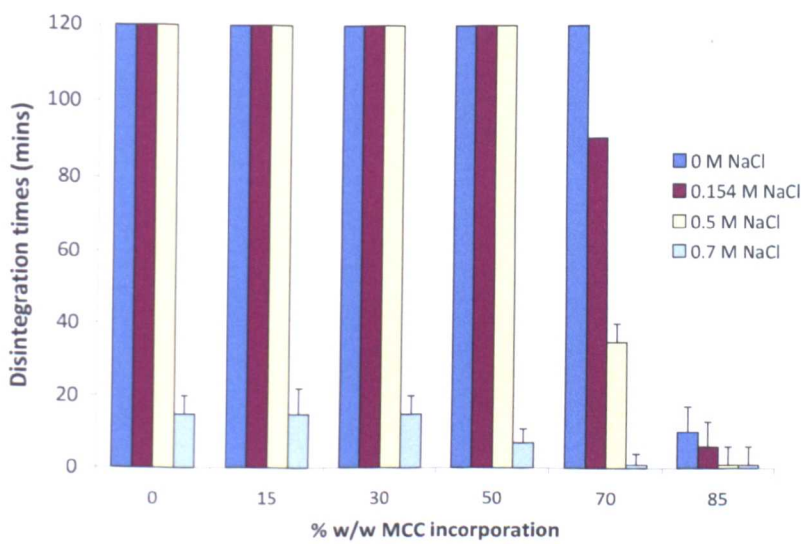
Figure 6.18 The effect of MCC incorporation on HPMC matrix disintegration time with respect to increasing sodium chloride concentration
USP Standard methodology, 37°C, carried out maximally for 120 minutes. Mean (n=4) ± 1 SD. (0.154 M = 0.9% NaCl)
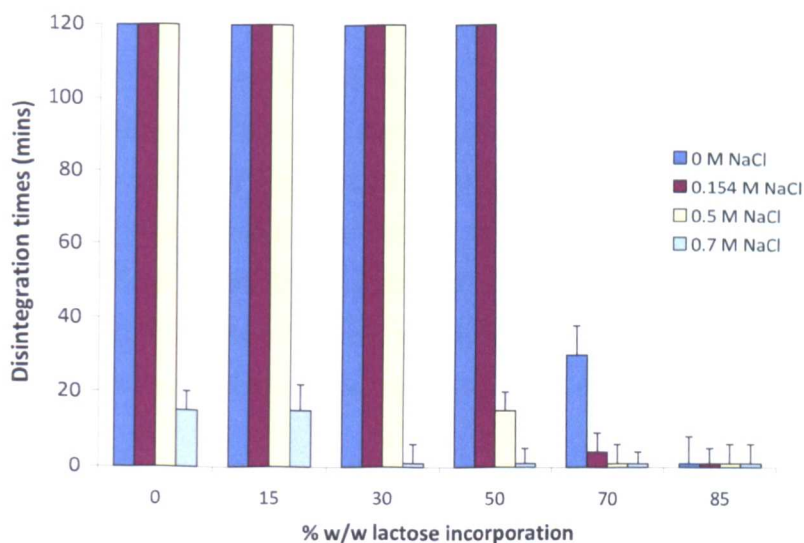
Figure 6.19 The effect of increasing lactose content on HPMC matrix disintegration time with respect to increasing sodium chloride concentration
USP Standard methodology, 37°C, carried out maximally for 120 minutes. Mean (n=4) ± 1 SD. (0.154 M = 0.9% NaCl)

6.5 Discussion

These results suggest that the physicochemical properties of diluents influence early gel layer formation and disintegration. These changes include alterations to the rate of swelling, disruption of coherent gel layer formation and diffusion barrier resistance to NaCl challenge. This study has provided novel imaging evidence to support previous literature findings (e.g Ford *et al.* 1987, Levina and Rajabi-Siahboomi 2004 and Jamzad *et al.* 2005). The effects of each diluent on the gel layer formation and matrix disintegration will now be discussed in more detail.

6.5.1 The effect of lactose

The effect of lactose on drug release rates from HPMC hydrophilic matrices has been described previously (Levina and Rajabi-Siahboomi 2004, Jamzad *et al.* 2005) in which an increase in lactose content results in more rapid drug release. The key difference of lactose in comparison with MCC and DCP is its high solubility, and consequently it exerts an osmotic pressure on gel layer coherence. From the confocal images presented in this chapter, it appears that lactose would influence drug release since the gel layer porosity will be increased by the rapidly dissolving lactose, resulting in an osmotic pressure increasing the hydration and dissolution of the gel layer. This would effectively expand the volume of the gel layer, and consequently lowering the concentration of HPMC across the gel layer and reducing its molecular tortuosity.

An additional influence that may be exerted by lactose is its capability of 'salt-out' HPMC in solution and reducing its sol:gel transition temperature. The capability of saccharides to affect the behaviour of thermo-sensitive polymers has been noted in the literature (Kim *et al.* 1995, Kawasaki *et al.* 1996, Kato *et al.* 2001, Lee *et al.* 2003). In this chapter, it has been seen

that the individual particle swelling and coalescence appeared to be affected by the content of lactose in the matrix, with a particulate gel layer appearing to form when the lactose content in the matrix exceeded 50(w/w. This acts as an additional explanation to the influence of lactose o HPMC gel layer swelling and functionality, particularly its affording (lesser resistance to the 'salting out' NaCl in the hydration medium.

In summary, the effect of lactose on gel layer formation may be proposed as being a combination of: (i) increasing the lactose content increases the soluble material within the matrix, which increases diffusion pathways, facilitating drug egress and water ingress, (ii) the osmotic potential of lactose in solution (Whittier 1933) results in a driving force which leads to increased water uptake and consequently greater gel layer hydration and (iii) the water structuring effect of lactose leads to dehydration of the hydrophobic regions of the polymer, with a consequential reduction in HPMC particle swelling and coalescence. It may also reduce the amount of polymer available to contribute to the gel layer.

6.5.2 The effect of MCC

MCC has been found to influence the early gel layer formation (Ford *et al.* 1987, Jamzad *et al.* 2005). The fluorescence of MCC in the presence of Congo red allowed it to be identified within the gel layer with the extent of its appearance being directly related to the original level of incorporation. Unlike lactose, the insoluble nature of MCC means that it does not affect the solution properties of HPMC. This insolubility means that it did not result in uncontrolled gel layer expansion up to the highest diluent content investigated, possessing a different mechanism of disruption of the gel layer formation.

With low MCC content, the insoluble particles of MCC will act as a physical barrier to the diffusion pathways through the gel layer, both for the entry of water and release of drugs. However, it was apparent that when MCC content relative to HPMC exceeded a critical threshold, there was impairment of effective barrier formation, resulting in underlying matrix disintegration as a result of MCC wicking and imbiding of water.

The disruption of gel layer formation by insoluble materials has been noted in other papers investigating polymer particle erosion and its effects on drug release (Zuleger and Lippold 2001, Zuleger *et al.* 2002, Freichel and Lippold 2004). Zuleger and Lippold (2001) proposed that polymer particle erosion processes were the result of insoluble fibres contained in a hydrophilic matrix based on methylhydroxy ethylcellulose (MHEC). These particles acted to impede the matrix swelling, weakened the gel layer and lead to attrition of polymer material.

The apparent 'protective' effect of MCC in response to electrolyte challenge is potentially a consequence of its disruption mechanism. When a 'salting out' electrolyte such NaCl is present in the swelling medium, this may reduce the swelling of MCC and hence counteract the mechanism by which this filler would disrupt HPMC gel layer formation.

These results conflict with the findings of Cao *et al.* (2005) who found, that increasing the level of MCC within a matrix formulation led to increased drug release rates. However, these matrices were formulated with other disintegrants, which would have led to a lowering of the threshold described above and consequently immediate release.

6.5.3 The effect of DCP

The insoluble and non-swelling filler DCP was found to influence the morphology and swelling of the gel layer. This influence is unlikely to be the result of a chemical interaction between HPMC and the insoluble calcium salts since a study by Dorozhkin (2001) has confirmed no interaction between calcium phosphate and HPMC used FTIR, X-ray diffraction and SEM. From the confocal images, DCP appears to act as a physical barrier to HPMC particles coalescing. This effect appears to only become significant in leading to matrix disintegration at high DCP loading (85% w/w). Below this threshold (~50% w/w) there appeared to be little difference between the morphology of the gel layers formed between the three different fillers suggesting that a coherent gel layer forms, but with the presence of insoluble material in it, increasing drug diffusion pathways and slowing drug release. This confirms the findings of Ford *et al.* (1987) who suggested that only at high (>50%) content levels do differences between insoluble and soluble fillers manifest as changes in drug release profiles and contradicts Alderman (1984) that as little as 10% insoluble solid may prevent HPMC matrices extending drug release. The caveat to this is that this applies to a binary system of DPC and HPMC only, and as has been shown in the previous chapter, drugs can exert a considerable influence on the development and properties of the gel layer.

6.6 Conclusions

The confocal images presented provide unprecedented microscopic evidence to support the many literature reports of the effects of different diluents on drug release from HPMC matrices. This study confirms that diluents may have significant effects on the early gel layer formation in HPMC hydrophilic matrices with diluent solubility and physical nature appearing to exert considerable influence on the emerging gel layer.

Lactose appears to have a particularly detrimental effect compared with DCP and MCC, which may be related to high solubility and its 'salting out' capability. The presence of lactose within the matrix places an increased burden upon gel layer formation capacity which was evidenced by increased susceptibility to disintegration upon NaCl challenge. This confirms the hypothesis rationalised in chapter 3 that lactose exerts a considerable influence on drug release through effects on the gel layer.

The next stage is to investigate if the detrimental effect of lactose and the relatively neutral effect of MCC manifest as changes in gel layer properties in matrices containing diclofenac Na and meclofenamate Na.

Chapter 7

The combined effects of drugs and diluents on early gel layer formation in HPMC hydrophilic matrices

7.1 Chapter aims and objectives

This chapter aimed to build on the previous experimental findings by examining the effects of drugs and diluents on gel layer formation when they are co-formulated in HPMC matrices.

Specifically the objectives were:

- To investigate the effects of drugs and diluents when formulated concomitantly in hydrophilic matrices

- To study the early gel layer morphology of matrices containing various ratios of drug:HPMC with high and low diluent content

- To determine the influence of NaCl on the interactive effects of drug and diluents on HPMC hydrophilic matrix gel layer formation.

7.2 Materials and Methods

7.2.1 Materials

7.2.1.1 HPMC

A sieve fraction of 63-90 μm HPMC (Methocel E4M CR Premium) was used in matrix manufacture. Details of the source and batch number are detailed in appendix 1.

7.2.1.2 Drugs

Diclofenac Na and meclofenamate Na were used as supplied. Details of the source and batch number are detailed in appendix 1.

7.2.1.3 Diluents

Lactose and MCC were used as supplied. Details of the source and batch number are detailed in appendix 1.

7.2.1.4 Water

Solutions were prepared using Maxima HPLC grade water. Details are in appendix 1.

7.2.2 Turbimetric determination of the sol:gel phase transition temperature

Turbimetric determinations of the sol:gel transition temperature of HPMC solutions containing drugs and lactose were undertaken as described in section 3.2.2.

7.2.3 Manufacture of matrix tablets

Fractionation of HPMC by sieving was undertaken using the method described in section 3.2.6.1. HPMC matrices containing drugs and diluents were manufactured using the method described in section 3.2.6.3.

The formulations investigated are detailed in table 7.1 and 7.2 for 19% w/w and 59% w/w diluent containing matrices respectively.

7.2.3.1 Matrix storage

HPMC matrices were stored under the conditions described in section 3.2.6.4.

7.2.4 Confocal laser scanning microscopy imaging

Confocal laser scanning imaging was undertaken using the method as described in section 5.4.6.

7.2.5 Tablet disintegration studies

Disintegration studies were undertaken using the method as described in as section 3.2.7.

Drug	% w/w drug	Diluent	% w/w diluent	% w/w HPMC
Meclofenamate Na	20	MCC	19	60
Meclofenamate Na	20	Lactose	19	60
Diclofenac Na	20	MCC	19	60
Diclofenac Na	20	Lactose	19	60
Meclofenamate Na	40	MCC	19	40
Meclofenamate Na	40	Lactose	19	40
Diclofenac Na	40	MCC	19	40
Diclofenac Na	40	Lactose	19	40
Meclofenamate Na	50	MCC	19	30
Meclofenamate Na	50	Lactose	19	30
Diclofenac Na	50	MCC	19	30
Diclofenac Na	50	Lactose	19	30
Meclofenamate Na	60	MCC	19	20
Meclofenamate Na	60	Lactose	19	20
Diclofenac Na	60	MCC	19	20
Diclofenac Na	60	Lactose	19	20

Table 7.1 Formulations to investigate drug effects in matrices containing 19% w/w diluent

Matrices weighed 200 mg, compressed to 180 MPa. All matrices contained 1% magnesium stearate to aid tablet compression.

Drug	% w/w drug	Diluent	% w/w diluent	% w/w HPMC
Meclofenamate Na	10	MCC	59	30
Meclofenamate Na	10	Lactose	59	30
Diclofenac Na	10	MCC	59	30
Diclofenac Na	10	Lactose	59	30
Meclofenamate Na	20	MCC	59	20
Meclofenamate Na	20	Lactose	59	20
Diclofenac Na	20	MCC	59	20
Diclofenac Na	20	Lactose	59	20
Meclofenamate Na	30	MCC	59	10
Meclofenamate Na	30	Lactose	59	10
Diclofenac Na	30	MCC	59	10
Diclofenac Na	30	Lactose	59	10

Table 7.2 Formulations to investigate drug effects in matrices containing 59% w/w diluent
Matrices weighed 200 mg, compressed to 180 MPa. All matrices contained 1% magnesium stearate to aid tablet compression.

7.3 Results

7.3.1 The effects of diclofenac Na and meclofenamate Na with lactose on HPMC solution cloud point

The effect of drug addition on the CPT of an HPMC solution containing a constant concentration of lactose (250 mM) is shown in figure 7.1. The addition of diclofenac to an HPMC solution containing lactose led to a greater 'salting-out effect' of the HPMC solution than drug alone. Typically, there was a 6°C greater reduction in CPT upon diclofenac Na addition in the presence of lactose than the CPT reduction with drug alone. For solutions containing meclofenamate Na, the presence of lactose lowered the CPT compared to HPMC solutions containing drug alone as well as shifting the concentration at which an inflexion occurred in the HPMC solutions CPT containing meclofenamate Na (40 mM to 30 mM).

7.3.2 The effects of drugs and diluents on HPMC gel layer formation in water

7.3.2.1 The effects of drugs on gel layer formation in matrices containing low levels of diluent

The influence of low diluent content (19% w/w) on gel layer formation was determined in matrices containing variable contents of drug and HPMC. The rationale for examining this diluent content was that the drug release of diclofenac Na and meclofenamate Na presented in chapter 2 included formulations with this percentage or lower diluent content. Water was used as the hydration medium to eliminate the influence of ionic species on the drug-HPMC interactions
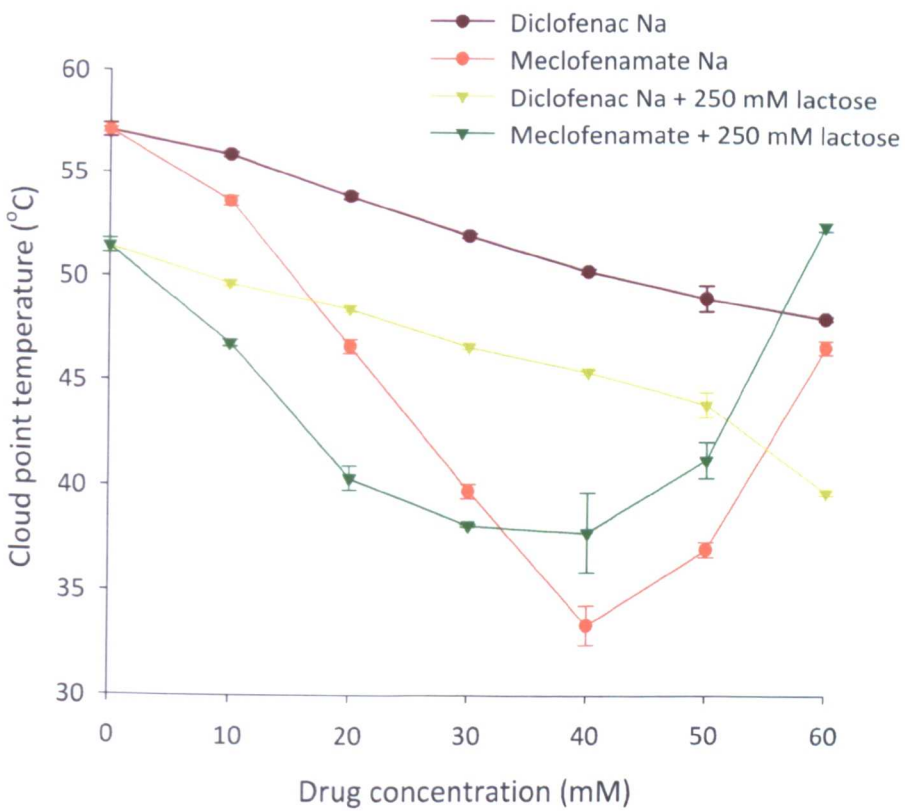
Figure 7.1 The effect of drug and lactose on the cloud point temperature (CPT) of 1% HPMC solutions

CPT measured turbimetrically as a reduction of 50% in light transmission (Sarkar 1979). Mean (n=3) ± SD

Figure 7.2 shows gel layer development in matrices containing 19% w/w MCC and increasing meclofenamate Na content. The gel layer growth is shown in figure 7.3. There was little difference between the matrix morphologies except at the highest meclofenamate Na content (60% w/w). The measurements of gel layer growth show only an increase in gel layer growth occurring for the formulation containing 60% w/w meclofenamate Na. The behaviour was analogous to the drug and HPMC matrices (chapter 5), in which increasing meclofenamate Na content increased the swelling of HPMC in the gel layer, therefore low MCC content did not appear to affect the influence of meclofenamate Na on HPMC particle swelling and coalescence.

Figure 7.4 shows the gel layer development of the matrices containing 19% w/w lactose and increasing meclofenamate Na content. The gel layer growth is shown figure 7.5. As with the MCC matrices, increased gel layer growth occurred with increasing meclofenamate content. The replacement of drug with lactose improved matrix integrity in comparison with binary mixtures of drug and HPMC alone. Lactose 'salts out' HPMC in solution but had little effect on gel layer formation up to 50% w/w content. The low lactose content apparently suppressed the effect of the meclofenamate Na and the gel layer maintained integrity. The gel layer growth shown in figure 7.5 supports this assertion, with a controlled swelling curve, typical in formulations with maintained matrix integrity, apparent for all meclofenamate Na contents.

| 20% meclofenamate 19% MCC 60% HPMC | 40% meclofenamate 19% MCC 40% HPMC | 50% meclofenamate 19% MCC 30% HPMC | 60% meclofenamate 19% MCC 20% HPMC |

Figure 7.2 The effect of increasing meclofenamate Na content in matrices containing low levels (19% w/w) of MCC on the evolution of the HPMC gel layer

Confocal microscopy images of the radial edge of a hydration matrix showing the development of the gel layer at 1, 5 and 15 minutes. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Images are coded for fluorescence intensity on a linear greyscale from white (highest) to black (lowest). Scale bar = 500 μm. Dotted line depicts the dry tablet boundary. All matrices contained 1% w/w magnesium stearate.

Figure 7.3 The effect of meclofenamate Na content on the radial gel layer growth of HPMC matrices containing 19% w/w MCC

Hydration in 0.008% w/v Congo red at 37°C. Swelling measured from dry tablet boundary to the edge of region B1. Mean (n=3) ±1 SD
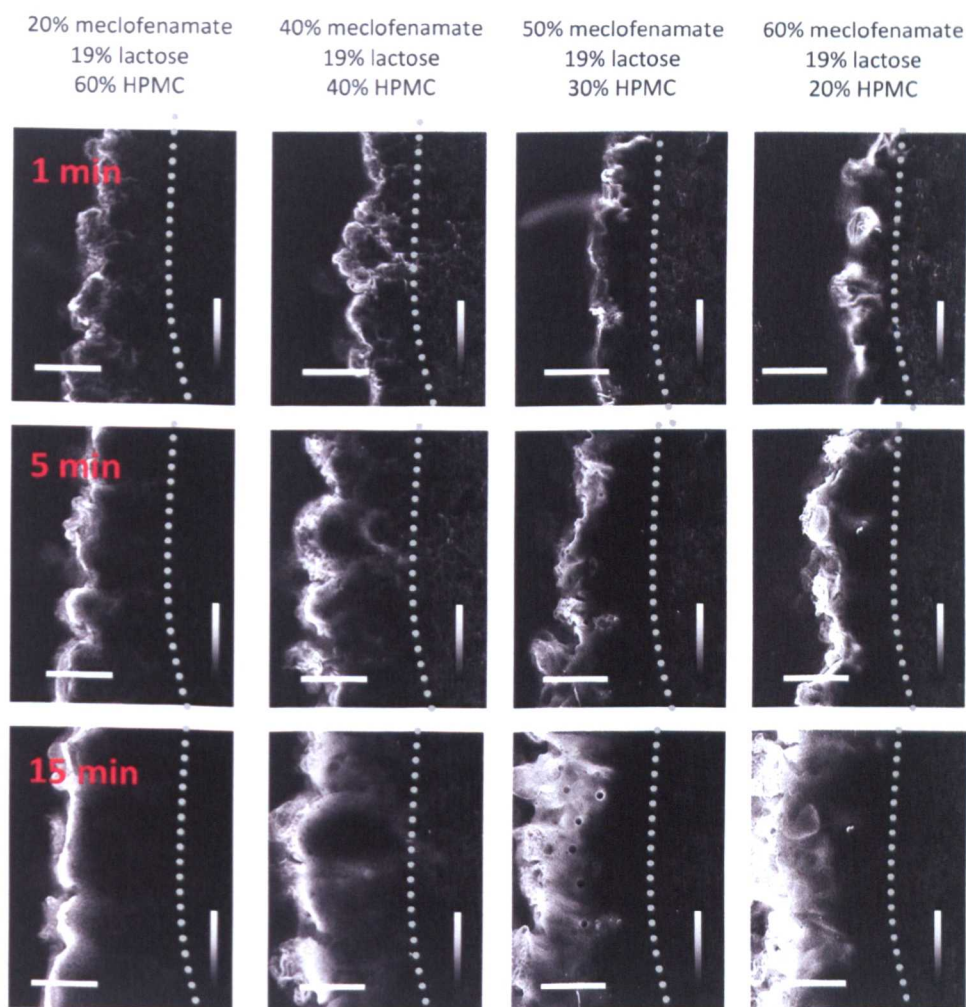
Figure 7.4 The effect of increasing meclofenamate Na content in matrices containing low levels (19% w/w) of lactose on the evolution of HPMC gel layer

Confocal microscopy images of the radial edge of a hydration matrix showing the development of the gel layer at 1, 5 and 15 minutes. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Images are coded for fluorescence intensity on a linear greyscale from white (highest) to black (lowest). Scale bar = 500 μm. Dotted line depicts the dry tablet boundary. All matrices contained 1% w/w magnesium stearate.
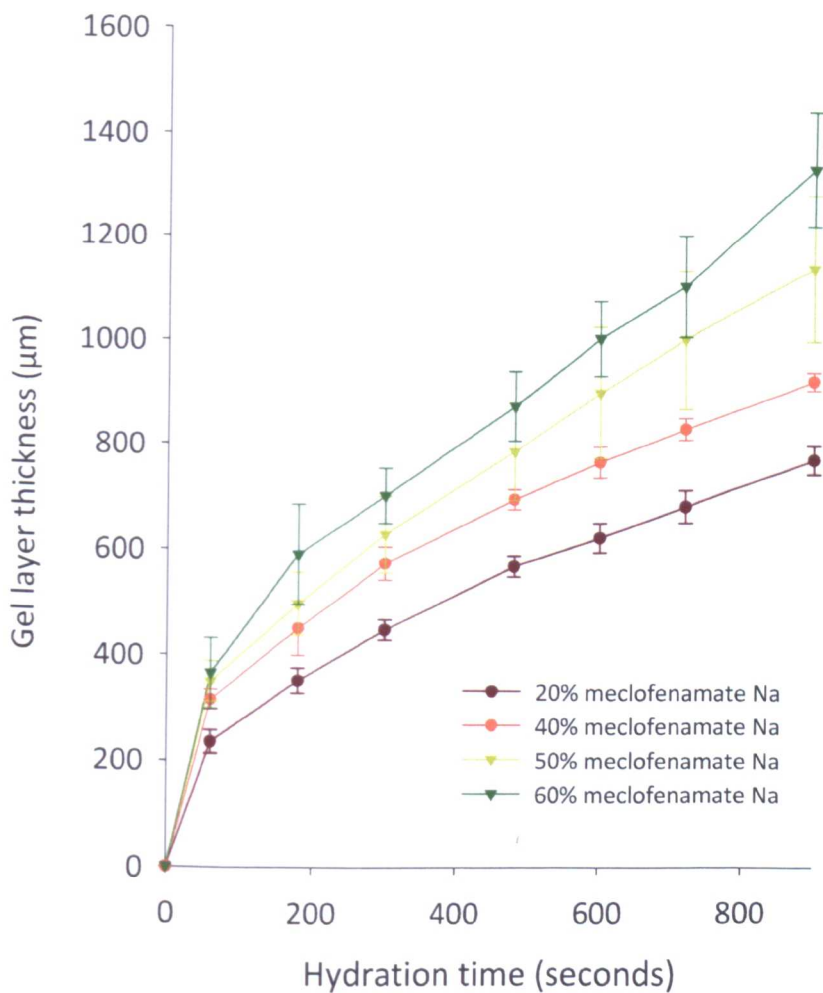
Figure 7.5 The effect of meclofenamate Na content on the radial gel layer growth of HPMC matrices containing 19% w/w lactose.

Hydration in 0.008% w/v Congo red at 37°C. Swelling measured from dry tablet boundary to the edge of region B1. Mean (n=3) ±1 SD

Figure 7.6 shows gel layer development in matrices containing 19% w/w MCC and increasing contents of diclofenac Na. The gel layer growth is shown in figure 7.7. Increasing the diclofenac Na content had a minimal effect on both the morphology and swelling of the gel layer. As with binary matrices of diclofenac Na and HPMC, a reduction in HPMC matrix content reduced the overall fluorescent intensity, particularly in the untangling and dissolving region at the gel layer periphery. The gel layer swelling suggested little difference between the formulations (figure 7.7).

Figure 7.8 shows gel layer development in matrices containing 19% w/w lactose and increasing diclofenac Na content. The gel layer growth is shown in figure 7.9. As with the MCC formulations, there was little effect on the overall swelling of the matrices supporting the assertions of Ford *et al.* (1987) that there is little difference in the effect of incorporation of low levels of soluble or insoluble diluents. However, there was an absence of fluorescent particulate matter in the gel layer and the 'classical' features in the immediate region were largely absent from the formulations as with the binary matrices of diclofenac Na and HPMC investigated in chapter 5.

20% diclofenac	40% diclofenac	50% diclofenac	60% diclofenac
19% MCC	19% MCC	19% MCC	19% MCC
60% HPMC	40% HPMC	30% HPMC	20% HPMC

Figure 7.6 The effect of increasing content of diclofenac Na in matrices containing low levels (19% w/w) of MCC on the evolution of HPMC gel layer

Confocal microscopy images of the radial edge of a hydration matrix showing the development of the gel layer at 1, 5 and 15 minutes. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Images are coded for fluorescence intensity on a linear greyscale from white (highest) to black (lowest). Scale bar = 500 µm. Dotted line depicts the dry tablet boundary. All matrices contained 1% w/w magnesium stearate.

Figure 7.7 The effect of diclofenac Na content on the radial gel layer growth of HPMC matrices containing 19% w/w MCC

Hydration in 0.008% w/v Congo red at 37°C. Swelling measured from dry tablet boundary to the edge of region B1. Mean (n=3) ±1 SD

Figure 7.8 The effect of increasing content of diclofenac Na in matrices containing low levels (19% w/w) of lactose on the evolution of HPMC gel layer microstructure after 1, 5 and 15 minutes hydration

Confocal microscopy images of the radial edge of a hydration matrix showing the development of the gel layer at 1, 5 and 15 minutes. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Images are coded for fluorescence intensity on a linear greyscale from white (highest) to black (lowest). Scale bar = 500 μm. Dotted line depicts the dry tablet boundary. All matrices contained 1% w/w magnesium stearate.
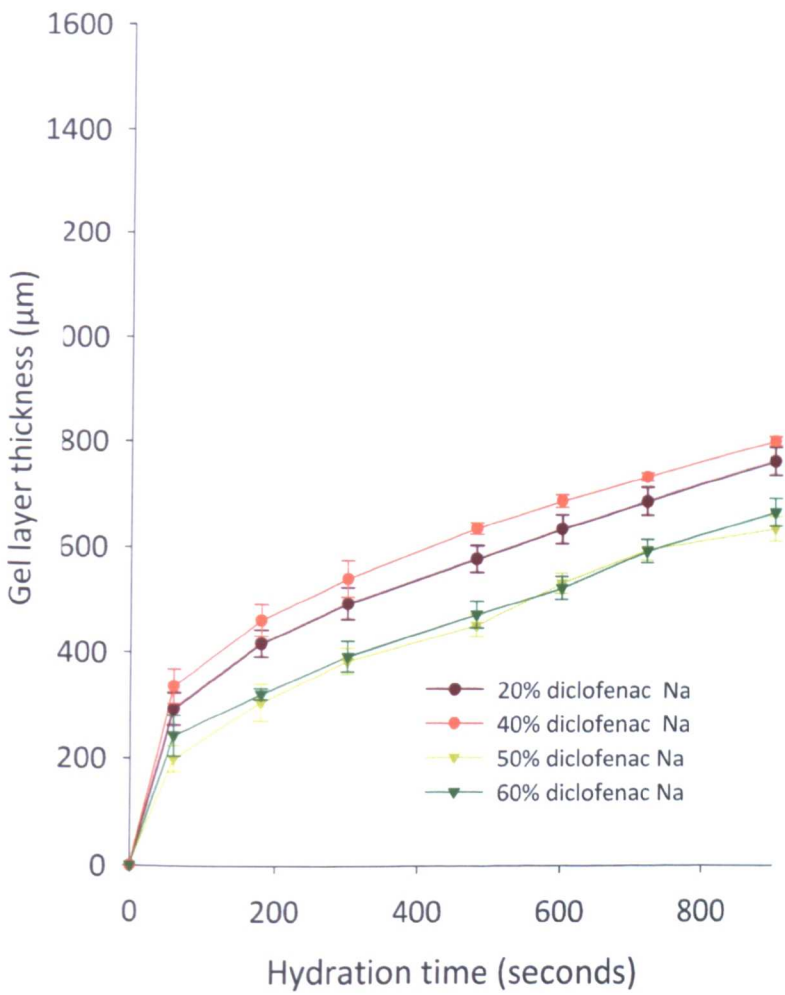
Figure 7.9 The effect of diclofenac Na content on the radial gel layer growth of HPMC matrices containing 19% w/w lactose

Hydration in 0.008% w/v Congo red at 37°C. Swelling measured from dry tablet boundary to the edge of region B1. Mean (n=3) ±1 SD

7.3.2.2 The effect of drug content on gel layer formation in matrices containing high levels of diluent

Figure 7.10 shows gel layer development in matrices containing 59% w/w MCC and increasing meclofenamate Na content. There was gradual loss of gel layer integrity as the meclofenamate Na content increased. With the lowest meclofenamate Na content (10% w/w), there was sufficient HPMC content to form a gel layer. As the drug loading increased, the internal swelling pressure and matrix disintegration capacity afforded by MCC resulted in disintegration of the more swollen and less concentrated HPMC gel layer. It appears the decrease in HPMC content and the association of meclofenamate Na with the HPMC to form a poly(electrolyte) material led to greater macromolecule chain extension, lowering the disintegration threshold of these matrices with respect to MCC.

Figure 7.11 shows gel layer development in matrices containing 59% w/w lactose and increasing meclofenamate Na content. At the lowest level of meclofenamate Na (10% w/w) the gel layer possessed a similar morphology to a high lactose: HPMC binary matrix (chapter 6). Therefore, the extent of the interaction between the drug and HPMC appeared insufficient to alter the polymer solution properties. However, when meclofenamate Na content was increased to 20% w/w, matrix integrity improved, possibly resulting from lactose counter-acting the 'salting-in' of meclofenamate Na. However, once the meclofenamate Na content was increased to 30% w/w, the burden of soluble material appeared to exceed the capacity of the remaining HPMC to form an adequate diffusion barrier and the gel layer failed.

Figure 7.12 shows the gel layer development in matrices containing 59% w/w MCC and increasing diclofenac Na content. There were clear

differences between the gel layer in each of the formulations. As the diclofenac Na content was increased there was an apparent decrease in HPMC particle swelling and a reduction in image fluorescence. At the lowest drug loading (10% w/w) the gel layer formed normally, but when the drug content was increased to 20% w/w, the presence of MCC appeared to exert a detrimental effect on gel layer development, with a pronounced 'bursting' of the gel layer. This may be as a result of the decreased HPMC content in the matrix unable to produce a sufficiently viscous gel layer to negate the swelling forces exerted by the MCC. This trend did not continue when drug content was increased to 30% w/w. The low levels of fluorescence from HPMC or the MCC suggests that the drug had suppressed matrix hydration almost completely and the 'bursting' effect evident at lower drug concentrations appeared to be suppressed. Diclofenac Na 'salts out' HPMC and reduced its swelling but it may also reduce the swelling of MCC, reducing the disintegration capacity of MCC within the gel layer. The image and measurement of the matrix swelling support this assertion.

Figure 7.13. shows the gel layer development in matrices containing 59% w/w lactose and increasing diclofenac Na content. An increase in diclofenac Na content resulted in a progressive decrease in the matrix swelling. The 10% w/w diclofenac Na matrix possessed the characteristic morphology of highly loaded lactose/HPMC binary matrix, with the drug appearing to exert little influence on the development of the gel layer. As the drug content increased, there was a reduction in particle swelling and gel layer growth, reduction in gel layer coherence, which allowed rapid dissolution of lactose from the matrix, eliminating matrix expansion.
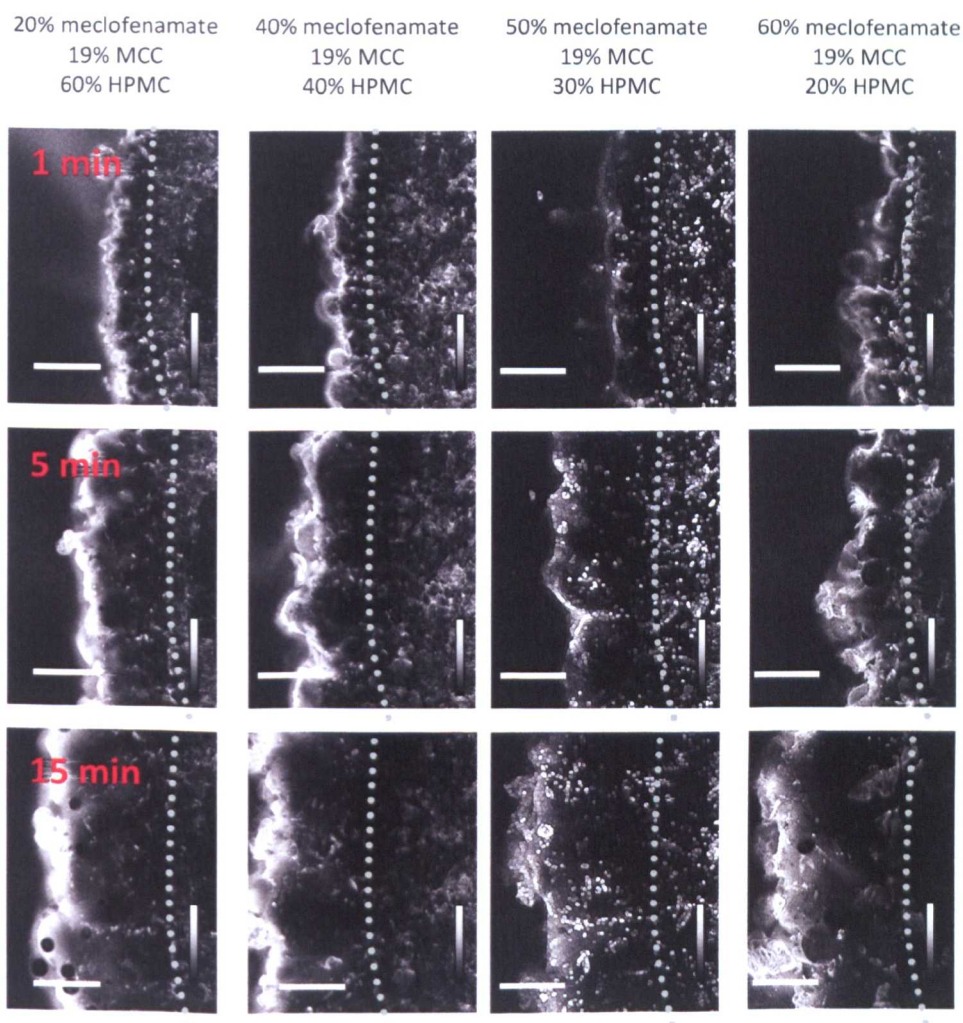
Figure 7.10 The effect of increasing content of meclofenamate Na in matrices containing high levels (59% w/w) of MCC on the evolution of HPMC gel layer

Confocal microscopy images of the radial edge of a hydration matrix showing the development of the gel layer at 1, 5 and 15 minutes. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Images are coded for fluorescence intensity on a linear greyscale from white (highest) to black (lowest). Scale bar = 500 μm. Dotted line depicts the dry tablet boundary. All matrices contained 1% w/w magnesium stearate.
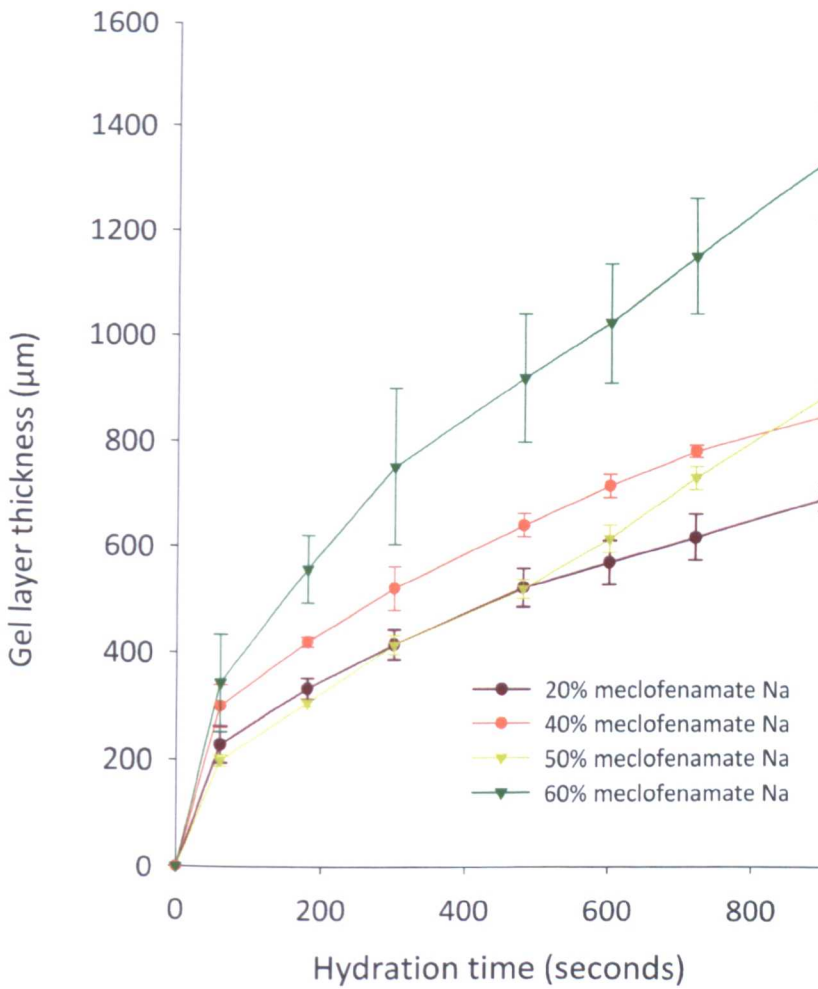
10% Meclofenamate	20% Meclofenamate	30% Meclofenamate
59% lactose	59% Lactose	59% lactose
30% HPMC	20% HPMC	10% HPMC

Figure 7.11 The effect of increasing content of meclofenamate Na in matrices containing high levels (59% w/w) of lactose on the evolution of HPMC gel layer

Confocal microscopy images of the radial edge of a hydration matrix showing the development of the gel layer at 1, 5 and 15 minutes. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Images are coded for fluorescence intensity on a linear greyscale from white (highest) to black (lowest). Scale bar = 500 μm. Dotted line depicts the dry tablet boundary. All matrices contained 1% w/w magnesium stearate.
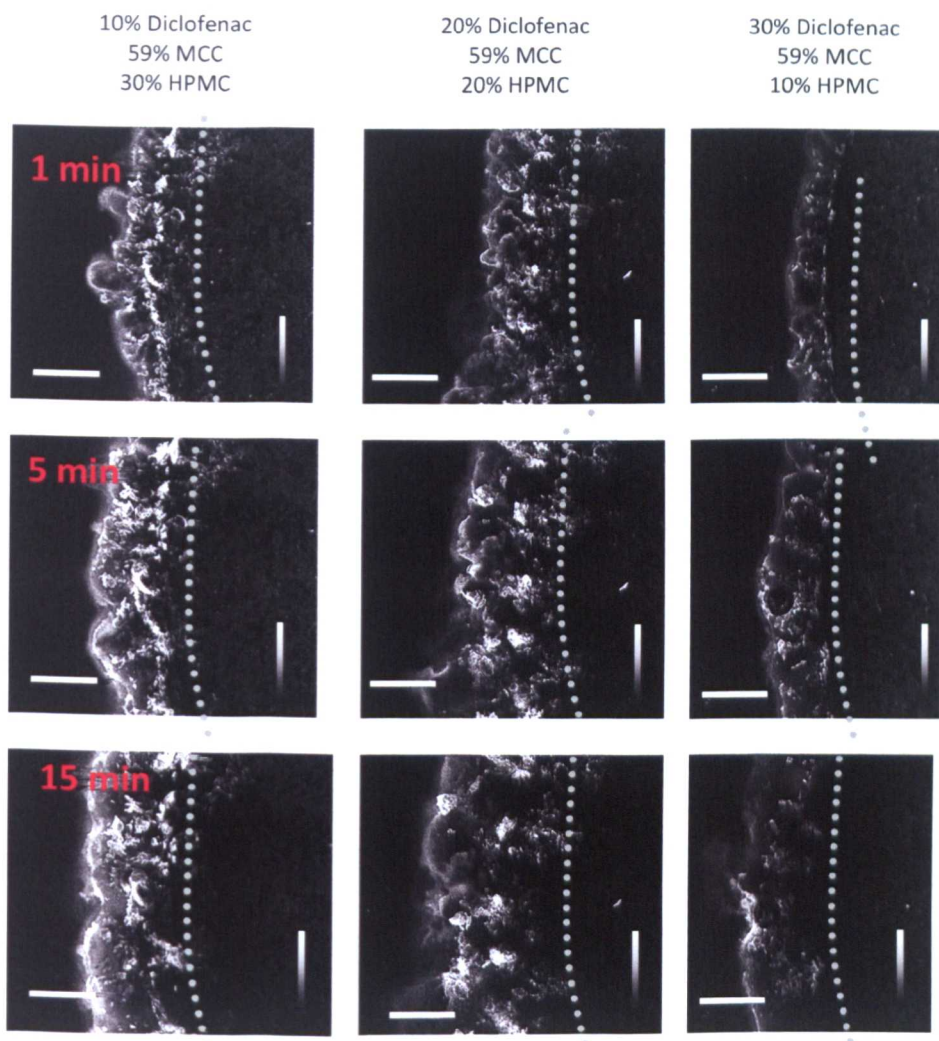
Figure 7.12 The effect of increasing content of diclofenac Na in matrices containing high levels (59% w/w) of MCC on the evolution of HPMC gel layer

Confocal microscopy images of the radial edge of a hydration matrix showing the development of the gel layer at 1, 5 and 15 minutes. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Images are coded for fluorescence intensity on a linear greyscale from white (highest) to black (lowest). Scale bar = 500 μm. Dotted line depicts the dry tablet boundary. All matrices contained 1% w/w magnesium stearate.

10% Diclofenac	20% Diclofenac	30% Diclofenac
59% lactose	59% lactose	59% lactose
30% HPMC	20% HPMC	10% HPMC

Figure 7.13 The effect of increasing content of diclofenac Na in matrices containing high levels (59% w/w) of lactose on the evolution of HPMC gel layer

Confocal microscopy images of the radial edge of a hydration matrix showing the development of the gel layer at 1, 5 and 15 minutes. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Images are coded for fluorescence intensity on a linear greyscale from white (highest) to black (lowest). Scale bar = 500 μm. Dotted line depicts the dry tablet boundary. All matrices contained 1% w/w magnesium stearate.

7.3.3 The effects of drugs and diluents on HPMC gel layer formation in 0.9% NaCl

In chapter 4, it was observed that the interaction between drugs and HPMC was influenced in the presence of NaCl. This appeared to manifest as an effect on the gel layer of binary matrices containing drugs and HPMC (chapter 5). This section aims to determine if NaCl also influences the combined effects of drugs and diluents in HPMC hydrophilic matrices.

7.3.3.1 The effects of drugs and NaCl on gel layer formation in matrices containing low levels of diluent

Figure 7.14 shows the effect of 19% w/w MCC on the gel layer development in hydrophilic matrices containing increasing meclofenamate Na content hydrating in 0.9% NaCl. Unlike the behaviour of the formulations in water, there were clear differences in the morphology of the gel layers. Matrices with low meclofenamate Na content (20% w/w), swelled rapidly and disintegrated. As the meclofenamate Na loading increased, gel layer integrity improved, correlating with extended release profiles of matrices with high meclofenamate Na content presented in chapter 2. The presence of NaCl salted the polymer out of solution, and increasing the viscosity of the gel layer.

Figure 7.15 shows the effects of 19% w/w lactose content on the gel layer development in matrices containing increasing meclofenamate Na content. Increased swelling and gelation occurred in the lowest meclofenamate content matrices and replacement of drug with lactose led to an increase in matrix integrity. The lactose in the dosage form, coupled with NaCl in the hydration medium, appeared to act synergistically to suppress the effect of increasing meclofenamate Na matrix content.
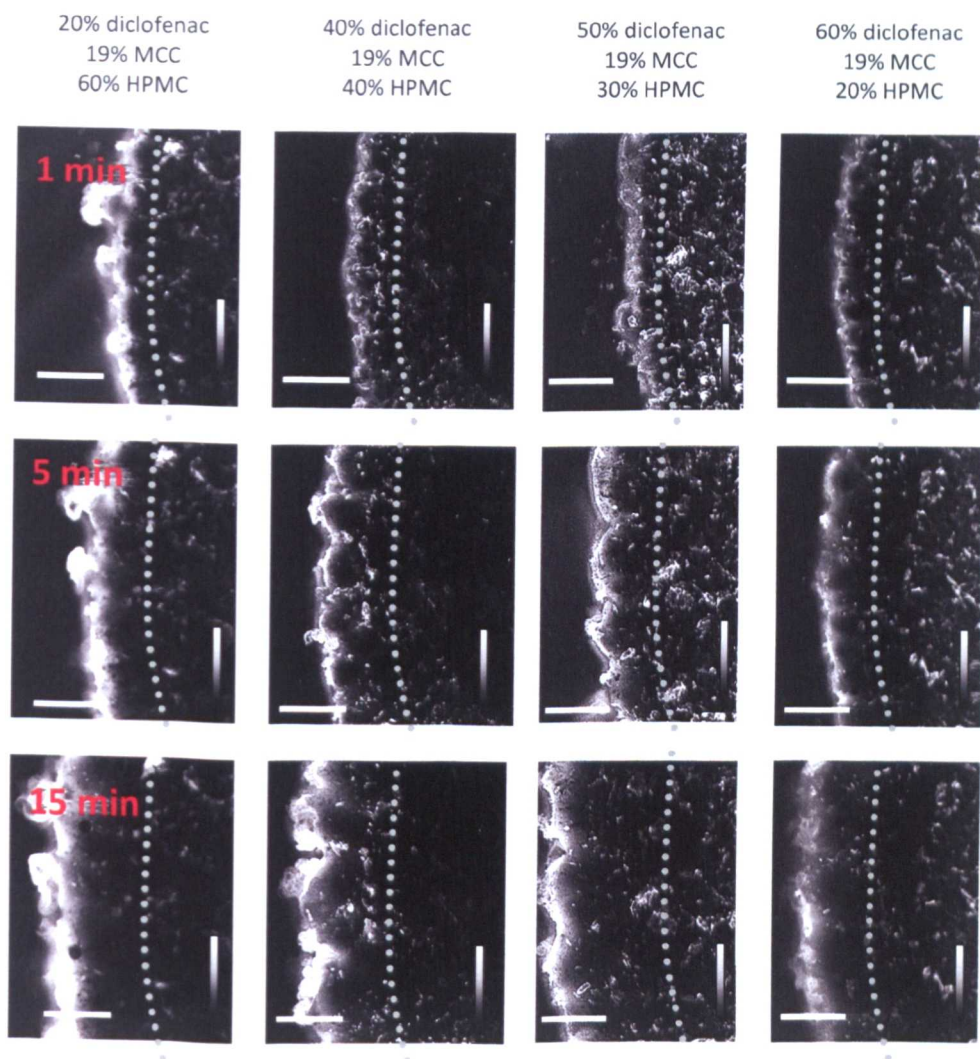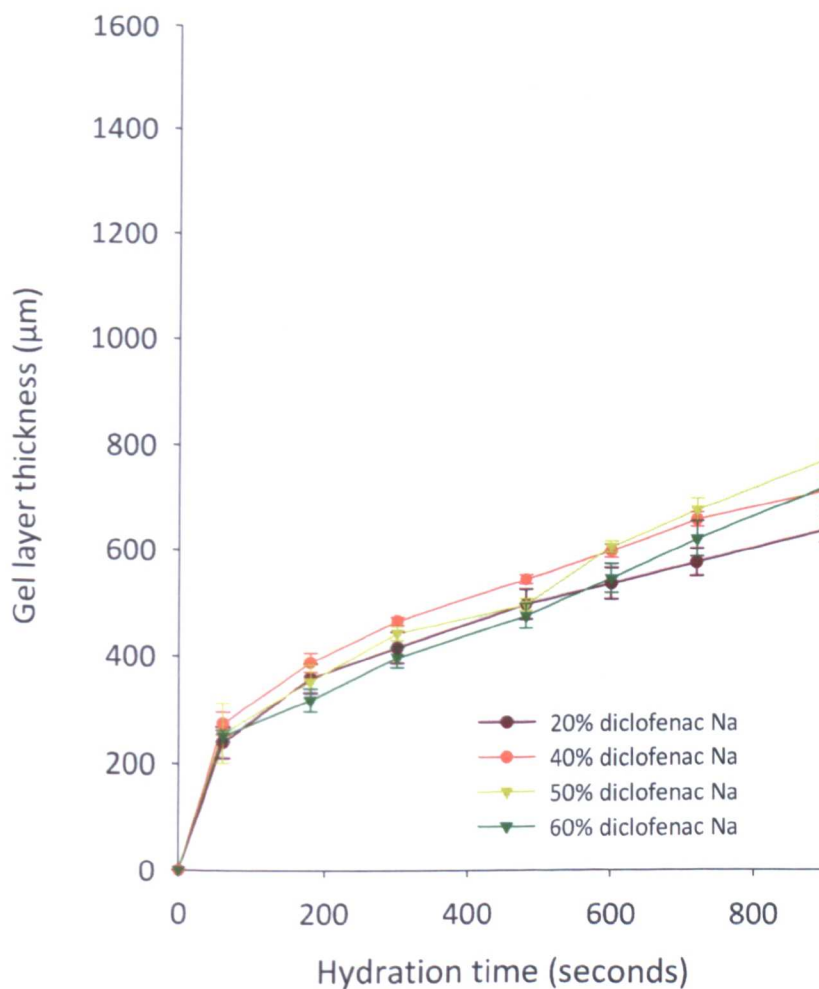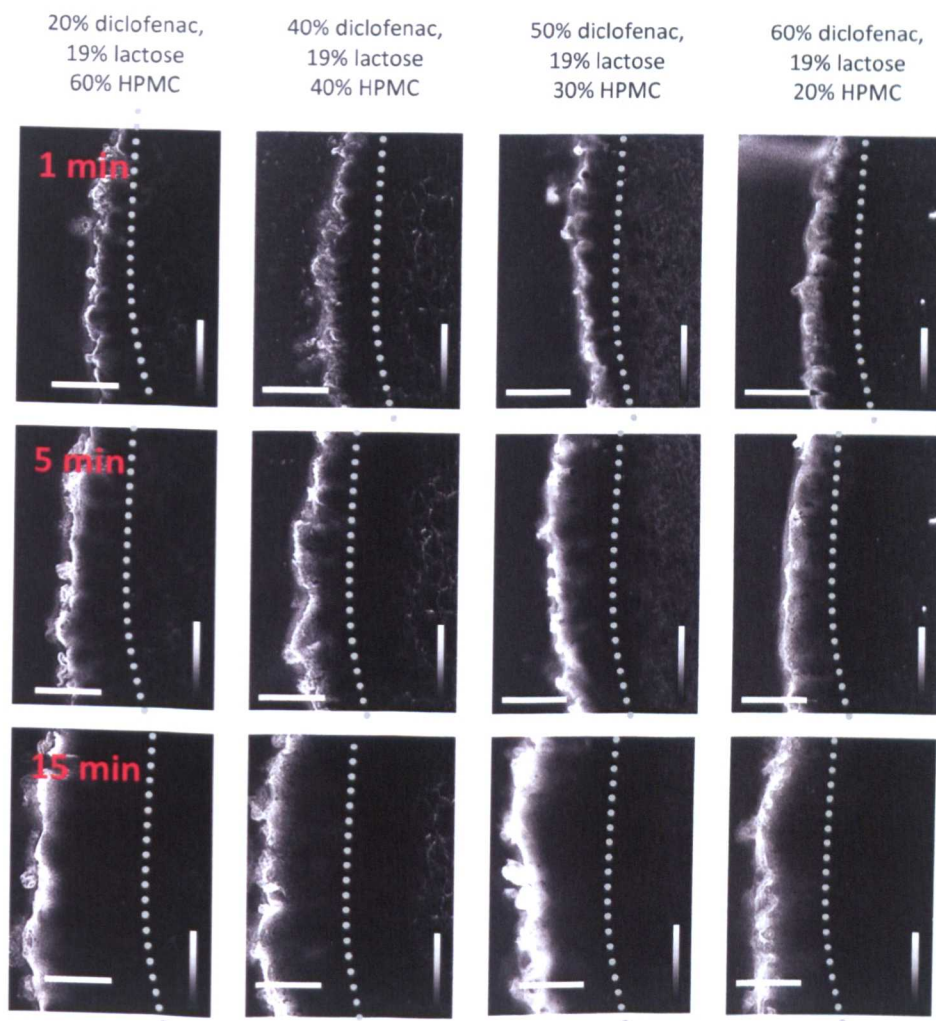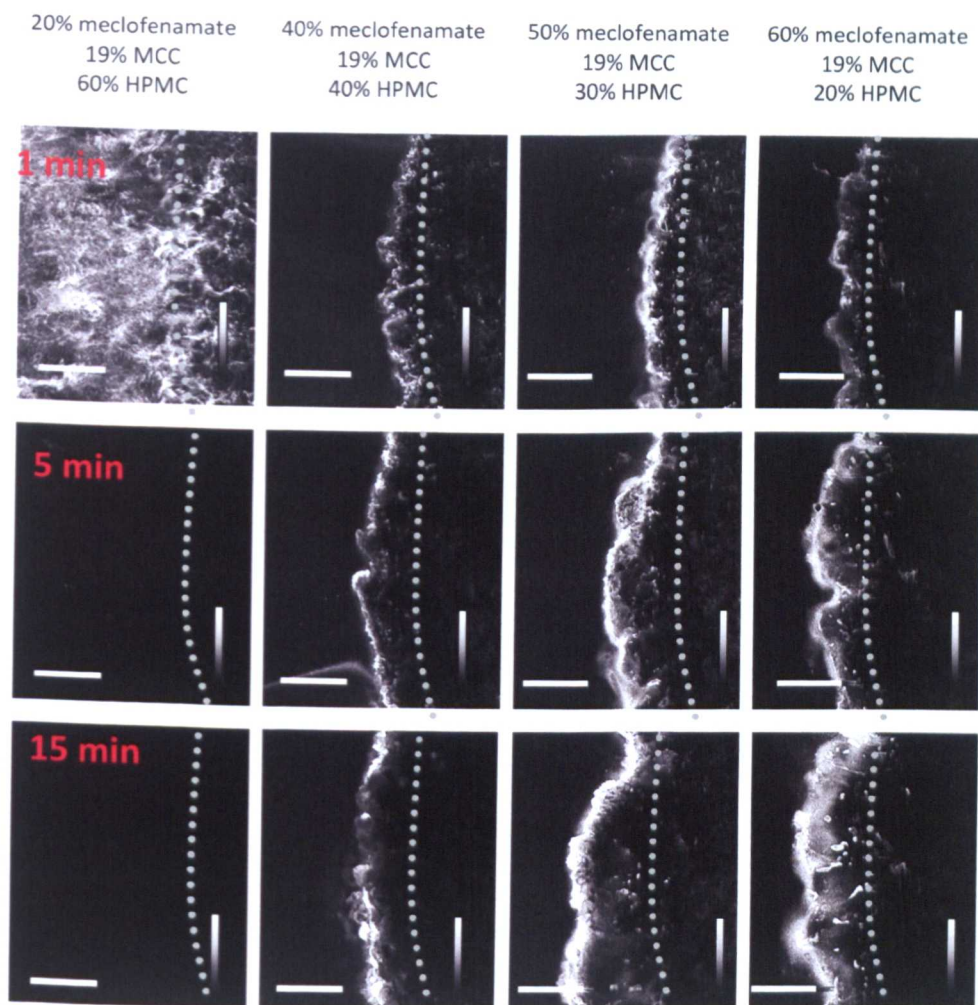
Figure 7.14 The effect of increasing content of meclofenamate Na in matrices containing low levels (19% w/w) of MCC on the evolution of HPMC gel layer in 0.9% NaCl

Confocal microscopy images of the radial edge of a hydration matrix showing the development of the gel layer at 1, 5 and 15 minutes. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Images are coded for fluorescence intensity on a linear greyscale from white (highest) to black (lowest). Scale bar = 500 μm. Dotted line depicts the dry tablet boundary. All matrices contained 1% w/w magnesium stearate.

| 20% meclofenamate 19% lactose 60% HPMC | 40% meclofenamate 19% lactose 40% HPMC | 50% meclofenamate 19% lactose 30% HPMC | 60% meclofenamate 19% lactose 20% HPMC |

Figure 7.15 The effect of increasing content of meclofenamate Na in matrices containing low levels (19% w/w) of lactose on the evolution of the HPMC gel layer in 0.9% NaCl

Confocal microscopy images of the radial edge of a hydration matrix showing the development of the gel layer at 1, 5 and 15 minutes. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Images are coded for fluorescence intensity on a linear greyscale from white (highest) to black (lowest). Scale bar = 500 μm. Dotted line depicts the dry tablet boundary. All matrices contained 1% w/w magnesium stearate.

Figure 7.16. shows gel layer development in matrices containing 19% w/w MCC and increasing contents of diclofenac Na, hydrating in NaCl. The gel layer appeared to form normally at the lowest diclofenac Na content. As the drug content was increased, HPMC hydration appeared to decrease until there was clear disruption of particle swelling and coalescence at 60% w/w. The images resembled those of 80% w/w MCC 20% HPMC (chapter 6), which suggests that the combined 'salting out' HPMC particles by internal diclofenac Na and external NaCl had lowered the gel layer disintegration threshold with respect to MCC

Figure 7.17 shows gel layer development in matrices containing 19% w/w lactose and increasing contents of diclofenac Na, hydrating in NaCl. All matrices were observed to fail. The failure of diclofenac Na-HPMC binary matrices when hydrating in NaCl manifested in these matrices with the lactose content appeared to act to synergistically to 'salt out' the HPMC with internal drug and external electrolyte in the dissolution medium.

| 20% diclofenac and 19% MCC 60% HPMC | 40% diclofenac and 19% MCC 40% HPMC | 50% diclofenac and 19% MCC 30% HPMC | 60% diclofenac and 19% MCC 20% HPMC |
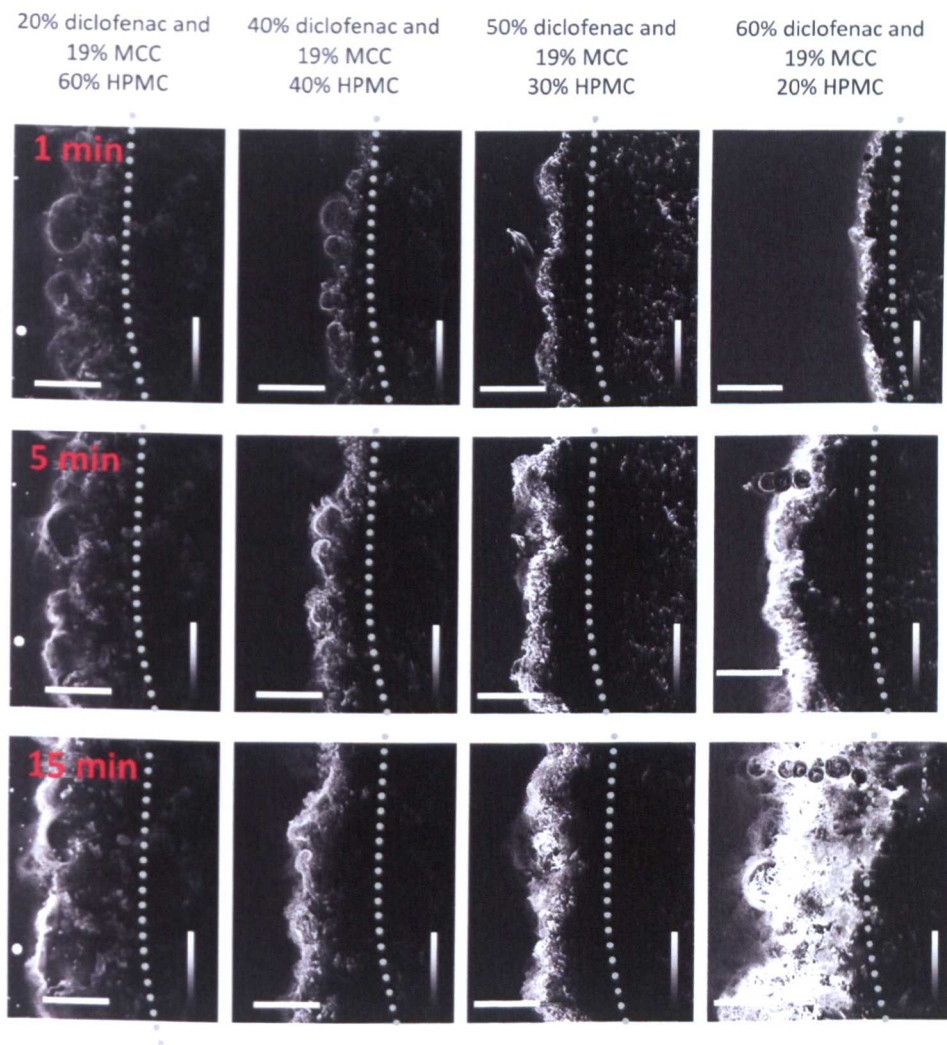
Figure 7.16 The effect of increasing content of diclofenac Na in matrices containing low levels (19% w/w) of MCC on the evolution of HPMC gel layer in 0.9% NaCl

Confocal microscopy images of the radial edge of a hydration matrix showing the development of the gel layer at 1, 5 and 15 minutes. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Images are coded for fluorescence intensity on a linear greyscale from white (highest) to black (lowest). Scale bar = 500 μm. Dotted line depicts the dry tablet boundary. All matrices contained 1% w/w magnesium stearate.

20% diclofenac	40% diclofenac	50% diclofenac	60% diclofenac
19% lactose	19% lactose	19% lactose	19% lactose
60% HPMC	40% HPMC	30% HPMC	20% HPMC
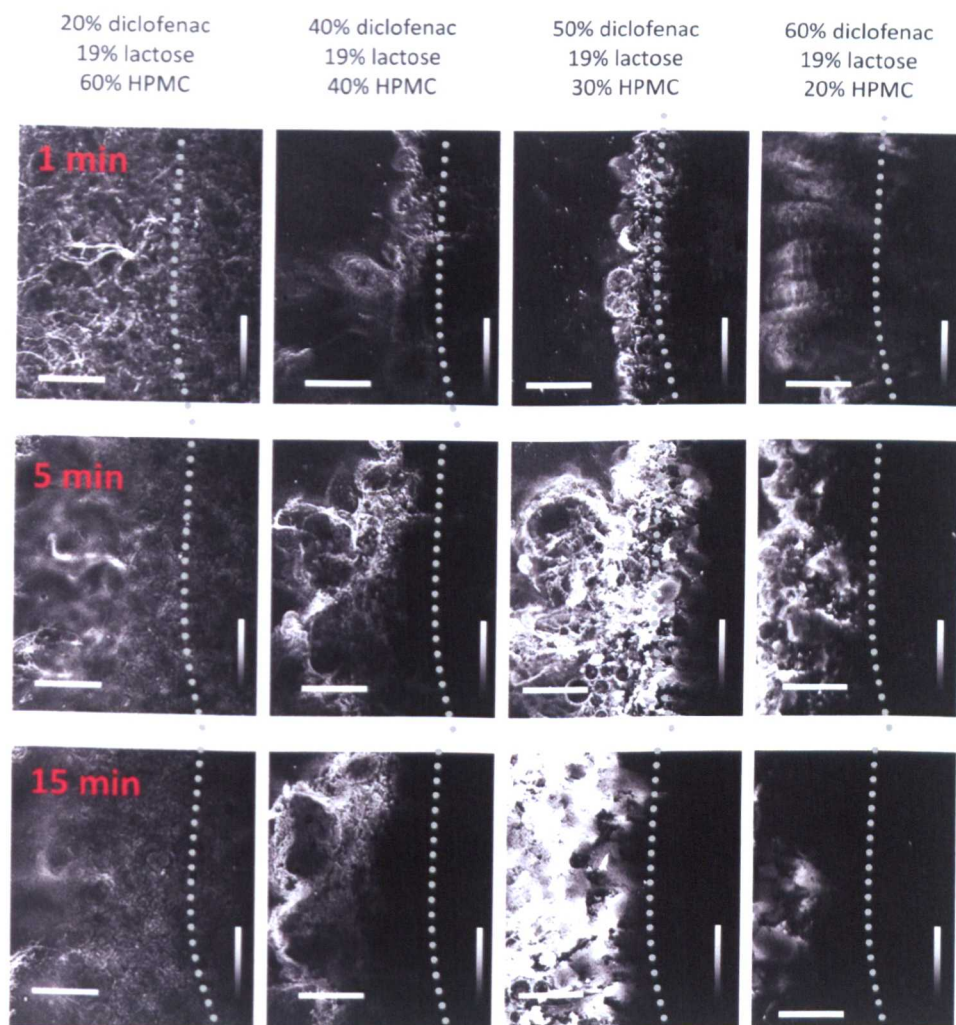
Figure 7.17 The effect of increasing content of diclofenac Na in matrices containing low levels (19% w/w) of lactose on the evolution of HPMC gel layer in 0.9% NaCl

Confocal microscopy images of the radial edge of a hydration matrix showing the development of the gel layer at 1, 5 and 15 minutes. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Images are coded for fluorescence intensity on a linear greyscale from white (highest) to black (lowest). Scale bar = 500 μm. Dotted line depicts the dry tablet boundary. All matrices contained 1% w/w magnesium stearate.

7.3.3.2 The effects of drugs and NaCl on gel layer formation in matrices containing high levels of diluent

Figure 7.18 shows gel layer development in matrices containing 59% w/w MCC and increasing meclofenamate Na content, hydrating in NaCl. Matrices containing 10% w/w drug and the highest (30% w/w) level of HPMC failed to form a coherent gel layer but as drug content was increased and HPMC content decreased, the hydration of HPMC particles improved, with the 30% w/w meclofenamate Na formulation forming a coherent gel layer.

Figure 7.19 shows gel layer development in matrices containing 59% w/w lactose and increasing meclofenamate Na content, hydrating in NaCl. The combined burden of drug, diluent and electrolyte in the hydration medium acted either antagonistically or synergistically. Matrices containing 10% meclofenamate Na failed, whereas increasing meclofenamate Na from 20% to 30% led to more coherent gel layer formation. This may be the result of the respective burdens placed on the HPMC particles by the drug, the diluent and NaCl with the level of coherence appeared to increase with respect to increasing meclofenamate Na content.

Figure 7.20 shows gel layer development in matrices containing 59% w/w MCC and increasing diclofenac Na content, hydrating in NaCl. With the lowest diclofenac Na content, there was a sufficient HPMC in the matrix to form a coherent gel layer but as diclofenac Na content increased, there was loss of gel layer integrity.

Figure 7.21 shows gel layer development in matrices containing 59% w/w lactose and increasing diclofenac Na content, hydrating in NaCl. All formulations failed to form a gel layer, irrespective of the diclofenac Na content.

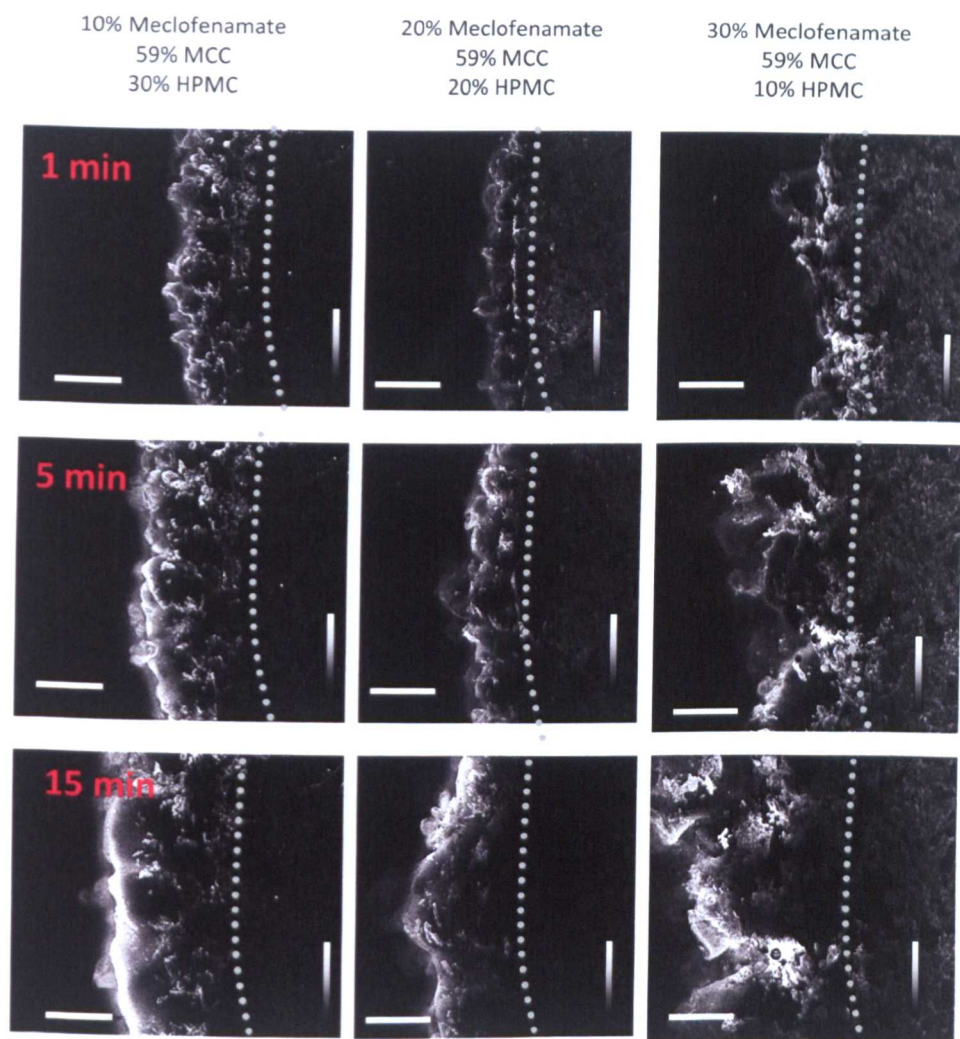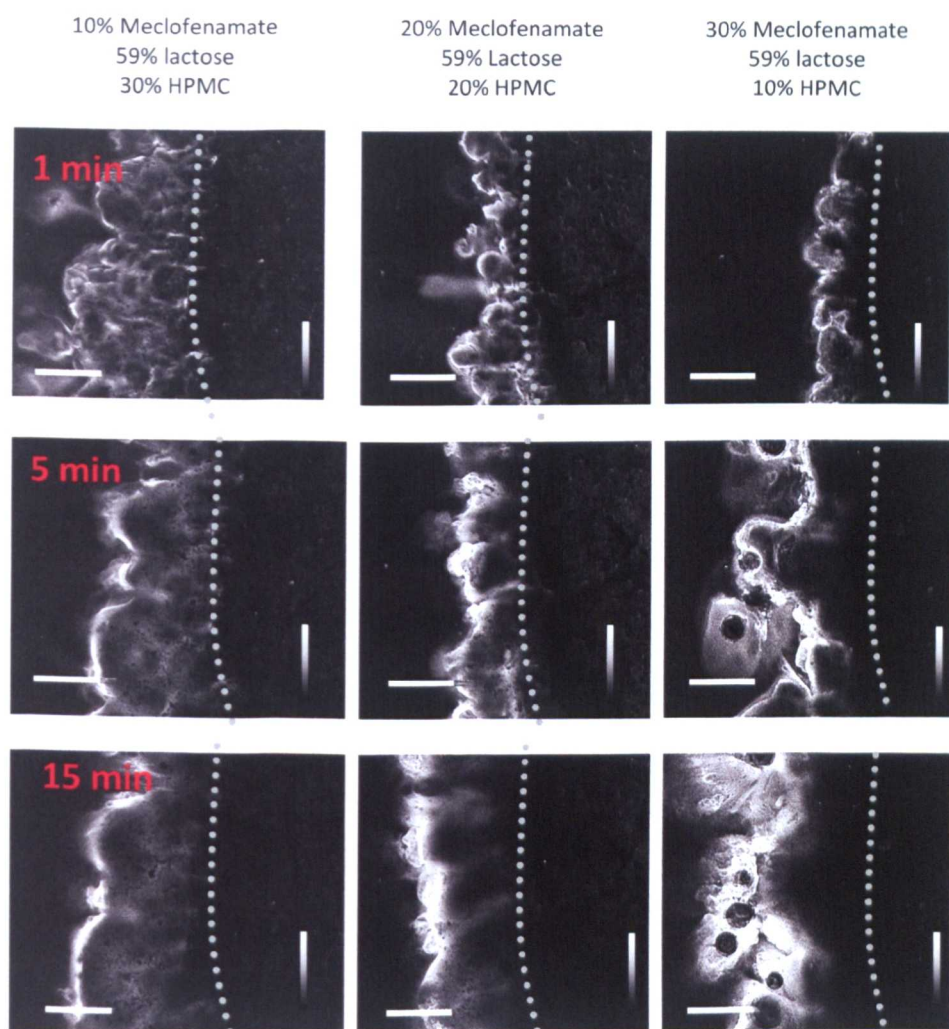| 10% meclofenamate | 20% meclofenamate | 30% meclofenamate |
| 59% MCC | 59% MCC | 59% MCC |
| 30% HPMC | 20% HPMC | 10% HPMC |
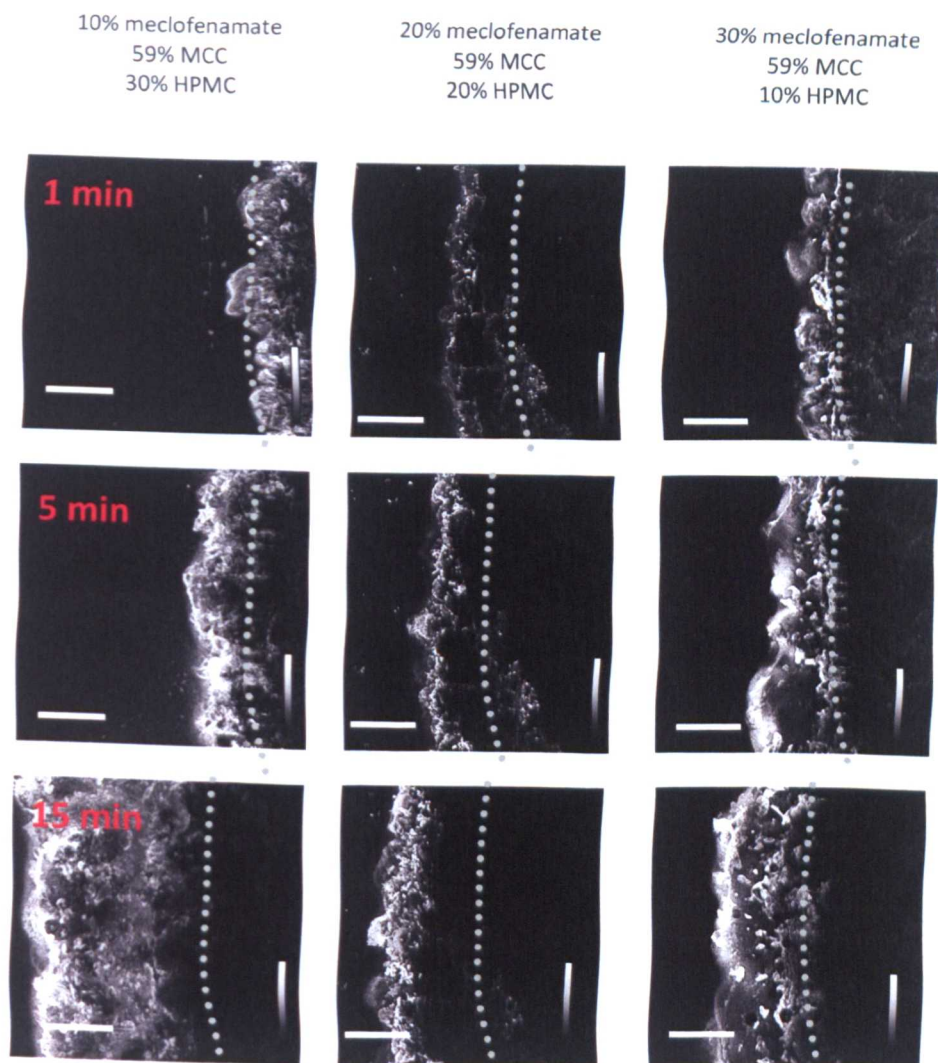
Figure 7.18 The effect of increasing content of meclofenamate Na in matrices containing high levels (59% w/w) of MCC on the evolution of HPMC gel layer in 0.9% NaCl

Confocal microscopy images of the radial edge of a hydration matrix showing the development of the gel layer at 1, 5 and 15 minutes. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Images are coded for fluorescence intensity on a linear greyscale from white (highest) to black (lowest). Scale bar = 500 μm. Dotted line depicts the dry tablet boundary
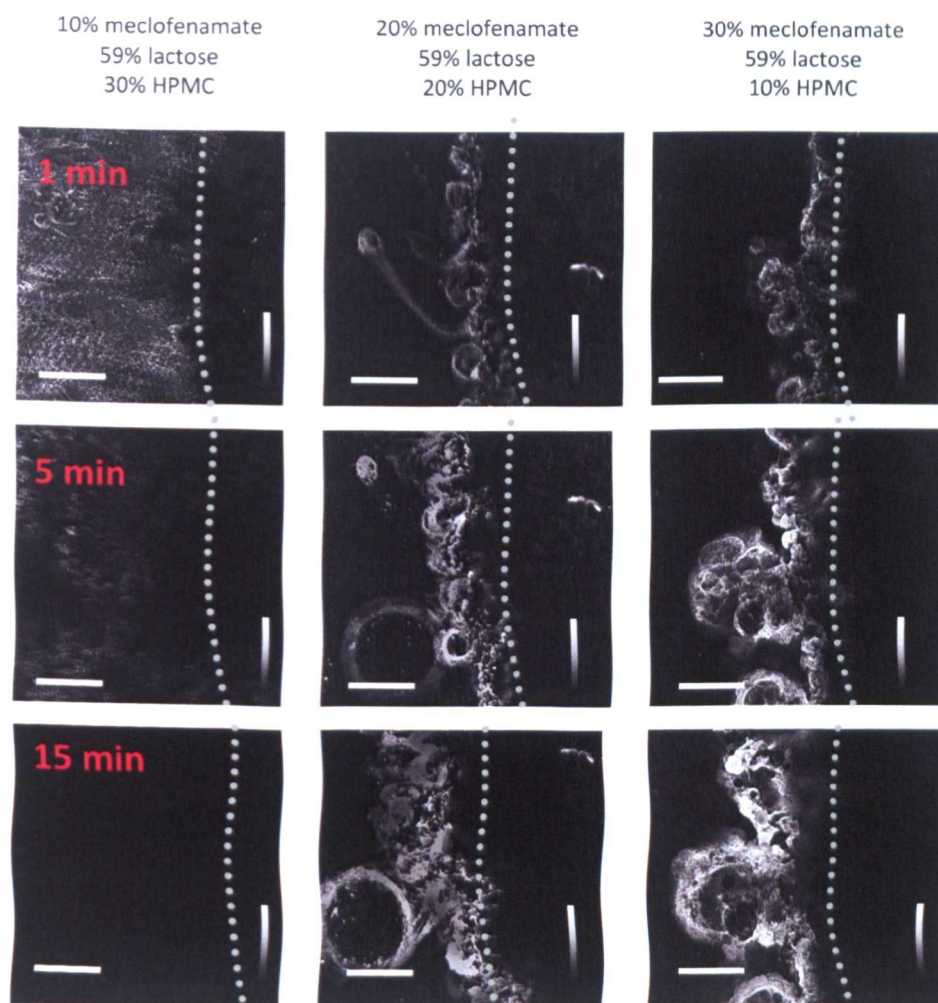
Figure 7.19 The effect of increasing content of meclofenamate Na in matrices containing high levels (59% w/w) of lactose on the evolution of HPMC gel layer in 0.9% NaCl

Confocal microscopy images of the radial edge of a hydration matrix showing the development of the gel layer at 1, 5 and 15 minutes. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Images are coded for fluorescence intensity on a linear greyscale from white (highest) to black (lowest). Scale bar = 500 μm. Dotted line depicts the dry tablet boundary. All matrices contained 1% w/w magnesium stearate.
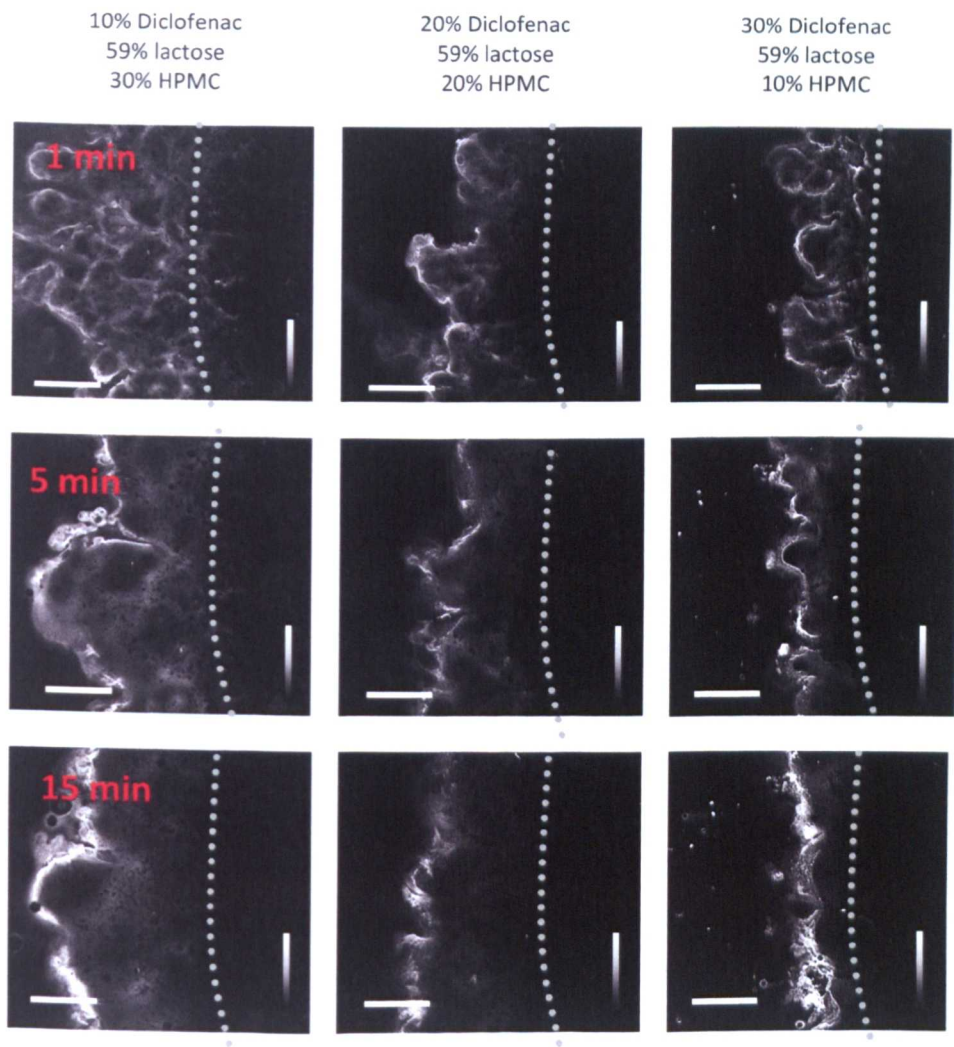
10% diclofenac	20% diclofenac	30% diclofenac
59% MCC	59% MCC	59% MCC
30% HPMC	20% HPMC	10% HPMC
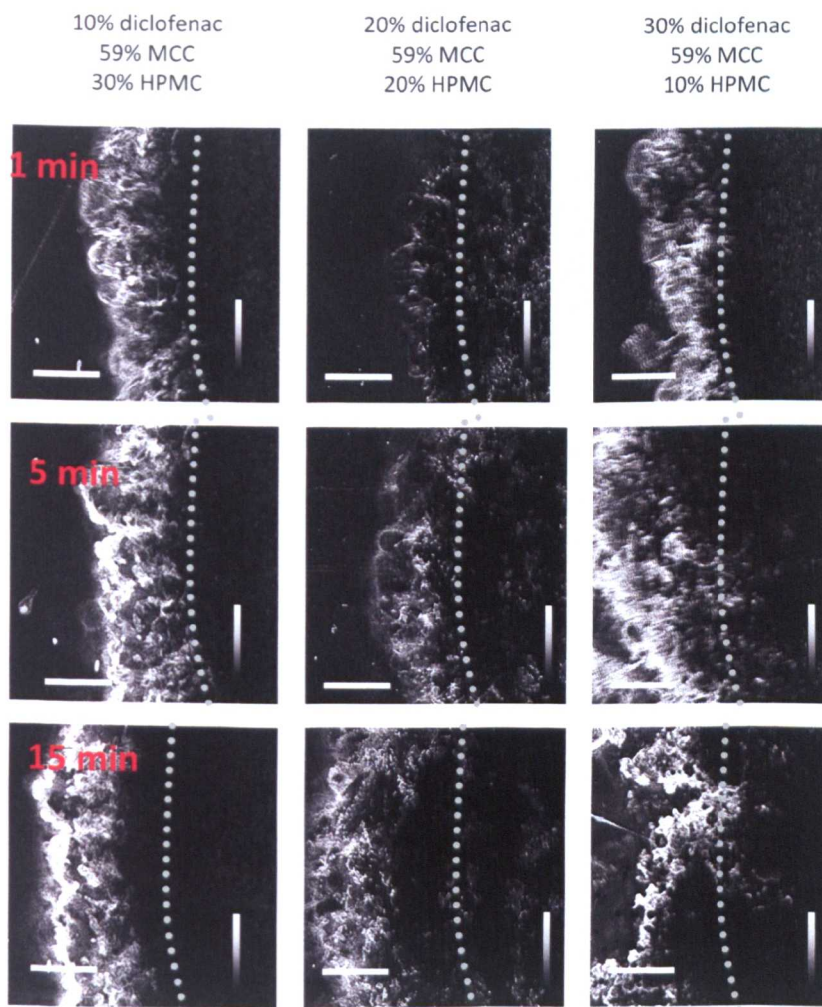
Figure 7.20 The effect of increasing content of diclofenac Na in matrices containing high levels (59% w/w) of MCC on the evolution of HPMC gel layer microstructure in 0.9% NaCl

Confocal microscopy images of the radial edge of a hydration matrix showing the development of the gel layer at 1, 5 and 15 minutes. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Images are coded for fluorescence intensity on a linear greyscale from white (highest) to black (lowest). Scale bar = 500 μm. Dotted line depicts the dry tablet boundary. All matrices contained 1% w/w magnesium stearate.

10% diclofenac	20% diclofenac	30% diclofenac
59% lactose	59% lactose	59% lactose
30% HPMC	20% HPMC	10% HPMC
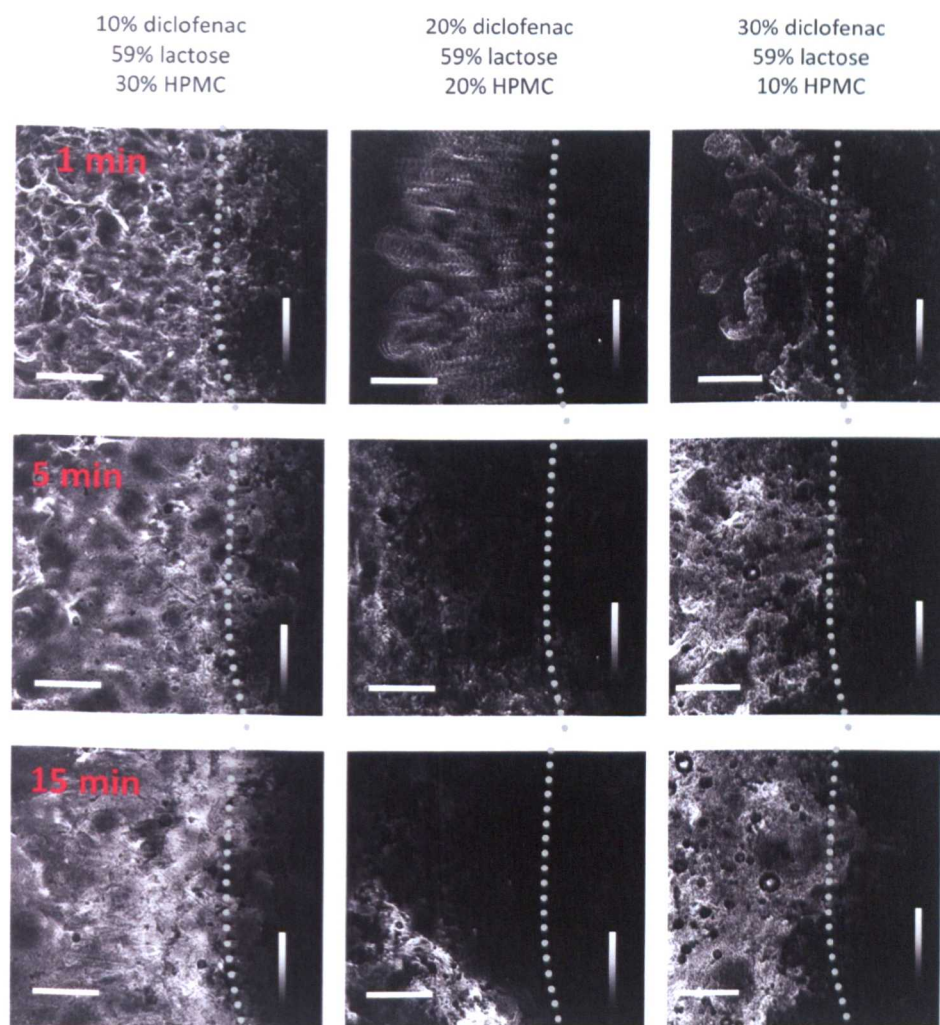
Figure 7.21 The effect of increasing content of diclofenac Na in matrices containing high levels (59% w/w) of lactose on the evolution of HPMC gel layer in 0.9% NaCl

Confocal microscopy images of the radial edge of a hydration matrix showing the development of the gel layer at 1, 5 and 15 minutes. Hydration medium containing 0.008% w/v Congo red maintained at 37°C. Images are coded for fluorescence intensity on a linear greyscale from white (highest) to black (lowest). Scale bar = 500 μm. Dotted line depicts the dry tablet boundary. All matrices contained 1% w/w magnesium stearate.

7.3.4 The effect of drug and diluent content on the disintegration behaviour of HPMC matrices

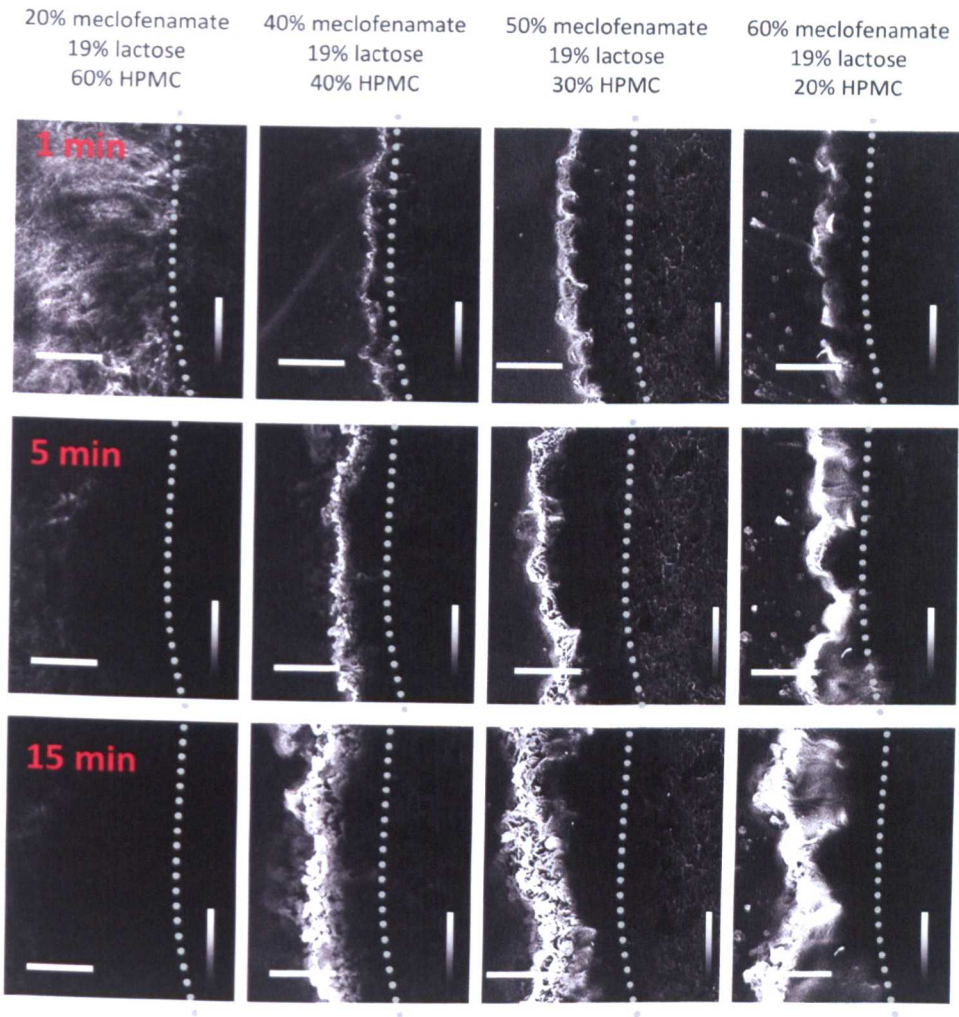Tables 7.3 and 7.4 show the influence of MCC or lactose on the disintegration behaviour of diclofenac Na matrices. In water, the majority of matrices did not disintegrate. The exceptions were formulations with high diclofenac content (60% w/w) and all high content lactose formulations. However, in NaCl solutions, there were clear differences between the formulations. In 0.154M NaCl, all matrices containing lactose were found to fail, irrespective of the content. Matrices containing 19% w/w MCC did not disintegrate except at the highest content of diclofenac Na (60% w/w). Higher content MCC matrices failed, but showed greater longevity in comparison with their lactose containing counterparts. Similar disintegration behaviour was observed in 0.5 M NaCl, with all formulation failing but with the MCC matrices outlasting lactose. All matrices failed rapidly in 0.7 and 1.0M NaCl.

Table 7.5 and 7.6 shows the influence of MCC or lactose on the disintegration behaviour of meclofenamate Na matrices. In water, matrices with a lower meclofenamate Na content did not fail within the experimental period, whereas at higher drug contents with 19% w/w diluent the matrices disintegrated, irrespective of the incorporated diluent. In 0.154M NaCl, matrices with low drug content disintegrated, but matrices with higher contents showed greater longevity. The exception were matrices containing high meclofenamate Na and lactose, which disintegrated rapidly, independent of the hydration medium. In 0.5M NaCl, only high meclofenamate Na content (>50% w/w) matrices including low diluent content did not disintegrate, with MCC matrices outlasting lactose. At 0.7 and 1.0 M NaCl concentrations, only matrices containing 50% w/w meclofenamate or greater did not disintegrate. Other formulations were observed to fail rapidly.

Formulation			Disintegration times of matrices (min)				
			Water	0.154M NaCl	0.5M NaCl	0.7M NaCl	1.0M NaCl
20% diclofenac	19% MCC	60% HPMC	>120	>120	15	1	1
20% diclofenac	19% lactose	60% HPMC	>120	40	5	1	1
40% diclofenac	19% MCC	40% HPMC	>120	>120	5	1	1
40% diclofenac	19% lactose	40% HPMC	>120	30	5	1	1
50% diclofenac	19% MCC	30% HPMC	>120	>120	5	1	1
50% diclofenac	19% lactose	30% HPMC	>120	30	5	1	1
60% diclofenac	19% MCC	20% HPMC	>120	25	15	1	1
60% diclofenac	19% lactose	20% HPMC	105	15	5	1	1

Table 7.3 Disintegration times of matrices of diclofenac Na with low MCC and lactose content in the presence of various concentrations of sodium chloride
Disintegration data obtained in 900 ml at 37°C, observations made from 4 tablets and taken to the nearest minute

Formulation			Disintegration times of matrices (min)				
			Water	0.154M NaCl	0.5M NaCl	0.7M NaCl	1.0M NaCl
10% diclofenac	59% MCC	30% HPMC	>120	40	20	5	1
10% diclofenac	59% lactose	30% HPMC	100	15	10	1	1
20% diclofenac	59% MCC	20% HPMC	>120	30	15	1	1
20% diclofenac	59% lactose	20% HPMC	70	10	10	1	1
30% diclofenac	59% MCC	10% HPMC	>120	25	15	1	1
30% diclofenac	59% lactose	10% HPMC	60	15	10	1	1

Table 7.4 Disintegration times of matrices of diclofenac Na with high MCC and lactose content in the presence of various concentrations of sodium chloride
Disintegration data obtained in 900 ml at 37°C, observations made from 4 tablets and taken to the nearest minute

Formulation			Disintegration times of matrices (min)				
			Water	0.154 M NaCl	0.5M NaCl	0.7M NaCl	1.0M NaCl
20% meclofenamate	19% MCC	60% HPMC	>120	2	2	1	1
20% meclofenamate	19% lactose	60% HPMC	>120	2	2	2	2
40% meclofenamate	19% MCC	40% HPMC	>120	>120	10	2	1
40% meclofenamate	19% lactose	40% HPMC	100	>120	10	10	5
50% meclofenamate	19% MCC	30% HPMC	>120	>120	>120	>120	>120
50% meclofenamate	19% lactose	30% HPMC	90	>120	>120	>120	>120
60% meclofenamate	19% MCC	20% HPMC	35	100	>120	>120	>120
60% meclofenamate	19% lactose	20% HPMC	35	100	>120	>120	>120

Table 7.5 Disintegration times of matrices of meclofenamate Na with low MCC and lactose content in the presence of various concentrations of sodium chloride
Disintegration data obtained in 900 ml at 37°C, observations made from 4 tablets and taken to the nearest minute

Formulation			Disintegration times of matrices (min)				
			Water	0.154M NaCl	0.5M NaCl	0.7M NaCl	1.0M NaCl
10% meclofenamate	59% MCC	30% HPMC	>120	1	1	1	1
10% meclofenamate	59% lactose	30% HPMC	>120	3	1	1	1
20% meclofenamate	59% MCC	20% HPMC	>120	>120	20	10	5
20% meclofenamate	59% lactose	20% HPMC	80	>120	3	1	1
30% meclofenamate	59% MCC	10% HPMC	90	>120	40	30	15
30% meclofenamate	59% lactose	10% HPMC	10	15	15	10	5

Table 7.6 Disintegration times of matrices of meclofenamate Na with high MCC and lactose content in the presence of various concentrations of sodium chloride
Disintegration data obtained in 900 ml at 37°C, observations made from 4 tablets and taken to the nearest minute

7.4 Discussion

The combined effects of drugs and diluents in these hydrophilic matrices appear to be a complex interplay between the solubility of the additives, drug interactions with the polymer and influence of the external electrolyte. To aid clarity, the results will be discussed in a separate section pertaining to the individual diluents.

7.4.1 The influence of lactose on drug-polymer interactions

Lactose appeared to influence the effects of both drugs. Lactose and diclofenac Na were found to both lower the CPT of HPMC and their combined effect was greater than each species individually. When co-formulated with diclofenac Na, both drug and diluent reduced HPMC particle swelling and growth of the gel layer. The high solubility of lactose exerts an osmotic pressure, and this led to matrix disintegration when HPMC particulate swelling and coalescence was impaired by the 'salting out' effects of diclofenac Na and lactose. This was exacerbated when the matrices were hydrated in NaCl. This correlates with the drug release data presented in chapter 2, in which diclofenac Na matrices were found to fail when in formulations containing high lactose content.

When formulated with meclofenamate Na, the influence of lactose appeared to be more complex. With low drug content, the drug is in insufficient concentration in the gel layer to interact with HPMC and change its properties, the most important of which will be an increase in viscosity and molecular tortuosity. When formulated with high levels of lactose, the soluble content in the matrices exceeds the extended release capacity of HPMC and the matrices fail. This supports the findings of Ford et al. (1987) that matrices cannot extend release when formulated with excessive soluble material. However, at intermediate contents of

meclofenamate Na, the interaction between the drug and HPMC resulted in changes to HPMC viscosity and solubility as a result of poly(electrolyte) formation. Whereas this did not provide a functional gel layer in binary matrices, the 'salting out' capability of the formulated lactose helps to stabilise the poly(electrolyte) gel layers. This stabilisation occurs to a greater extent when the hydration medium contains sodium chloride.

7.4.2 The influence of MCC on drug-polymer interactions

The insoluble nature of MCC means that it cannot exert a water restructuring effect within the gel layer. However, it possesses the ability to wick and imbibe water, the extent of which appears to be influenced by the formulated drug and composition of the swelling medium.

The low solubility but considerable water-imbibing properties of MCC provide an explanation for its influence on the drug effects on HPMC gel layer development. An increasing content of MCC in the matrix results in an increase in insoluble but swellable particles within the gel layer. This increases molecular tortuosity, resulting in elevated local drug concentration within the gel layer. This is supported by previous reports in the literature which have suggested that MCC acts to physically obstruct drug release (Xu and Sunada 1995, Lee et al. 1999). Consequently, this increases the potential for drug-HPMC interactions and the subsequent changes to HPMC solution properties resulting from these interactions. In the case of meclofenamate, this is an enhancement of swelling of HPMC particles, whereas in the case of diclofenac Na it increases the propensity of the drug to decrease HPMC solubility and particle swelling. The hypothesis holds if there is a sufficient ratio of HPMC in the hydrophilic matrix in relation to the level of MCC so that a gel layer forms and disintegration does not occur.

Studies from the literature have shown that the presence of MCC in a hydrophilic matrix formulation actually resulted in increases in drug release rates (Cao *et al.* 2005) which is attributed to the disintegrant characteristics of MCC. Other studies have noted that the drug release rate is only increased with the addition of superdisintegrants such as Ac-Di-Sol (croscarmellose sodium) and Explotab (sodium starch glycolate) (Lee *et al.* 1999). Evidence in this chapter suggests that MCC may exhibit 'superdisintegrant' characteristics in the highly swollen gel layer resulting from the meclofenamate Na interaction with HPMC.

7.4.3 The pharmaceutical consequences of the combined effects of drugs and diluents on HPMC gel layer formation

Previous studies have shown the importance of drug effects (Hino and Ford 2001, Mitchell *et al.* 1990), the level of polymer (Alderman 1984, Xu and Sunada 1995, Ebube *et al.* 1997, Ebube and Jones, 2004, Lee *et al.* 1999) and the importance of incorporated diluent (Jamzad *et al.* 2005, Williams *et al.* 2002, Levina and Rajabi-Siahboomi 2004) on the mechanisms of drug release from HPMC hydrophilic matrices.

All three factors may have combined importance depending on the drug-polymer level, the choice and physicochemical properties of the diluent and the interactive capability of the drug with HPMC. In meclofenamate Na matrices, the effect of drug on the gel layer is counteracted by the 'salting-out' burden from incorporated lactose. The apparent protective effect afforded by MCC matrices in response to NaCl challenge may be a result of an absence of burden on the HPMC particle swelling. The additional presence of a 'salting out' electrolyte in the hydration medium affected not only the behaviour of the drug in solution (i.e. its solubility and capability of forming self-associative structures) but also its interaction with HPMC.

These results support the assertion of Ford (1999) who made the explicit link between effects on HPMC cloud point and extended release properties of HPMC hydrophilic matrices. It can be seen that this concept holds in the formulations investigated in this chapter, with the combined effects on CPT of incorporated drugs and diluents with external ionic species appearing critical in determining if a HPMC based hydrophilic matrix will successfully extend release.

7.5 Conclusions

The combined influence of drugs and diluents on the HPMC matrix gel layer has been presented and discussed. Lactose and MCC exerted different influences on the effects of diclofenac Na and meclofenamate Na in HPMC matrices, which was dependent on the diluent content in the HPMC matrix. The influence of NaCl was dependent on the soluble or insoluble diluent content. Cloud point studies suggested that lactose acted synergistically in 'salting-out' HPMC in the presence of diclofenac Na and antagonise the effects of meclofenamate Na, manifested in changes in the morphology and physical properties of the gel layer.

The results support the hypothesis in chapter 2 and developed in chapter 6 that lactose plays a key role in influencing drug-mediated effects on HPMC gel layer development and functionality. It supports the assertion of Ford (Ford *et al.* 1987) that high levels of diluent are required in order for their effects to be exerted but with the additional consideration of how the drug effects on HPMC particle swelling and gel layer formation interplay with the effects of diluents.

Chapter 8

Conclusions and future Work

8.1 Summary

The principal aim of this thesis was to explore the critical processes in drug release from HPMC hydrophilic matrices. Specifically, the effects of diclofenac Na, meclofenamate Na and diluents on HPMC solution properties and gel layer formation have been investigated and related to patterns of drug release in a previous thesis. The following sections discuss the key findings of each chapter.

Chapter 2 Developing a hypothesis

In chapter 2, a hypothesis was developed from an interpretation of a previous study, which was subsequently tested in the experimental work in this thesis. The key aspects of the hypothesis were that:

- The differences in the release of diclofenac Na and meclofenamate Na from HPMC matrices are a consequence of drug surface activity and the capability of the drug to interact with HPMC.

- The incorporation of lactose in the matrix has a significant role in influencing the effects of drug on gel layer formation and release mechanisms

- The choice of 0.9% w/w sodium chloride as a dissolution medium influences the interaction of drugs with HPMC and the subsequent drug release.

The validity of this hypothesis was tested in the experimental work undertaken in the subsequent chapters of this thesis.

Chapter 4 Investigating interactions between drugs and HPMC

Chapter 4 investigated the nature of the interactions between diclofenac Na and meclofenamate Na with HPMC, using PGSE-NMR, SANS, turbimetry, tensiometry and rheology. In summary it was found that:

- Diclofenac Na and meclofenamate Na possess surface activity, while tensiometry suggested drug binding to HPMC in bulk solution, with an apparent saturation concentration for diclofenac Na but not meclofenamate Na.

- The interaction between polymer and drug examined using PGSE-NMR and SANS showed association between meclofenamate Na and HPMC but not diclofenac Na and HPMC.

- The addition of meclofenamate Na led to changes in the bulk properties such as cloud point temperature, viscosity and viscoelasticity. In contrast, diclofenac Na was found to have little effect on HPMC bulk solution properties.

- The interaction between meclofenamate Na and HPMC was influenced by sodium chloride, with the sodium chloride addition to a drug-HPMC solution resulting in decreased polymer solubility and altered viscoelastic properties at lower drug concentrations.

This provided supporting evidence for the hypothesis described above and developed in chapter 2 that drug surface activity and its interactive potential with HPMC can change alter HPMC solution properties. A theory was proposed detailing the phenomenon of association of drug with the polymer conferring polymer solubility increases, changes in the viscoelastic properties and increases in viscosity. This provides a mechanistic explanation for how increasing meclofenamate Na content in a matrix results in decreased drug release rates and vice versa for diclofenac Na matrices.

Chapter 5 Investigating the effects of drugs on the gel layer

In chapter 5, the effects of increasing the matrix content of meclofenamate Na and diclofenac Na on the early development of the gel layer was investigated using confocal laser scanning microscopy. It was found that:

- Drug effects on HPMC solution properties externalise in HPMC matrix gel layer morphology.

- In water, meclofenamate matrices swell rapidly in comparison with diclofenac matrices, producing a highly swollen, diffuse gel layer.

- When hydrated in sodium chloride, gel layer formation and matrix integrity for matrices including meclofenamate Na

improved, whereas diclofenac matrices produced a mass of discrete particles that disintegrated rapidly.

- Drug and HPMC matrices possessed different disintegration properties depending on formulated drug and the sodium chloride concentration in the hydration medium.

- Meclofenamate Na matrices disintegrated more rapidly in water than diclofenac Na matrices and this was reversed when challenged by sodium chloride in the hydration medium.

- Meclofenamate Na matrices exhibited an increased resistance to sodium chloride challenge beyond the disintegration threshold of 100% HPMC matrices. This may be explained by the poly(electrolyte) properties conferred by bound drug, resulting in a viscous gel layer that has improved functionality as sodium chloride concentration is increased.

- The inability of diclofenac Na to interact with HPMC resulted in an increased propensity for HPMC matrices to disintegrate, as a result of salting out from the incorporated drug and external electrolyte.

Chapter 6 Investigating the effects of diluents on the gel layer

In chapter 6, it was found that the physicochemical properties of the diluent had significant effects on gel layer development.

- Lactose reduced the cloud point temperature of HPMC in solution, but had minimal effect on the viscosity and viscoelastic properties of HPMC solutions.

- Lactose had little effect on gel layer formation at low matrix contents, but resulted in a highly diffuse gel at higher lactose contents. This suggested rapid diffusion of the soluble excipient through the gel layer, with a contributory effect from the capability of lactose to 'salt-out' HPMC from solution.

- MCC exerted little effect on early gel layer formation at low matrix content (<50% w/w) but at higher matrix contents (>50% w/w) apparently led to failure of HPMC to form a coherent gel layer, with a visible erosion and disintegration of the underlying matrix.

- DCP disrupted early gel layer formation and led to matrix failure at the highest content (85% w/w) but had minimal effect at lower contents.

- Increasing diluent content and reducing HPMC content led to an increased susceptibility to disintegration upon electrolyte challenge, with lactose having the most detrimental effect and MCC the least.

This chapter provided evidence supporting the hypothesis that the content and nature of the diluent can influence the early gel layer formation.

Chapter 7 Investigating the combined effects of drugs and diluents on the gel layer

The final chapter considered the influence of drug effects on gel layer formation by incorporated diluents (MCC and lactose). It was found that:

- Lactose antagonised the effects of meclofenamate at both low (19%) and high (59% w/w) levels of incorporation within the matrix.

- Lactose acted synergistically with diclofenac to 'salt out' the HPMC and reduce the gel layer integrity.

- MCC was found to have a relatively neutral effect on the drug-mediated effects on the gel layer formation and functionality

- NaCl was found to influence the drug effects on the gel layer formation. Diclofenac Na matrices were found to disintegrate and fail to form a gel layer, whereas it appeared to promote matrix integrity in tablets containing meclofenamate Na.

8.2 Overall Conclusions

It has been identified that drug surface activity and capability to interact with HPMC can affect the gel layer formation and that this would provide a mechanistic explanation for drug release profiles presented in chapter 2 of this thesis. It is proposed that a balance exists between the influences of different species on the capability of HPMC particles to form an adequate

gel layer, both internally from the incorporated drug and excipients, and externally from ionic species present in the hydration medium.

Tailoring matrix formulations to overcome the potential effects of each component may lead to the production of more robust future dosage forms through informed choice of excipient and consideration of these interactive effects.

8.3 Future work

Future work should be concerned with providing further insights into the mechanisms and the potential for interactions in other hydrophilic matrix formulations.

8.3.1 Influence of other surface active drugs

Several important classes of drugs possess surface activity including (i) beta-blockers, (ii) phenothiazides and (iii) local anaesthetics (Attwood 1995). The work in this thesis has shown that the effect of drugs on HPMC hydrophilic matrix performance may be partially a result of surface activity, subsequent association with the polymer, with consequent changes to the properties of the gel layer. It would be of value to consider classes of drugs possessing surface active, e.g. beta-blockers, in an attempt to discern the importance of concomitant properties such as drug solubility in the drug-polymer association.

8.3.2 Influence of HPMC grade

Other studies have noted no differences between the swelling of particles and gel layer formation of different HPMC grades (Mitchell *et al.* 1990,

Rajabi-Siahboomi *et al.* 1993) although this has been disputed (Conti *et al.* 2006). It would be interesting to determine if a grades of HPMC which were more susceptible to drug-mediated changes in its solution properties promotes extended drug release in the example of a 'salting-in' drug such as meclofenamate Na, whereas a choice of less susceptible grade would help negate the 'salting out' effects of a drug such as diclofenac Na.

8.3.3 Behaviour of surface active drugs with other polymers and polymer blends

The interaction between surface active drugs and polymers is unlikely to be confined to hydrophilic matrices based on HPMC. Other polymers used in hydrophilic matrix dosage forms including alginates, xanthan gum, poly(ethylene oxide) and their hydrophobic equivalents, possess the basic chemical structure to interact with surface active drugs and this may influence their performance within pharmaceutical dosage forms.

Polymer blends are being increasingly investigated as the possible basis of hydrophilic matrix dosage forms. Again, interactions between drugs and blends of polymers may provide a fertile area for future work.

References

ADLER, J., JAYAN, A. & MELIA, C. D. (1999) A method for quantifying differential expansion within hydrating hydrophilic matrixes by tracking embedded fluorescent microspheres. *Journal of Pharmaceutical Sciences*, 88, 371-377.

ALBERTSSON, P. A. (1995) Aqueous polymer phase systems: Properties and applications in bioseparation. IN HARDING, S. E., HILL, S. E. & MITCHELL, J. R. (Eds.) *Biopolymer Mixtures.* Loughborough, Nottingham University Press.

ALDERMAN, D. A. (1984) A Review of Cellulose Ethers in Hydrophilic Matrices for Oral Controlled-Release Dosage Forms. *International Journal of Pharmaceutical Technology and Product Manufacture*, 5, 1-9.

ALMOND, A. (2005) Towards understanding the interaction between oligosaccharides and water molecules. *Carbohydrate Research*, 340, 907-920.

ANTALEK, B. (2007) Using PGSE NMR for chemical mixture analysis: Quantitative aspects. *Concepts in Magnetic Resonance Part A*, 30A, 219-235.

ATTWOOD, D. & UDEALA, O. K. (1975) Surface-Activity of Some Antihistamines at Air-Solution Interface. *Journal of Pharmacy and Pharmacology*, 27, 754-758.

ATTWOOD, D. (1995) The Mode of Association of Amphiphilic Drugs in Aqueous-Solution. *Advances in Colloid and Interface Science*, 55, 271-303.

BADAWY, S. I. F. & HUSSAIN, M. A. (2007) Microenvironmental pH modulation in solid dosage forms. *Journal of Pharmaceutical Sciences*, 96, 948-959.

BAI, G., CATITA, J. A. M., NICHIFOR, M. & BASTOS, M. (2007) Microcalorimetric evidence of hydrophobic interactions between hydrophobically modified cationic polysaccharides and surfactants of the same charge. *Journal of Physical Chemistry B*, 111, 11453-11462.

BAJWA, G. S., HOEBLER, K., SAMMON, C., TIMMINS, P. & MELIA, C. D. (2006) Microstructural imaging of early gel layer formation in HPMC matrices. *Journal of Pharmaceutical Sciences,* 95, 2145-2157.

BANKS, S.R. (2003) Incompatibilities between HPMC and model drugs: consequences for extended drug release. *Pharmaceutical Sciences.* Nottingham, University of Nottingham.

BANKS, S. R., SAMMON, C., MELIA, C. D. & TIMMINS, P. (2005) Monitoring the thermal gelation of cellulose ethers in situ using attenuated total reflectance Fourier transform infrared spectroscopy. *Applied Spectroscopy,* 59, 452-459.

BARBOSA, L. R. S., ITRI, R. & CAETANO, W. (2008) Self-assembling of phenothiazine compounds investigated by small-angle X-ray scattering and electron paramagnetic resonance spectroscopy. *Journal of Physical Chemistry B,* 112, 4261-4269

BATCHELOR, J. D., OLTEANU, A., TRIPATHY, A. & PIELAK, G. J. (2004) Impact of protein denaturants and stabilizers on water structure. *Journal of the American Chemical Society,* 126, 1958-1961.

BAUMGARTNER, S., LAHAJNAR, G., SEPE, A. & KRISTL, J. (2005) Quantitative evaluation of polymer concentration profile during swelling of hydrophilic matrix tablets using H-1 NMR and MRI methods. *European Journal of Pharmaceutics and Biopharmaceutics,* 59, 299-306.

BELL, C. G., BREWARD, C. J. W., HOWELL, P. D., PENFOLD, J. & THOMAS, R. K. (2007) Macroscopic modeling of the surface tension of polymer-surfactant systems. *Langmuir,* 23, 6042-6052

BENCHERIF, S. A., SRINIVASAN, A., HORKAY, F., HOLLINGER, J. O., MATYJASZEWSKI, K. & WASHBURN, N. R. (2008) Influence of the degree of methacrylation on hyaluronic acid hydrogels properties. *Biomaterials,* 29, 1739-1749.

BERGFELDT, K., PICULELL, L. & LINSE, P. (1996) Segregation and association in mixed polymer solutions from Flory-Huggins model calculations. *Journal of Physical Chemistry,* 100, 3680-3687

BETTINI, R., COLOMBO, P., MASSIMO, G., CATELLANI, P. L. & VITALI, T. (1994) Swelling and drug release in hydrogel matrices: polymer viscosity and matrix porosity effects. *European Journal of Pharmaceutical Sciences*, 2, 213-219.

BETTINI, R., CATELLANI, P. L., SANTI, P., MASSIMO, G., PEPPAS, N. A. & COLOMBO, P. (2001) Translocation of drug particles in HPMC matrix gel layer: effect of drug solubility and influence on release rate. *Journal of Controlled Release*, 70, 383-391.

BOSCO, S. J., ZETTL, H., CRASSOUS, J. J., BALLAUFF, M. & KRAUSCH, G. (2006) Interactions between methyl cellulose and sodium dodecyl sulfate in aqueous solution studied by single molecule fluorescence correlation spectroscopy. *Macromolecules*, 39, 8793-8798.

BOWTELL, R. W., SHARP, J. C., PETERS, A., MANSIELD, P., RAJABI-SIAHBOOMI, A. R., DAVIES, M. C. & MELIA, C. D. (1994) NMR Microscopy of Hydrating Matrix Pharmaceutical Tablets. *Magnetic Resonance Imaging*, 12, 361-364.

BRITISH PHARMACOPOEIA (2007) HMSO, London, UK

BRYAN, J. W. & MCCALLISTER, J. D. (1992) Matrix Forming Capabilities of 3 Calcium Diluents. *Drug Development and Industrial Pharmacy*, 18, 2029-2047.

BU, H. T., KJONIKSEN, A. L., ELGSAETER, A. & NYSTROM, B. (2006) Interaction of unmodified and hydrophobically modified alginate with sodium dodecyl sulfate in dilute aqueous solution - Calorimetric, rheological, and turbidity studies. *Colloids and Surfaces a-Physicochemical and Engineering Aspects*, 278, 166-174.

BU, H., KJONIKSEN, A. L., KNUDSEN, K. D. & NYSTROM, B. (2007) Characterization of interactions in aqueous mixtures of hydrophobically modified alginate and different types of surfactant. *Colloids and Surfaces a-Physicochemical and Engineering Aspects*, 293, 105-113.

CAMPOS-ALDRETE, M. E. & VILLAFUERTE-ROBLES, L. (1997) Influence of the viscosity grade and the particle size of HPMC on metronidazole release from matrix tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, 43, 173-178.

CAO, Q.-R., CHOI, Y.-W., CUI, J.-H. & LEE, B.-J. (2005) Formulation, release characteristics and bioavailability of novel monolithic hydroxypropylmethylcellulose matrix tablets containing acetaminophen. *Journal of Controlled Release*, 108, 351-361.

CARLSSON, A., KARLSTROM, G. & LINDMAN, B. (1990) Thermal Gelation of Nonionic Cellulose Ethers and Ionic Surfactants in Water. *Colloids and Surfaces,* 47, 147-165.

CHEEMA, M. A., SIDDIQ, M., BARBOSA, S., TABOADA, P. & MOSQUERA, V. (2008) Surface and bulk properties of two amphiphilic phenothiazine drugs in different aqueous media. *Journal of Chemical and Engineering Data,* 53, 368-373.

CLARO, C., MUNOZ, J., DE LA FUENTE, J., JIMENEZ-CASTELLANOS, M. R. & LUCERO, M. J. (2008) Surface tension and rheology of aqueous dispersed systems containing a new hydrophobically modified polymer and surfactants. *International Journal of Pharmaceutics,* 347, 45-53.

COLOMBO, P. (1993) Swelling-Controlled Release in Hydrogel Matrices For Oral Route. *Advanced Drug Delivery Reviews,* 11, 37-57.

COLOMBO, P., BETTINI, R., MASSIMO, G., CATELLANI, P. L., SANTI, P. & PEPPAS, N. A. (1995) Drug Diffusion Front Movement Is Important in Drug-Release Control from Swellable Matrix Tablets. *Journal of Pharmaceutical Sciences,* 84, 991-997.

COLOMBO, P., BETTINI, R., SANTI, P., ASCENTIIS, A. D. & PEPPAS, N. (1996) Analysis of the swelling and release mechanisms from drug delivery systems with emphasis on drug solubility and water transport. *Journal of Controlled Release,* 39, 231-237.

COLOMBO, P., BETTINI, R., CATELLANI, P. L., SANTI, P. & PEPPAS, N. A. (1999) Drug volume fraction profile in the gel phase and drug release kinetics in hydroxypropylmethyl cellulose materials containing soluble drug. *European Journal of Pharmaceutical Sciences,* 9, 33-40.

CONTE, U. & MAGGI, L. (1996) Modulation of the dissolution profiles from Geomatrix(R) multi-layer matrix tablets containing drugs of different solubility. *Biomaterials,* 17, 889.

CONTI, S., MAGGI, L., SEGALE, L., MACHISTE, E. O., CONTE, U., GRENIER, P. & VERGNAULT, G. (2007) Matrices containing NaCMC and HPMC 1. Dissolution performance characterization. *International Journal of Pharmaceutics,* 333, 136-142.

COX, P. J., KHAN, K. A., MUNDAY, D. L. & SUJJA-AREEVATH, J. (1999) Development and evaluation of a multiple-unit oral sustained release dosage form for S(+)-ibuprofen: preparation and release kinetics. *International Journal of Pharmaceutics*, 193, 73-84.

DABBAGH, M. A., FORD, J. L., RUBINSTEIN, M. H., HOGAN, J. E. & RAJABI-SIAHBOOMI, A. R. (1999) Release of Propranolon Hydrochloride from Matrix Tablets Containing Sodium Carboxymethylcellulose and Hydroxypropylmethylcellulose. *Pharmaceutical Development and Technology*, 4, 313-324.

DAHL, T. C., CALDERWOOD, T., BORMETH, A., TRIMBLE, K. & PIEPMEIER, E. (1990) Influence of Physicochemical Properties of Hydroxypropyl Methylcellulose On Naproxen Release From Sustained-Release Matrix Tablets. *Journal of Controlled Release*, 14, 1-10.

DAHLBERG, C., FUREBY, A., SCHULEIT, M., DVINSKIKH, S. V. & FURO, I. (2007) Polymer mobilization and drug release during tablet swelling. A H-1 NMR and NMR microimaging study. *Journal of Controlled Release*, 122, 199-205.

DAVIES, J. A. & GRIFFITHS, P. C. (2003) A phenomenological approach to separating the effects of obstruction and binding for the diffusion of small molecules in polymer solutions. *Macromolecules*, 36, 950-952.

DE LA TORRE, P. M., ENOBAKHARE, Y., TORRADO, G. & TORRADO, S. (2003) Release of amoxicillin from polyionic complexes of chitosan and poly(acrylic acid). study of polymer/polymer and polymer/drug interactions within the network structure. *Biomaterials*, 24, 1499-1506.

DEGIM, Z. & KELLAWAY, I. W. (1998) An investigation of the interfacial interaction between poly(acrylic acid) and glycoprotein. *International Journal of Pharmaceutics*, 175, 9-16.

DOELKER, E. (1987) Water-Swollen Cellulose Derivatives in Pharmacy. IN PEPPAS, N. A. (Ed.) *Hydrogels in Medicine and Pharmacy.* Florida, CRC Press, Inc.

DONGES, R. (1990) Nonionic Cellulose Ethers. *British Polymer Journal*, 23, 315-326.

DOROZHKIN, S. V. (2001) Is there a chemical interaction between calcium phosphates and hydroxypropylmethylcellulose (HPMC) in organic/inorganic composites? *Journal of Biomedical Materials Research*, 54, 247-255.

EBUBE, N. K., HIKAL, A. H., WYANDT, C. M., BEER, D. C., MILLER, L. G. & JONES, A. B. (1997) Effect of drug, formulation and process variables on granulation and compaction characteristics of heterogeneous matrices. Part 1: HPMC and HPC systems. *International Journal of Pharmaceutics*, 156, 49-57.

EBUBE, N. K. & JONES, A. B. (2004) Sustained release of acetaminophen from a heterogeneous mixture of two hydrophilic non-ionic cellulose ether polymers. *International Journal of Pharmaceutics*, 272, 19-27.

EECKMAN, F., AMIGHI, K. & MOËS, A. J. (2001) Effect of some physiological and non-physiological compounds on the phase transition temperature of thermoresponsive polymers intended for oral controlled-drug delivery. *International Journal of Pharmaceutics*, 222, 259-270.

ESPINOZA, R., HONG, E. & VILLAFUERTE, L. (2000) Influence of admixed citric acid on the release profile of pelanserin hydrochloride from HPMC matrix tablets. *International Journal of Pharmaceutics*, 201, 165-173.

EVERTSSON, H. & HOLMBERG, C. (1997) Salt influence in the polymer-surfactant interaction in solution. A fluorescence probe investigation of the EHEC/SDS/water system. *Colloid and Polymer Science*, 275, 830-840.

EVERTSSON, H. & NILSSON, S. (1998) Microviscosity in dilute aqueous solutions of SDS and non-ionic cellulose derivatives of different hydrophobicity: fluorescence probe investigations. *Carbohydrate Polymers*, 35, 135-144.

FAGAN, P. G., HARRISON, P. J. & SHANKLAND, N. (1989) A correlation between cloud point and disintegration of hydroxyalkylcellulose controlled release matrices. *Journal of Pharmacy and Pharmacology*, 41, 25P.

FEELY, L. C. & DAVIS, S. S. (1988) Influence of surfactants on drug release from hydroxypropylmethylcellulose matrices. *International Journal of Pharmaceutics*, 41, 83-90.

FINI, A., FAZIO, G. & FEROCI, G. (1995) Solubility and solubilization properties of non-steroidal anti-inflammatory drugs. *International Journal of Pharmaceutics*, 126, 95-102.

FLORENCE, A. T. & ATTWOOD, D. (1998) *Physicochemical Principles of Pharmacy*, London, The MacMillan Press, Ltd.

FLORY, P. J. (1941) Thermodynamics of High Polymer Solutions. *The Journal of Chemical Physics*, 9, 660-660.

FORD, J. L., RUBINSTEIN, M. H. & HOGAN, J. E. (1985) Formulation of sustained release promethazine hydrochloride tablets using hydroxypropyl-methylcellulose matrices. *International Journal of Pharmaceutics*, 24, 327-338.

FORD, J. L., RUBINSTEIN, M. H. & HOGAN, J. E. (1985) Propranolol hydrochloride and aminophylline release from matrix tablets containing hydroxypropylmethylcellulose. *International Journal of Pharmaceutics*, 24, 339-350.

FORD, J. L., RUBINSTEIN, M. H. & HOGAN, J. E. (1985) Dissolution of Poorly Water Soluble Drug, Indomethacin from Hydroxypropylmethylcellulose Controlled Release Tablets. *Journal of Pharmacy and Pharmacology*, 37, 33.

FORD, J. L., RUBINSTEIN, M. H., MCCAUL, F., HOGAN, J. E. & EDGAR, P. J. (1987) Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. *International Journal of Pharmaceutics*, 40, 223-234.

FORD, J. L. & MITCHELL, K. (1995) Thermal analysis of gels and matrix tablets containing cellulose ethers. *Thermochimica Acta*, 248, 329-345.

FORD, J. L. (1999) Thermal analysis of hydroxypropylmethylcellulose and methylcellulose: powders, gels and matrix tablets. *International Journal of Pharmaceutics*, 179, 209-228.

FREICHEL, O. L. & LIPPOLD, B. C. (2004) Artificially induced polymer particle erosion of oral hydrocolloid systems by the addition of insoluble cellulose fibres to fibre-free methylhydroxy ethylcellulose (MHEC). *European Journal of Pharmaceutics and Biopharmaceutics*, 57, 527-532.

FURLANETTO, S., CIRRI, M., MAESTRELLI, F., CORTI, G. & MURA, P. (2006) Study of formulation variables influencing the drug release rate from matrix tablets by

experimental design. *European Journal of Pharmaceutics and Biopharmaceutics*, 62, 77-84.

FUERTES, I., MIRANDA, A., MILLAN, M. & CARABALLO, I. (2006) Estimation of the percolation thresholds in acyclovir hydrophilic matrix tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, 64, 336-342.

FYFE, C. A. & BLAZEK-WELSH, A. I. (2000) Quantitative NMR imaging study of the mechanism of drug release from swelling hydroxypropylmethylcellulose tablets. *Journal of Controlled Release*, 68, 313-333

GABR, K. E. (1992) Effect of organic acids on the release patterns of weakly basic drugs from inert sustained release matrix tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, 38, 199.

GAFOURIAN, T., SAFARI, A., ADIBKIA, K., PARVIZ, F. & NOKHODCHI, A. (2007) A drug release study from hydroxypropylmethylcellulose (HPMC) matrices using QSPR modeling. *Journal of Pharmaceutical Sciences*, 96, 3334-3351.

GAO, P. & MEURY, R. H. (1996) Swelling of hydroxypropyl methylcellulose matrix tablets. 1. Characterization of swelling using a novel optical imaging method. *Journal of Pharmaceutical Sciences*, 85, 725-731.

GIANGIACOMO, R. (2006) Study of water-sugar interactions at increasing sugar concentration by NIR spectroscopy. *Food Chemistry*, 96, 371-379.

GODDARD, E. D. (2002) Polymer/surfactant interaction: Interfacial aspects. *Journal of Colloid and Interface Science*, 256, 228-235.

GONZALEZ-RODRIGUEZ, M. L., HOLGADO, M. A., SANCHEZ-LAFUENTE, C., RABASCO, A. M. & FINI, A. (2002) Alginate/chitosan particulate systems for sodium diclofenac release. *International Journal of Pharmaceutics*, 232, 225-234

GOYAL, P. S. & ASWAL, V. K. (2001) Micellar structure and inter-micelle interactions in micellar solutions: Results of small angle neutron scattering studies. *Current Science*, 80, 972-979.

GREMINGER, J. G. K. & KRUMEL, K. L. (1980) Alkyl and Hydroxyalkylcellulose. IN DAVIDSON, R. L. (Ed.) *Handbook of Water Soluble Gums and Resins.* San Diego, Academic Press, Inc.

GRIFFITHS, P. C., CHEUNG, A. Y. F., DAVIES, J. A., PAUL, A., TIPPLES, C. N. & WINNINGTON, A. L. (2002) Probing interactions within complex colloidal systems using PGSE-NMR. *Magnetic Resonance in Chemistry,* 40, S40-S50.

GRIFFITHS, P. C., HIRST, N., PAUL, A., KING, S. M., HEENAN, R. K. & FARLEY, R. (2004) Effect of Ethanol on the Interaction between Poly(vinylpyrrolidone) and Sodium Dodecyl Sulfate. *Langmuir,* 20, 6904-6913.

GRIFFITHS, P. C., PAUL, A., FALLIS, I. A., WELLAPPILI, C., MURPHY, D. M., JENKINS, R., WATERS, S. J., NILMINI, R., HEENAN, R. K. & KING, S. M. (2007) Derivatizing weak polyelectrolytes - Solution properties, self-aggregation, and association with anionic surfaces of hydrophobically Modified poly(ethylene imine). *Journal of Colloid and Interface Science,* 314, 460-469.

GROVER, J. A. (1993) Mehtylcellulose and its Derivatives. IN WHISTLER, R. L. & BEMILLIER, J. N. (Eds.) *Industrial Gums.* Third ed. San Diego, Academic Press, Inc.

GUMBLETON, M. & STEPHENS, D. J. (2005) Coming out of the dark: the evolving role of fluorescence imaging in drug delivery research. *Advanced Drug Delivery Reviews,* 57, 5-15.

GURAU, M. C., CASTELLANA, E. T., ALBERTORIO, F., KATAOKA, S., LIM, S. M., YANG, R. D. & CREMER, P. S. (2003) Thermodynamics of phase transitions in Langmuir monolayers observed by vibrational sum frequency spectroscopy. *Journal of the American Chemical Society,* 125, 11166-11167.

HAHN, E. L. (1950) Spin Echoes. *Physical Review,* 80, 580-594.

HARDY, I. J., WINDBERG-BAARUP, A., NERI, C., BYWAY, P. V., BOOTH, S. W. & FITZPATRICK, S. (2007) Modulation of drug release kinetics from hydroxypropyl methyl cellulose matrix tablets using polyvinyl pyrrolidone. *International Journal of Pharmaceutics,* 337, 246-253.

HAQUE, A. & MORRIS, E. R. (1993) Thermogelation of Methylcellulose. Part 1: molecular strucures and processes. *Carbohydrate Polymers,* 22, 161-173.

HAQUE, A., RICHARDSON, R. K., MORRIS, E. R., GIDLEY, M. & CASWELL, D. (1993) Thermogelation of Methylcellulose. Part II: effect of hydroxypropyl substituents. *Carbohydrate Polymers,* 22, 175-186.

HARSH, D. C. & GEHRKE, S. H. (1991) Controlling the Swelling Characteristics of Temperature- Sensitive Cellulose Ether Hydrogels. *Journal of Controlled Release,* 17, 175-185.

HENG, P. W. S., CHAN, L. W., EASTERBROOK, M. G. & LI, X. (2001) Investigation of the influence of mean HPMC particle size and number of polymer particles on the release of aspirin from swellable hydrophilic matrix tablets. *Journal of Controlled Release,* 76, 39-49.

HEYMAN, E. (1935) Studies on Sol-Gel Transformations 1. The Inverse Sol-Gel Transformation of Methylcellulose in Water. *Trans. Faraday Soc.,* 31, 846-864.

HINO, T. & FORD, J. L. (2001) Effect of nicotinamide on the properties of aqueous HPMC solutions. *International Journal of Pharmaceutics,* 226, 53-60.

HOGAN, J. E. (1989) Hydroxypropylmethylcellulose Sustained-Release Technology. *Drug Development and Industrial Pharmacy,* 15, 975-999.

HOROBIN, R. W. (2002) Biological staining: mechanisms and theory. *Biotechnic & Histochemistry,* 77, 3-13.

HUANG, Y. B., TSAI, Y. H., YANG, W. C., CHANG, J. S. & WU, P. C. (2004) Optimization of sustained-release propranolol dosage form using factorial design and response surface methodology. *Biological & Pharmaceutical Bulletin,* 27, 1626-1629

HUSSAIN, S., KEARY, C. & CRAIG, D. Q. M. (2002) A thermorheological investigation into the gelation and phase separation of hydroxypropyl methylcellulose aqueous systems. *Polymer,* 43, 5623-5628.

ISHIKAWA, T., WATANABE, Y., TAKAYAMA, K., ENDO, H. & MATSUMOTO, M. (2000) Effect of hydroxypropylmethylcellulose (HPMC) on the release profiles and

bioavailability of a poorly water-soluble drug from tablets prepared using macrogol and HPMC. *International Journal of Pharmaceutics,* 202, 173-178.

JIMENEZ-KAIRUZ, A., ALLEMANDI, D. & MANZO, R. H. (2002) Mechanism of lidocaine release from carbomer-lidocaine hydrogels. *Journal of Pharmaceutical Sciences,* 91, 267-272.

JAMZAD, S., TUTUNJI, L. & FASSIHI, R. (2005) Analysis of macromolecular changes and drug release from hydrophilic matrix systems. *International Journal of Pharmaceutics,* 292, 75-85.

JAYAN, A. (2001) Investigating the Drug Release Mechanisms of Mixed HPMC/PEO Hydrophilic Martices. *Pharmaceutical Sciences.* Nottingham, The University of Nottingham.

JELCIC, Z., HAUSCHILD, K., OGIERMANN, M. & PICKER-FREYER, K. M. (2007) Evaluation of tablet formation of different lactoses by 3D modeling and fractal analysis. *Drug Development and Industrial Pharmacy,* 33, 353-372.

JONES, M. N. (1967) Interaction of Sodium Dodecyl Sulfate with Polyethylene Oxide. *Journal of Colloid and Interface Science,* 23, 36-&.

JU, R. T. C., NIXON, P. R., PATEL, M. V. & TONG, D. M. (1995) A Mechanistic Model for Drug Release from Hydrophilic Matrices Based on the Structure of Swollen Matrices. *Proceedings of the International Symposium on Controlled Release of Bioactive Materials.* Controlled Release Society Inc.

KAJIYAMA, A., TAKAGI, H., MORIBE, K. & YAMAMOTO, K. (2008) Improvement of HPMC tablet disintegration by the addition of inorganic salts. *Chemical & Pharmaceutical Bulletin,* 56, 598-601.

KATO, N., SAKAI, Y. & TAKAHASHI, F. (2001) Saccharide effect on the deswelling process of the thermosensitive poly(N-isopropylacrylamide) gel. *Bulletin of the Chemical Society of Japan,* 74, 2025-2029.

KATZHENDLER, I., AZOURY, R. & FRIEDMAN, M. (1998) Crystalline properties of carbamazepine in sustained release hydrophilic matrix tablets based on hydroxypropyl methylcellulose. *Journal of Controlled Release*, 54, 69-85.

KATZHENDLER, I., MADER, K. & FRIEDMAN, M. (2000) Structure and hydration properties of hydroxypropyl methylcellulose matrices containing naproxen and naproxen sodium. *International Journal of Pharmaceutics*, 200, 161-179.

KAWASAKI, H., SASAKI, S., MAEDA, H., MIHARA, S., TOKITA, M. & KOMAI, T. (1996) Saccharide-induced volume phase transition of poly(N-isopropylacrylamide) gels. *Journal of Physical Chemistry*, 100, 16282-16284.

KIIL, S. & DAM-JOHANSEN, K. (2003) Controlled drug delivery from swellable hydroxypropylmethylcellulose matrices: model-based analysis of observed radial front movements. *Journal of Controlled Release*, 90, 1-21.

KIM, Y. H., KWON, I. C., BAE, Y. H. & KIM, S. W. (1995) Saccharide Effect on the Lower Critical Solution Temperature of Thermosensitive Polymers. *Macromolecules*, 28, 939-944.

KJONIKSEN, A. L., NYSTROM, B., IVERSEN, C., NAKKEN, T., PALMGREN, O. & TANDE, T. (1997) Viscosity of dilute aqueous solutions of hydrophobically modified chitosan and its unmodified analogue at different conditions of salt and surfactant concentrations. *Langmuir*, 13, 4948-4952

KLEMM, D., HEUBLEIN, B., FINK, H. P. & BOHN, A. (2005) Cellulose: Fascinating biopolymer and sustainable raw material. *Angewandte Chemie-International Edition*, 44, 3358-3393.

KOESTER, L. S., ORTEGA, G. G., MAYORGA, P. & BASSANI, V. L. (2004) Mathematical evaluation of in vitro release profiles of hydroxypropylmethylcellulose matrix tablets containing carbamazepine associated to [beta]-cyclodextrin. *European Journal of Pharmaceutics and Biopharmaceutics*, 58, 177-179.

KONRAD, R., CHRIST, A., ZESSIN, G. & COBET, U. (1998) The use of ultrasound and penetrometer to characterize the advancement of swelling and eroding fronts in HPMC matrices. *International Journal of Pharmaceutics*, 163, 123-131.

KOWALCZUK, J., TRITT-GOC, J. & PISLEWSKI, N. (2004) The swelling properties of hydroxypropyl methyl cellulose loaded with tetracycline hydrochloride: magnetic resonance imaging study. *Solid State Nuclear Magnetic Resonance,* 25, 35-41.

KULICKE, W. M., ARENDT, O. & BERGER, M. (1998) Rheological characterization of the dilatant flow behavior of highly substituted hydroxypropylmethylcellulose solutions in the presence of sodium lauryl sulfate. *Colloid and Polymer Science,* 276, 617-626.

KUMAR, S., ALAM, M. S., PARVEEN, N. & KABIR UD, D. (2006) Influence of additives on the clouding behavior of amphiphilic drug solutions. *Colloid and Polymer Science,* 284, 1459-1463.

LAPIDUS, H. & LORDI, N. G. (1968) Drug Release from Compressed Hydrophilic Matrices. *Journal of Pharmaceutical Sciences,* 57, 1292-1301.

LARSON, R. G. (2005) The rheology of dilute solutions of flexible polymers: Progress and problems. *Journal of Rheology,* 49, 1-70.

LEE, B.-J., RYU, S.-G. & CUI, J.-H. (1999) Controlled release of dual drug-loaded hydroxypropyl methylcellulose matrix tablet using drug-containing polymeric coatings. *International Journal of Pharmaceutics,* 188, 71-80.

LEE, S. B., SOHN, Y. S. & SONG, S. C. (2003) Saccharide effect on the lower critical solution temperature of poly(organophosphazenes) with methoxy-poly(ethylene glycol) and amino acid esters as side groups. *Bulletin of the Korean Chemical Society,* 24, 901-905.

LERK, C. F., BOLHUIS, G. K. & DEBOER, A. H. (1979) Effect of Microcrystalline Cellulose on Liquid Penetration in and Disintegration of Directly Compressed Tablets. *Journal of Pharmaceutical Sciences,* 68, 205-211.

LERK, C. F. (1993) Consolidation and Compaction of Lactose. *Drug Development and Industrial Pharmacy,* 19, 2359-2398.

LEVINA, M. & RAJABI-SIAHBOOMI, A. R. (2004) The influence of excipients on drug release from hydroxypropyl methylcellulose matrices. *Journal of Pharmaceutical Sciences,* 93, 2746-2754.

LEVY, G. & SCHWARZ, T. W. (1958) The Effect of Certain Additives on the Gel Point of Methylcellulose. *Journal of the American Pharmaceutical Association*, 47, 44-46.

LI, C. L., MARTINI, L. G., FORD, J. L. & ROBERTS, M. (2005) The use of hypromellose in oral drug delivery. *Journal Of Pharmacy And Pharmacology*, 57, 533-546.

LIU, Y. & GUO, R. (2007) Interaction between casein and the oppositely charged surfactant. *Biomacromolecules*, 8, 2902-2908.

LIU, S. Q., JOSHI, S. C. & LAM, Y. C. (2008) Effects of salts in the Hofmeister series and solvent isotopes on the gelation mechanisms for hydroxypropylmethylcellulose hydrogels. *Journal of Applied Polymer Science*, 109, 363-372.

LOTFIPOUR, F., NOKHODCHI, A., SAEEDI, M., NOROUZI-SANI, S., SHARBAFI, J. & SIAHI-SHADBAD, M. R. (2004) The effect of hydrophilic and lipophilic polymers and fillers on the release rate of atenolol from HPMC matrices. *Farmaco (Lausanne)*, 59, 819-825.

LUNDIN, M., MACAKOVA, L., DEDINAITE, A. & CLAESSON, P. (2008) Interactions between chitosan and SDS at a low-charged silica substrate compared to interactions in the bulk - The effect of ionic strength. *Langmuir*, 24, 3814-3827

MANGIAPIA, G., RICCIARDI, R., AURIEMMA, F., DE ROSA, C., LO CELSO, F., TRIOLO, R., HEENAN, R. K., RADULESCU, A., TEDESCHI, A. M., D'ERRICO, G. & PADUANO, L. (2007) Mesoscopic and microscopic investigation on poly(vinyl alcohol) hydrogels in the presence of sodium decylsulfate. *Journal of Physical Chemistry B*, 111, 2166-2173.

MARSHALL, P., SNAAR, J. E. M., NG, Y. L., BOWTELL, R. W., HAMPSON, F. C., DETTMAR, P. W. & MELIA, C. D. (2001) A novel application of NMR microscopy: measurement of water diffusion inside bioadhesive bonds. *Magnetic Resonance Imaging*, 19, 487-488.

MARTINDALE: THE EXTRA PHARMACOPOEIA (1996) Royal Pharmaceutical Society, London, UK

MARTINEZ, K. D., SANCHEZ, C. C., RUIZ-HENESTROSA, V. P., PATINO, J. M. R. & PILOSOF, A. M. R. (2007) Soy protein-polysaccharides interactions at the air-water interface. *Food Hydrocolloids*, 21, 804-812

MASUDA, Y., HIRABAYASHI, K., SAKUMA, K. & NAKANISHI, T. (2002) Swelling of poly(ethylene oxide) gel in aqueous solutions of sodium dodecyl sulfate with added sodium chloride. *Colloid and Polymer Science*, 280, 490-494.

MCCONVILLE, J. T., ROSS, A. C., FLORENCE, A. J. & STEVENS, H. N. E. (2005) Erosion characteristics of an erodible tablet incorporated in a time-delayed capsule device. *Drug Development and Industrial Pharmacy*, 31, 79-89.

MCCRYSTAL, C. B., FORD, J. L. & RAJABI-SIAHBOOMI, A. R. (1999) Water distribution studies within cellulose ethers using differential scanning calorimetry. 1. Effect of polymer molecular weight and drug addition. *Journal of Pharmaceutical Sciences*, 88, 792-796.

MCCRYSTAL, C. B., FORD, J. L. & RAJABI-SIAHBOOMI, A. R. (1999) Water distribution studies within cellulose ethers using differential scanning calorimetry. 2. Effect of polymer substitution type and drug addition. *Journal of Pharmaceutical Sciences*, 88, 797-801.

MELIA, C. D., BINNS, J. S. & DAVIES, M. C. (1990) Polymer Hydration and Drug Distribuion within the Gel Layer of Hydrophilic Matrix Devices during Drug Release. *Journal of Pharmacy and Pharmacology*, 42, 125.

MELIA, C. D. (1991) Hydrophilic Matrix Sustained-Release Systems Based on Polysaccharide Carriers. *Critical Reviews in Therapeutic Drug Carrier Systems*, 8, 395-421.

MELIA, C. D., RAJABI-SIAHBOOMI, A. R. & DAVIES, M. C. (1992) The Development of Structural Features in the Surface Gel Layer of Hydrating HPMC Hydrophilic Matrices. *Proceedings of the International Symposium of Controlled Release of Bioactive Materials.* Controlled Release Society, Inc.

MELIA, C. D., RAJABI-SIAHBOOMI, A. R., HODSDON, A. C., ADLER, J. & MITCHELL, J. R. (1993) Structure and Behavior of Hydrophilic Matrix Sustained-Release Dosage Forms .1. the Origin and Mechanism of Formation of Gas-Bubbles in the Hydrated Surface-Layer. *International Journal of Pharmaceutics*, 100, 263-269

MELIA, C. D., MARSHALL, P., STARK, P., CUNNINGHAM, S., KINAHAN, A. & DEVANE, J. (1997) Investigating In Vitro Drug Release Mechanisms Inside Dosage Forms. Monitoring Liquid Ingress in HPMC Hydrophilic Matrices using Confocal Microscopy. IN YOUNG (Ed.) *In Vitro-In Vivo Correlations.* New York, Plenum Press.

MERCK INDEX (1989), Merck & Co. Inc., Rahway, New Jersey, USA

MINSKY, M. (1988) Memoir in inventing the confocal scanning microscope. *Scanning,* 132.

MIRANDA, A., MILLAN, M. & CARABALLO, I. (2006) Study of the critical points of HPMC hydrophilic matrices for controlled drug delivery. *International Journal of Pharmaceutics,* 311, 75-81.

MIRANDA, A., MILLAN, M. & CARABALLO, I. (2006) Study of the critical points in lobenzarit disodium hydrophilic matrices for controlled drug delivery. *Chemical & Pharmaceutical Bulletin,* 54, 598-602.

MITCHELL, K., FORD, J. L., ARMSTRONG, D. J., ELLIOTT, P. N. C., ROSTRON, C. & HOGAN, J. E. (1990) The Influence of Additives on the Cloud Point, Disintegration and Dissolution of Hydroxypropylmethylcellulose Gels and Matrix Tablets. *International Journal of Pharmaceutics,* 66, 233-242.

MIRZA, M. L., IQBAL, J. & AZIZ, H. (1996) Sorption of congo red on cellulose. *Journal of the Chemical Society of Pakistan,* 18, 233-236.

MITCHELL, K., FORD, J. L., ARMSTRONG, D. J., ELLIOTT, P. N. C., HOGAN, J. E. & ROSTRON, C. (1993) The influence of substitution type on the performance of methylcellulose and hydroxypropylmethycellulose in gels and matrices. *International Journal of Pharmaceutics,* 100, 143-154.

MITCHELL, K., FORD, J. L., ARMSTRONG, D. J., ELLIOTT, P. N. C., ROSTRON, C. & HOGAN, J. E. (1993) The influence of concentration on the release of drugs from gels and matrices containing Methocel. *International Journal of Pharmaceutics,* 100, 155-163.

MITCHELL, K., FORD, J. L., ARMSTRONG, D. J., ELLIOT, P. N. C., HOGAN, J. E. & ROSTRON, C. (1993) The Influence of the particle size of hydroxypropylmethylcellulose K15M on its

hydration and performance in matrix tablets. *International Journal of Pharmaceuics*, 100, 175-179.

MITCHELL, K., FORD, J. L., ARMSTRONG, D. J., ELLIOTT, P. N. C., HOGAN, J. E. & ROSTRON, C. (1993) The Influence of Drugs on the Properties of Gels and Swelling Characteristics of Matrices Containing Methylcellulose or Hydroxypropylmethylcellulose. *International Journal of Pharmaceutics*, 100, 165-173.

MITCHELL, S. A. & BALWINSKI, K. M. (2007) Investigation of hypromellose particle size effects on drug release from sustained release hydrophilic matrix tablets. *Drug Development and Industrial Pharmacy*, 33, 952-958.

MITCHELL, S. A. & BALWINSKI, K. M. (2008) A framework to investigate drug release variability arising from hypromellose viscosity specifications in controlled release matrix tablets. *Journal of Pharmaceutical Sciences*, 97, 2277-2285.

MORI, T., FUKUDA, Y., OKAMURA, H., MINAGAWA, K., MASUDA, S. & TANAKA, M. (2004) Thermosensitive copolymers having soluble and insoluble monomer units, poly(N-vinylacetamide-co-methyl acrylate)s: Effect of additives on their lower critical solution temperatures. *Journal of Polymer Science Part a-Polymer Chemistry*, 42, 2651-2658.

MORTAZAVI, S. A. & SMART, J. D. (1993) An Investigation into the Role of Water-Movement and Mucus Gel Dehydration in Mucoadhesion. *Journal of Controlled Release*, 25, 197-203.

MOUSSA, I. S. & CARTILIER, L. H. (1996) Characterization of moving fronts in cross-linked amylose matrices by image analysis. *Journal of Controlled Release*, 42, 47.

NAIR, A., GUPTA, R. & VASANTI, S. (2007) In vitro controlled release of alfuzosin hydrochloride using HPMC-based matrix tablets and its comparison with marketed product. *Pharmaceutical Development and Technology*, 12, 621-625.

NAKANO, T., YUASA, H. & KANAYA, Y. (1999) Suppression of agglomeration in fluidized bed coating. III. Hofmeister series in suppression of particle agglomeration. *Pharmaceutical Research*, 16, 1616-1620.

NAKAMURA, K., KINOSHITA, E., HATAKEYAMA, T. & HATAKEYAMA, H. (2000) TMA measurement of swelling behavior of polysaccharide hydrogels. *Thermochimica Acta*, 352, 171-176.

NILSSON, S. (1995) Interactions between Water-Soluble Cellulose Derivatives and Surfactants .1. the HPMC/SDS/Water System. *Macromolecules*, 28, 7837-7844.

NOKHODCHI, A., NOROUZI-SANI, S., SIAHI-SHADBAD, M.-R., LOTFIPOOR, F. & SAEEDI, M. (2002) The effect of various surfactants on the release rate of propranolol hydrochloride from hydroxypropylmethylcellulose (HPMC)-Eudragit matrices. *European Journal of Pharmaceutics and Biopharmaceutics*, 54, 349-356.

OMTA, A. W., KROPMAN, M. F., WOUTERSEN, S. & BAKKER, H. J. (2003) Negligible effect of ions on the hydrogen-bond structure in liquid water. *Science*, 301, 347-349.

ONESIPPE, C. & LAGERGE, S. (2008) Study of the complex formation between sodium dodecyl sulfate and chitosan. *Colloids and Surfaces a-Physicochemical and Engineering Aspects*, 317, 100-108.

PAULSSON, M. & EDSMAN, K. (2001) Controlled drug release from gels using surfactant aggregates. II. Vesicles formed from mixtures of amphiphilic drugs and oppositely charged surfactants. *Pharmaceutical Research*, 18, 1586-1592

PENOTT-CHANG, E. K., GOUVEIA, L., FERNANDEZ, I. J., MULLER, A. J., DIAZ-BARRIOS, A. & SAEZ, A. (2007) Rheology of aqueous solutions of hydrophobically modified polyacrylamides and surfactants. *Colloids and Surfaces a-Physicochemical and Engineering Aspects*, 295, 99-106.

PEREZ, O. E., SANCHEZ, C. C., PATINO, J. M. R. & PILOSOF, A. M. R. (2006) Thermodynamic and dynamic characteristics of hydroxypropylmethylcellulose adsorbed films at the air-water interface. *Biomacromolecules*, 7, 388-393.

PHAECHAMUD, T. & RITTHIDEJ, G. C. (2007) Sustained-release from layered matrix system comprising chitosan. *Drug Development and Industrial Pharmacy*, 33, 595-605.

PICULELL, L., BERGFELDT, K. & NILSSON, S. (1995) Factors determining phase behaviour of multi component polymer systems. IN HARDING, S. E., HILL, S. E. & MITCHELL, J. R. (Eds.) *Biopolymer Mixtures.* Loughborough, Nottingham University Press.

PILLAY, V. & FASSIHI, R. (2000) A novel approach for constant rate delivery of highly soluble bioactives from a simple monolithic system. *Journal of Controlled Release,* 67, 67-78.

PINI, R., STORTI, G., MAZZOTTI, M., TAI, H. Y., SHAKESHEFF, K. M. & HOWDLE, S. M. (2008) Sorption and swelling of poly(DL-lactic acid) and poly(lactic-co-glycolic acid) in supercritical CO_2: An experimental and modeling study. *Journal of Polymer Science Part B-Polymer Physics,* 46, 483-496.

PERON, N., MESZAROS, R., VARGA, I. & GILANYI, T. (2007) Competitive adsorption of sodium dodecyl sulfate and polyethylene oxide at the air/water interface. *Journal of Colloid and Interface Science,* 313, 389-397.

POSE-VILARNOVO, B., RODRÍGUEZ-TENREIRO, C., ROSA DOS SANTOS, J. F., VÁZQUEZ-DOVAL, J., CONCHEIRO, A., ALVAREZ-LORENZO, C. & TORRES-LABANDEIRA, J. J. (2004) Modulating drug release with cyclodextrins in hydroxypropyl methylcellulose gels and tablets. *Journal of Controlled Release,* 94, 351-363.

PURCELL, I. P., LU, J. R., THOMAS, R. K., HOWE, A. M. & PENFOLD, J. (1998) Adsorption of sodium dodecyl sulfate at the surface of aqueous solutions of poly(vinylpyrrolidone) studied by neutron reflection. *Langmuir,* 14, 1637-1645.

PUTTIPIPATKHACHORN, S., NUNTHANID, J., YAMAMOTO, K. & PECK, G. E. (2001) Drug physical state and drug-polymer interaction on drug release from chitosan matrix films. *Journal of Controlled Release,* 75, 143-153.

PYGALL, S. R., WHETSTONE, J., TIMMINS, P. & MELIA, C. D. (2007) Pharmaceutical applications of confocal laser scanning microscopy: The physical characterisation of pharmaceutical systems. *Advanced Drug Delivery Reviews,* 59, 1434-1452.

RADES, T. & MUELLER-GOYMANN, C. C. (1998) Interactions between fenoprofen sodium and poly (ethylene oxide). *European Journal of Pharmaceutics and Biopharmaceutics,* 46, 51-59.

RAJABI-SIAHBOOMI, A. R. (1993) Hydroxypropylmethylcellulose in Hydrophilic Matrix Dosage Forms. *Department of Pharmaceutical Sciences.* Nottingham, University of Nottingham.

RAJABI-SIAHBOOMI, A. R., BOWTELL, R. W., MANSFIELD, P., HENDERSON, A., DAVIES, M. C. & MELIA, C. D. (1994) Structure and behaviour in hydrophilic matrix sustained release dosage forms: 2. NMR-imaging studies of dimensional changes in the gel layer and core of HPMC tablets undergoing hydration. *Journal of Controlled Release,* 31, 124-128.

RAJABI-SIAHBOOMI, A. R., BOWTELL, R. W., MANSFIELD, P., DAVIES, M. C. & MELIA, C. D. (1996) Structure and behavior in hydrophilic matrix sustained release dosage forms .4. Studies of water mobility and diffusion coefficients in the gel layer of HPMC tablets using NMR imaging. *Pharmaceutical Research,* 13, 376-380.

RAO, M. A. (1999) *Rheology of Fluid and Semisolid Foods - Principles and Applications,* Gaithersburg, Aspen.

REKHI, G. S., NELLORE, R. V., HUSSAIN, A. S., TILLMAN, L. G., MALINOWSKI, H. J. & AUSBERGER, L. L. (1999) Identification of critical formulation and processing variables for metoprolol tartrate extended-release (ER) matrix tablets. *Journal of Controlled Release,* 59, 327-342.

RICHARDSON, J.C. (2002) Bioadhesive sodium alginate suspensions as oesophageal protectants. *Pharmaceutical Sciences.* Nottingham, University of Nottingham.

RICHARDSON, J. C., FOSTER, C. S., DOUGHTY, S. W., BURTON, J. S., MACRAE, R. J. & MELIA, C. D. (2006) The influence of L-amino acid molecular structure on the phase transition temperature of hydroxypropyl methylcellulose. *Carbohydrate Polymers,* 65, 22-27.

RIDELL, A., EVERTSSON, H. & NILSSON, S. (2002) Influence of counterion on the interaction of dodecyl sulfates and cellulose ethers. *Journal of Colloid and Interface Science,* 247, 381-388.

RIEPMA, K. A., DEKKER, B. G. & LERK, C. F. (1992) The Effect of Moisture Sorption on the Strength and Internal Surface-Area of Lactose Tablets. *International Journal of Pharmaceutics,* 87, 149-159.

RIDELL, A., EVERTSSON, H., NILSSON, S. & SUNDELOF, L. O. (1999) Amphiphilic association of ibuprofen and two nonionic cellulose derivatives in aqueous solution. *Journal of Pharmaceutical Sciences*, 88, 1175-1181.

RIGGS, P. D., CLOUGH, A. S., JENNESON, P. M., DREW, D. W., BRADEN, M. & PATEL, M. P. (1999) He-3 ion-beam analysis of water uptake and drug delivery. *Journal of Controlled Release*, 61, 165-174.

RODRIGUEZ, R., ALVAREZ-LORENZO, C. & CONCHEIRO, A. (2003) Influence of cationic cellulose structure on its interactions with sodium dodecylsulfate: implications on the properties of the aqueous dispersions and hydrogels. *European Journal of Pharmaceutics and Biopharmaceutics*, 56, 133-142.

ROSHDY, M. N., SCHNAARE, R. L. & SCHWARTZ, J. B. (2001) THe Effect of Formulation Composition and Dissolution Parameters on the Gel Strength of Controlled Release Hydrogel Tablets. *Pharmaceutical Development and Technology*, 6, 583-593.

ROSS-MURPHY, S. B. (1988). Small deformation measurements. Food Structure - Its creation and evaluation. J. M. V. Blanshard and J. R. Mitchell. London, Butterworths: 387-400

SAKO, K., SAWADA, T., NAKASHIMA, H., YOKOHAMA, S. & SONOBE, T. (2002) Influence of water soluble fillers in hydroxypropylmethylcellulose matrices on in vitro and in vivo drug release. *Journal of Controlled Release*, 81, 165-172.

SARKAR, N. (1979) Thermal Gelation Properties of Methyl and Hydroxypropyl Methylcellulose. *Journal of Applied Polymer Science*, 24, 1073-1087.

SARKAR, N. (1984) Structural Interpretation of the Interfacial Properties of Aqueous-Solutions of Methylcellulose and Hydroxypropyl Methylcellulose. *Polymer*, 25, 481-486.

SARKAR, N. & WALKER, L. C. (1995) Hydration--dehydration properties of methylcellulose and hydroxypropylmethylcellulose. *Carbohydrate Polymers*, 27, 177-185.

SASA, B., ODON, P., STANE, S. & JULIJANA, K. (2006) Analysis of surface properties of cellulose ethers and drug release from their matrix tablets. *European Journal of Pharmaceutical Sciences,* 27, 375-383.

SAVOLAINEN, J., JARVINEN, K., TAIPALE, H., JARHO, P., LOFTSSON, T. & JARVINEN, T. (1998) Co-administration of a water-soluble polymer increases the usefulness of cyclodextrins in solid oral dosage forms. *Pharmaceutical Research,* 15, 1696-1701.

SCHERLUND, M., BRODIN, A. & MALMSTEN, M. (2000) Micellization and gelation in block copolymer systems containing local anesthetics. *International Journal of Pharmaceutics,* 211, 37-49.

SCHMIDT, P. C. & HERZOG, R. (1993) Calcium Phosphates in Pharmaceutical Tabletting .1. Physico-Pharmaceutical Properties. *Pharmacy World & Science,* 15, 105-115.

SCHREIER, S., MALHEIROS, S. V. P. & DE PAULA, E. (2000) Surface active drugs: self-association and interaction with membranes and surfactants. Physicochemical and biological aspects. *Biochimica Et Biophysica Acta-Biomembranes,* 1508, 210-234

SHEPPARD, C. J. R. & SHOTTON, D. M. (1997) *Confocal Laser Scanning Microscopy,* Oxford, UK, BIOS Scientific Publishers LTD.

SHESKEY, P., ROBB, R., MOORE, R. & BOYCE, B. (1995) Effects of lubricant level, method of mixing and duration of mixing on controlled release matrix tablet containing hydroxypropyl methyl cellulose. *Drug Development and Industrial Pharmacy,* 21, 2151-2165.

SIEPE, S., LUECKEL, B., KRAMER, A., RIES, A. & GURNY, R. (2006) Strategies for the design of hydrophilic matrix tablets with controlled microenvironmental pH. *International Journal of Pharmaceutics,* 316, 14-20.

SINGH, S. K. & NILSSON, S. (1999) Thermodynamics of interaction between some cellulose ethers and SDS by titration microcalorimetry - I. EHEC and HPMC. *Journal of Colloid and Interface Science,* 213, 133-151.

SMITH, R. W., BOOTH, J., MASSINGHAM, G. & CLOUGH, A. S. (2004) A study of water diffusion, in both radial and axial directions, into biodegradable monolithic depots using ion beam analysis. *Polymer*, 45, 4893-4908

SOVILJ, V. J. & PETROVIC, L. B. (2006) Influence of hydroxypropylmethyl cellulose-sodium dodecylsulfate interaction on the solution conductivity and viscosity and emulsion stability. *Carbohydrate Polymers*, 64, 41-49.

SRIAMORNSAK, P., THIRAWONG, N. & KORKERD, K. (2007) Swelling, erosion and release behavior of alginate-based matrix tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, 66, 435-450.

STREUBEL, A., SIEPMANN, J., DASHEVSKY, A. & BODMEIER, R. (2000) pH-independent release of a weakly basic drug from water-insoluble and -soluble matrix tablets. *Journal of Controlled Release*, 67, 101.

STUBENRAUCH, C., ALBOUY, P. A., V. KLITZING, R. & LANGEVIN, D. (2000) Polymer/Surfactant Complexes at the Water/Air Interface: A Surface Tension and X-ray Reflectivity Study. *Langmuir*, 16, 3206-3213.

STRUGALA, G. J., ELSENHANS, B. & FORTH, W. (2000) Active transport inhibition in rat small intestine by amphiphilic amines: An in vitro study with various local anaesthetics. *Biochemical Pharmacology*, 59, 907-913.

SUNG, K. C., NIXON, P. R., SKOUG, J. W., JU, T. R., GAO, P., TOPP, E. M. & PATEL, M. V. (1996) Effect of formulation variables on drug and polymer release from HPMC-based matrix tablets. *International Journal of Pharmaceutics*, 142, 53-60.

TAHARA, K., YAMAMOTO, K. & NISHIHATA, T. (1995) Overall mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropyl methylcellulose 2910. *Journal of Controlled Release*, 35, 59-66.

TAKKA, S., RAJBHANDARI, S. & SAKR, A. (2001) Effect of anionic polymers on the release of propranolol hydrochloride from matrix tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, 52, 75-82.

TAM, K. C. & WYN-JONES, E. (2006) Insights on polymer surfactant complex structures during the binding of surfactants to polymers as measured by equilibrium and structural techniques. *Chemical Society Reviews*, 35, 693-709.

TANG, Y. & SINGH, J. (2008) Controlled delivery of aspirin: Effect of aspirin on polymer degradation and in vitro release from PLGA based phase sensitive systems. *International Journal of Pharmaceutics*, 357, 119-125.

TAPIA, M. J., BURROWS, H. D., VALENTE, A. J. M., PRADHAN, S., SCHERF, U., LOBO, V. M. M., PINA, J. & DE MELO, J. S. (2005) Interaction between the water soluble poly{1,4-phenylene-[9,9-bis(4-phenoxy butylsulfonate)]fluorene-2,7-diyl} copolymer and ionic surfactants followed by spectroscopic and conductivity measurements. *Journal of Physical Chemistry B*, 109, 19108-19115

TAYLOR, D. J. F., THOMAS, R. K. & PENFOLD, J. (2007) Polymer/surfactant interactions at the air/water interface. *Advances in Colloid and Interface Science*, 132, 69-110.

THOMA, K. & ZIEGLER, I. (1998) The pH-independent release of fenoldopam from pellets with insoluble film coats. *European Journal Of Pharmaceutics And Biopharmaceutics*, 46, 105-113.

THONGNGAM, M. & MCCLEMENTS, D. J. (2005) Influence of pH, ionic strength, and temperature on self-association and interactions of sodium dodecyl sulfate in the absence and presence of chitosan. *Langmuir*, 21, 79-86.

THURESSON, K. & LINDMAN, B. (1997) Effect of hydrophobic modification of a nonionic cellulose derivative on the interaction with surfactants. Phase behavior and association. *Journal of Physical Chemistry B*, 101, 6460-6468.

THURESSON, K. & LINDMAN, B. (1999) Association in nonionic cellulose ether solutions due to microcrystallites. *Colloids and Surfaces a-Physicochemical and Engineering Aspects*, 159, 219-226.

TILLMAN, W. J. & KURAMOTO, R. (1957) A Study of the Interaction Between Methylcellulose and Preservatives. *Journal of the American Pharmaceutical Association (Scientific Edition)*, 46, 211-214.

TOLSTOGUZOV, V. (2003) Thermodynamic considerations on polysaccharide functions. Polysaccharides came first. *Carbohydrate Polymers*, 54, 371-380.

TOUITOU, E. & DONBROW, M. (1982) Influence of Additives on (hydroxyethyl) methylcellulose properties: Relation between Gelation Temperature Change, Compressed Matrix Integrity and Drug Release Profile. *International Journal of Pharmaceutics*, 11, 131-148.

VARMA, M. V. S., KAUSHAL, A. M. & GARG, S. (2005) Influence of micro-environmental pH on the gel layer behavior and release of a basic drug from various hydrophilic matrices. *Journal of Controlled Release*, 103, 499-510.

VELASCO, M. V., FORD, J. L., ROWE, P. & RAJABI-SIAHBOOMI, A. R. (1999) Influence of drug:hydroxypropylmethylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets. *Journal of Controlled Release*, 57, 75-85.

VLACHOU, M., NASEEF, H. & EFENTAKIS, M. (2004) Image analysis studies of dimensional changes in swellable hydrophilic polymer matrices. *Polymers for Advanced Technologies*, 15, 683-689.

WAN, L. S. C. & PRASAD, K. P. P. (1990) A Study of the Swelling of Tablet Excipients Using Video Recording. *Drug Development and Industrial Pharmacy*, 16, 921-933.

WANG, Y., HAN, B., YAN, H. & KWAK, J. C. T. (1997) Microcalorimetry Study of Interaction between Ionic Surfactants and Hydrophobically Modified Polymers in Aqueous Solutions. *Langmuir*, 13, 3119-3123.

WANGSAKAN, A., CHINACHOTI, P. & MCCLEMENTS, D. J. (2006) Isothermal titration calorimetry study of the influence of temperature, pH and salt on maltodextrin-anionic surfactant interactions. *Food Hydrocolloids*, 20, 461-467.

WHITE, N. S. & ERRINGTON, R. J. (2005) Fluorescence techniques for drug delivery research: theory and practice. *Advanced Drug Delivery Reviews*, 57, 17-42.

WHITTIER, E. O. (1933) Freezing points and osmotic pressures of lactose solutions. *Journal of Physical Chemistry*, 37, 847-849.

WILLIAMS, R. O., REYNOLDS, T. D., CABELKA, T. D., SYKORA, M. A. & MAHAGUNA, V. (2002) Investigation of excipient type and level on drug release from controlled release tablets containing HPMC. *Pharmaceutical Development and Technology*, 7, 181-193.

WITTGREN, B., STEFANSSON, M. & PORSCH, B. (2005) Interactions between sodium dodecyl sulphate and non-ionic cellulose derivatives studied by size exclusion chromatography with online multi-angle light scattering and refractometric detection. *Journal of Chromatography A*, 1082, 166-175.

WONG, E.B. (2008) Use of Starch 1500 in HPMC hydrophilic matrices. *Pharmaceutical Sciences*. Nottingham, University of Nottingham.

WOOD, P. J. (1980) Specificity in the Interaction of Direct Dyes with Polysaccharides. *Carbohydrate Research*, 85, 271-287.

WU, H. L., HUANG, C. H., CHEN, S. H. & WU, S. M. (1998) Micellar electrokinetic chromatography of scopolamine-related anticholinergics. *Journal of Chromatography A*, 802, 107-113.

WU, N., WANG, L. S., TAN, D. C. W., MOOCHHALA, S. M. & YANG, Y. Y. (2005) Mathematical modeling and in vitro study of controlled drug release via a highly swellable and dissoluble polymer matrix: polyethylene oxide with high molecular weights. *Journal of Controlled Release*, 102, 569-581.

XU, G. J. & SUNADA, H. (1995) Influence Of Formulation Change On Drug-Release Kinetics From Hydroxypropylmethylcellulose Matrix Tablets. *Chemical & Pharmaceutical Bulletin*, 43, 483-487.

YANG, J., ZHAO, J. & FANG, Y. (2008) Calorimetric studies of the interaction between sodium alginate and sodium dodecyl sulfate in dilute solutions at different pH values. *Carbohydrate Research*, 343, 719-725.

YAMAKI, S. B., BARROS, D. S., GARCIA, C. M., SOCOLOSKI, P., OLIVEIRA, O. N. & ATVARS, T. D. Z. (2005) Spectroscopic studies of the intermolecular interactions of Congo red and tinopal CBS with modified cellulose fibers. *Langmuir*, 21, 5414-5420.

YASUEDA, S., INADA, K., MATSUHISA, K., TERAYAMA, H. & OHTORI, A. (2004) Evaluation of ophthalmic suspensions using surface tension. *European Journal of Pharmaceutics and Biopharmaceutics,* 57, 377-382.

YOMOTA, C. & OKADA, S. (2003) Various interactions of drugs with cross-linked hyaluronate gel. *Polymer Gels: Fundamentals and Applications.* Washington, Amer Chemical Soc.

ZATLOUKAL, Z. & SKLUBALOVA, Z. (2007) Sterilized ophthalmic hydrogels with hydroxypropyl methylcellulose: Determination and mathematical treatment of flow properties. *Pharmaceutical Development and Technology,* 12, 55-60.

ZHANG, Y. J. & CREMER, P. S. (2006) Interactions between macromolecules and ions: the Hofmeister series. *Current Opinion in Chemical Biology,* 10, 658-663.

ZHAO, G. & CHEN, S. B. (2007) Nonlinear rheology of aqueous solutions of hydrophobically modified hydroxyethyl cellulose with nonionic surfactant. *Journal of Colloid and Interface Science,* 316, 858-866.

ZULEGER, S. & LIPPOLD, B. C. (2001) Polymer particle erosion controlling drug release. I. Factors influencing drug release and characterization of the release mechanism. *International Journal of Pharmaceutics,* 217, 139-152.

ZULEGER, S., FASSIHI, R. & LIPPOLD, B. C. (2002) Polymer particle erosion controlling drug release. II. Swelling investigations to clarify the release mechanism. *International Journal of Pharmaceutics,* 247, 23-37.

Appendix 1

Materials

Material	Manufacture	Batch no
Congo red	Sigma-Aldrich Company Ltd, Dorset, UK	126H2510
Deuterium oxide	Fluorochem, Derbyshire , UK	X3191
Diclofenac sodium salt	MP Biomedicals, Germany	7721E
HPMC (Methocel E4M CR Premium USP/EP)	Colorcon Ltd, Dartford, UK	OD16012N32
Lactose (Lactopress)	Borculo Ltd,	S0410410034
Magnesium stearate	Sigma-Aldrich Company Ltd, Dorset, UK	S03492-325
Meclofenamate sodium	Cayman Chemical Company	17116A
Sigmacote®	Sigma-Aldrich Company Ltd, Dorset, UK	103K4360
Silicon dioxide	Sigma-Aldrich Company Ltd, Dorset, UK	10626JD
Silicone Oil (low viscosity 100 mPa.s)	Sigma-Aldrich Company Ltd, Dorset, UK	448742/1 11904174
Sodium chloride	Fisher Scientific, Loughborough, UK	0585645
Water (Maxima HPLC grade with a maximum conductance of 18.2 $M\Omega cm^{-1}$)	USF Elga, Buckinghamshire, UK	

Appendix 2

Moisture content of HPMC batch

Powdered HPMC absorbs moisture and can contain significant equilibrium moisture content varying between 2-10% w/w water (Doelker 1993). The moisture content of the HPMC batch utilized throughout the study was therefore monitored periodically at 3 month intervals using a MB45 Moisture Analyser (Ohaus Corporation, Florham Park, NJ). The water content was found to be maintained between 3.5-4.5% w/w, as shown in figure A.1.
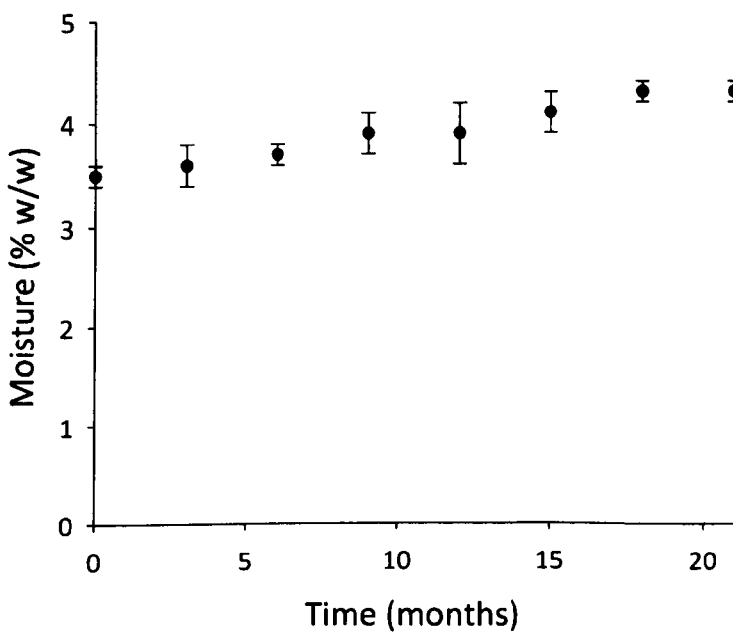

Figure A.1 Moisture content (% w/w) of the HPMC batch used in the thesis

Moisture content monitored periodically at 3 month intervals. Mean (n = 5) ±1 SD