Exploring low polymer content HPMC hydrophilic matrices

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Abstract

Extended release oral drug delivery (ER) offers many therapeutic benefits. Hydroxypropyl methylcellulose (HPMC) hydrophilic matrices provide a widely-accepted industrial technology to achieve ER. However, there are significant limitations and the mechanism of drug release is complex. One limitation is polymer content. Manufacturers recommend that at least 30% w/w of a high viscosity HPMC should be included in the dosage form, but lower polymer contents are desirable, for example, when (i) a high drug load restricts tablet size or (ii) *in-vivo* studies show drug release kinetics to be too slow.

The widely-held view has been that matrix properties will worsen as polymer content is lowered, and that matrices will fail, or become erratic in their drug release behaviour. This is thought to be due to increased sensitivity to formulation parameters, manufacturing conditions or external dissolution factors, including the fed or fasted state *in-vivo*. These failures have been attributed to the belief that a lower polymer content will provide a less stable gel layer, in terms of its diffusion barrier properties, its physical strength and resistance to erosion. These principles have scarcely been challenged, even though there is only sparse evidence in the literature to support them. This thesis aims to address this lack of knowledge by providing a series of systematic studies on the behaviour of 'low polymer' matrices, those with a polymer content between 5% and 20% w/w of a high viscosity HPMC. Overall, the presented studies have shown that hydrophilic matrices containing less than 30% w/w HPMC can be designed with effective ER control, thus expanding the formulation space for HPMC-based ER medicines.

The first experimental chapter (Chapter 3) focused on the formation and structure of the early gel layer with respect to HPMC polymer content. Confocal laser scanning microscopy was used to visualise and compare the emerging gel layer of matrices with different HPMC contents, and was combined with theoretical predictions from percolation theory, one of the few techniques that provides a guide for formulators on the necessary matrix polymer content. The images showed that at polymer contents above the estimated percolation threshold a continuous gel layer was formed within 15 min, whereas matrices with polymer contents below the threshold were characterized by irregular gel layer formation with little evidence of HPMC particle coalescence. The studies provide, for the first time, physical evidence to validate the use of percolation theory in HPMC matrices and they provide support for use of this theory in the development of low polymer content matrices.

Chapter 4 examined the drug release sensitivity of low polymer matrices to dissolution factors such as ionic strength and paddle speed. The presence of salts is known to influence HPMC swelling behaviour, and can affect matrix drug release. It was found in USP apparatus II that, as the matrix polymer content was lowered, drug release rate was faster as paddle speed increased from 25 to 150 RPM. In contrast, dissolution sensitivity was found to be independent of sodium chloride (NaCl) concentration, suggesting that the effects of NaCl are polymer, rather than formulation, mediated. This was a rather surprising result, given that salt is known to influence the rate of polymer swelling, a necessary process for gel layer formation and diffusion barrier development.

Chapter 5 compared the behaviour of low polymer matrices in the fed and fasted state under simulated *in-vivo* conditions. The Dynamic Gastric Model, was used to compare drug release from formulations in the presence or absence of food. This work was one of the first published studies where a series of matrix formulations had been evaluated in the DGM. The studies demonstrated that the drug release from formulations with a matrix polymer content below 30% w/w varied according to prandial state, being slower in the presence of food. Formulations containing 30% w/w HPMC did not show a change in drug release rate according to prandial state, beyond a lag in the fed state. The reasons for this are speculated to be due to the deposition of fats on the matrix surface limiting the initial burst in drug release associated with matrices containing lower polymer contents

Chapter 6 and 7 examined formulation variables including HPMC particle size and viscosity grade, tabletting excipients and complementary polymers. It showed how judicious formulation selection could reduce the sensitivity of low polymer content matrices to challenging dissolution conditions. A series of numerical rules were developed which could assist in the development of low polymer content matrices in an industrial context.

The thesis has identified several key considerations for developing successful low polymer content matrices and should be helpful in guiding the development of medicines that contain lower than the currently recommended levels of HPMC. It corroborates percolation theory and has shown that the percolation threshold is important in influencing matrix sensitivity to dissolution conditions. It should aid the rational design of formulations that have better *in-vivo* reproducibility and drug release that is less influenced by gastro-intestinal conditions.

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I am the product of my Kendalian upbringing, and my amazing family have instilled the determination, moral values and healthy dose of stubbornness that have kept me going when times get tough. A special Auntie hello to my nephews Flynt and Eryck who have been born in the time it has taken me to complete my studies.

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Abbreviations

API	Active pharmaceutical ingredient
BCS	Biopharmaceutics Classification System
BP	British Pharmacopeia
CLSM	Confocal laser scanning microscopy
cm	centimetre
cP	Centipoise
CPT	Cloud point temperature
DGM	Dynamic gastric model
DR10min	Drug release (%) in 10 minutes
ER	Extended-release
FaSSGF	Fasted state simulated gastric fluid
FaSSIF	Fasted state simulated intestinal fluid
FDA	Food and Drug Administration
FeSSGF	Fed state simulated gastric fluid
FeSSIF	Fed state simulated intestinal fluid
FTIR	Fourier-transform infrared
g	Gram
GI	Gastro-intestinal
GRAS	Generally regarded as safe
h, hr	Hour
HCl	Hydrochloric acid
HPLC	High performance liquid chromatography
HPMC	Hydroxypropyl methylcellulose
Hz	Hertz (1/seconds)
IFR	Institute for Food Research
IGT	Incipient gelation temperature
IR	Immediate-release
kN	Kilonewton
LUT	Lookup table
MCC	Microcrystalline cellulose
µm	micrometre
mg	Milligram
mg/mL	milligram per millilitre
min	Minute
mm	Millimetre
MMC	Migrating motor complex
mmol	Millimolar
MPa	Megapascal
MRI	Magnetic Resonance Imaging
MW	Molecular weight
N	Newton
NaCl	Sodium chloride
NaCMC	Sodium carboxymethyl cellulose
NaOH	Sodium hydroxide

nm	nanometre
PEO	Polyethylene oxide
pHEMA	poly-2-hydroxyethyl methacrylate
QbD	Quality-by-Design
R/F	Relaxational (Erosional) to Fickian release mechanism
RPM	Revolutions per minute
RSD	Relative standard deviation
RSD	Relative standard deviation
SA/V	Surface Area/Volume
SCrit	Critical concentration of solute
SD	Standard Deviation
SEM	Standard error of the mean
SGF	Simulated gastric fluid
SIF	Simulated intestinal fluid
$T_{80\%}$	Time for 80% release
Tg	Glass transition temperature
THAM	Trisaminomethane
TIM	TNO-intestinal model
TSC	Trisodium citrate
USP	United States Pharmacopeia
UV	Ultraviolet
v/v	volume in volume
w/v	weight in volume
w/w	weight in weight

Symbols

%	Percent
k_1	First order rate constant
k_0	Zero order rate constant
k_h	Higuchi rate constant
k_{kp}	Korsmeyer-Peppas rate constant
k_d	Diffusional release (Peppas-Sahlin)
k_r	Diffusional release (Peppas-Sahlin)
n	release exponent (Korsmeyer-Peppas)
>	Greater than
<	Less than
Ø	diameter
σ_{TS}	Tensile Strength
λ	wavelength
r^2	Coefficient of determination
°C	degrees Celsius

Chapter 1
Introduction

1.1 The use of hydrophilic matrices as extended-release dosage forms

The oral route is the most frequent way to deliver drugs. Tablets and capsules comprised of 55% of novel drug approvals by the FDA in 2015 (U.S. Food and Drug Administration, 2016). The oral route remains popular due to the simplicity and convenience of administration for the patient, and relative ease of manufacture. The majority of these are "immediate release" dosage forms, in which drug is liberated rapidly from the dosage form, with the aim of achieving rapid onset of the therapeutic effects. However drug plasma concentrations can quickly fall and therefore immediate release (IR) dosage forms often require repeated dosing (Figure 1.1).

Extended-release (ER) dosage forms aim to increase the time period over which a therapeutic drug plasma concentration is maintained (Collett and Moreton, 2007). The advantages and disadvantages of ER formulations are well known and some are listed in Table 1.1. Developing ER formulations is often considered a form of product life-cycle management. Producing ER forms of existing IR products can enable a company to claim new therapeutic benefits and maintain the exclusivity of its proprietary product (Wright, 2014). However, ER formulations are increasingly being used as an 'enabling technology' much earlier in the drug development programme during early formulation development and Phase I and II clinical trials. As peak plasma concentrations are lower, ER formulations can facilitate dose tolerability studies and advance drug candidates that may have otherwise failed to progress (Martini and Crowley, 2011, Nicholson et al., 2012, Good et al., 2015).

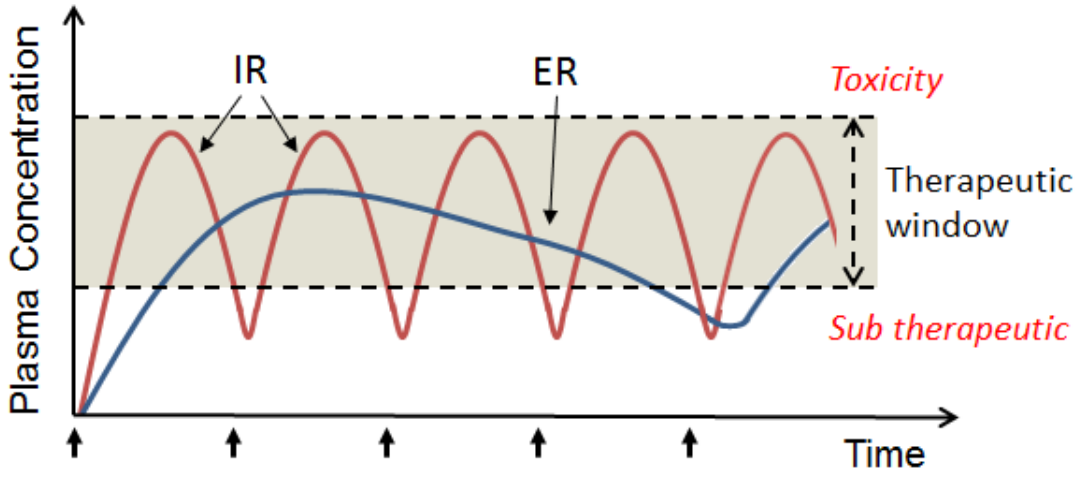

Figure 1.1: Schematic representation of drug-plasma profiles for conventional, immediate release (IR) dosage forms (red line) and extended release (ER) dosage forms (blue line). Arrows on *x* axis represent dosing points. The grey band represents the therapeutic window which is a range of doses that produce a therapeutic response without any significant adverse event.

Advantages and disadvantages of extended-release dosage forms	
Advantages	Longer duration of action which enables once-daily or twice-daily administration for drugs with short half-lives. This can improve patient compliance. e.g. *opioids*
	The dug plasma concentration remains in therapeutic window for longer. This can result in more effective treatment *e.g. anti-psychotics, beta-blockers*
	Can avoid peak plasma concentrations and dose-related adverse effects e.g. *to avoid reflex tachycardia and hypotension with nifedipine*
Disadvantages	Drug release rate can depend on the presence of foods or the rate of gut transit
	Cannot be stopped abruptly in case of adverse drug reactions
	Large dosage form that cannot be chewed or crushed. This can be troublesome for some patient populations.

Table 1.1: Advantages and disadvantages of extended release formulations. Information from: Sansom (1999), Richter et al. (2003), Minami et al. (2004), Wilson and Crowley (2011), Kuentz et al. (2016)

Many different oral dosage systems have been developed to extend drug release, with some outlined in Table 1.2. They can be broadly categorised into reservoir and matrix systems. In reservoir type systems the drug is surrounded by a coat that stops the immediate release of the drug on swallowing. The drug release is controlled by the coat, typically formed from a high molecular weight polymer. The drug may diffuse through the coat, often through pores left as water soluble components of the membrane dissolve. In the case of osmotic systems, an osmotic agent drives an osmotic pressure which forces drug out of a hole in the membrane (am Ende et al., 2000). Whilst drug release rates can be well controlled using reservoir systems, dose dumping can occur if the membrane integrity is damaged or manufactured with defects. Thus, these tablets cannot be divided and maintain their designed drug release profiles (Collett and Moreton, 2007).

Matrix tablets are also known as monolithic matrices, and contain drug that is '*finely, intimately and thoroughly dispersed in the tablet itself'* (Goldman, 1962). Typically, these formulations contain polymers, fats or waxes as the matrix. Unlike reservoir systems, matrix tablets can be easily manufactured by compression with normal tabletting excipients, and using conventional tabletting processes. Extended release kinetics will still be expected if there are small defects in the surface of the tablet. Excipient selection influences the mechanism of drug release from matrix tablets. Depending on the content and solubility of the rate controlling excipient, drug will be released by erosional mechanisms, diffusional mechanisms or a combination of the two (Wilson and Crowley, 2011, Timmins et al., 2014).

Extended-release system		Properties	Predominant release mechanisms	Materials employed
Reservoir type	Barrier coated	Coating on the dosage form that limits drug release rate. Can be excreted intact	Diffusion	Cellulose acetate
	Osmotic controlled	Semi-permeable membrane coat, with an osmotic agent in the core	Drug driven out of matrix by osmotic pressure providing a mechanical force	Cellulose acetate coat. Osmotic agents such as sorbitol, sodium chloride, potassium chloride and xylitol.
Matrix type	Inert matrix	Insoluble matrix which does not swell. Can be excreted intact.	Drug release by diffusion through channels	Ethylcellulose Methacrylate acid co-polymers Polyvinyl acetate
	Swelling	Polymer swells without eroding, usually due to a cross-linked polymer	Drug release by diffusion	poly(HEMA) with dextrin or collagen
	Hydrophilic matrix	Swellable, and polymer erodes over time	Diffusion and polymer erosion	HPMC NaCMC Alginate Xanthan gum Polyethylene oxide
	Surface eroding	Limited swelling, but erodes over time	Erosion	Wax or lipids hydrogenated castor oil Carnauba wax
	Ion-exchange resins	Contains an insoluble, commonly synthetic matrix with ionisable groups	Counter-ion diffuses into matrix, exchanges with bound drug and free drug is released	Anionic and cationic polymers i.e. Amberlite resins.

Table 1.2: Oral dosage systems designed to extended drug release. Information from: Florence and Attwood (1998), am Ende et al. (2000), Collett and Moreton (2007), Wilson and Crowley (2011), Timmins et al. (2014).

1.1.1 Hydrophilic matrices

When matrices contain non-crosslinked, water-swellable, hydrophilic polymers they are known as hydrophilic matrices. These systems are capable of releasing drug by both swelling and erosion. The detailed mechanism of drug release from hydrophilic matrices is more fully explained in section 1.1.3.

Hydrophilic matrices have been used as extended release dosage forms since the 1960s (Christenson and Dale, 1962, Lapidus and Lordi, 1966), and they have continued to be a mainstay formulation strategy when extended drug release kinetics are desired (Melia, 1991, Timmins et al., 2014). It has been shown that drugs with varying solubilities, and loadings can easily be formulated into hydrophilic matrices. There is a wealth of academic literature and industrial experience that can guide formulation development (Hogan, 1989, Melia, 1991, Dow Chemicals, 2000, Li et al., 2005, Maderuelo et al., 2011, Timmins et al., 2014). Some commercially successful formulations in the UK are listed in Table 1.4. Examples of polymers used in hydrophilic matrices are listed in Table 1.3. These polymers can be categorised by their charge and chemistry. Polysaccharides are long chains of repeating sugar units bound by glycosidic linkages. Cellulose is a specific example of a polysaccharide, where D-glucose units are joined by β(1→4) linkages.

Neutral polysaccharides	Cellulosic	Hydroxypropyl methylcellulose
		Hydroxypropyl cellulose
	Non-cellulosic	Galactomannans
		Starches
Charged polysaccharides	Cellulosic	Sodium carboxymethyl cellulose
	Non-cellulosic	Sodium alginate
		Carrageenans
		Xanthan gum
High molecular weight polymer chains (non-cellulosic)		Polyacrylic acid (Carbopol)
		Polyethylene oxide

Table 1.3: Polymers used in studies of hydrophilic matrices in the scientific literature. (Melia, 1991, Melia and Timmins, 2014)

Brand	Drug	Polymer (s) (% w/w)	Company	Patent	Year of MA
Natrilix SR	Indapamide	A mixture of two HPMC viscosity grades (30 – 35%)	Servier	EP 1902709 A1	1996
Mirapexin PR	Pramipexole	Combination of HPMC (25 – 65%) and Carbopol	Boehringer	WO 2006015942 A1	1998
Plendil	Felodipine	HPMC (20 – 80%)	AstraZeneca	US 4,803,081	2002
Triapin	Felodipine Ramipril	HPMC (in felodipine tablet core, 49%)	Sanofi / AstraZeneca	WO 1996007400 A1	2002
Zydol SR	Tramadol	HPMC (10 – 40%)	Grünenthal	EP 0642788 B1	2002
Lescol XL	Fluvastatin	Hydroxyethyl cellulose (5 – 35%)	Novartis	WO 2008102379 A1	2004
Glucophage XR	Metformin	NaCMC, HPMC (35 – 60%)	Merck Serono	US 6,475,521	2004
Toviaz XL	Festerodine	HPMC (20 – 65%)	Ucb Pharma, Pfizer	US 7,807,715 B2	2007
Seroquel XL	Quetiapine	HPMC (5 – 50%)	AstraZeneca	US 5,948,437	2008
Niaspan	Nicotinic acid	HPMC (14 – 18%)	Abbott Respiratory	WO 2007120385 A2	2007
Requip XL	Ropinirole	HPMC 2208, carmellose, povidone in multilayers (1 – 75%)	GlaxoSmithKline	US 20040247676 A1	2008
Ralnea XL	Ropinirole	HPMC (40 – 80%)	KRKA	WO 2010012482 A1	2010
Cositam XL	Tamsulosin	HPMC (mixed) (30 – 35%)	Synthon BV	WO 2003039531 A1	2010
Palexia SR	Tapentadol	HPMC (10 – 30%)	Grünenthal	WO 20050058706 A1	2011

Table 1.4: A subset of commercial hydrophilic matrix formulations launched to the market since 1996. Patents accessed via patents.google.com [online], and HPMC content taken from patent application. Company and year of marketing authorisation (UK) taken from the Summary of Product Characteristics accessed via the electronic Medicines Compendium [online]. Accessed June 2016.

1.1.2 Hydroxypropyl methylcellulose

Hydroxypropyl methylcellulose (HPMC, hypromellose) is one of the most commonly used polymers in hydrophilic matrices worldwide (Tiwari and Rajabi-Siahboomi, 2009). HPMC and other cellulose ethers have been used in these formulations since the early patents of the 1960s (Christenson and Dale, 1962). HPMC has good compression properties, is relatively low cost and has GRAS status. In addition, the performance of HPMC is essentially pH independent. Most importantly, HPMC can rapidly swell to form the gel layer necessary to control drug release kinetics (Alderman, 1984, Melia, 1991, Li et al., 2005, Tiwari and Rajabi-Siahboomi, 2008).

HPMC is derived from pulp cellulose obtained from wood and cotton. The pulp is first treated with sodium hydroxide, and then treated with methyl chloride and propylene oxide. This results in chemical substitution of chain hydroxyl groups with methyl ($-CH_3$) and hydroxypropyl ($-CH_2-CH(OH)-CH_3$) substituents (Figure 1.2). Substitution along the cellulose backbone is random and therefore it breaks up the natural crystallinity of cellulose. This increases its water solubility as more hydroxyl groups become available to hydrogen bond with water. The methyl substitution also introduces a degree of hydrophobicity into the chain, but overall the modified cellulose remains highly hydrophilic and water soluble (Dow Chemicals, 2000, Viriden et al., 2009a, Ford, 2014).

Polymer properties are strongly influenced by the ratio of methyl and hydroxypropyl substitution, and The United States Pharmacopeia (USP) details different HPMC types that are classified by their substitution levels (Table 1.5). The first two numbers in the USP description corresponds to the percentage degree of methyl substitution, and the second two numbers indicate the percentage degree of hydroxypropyl substitution (Siepmann and Peppas, 2001, The U.S. Pharmacopeial Convention, 2016). USP 2208 and USP 2910 are the two types most commonly used for hydrophilic matrices (Ford, 2014).

Each USP type of HPMC is also available in a range of viscosities, which is proportional to the polymer molecular weight. As molecular weight is cumbersome to measure, these types are denoted by the viscosity of a 2% w/v aqueous solution. Viscosity grades range from 3 to 200,000 cP, and typically grades with a viscosity of at least 4000 cP are used in extended release formulations (Dow Chemicals, 2000, Li et al., 2005).

There are many commercial manufacturers of HPMC, but the most widely used HPMCs in the western world come from Dow Chemicals (METHOCEL™), Ashland (BENECEL™) and Shin-Etsu (METOLOSE® SR) (Dow Chemicals, 2000, Shin-Etsu Chemical Co., Tiwari and Rajabi-Siahboomi, 2008, Ashland Speciality Ingredients, 2014). The naming of the different types and grades varies according to the different manufacturers. Dow Chemicals and Ashland use the letter A, E, F, J and K to denote each USP type, whereas Shin-Etsu use a combination of numbers and letters, as shown in Table 1.5. The viscosity grades are denoted by the viscosity in cP of a 2% w/v aqueous solution at 20 °C, measured according to the USP method (The U.S. Pharmacopeial Convention, 2016). Dow Chemicals and Ashland abbreviate the viscosity using the modifiers C (x100) and M (x1000) so that, for example, 15C and 15M indicate a nominal viscosity of 1500 cP and 15000 cP respectively. This thesis has solely studied USP 2208, which is designated as METHOCEL™ K by Dow Chemicals (Dow Chemicals, 2000). Four viscosity grades of METHOCEL™ K have been used: 100LV, 4M, 100M and K200M. These grades have nominal viscosities of 100 cP, 4000 cP, 100000 cP and 200000 cP respectively.

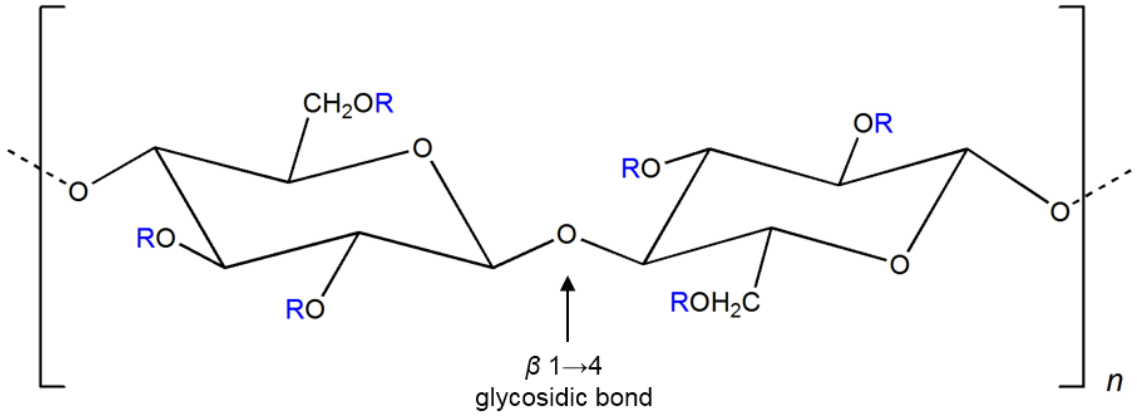

Figure 1.2: The chemical structure of hydroxypropyl methylcellulose. Figure from Williams (2009). Adapted from Doenges (1990) "R" substituents can be -H, $-CH_3$, $-CH_2CH(OH)CH_3$

USP Type	Methyl	Hydroxypropyl	Example Products
	Percent degree of substitution (%)		
Methylcellulose	26.0 to 33.0	-	METHOCEL A BENECEL MC
USP 2910	28.0 to 30.0	7.0 to 12.0	METHOCEL E10M METOLOSE SR 60SH
USP 2906	27.0 to 30.0	4.0 to 7.5	METHOCEL F METOLOSE SR 65SH
USP 1828	16.5 to 20.0	23.0 to 32.0	METHOCEL J
USP 2208	19.0 to 24.0	4.0 to 12.0	METHOCEL K4M METHOCEL K100LV METOLOSE SR 90SH BENECEL K250

Table 1.5: List of USP types of HPMC with corresponding USP specification and example commercial products. Dow Chemicals (2000), Aqualon (2004), Shin-Etsu Chemical Co. (2005), The U.S. Pharmacopeial Convention (2016).

1.1.3 The mechanisms of drug release from hydrophilic matrices

Figure 1.3 shows a schematic illustration of HPMC matrix hydration. The extended release properties of HPMC matrices results from the formation and physical properties of a mucilaginous surface barrier, also termed a 'gel layer'. This layer is formed by the hydration and swelling of HPMC at the matrix surface (Melia, 1991). This layer limits further diffusion of water into the matrix and prevents the immediate disintegration of the tablet. Subsequent regions of the matrix are hydrated as the surface layer erodes away (Alderman, 1984, Ford et al., 1985a). Although the hydrated polymer is commonly termed a 'gel', to a polymer chemist they are not 'true gels' as their viscosity is a result of simple entanglement of polymer chains without crosslinking structures (Morris et al., 1981, Collett and Moreton, 2007). Although 'gel' is the conventional terminology used in most publications, they are better termed as a 'concentrated mucilage'.

The properties of the surface gel barrier determines the rate of water movement into the core of the matrix and the release of drug (Kim and Fassihi, 1997, Li et al., 2005). There are a number of gradients within the gel. As we move from the dry core to the gel periphery we encounter a decreasing polymer concentration gradient and an increasing water concentration gradient. Fronts have been identified in the gel layer, which are shown in Figure 1.3, and pertain to the hydration state of the polymer (Peppas et al., 1980, Harland et al., 1988, Pham and Lee, 1994, Colombo et al., 1995, Ju et al., 1995a, Caccavo et al., 2015). The principal boundaries occur:

(i) Between the glassy tablet core and the rubbery gel (the swelling front)

(ii) The point at which there is sufficient water to dissolve soluble materials within the gel (the diffusion front), and,

(iii) The interface between the gel and the dissolution medium (the erosion front).

The relative movement of these fronts can influence both the drug release rate and the mechanisms of release. These fronts can be distinguished by water content (Barba et al., 2009) and have also been imaged using MRI (Tajarobi et al., 2009a, Chen et al., 2010, Dorozynski et al., 2012).

As the water content of hydrated polymer increases, the entanglement between the polymer chains becomes weaker. This enables polymer chains to dissociate from the gel, either by dissolution or by physical attrition at the gel periphery. This process is termed 'erosion' (Alderman, 1984, Ju et al., 1995a). Polymer hydration and matrix erosion occur simultaneously, and drug can be released throughout, depending on its

aqueous solubility. In simple terms, poorly soluble drugs tend to be released from the matrix as erosion occurs, whereas water soluble drugs can additionally diffuse through the hydrated polymer layer (Harland et al., 1988, Ford et al., 1991).

Understandably, the properties of the gel layer, especially gel strength and the internal morphology, can greatly influence extended release kinetics. Therefore, the hydration and swelling of HPMC is critical to its functionality in extended release (ER) formulations. When HPMC hydrates, hydrogen bonds are formed between water and the polymer hydroxypropyl side groups. Structured water cages form around the hydrophobic regions of the HPMC chain, predominantly where methyl groups have been substituted (Liu et al., 2008a). With continued hydration, surface polymer chains begin to uncoil and extend. This breaks inter-polymer hydrogen bonds allowing the polymer to bond with more water molecules (Ju et al., 1995b, Kim and Fassihi, 1997, Li et al., 2005), resulting in a rapid increase in viscosity (Liu et al., 2008a). This plasticisation of HPMC by water, has been described as a phase transition of the polymer from the glassy to the rubbery state (Harland et al., 1988).

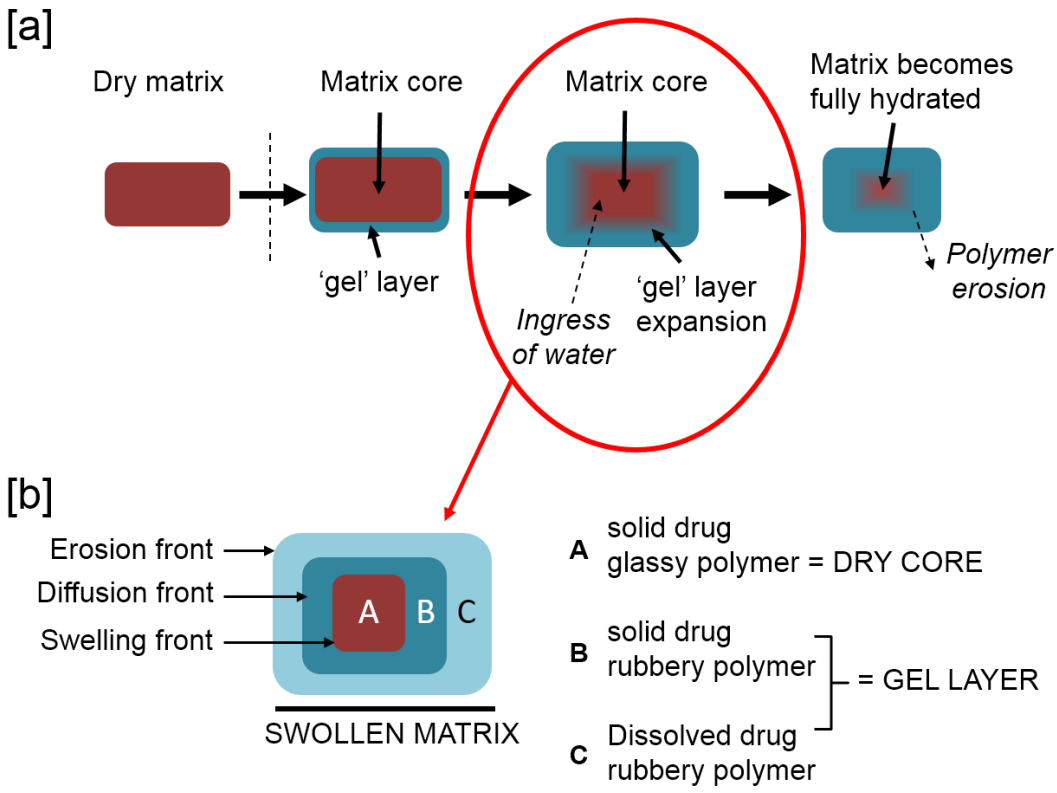

Figure 1.3: Schematic illustration of the hydration of HPMC matrices. (a) Cross-section of matrix hydration (b) Illustration of fronts within the gel layer. Blue represents hydrated polymer, maroon is dry tablet. Adapted from Alderman (1984), Colombo et al. (1995) and Williams (2009).

1.1.4 Measuring drug release from ER dosage forms

When a drug is administered in an immediate-release dosage form, the drug is generally available for dissolution in the GI fluids within 15 minutes. Depending on the drug solubility, the rate limiting step for bioavailability is either the rate of drug dissolution or the rate of drug absorption through the gut wall. However, when drug is administered in an ER dosage form, the rate of drug release from the dosage form will typically be the rate-limiting step. Release of drug from oral dosage forms is typically measured using i*n-vitro* dissolution testing. Dissolution testing is a key method used throughout this thesis, and has therefore been explained in detail here. Drug that is released when the polymer erodes might not be in solution, however dissolution testing is generally conducted under sink conditions, and therefore the drug should quickly dissolve once it is released from the matrix. Therefore, a measurement of the concentration of drug in the dissolution media provides an indication of the rate that drug has been released from the dosage form.

1.1.4.1 Compendial methods for measuring drug release

Four dissolution apparatus are outlined in the United States Pharmacopeia, and are listed below (The U.S. Pharmacopeial Convention, 2016)

- USP Apparatus I – Basket
- USP Apparatus II – Paddle
- USP Apparatus III – Reciprocating cylinder (BIO-DIS)
- USP Apparatus IV – Flow-through cell

All apparatus consist of one or more vessels with a lid, release media, and some means of agitation. USP apparatus I and USP apparatus II are those mostly commonly used. The design of each apparatus, such as the vessel dimensions and method of agitation, are tightly controlled in the compendia so that dissolution testing is universally consistent (British Pharmacopoeia Commission, 2016, The U.S. Pharmacopeial Convention, 2016).

A typical dissolution test would involve (i) the dosage form being placed into the media, (ii) at set time points, aliquots of filtered medium being removed and (iii) the analysis of the sample for drug content using UV (ultraviolet) spectroscopy or HPLC (high performance liquid chromatography). This enables a concentration versus time profile, or “dissolution profile” to be produced. Typically, the drug release is plotted as a percentage of either the expected maximum concentration based on the labelled strength, or as a fraction of the maximum measured drug concentration (Rathbone and Butler, 2011). Figure 1.4 shows some example dissolution profiles, for an immediate

release dosage form, and two hydrophilic matrix extended release dosage forms. The extended drug release profiles differ in the percentage of drug that is released in the first few 30 minutes of dissolution. This effect can be described as an initial burst of drug release (Huang and Brazel, 2001).

The rate of drug release observed in a dissolution test depends not only on the rate limiting steps within the dosage form, but the specific set-up of the test apparatus and the dissolution medium (Rathbone and Butler, 2011). Some factors include temperature, rate of agitation and dissolution media components. A selection of external factors that can influence drug release rate are further discussed in Section 1.4.

Numerous mathematical models have been developed which, when fitted to dissolution profile data can be used to estimate the rate of drug release and the drug release mechanism from hydrophilic matrices. Some models can be used to estimate the drug release rates attributable to diffusion and erosion processes. A number have been used in this thesis, and these have been explained in greater detail in Section 2.3.3. There are several publications which critically assess the use of these models for evaluating drug release from hydrophilic matrices (Costa and Sousa Lobo, 2001, Siepmann and Peppas, 2001, Siepmann and Siepmann, 2008, Gao, 2011).

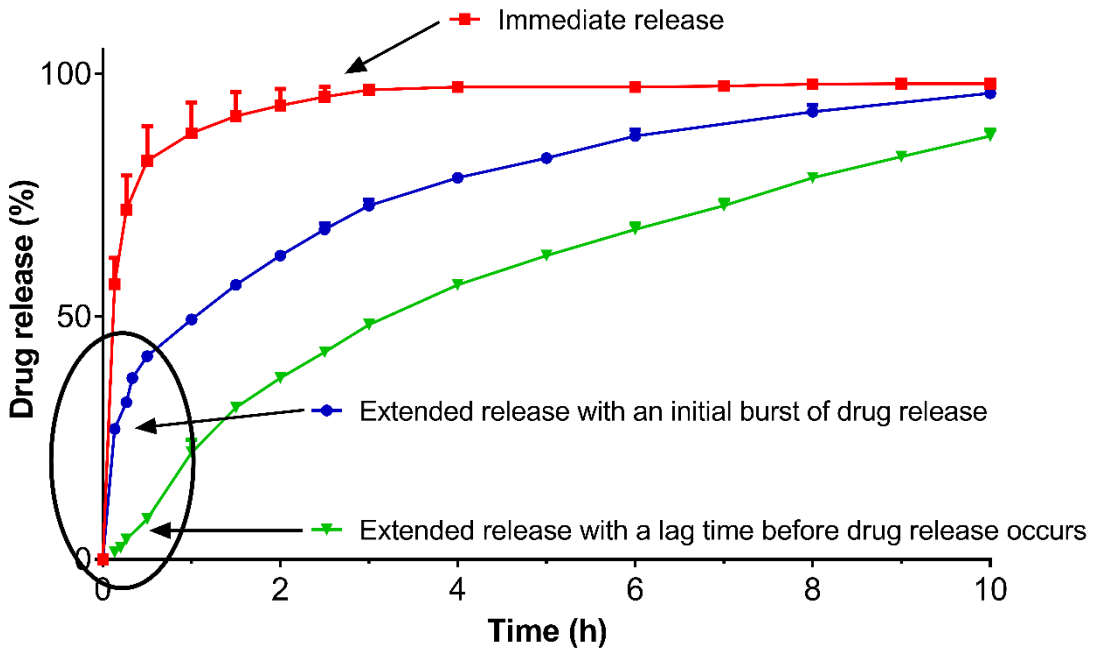

Figure 1.4: Typical dissolution profiles showing drug release from (i) an immediate release tablet or (ii) and (iii) a hydrophilic matrix tablet, as generated using USP I or II dissolution apparatus.

1.2 The importance of HPMC content in matrix formulations

Early patents stated that *"when a drug … is mixed with a hydrophilic mucilaginous gum … the resulting tablet will not immediately dissolve or disintegrate on contact with the gastric fluids* ***if the proportion of the hydratable gum in the tablet is sufficiently large"*** (Christenson and Dale, 1962). This patent suggested that matrices should contain at least 33% w/w HPMC to obtain extended drug release kinetics. A subsequent patent suggested that use of lower levels of HPMC (< 30% w/w) was feasible if the HPMC was substituted with more than 9% hydroxypropyl groups (typically HPMC 2910) (Schor et al., 1983). Generally, it has been found that increases in polymer content result in slower drug release (Alderman, 1984, Ford et al., 1985a, Sung et al., 1996, Mohamed et al., 2013), and the drug:HPMC ratio has been found to be one of the major factors that controls the drug release rate (Ford et al., 1985b, Dahl et al., 1990). The rate of water uptake into matrices has been shown to increase as the matrix polymer content increases, as HPMC has a high liquid uptake capacity (Wan et al., 1991). This could increase the tortuosity and length of the d]rug diffusion path (Xu and Sunada, 1995). It has been shown that the drug diffusion coefficient decreases as the matrix polymer content increases (Mitchell et al., 1993d).

A commonly cited paper which has become part of the received wisdom in hydrophilic matrix technology is that of Alderman (1994). In this paper, the author used formulations containing 10% w/w of a high viscosity HPMC, and demonstrated significant effects on changing viscosity grade, degree of substitution and ion concentration of the hydration fluid. This fuelled the idea that low polymer content might give rise to formulation sensitivity to HPMC polymer characteristics and environmental conditions. Therefore, manufacturers have recommended that at least 30% w/w HPMC should be used within matrix dosage forms, to ensure extended release kinetics (Hughes, 2013).

1.2.1 Percolation theory

Classical percolation theory discusses the probability that an open path (i.e. one where adjacent components are interconnected) exists from one side to the other (Broadbent and Hammersley, 1957). Percolation is a different physical process than diffusion, as it is the random properties of the material that matter, not the random properties of the fluid. Percolation processes can be applied to many scenarios, in many different fields of study. Examples include electrical conductivity (Scher and Zallen, 1970), epidemics

infecting a community (Moore and Newman, 2000), and molecules penetrating a porous solid (Broadbent and Hammersley, 1957).

Percolation theory was first applied to pharmaceutical tablets by Leuenberger et al. (1987). A schematic illustration of percolation theory is shown in Figure 1.5. Each rectangle represents a tablet, with black squares denoting the location of the soluble or swellable excipient of interest. From left to right in Figure 1.5, the content of this excipient within the overall rectangle increases, from 10 to 50% v/v. As the content increases, it can be seen that there are more adjoining black squares. When the excipient is soluble or swellable, these connections provide possible channels through which liquid can permeate. Leuenberger et al. (1987) related percentage content of excipient to the disintegration properties and intrinsic dissolution rates of binary compacts (Leuenberger et al., 1987). They found that in all cases, a particular drug:excipient ratio resulted in significant changes to the tablet disintegration time or drug dissolution rate. This ratio was termed the percolation threshold which, in accordance with percolation theory, is thought to signify the excipient content at which a continuous network of that excipient is formed. In Figure 1.5, the percolation threshold would be estimated to be between 25 and 33% v/v.

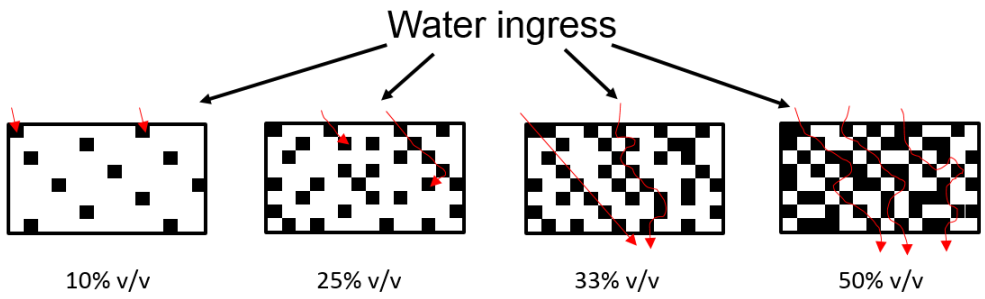

Figure 1.5: Schematic figure to illustrate percolation theory. Each rectangle represents a matrix tablet, and black squares denote regions containing polymer. Red lines show possible paths of water penetration through the matrix from the upper face to the bottom

Caraballo at al. have used percolation theory to explain drug release profiles from inert matrices containing ethyl acrylate, Eudragit® RS (Caraballo et al., 1993), and reported a drug percolation threshold of 35.5% w/w. A later publication reported the Eudragit® percolation threshold for a different formulation as between 40 and 60% v/v (Caraballo et al., 1994). The method estimates the percolation threshold from plots of Higuchi rate constants (derived from dissolution profiles) against matrix polymer content. An inflection in the graph extrapolated to the x-axis provides an estimate of the excipient percolation threshold. Further detail on the method can be found in Section 2.3.4.

Percolation thresholds for HPMC based hydrophilic matrix formulations containing many different drugs have since been estimated (Fuertes et al., 2006, Miranda et al., 2006a, Miranda et al., 2006b, Maghsoodi and Barghi, 2011, Aguilar-de-Leyva et al., 2012, Mohamed et al., 2013). Typically, it is the threshold concentration of HPMC that is reported. When the HPMC content of a matrix is above the percolation threshold, the excipient (HPMC) is present in sufficient quantity for clusters to form which percolate the whole tablet (Gonçalves-Araújo et al., 2010). Researchers hypothesised that a coherent gel layer would be formed only when the matrix polymer content is above the percolation threshold, thus resulting in extended drug release kinetics. This is a rational argument because swelling polymer particles have been shown to play an important role in blocking pores and forming a barrier that prevents water ingress (Wong, 2009).

Several publications have outlined the impact of various formulation properties on the matrix percolation threshold. These include:

- HPMC particle size (Campos-Aldrete and Villafuerte-Robles, 1997, Miranda et al., 2007)
- Drug particle size (Miranda et al., 2006a, Miranda et al., 2007)
- Drug solubility (Fuertes et al., 2010, Gonçalves-Araújo et al., 2010)
- HPMC viscosity grade (Gonçalves-Araújo et al., 2008, Aguilar-de-Leyva et al., 2012).

Threshold concentrations are typically reported as being between 10 and 35% w/w HPMC. It has been recommended that formulators use a matrix polymer content that is 10% greater than the threshold concentration, in order to ensure a robust matrix. This corresponds with manufacturer's recommendations to use at least 30% w/w HPMC within matrix dosage forms (Hughes, 2013).

1.2.3 Rationale for low polymer content formulations

As we have discussed above, it is necessary to include sufficient polymer in hydrophilic matrices to ensure the extended release of drug. However, there may be occasions where the polymer content is required to be lower than the recommended 30% w/w. Achieving a reasonable sized tablet that is easy to swallow, can be difficult if a high dose of drug (e.g. 500 to 1000 mg) is necessary (Tiwari and Rajabi-Siahboomi, 2009). Low polymer content HPMC matrix systems are also common-place during formulation development due to drivers to explore different release rates and achieve pharmacokinetic targets (Pygall, S. R. personal communication, September 2012). In simple terms, depending on the characteristics of the drug, drug release from HPMC matrices containing 30% w/w polymer can be just too slow to achieve an optimal plasma profile.

Despite low polymer content matrices sometimes achieving desirable *in-vitro* and *in-vivo* dissolution profiles, there are often concerns about proceeding with these formulations due to changes in gel layer strength and the associated risks of dose dumping (McDermott et al., 2014). In addition, Quality-by-Design (QbD) studies have shown that matrices containing a lower polymer content show a greater sensitivity to certain 'critical quality attributes' of HPMC, such as particle size and levels of substitution (Robertson et al., 2012, Tayade et al., 2014). QbD is an important concept in pharmaceutical development, in which formulators must be able to demonstrate a full and complete understanding of the impact of product or process change on product quality and performance (International Committee for Harmonisation, 2009, McDermott et al., 2014). This includes the impact of batch variability in the key rate-controlling excipient, HPMC.

1.3 Other formulation factors that can influence drug release from HPMC matrices

There are many other formulation and process variables that can affect the rate and mechanism of drug release from HPMC hydrophilic matrices. Low polymer content formulations may be unduly sensitive to these. The most important variables influencing drug release are discussed below.

1.3.1 HPMC factors

1.3.1.1 HPMC substitution

Typically, HPMC 2208 (K grades) and HPMC 2910 (E grades) are utilised in controlled release formulations (Dow Chemicals, 2000). Random substitution of the cellulose chain during polymer manufacture results in hydrophilic, hydrophobic and mixed substituent regions on the cellulose backbone (Maderuelo et al., 2011) which influences polymer solubility, hydration, swelling and the thermo-gelation properties of HPMC solutions (Dahl et al., 1990, Mitchell et al., 1993b, Dow Chemicals, 2000). In addition, more heterogeneous substitution along the polymer chain can result in slower drug release (Viriden et al., 2009b, Viriden et al., 2010).

Changes in drug release have been attributed to the USP type used (Alderman, 1984). However, the rank ordering of USP types in terms of impact on drug release rate is not clear. Increased levels of substitution may increase polymer hydrophobicity, which may decrease water transport into the gel layer and decrease swelling (Viriden et al., 2009c). It has been suggested that USP type may influence the release of poorly soluble drugs more than soluble drugs. This may indicate that USP type influences matrix erosion rate (Mitchell et al., 1993b). There is some evidence that differences between USP types may only be apparent when the matrix contains low levels of HPMC (Mitchell et al., 1993b).

1.3.1.2 HPMC viscosity grade

There are various commercially available viscosity grades of HPMC, with viscosities ranging from 3 to 200000 cP (for a 2% w/v solution at 20 °C) (Dow Chemicals, 2013).

The molecular weight of a polymer is indicative of the chain length. Physical properties of the polymer, such as viscosity and glass transition temperature (T_g) increase with increasing chain length (Wan et al., 1992, Meena et al., 2014) because as the polymer chain length increases, there are an increased number of chain entanglements that tend

to fix the individual chains more strongly in position (Baumgartner et al., 2002, Tritt-Goc and Kowalczuk, 2005).

Generally, it has been found that the use of lower viscosity grades of HPMC elicits faster drug release than the use of higher viscosity grades (Huber and Christenson, 1968, Harwood and Schwartz, 1982, Nakano et al., 1983, Alderman, 1984, Daly et al., 1984). This is thought to be due to the reduced swelling of lower viscosity grades resulting in a less tortuous gel layer (Ford et al., 1985b) but it has also been found that the lower the polymer viscosity, the lower the intrinsic water uptake (Wan et al., 1991). The rate of polymer erosion has also been found to increase as viscosity decreases, but diffusion rates showed far less dependence on viscosity grades (Reynolds et al., 1998). Other studies have indicated that reductions in HPMC viscosity do not universally increase drug release rates. It has been found that drug release for K4M, K15M and K100M were similar at the same HPMC:drug ratio, whereas drug release from matrices containing K100LV were faster (Ford et al., 1985a, Ford et al., 1985b).

Some differences between the K4M and K100M grades of HPMC were seen when the matrix polymer content was lowered (Ford et al., 1985b). Similarly, differences were seen in the water uptake of different HPMC grades at matrix polymer contents of 5% and 10% w/w which were not apparent at 50% w/w (Wan et al., 1991). In contrast, Aguilar-de-Leyva (2012) reported that polymer viscosity had minimal impact at a polymer content below the percolation threshold (15% w/w) but a greater impact at 30% w/w polymer loading. These results suggest that the influence of viscosity grade on drug release may be related to the matrix polymer content.

1.3.1.3 HPMC particle size

Using smaller particle size fractions of HPMC can decrease drug release rates and as the HPMC particle size decreases, lag times correspondingly increase (Alderman, 1984, Mitchell et al., 1993c, Campos-Aldrete and Villafuerte-Robles, 1997, Velasco et al., 1999). A dissolution profile with a lag time is shown in Figure 1.4. A lag time indicates that drug release is inhibited during early dissolution time points, which suggests that gel layer formation is more rapid when smaller particle sizes are used (Velasco et al., 1999). This effect is thought to be due to the increased particle surface area which results in more rapid hydration of HPMC particles and subsequently a quicker formation of the gel layer.

Burst release of drug can occur when large particle size HPMC fractions are used at low content in the matrix (Mitchell et al., 1993c, Dabbagh et al., 1996, Campos-Aldrete and Villafuerte-Robles, 1997). The effect of particle size was dependent upon the content of HPMC in the matrix, with greater sensitivity being seen below 20% w/w (Campos-Aldrete and Villafuerte-Robles, 1997, Heng et al., 2001) and below 50% w/w (Mitchell et al., 1993c). A linear relationship has been found between the necessary HPMC content (determined as the percolation threshold) and HPMC particle size (Miranda et al., 2007).

1.3.2 Non HPMC formulation factors

1.3.2.1 Drug properties

Drug characteristics are known to affect release profiles from HPMC matrices. Aqueous drug solubility is one of the most important factors. Generally, drug release is slower when a poorly soluble drug is included. This is because the drug can no longer readily diffuse through the gel layer (Ford et al., 1987, Bettini et al., 2001). Changes in drug solubility are not thought to influence the excipient percolation threshold (Fuertes et al., 2010, Gonçalves-Araújo et al., 2010).

Other drug characteristics can affect drug release rates and mechanisms. The drug particle size has been shown to influence both the percolation threshold (Miranda et al., 2007) and drug release rate (Velasco et al., 1999), although in other studies, particle size had no significant influence in the case of soluble drugs (Ford et al., 1985a, Ford et al., 1985b). Differences in drug release rate for drugs of similar solubilities have been attributed to differences in accessible surface area, which is related to the molecular shape and size of the drug (Baveja et al., 1988).

There have also been reports of direct drug:HPMC interactions which can result in the molecular association of drug and polymer which subsequently results in retardation of drug release (Mitchell et al., 1993a, Pygall et al., 2011, Banks et al., 2014). HPMC offers no buffering capacity thus, whilst the functionality of HPMC is said to be pH insensitive, drug release can be affected by a change in pH if the drug has a pH-dependant solubility (Pygall et al., 2009, Ramos Pezzini and Gomes Ferraz, 2009).

1.3.2.2 Other diluents

Hydrophilic matrix formulations usually include other excipients to aid the manufacture of quality tablets, and to achieve the desired drug release profiles. The impact of such excipients on HPMC matrix tablet formulations manufactured by direct compression has

been studied and the general consensus is that when the matrices contain a sufficient level of polymer (> 30 - 50% w/w), other excipients have limited impact on drug release. HPMC content has been shown to be the presiding determinant of drug release rate (Xu and Sunada, 1995, Nellore et al., 1998). It has been found that a high level of diluent is necessary to impact on drug release from matrices (Ford et al., 1987). One research group has reported that a matrix containing a low viscosity HPMC (100LV) had drug release that was affected by just 4% w/w microcrystalline cellulose (Lee et al., 1999).

Soluble excipients, such as lactose, have been found to decrease the tortuosity of the diffusion pathway and decrease gel strength (Nellore et al., 1998). The impact of insoluble or poorly soluble diluents is more varied, although this only seems to have an effect when polymer content is reduced. Dicalcium phosphate, a poorly soluble excipient which can be included as a binder, has typically been shown to result in slower drug release than when lactose is used (Jamzad et al., 2005), although there are examples where use of either filler had no significant effect on release profile (Lotfipour et al., 2004). The evaluation of the impact of diluents is difficult where studies have adjusted for a change in diluent level with an opposite change in the matrix HPMC content (Lotfipour et al., 2004). Starch 1500, a partially pre-gelatinized grade of starch, is thought to decrease release rate through a direct interaction with the gel layer rather than solely through a solubility effect, as it is more soluble than Avicel 102, for which release was faster (Levina and Rajabi-Siahboomi, 2004). The water soluble component of Starch 1500 may also add to gel layer viscosity, whilst the less soluble fractions increase the diffusion path length within the gel layer (Wong, 2009).

Some studies have reported that diluents may have a greater impact when the matrix contains lower amounts of HPMC (< 20% w/w). Alderman (1984) reported that a small amount of di-calcium phosphate (10% w/w) may destroy the integrity of the gel layer when the tablet contains 10% w/w HPMC, and cause premature disintegration. Another report suggested that when the matrix contains 20% w/w HPMC, a sufficiently thick gel layer is formed so that di-calcium phosphate doesn't affect the integrity of the gel layer (Nellore et al., 1998). The possible local influence of the small amounts of dissolved calcium and phosphate ions has yet to be investigated.

Overall, it is clear from the literature that the impact of diluents is dependent upon the polymer content, the drug solubility and the level of diluent within the formulation.

1.3.2.3 The addition of other polymers

The concept of combining HPMC with other polymers may have a number of potential benefits (Tiwari and Rajabi-Siahboomi, 2009). Synergy has been shown between combinations of HPMC and some other polymers, so that a higher viscosity can be achieved at a lower overall polymer concentration (Samani et al., 2003).

Early research by Walker and Wells (1982) found that HPMC and sodium carboxymethyl cellulose (NaCMC) show rheological synergy (Walker and Wells, 1982). Subsequently, NaCMC was used in combination formulations (Baveja et al., 1987, Ranga Rao et al., 1988). Unfortunately, HPMC: NaCMC matrices can show pH sensitivity, which can be attributed to NaCMC ionisation (Bonferoni et al., 1993, Dabbagh et al., 1999). Zero-order drug release has been achieved using HPMC: NaCMC systems, which is not usually achieved in HPMC-based formulations. Zero-order release has also been achieved using HPMC in combination with polyacrylic acid (Carbopol) (Perez-Marcos et al., 1991, Samani et al., 2003).

One of the known weaknesses of HPMC based formulations is a delay before the gel layer establishes, which can result in burst release of drug (Ford et al., 1985a, Huang and Brazel, 2001). The inclusion of polymers, such as polyacrylic acid (Carbopol) (Samani et al., 2003) and λ-carrageenan (Bonferoni et al., 1993) have been shown to reduce this initial burst. Any polymer that swells faster than HPMC, or that can limit the initial water uptake could reduce the burst release of drug during early dissolution.

1.3.3 Matrix manufacturing factors

1.3.3.1 Compression force

It has commonly been reported that drug release profiles from HPMC matrices are generally insensitive to matrix compression force, once a critical hardness has been achieved (Ford et al., 1985a, Dahl et al., 1990, Kim and Fassihi, 1997, Rekhi et al., 1999, Velasco et al., 1999). Below this critical hardness, the initial tablet porosity is higher and this can result in increased water uptake (Castellanos Gil et al., 2009).

However work related to this has primarily studied matrices with "standard" polymer contents (e.g. > 20-30% w/w HPMC). Matrices with a lower polymer content have rarely been investigated. One study found that the percolation threshold values were similar for matrices of different initial porosity (Castellanos Gil et al., 2009). This might suggest that polymer content has little impact on matrix sensitivity to porosity.

1.3.3.2 Tablet size and shape

The size of the tablet has been found to influence both the drug release rate and the amount of polymer needed to achieve the desired results. Faster drug release is observed when the tablet surface area to volume (SA/V) ratio is increased (Alderman, 1984, Ford et al., 1987, Rekhi et al., 1999). Different tablet shapes can have the same release profile when the SA/V ratio is constant (Reynolds et al., 2002) and it can be is possible to calculate the tablet size and shape required to achieve a given drug release profile (Siepmann et al., 2000).

Smaller tablets require a higher HPMC content (Alderman, 1984, Mohamed et al., 2013), and for very small tablets ('mini-matrices') with a diameter of 2 mm, 30% w/w HPMC was not sufficient to retard drug release, whereas 4 mm tablets showed extended release (Mohamed et al., 2013). These results suggest that there is a relationship between tablet size (SA/V) and the necessary matrix polymer content.

1.4 External factors affecting drug release from HPMC matrices

1.4.1 *In-vivo* HPMC hydrophilic matrix food effect

Despite their extensive use in the pharmaceutical industry, HPMC hydrophilic matrices have shown an occasional *in-vivo* variability in which plasma profiles vary between the fed and fasted state (Pargal et al., 1996, Abrahamsson et al., 1998a). In some studies, this has led to greatly accelerated drug release from HPMC matrices after the intake of food, in an effect termed the "postprandial effect" (Abrahamsson et al., 1999). This effect has been attributed to higher matrix erosion rates under fed conditions (Abrahamsson et al., 1998a, Davis et al., 2009, Jain et al., 2014), whereas other studies show a delay in the onset of drug release under fed conditions. It has been postulated that this may result from the formation of a fat film on the surface of the tablet, which can impede water ingress (Abrahamsson et al., 2004, Williams et al., 2011). It is worth noting that there are several examples in the hydrophilic matrix literature where the prandial state has been shown to have little impact on *in-vivo* drug release (Abrahamsson et al., 1993, Gai et al., 1999, Delrat et al., 2002).

There are several theories that attempt to explain the mechanism behind this HPMC-food 'interaction' (Garbacz and Klein, 2012, Nokhodchi and Asare-Addo, 2014). One theory attributes the food effect to a change in the gastric contents, exposing the matrix to a high salt or sugar environment (Abrahamsson et al., 1999, Williams et al., 2009, Williams et al., 2010b). Another suggests that hydrophilic matrix tablets may be subjected to higher agitation intensity in the fed state, which can increase matrix erosion rates. Gastric wall contractions increase with food intake, caused by a change in the migrating motor complex (MMC) cycles and the increase in frequency and duration of these contractions may result in increased hydrodynamic forces. There may also be increased mixing due to increased fluid volumes (Lindner and Lippold, 1995, Abrahamsson et al., 1998b, Klancar et al., 2012). The exploration of these mechanisms *in-vitro* is discussed in Section 1.4.2.

1.4.1.1 Impact of matrix formulation on the prevalence of the food effect

Although it is known that food can affect drug solubility (Welling, 1989), the evidence suggests that the food effect in HPMC matrices is formulation and not drug dependant (Abrahamsson et al., 1999). However, in this study they did not identify which aspects of the formulation were suspected of inducing the food effect. Therefore, it is not clear how

the polymer content of the matrix tablet influences the prevalence of matrix-food effects. Ghimire et al. found that post-prandial effects occurred only when the polymer content was lowered below the percolation threshold (around 20% w/w HPMC) (Ghimire et al., 2010). In contrast, Abrahamsson et al. have reported two formulations, both containing approximately 50% w/w HPMC, where one showed an *in-vivo* food effect whilst the other was insensitive to food (Abrahamsson et al., 1999). This result may indicate that the polymer content is not the only property of a formulation that can influence its sensitivity to food, although Ghimire et al.'s work suggests that the impact of HPMC content should be considered as a contributing factor.

1.4.2 *In-vitro* dissolution conditions

1.4.2.1 Salts

Dissolved ionic species are known to have an impact on both HPMC solutions and HPMC matrices. The mechanism behind this interaction is well reported in the literature, and is due to a "salting out" of the polymer. Ions that have a greater affinity for water than HPMC are able to remove the water of hydration from the polymer and therefore disrupt the water sheath that solubilises the polymer (Sarkar, 1979, Liu et al., 2008b). The molecular aggregation of hydrophobic chain regions become more favourable. This results in a dehydration or 'salting out' of the polymer which becomes less soluble in the media (Touitou and Donbrow, 1982). Polymer-polymer interactions become more favourable. The rank order in which ionic salts 'salt out' non-ionic cellulose ethers follows the Hofmeister (lyotropic) series (Hofmeister, 1888, Fagan et al., 1989, Mitchell et al., 1990, Chen et al., 2007, Liu et al., 2008a, Sardar et al., 2011). Rank ordering has typically been determined by turbidimetric measurements on HPMC solutions (Mitchell et al., 1990).

Previous work, primarily from the Ford and Melia groups, has shown that salts can also affect drug release from HPMC matrices. Enhanced matrix swelling has been seen as the ionic strength of dissolution media increases. This leads to increasingly slower drug dissolution rates due to the increased diffusional path length (Mitchell et al., 1990, Johnson et al., 1993). Above a certain ionic strength, water activity was reduced to such an extent that uniform hydration of the polymer did not occur, and incomplete gel layer formation resulted in burst release of drug from the matrix. The necessary salt concentration was dependent on the matrix formulation, polymer type and Hofmeister classification of the salt (Maderuelo et al., 2011). For sodium chloride, this concentration has been reported as 0.52 M (Krese et al., 2016), 0.75 M (Bajwa et al., 2006) and 2.0 M

(Mitchell et al., 1990) for various HPMC based formulations. Confocal images (Bajwa et al., 2006) have illustrated the early gel layer growth of HPMC matrices in a salt environment. Images show increased swelling of matrices at low ionic concentrations, which serves as a greater barrier to drug release. Once the concentration was increased to 0.75 M NaCl, polymer particles clearly failed to coalesce into a gel layer. The failure to form a rate-limiting diffusion barrier, resulted in enhanced liquid penetration of the core, and particle swelling without coalescence resulted in surface disintegration.

Sodium chloride (NaCl) has been the most extensively studied food substance to date. This is appropriate as NaCl is often present in excessive quantities in the western diet (World Health Organisation, 2013), and very salty food may therefore pose a risk to hydrophilic matrices if the salt concentration is sufficiently high to inhibit the swelling of HPMC. There are additional classes of salts that can be found in processed foods and drinks, including citrates, phosphates, nitrates and sulphates and these may also affect hydrophilic matrices. Multivalent cations are particularly strong in their Hofmeister effects, and di- and tri-valent phosphate (Hodsdon et al., 1993) and trivalent citrate ions (Pygall et al., 2009, Pygall et al., 2010) have been found to accelerate drug release from matrices. Similar effects have also been reported for many sugars (Williams et al., 2010a) and soluble L-amino acids (Richardson et al., 2006). Changes in HPMC hydration are likely to impact on the properties of the surface gel layer.

The ionic strength of the stomach is typically reported as 0.1 M (Bergstrand et al., 2009). However, this can increase upon dietary intake of salt and the presence of micro-environments next to dissolving particles where the ionic strength may be artificially higher (Abrahamsson et al., 1999). Moreover, combinations of salts and sucrose have been shown to have an additive effect on hydrophilic matrices (Williams et al., 2010b). To date, it is unknown how the matrix polymer content influences sensitivity to salts. If lowering the matrix polymer content renders the formulation more sensitive to a lower concentration of ionic salts, this may manifest in a change in release kinetics *in-vivo*.

1.4.2.2 Hydrodynamics

Matrices are exposed to varying hydrodynamic forces which change depending on food intake and the part of the GI tract through which they are travelling. These forces are difficult to replicate *in-vitro* due to their transient nature.

One simple test to change the dissolution hydrodynamics has been to adjust the paddle speed of the USP apparatus II dissolution test. This has been used as a surrogate

measure to assess the impact of hydrodynamic conditions on the dosage forms. Several research groups have used this method to study the impact of hydrodynamic conditions on drug release from hydrophilic matrix tablets (Kim and Fassihi, 1997, Abrahamsson et al., 1998b, Scholz et al., 2003). The general finding has been that increasing the paddle speed results in faster drug release due to surface erosion (Abrahamsson et al., 1998b). In increased stirring conditions, polymer chains were found to detach from the matrix surface at a faster rate relative to increases in drug diffusion (Reynolds et al., 1998).

A study by Abrahamsson et al (1998) found that the best *in-vitro/in-vivo* correlations for a HPMC matrix when taken on a fed stomach, were obtained using a paddle speed (USP apparatus II) of 140 RPM. This is far higher than the USP compendial speed of 50 RPM. It has also been suggested that varying the paddle speed can be used as a discriminatory test to detect formulations that may be sensitive to a post-prandial effect (Abrahamsson et al., 1999). No published studies have explored how changes in the HPMC polymer content of the matrix tablet influences their susceptibility to changes in hydrodynamic conditions *in-vitro*.

1.4.3 Biorelevant dissolution

It is widely acknowledged that when performed using compendial methods, USP apparatus I and II dissolution testing does not realistically represent the hydrodynamic forces and conditions exerted *in-vivo*. There has been a move to improve the bio-relevance of *in-vitro* test methods, so that they use more biorelevant media and generate realistic hydrodynamic forces. Predicting the performance of orally-administered drugs is a key objective of a 5-year, €24.5 million European project called “OrBiTo” (Kostewicz et al., 2014). Predicting *in-vivo* performance is more difficult for extended release dosage forms than for immediate release dosage forms, because of the extended time period and the different environments the dosage form encounters as it traverses the GI tract (Khan, 1996, Van Den Abeele et al., 2016). There are many publications that summarise the recent technologies designed to facilitate more biorelevant dissolution testing (McAllister, 2010, Garbacz and Klein, 2012, Koziolek et al., 2013, Kostewicz et al., 2014). Some current methods that have been used for the testing of hydrophilic matrices, are listed in Table 1.6.

Biorelevant media has primarily been developed by the Dressman research group (Galia et al., 1998, Dressman, 2014). Whilst compendial media such as simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) can reflect relevant *in-vivo* pHs, biorelevant media can better reflect the osmolality, surface tension, buffer capacity, and reflect

different conditions according to the prandial state. The biorelevant media can be cumbersome to prepare, and so since 2007, powders have been commercially available to prepare each version (Biorelevant.com, 2016). The use of biorelevant dissolution media is fairly commonplace when investigating food effects, especially when studying poorly soluble drugs. However, these media tend not to be used for routine quality control due to high costs of the materials used and challenges in reproducible preparation (Vertzoni et al., 2004). Biorelevant media has the advantage of being able to be used with all compendial dissolution apparatus, and is often used with USP apparatus III (reciprocating cylinder, BIO-DIS).

The dissolution stress tester (from Physiolution), TNO-Gastro Intestinal Model (TIM) and Dynamic Gastric Model (DGM) are newer systems that apply pressure as a means to generate forces akin to peristaltic forces *in-vivo*. The forces are transient and cycles can be changed to reflect anticipated physiological responses to food. This contrasts with USP apparatus I and II, where the mechanical agitation remains constant throughout the experiment. All three have been used to study oral dosage forms (Blanquet et al., 2004, Garbacz et al., 2009, Mann and Pygall, 2012, Chessa et al., 2014, Garbacz et al., 2014), and suggested that compendial USP apparatus underestimates the mechanical forces a dosage form may be exposed to *in-vivo*. There have been no published reports to suggest how the matrix polymer content may impact on sensitivity to these higher stress forces.

Model	Summary	References
Biorelevant media (FaSSGF, FaSSIF, FeSSGF and FeSSIF)	Aim to better reflect the *in-vivo* gastrointestinal fluids in terms of buffering capacity, pH and surface tension. Particularly useful where solubility and hence dissolution is a limit to drug absorption (Class II and IV BCS, poorly soluble APIs). Can be used with conventional USP and developing dissolution systems.	Galia et al. (1998), Jantratid et al. (2008), Dressman (2014), Markopoulos et al. (2015)
USP Apparatus III (Bio-Dis)	Reciprocating cylinder apparatus where dip rate can be altered to change the hydrodynamics. Typically used for pH profiling as apparatus can test one formulation in multiple vessels of different pH's. Can use with beads to apply additional mechanical stress and/or biorelevant media.	Klein et al. (2008), Fotaki et al. (2009), Asare-Addo et al. (2011), Asare-Addo et al. (2013), Klancar et al. (2013), Mercuri et al. (2015), Andreas et al. (2016)
Dissolution stress tester	Dissolution stress tester exposes a formulation to sequences of agitation and relative calm, akin to *in-vivo.* The force is generated using a balloon which inflates and deflates to force the tablet against wire netting. Any media can be used with the system	Garbacz et al. (2008), Garbacz et al. (2009), Garbacz et al. (2014)
TIM (TNO intestinal model)	A multi-compartment system which simulates the human stomach and small intestine (separate chambers for the duodenum, jejunum and ileum). Mixes by alternating the pressure on flexible walls Provides information on site specific release of APIs. TinyTIM has been developed with fewer compartments to increase throughput.	Minekus et al. (1995), Blanquet et al. (2004), Souliman et al. (2007), Brouwers et al. (2011), Minekus (2015), Verwei et al. (2016)
Dynamic Gastric Model (DGM)	The model aims to closely replicate the complex mixing, dynamic biochemical release and emptying patterns of the human stomach (separate fundus and antrum). Can accommodate real food items and can dynamically process meals Faster set-up time than TIM, but lacks the intestinal model.	Mann and Pygall (2012), Wickham et al. (2012), Chessa et al. (2014), Thuenemann et al. (2015), Mason et al. (2016)

Table 1.6: Some current tools for biorelevant dissolution testing

1.5 Thesis aims and an overview of the thesis

Hydrophilic matrices containing HPMC are a common extended-release dosage form, and this thesis introduction has attempted to illustrate the wealth of literature that has been published since their introduction in the 1960s. Many publications outline the mechanism of drug release and discuss many of the formulation factors that can affect release in these systems. Polymer content is a key variable that determines drug release rate, and lowering polymer content is a formulation strategy that can be used to increase the drug release rate. However, as highlighted by this introduction, the literature is currently incomplete in the following areas:

- There is a lack of physical evidence to corroborate the application of percolation theory to HPMC systems. Percolation theory could offer a means to design matrix formulations that will contain sufficient polymer for extended drug release.
- The influence of matrix polymer content on how drug release from HPMC matrices is affected by variable dissolution conditions.
- The effect of HPMC viscosity grade and particle size on drug release, especially in the context of low polymer content matrices.
- The effect on drug release of other excipients in matrix tablet formulations, in the context of low polymer content matrices.

Therefore, the overall aims of this thesis are:

- To develop a holistic understanding of the impact of reducing HPMC content on the swelling behaviour and release of drug from hydrophilic matrices. This will include a thorough evaluation of percolation theory, supported by confocal laser scanning microscopy.
- To consider drug release under various dissolution conditions in an attempt to uncover the potential *in-vitro* liabilities of lowering the matrix polymer content.
- Investigate potential formulation strategies that minimise the *in-vitro* liabilities of low polymer content matrices.

The thesis is divided into the following experimental chapters, with the explicit aims and objectives outlined in each chapter introduction.

Chapter 3: An evaluation of drug release mechanism from matrices containing 5 to 30% w/w HPMC, using both theoretical and practical evidence.

Chapter 4: The uncovering of matrix sensitivities using variable USP dissolution conditions, including the presence of salt and increase in paddle speed.

Chapter 5: Exploring matrix dissolution sensitivities under fasted and fed conditions, using the Dynamic Gastric Model.

Chapter 6: The development of HPMC based formulation strategies to improve matrix robustness.

Chapter 7: The development of non-HPMC based formulation strategies to improve matrix robustness.

We hoped that this work might provide a better understanding of how matrix polymer content influences drug release, and offer mitigating strategies to avoid deleterious consequences from lowering matrix polymer content. This would increase industrial confidence when the development of low polymer content matrices is necessary.

Chapter 2
Materials, Methods and Manufacturing Method Development

2.1 Materials

Comprehensive details of all other chemicals, reagents and excipients used in this work can be found in Chapter 9 (Appendix).

2.1.1 Hydroxypropyl methylcellulose

Four viscosity grades of HPMC 2208 were used in this thesis, each being METHOCEL™ CR Premium (Colorcon, Dartford, UK). They are listed in Figure 2.1. METHOCEL™ K4M CR Premium was the main focus of the studies.

METHOCEL Grade	**Nominal Viscosity (cP)**	**Methoxyl substitution (%)** *(CoA limit 22.0-24.0)*	**Hydroxypropoxy substitution (%)** (*CoA limit in brackets)*	**Thesis chapter**
K100LV	95	22.9	8.6 (7.5 - 9.5)	6
K4M	3990	22.7	8.6 (7.5 - 9.5)	3,4,5,6,7
K100M	102634	23.2	10.4 (9.5 - 11.5)	6
K200M	212355	23.2	10.1 (9.5 - 11.5)	6

Figure 2.1: HPMC grades investigated in this thesis. All grades were METHOCEL CR Premium. CoA limit is the range of acceptable values listed on the Colorcon Certificate of Analysis (CoA).

2.1.2 Formulation rationale

The rationale for excipient selection and formulation compositions are detailed in this section. The actual formulations used in each chapter are listed in the respective chapter introductions.

2.1.2.1 Matrix HPMC content

It has been suggested by manufacturers that HPMC matrices should contain at least 30% w/w of a high viscosity grade of HPMC, in order to ensure extended release kinetics are maintained (Hughes, 2013). In order to explore the impact of matrix polymer content on drug release, it was decided that the matrix polymer content should initially be varied between 5 and 30% w/w (Chapter 3).

2.1.2.2 Drug selection and matrix drug content

Caffeine was used as a model, water-soluble drug throughout the thesis. Caffeine has been chosen as a model high solubility drug in many previous PhD theses, because of its good aqueous solubility (16 mg/mL at room temperature), lack of pH dependence (pKa = 10.4, 14), and good UV absorption characteristics (λ = 273 nm, A_1^1 = 504a) (Sigma-Aldrich, 1999, Moffat et al., 2004, Williams, 2009). Previous work has determined that caffeine does not have a direct interaction with HPMC. Matrix drug load was fixed at 10% w/w to ensure dissolution sink conditions and to enable the use of on-line, automated dissolution testing, of a 250 mg tablet.

2.1.2.3 Diluents

Lactose (Lactose Fast Flo 316, Foremost Farms, USA), a diluent, and microcrystalline cellulose (Avicel PH102, FMC Biopolymer, Ireland), a binder, were used as fillers within the formulation. Both these excipients had been used in a 2:1 ratio in a previous thesis investigating 30% w/w HPMC matrices (Williams, 2009), and are commonly used within the industrial sponsor (MSD, private communication, 2012). It was decided that the 2:1 ratio of lactose to microcrystalline cellulose should be maintained when the HPMC content of the matrices was lowered, thus increasing the quantity of each excipient. Substituting HPMC for other diluents avoided changes in the weight of the matrix, which may change the matrix surface area/volume ratio. This is known to impact on drug release rates (Reynolds et al., 2002).

2.1.2.4 Lubricant

It is known that changing the level of lubricant can make tablets softer, impacting on the tablet crushing strength, but adjusting the magnesium stearate content between 0.2 and 2.0 % w/w has been found to only slightly affect drug release from HPMC matrices (Sheskey et al., 1995), and a content between 1 and 2% had no effect on metoprolol tablets (Rekhi et al., 1999). Therefore, magnesium stearate was used as a lubricant in the matrix formulations, at a constant load of 0.5% w/w.

Methods

The following techniques were used repeatedly throughout this thesis, and have been collated into the following categories:

- Matrix manufacturing
- Matrix characterisation
- Powder characterisation
- Solution manufacture and characterisation

Details of additional techniques are described in the appropriate chapters.

2.2 Methods: Manufacture of Matrices

The excipient blending process and compression force required investigation before the manufacturing method could be finalised, and these studies are described in Section 2.6. The developed manufacturing method used to make tablets in this thesis is described below.

Excipients

- **Drug**: 10% w/w caffeine (< 125 µm sieve fraction).
- **Excipients**: As detailed in each chapter methods. Model HPMC formulations contained a 2:1 mixture of lactose:microcrystalline cellulose 102.
- **Lubricant**: 0.5% w/w magnesium stearate

Powder blending

The excipients, less magnesium stearate, were prepared into batches by mixing using a TURBULA® mixer. Magnesium stearate (0.5% w/w) was added during a second mixing step. Mixing parameters are detailed below. The final batch sizes were 60 – 100 g.

- **Blend time:** 15 minutes at 47 RPM
- **Blending Apparatus:** TURBULA® mixer T2F (W. A. Bachofen, Switzerland) with powders in a 500 mL amber glass powder jar.
- **Lubrication mix:** 2 minute mix at 47 RPM

Tablet compression

Matrices were manufactured by dry compression of powder blends on a rotary tablet press. Compression parameters are detailed below.

- **Tablet Press:** Riva Piccola multi-station tablet press (Riva S.A, Argentina)

- **Punches:** 8 mm, flat faced, round
- **Press parameters:** Turret Head speed of 10 RPM
  Feeder speed of 15 RPM
- **Target compression:** 158 MPa (8 kN force)
- **Target fill weight:** 250 mg ± 5 mg

2.3 Methods: Characterisation of matrices

2.3.1 Diametral crushing force and tensile strength

The diametral crushing force was determined for 10 tablets of each batch using an electronic crushing force tester (C50 Benchtop Tablet Hardness Tester, I Holland, Nottingham, UK). The matrix diameter and thickness was measured using a micrometer screw gauge, and the mean tablet tensile strength was calculated using Equation 2.1.

Equation 2.1: $$\sigma_{TS} = \frac{2F}{\pi DH}$$

where: σ_{TS} = Tensile strength (MPa), F = Breaking force (N), D = diameter of matrix (mm) and H = height of matrix (mm).

2.3.2 Dissolution testing

The standard dissolution test used in this thesis utilised the USP apparatus II (paddle) (Dissolutest, Prolabo, UK) to evaluate the rate of caffeine release from the matrices into aqueous media. Paddles were rotated at 50 RPM, except where paddle speed was a variable. The tablet was held within a capsule sinker (stainless steel, 10 spirals, 31.0 x 11.0 mm capacity) to prevent floating or adhesion to the dissolution vessel wall. In Chapter 5, USP apparatus I (basket) was used, with baskets rotated at 100 RPM, and the tablets placed directly into the baskets (The U.S. Pharmacopeial Convention, 2016).

Water was used for paddle and basket apparatus, with the addition of salt to dissolution media for certain experiments. No pH adjustment of media was made, as caffeine release from 10% and 30% w/w HPMC formulations showed no sensitivity to pH 1.2 (simulated gastric fluid (SGF) with pepsin) or pH 7.0 (phosphate buffer) (Figure 2.2).

The USP apparatus I and II were attached to an on-line, closed loop dissolution system, facilitating the automatic sampling and quantification of caffeine during dissolution testing. Samples were removed from the dissolution vessel at intervals by a peristaltic pump (60 s pump time), which filtered the sample through 10 µm ultra-high molecular weight polyurethane filters (Copley Scientific, Nottingham UK). The samples then flowed into 10 mm flow-through quartz cells for the spectrophotometric determination of absorbance at a wavelength of 273 nm. Absorbance was measured and recorded using an 8453 Agilent UV/Vis spectrophotometer system equipped with Chemstation software version 08(03) (Agilent Technologies, Stockport, UK). Caffeine content in solution was calculated from a standard curve, where; caffeine concentration (mg/mL) = 0.0206 x Absorbance - 0.00003.

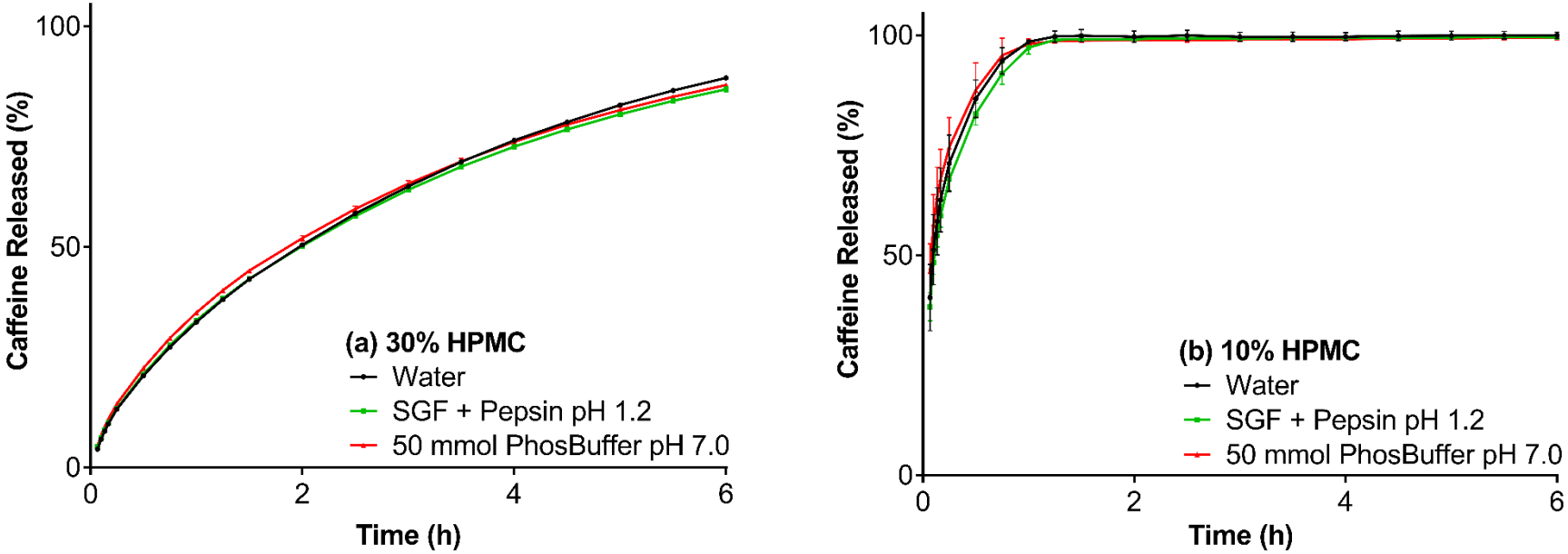

Figure 2.2: Release of caffeine from HPMC matrices in different dissolution media. (a) 30% w/w HPMC K4M and (b) 10% w/w HPMC K4M matrices tested in USP II (paddle) 50 RPM at 37 °C with 3 dissolution media; (1) water, (2) simulated gastric fluid (SGF) containing Pepsin and adjusted to pH 1.2 using HCl and (3) 50 mmol sodium phosphate (dihydrogen) monohydrate adjusted to pH 7.0 using NaOH. Mean (n=3) ± 1 SD. SGF contained 2 g NaCl, 3.2 g pepsin powder and 80 mL of 1 M HCl in 1 L of water.

2.3.3 Analysis of dissolution data

Drug release profiles from the dissolution tests provided a graphical representation of drug release with respect to time. However, when the data is in this format, it is not easy to compare drug release between different matrices. One of the few methods that can deal with whole curves is f_2, which is described in Section 2.3.3.2. As a result, single time or % release points and curve fitting are used to provide parameters that can be used to compare drug release profiles. Some of the models can also provide an indication of the dominant mechanism of drug release. Several publications describe these models in detail (Costa and Sousa Lobo, 2001, Siepmann and Peppas, 2001, Siepmann and Siepmann, 2008, Maderuelo et al., 2011), and thus only a brief summary of each model is provided here.

In this thesis, two single dissolution point references, similar factor (f_2) and five mathematical models have been applied to dissolution data. A summary of mathematical models used is provided in Table 2.1. Mathematical models were applied by non-linear fitting using GraphPad Prism (version 7.01).

2.3.3.1 Single-point dissolution reference

$T_{80\%}$ and DR10min have been used as single point parameters to represent the data. $T_{80\%}$ is the time taken for 80% drug release. It was calculated from a linear interpolation of the two nearest dissolution time points, and provides a measure of the duration of extended release. DR10min is the % drug release in the first 10 minutes, and provides a measure of the initial burst release of drug seen at the beginning of many dissolution tests. DR10min was taken directly from the dissolution data.

2.3.3.2 Similarity factor (f_2)

The similarity factor compares two dissolution curves by calculating the sum of squared error between the two curves at each time point. It is the equation provided by FDA guidance for assessing bioequivalence between ER dosage forms (Center for Drug Evaluation and Research (CDER), 1997a). The profiles are considered similar when the f_2 value is > 50

Equation 2.2: $$f2 = 50 \log \left(100 \left[1 + \left(\frac{1}{n}\right) \sum (R_t - T_t)^2\right]^{-0.5}\right)$$

Similarity equation, where n is number of time points where drug release values are < 85%, R_t is the drug released at a timepoint, t, for a reference matrix, and T_t the drug released at the time point t for the test matrix

Name of Model	Summary	Equation	Parameters	Range of dissolution data used to fit the model (w/v)
Zero Order	Concentration independent release of drug Constant drug release rate due to controlled drug diffusion Usually during middle phase of release curve	$Q = k_o\, t$	k_0 = zero order kinetic	5 - 70%
First Order	Concentration dependent release of drug Rate changes as concentration of drug in the system changes Usually final stages of release (> 70%).	$\log Q = \log C_0 - \frac{kt}{2.303}$	C_0 = matrix drug content k = rate constant	5 - 70%
Higuchi	Drug release is proportional to square root of time, due to underlying diffusion mechanisms	$Q = k_h\sqrt{t}$	k_h = Higuchi rate constant	5 - 70%
Power Law (Korsmeyer-Peppas)	Flexible release exponent *n* accounts for different release mechanisms, being diffusion or polymer erosion.	$Q = k_{kp}t^n$	k_{kp} = Korsmeyer-Peppas rate constant *n* = diffusional exponent	5 - 70%
Peppas-Sahlin	Two components that consider the release rate attributable to each mechanism. *m* is a fixed diffusional exponent dependant on the geometric shape of the tablet.	$Q = k_d t^m + k_r t^{2m}$	k_d = diffusional rate k_r = erosional rate *m* = parameter related to aspect ratio (fixed at 0.44)	5 - 60%

Table 2.1: Mathematical models used to analyse dissolution data in this thesis. Q is the fraction of drug released and t is time. Other parameters are detailed in the table.

2.3.3.3 Zero Order

Zero order kinetics can be generated by matrix systems when there is constant replenishment of fresh drug from the matrix core. If zero order kinetics are true, the rate of drug release from hydrophilic matrices will remain constant and independent of the content of drug in the system (Costa and Sousa Lobo, 2001, Collett and Moreton, 2007). In hydrophilic matrices, zero order kinetics are more likely to occur during the middle phase of release once there is saturation of drug into the hydrated pores of the matrix (Caraballo et al., 1996). At other times, e.g. during initial swelling, the tablet is hydrating inwards and there will either be minimal drug release or a burst release of drug before complete gel layer formation, and during the latter stages of drug release the rate slows as the concentration of drug remaining in the matrix falls below the minimum threshold (Caraballo et al., 1996).

2.3.3.4 First Order

In first order kinetics, the drug release rate changes as the drug concentration within the dosage form changes over time (Costa and Sousa Lobo, 2001). This model is rarely applied to controlled release matrices but the model has been applied to matrices containing very soluble drugs (Mulye and Turco, 1995). It could be used to describe the final stages of release (> 70% w/v) when a system stops obeying zero order kinetics and the release rate depends upon the concentration of drug remaining in the matrix.

2.3.3.5 Higuchi

The Higuchi equation is one of the earliest and probably most recognisable models representing drug release from HPMC matrix tablets. Initially, it was used to model drug release from a planar surface, but has been adapted to relate to release from a sphere (Higuchi, 1963). The principles are based within Fick's law of diffusivity, in which the distance drug diffuses is proportional to the square root of time ($t^{0.5}$) (Costa and Sousa Lobo, 2001).

2.3.3.6 Power Law (Korsmeyer-Peppas)

The Power Law, also known as Korsmeyer-Peppas equation, is an extension of the Higuchi principle, and states that the release rate is proportional to time to the power of *n*. *n* is commonly termed the release exponent. The Higuchi equation is a specific example of the Power Law, in which the release exponent *n* equals 0.5.

The Power Law can be used to interrogate the overall mechanism of drug release from a matrix. When *n* equals 0.45 release is diffusion controlled, i.e. limited by the diffusivity of the drug through the gel layer as the tablet swells. Drug is following a Fickian mechanism (Korsmeyer et al., 1983), as discussed under Higuchi above (Section 2.3.3.5). However, in hydrophilic matrices, drug release rate may not always follow square root of time kinetics, as polymer erosion and change in matrix surface area can occur. The polymer configuration and subsequently volume can change as the polymer changes from glassy to rubbery state during hydration, which can slow or accelerate the uptake of water. When polymer erosion dominates the release mechanism, exponent *n* increases up to 0.89 in the case of a cylinder. Values between the two show a mixed control of release rate. This is often described as 'anomalous' release, which is simply the combination of diffusional and erosional mechanisms (Langer and Peppas, 1981). The table below shows the anticipated range of *n* values for hydrophilic matrix tablets.

Release exponent (n)	**Overall solute diffusion mechanism**	**Time dependence of solute release rate (dMt/dt)**
0.45	Fickian Diffusion	$T^{-0.5}$ (Higuchi)
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion	$T^{(n-t)}$
0.89	Case II transport (Relaxational, Erosion)	Zero order (concentration-independent) release
n > 0.89	Super Case II transport	$T^{(n-t)}$

Table 2.2: Diffusion exponent and solute release mechanism for cylindrical shape. (Adapted from Korsmeyer et al. (1983) and Peppas (1985).

2.3.3.7 Peppas-Sahlin

The Peppas-Sahlin equation aims to attribute drug release to two principal mechanisms: drug diffusion and polymer erosion. The equation requires tablet dimensions to be recorded in order to calculate the aspect ratio, using Equation 2.3, from which *m* is determined from Figure 2.3. An aspect ratio of 100 would represent a thin film, whereas 0.01 would represent a long cylinder. Matrix tablets generally have a greater diameter than thickness, so an aspect ratio from 1 to 4 would be expected. The ratio between k_d and k_r (R/F) is often used to interpret the proportion of diffusional to relaxational release (Siepmann and Peppas, 2001).

Equation 2.3: $$\boldsymbol{Aspect\ Ratio = 2a/l}$$

where: *a* is the matrix radius, and *l* is the thickness*.*

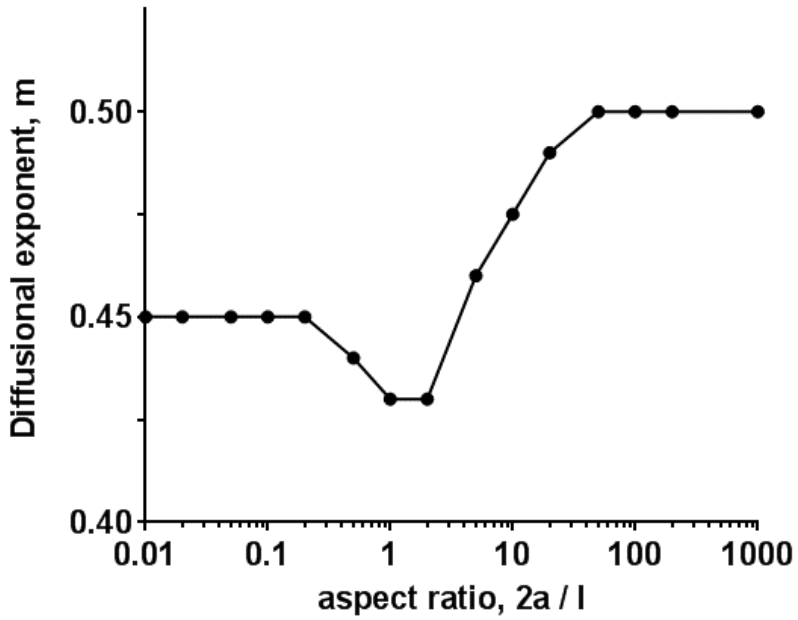

Figure 2.3: Diffusional exponent, *m*, for Fickian diffusional drug release from tablets, as a function of their aspect ratio. Adapted from Ritger and Peppas (1987). a is the tablet radius, and l is the tablet height.

2.3.4 Percolation theory

Percolation theory has been applied to HPMC matrices and this has been earlier discussed in the thesis introduction (Section 1.2.1). This theory suggests that there is a polymer content at which there is a sufficient volume of polymer to form a continuous network (or phase) within the tablet. In this thesis, we have defined this as the HPMC percolation threshold. Below the percolation threshold, the HPMC cannot form a percolating cluster and the matrix is therefore less likely to have extended release properties. Matrix properties are expected to change around the percolation threshold, and therefore the percolation threshold can be estimated using release rates derived from dissolution data (Fuertes et al., 2006).

In our study, the percolation threshold has been estimated using Higuchi rate parameters (k_h) calculated from the dissolution curves. The Higuchi rate has been normalised by dividing by the volumetric fraction of HPMC at time zero (k_h/% v/v HPMC). This takes into account that a cluster of polymer will be linked to the volume of HPMC and not the weight (%). The volumetric fraction of HPMC in a matrix was determined by measuring the true density of each tablet excipient using helium pycnometry (Section 2.4.2).

To estimate the excipient percolation threshold, the normalised Higuchi rate constant was then plotted against the HPMC volumetric fraction. Two linear regressions were fitted and the percolation threshold estimated from the point of intersection (Fuertes et al., 2006, Miranda et al., 2006a, Gonçalves-Araújo et al., 2008).

2.3.5 Confocal laser scanning microscopy (CLSM)

Confocal laser scanning microscopy (CLSM) is a type of high resolution fluorescence microscopy, which has been used in our group to investigate the development of the early gel layer in HPMC matrices. Bajwa et al. (2006) have used this method to provide an insight into how ionic salts influence HPMC gel layer formation, with subsequent publications studying the impact of citrate (Pygall et al., 2009), sucrose (Williams et al., 2009, Williams et al., 2010a), THAM (Pygall et al., 2010), and milk and fats (Williams et al., 2011).

2.3.5.1 Theory of confocal microscopy

Figure 2.4 shows a schematic diagram of the general workings of a confocal microscope. Both 3D and 2D imaging is possible by scanning the sample with a laser beam in a raster pattern, in either the vertical or horizontal plane, using galvanometer driven mirrors. 3D images can be built up by the stacking of successive slices into a 'z-stack'. The slice thickness can be as thin as 0.5 to 1.5 µm, but is dependent on the wavelength of light, the numerical aperture of the objective lens, the confocal aperture setting and the refractive index of the sample (Pygall et al., 2007).

The main advantage of CLSM over conventional (i.e. wide-field) fluorescent microscopy is that optical resolution is increased by adding a pinhole, or confocal aperture, which eliminates out-of-focus light. This light comes from areas adjacent to the plane of interest, and contributes little to the image but may cause blurring (Pygall et al., 2007, Melia et al., 2010).

The signal intensity can be decreased compared to that of conventional, fluorescent microscopes, which means longer exposure times can be necessary. However, in our confocal microscope, this is only in the order of a few seconds as this disadvantage can be overcome by the use of a laser source to give high light intensity, a good fluorophore and a photo-multiplier tube (PMT) which transforms the light signal into an electrical one.

Fluorescent signals arise either from natural auto fluorescence of incorporated drugs and excipients, or from the addition of specific fluorophore markers. The fluorescent intensity of each pixel in the image can be colour coded using a false 'lookup table' (LUT), but in our experience the use of a simple greyscale provides better visual identification of features within the scanned image.

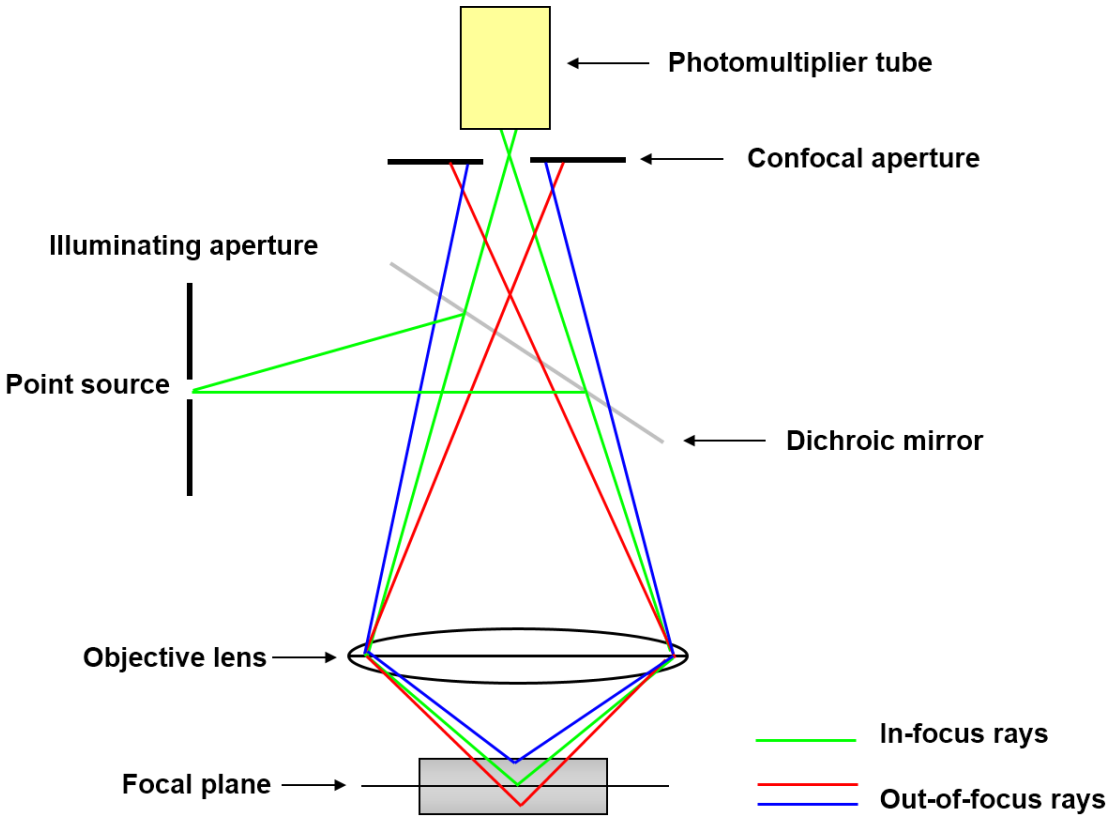

Figure 2.4: Schematic diagram of the light path within a confocal laser scanning microscope.
Adapted from Sheppard and Shotton (1997), Bajwa (2006), Williams (2009).

2.3.5.2 Experimental method of CLSM for HPMC based hydrophilic matrices

Imaging of matrices was undertaken using a Bio-Rad MRC-600 confocal microscope (Bio-Rad, Hemel Hempstead, UK) equipped with a 15 mW Krypton Argon laser, attached to a Nikon Optiphot upright microscope using a plan x4 air objective. The 488 nm laser line at 5 mW was used for sample excitation and the fluorescence emission collected at 510 nm using the BHS filter block.

Congo red was used as a fluorescent marker in these studies. Congo red binds to cellulose through a combination of (i) electrostatic, (ii) hydrophobic interactions and (iii) H-bonds between the azo and amino groups of the dye, and native cellulose sequences (Yamaki et al., 2005). As the cellulose derivative hydrates, there is increased access of the dye to available binding sites so that Congo red selectively and disproportionately highlights hydrated regions of HPMC within the matrix. Bajwa et al. found that a concentration of 0.008% w/v Congo red in the hydration medium had no significant effect on polymer swelling and hydration but offered excellent resolution of individual HPMC particles (Bajwa et al., 2006).

In the confocal microscopy work undertaken in this thesis HPMC. Matrices were hydrated in a fixed observational geometry (FOG) cell, first described by the Colombo research group in Parma (Bettini et al., 1994). In this cell the tablet is held between two Perspex discs secured with Teflon screws (as illustrated in Figure 2.5). This allows imaging of the matrix from overhead and in this way we can capture the development and growth of the gel at the radial edge of the tablet.

The confocal aperture was set between 2 and 4 as necessary for image intensity, and black level and gain were adjusted to optimise image quality. Images taken at $t > 4.5$ min were a Kalman average of 3, but for images at $t < 4.5$ min only a single scan was taken. This was because in the earliest stages of polymer hydration rapid swelling results in very rapid movement of the gel layer and would lead to blurring between Kalman scans.

Images were captured every 30 seconds for 15 minutes. Image resolution was 512x768, and each pixel was coded for fluorescent intensity between 0 - 255 using a continuous grey-scale lookup table (LUT). Images were processed using Image-Pro Plus (Media Cybernetics, USA)

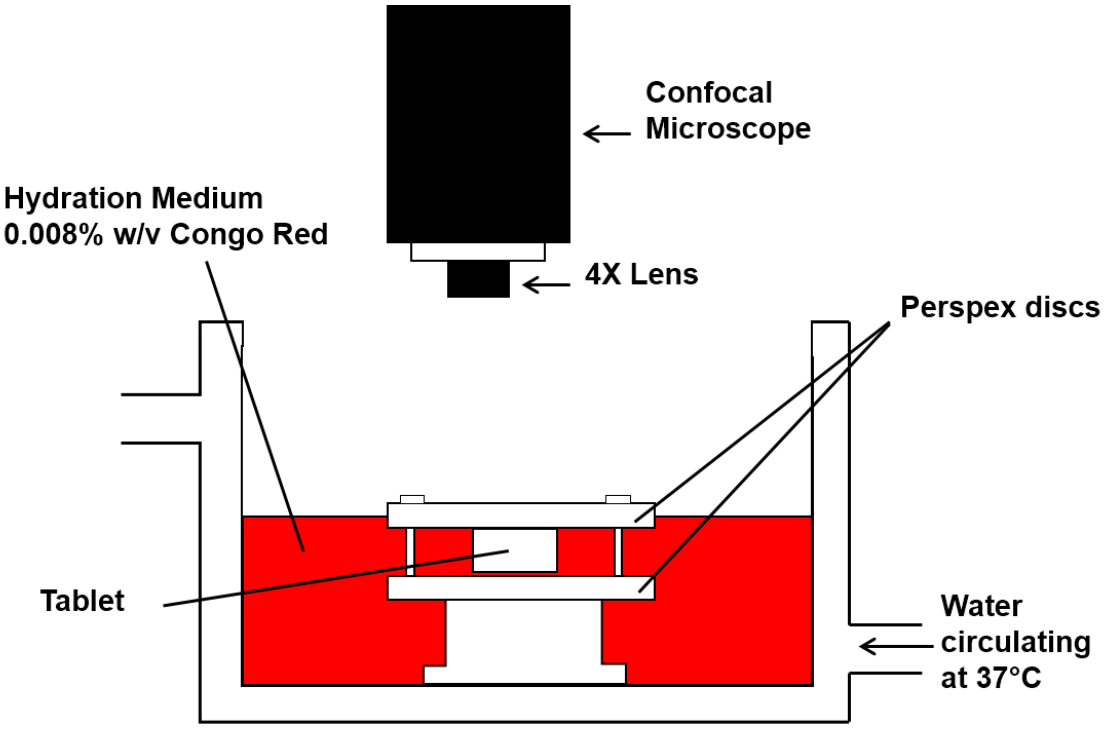

Figure 2.5: Sample cell geometry for monitoring early gel formation by confocal laser scanning microscopy. Adapted from Bajwa et al. (2006).

2.3.6 Digital photography of matrices using a macro lens

Optical images of the whole tablet were taken from the side as the tablet hydrated in degassed media (600 mL) at 37 °C. Images were taken every 30 seconds for 30 minutes. The configuration is shown in Figure 2.6. The tablet was fixed flat to a Perspex® stand (covered in black tape) using Blu-Tack™ inside a water-jacketed beaker. Images were taken through the wall of the beaker to enable image capture without touching the tablet. Images were captured using Image-Pro Plus (v.4.0. Media Cybernetics, USA) in grayscale using a CoolSNAP-pro CF camera (Photometrics, USA) fitted with an AF micro Nikkor lens (Nikon, Japan) mounted on a stand with adjustable height.

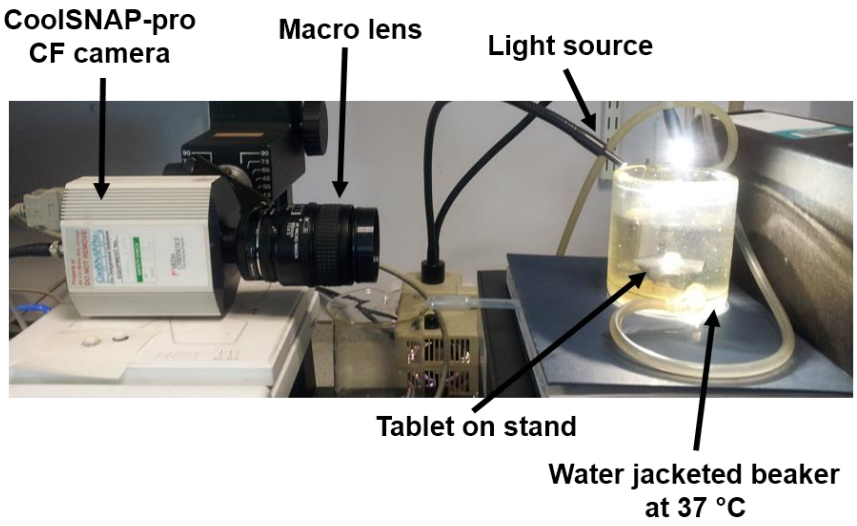

Figure 2.6: Experimental apparatus for time lapse photography.

2.4 Methods: Powder characterisation

2.4.1 Sieve analysis to determine particle size distribution

The particle size distribution of HPMC was determined using sieve analysis according to USP methods (The U.S. Pharmacopeial Convention, 2016). A weighed (approx. 30 g) representative sample was fractionated using a nest of sieves. The largest mesh size was 355 µm, with sieves of descending mesh size underneath: 180 µm, 125 µm, 90 µm, 63 µm, 45 µm and receiver pan (Endecotts Laboratory Test Sieves Ltd, London, UK). The sample was mechanically agitated using a mechanical sieve shaker (Copley Scientific, Nottingham, UK) for 10 minutes, and then agitated at intervals of 5 minutes, until the weight on the test sieves did not change by more than 5% w/w or 0.1 g. This first analysis was used to determine the sieving time, and the analysis was then repeated with a fresh sample that was agitated for the total duration of 20 minutes without disturbing. This second run was used to measure the particle size distribution.

2.4.2 Determination of particle true density using helium pycnometry

The true density of powders was measured using an AccuPyc II 1340 pycnometer (Micromeritics, Norcross, USA). A steel sphere of known volume was placed into a 10 cm^3 cylinder which was flushed with helium, closed, and the pressure recorded. A second cylinder, filled tightly with an accurately weighed sample of blend, is also flushed with helium and closed with the pressure recorded. The ratio between the two pressures is directly related to the volume occupied by the solid material in the sample. This provides the true density of the particles. Each sample was filled with helium and pressures recorded a minimum of 5 times until the results fall within a specified error band.

2.5 Methods: solution manufacture and characterisation

2.5.1 Manufacture of HPMC solutions

HPMC solutions were manufactured by adding powder to media (either DI water or salt solution, 80 °C) using an overhead, high-shear mixer (1000 RPM) for 15 minutes. If two powders were to be included in the solution, these were mixed whilst dry using a spatula prior to high shear mixing. Solutions were then stored at 2 - 8 °C for 24 hours before use.

2.5.2 Determination of solution cloud point temperature by turbidimetry

2.5.2.1 The use of turbidimetric methods to evaluate HPMC solutions

When aqueous solutions of HPMC are heated, a reversible gelling process occurs at a temperature which depends on the degree of methoxyl and hydroxypropyl substitution. At low temperatures, there is little polymer-polymer interaction beyond simple entanglements. When the temperature rises, molecules lose their water of hydration, causing a decrease in viscosity. When sufficient dehydration occurs, a three-dimensional, insoluble gel network forms through hydrophobic polymer associations between methoxyl rich regions and the viscosity rapidly increases (Ford, 2014). The temperature at which this occurs is termed the thermal gelation temperature (TGT) (Sarkar, 1979).

Visual precipitation can also occur in dilute solution around the TGT, and this is often termed cloud point behaviour. Cloud point can be determined by turbidity measurements which monitor the transmission of light through the sample with respect to temperature. The cloud point temperature (CPT) is generally taken as the temperature at which there has been a 50% drop in light transmission. Another common measurement is the Incipient Gelation Temperature (IGT) which corresponds to a 5% drop in light transmission. The IGT is less dependent on polydispersity but it is also less easy to measure. Although they arise from the same underlying thermal gelation mechanism, the cloud point and thermal gelation temperatures do not always coincide, due to variations in polymer polydispersity, substitution and concentration effects.

Although the response of dilute HPMC solutions to increasing temperature is not identical to the processes which occur as a polymer hydrates, if a soluble species or drug affects

the cloud point of a HPMC solution, then it is likely to affect the hydration of HPMC within the matrix. Therefore, the cloud point has been used in many pharmaceutical studies to assess the effects of ionic solutes and drug-polymer interactions (Mitchell et al., 1990, Ford, 1999, Hino and Ford, 2001, Khan et al., 2013, Banks et al., 2014).

2.5.2.2 Method of cloud point testing

The cloud point temperature (CPT) of HPMC solutions was determined using an FP81 MBC module attached to an FP900 processor (Mettler-Toledo, UK). A schematic of this testing module is shown in Figure 2.7. A boiling tube (Ø 2.9 – 3.1 mm) was filled with approximately 2 cm of HPMC solution using a 1 mL syringe with an 80 mm, 21G needle. The tubes were then placed into the FP81 MBC accessory and heated at 1 °C/min whilst being illuminated by the light pipe. The experiment ran from a temperature at least 15 °C below the expected cloud point, to 90 °C at which maximum turbidity was reached. Three photo sensors continuously measured the intensity of the light transmitted through the samples. Data values were exported to Microsoft Excel, and the temperature at which the transmission of light had dropped by 50%, was taken as the cloud point temperature.

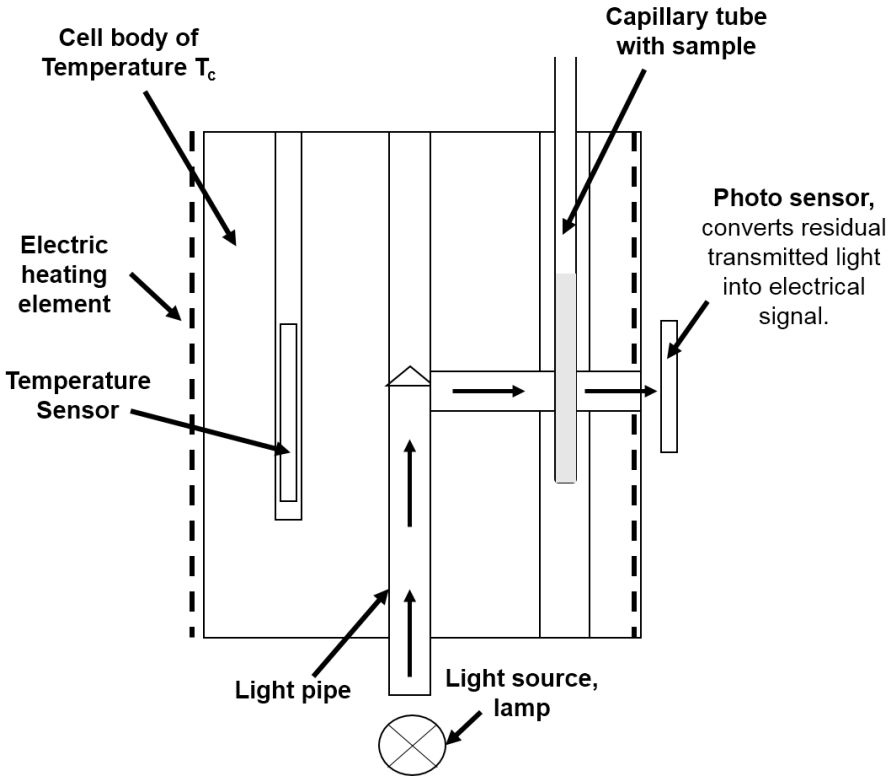

Figure 2.7: Schematic cross-section through the FP81 measuring cell. Adapted from product literature (Mettler-Toledo)

2.5.3 Measurement of solution viscosity

2.5.3.1 Practical considerations of measuring viscosity

The viscosity of HPMC in dilute solutions is one of the defining properties of different HPMC grades, as detailed in Section 1.3.1.2. Solution viscosity is related to the polymer molecular weight and the solution concentration. The viscosity of a fluid is a measure of its resistance to gradual deformation by shear or tensile stress. Viscosity can be affected by parameters such as the molecular structure in solution (ordered, disordered), concentration, temperature, pressure, shear rate and time (Schramm, 2000).

There are several definitions of viscosity, of which the most widely used are:

- **Dynamic (shear) Viscosity, η (IUPAC) or μ (mPa.s or cP):** The measure of resistance of a fluid to shear i.e. when two adjacent layers move parallel to each other at different speeds. In a Newtonian liquid, the viscosity is independent of the shear rate applied to the sample.
- **Apparent Viscosity, η (mPa.s or cP):** This is the same measurement as dynamic viscosity, but where the viscosity of the fluid is influenced by the shear rate (non-Newtonian). The shear conditions need to be stated when apparent viscosity values are given.
- **Intrinsic Viscosity [η] (dL/g):** A measure of a solute's contribution to the viscosity, η, of a solution as measured by an Ubbelohde or Ostwald viscometer. This value is independent of polymer concentration.

HPMC solutions are non-newtonian and exhibit pseudo-plastic behaviour in which the viscosity decreases as the shear rate increases. Therefore, different methods and viscometers do not necessarily correlate with each other. Viscosity measurements should be always interpreted with the shear rate in mind. Given the relatively high viscosity of 2% w/v HPMC solutions, a shear rheometer was used to measure the apparent viscosity of HPMC solutions.

2.5.3.2 Method of measuring solution viscosity using the rheometer

A shear rheometer (MCR302, Anton-Paar GmbH, Graz, Austria) and Rheoplus software (v3.61) were used to measure the apparent viscosity of polymer solutions at a range of shear rates. The rheometer was fitted with a 50 mm, 2° (top) cone and plate geometry (CP50-2). The apparatus is pictured in Figure 2.8. The cone-plate geometry has the advantage that the shear rate is constant along the complete gap. The plate remains stationary as the cone is rotated, and the torque is measured (Schramm, 2000). The Peltier stage was temperature-controlled at 37 °C for all measurements.

The sample was carefully loaded onto the Peltier stage using a plastic spoon. Care was taken not to introduce bubbles into the sample, as they can greatly influence the measured value. The cone was lowered down onto the sample to the set gap of 200 µm, with any excess material being pushed out. This sample was trimmed using a spatula from the edge, taking care not to trim under the cone. The samples were held for 30 seconds in the test position to ensure the sample reached 37 °C before testing.

The sample was subjected to increasing shear rate, from 0.001 to 10 Hz, and the viscosity at each rate was recorded as an average over 10 seconds. For the standardised measurements in this thesis, the viscosity was measured at a shear rate of 6.81 Hz, based on the results of Section 2.6.3. Each measurement was repeated 3 times.

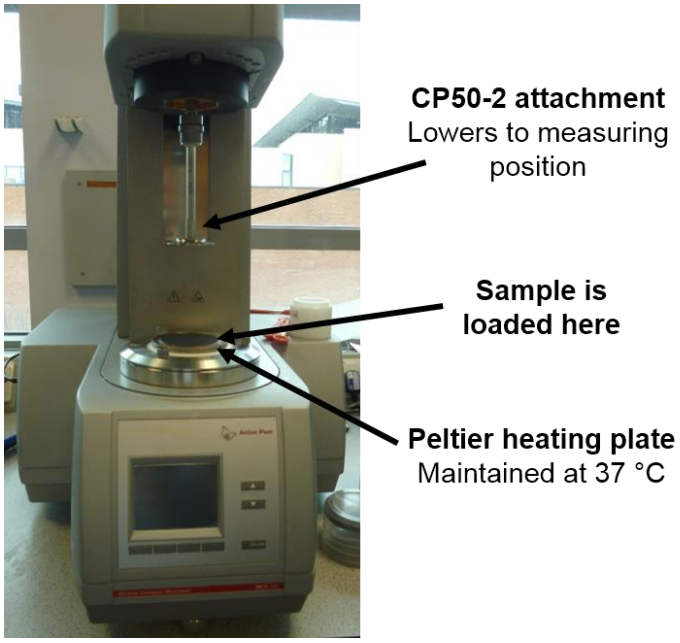

Figure 2.8: Picture of rheometer with cone and plate geometry attached. MCR302 with CP50-2 geometry, Anton-Paar GmbH, Graz, Austria

2.6 Method development

This section details experiments undertaken to optimise (i) the excipient blending process, (ii) compression force used during tablet manufacturing and (iii) the shear rate for rheology studies.

2.6.1 Optimisation of blend uniformity

Powders were blended using a TURBULA® mixer T2F (Willy A Bachofen, Switzerland) rotating at 47 RPM in amber glass jars (500 mL) with batch sizes of 60 – 100 g. Following a previous standard procedure, caffeine, lactose, MCC and HPMC were blended together for 20 minutes. Magnesium stearate was then added and blending continued for a further 5 minute mix. However, poor matrix content uniformity was seen in the initial batches of tablets, with drug content (assessed by UV-vis at λ = 273 nm) varying from 90 – 116% of expected.

Consequently, a blending experiment was carried out. In this study, a 1 g sample was removed after 2, 5, 10, 15 and 20 minutes from three positions in the powder jar (top, middle and bottom). The caffeine content of each aliquot was quantified using UV-vis (λ = 273 nm). Three methods were trialled:

- A ONE STAGE MIX. As previously; ingredients weighed individually and added to powder jar. Large caffeine aggregates were broken by spatula. Caffeine weighing boat was “rinsed” with lactose to ensure all drug was added to blend.
- A TWO STAGE MIX. Caffeine was mixed with an equal volume of lactose, and blended for one minute. The remaining excipients were added, and the sample mixed.
- USING A SIEVE FRACTION OF CAFFEINE. Caffeine was screened through a 125 µm sieve and then mixed as per one stage mix.

Figure 2.9 shows the variance in the caffeine content across the three sampling positions, with respect to blend time and mixing method. The extent of variance was determined by the relative standard deviation (RSD). The lower the RSD, the more similar the caffeine content in each aliquot, indicating that the blend was more uniform. An RSD value of 10% was used as an acceptability limit.

The one stage mix and the two stage mix at early time points exhibited high RSD values (> 10%) suggesting an uneven mix. However the RSD fell below 10% when the < 125 µm fraction of caffeine was used. At mixing times of 10 minutes or more, the RSD values

for all samples dropped below 10%. However, the one stage and caffeine sieved mixtures showed a slight increase in RSD between 15 and 20 minutes. It is well know that over-mixing in a rotational blender can lead to de-mixing (Larson, 1992). A blending time of 15 minutes was selected as, except for the 2 stage mix, the RSD was at a nadir. Blends containing sieved caffeine generally had a lower RSD, and have the added advantage of making the drug particle size more uniform. Magnesium stearate was added after the other excipients had been blended for 15 minutes and the whole mixture was then blended for 2 minutes, based on industrial experience.

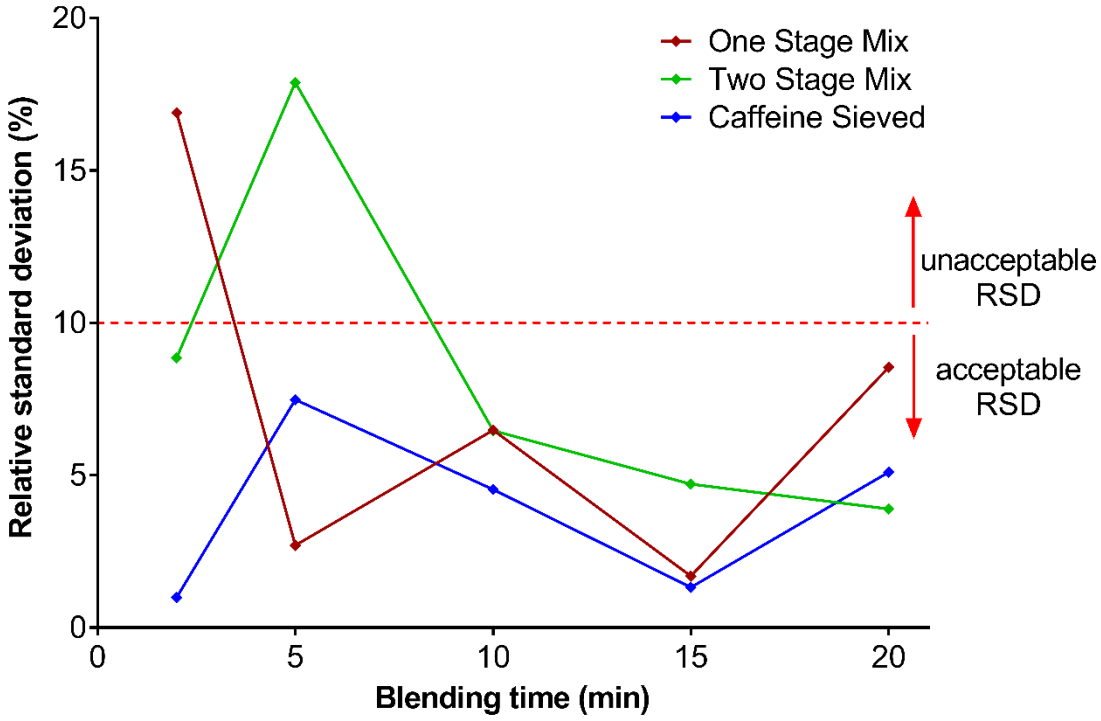

Figure 2.9: Blending experiment: Relative Standard Deviation (RSD) with respect to blending time and method. Each point represents the mean content of three samples, one each from the top, middle and bottle of the powder jar. Blending was undertaken using TURBULA® mixer at 47 RPM.

2.6.2 Optimisation of compression force

Although it is reported that above a critical hardness compression force has little impact on drug release from hydrophilic matrices (Section 1.3.3.1), compression force studies have rarely considered matrices with low polymer contents. Therefore, a study was undertaken to explore the effect of compression force on drug release rate from low polymer matrices.

Tablets were manufactured on a Riva Piccola multi-station press (Riva S.A., Argentina) using 8 mm flat round tooling (I Holland, UK). Matrices containing 5, 10, 15, 20 or 30% w/w HPMC K4M were manufactured at compression forces between 2.5 and 20 kN, which equated to compression pressures between 49.2 and 394 MPa. The tensile strength of matrices was calculated from the breaking force using the equation in section 2.3.1.

Figure 2.10 shows how tablet tensile strength varied with increasing compression force. The tablet tensile strength increased almost linearly with increases in compression force up to 10 kN. Increasing the compression force further resulted in progressively smaller increases in tensile strength. The literature advises using compression forces within the linear region for tablet compaction. This avoids capping and lamination (Carstensen et al., 1985).

The time for 80% drug release ($T_{80\%}$) in USP apparatus II (50 RPM, water) were compared for each formulation in Figure 2.11. This method is further described in Section 2.3.2. It can be seen that in general $T_{80\%}$ values increase as the compression pressure was increased. The pattern was similar at matrix polymer contents between 10% and 30% w/w HPMC. The results suggest that it is important to have a standard compression pressure for all studies and 8 kN (158 MPa) was chosen as this was in the linear region of the compressibility curve for all formulations. In addition, Figure 2.11 suggests that the difference in $T_{80\%}$ between 8 and 10 kN (158 – 197 MPa) was marginal, and therefore slight variations in compression force would not be expected to dramatically impact on drug release rate.

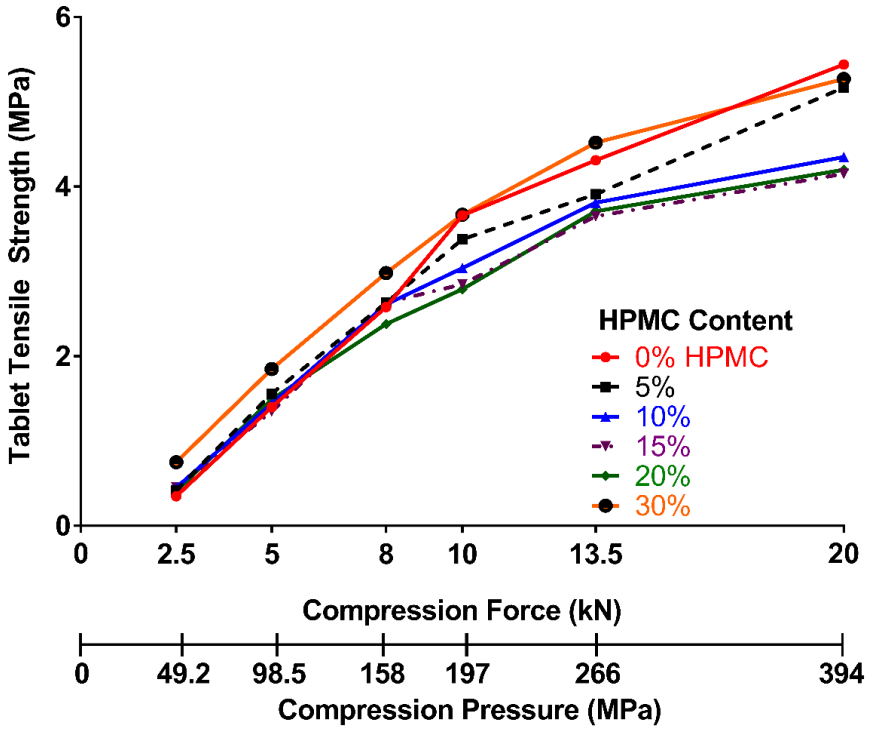

Figure 2.10: The effect of compression force on tablet tensile strength with respect to matrix polymer content. Mean (n=3). Matrix polymer content between 0 and 30% w/w HPMC K4M. 8 mm flat round tablets (250 mg ± 5 mg) manufactured using a Riva Piccola multi-station tablet press.

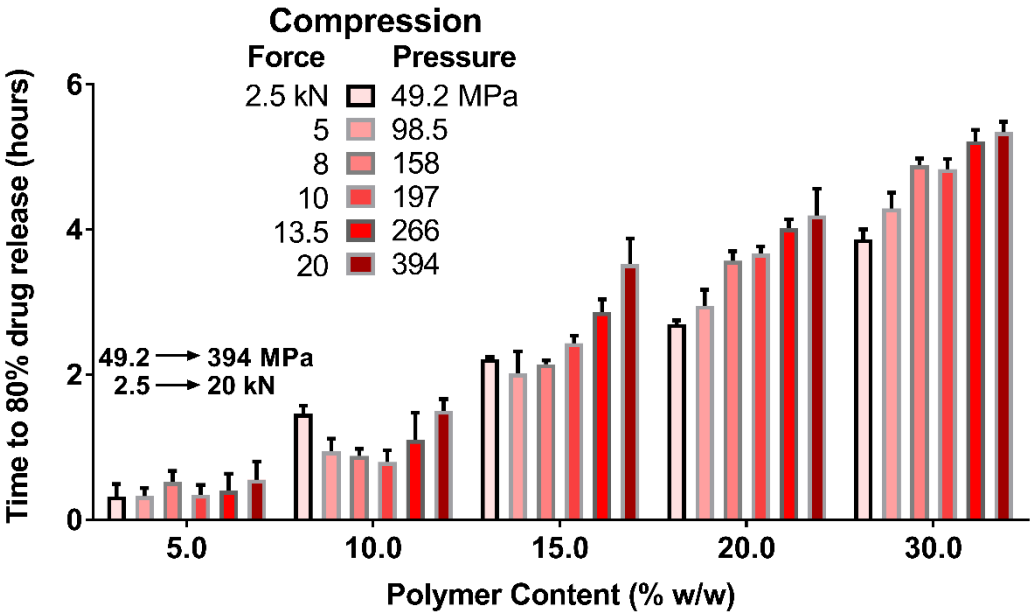

Figure 2.11: The effect of compression pressure on time for 80% drug release with respect to matrix polymer content Mean (n=3) + 1 SD. 8 mm flat round tablets (250 mg ± 5 mg). Time for 80% drug release ($T_{80\%}$) calculated from dissolution data (USP apparatus II, paddle, 50 RPM, water at 37 °C, capsule sinkers).

2.6.3 Selection of a standard shear rate for viscosity measurements

The measured viscosity of an HPMC solution will depend on the shear rate. Figure 2.12 shows the viscosity of HPMC solutions between 0.25% and 5.0% w/v. In the case of solutions containing less than 1.5% w/v HPMC, a viscosity plateau is seen at shear rates of less than 0.3 Hz. Under these circumstances, viscosity values at very low shear rates will be close to the zero shear viscosity (the viscosity of the solution at rest). Above 0.3 Hz, there is a clear decrease in viscosity as the shear rate increases, which highlights the shear-thinning, non-newtonian behaviour of HPMC solutions. In the case of solutions with an HPMC concentration greater than 1.5% w/v, the decrease in viscosity as the shear rate increases is more gradual. It is known that there is roughly a $1/8^{th}$ power relationship between HPMC concentration and solution viscosity (Dow Chemicals, 2002). Figure 2.13 shows the apparent viscosities measured at 0.00463 Hz and 6.81 Hz for two HPMC solutions. At the low shear rate, there was a large variation in the measured viscosity between different runs on the same solution. In addition, the two batches had different gradients, suggesting a high degree of error in the measurements at the lower shear rate. In contrast, at the higher shear rate (6.81 Hz), a linear relationship was observed between solution concentration and viscosity$^{1/8}$. The relationship was very similar when a second batch of solutions was manufactured, suggesting that a shear rate of 6.81 Hz enabled a reliable comparison between the viscosities of different solutions.

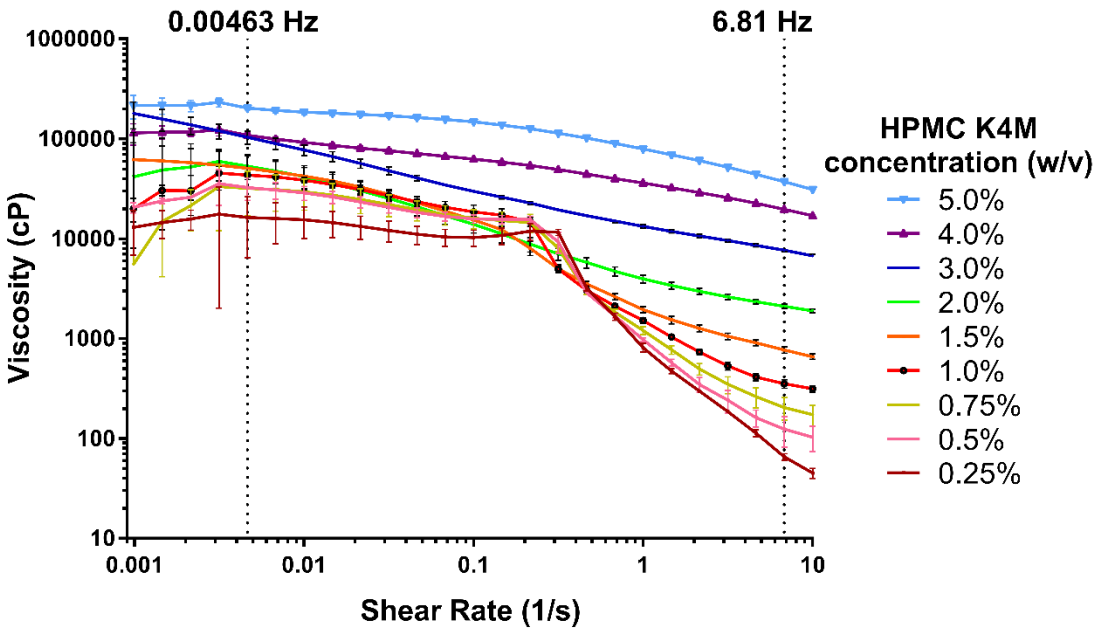

Figure 2.12: Rheology flow curves for HPMC K4M solutions. Polymer concentration was varied between 0.25 and 5.0% w/v. Mean ±1 SD (n=3), 37 °C. Measured using an MCR 302 Rheometer fitted with a CP50-2 geometry (50 mm, 2° cone and plate).

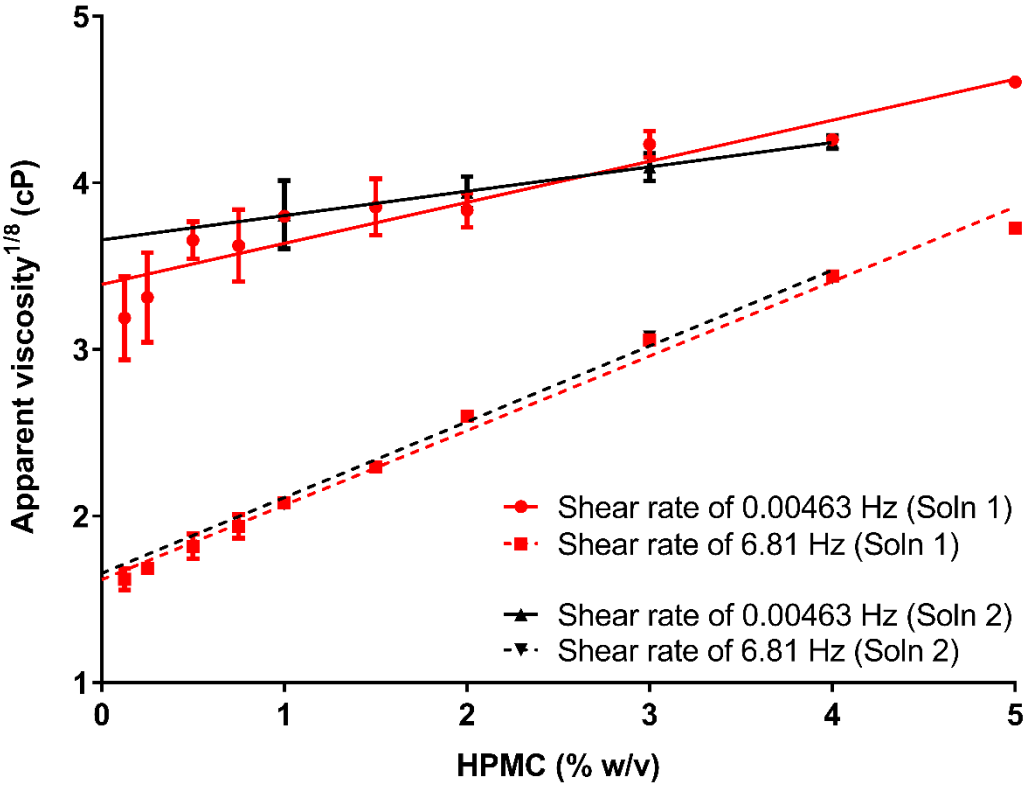

Figure 2.13: Apparent viscosity of two HPMC K4M solutions with polymer concentration between 0.25 and 5.0% w/v, measured at 0.00463 Hz and 6.81 Hz. Mean ±1 SD (n=3), 37 °C. Each solution used the same batch of HPMC. Measured using MCR 302 Rheometer fitted with a 50 mm, 2° cone and plate.

Chapter 3
The Impact of Polymer Content on HPMC Hydrophilic Matrices

3.1 Introduction

Reducing the content of rate-controlling polymer within a formulation can be a necessary modification if drug release is too slow, or if there are constraints on the tablet size (Section 1.2). Despite being a useful and regularly employed formulation strategy, there have been few systematic investigations that describe the impact of lowering matrix polymer content on the underlying mechanisms of drug release. We believe that the development of successful and reliable low polymer content formulations is impossible without a detailed understanding of how polymer content influences (i) the drug release rate and mechanism, (ii) the establishment of a rate-limiting gel layer and (iii) matrix erosion rates.

In this chapter, a combination of mathematical tools and physical studies have been used to probe the mechanism of drug release as polymer content is lowered below the typical 30% w/w.

3.2 Aims

The aims of this chapter are:

1) To study the impact of matrix polymer content on drug release rates, in conventional USP dissolution tests.
2) To fit the dissolution data to common mathematical models, in order to further describe the impact of polymer content on the drug release mechanisms.
3) To use *in-situ* imaging techniques to validate the mechanisms of drug release predicted by the mathematical models.
4) To use other physical methods to understand how polymer content influences matrix erosion.

3.3 Materials and Methods

3.3.1 Materials

Full details of the materials used are described in Chapter 9 (Appendix). The HPMC used was METHOCEL™ K4M CR premium (Colorcon, UK).

3.3.2 Manufacture of HPMC matrices

The matrix tablet formulations are listed in Table 3.1 and the HPMC content was varied between 5% and 30% w/w. The manufacturing methods are described in Section 2.1. Tablet hardness was measured as between 2.36 and 2.76 MPa for all formulations.

3.3.3 USP apparatus II (paddle) dissolution testing

Drug release kinetics were determined in 900 mL degassed, de-ionised water 37 ± 0.5 °C in USP apparatus II (paddle, 50 RPM).

Caffeine was quantified at a UV absorbance of λ = 273 nm as fully described in Section 2.3.2. Dissolution data was characterised using the mathematical models discussed in Section 2.3.3.

	Quantity of excipient (% w/w)							
METHOCEL K4M	5	7.5	10	12.5	15	17.5	20	30
Caffeine	10	10	10	10	10	10	10	10
Lactose	56.3	54.7	53.0	51.3	49.7	48.0	46.3	39.7
MCC	28.2	27.3	26.5	25.7	24.8	24.0	23.2	19.8
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Table 3.1: HPMC matrix tablet formulations. Caffeine was sieved through a 125 µm sieve, other excipients were used as received. Materials were blended for 15 minutes with magnesium stearate added for a final 2-minute lubrication step. Tablets were 250 ± 5 mg (8 mm Ø, flat-faced, round) and manufactured using direct compression at 150 MPa.

3.3.4 Estimation of the percolation threshold from dissolution kinetic parameters

Percolation threshold estimates were made using linear regressions of the normalised Higuchi rate constants against the matrix HPMC content, as fully described in Section 2.3.4.

3.3.5 Confocal microscopy imaging of early gel layer formation

Imaging of early gel formation was undertaken in 0.008% w/v Congo red using a Bio-Rad MRC-600 confocal microscope (Bio-Rad, UK) and using the methods described in Section 2.3.5. The tablet was held between two Perspex® discs allowing imaging of the matrix from overhead, to capture the processes of gel layer formation at the radial edge of the tablet. A series of images were taken every 30 seconds for the first 15 minutes of hydration.

3.3.6 Time lapse photography of hydrating matrices

Matrices, fixed to a Perspex® stand and held in a water-jacketed beaker were photographed every 30 seconds from the addition of media at 37 ± 1 °C. A series of images were obtained for the first 30 minutes of hydration. Full methods are described in Section 2.3.6.

3.3.7 Hydration of matrices in a USP disintegration apparatus prior to texture analysis and erosion studies

The USP disintegration apparatus was used to hydrate matrix tablets prior to texture analysis testing and erosion studies, as the tablet could be removed from the basket-rack with minimal damage, and because tablets could not be easily recovered from the capsule sinkers used in USP dissolution apparatus II. Tablets were placed into individual tubes of the disintegration basket-rack and then lowered into 700 mL of water (37 ± 1 °C) in a disintegration bath (Copley Scientific, UK). The disintegration apparatus raises and lowers the basket-rack in media, in accordance with the USP method (The U.S. Pharmacopeial Convention, 2016). The tablets were hydrated for set periods of time (between 4 and 120 minutes) before being carefully removed and placed flat surface down on a glass cover slip.

3.3.8 Measurement of core breaking force using the texture analyser

A texture analyser (TA.XT Plus, Stable Micro Systems. Surrey) calibrated with a 5 kg load cell was used to measure the core strength of the matrix tablet, by performing a probe penetration test. The texture analyser is able to record instantaneous force with respect to probe location (i.e. depth into the sample), using Exponent software (version 6.1.9.0, Stable Micro Systems. Surrey).

A graphical representation of the test method is shown in Figure 3.2. A tablet, removed from the disintegration bath at the desired time interval, was placed onto a glass cover slip and positioned underneath the 2 mm diameter stainless steel probe. The probe travelled downwards at a speed of 0.2 mm/s from a starting position of 15 mm above the base plate [position 1]. As the probe travelled downwards, force and distance measurements (50 per second) were collected. The probe continued moving downwards until the maximum measurable force of 58.5 N was reached, which was either as a result of the probe hitting the base plate or when the tablet core was harder than this value [position 3 or 4].

Results were exported to Microsoft Excel. There were small fluctuations in the force reading as the probe moved at low speeds. Therefore, force measurements were averaged with the previous 10 readings (approx. 0.022 mm), in order to determine when the gel layer had been reached. The start of the gel layer was taken as the distance where the average force reading was more than 0.001 N (Position 2 in Figure 3.2).

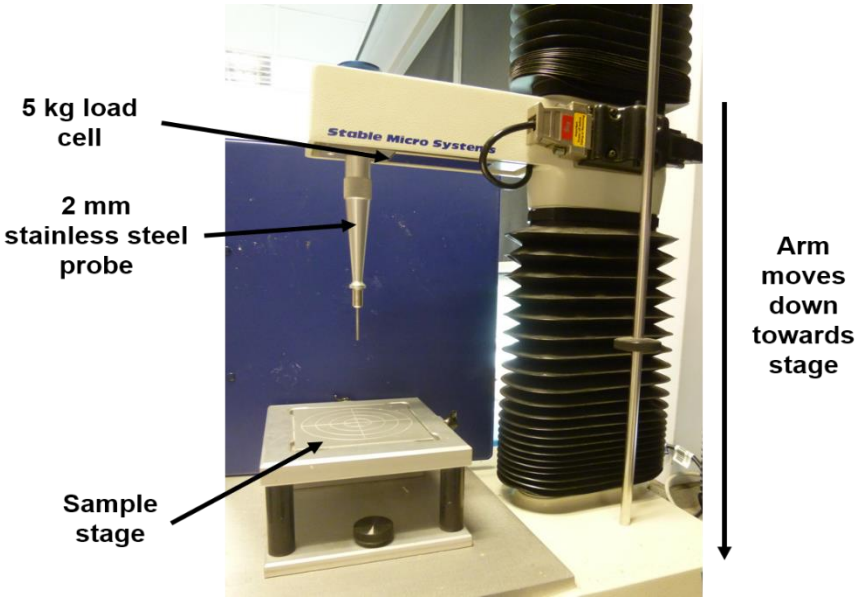

Figure 3.1: Texture analyser fitted with 2 mm diameter probe.

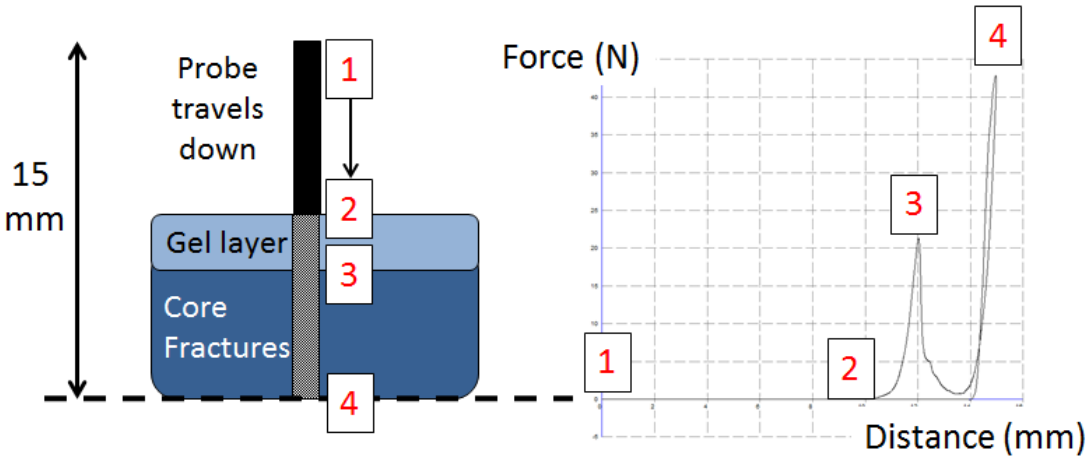

Figure 3.2: Schematic depiction of texture analysis probe test with example results trace.
20% HPMC, 24 mins hydration in water (37 °C) in the disintegration test.
1) The 2 mm diameter probe moves downwards from a height of 15 mm.
2) The probe enters the gel layer
3) The force increases as the probe pushes on the harder core, until the core breaks.
4) The probe continues to travel until it reaches the distance of 15 mm / a force of 58.5 N is reached.

3.3.9 The measurement of matrix erosion by gravimetric analysis

Gravimetric analysis was used to determine the total weight loss from the tablet as a function of hydration time and matrix polymer content.

The dry tablet was weighed before being hydrated in a USP disintegration apparatus as described according to methods 3.3.7. After a period of time (between 4 mins and 2 hours), the hydrated tablet was placed onto a glass cover slip and dried in an oven for 24 hours at 40 °C to a constant weight. Tablets were weighed again, and the matrix erosion (% w/w) calculated from the weight loss using Equation 3.1.

Equation 3.1: $$\boldsymbol{Erosion}\ (\%) = \mathbf{100} \times \frac{(\boldsymbol{initial\ weight - dried\ weight})}{\boldsymbol{initial\ weight}}$$

3.4 Results

3.4.1 Investigating the extended release properties of HPMC matrices containing different HPMC contents

Figure 3.3 shows caffeine release from HPMC matrices as a function of HPMC content. Table 3.2 reports the mean drug release in 10 minutes (DR10min), mean time for 80% drug release ($T_{80\%}$) and the results of fitting the dissolution data to zero order, first order, Higuchi, Korsmeyer-Peppas and Peppas-Sahlin mathematical models, as described in Section 2.3.3.

Figure 3.3 shows that as the matrix polymer content was increased, drug release became progressively slower, with mean $T_{80\%}$ value ranging from 0.49 hours for the 5% w/w HPMC formulation, to 5.17 hours for formulations containing 30% w/w HPMC. All the dissolution curves appear to have a similar shape, drug release being faster at earlier time points (up to 30 minutes), before a slower release of drug over the remaining time.

The mean DR10min ranged from 57.9% to 8.8% drug release as the matrix polymer content increased from 5% to 30% w/w HPMC. The ability of a hydrophilic matrix to limit the initial burst release of the drug is important, as extended release formulations are often utilised to reduce the peak plasma concentrations for drugs with dose-dependent side effects. Even when the formulation contained 30% w/w HPMC, the drug release in the first 10 minutes (8.8% drug in 10 minutes) was disproportional to the eventual $T_{80\%}$ (80% drug in 310 minutes). The presence of a rapid burst release of soluble drug during the initial stages of matrix hydration is a known phenomenon of HPMC matrices and has been reported to be a result of drug release during the time taken for the gel layer to establish (Ford, 2014).

Formulations containing 5% w/w HPMC had a $T_{80\%}$ of 0.49 hr and matrices containing 0% HPMC had a mean $T_{80\%}$ of 0.08 hr. The FDA definition states than an extended release dosage form is “a dosage form that allows a reduction in dosing frequency as compared to that presented by a conventional dosage form” (Center for Drug Evaluation and Research (CDER), 1997b). Whilst we do not know how the *in-vitro* dissolution rate will translate into *in-vivo* drug release kinetics, it is arguable that formulations containing just 5% w/w HPMC are not ‘true’ extended release dosage forms.

Figure 3.4 provides an expanded view of drug release over the first 15 minutes of the dissolution test. It can be seen that even in these early stages, the drug release rate is closely related to the polymer content and differentiation between profiles can be seen very early (four minutes) into the test. This suggests that the early behaviour of the matrix might provide a prediction of subsequent matrix performance over the complete dissolution time frame of many hours.

Drug release kinetic parameters, as calculated using zero order, first order, Higuchi, Korsmeyer-Peppas and Peppas-Sahlin equations, are shown in Table 3.2. In line with the graphs, the rate of caffeine release decreased as the polymer content was increased.

These mathematical models have been developed using idealised systems, for example where there is negligible swelling of the formulation, perfect sink conditions and limited edge release (Siepmann and Peppas, 2001). The drug release from matrices containing lower HPMC content is likely to deviate from these model conditions. Therefore, an evaluation of how the models fit drug release data from low polymer content formulations is made in the next section.

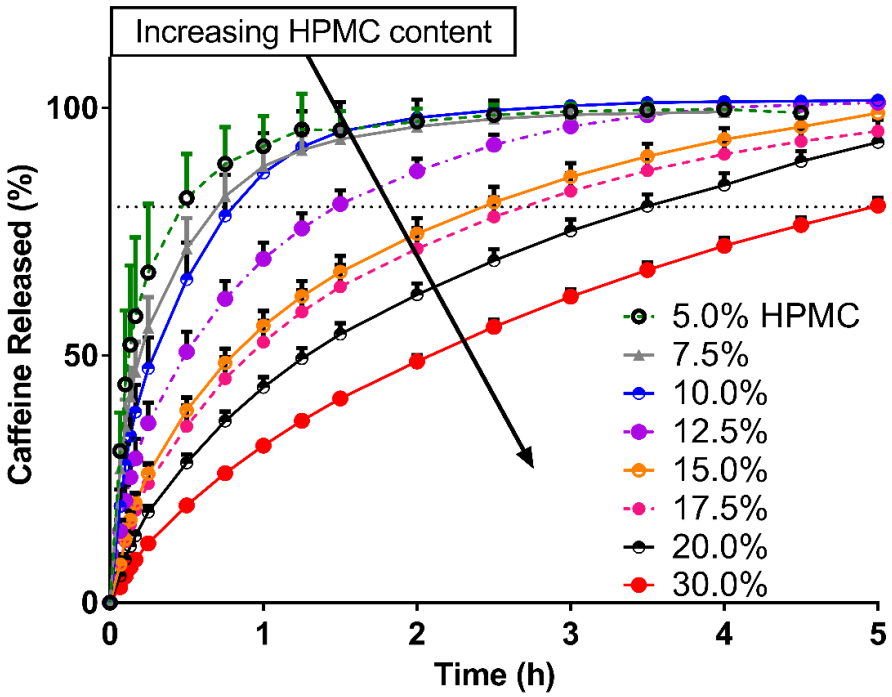

Figure 3.3: Release of caffeine from HPMC matrices as a function of polymer content. HPMC content as % w/w. USP apparatus II (paddle), 50 RPM, 900 mL water, 37 ± 0.5 °C. Mean (n=6) + 1 SD. Dotted line represents T80%. From: Mason et al. (2015), see footer.

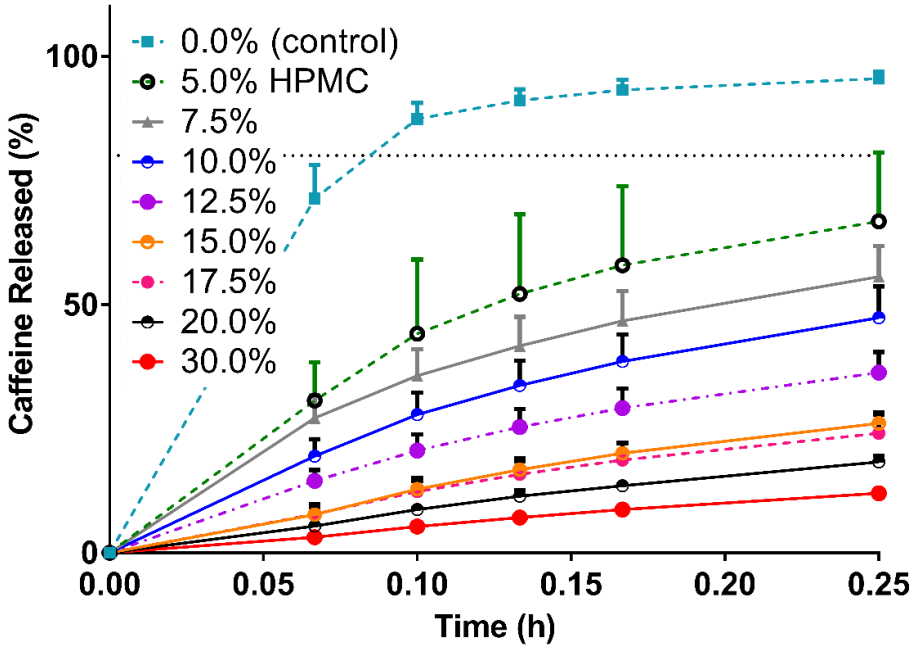

Figure 3.4: Release of caffeine from HPMC matrices as a function of polymer content over the first 15 minutes of the dissolution test. HPMC content as % w/w. USP apparatus II (paddle), 50 RPM, 900 mL water, 37 ± 0.5 °C. Mean (n=6) + 1 SD. Dotted line represents T80%.

Figure 3.3 and Figure 3.4 reprinted from European Journal of Pharmaceutics and Biopharmaceutics, Volume 94, Mason LM et al, The influence of polymer content on early gel-layer formation in HPMC matrices: The use of CLSM visualisation to identify the percolation threshold, 485-492., Copyright (2015), with permission from Elsevier

HPMC Content (% w/w)	DR10min (%)	$T_{80\%}$ (h)	Zero Order		First Order		Higuchi		Korsmeyer-Peppas			Peppas-Sahlin			
			k_0 ($mins^{-1}$)	r^2	k_1 (mins)	r^2	k_h ($mins^{-0.5}$)	r^2	k_{kp} ($mins^{-n}$)	*n*	r^2	k_d ($mins^{-0.44}$)	k_r ($mins^{0.88}$)	$\frac{k_r}{k_d} = \frac{R}{F}$	r^2
5.0	57.9 ± 15.9	0.49 ± 0.22	3.11	0.435	0.066	0.505	18.92	0.459	14.04	0.59	0.573	16.47	1.37	0.08	0.456
7.5	46.7 ± 6.0	0.70 ± 0.14	2.51	0.750	0.062	0.717	15.10	0.773	13.01	0.55	0.783	13.71	1.05	0.08	0.770
10.0	37.7 ± 5.4	0.88 ± 0.27	1.65	0.846	0.040	0.731	12.89	0.886	9.32	0.59	0.869	7.79	2.10	0.27	0.795
12.5	29.6 ± 3.4	1.43 ± 0.13	1.09	0.914	0.031	0.791	9.76	0.951	7.14	0.58	0.931	7.73	0.86	0.11	0.911
15.0	19.0 ± 1.9	2.54 ± 0.30	0.67	0.941	0.021	0.782	7.86	0.984	3.94	0.65	0.960	4.77	0.79	0.17	0.972
17.5	18.6 ± 3.3	2.74 ± 0.33	0.64	0.933	0.021	0.789	7.45	0.968	3.80	0.64	0.948	4.47	0.73	0.16	0.948
20.0	13.1 ± 0.8	3.72 ± 0.17	0.43	0.940	0.014	0.754	6.27	0.992	2.81	0.66	0.980	3.54	0.58	0.16	0.985
30.0	8.8 ± 0.2	5.17 ± 0.09	0.31	0.961	0.012	0.743	5.16	0.998	1.46	0.74	0.986	2.22	0.46	0.21	0.991

Table 3.2: The effect of matrix polymer content on drug release kinetics: $T_{80\%}$ DR10min, zero order, first order, Higuchi, Korsmeyer-Peppas and Peppas-Sahlin. Calculated from mean dissolution profiles (n=6) (± 1 SD for DR10min and $T_{80\%}$). DR10min is the drug release (%) after 10 minutes dissolution, $T_{80\%}$ is the time for 80% drug release, k_x = rate constant for each equation and in the case of the Peppas-Sahlin equation k_d is diffusional release and k_r erosional release. n is the Korsmeyer-Peppas time exponent that relates to the drug release mechanism.

3.4.2 A comparison of model fit assessed using coefficient of determination (r^2)

Correlation coefficients (r^2) for each model were compared to establish how well the respective models fitted the dissolution data. In the literature, r^2 has been suggested as a useful way to choose the 'best' model to represent dissolution data, being appropriate to compare fitting when models have the same number of parameters (Costa and Sousa Lobo, 2001). As all models (except Peppas-Sahlin) could be formatted to resemble a linear equation ($y = mx + c$), a perfectly fitting model would have an r^2 value of 1, and a model which in no way describes the data would have an r^2 value of 0. Therefore, the closer the r^2 value is to 1, the better the model fits the data.

Figure 3.5 shows the relationship between r^2 and the matrix polymer content. When the matrix contains just 5% HPMC, the r^2 values for all models was between 0.4 and 0.6. As the matrix polymer content increased from 5% to 15%, the r^2 values increased to above 0.93 for models, with the exception of the first order equation. As the polymer content increased further from 15% to 30%, a small increase in r^2 was observed.

An increase in r^2 value as the polymer content increases may suggest that the mathematical model used describes the drug release characteristics of matrices with higher polymer contents better than those with lower polymer contents. This may be because higher concentrations of HPMC in the gel layer provide greater and more consistent control of drug release processes such as diffusion and erosion. Therefore, when polymer content is higher, drug release appears to correlate better with the idealised scenario upon which the models are based. Higuchi, Korsmeyer-Peppas and Peppas-Sahlin have similar r^2 values with respect to matrix polymer content.

The first order model displays a poorer fit (r^2 below 0.8) at all matrix polymer contents. As the first order model suggests that drug release rate is dependent on the matrix drug concentration, lower r^2 values indicate that drug concentration is not driving slower drug release rates.

A discussion of the appropriateness of these models is made in Section 3.5.1.

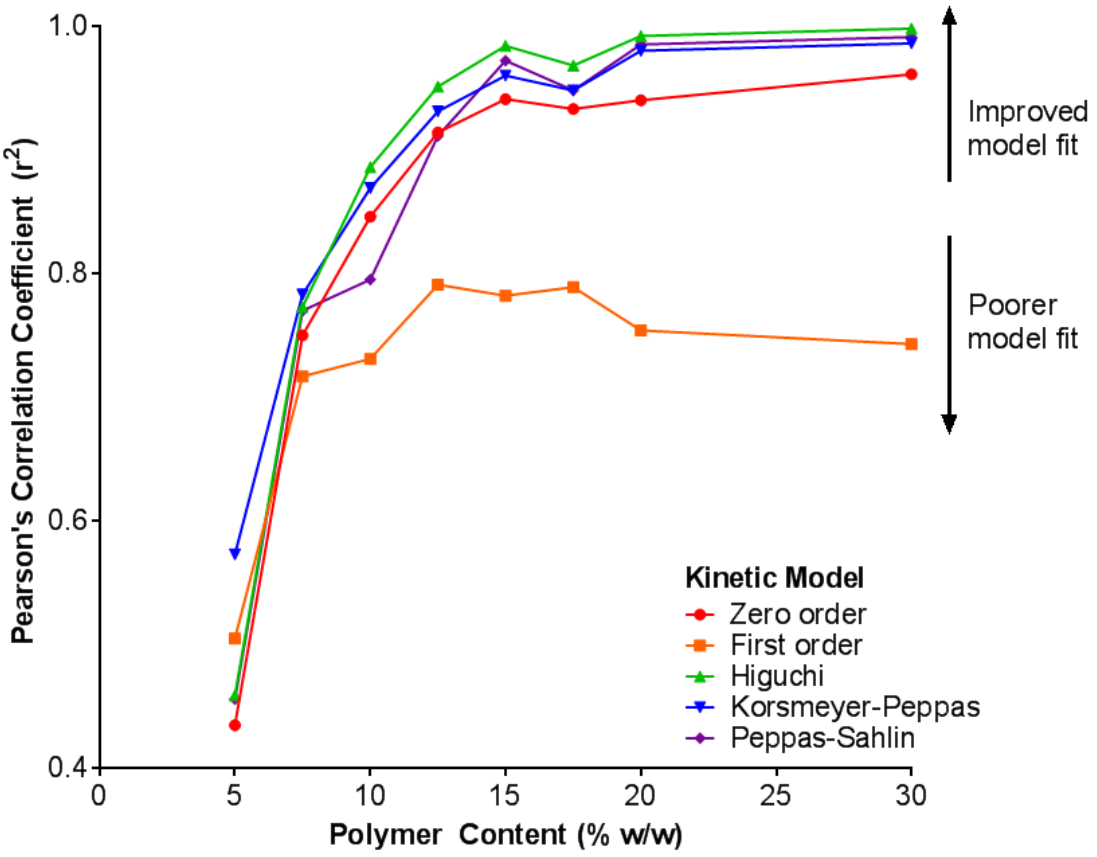

Figure 3.5: The coefficient of determination (r^2) for mathematical models fitted to drug release data from matrices of varying HPMC content with respect to mathematical model applied. Models applied: Zero order, first order, Higuchi, Korsmeyer-Peppas and Peppas-Sahlin models (fitted to the mean of dissolution data (n=6), of between 0 – 60 % drug release for Peppas-Sahlin model and 0 – 70% drug release for the remaining models).

3.4.3 The use of mathematical models to determine drug release mechanism

Table 3.2 shows the calculated kinetic parameters for the Korsmeyer-Peppas and Peppas-Sahlin models, which have been reported to offer insights into the predominant mechanism by which drug may be released (Siepmann and Peppas, 2001, Siepmann and Siepmann, 2008). In the case of a cylindrically shaped matrix tablet, Korsmeyer-Peppas reported that *n* values near 0.45 suggest a mechanism in which drug diffusion predominates, whereas values approaching 0.89 suggest erosion-dominated release. Values between 0.45 and 0.89 indicate a mixed mechanism of the two, which is often defined as 'anomalous' (Korsmeyer et al., 1983).

Table 3.2 shows that the Korsmeyer-Peppas *n* exponent lies between 0.55 and 0.74 for all polymer content formulations studied. This suggests an anomalous drug release mechanism irrespective of the matrix polymer content. There is a slight correlation with polymer content as matrices containing 15 - 30% w/w HPMC show closely similar *n* values (0.64 - 0.74) whereas those with less than 15% HPMC show values between 0.55 - 0.59. This suggests a shift in drug release towards diffusional release in low polymer content matrices. However, as discussed in the previous section (3.4.2), it would be reasonable to be wary of attributing too much weight to *n* values calculated for 5% to 10% w/w HPMC matrices, because the kinetic models show a reduced fit to the dissolution data. Nonetheless, the subtle change in *n* value between 15% and 12.5% w/w HPMC matrices may indicate a difference in the properties of the gel layer.

The Peppas-Sahlin model aims to report the rate of drug release attributed to erosion (relaxation, R) compared to diffusion (Fickian, F), which is known as the parameter R/F (Peppas and Sahlin, 1989). Table 3.2 shows that R/F generally increased as the matrix polymer content increased. This suggests a greater component of erosional release when there was a higher level of HPMC in the matrix. However, in all cases, the diffusional rate constant (k_d) was greater than the erosional rate (k_r).

The results from Korsmeyer-Peppas and Peppas-Sahlin both agreed that the mechanism of drug release from formulations was similar and was predominantly unaffected by the matrix polymer content.

3.4.4 Estimation of the HPMC percolation threshold

A detailed explanation of percolation theory and its relevance and application to the design of hydrophilic matrices is provided in Section 1.2.1. In brief, percolation theory states that there is a minimum threshold (% w/w or % v/v) of the rate controlling excipient that must be present in a matrix tablet to ensure the formation of a drug-retarding network which extends the release of the drug. In the case of hydrophilic matrices, this can be interpreted as there being sufficient polymer to form a coherent and complete surface gel layer.

The method, detailed in Section 2.3.4, required two regression lines to be fitted to Higuchi rate constants that had been calculated for matrices of different HPMC content. This is shown in Figure 3.6. The intercept of the two regression lines was 12.6% v/v, which corresponds to 11.1% w/w HPMC.

The Higuchi rate constant for the 12.5% w/w HPMC matrix was omitted from both regression lines as it was difficult to determine which regression line should include it. This data point omission highlights an inherent bias with the estimation of percolation thresholds, and is one reason why percolation threshold values are estimates and not definitive. Small variations in experimental conditions and intra-batch variability in drug release can also change the precise co-ordinates of each regression line, and therefore influence the percolation threshold calculated. In addition, any conclusions drawn from percolation theory are dependent on the fitting of dissolution data to kinetic models which was found to be poorer for matrices with low HPMC content (5 – 12.5% w/w) (section 3.4.2). Finally, this analysis provides little in the way of understanding of the internal processes underlying the change in behaviour and for these reasons confocal laser scanning microscopy (CLSM) imaging was undertaken to understand the impact of polymer content on the formation of a coherent gel layer.

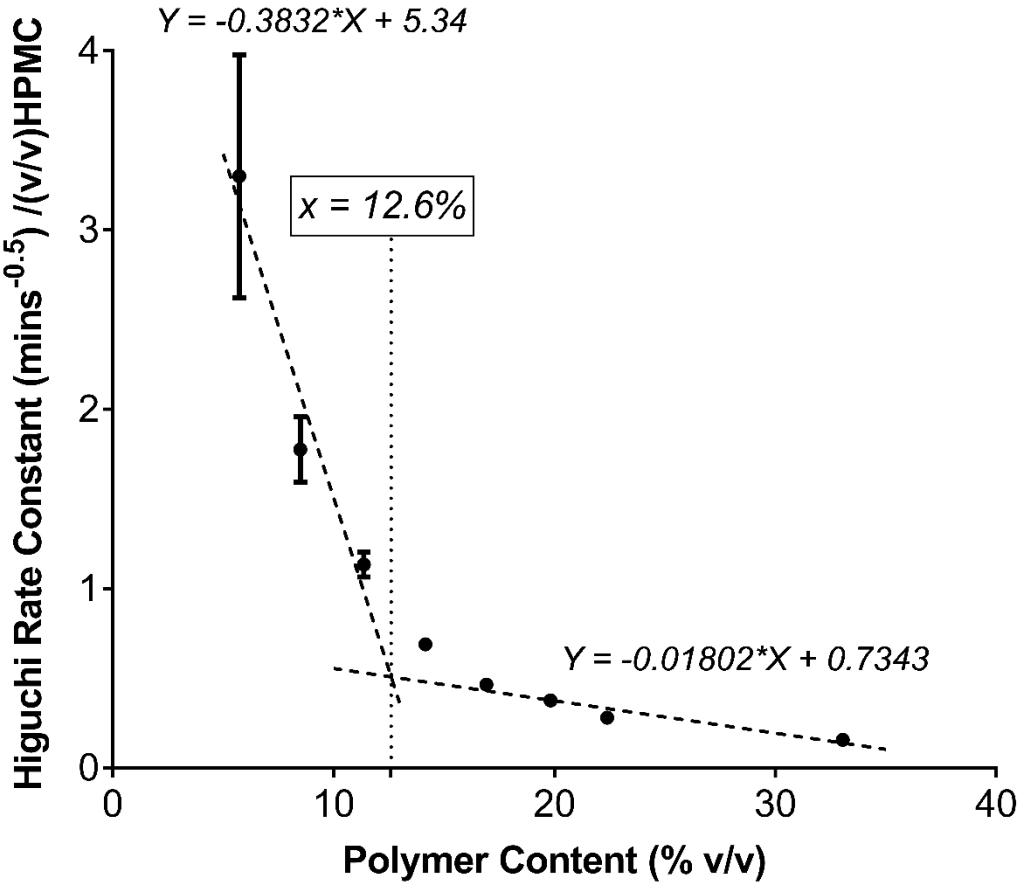

Figure 3.6: Mathematical determination of percolation threshold concentration x is the estimated percolation threshold, taken as the intersection of the two linear regressions. Higuchi rate constants (mean ± 1 SD) calculated from mean dissolution data (n=6, USP II 50 RPM paddle water 37 °C).

Figure 3.6 is reprinted from European Journal of Pharmaceutics and Biopharmaceutics, Volume 94, Mason LM et al, The influence of polymer content on early gel-layer formation in HPMC matrices: The use of CLSM visualisation to identify the percolation threshold, 485-492., Copyright (2015), with permission from Elsevier.

3.4.5 The effect of matrix polymer content on early gel layer development visualised by confocal laser scanning microscopy

Confocal laser scanning microscopy (CLSM) was used to examine early gel layer development (Bajwa et al., 2006). The fluorophore, which is dissolved in the hydrating fluid is Congo red. This exhibits low fluorescence in water, but high fluorescence when bound to cellulose. In these studies, Congo red therefore functions as a marker for regions of hydrated HPMC, and MCC.

A typical CLSM image from our current study is shown in Figure 3.7. This figure is annotated to illustrate the general features that can be seen in this type of image. The bulk of the hydration liquid exhibits a low overall fluorescence, except for nebulous plumes which probably represent HPMC dissolving away from the gel surface. The highly fluorescent region in the centre of the image, represents the emerging gel layer, within which can be seen hydrating individual polymer particles. Polymer swelling in this region allows extensive access of fluorophore molecules to the polymer chain, and the resulting binding of fluorophore molecules generates the intense fluorescence to provide the contrast we see in these images. The dark region to the right of the gel layer corresponds to the unhydrated matrix core, in which only a weak autofluorescence delineates individual dry particles.

Figure 3.8 shows a series of time-resolved images depicting matrices, containing 5 to 30% w/w HPMC, undergoing hydration. Representative images are provided of gel layer formation at 1 min, 5 min and 15 min. To allow visual comparison, all images have been obtained under standardised experimental conditions and using the same confocal microscope settings. The periphery of the dry tablet prior to hydration (time, t = 0) is shown by the white dashed line, providing a reference position with which to compare the extent of gel layer swelling.

30% w/w has been suggested as the recommended amount of high viscosity HPMC (Methocel K4M or similar) for use in hydrophilic matrices (Dow Chemicals, 2000, Hughes, 2013). In our 30% w/w HPMC formulations, individual particle swelling at the matrix surface can be seen during the initial few minutes, and by 15 minutes these hydrating particles have coalesced into a continuous gel layer. In matrices containing 20% and 15% w/w HPMC, the 1 min and 5 min images show swelling that is both greater and more irregular than observed for 30% w/w matrices. This suggests there had been

greater penetration of liquid into the matrix before the swelling particles stuck together, yet ultimately, both formulations after 15 minutes have formed a continuous gel layer of similar thickness to that formed by the 30% w/w HPMC matrix.

Images of the matrices that contained 5 or 10% w/w HPMC show a different pattern of hydration in that after 15 minutes, no obvious surface gel layer is apparent. Both formulations initially show an outward swelling beyond the tablet dry boundary, but after 5 minutes, the gel appears thin and irregularly formed. This is in contrast to the 15% - 30% w/w HPMC matrix images. In the case of 5% w/w matrices, there is also evidence of (i) matrix erosion and (ii) liquid penetration into the core. These can be seen by (i) particles separating from the surface and (ii) fluorescent regions appearing behind the dashed line of the original tablet boundary. This suggests a complete failure of gel barrier function with significant surface disintegration.

This series of CLSM images suggest that matrices containing 10% w/w HPMC or less are simply unable to form a continuous gel layer capable of adequately restricting water uptake within 15 minutes. This proposed failure mechanism of low polymer content matrices is different to failure modes that have been seen before for 30% w/w HPMC matrices. In previous studies, high concentrations of salt (Bajwa et al., 2006) or sugar (Williams et al., 2009), and fat emulsions (Williams et al., 2011) have resulted in extensive surface channelling or disintegration involving large lumps of the HPMC tablet surface being ejected due to the swelling of isolated regions of polymer. There was no evidence of these processes in the case of our low polymer content formulations.

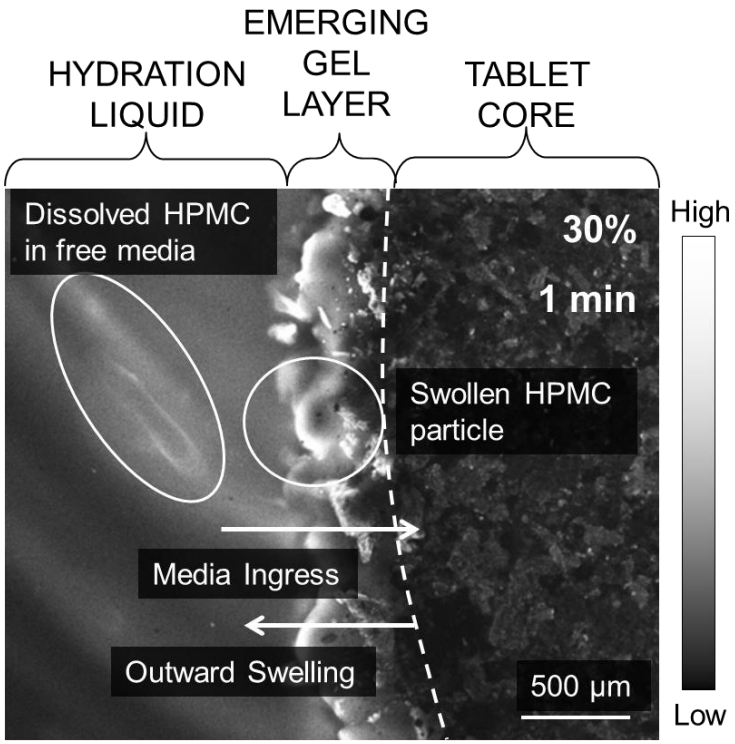

Figure 3.7: Confocal microscopy image of the emerging gel layer in a hydrating HPMC matrix tablet. This image shows a 30% w/w HPMC matrix, hydrated for 1 min in aqueous Congo Red 0.008% w/v. at 37°C. The images are coded for fluorescence intensity from white (highest) to black (lowest) in a continuous greyscale, as indicated by the colour bar on the right. The bright regions indicate areas of high fluorescence, highlighting regions of polymer hydration where the fluorophore has penetrated and bound with the swelling polymer. Ex 488/ Em>510 nm. Scale bar = 500 µm.

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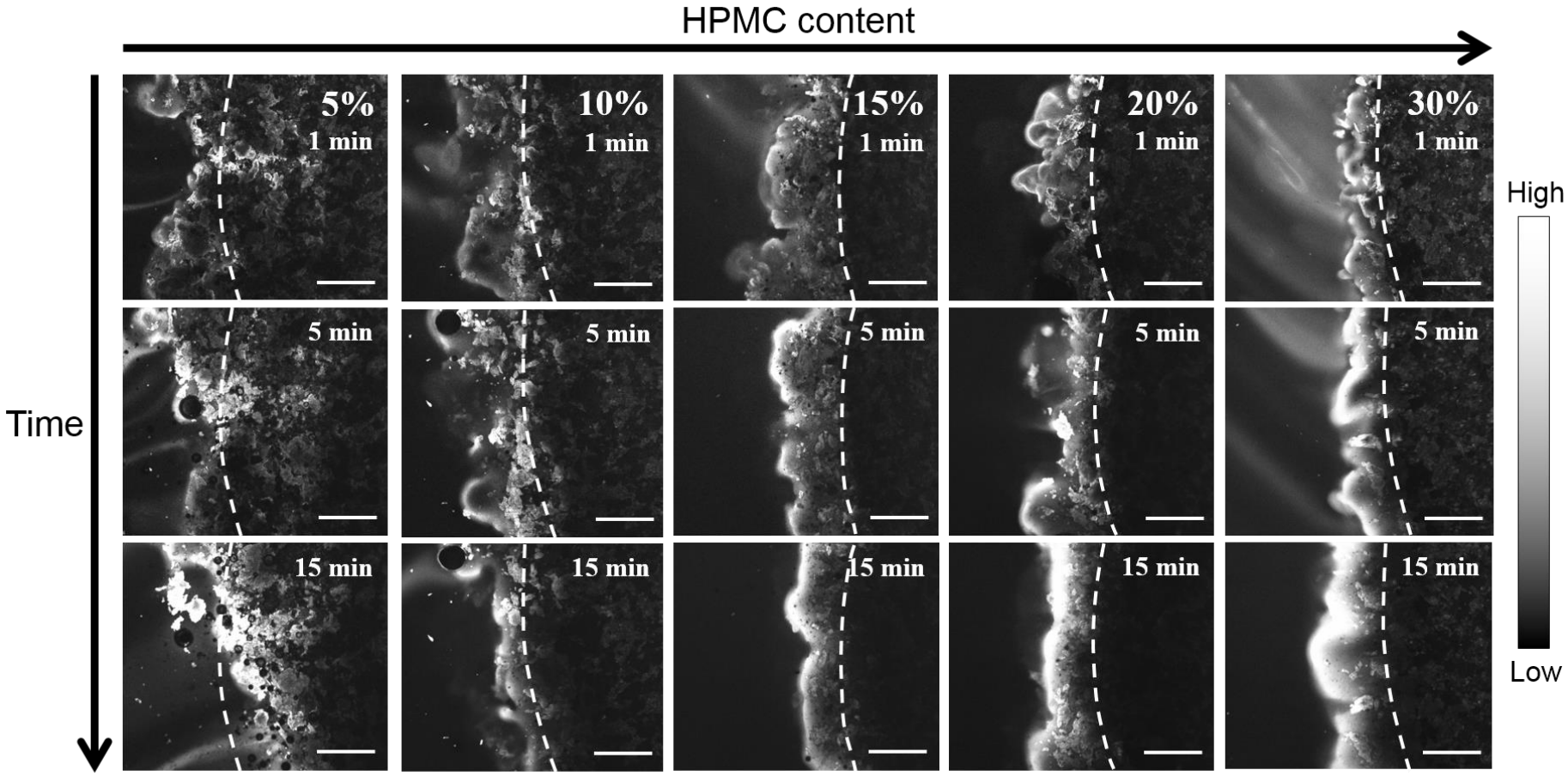

Figure 3.8: Confocal imaging of early gel formation in HPMC matrices with different HPMC contents. Matrix polymer content reported as % w/w HPMC. Hydration fluid: Congo red 0.008% w/v in water at 37°C. Images are coded for fluorescent intensity (highest, white; lowest, black) on a continuous grayscale. White dashed line denotes the dry matrix boundary at t = 0. Ex 488/ Em>510 nm. White scale bar = 500 µm.

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3.4.6 The impact of matrix polymer content on matrix swelling as visualised by time-lapse photography

Figure 3.9 shows the hydration behaviour of HPMC matrices in water as a time series of digital images over 30 minutes.

Matrices containing 30% w/w HPMC maintained a cylindrical shape and the gel layer appeared compact and well-defined throughout the 30 minute hydration period. The matrix swells only slightly in both axial and radial directions over time, and there is no evidence of surface disintegration. In matrices containing 20% or 15% w/w HPMC, the swelling was anisotropic and there was more axial expansion in the first minute than in matrices containing 30% w/w HPMC. The 20% and 15% w/w matrices were more rounded on the corners after one minute hydration, but showed little dimensional change between 5 and 30 minutes. This suggests that the processes of matrix swelling and matrix erosion were occurring at similar rates.

At a matrix polymer content of 10% or 5% w/w, we can see that the tablet reduces in size, both axially and radially, as it hydrates over time. The images also show a build-up of eroded material at the base of the tablet, suggesting surface disintegration has occurred, which may account for why the matrices became smaller over time. The reduction in tablet size is especially clear for the 5% w/w formulation, which appears to split over time. This may suggest that HPMC can act as a disintegrant through swelling, which is uninhibited when the gel layer is incompletely formed.

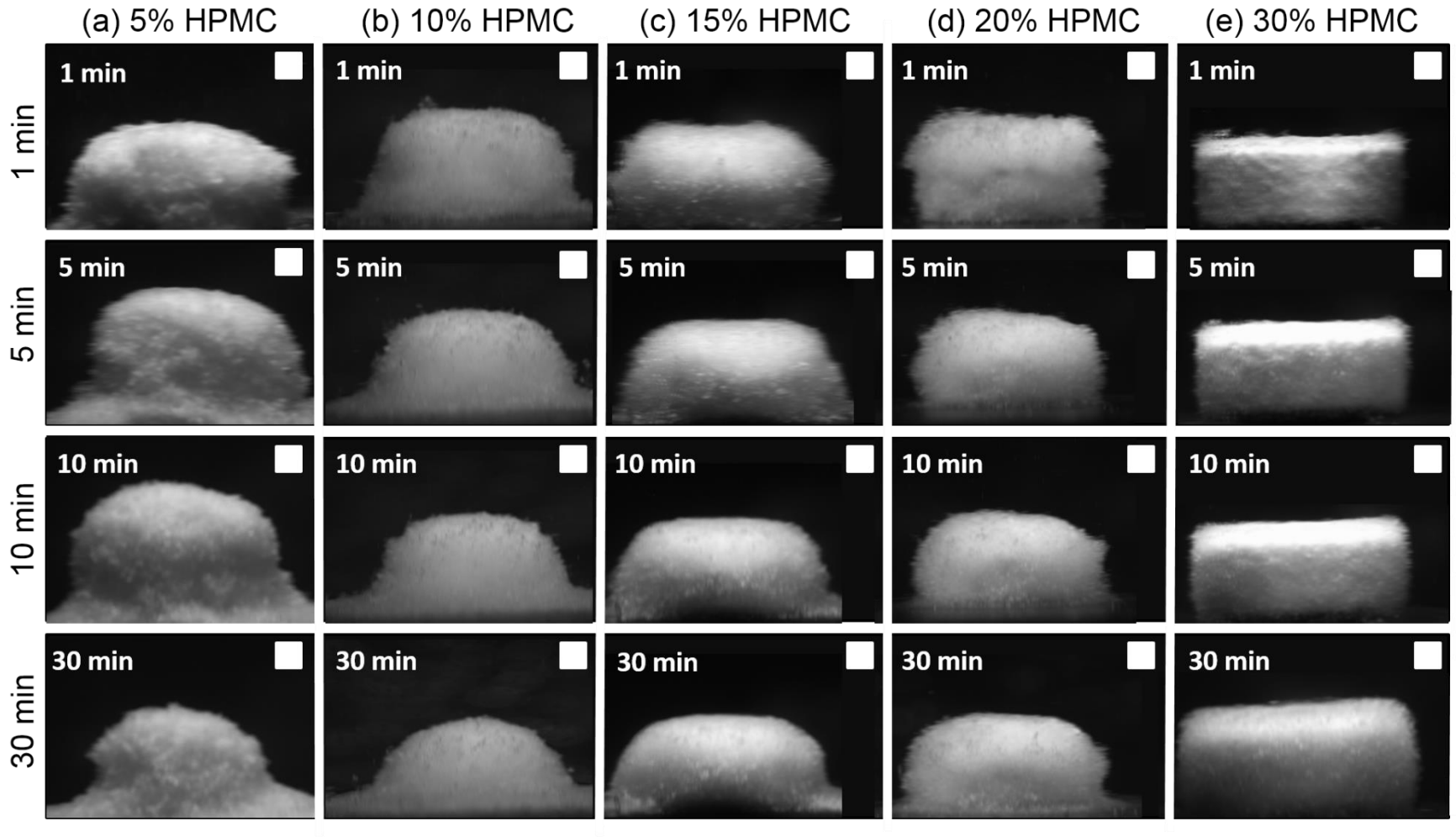


Figure 3.9: Time-lapse photographs of hydrating HPMC matrices with different polymer contents. Matrix polymer content reported as % w/w HPMC. Hydration media: 600 mL water at 37 ± 1 °C under static conditions. The white square is a scale bar of 1 x 1 mm.

3.4.7 Use of the texture analyser to compare gel layer development and crushing force of matrices with respect to polymer content

The aim of texture analysis experiments was to compare the height of the hydrated matrices and the strength of the tablet core. Only matrices with a polymer content from 10 – 30% w/w HPMC were studied as the 5% w/w matrix had shown clear signs of rapid disintegration in Section 3.4.6. An extra matrix at 12.5% w/w was added as this was in the region of the percolation threshold determined in Section 3.4.4. Matrices were pre-hydrated in a USP disintegration apparatus for between 4 min and 2 hours before texture analysis testing, using the methods described in Section 3.3.7.

The texture analyser comprised of a probe which moved downwards towards the matrix, recording the instantaneous distance and force. The surface of the hydrated gel was defined as the point where the mean of 10 force readings (a distance of approx. 0.022 mm) was more than 0.001 N. The height measurement is, therefore, the axial height of the hydrated matrix. Figure 3.10 shows the mean hydrated height for matrices of different polymer contents after hydration for 4 and 24 minutes. After 4 minutes, matrices containing 12.5 to 30% HPMC had swollen from a dry tablet height of between 3.7 and 3.9 mm, to a mean hydrated height between 5.4 and 6.1 mm, an approximate 2 mm increase in axial height. In contrast, the matrices containing 10% HPMC showed negligible swelling, with a mean swollen height of 3.9 mm. At the longer hydration time of 24 min, the 10% matrix had reduced in height to 2.5 mm (a 36% reduction compared to 4 min), whereas matrices containing 12.5%, 15% and 17.5% HPMC showed more modest 8.1%, 9.5% and 9.5% reduction in height respectively. Matrices containing 20% and 30% w/w HPMC showed an even smaller reduction in tablet height between 4 and 24 minutes of 4.4% and 2.9% respectively. The texture analysis measurements correspond with findings from photography studies in Section 3.4.6 and show a dramatic difference in swelling behaviour of 10% and 12.5% w/w HPMC matrices.

The force required to fracture the core of the hydrated matrices can be seen in Figure 3.11. For all formulations, the tablet became weaker with hydration time. Additionally, the lower the HPMC content, the lower is the necessary force to penetrate the tablet core at each time point. Using a different load cell, the breaking strength of the dry tablet was determined as approx. 150 N. The maximum force that the texture analyser could apply with a 5 kg load cell was 58.5 N, and if this force was reached the probe stopped moving. The cores of the 15%, 12.5% and 10% w/w HPMC matrix tablets had breaking forces

below 58.5 N after only 4 minutes of hydration. In the case of 10% w/w HPMC matrices, the breaking force of the tablet dropped to less than 2 N within 4 minutes. In the case of 30% w/w HPMC matrices, the breaking force remained greater than 58.5 N until 8 minutes, when one tablet broke under this force. It is clear that the tablets with higher polymer content retain greater strength for longer hydration periods than those with lower polymer contents.

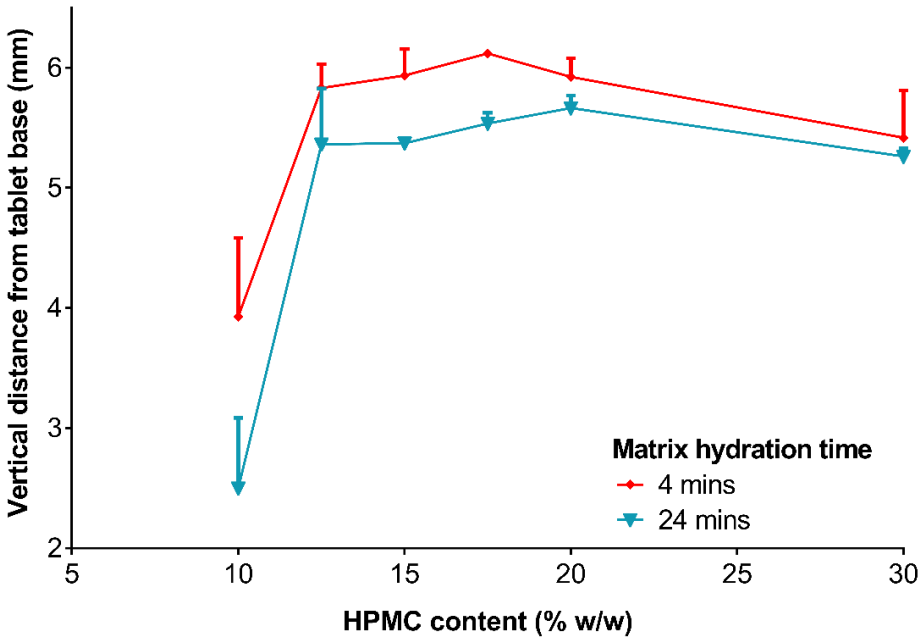


Figure 3.10: Height of hydrated matrices with respect to polymer content, as measured using texture analysis. Matrices hydrated in USP disintegration tester in water (37 °C) for 4 or 24 minutes and probed using Texture Analyser (2 mm Ø diameter probe, top of tablet defined as a force of 0.001N) n=3 + 1 SD.

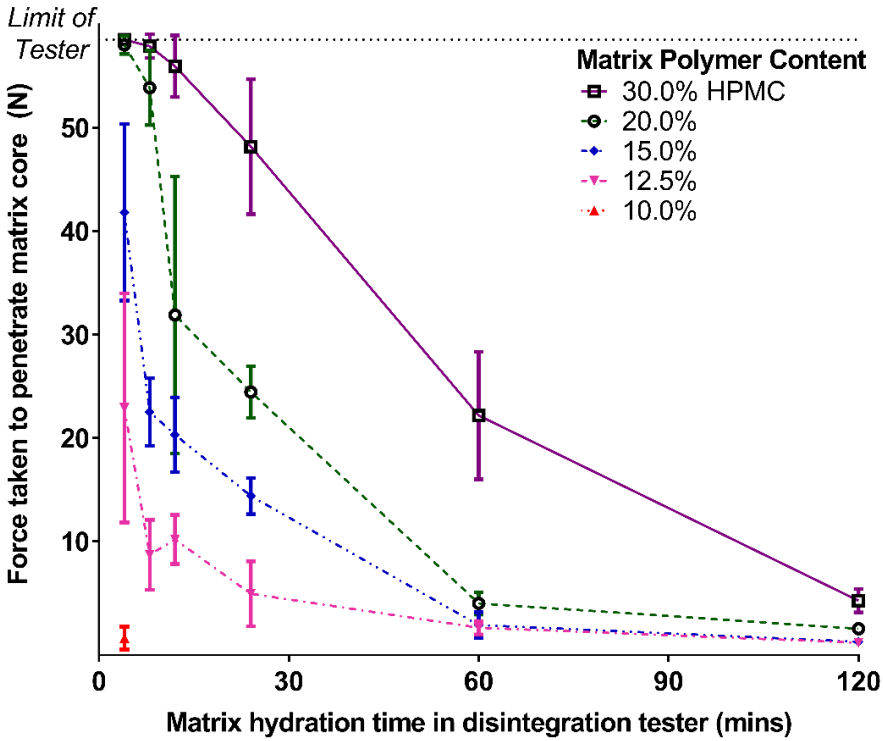


Figure 3.11: The force taken to fracture the HPMC matrix core after hydration in the disintegration tester with respect to polymer content. Matrix polymer content reported as % w/w HPMC. Tablets hydrated in disintegration apparatus for different times before removal and testing using Texture Analyser (2 mm Ø diameter probe) (water, 37 °C, n=3 ± 1 SD.)

3.4.8 Matrix erosion determined by the gravimetric method

Gravimetric methods are often used to measure erosion of hydrophilic matrices, but the main limitation is that we cannot easily determine whether it is the polymer, drug or other excipients that have been lost.

Figure 3.12 shows matrix weight loss, “matrix erosion” expressed as a percentage of the initial tablet weight, with respect to matrix polymer content and hydration time. As expected, matrix erosion increased when the matrices were hydrated for longer. Matrix erosion is in rank order of polymer content, with less erosion when the matrix has a higher polymer content. It is interesting how rapidly weight was lost from the formulations with low polymer content; the 12.5%, 10% and 7.5% w/w formulations exhibited over 50% weight loss within 4 minutes. In contrast, formulations containing 17.5%, 20% and 30% w/w HPMC were less than 50% eroded after 60 minutes. These differences highlight the importance of the rapidly developing gel layer, as a diffusional barrier to prevent excessive ingress of liquid into the tablet. Until the gel layer is formed, a hydrophilic matrix containing high levels of soluble diluents, such as caffeine and lactose in the studied formulations, will rapidly disintegrate as there is no barrier to erosion in this time. For 17.5, 20 and 30% w/w HPMC formulations, the rates of matrix erosion are near linear and have similar gradients between 12 and 60 min, suggesting that the initial burst release of the drug is the primary difference between these formulations.

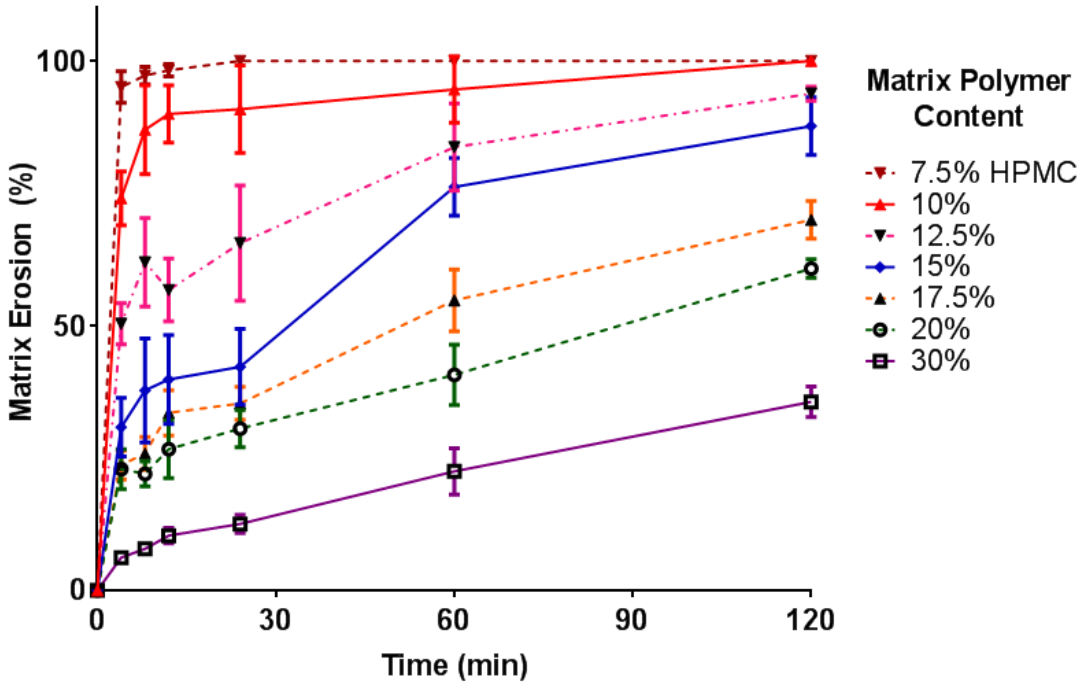


Figure 3.12: Weight loss (erosion, %) of HPMC matrices of different polymer contents with respect to time. Mean (n=6) ± 1 SEM. Matrix polymer content reported as % w/w HPMC. Matrices were hydrated in a USP disintegration apparatus (water at 37 °C) and then dried to a constant weight. Erosion (%) was determined as the difference between the initial dry weight and weight after hydration and drying.

3.5 Discussion

3.5.1 The suitability of standard mathematical models for studying low polymer content matrices

The mathematical models we studied, zero order, first order, Higuchi, Korsmeyer-Peppas and Peppas-Sahlin have been frequently used to describe the release of drug from hydrophilic matrices. However, we must always bear in mind that they were developed on the basis of near-perfect systems, with stipulations and assumptions that in many cases simply do not apply in real world situations. For example in the Higuchi model, there are unrealistic assumptions of negligible swelling of the formulation, perfect sink conditions and limited edge release. The general limitations of the different models have been widely discussed in the literature (Costa and Sousa Lobo, 2001, Siepmann and Peppas, 2001, Siepmann and Siepmann, 2008).

In section 3.4.2, the fitting of dissolution data to five commonly used mathematical models was compared with respect to matrix polymer content. First order equations showed a poor fit to the dissolution data ($r^2 < 0.8$), irrespective of the matrix polymer content, indicating that the content of drug in the formulation was not the main driver of the drug release rate. This is not unexpected given the high aqueous solubility of caffeine. The four other models studied; zero order, Higuchi, Korsmeyer-Peppas and Peppas-Sahlin equations, showed a goodness of fit that was dependent on the polymer content. As the polymer content was increased from 7.5% to 15% w/w, the fit improved from r^2 values of 0.4 - 0.6 to r^2 values over 0.9. Matrices with a polymer content over 15% w/w HPMC had r^2 values exceeding 0.95.

The results suggest that the models do not fully describe drug release from HPMC matrices containing lower polymer contents. This may indicate that there is a degree of immediate release of drug from the dosage form, and with multiple drug release mechanisms occurring simultaneously so that no one mechanism predominates. In any case, results derived from mathematical models should always be interpreted with a degree of caution as the systems under analysis often do not resemble the systems upon which the models were designed. Results from Higuchi, Korsmeyer-Peppas and Peppas-Sahlin models will be used throughout the thesis, as a means to interpret dissolution profiles, but the caveats above must always be borne in mind when using these equations. The parameters of $T_{80\%}$ and DR10min do not rely upon fitting of the

data to a kinetic model, and have been used as simple assessments of extended release and burst release of drug from the matrices respectively.

3.5.2 Effect of polymer content on rate of drug release

The mathematical models all showed that increasing the matrix polymer content decreased the drug release rate, as expected from the literature (Alderman, 1984, Ford et al., 1985a, Ford et al., 1985b, Gao et al., 1996, Sung et al., 1996, Mohamed et al., 2013). It is generally held that at the higher levels of HPMC, there is an HPMC content where further increases in polymer content do not result in substantially slower release (Mitchell et al., 1993d). This was not apparent from the results of our study, probably because the polymer content used was below this upper threshold.

The mechanisms by which increases in polymer content may cause prolongation of drug release is worthy of further discussion. It has been proposed that increasing the content of HPMC in the formulation results in a greater degree of swelling which increases the tortuosity and length of the drug diffusion path, thus slowing the rate of drug release (Wan et al., 1993, Xu and Sunada, 1995). Several groups have shown increasing drug diffusivity within the gel layer as the polymer content decreases which, they say, is the main driver for the increased drug release rates of soluble drug as the matrix polymer content is lowered (Mitchell et al., 1993d, Gao and Fagerness, 1995, Gao et al., 1996). At high loadings of soluble drugs, or where poorly soluble drugs are included, matrix dissolution rate has been reported to determine release rate (Ranga Rao et al., 1990, Skoug et al., 1993, Tahara et al., 1996). Matrix dissolution has been found to be faster as the HPMC content is decreased (Ghori et al., 2014), and therefore both erosional and diffusional rates are expected to increase as the matrix polymer content is lowered. The mechanism of drug release is further discussed in Section 3.5.3.

In the work undertaken in this chapter, we also observed significant burst release of drug from all formulations, with DR10min increasing as the matrix polymer content was lowered. This effect has been reported before, with 10% w/w HPMC matrices showing a much larger initial burst than 20% and 30% w/w matrices (Campos-Aldrete and Villafuerte-Robles, 1997). The initial burst release of the drug, before extended release kinetics ensue can be attributed to the infiltration of the medium into the matrix before the gel layer is fully established. This can be influenced by the presence of soluble excipients, as well as the polymer content of the formulation (Tahara et al., 1995, Ford, 2014). The initial burst occurs from the dissolution of the drug within the outer regions of the matrix before a coherent gel layer diffusion barrier is formed, and further by the

release of dissolved drug within the gel layer whilst the concentration gradient is being established.

3.5.3 Effect of polymer content on the mechanism of drug release

All formulations in this study exhibited a Korsmeyer-Peppas release exponent (*n)* of between 0.59 and 0.74 irrespective of the matrix polymer content. This suggests an anomalous release mechanism, whereby drug release is due to a mixture of diffusional and erosional processes. A mixed release mechanism would be expected for the release of a soluble drug such as caffeine, as the drug would be expected to be able to diffuse through the gel layer throughout matrix hydration. It has previously been reported that HPMC content has little impact on diffusional exponent *n*, but can result in large changes in kinetic rate (Fu et al., 2004), similar to the findings of our study. In our study, there was a small decrease in *n* value in matrices containing less than 12.5% w/w HPMC. This might suggest a higher proportion of diffusion-led release, but overall there appears to be no clear change in the drug release mechanism with respect to matrix polymer content.

The results of the gravimetric analysis (Section 3.4.8) suggested that the rate of matrix erosion was increased as the polymer content was lowered. This corresponds to findings in other studies (Ghimire et al., 2010, Ghori et al., 2014). In our study, higher levels of erosion were observed for 5 and 10% w/w HPMC matrices than for matrices containing 15 to 30% w/w HPMC in photographic images (Section 3.3.6). Our gravimetric analysis similarly showed that matrices containing 5 to 12.5% w/w HPMC eroded by over 50% after only 4 minutes of hydration. This suggests that a significant amount of erosion is able to occur before the gel layer forms if the matrix contains a lower polymer content, and explains the high levels of drug release during the initial burst. This could be one of the major limitations of using low levels of a polymer as in clinical applications, this could result in a bolus dose of drug being released and potential toxicity to the patient.

Whilst there is some apparent discrepancy between the mathematical analysis, which suggests greater levels of diffusion, and physical erosion measurements which suggest higher erosion rate as the matrix polymer content decreases, it is likely that both rates increase when the polymer content is lowered, resulting in an overall increase in drug release.

Early work by Ford et al. found that promethazine matrices containing lower polymer contents showed deviation from root time kinetics, unlike matrices with higher polymer contents. They suggested this meant that drug release could also be attributed in part to attrition of the matrix (Ford et al., 1985a). Unusually, similar results were not found with low polymer content formulations of aminophylline or propranolol (Ford et al., 1985b). There are other contrasting reports elsewhere in the literature; for example, it has been reported that the mechanism of indomethacin release from matrices became more diffusion controlled as the polymer content was lowered to 20% w/w (Xu and Sunada, 1995). However, Ford et al. found no significant changes in *n* value for similar indomethacin formulations when using a higher molecular weight HPMC at a higher HPMC content (> 50% w/w) (Ford et al., 1987). It may be that the higher polymer content in the Ford studies masked changes in the mechanism that may be apparent at lower polymer contents. Many other studies conclude that the mechanism of drug release from hydrophilic matrices depends, to a greater extent, on the solubility of the drug than changes in matrix polymer content (Ford et al., 1987, Hogan, 1989).

3.5.4 Effect of polymer content on gel layer formation

The HPMC content of the matrices appeared to influence the formation of the gel layer. This was seen in confocal (Section 3.4.5) and photographic (Section 3.4.6) studies. When the matrix polymer content was low (5 - 10% w/w HPMC), the gel layer was very thin and irregular. Texture analysis results (Section 3.4.7) showed that water could rapidly penetrate into the matrix within 4 minutes, which resulted in the lack of a breakable core. At intermediate polymer contents (15 - 20% w/w HPMC), the gel layer can be clearly distinguished in the confocal images and it remained a consistent size over the first 15 minutes. In a 30% w/w HPMC matrix, the gel layer continues to swell over time with outward swelling of the tablet. Several groups have reported that a higher rate of matrix swelling is observed as the HPMC content is increased (Wan et al., 1993, Gao et al., 1996). It has previously been reported that HPMC matrices exhibit anisotropic swelling with a preference for axial swelling (Colombo et al., 1990, Papadimitriou et al., 1993, Gao et al., 1996), and matrices in this study showed a similar result in photography images. This can be explained by the release of stored elastic energy from uniaxial compression of the tablet during manufacture.

Whilst other groups have used techniques such as magnetic resonance imaging (MRI) (Fyfe and Blazek-Welsh, 2000, Baumgartner et al., 2005, Chen et al., 2010), Fourier transform infrared spectroscopy (FTIR) (Kazarian and van der Weerd, 2008, Wray et al., 2013), ultrasound (Konrad et al., 1998, Leskinen et al., 2011), near infrared (IR)

spectroscopy (Avalle et al., 2011, Avalle et al., 2013) and confocal laser scanning microscopy (Bajwa et al., 2006) to assess the dynamic swelling / gel layer formation of specific matrix formulations, the confocal study in this thesis is one of the first to image the formation of the gel layer of several matrices with respect to matrix polymer content.

3.5.5 Explaining the effect of matrix polymer content using percolation theory

The mathematical estimation of percolation threshold, calculated from drug release data in USP apparatus II, has estimated a percolation threshold of approximately 11% w/w HPMC (Section 3.3.4). Correspondingly the confocal imaging shows that there are clear differences in gel layer formation between matrices containing 10 and 15% w/w HPMC, values which sit either side of the estimated threshold concentration. Similar findings were seen in photographic images (Section 3.4.6) and texture analysis results (Section 3.4.7), where 10% w/w HPMC matrices displayed substantial matrix erosion and minimal swelling in comparison with the 12.5% w/w HPMC matrices.

According to percolation theory, if the matrix polymer content is above the polymer percolation threshold a continuous phase of polymer throughout the gel layer is expected. As a result, extended drug release kinetics will be observed. To date, there has been limited physical evidence to support this theory in hydrophilic matrices, but the confocal images above provide some direct physical evidence of the percolation threshold, perhaps for the first time. Confocal imaging showed that sufficient polymer content was key to the establishment of a surface barrier, which is formed due to water uptake by the surface polymer particles, which then undergo sufficient swelling, attachment and coalescence to form a continuous gel layer. This must happen at the very earliest stages of matrix hydration, and it must dominate over the competing processes of capillary liquid penetration of the matrix and the dissolving of soluble components, both of which would contribute to disintegration at the matrix surface. It can be seen that when the matrix polymer content is 10% w/w or below, water can rapidly penetrate into the matrix, to the extent that the core becomes very soft (< 2 N) in 4 minutes. We predict that this is a result of the lack of formation of a rate limiting gel layer within this time frame.

3.6 Conclusions

The polymer content of HPMC matrices has a clear impact on the rate of drug release, which accelerates as the polymer content is reduced. According to Korsmeyer-Peppas and Peppas-Sahlin modelling, the increase in release rate does not appear to be the result of a dramatic change in the release mechanism from erosion to diffusion (or vice-versa). All results highlight a discontinuity between 10 and 15% HPMC, which directs us towards a failure mechanism suggested by percolation theory. This theory suggests that at low polymer levels, the distance between hydrating HPMC particles is too great for them to meet on swelling and to mutually attach. This results in excessive water ingress into the matrix before the gel layer can from a coherent diffusion barrier. During this delay, rapid dissolution and diffusion of drug and soluble excipients can occur with the result of significant erosion of the matrix.

The drug release rate decreases as the polymer content is increased across all the polymer contents studied (5 – 30%), and extended drug release kinetics were still possible below the estimated percolation threshold. At sub percolation threshold concentrations, we would expect polymer-rich regions to gel, but into a discontinuous layer with diffusion barrier weaknesses in areas where the polymer content is lower. This would explain why matrices with polymer contents below the percolation threshold exhibit more variable release profiles. The hydrated polymer would, however, also act to retard complete tablet disintegration, as the swollen regions of HPMC would act as an adhesive to other tablet excipients. The effect would be the opposite of that seen with tablet disintegrant.

Changing the matrix polymer content remains a useful tool in the formulation of HPMC matrices, however, to avoid failure of these formulations, it is vital to ensure that the polymer content is above the percolation threshold. In addition, a major weakness of low polymer content formulations appears to be the rapid release of drug through matrix erosion in the first 5 minutes of dissolution. This has a dramatic influence on the overall release profile.

The next chapter aims to explore how matrix polymer content influences drug release in non-standard dissolution conditions, to further understand the liabilities of using low polymer content HPMC matrices.

Chapter 4
Examining drug release in challenging dissolution environments

4.1 Introduction

The importance of the HPMC content in enabling extended drug release from matrix tablets has been discussed in the previous chapter (Chapter 3). We established experimentally that the matrix polymer content must be above the percolation threshold (% w/w) to ensure that a continuous, rate limiting gel layer is formed. The percolation threshold was estimated at 12.6% v/v of HPMC for the formulations studied. HPMC manufacturers recommend that matrices should be formulated with a polymer content of 30% w/w and/or 10% higher than the percolation threshold in order to ensure reliable drug release (Levina and Rajabi-Siahboomi, 2014). In some cases this is not always practical.

The drug release kinetics of HPMC matrices are known to be affected by *in-vitro* dissolution conditions, such as the presence of salts in the dissolution media (Section 1.4.2.1) and the hydrodynamics of dissolution (Section 1.4.2.2). In this chapter, experiments are undertaken to understand how the factors influence drug release kinetics with respect to the matrix polymer content. We hoped that these studies would enable us to understand the sensitives that are introduced when the matrix polymer content is lowered.

4.2 Aims

The aims of this chapter are:

- To investigate the influence of trisodium citrate (TSC) and sodium chloride (NaCl) on HPMC matrices with respect to lower polymer content,
- To study how polymer content influences the sensitivity of the matrix tablet to changes in hydrodynamic conditions, such as a change in USP II paddle speed.
- Develop a screening test to explore the dissolution sensitivity of subsequent formulations.

4.3 Materials and Methods

4.3.1 Materials

Full details of the materials used are described in Appendix 1. The HPMC used was METHOCEL™ K4M CR premium (Colorcon, Dartford, UK).

4.3.2 Manufacture of HPMC matrices

The matrix tablet formulations are listed in Table 4.1. HPMC content was varied between 7.5% and 30% w/w. The manufacturing methods are described in Section 2.1. Tablet hardness was between 2.36 and 2.76 MPa for all formulations.

	Quantity of excipient (% w/w)						
HPMC K4M	7.5	10	12.5	15	17.5	20	30
Caffeine	10	10	10	10	10	10	10
Lactose	54.7	53.0	51.3	49.7	48.0	46.3	39.7
MCC	27.3	26.5	25.7	24.8	24.0	23.2	19.8
MgSt	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Table 4.1: HPMC matrix tablet formulations. Caffeine was sieved through a 125 µm sieve, other excipients as received. Materials were blended for 15 minutes with magnesium stearate added for the final 2-minute lubrication step. Tablets were 250 ± 5 mg (8 mm Ø, flat-faced, round) and manufactured using direct compression at 150 MPa.

4.3.3 USP apparatus II (paddle) dissolution testing

Drug release kinetics were determined in 900 mL de-gassed, de-ionised media 37 ± 0.5 °C in USP apparatus II (paddle). Salt concentration and paddle speed were adjusted according to the objectives of each experiment. Caffeine was quantified at a UV absorbance of λ = 273 nm as fully described in Section 2.3.2. Dissolution data was characterised using the mathematical models discussed in Section 2.3.3.

Trisodium citrate (TSC) and sodium chloride (NaCl) were selected as model salts to provide this ionic challenge. Both are commonly found in foods, and trisodium citrate is additionally often found in medicines as a buffering agent and as a treatment in cystitis products. Both salts contain sodium, but it has been found that the effects of anions are

more important than cations in salting out polymers (Mitchell et al., 1990, Nakano et al., 1999). As trisodium citrate contains a trivalent anion and 3 times the number of sodium ions per mol, it would be anticipated that trisodium citrate will be more potent than sodium chloride at 'salting out' HPMC.

4.3.4 Manufacture of HPMC solutions

HPMC solutions were manufactured by high shear mixing as described in Section 2.5.1**.**

4.3.5 Determination of HPMC cloud point temperature by turbidimetry

The cloud point temperature was measured using the method described in Section 2.5.2. The cloud point temperature was taken as the temperature at which the transmission of light had dropped to 50% of the original transmittance.

4.3.6 Confocal microscopy imaging of early gel layer formation

Imaging of early gel formation was undertaken in 0.008% w/v Congo red using a Bio-Rad MRC-600 confocal microscope (Bio-Rad, Hemel Hempstead, UK). The tablet was held between two Perspex® discs allowing imaging of the matrix from overhead, to capture the processes of gel layer formation at the radial edge of the tablet. A series of images were obtained for the first 15 minutes of hydration. Full methods are described in Section 2.3.5.

4.3.7 Time lapse photography of hydrating matrices

Matrices, fixed to a Perspex® stand and held in a water-jacketed beaker were photographed every 30 seconds from the addition of media at 37 ± 1 °C. A series of images were obtained for the first 30 minutes of hydration. Full methods are described in Section 2.3.6.

4.3.8 Measurement of core breaking force using the Texture Analyser

The tablets were pre-hydrated in USP disintegration apparatus (as described in Section 3.3.7) or USP I dissolution apparatus (basket, 100 RPM) and probed using the texture analyser according to the methods in Section 0.

4.4 Results and Discussions

The chapter is formatted into 4 sections.

Section A	The effect of **salts**	4.4.1 - 4.4.2
Section B	The effect of **hydrodynamic forces**	4.4.3 - 4.4.4
Section C	The **combined** influence of salts and hydrodynamics	4.4.5 - 4.4.6
Section D	Development of an *in-vitro* dissolution **screening tool**	4.4.7

Section A:

The influence of salts on drug release from low polymer content HPMC matrices

4.4.1 Results: The effect of salts on HPMC matrices

In this section we investigated how two ionic salts, trisodium citrate and sodium chloride, can impact on polymer behaviour, matrix swelling and drug release. Upper salt concentrations were selected so that failure of matrices was observed. As discussed in the thesis introduction (Section 1.4.2.1), the total ionic concentration of the stomach is not thought to be higher than 0.2 M, comprising of a combination of different salts. The bio-relevance of the presented results is discussed in Section 4.4.2.4.

4.4.1.1 Extended release properties of HPMC matrices with respect to salt concentration

Figure 4.1 and Figure 4.2 show how caffeine is released from HPMC matrices in USP dissolution apparatus II as a function of increasing trisodium citrate (TSC) (Figure 4.1) or sodium chloride (NaCl) (Figure 4.2) concentration in the dissolution medium. The polymer content of the matrix tablets ranged from 7.5% to 30% w/w HPMC. Dissolution curves for 7.5, 10, 12.5, and 15% w/w HPMC matrices are shown the first 4 hours of release, and those for 20 and 30% w/w HPMC matrices shows the first 6 hours of caffeine release data.

Trisodium citrate (TSC) concentration was varied from 0.0 to 0.2 M. Figure 4.1 shows how in water and 0.05 M TSC, drug release was similar with respect to matrix polymer content. For matrices containing 10, 12.5, 20 and 30% w/w HPMC, drug release was also similar in 0.1 M TSC. When the TSC concentration was increased to 0.15 M and above, the drug release was faster, with more than 80% drug released in the first 30 minutes.

Figure 4.2 shows how increases in sodium chloride (NaCl) concentration from 0.0 to 1.0 M elicited a similar response. Drug release changed little in dissolution media containing water to 0.6 M NaCl, with respect to matrix polymer content. In addition, little change in drug release was seen in 0.7 and 0.8 M when matrices contained a polymer content between 7.5 and 15% w/w HPMC. A clear increase in the caffeine release rate was observed when the salt concentration increased to 1.0 M NaCl. More than 80% drug was released in 30 minutes for all formulations.

Formulations containing 20% or 30% w/w HPMC show a different response to the intermediate concentrations of 0.7 M and 0.8 M NaCl than the formulations containing 15% w/w HPMC or less. Figure 4.2(e) and (f) show that the first 1 hour of drug release

is similar to when the dissolution media has a lower salt concentration (0.6 M or below). However, the drug release rate then accelerates with a sharp increase in the slope of the dissolution curve for 20% and 30% w/w matrices in 0.8 M NaCl. A similar increase is seen after 3 hours for 30% w/w HPMC matrices in 0.7 M NaCl.

The time taken for 80% caffeine to be released ($T_{80\%}$) was taken as a single value which represents the extended release properties of the formulation. Figure 4.3 and Figure 4.4 show how the $T_{80\%}$ of HPMC matrices is related to the concentration of salt in the dissolution media. Matrices tested in water show a rank ordering of $T_{80\%}$ values, which is related to the matrix HPMC content, as discussed in Section 3.4.1. As the salt concentration progressively increased to 0.1 M (TSC) and 0.6 M (NaCl), little change is seen in the $T_{80\%}$ values. However, when the salt concentration increased further (above 0.8 M for NaCl, 0.15 M for TSC), a significant drop in the $T_{80\%}$ value is seen for all formulations. Beyond these salt concentrations, the $T_{80\%}$ values are less than 30 minutes for all formulations. The concentration of the salts which induced failure of the HPMC matrices (termed the *SCrit*) was 0.15 M for TSC and 0.8 - 1.0 M NaCl.

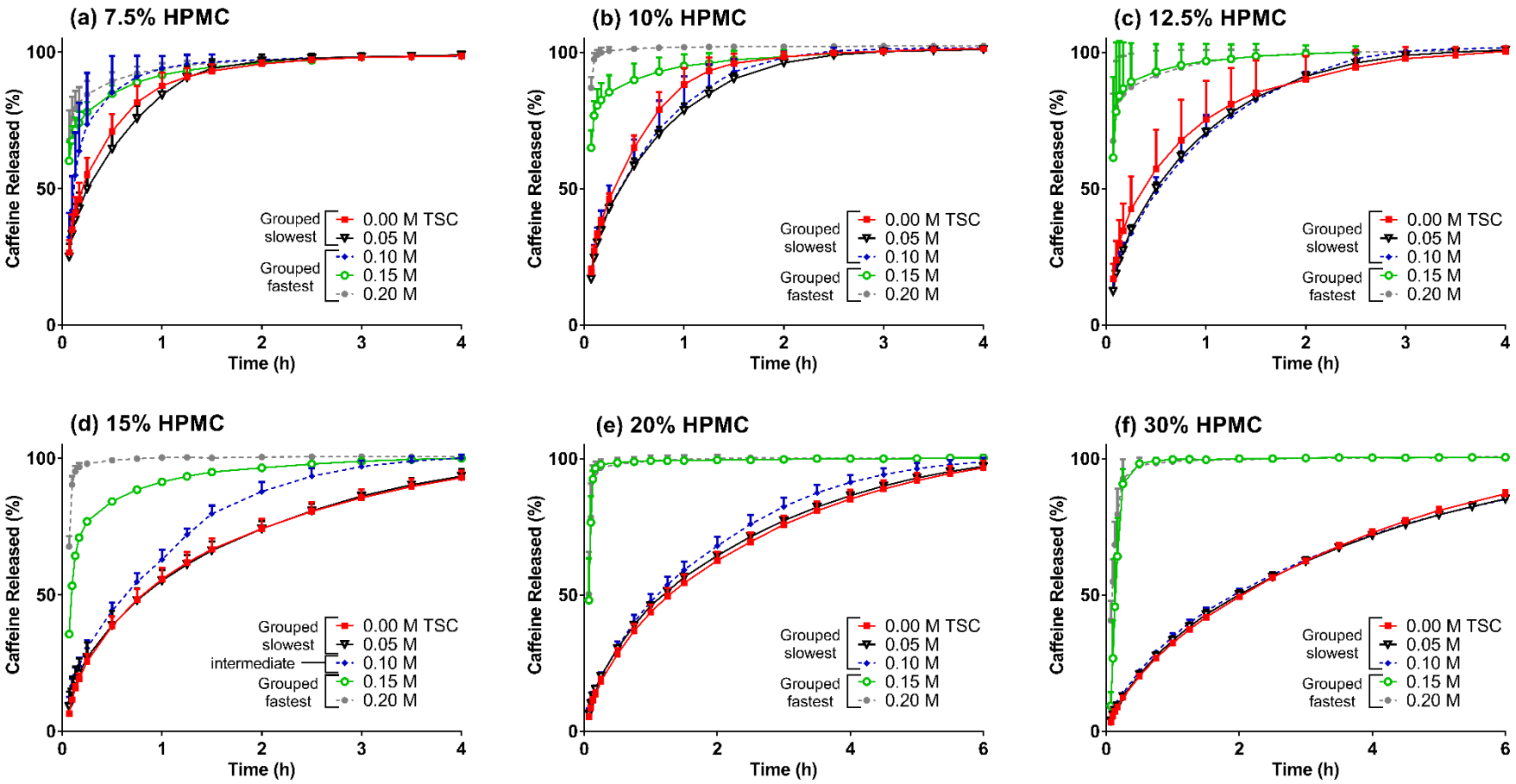


Figure 4.1: Release of caffeine from HPMC matrices as a function of trisodium citrate concentration for formulations containing different HPMC contents. Figures over different time frames of either 4 or 6 hours. HPMC contents, reported in % w/w, were (a) 7.5% HPMC, (b) 10% HPMC, (c) 12.5% HPMC, (d) 15% HPMC, (e) 20% HPMC and (f) 30% HPMC.USP apparatus II, 50 RPM, 900 mL, 37 ± 0.5 °C. Mean (n=3) + 1 SD.

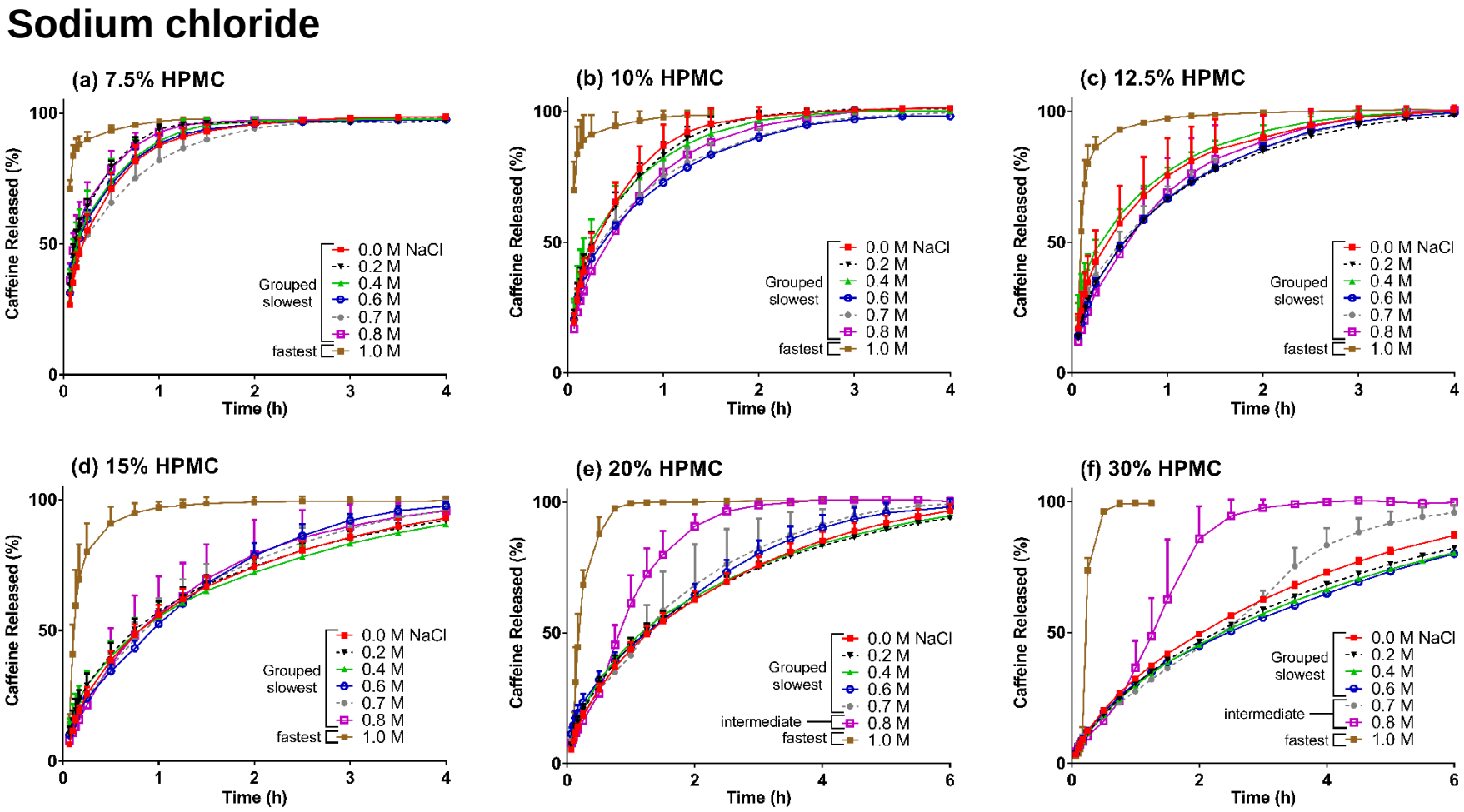


Figure 4.2: Release of caffeine from HPMC matrices as a function of sodium chloride concentration for formulations containing different HPMC contents. Figures over different time frames of either 4 or 6 hours. HPMC contents, reported in % w/w, were (a) 7.5% HPMC, (b) 10% HPMC, (c) 12.5% HPMC, (d) 15% HPMC, (e) 20% HPMC and (f) 30% HPMC. USP apparatus II, 50 RPM, 900 mL, 37 ± 0.5 °C. Mean (n=3) + 1 SD.

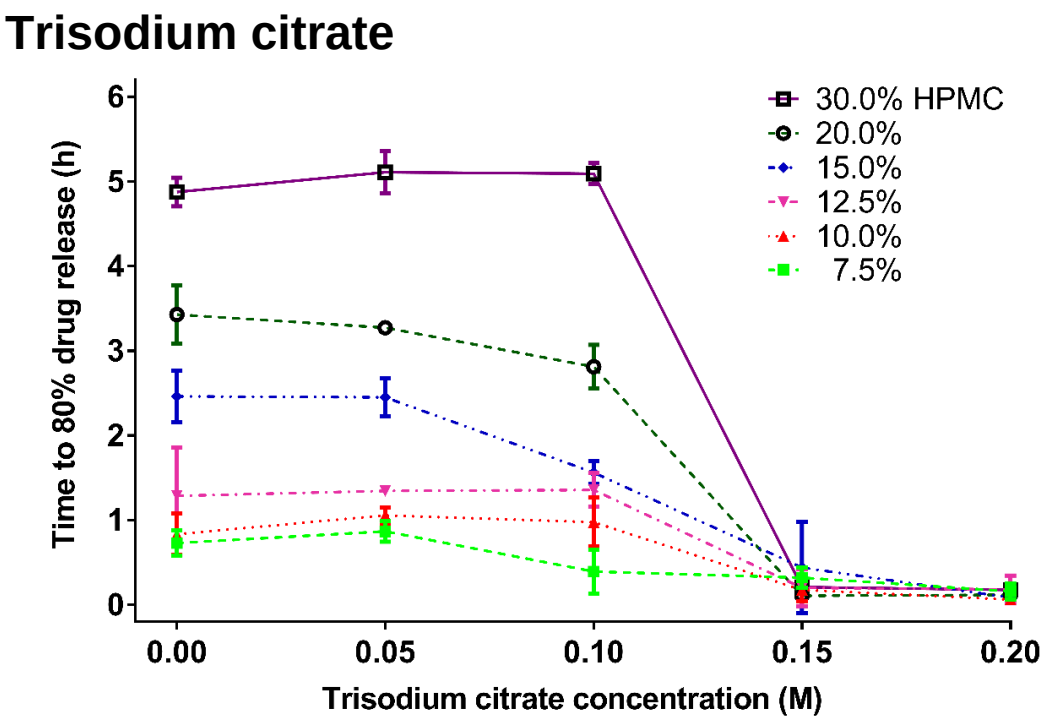


Figure 4.3: Time for 80% caffeine release from HPMC matrices as a function of trisodium citrate concentration and matrix HPMC content. Matrix polymer content reported as % w/w HPMC. Dissolution in USP apparatus II, 50 RPM, 900 mL, 37 ± 0.5 °C. Mean (n=3) + 1 SD

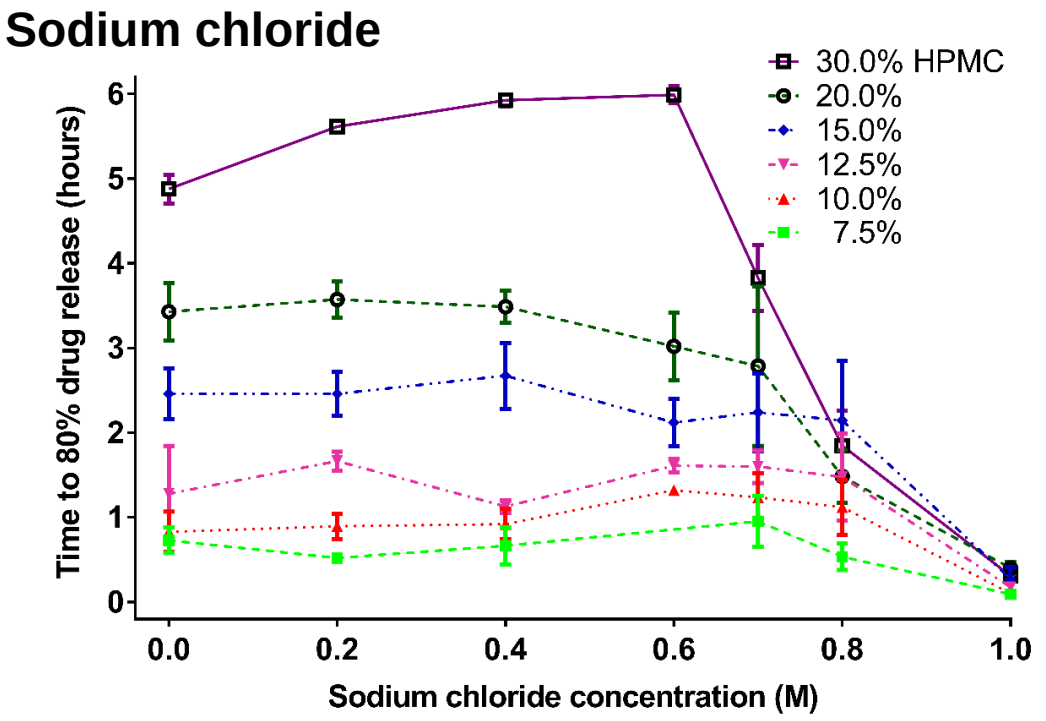


Figure 4.4: Time for 80% caffeine release from HPMC matrices as a function of trisodium citrate concentration and matrix HPMC content. Matrix polymer content reported as % w/w HPMC. Dissolution in USP apparatus II, 50 RPM, 900 mL, 37 ± 0.5 °C. Mean (n=3) + 1 SD

4.4.1.2 The effect of salts on the cloud point temperature of HPMC

Figure 4.5 shows the cloud point temperature (CPT) of 1% w/v HPMC K4M solutions containing trisodium citrate or sodium chloride. It can be seen that as the salt concentration was progressively increased, the CPT decreased and that TSC caused a greater drop in CPT than NaCl at similar molarities. The gradient of the line (ΔCPT) is a measure of the potency of the salt to depress the cloud point of HPMC and was -196.75 $°C.M^{-1}$ (SEM = 7.14 $°C.M^{-1}$) for TSC and -22.91 $°C.M^{-1}$ (SEM = 7.86 $°C.M^{-1}$) for NaCl. By this measure, TSC appeared to be approximately 8.5 times more potent at depressing the CPT than NaCl.

Figure 4.6 shows the relationship between polymer solution concentration and CPT in the presence of NaCl. The gradients at the different concentrations studied (ΔCPT ± SEM) of -23.43 ± 0.59 $°C.M^{-1}$, -23.45 ± 0.88 $°C.M^{-1}$ and -23.35 ± 0.59 $°C.M^{-1}$ were similar ($p = 0.9942$), whereas the intercepts were statistically different ($p = 0.0014$). The actual differences were only modest (74.21 ± 0.31 °C, 72.97 ± 0.46 °C and 72.02 ± 0.31 °C respectively) and it is unlikely that these differences would manifest as important differences in solution behaviour.

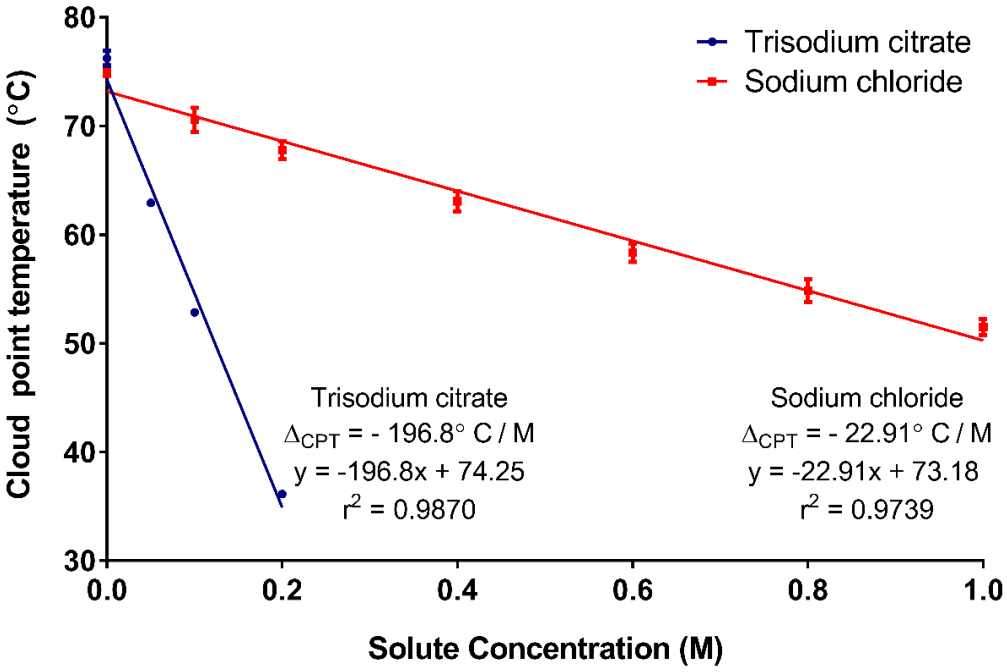


Figure 4.5: The cloud point temperature of 1% w/v HPMC solutions with respect to solute concentration. The HPMC is Methocel™ K4M. Cloud point temperature determined by a drop in light transmission of 50%. Mean (n=3) + 1 SD

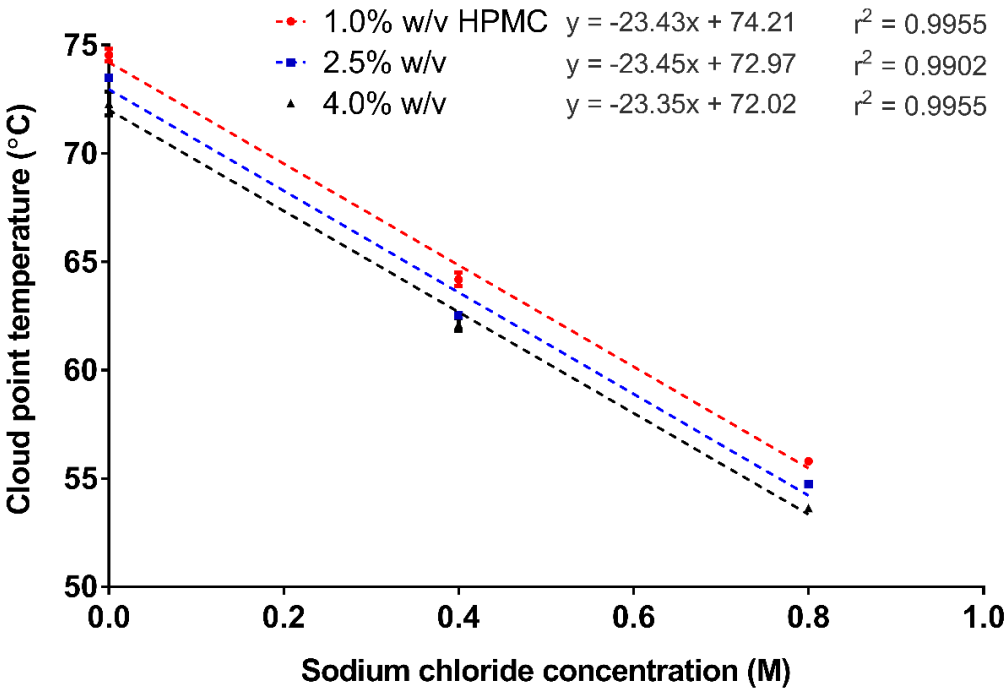


Figure 4.6: The cloud point temperature of HPMC K4M solutions of varying concentration (w/v) with respect to increasing concentration of sodium chloride. The HPMC is Methocel™ K4M. Cloud point temperature determined by a drop in light transmission of 50%. Mean (n=3) + 1 SD.

4.4.1.3 Early gel layer formation in the presence of salt

Figure 4.7 and Figure 4.8 show confocal microscopy images of early gel layer development, in matrices containing 30% and 15% w/w HPMC, in hydration media containing trisodium citrate.

In the absence of TSC, both 30 and 15% w/w matrix tablets show the previously reported pattern of hydration and gel layer formation described in Section 3.3.5. In both formulations, the gel layer forms quickly, with limited gel layer growth after the first minute. The bright outer surface of the gel and limited fluorescence within the matrix tablet suggests Congo red can no longer diffuse into the matrix. This suggests the rapid formation of a rate controlling barrier.

In contrast, in 0.1 M TSC both formulations show a large and irregular gel layer about twice the thickness of the formulations tested in water. The gel layer shows high brightness throughout, indicating that Congo red solution can penetrate this gel layer and matrix. This may be because the gel diffusion barrier takes longer to form, and there is time for the Congo red solution to penetrate further into the matrix. Alternatively, it may suggest that the resultant gel layer provides less of a diffusional barrier.

In 0.2 M TSC matrices show significant swelling, and for 30% w/w matrices, this swelling continues throughout the 15-minute timescale of the experiment. In the case of the 15% w/w matrix tablet, fluorescence is seen inside the initial dry periphery which suggests that the hydration medium is able to diffuse into the core of the tablet and that the gel layer that is formed is insufficient to control media penetration.

Figure 4.9 and Figure 4.10 show early gel layer development for matrices containing 30% and 15% w/w HPMC, in sodium chloride media. Gel formation in 0.2 M NaCl appears to be similar to that in water as there is a similar gel layer thickness. However, the outer edge of the gel layer formed in 0.2M NaCl is not as smooth as the gel layer formed in water. In 0.8 M and 1.0 M NaCl, the matrix containing 30% w/w HPMC exhibits substantial gel layer swelling between 1 minute and 5 minutes, suggesting there is a delayed swelling of the matrix that is not apparent in the 15% w/w HPMC formulations. The matrix containing 15% w/w HPMC swells beyond the field of view when hydrated in 1.0 M NaCl, indicating rapid penetration of medium through the surface gel layer with no delay in swelling. In contrast to 15% w/w HPMC matrices exposed to 0.2 M TSC, none of the matrices in NaCl shows the ingress of water beyond the initial dry boundary.

The highest concentrations of salts used in these imaging studies were 0.2 M TSC and 1.0 M NaCl. These concentrations were selected because they caused failure of all formulations under USP II dissolution testing. In the confocal images, complete failure of gel layer formation was not seen, perhaps with the exception of the 15% w/w HPMC matrix in 0.2 M TSC, where no apparent gel layer was established. This may be because the media is static under confocal imaging so there are no erosional forces acting on the gel layer. In addition, matrices are only being hydrated at the rounded edge, limiting the matrix surface area available for liquid ingress. This may be why concentrations that cause failure in dissolution testing do not result in the failure of gel layer development in these confocal microscopy experiments.

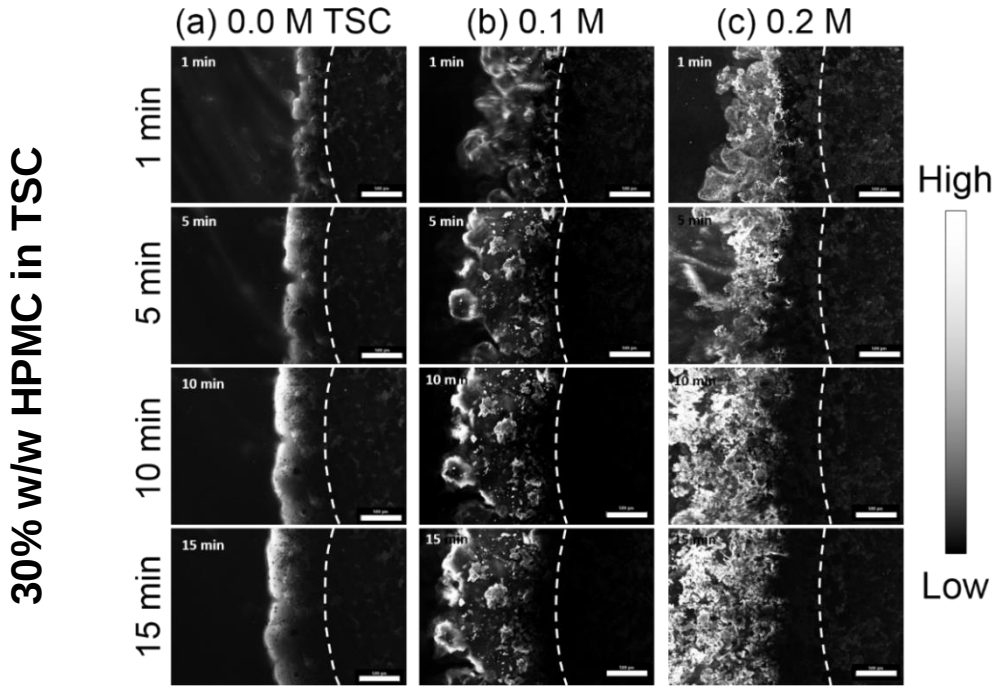


Figure 4.7: Early gel layer formation at the boundary of hydrating 30% w/w HPMC matrices as a function of time and trisodium citrate concentration. Confocal fluorescence imaging at Ex 488/Em >510 nm. Experiments conducted at 37 ± 1 °C using trisodium citrate media containing 0.008% w/v Congo red as a visualisation aid. Dotted white lines represent the dry matrix boundary at t=0 minutes. Scale bar = 500 µm.

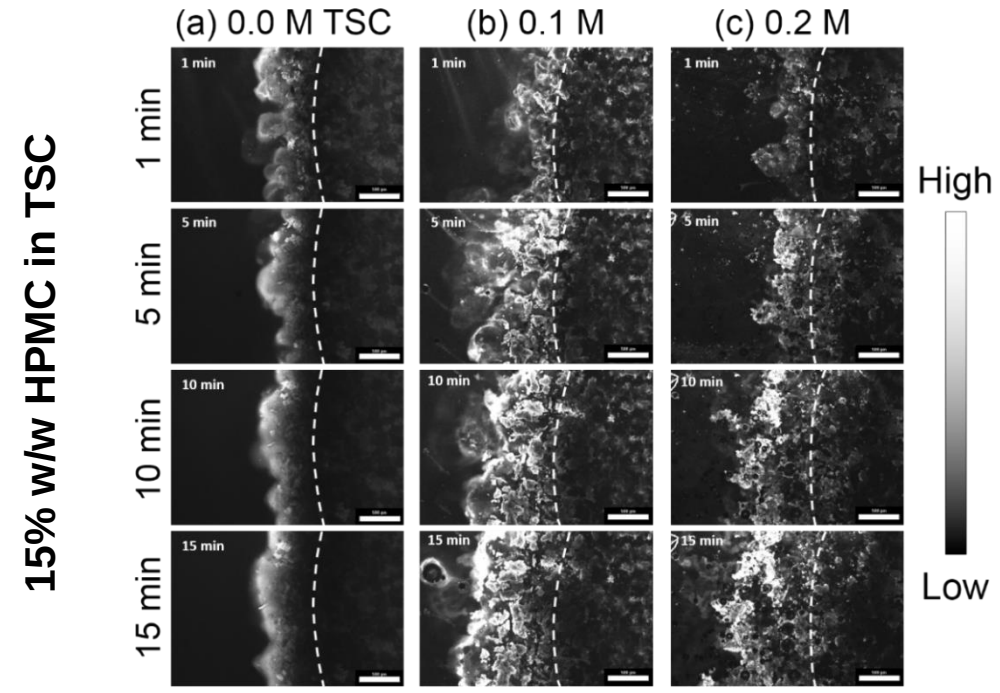


Figure 4.8: Early gel layer formation at the boundary of hydrating 15% w/w HPMC matrices as a function of time and trisodium citrate concentration. Confocal fluorescence imaging at Ex 488/Em >510 nm. Experiments conducted at 37 ± 1 °C using trisodium citrate media containing 0.008% w/v Congo red as a visualisation aid. Dotted white lines represent the dry matrix boundary at t=0 minutes. Scale bar = 500 µm.

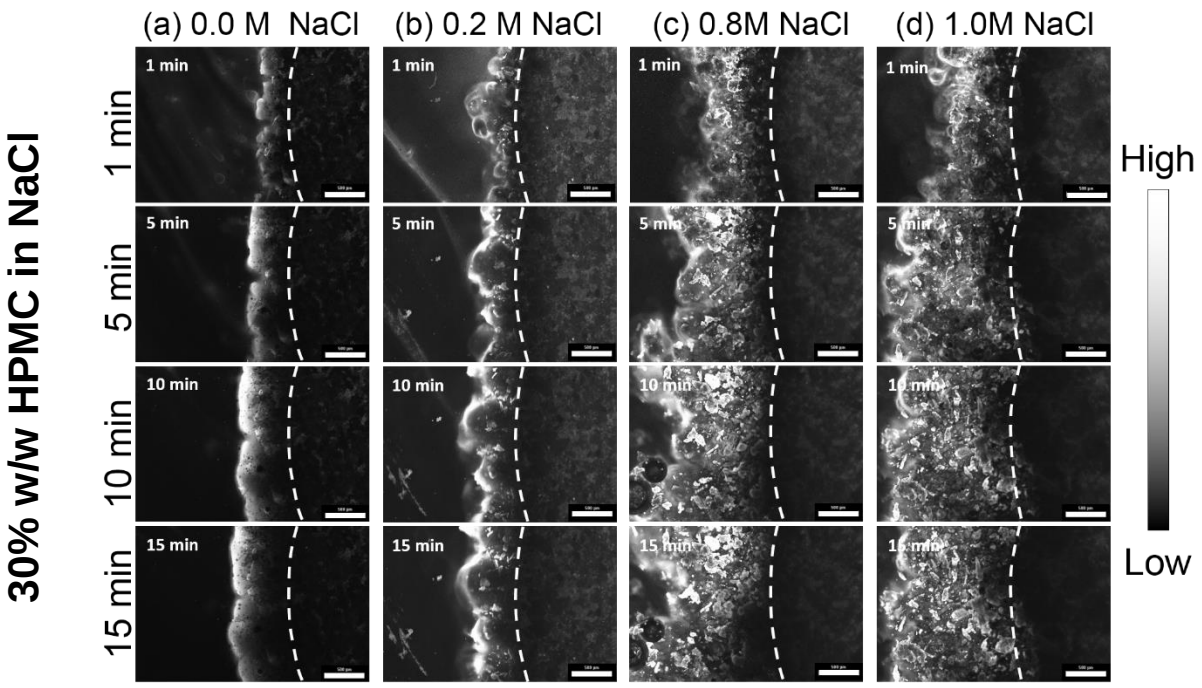


Figure 4.9: Early gel layer formation at the boundary of hydrating 30% w/w HPMC matrices as a function of time and sodium chloride concentration. Confocal fluorescence imaging at Ex 488/Em >510 nm. Experiments conducted at 37 ± 1 °C using sodium chloride media containing 0.008% w/v Congo red as a visualisation aid. Dotted white lines show the dry boundary at t=0 minutes. Scale bar = 500 µm.

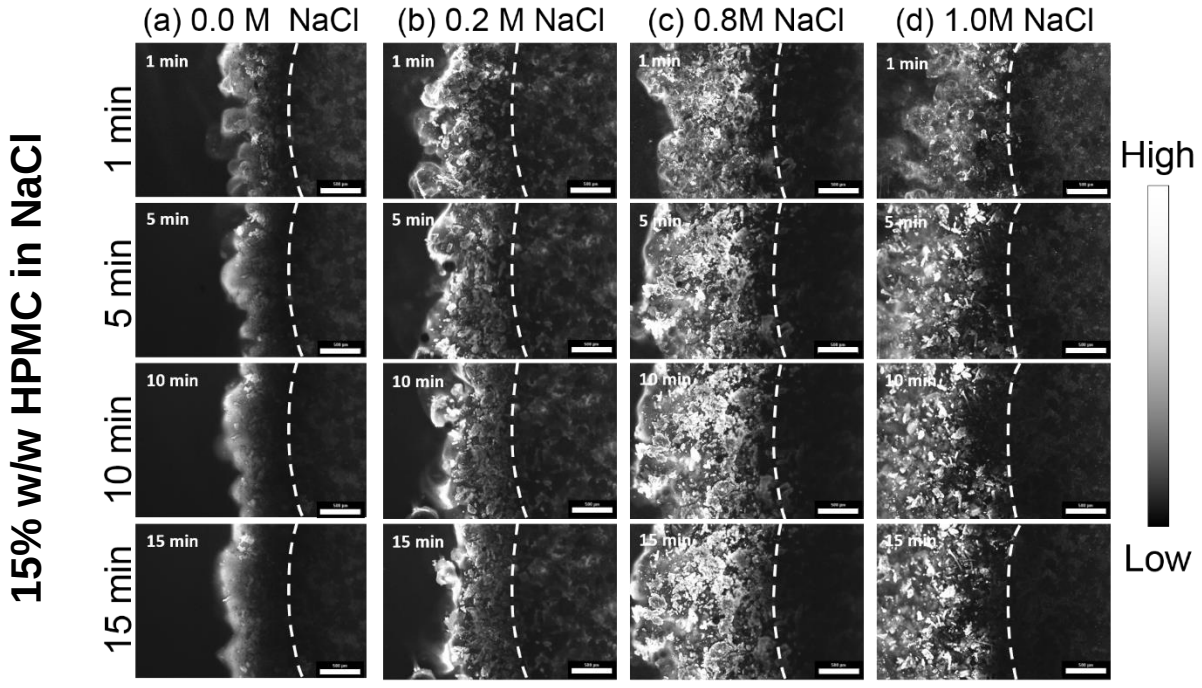


Figure 4.10: Early gel layer formation at the boundary of hydrating 15% w/w HPMC matrices as a function of time and sodium chloride concentration. Confocal fluorescence imaging at Ex 488/Em >510 nm. Experiments conducted at 37 ± 1 °C using sodium chloride media containing 0.008% w/v Congo red as a visualisation aid. Dotted white lines show the dry boundary at t=0 minutes. Scale bar = 500 µm.

4.4.1.4 Time-lapse photography imaging of hydrating HPMC matrices in salt solutions

Figure 4.11 and Figure 4.12 show time-lapse photography images which show the swelling behaviour of 30% and 15% w/w HPMC matrix tablets in water of different trisodium citrate concentrations.

In water, significant matrix swelling is confined to the first minute. The 15% w/w HPMC matrix swells to a greater extent in the first minute, but there appears to be no additional change in tablet size thereafter. This suggests that the processes of erosion and swelling are occurring at similar rates. The 30% w/w matrix tablet increases in size radially between 10 and 30 minutes, suggesting the matrix tablet is continuing to hydrate with more polymer swelling than erosion.

In 0.1 M TSC, rapid swelling of matrices is observed in both radial and axial directions in the first minute. Due to the rapid axial expansion, the 15% w/w HPMC tablet splits into two after 5 minutes. In contrast, the 30% w/w matrix remains in one piece, with little change in tablet size over 30 minutes.

In 0.2 M TSC, rapid swelling is observed for the 30% w/w matrix. The matrix forms a dumbbell shape, and the matrix tablet separates into two pieces at 16.5 minutes (image not shown). The 15% w/w matrix tablet swells in the first minute, but thereafter rapid erosion and disintegration of the tablet occurs.

Figure 4.13 and Figure 4.14 show similar images for matrices hydrating in sodium chloride solutions up to a concentration of 1.0 M NaCl. In water and 0.2 M NaCl, there is little change in the physical appearance of both formulations over time. For both formulations, there is somewhat more axial swelling in 0.8 M than in 0.2 M NaCl. At 1.0 M NaCl, considerable axial swelling of the formulations can be seen, with surface polymer disintegration. There appears to be a radial splitting of the matrix tablet, and in the case of the 15% w/w HPMC matrix, the tablet completely separates.

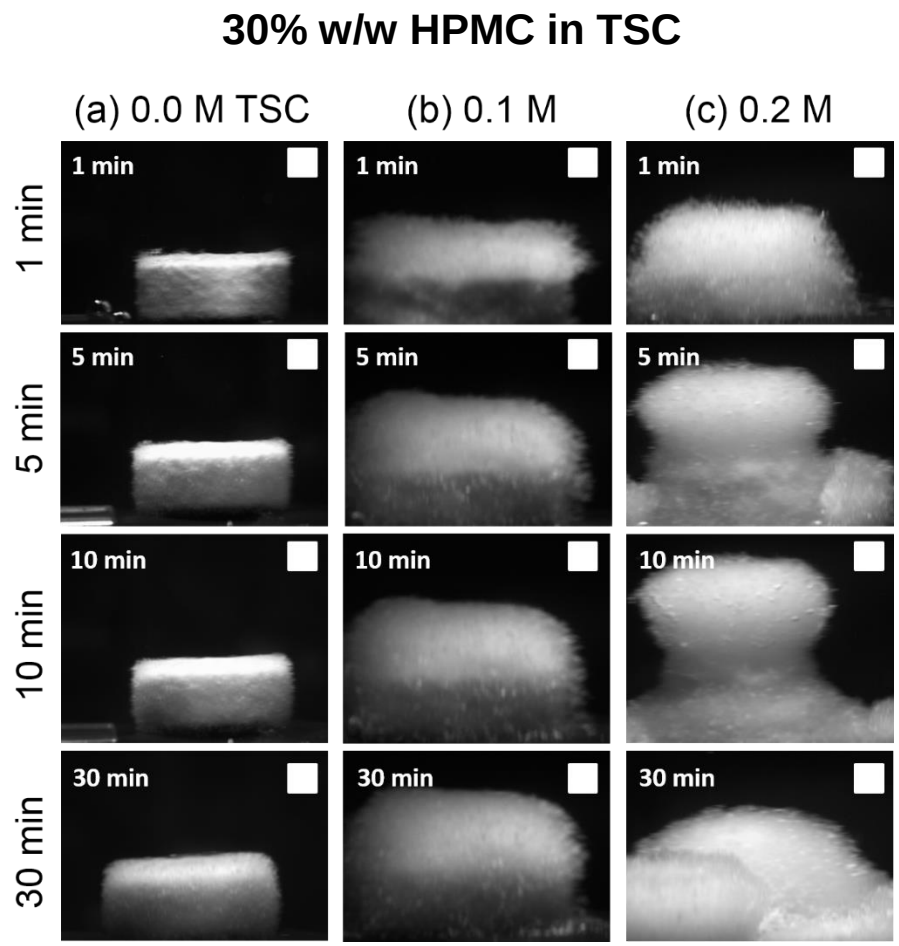


Figure 4.11: Time-lapse photography of hydrating 30% w/w HPMC matrix tablets in (a) water, (b) 0.1 M TSC and (c) 0.2 M TSC. 600 mL media at 37 ± 1 °C

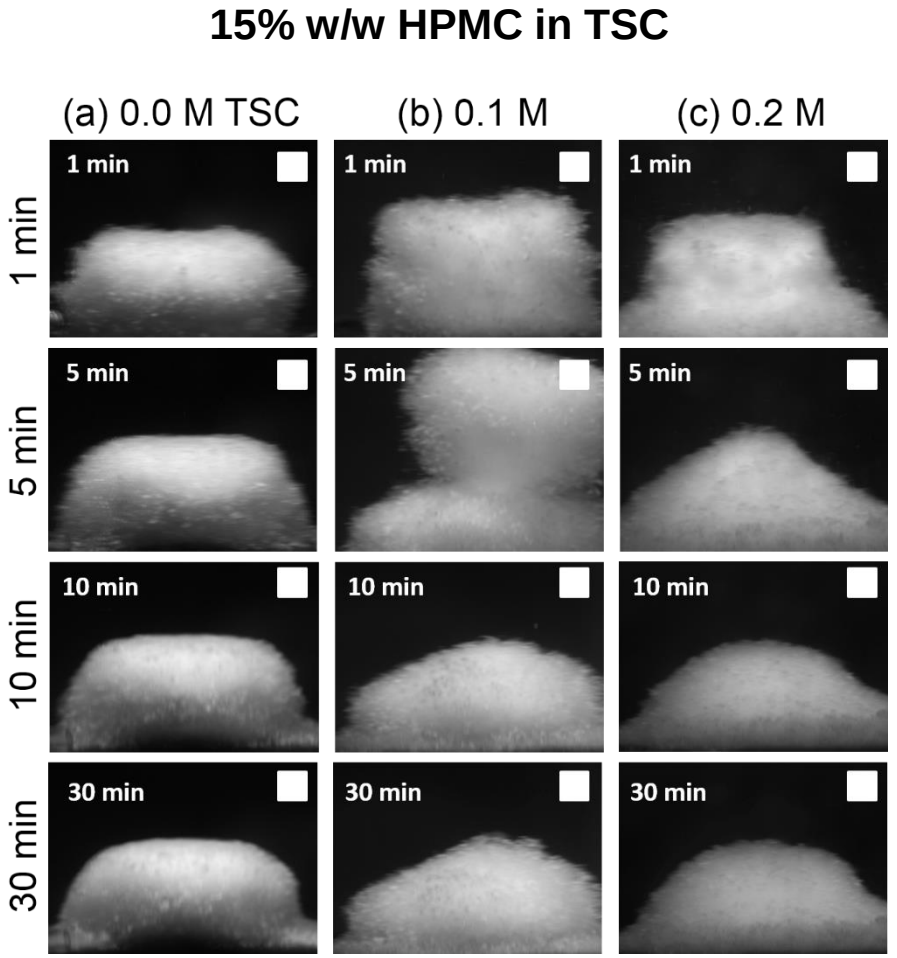


Figure 4.12: Time-lapse photography of hydrating 15% w/w HPMC matrix tablets in (a) water, (b) 0.1 M TSC and (c) 0.2 M TSC. 600 mL media at 37 ± 1 °C

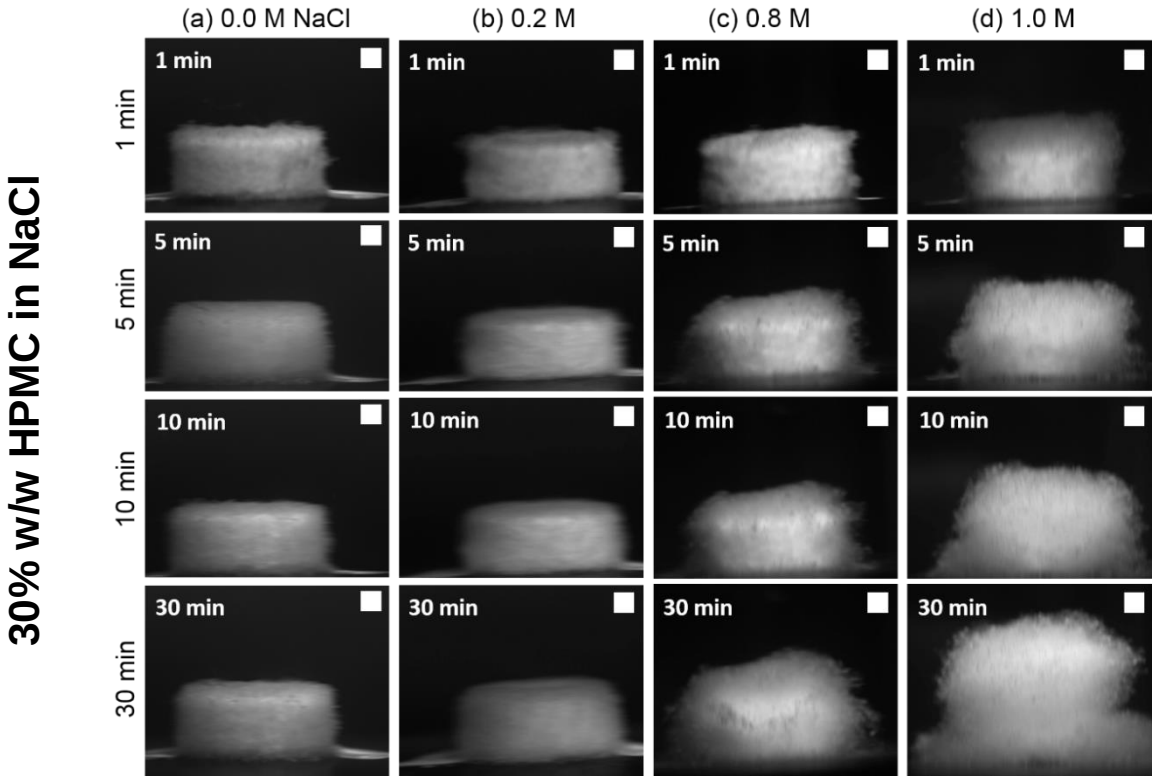


Figure 4.13: Time-lapse photography of hydrating 30% w/w HPMC matrix tablets in (a) water, (b) 0.2 M NaCl and (c) 0.8 M NaCl and (d) 1.0 M NaCl 600 mL media at 37 ± 1 °C

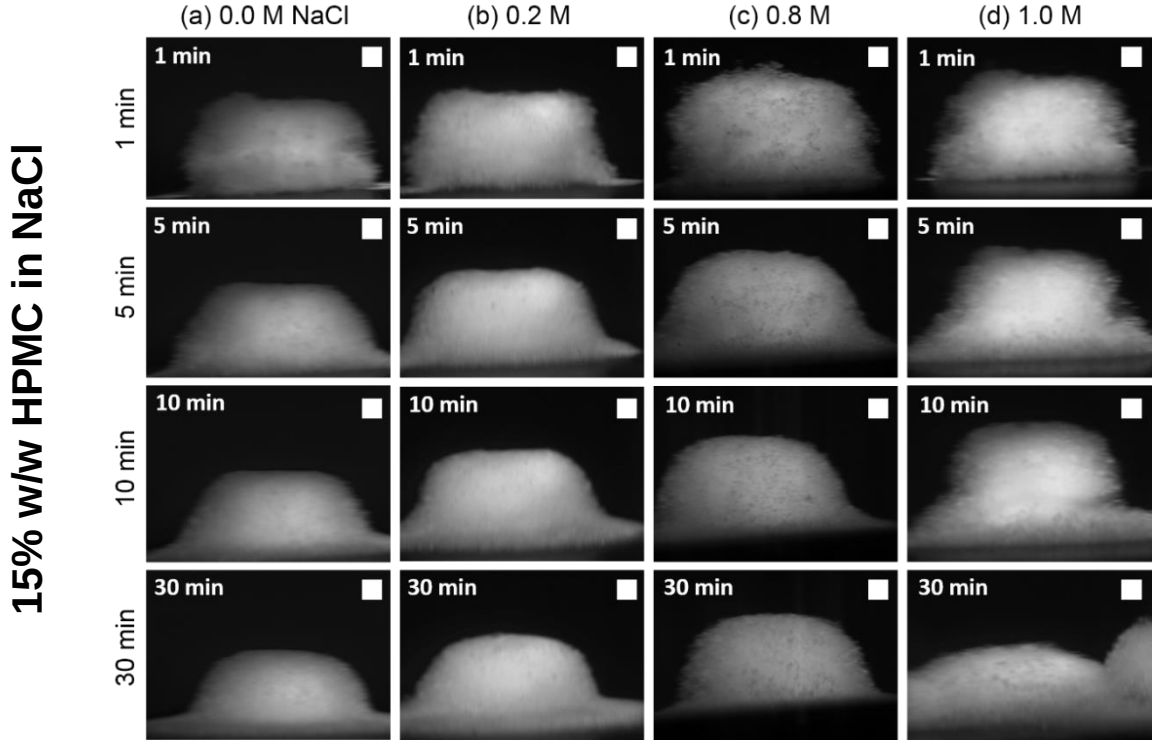


Figure 4.14: Time-lapse photography of hydrating 15% HPMC w/w matrix tablets in (a) water, (b) 0.2 M NaCl and (c) 0.8 M NaCl and (d) 1.0 M NaCl 600 mL media at 37 ± 1 °C

4.4.2 Discussion: Effect of salts

4.4.2.1 The impact of salts on HPMC matrices

The results of the previous section show that salts can affect the swelling of HPMC. With increasing salt concentrations, increased gel layer thickness, greater tablet swelling, or complete failure of the tablet with rapid disintegration has been observed.

Ionic salts are known to interfere with the hydration of HPMC, due to their greater affinity for water. Chaotropes, such as TSC and NaCl, have been found to change the surface tension of bound water and increase the polarity of adjacent water molecules (Zhang et al., 2007). This can result in destabilising of the water clathrates which hydrate the hydrophobic regions of the polymer. Subsequently, 'salting out' of the polymer can occur. At high salt concentrations, this effect can ultimately impede the hydration of HPMC, thus preventing the formation of a coherent gel layer (Sarkar, 1979, Touitou and Donbrow, 1982, Mitchell et al., 1990, Ford, 1999).

It was found that at intermediate salt concentrations (< 0.1 M TSC, < 0.8 M NaCl), there were no substantial differences in $T_{80\%}$ or calculated kinetic parameters for each formulation. The gel layer typically became thicker as the salt concentration increased, as shown in confocal imaging (Figure 4.7 – 4.10) and time-lapse photography (Figure 4.11 – 4.14). However, no resulting difference in drug release profiles was observed. It seems that the matrix can still form a rate limiting gel layer that controls drug release at these intermediate salt concentrations.

Higher salt concentrations (0.2 M TSC, 1.0 M NaCl) resulted in dramatic changes in the swelling behaviour of matrices and release of drug. The time for 80% caffeine to be released ($T_{80\%}$) was taken a single value to represent the extended release kinetics of the formulation. If the $T_{80\%}$ was shorter than 30 minutes, the formulation was deemed to have failed in those dissolution conditions. By that definition, all matrices failed in the higher salt concentrations. Confocal imaging and time-lapse photography suggested this formulation failed to establish a rate limiting gel layer, with rapid axial swelling of the formulations at higher concentrations.

These high concentrations resulted in 'dumbbell' shaped swelling with the matrix splitting at the radial edges into two halves. The splitting of HPMC matrix tablets has been reported by Cahyadi et al. who coined it the 'butterfly effect' (Cahyadi et al., 2011)

because sometimes the layers did not fully separate, resulting in a butterfly shaped tablet. They attributed this to the penetration of fracture lines by hydration medium, resulting in a large internal swelling pressure in a specific plane. The expansion of the inner layer forced the tablet edges to curl outwards, forming either a 'butterfly' shape or causing the two halves of the tablet to separate completely. The effect is similar to that of lamination, and Cahyadi et al. found a minimum compression force of 3 kN was necessary for the effect to occur. Unfractionated HPMC, thinner tablets and the ratio of HPMC to other excipients predisposed a formulation to the effect.

In our studies, we never observed the butterfly effect in water but have often observed it during dissolution testing in intermediate salt concentrations (< 0.1 M TSC, < 0.8 M NaCl). Under these conditions, the tablets sometimes split into two discrete swollen masses that continued to individually maintain extended drug release.

4.4.2.2 The impact of matrix polymer content on sensitivity to salt effects

SCrit values, the concentration of salt that induces failure of matrices in dissolution testing, have been reported for many salts and for different cellulosic polymers (Mitchell et al., 1990, Johnson et al., 1993). However, there have been no published comparisons of how the *SCrit* value is influenced by the matrix polymer content.

Our work, using two salts of different potency, suggest that the *SCrit* value is independent of the content of HPMC polymer in the matrix tablet, in the case of our formulations. This conclusion seems reasonable given that these salts induce failure of matrices through the suppression of HPMC hydration. However, we might have expected a difference in the response of matrices to the intermediate salt concentrations. The presence of salt in hydration media might result in regions along the polymer chain where water sheaths have been disrupted. As discussed above and in section 1.4.2.1, disruption of water sheaths may result in polymer-polymer interactions becoming more favourable. This might result in contraction of the polymer chains, subsequently reducing the number of chain entanglements between adjacent HPMC particles. In addition, a lower matrix polymer content means the distance between adjacent HPMC particles is greater. Both effects could combine to result in polymer content dependent sensitivity to salt. However, no manifestation of this theory was observed in this study.

Biphasic release profiles (Figure 4.2) were observed for 30% and 20% w/w HPMC matrices in 0.7 M NaCl. Similar biphasic release profiles were observed by Williams et

al. when studying the effect of sucrose solutions on 30% w/w HPMC K4M matrices (Williams et al., 2009). They hypothesised that this was the result of pronounced matrix swelling during the first few hours of hydration, with the formation of a large swollen mass which then disintegrated. They did not describe the trigger for this abrupt change, although they found that the swollen mass "collapsed" on removal from the dissolution media, suggesting that the gel layer formed was weak or dilute. In our studies, the effect was not seen in matrices with 15% w/w or lower HPMC contents. This may be because drug release is too rapid to show a biphasic curve, although, in 0.8 M NaCl the release rate of 30% w/w HPMC matrix tablets accelerated to such a degree that the $T_{80\%}$ was faster than for 15% w/w matrices.

Despite the differences in release profile in 0.7 M and 0.8 M NaCl, the salt concentration which caused absolute failure (*SCrit*) was similar for all matrices (0.15 M TSC, 1.0 M NaCl). This was irrespective of the matrix polymer content.

4.4.2.3 The potency of different salts to affect HPMC matrices

When comparing *SCrit* values, TSC was found to be 6 - 7 times more potent than NaCl in causing failure of HPMC matrices (0.15 M TSC v 1.0 M NaCl). Cloud point testing reported that TSC appeared to be 7 - 8 times more potent at depressing the cloud point temperature than NaCl (-197 $°C.M^{-1}$ TSC v (-22.9 $°C.M^{-1}$ NaCl). Ions with higher affinity for water would be expected to have lower *SCrit* values as they should be better able to disrupt the hydration of HPMC (Fagan et al., 1989, Mitchell et al., 1990).

The difference in potency between TSC and NaCl was as expected. TSC contains 3 times the number of sodium cations than NaCl. In addition, TSC contains a trivalent citrate anion, which is highly disruptive compared to monovalent chloride.

4.4.2.4 Practical application in the development of HPMC-based dosage forms

We had anticipated that reducing the matrix polymer content would result in a formulation which was more sensitive to salt, however, our results show similar *SCrit* values for all 6 formulations.

The ionic strength of the gastric contents *in-vivo* is routinely reported as in the region of 0.1 M NaCl (Lindahl et al., 1997). Although there may be regions of locally higher concentrations, such as adjacent to a high salt food, the ionic strength of the stomach is unlikely to reach the salt concentrations that affected our formulations (0.7 - 0.8 M NaCl)

for extended periods of time. However, low levels of ionic salt, close to concentrations that could be reasonable *in-vivo,* may influence the thickness of the gel layer and swelling of the tablet. In addition, it is not clear how other components of the tablet formulation influence sensitivity to salts. It is, therefore, important to consider the possible impact of salts during the development of HPMC matrices, irrespective of the matrix polymer content.

Section B:

The influence of mechanical stress on drug release from low polymer content HPMC matrices

4.4.3 Results: The impact of mechanical stress on HPMC matrices

It is important that oral, ER dosage forms can withstand the forces of the stomach. The matrix must not break apart prematurely, as this could result in faster release and clinical toxicity. In this section, we investigated how physical stress influenced drug release as a function of matrix polymer content.

4.4.3.1 Use of the Texture Analyser to show deterioration in tablet strength during hydration

Figure 4.15, replicated from Section 3.4.7, shows the force required for a 2 mm diameter probe to penetrate a matrix tablet after hydration in water. The dry tablets had a breaking force of over 150 N (tested with a 50 kg load cell). Tablets were weaker with respect to increased hydration time and lower polymer content. The maximum force that the texture analyser could apply with the 5 kg load cell was 58.5 N, and if this force was reached the probe stopped moving. The 15%, 12.5% and 10% w/w HPMC matrix tablets exhibited breaking forces below 58.5 N after only 4 minutes of hydration. In the case of 10% w/w HPMC matrices, the breaking force of the tablet dropped from more than 150 N dry to less than 2 N within 4 minutes, suggesting rapid liquid penetration and extensive destruction of internal tablet bonding. In the case of 30% w/w HPMC matrices, the breaking force remained higher than 58.5 N for 8 minutes, when one tablet broke under this force. It is clear that the tablets with higher polymer content retained greater overall strength for longer hydration periods than those with lower polymer contents.

The sensitivity of the instrument was not sufficient to confidently measure force gradient within the gel layer. However, the images in Figure 4.16 show how forces up to a maximum of 0.2 N, 0.5 N and 5 N were sufficient to damage the outer gel layer of 30% w/w HPMC matrices after hydration in USP II apparatus for 90 minutes. It is clear that forces of 0.2 N and above can penetrate through the outermost layer of the gel, which is far lower than the force to penetrate the tablet core.

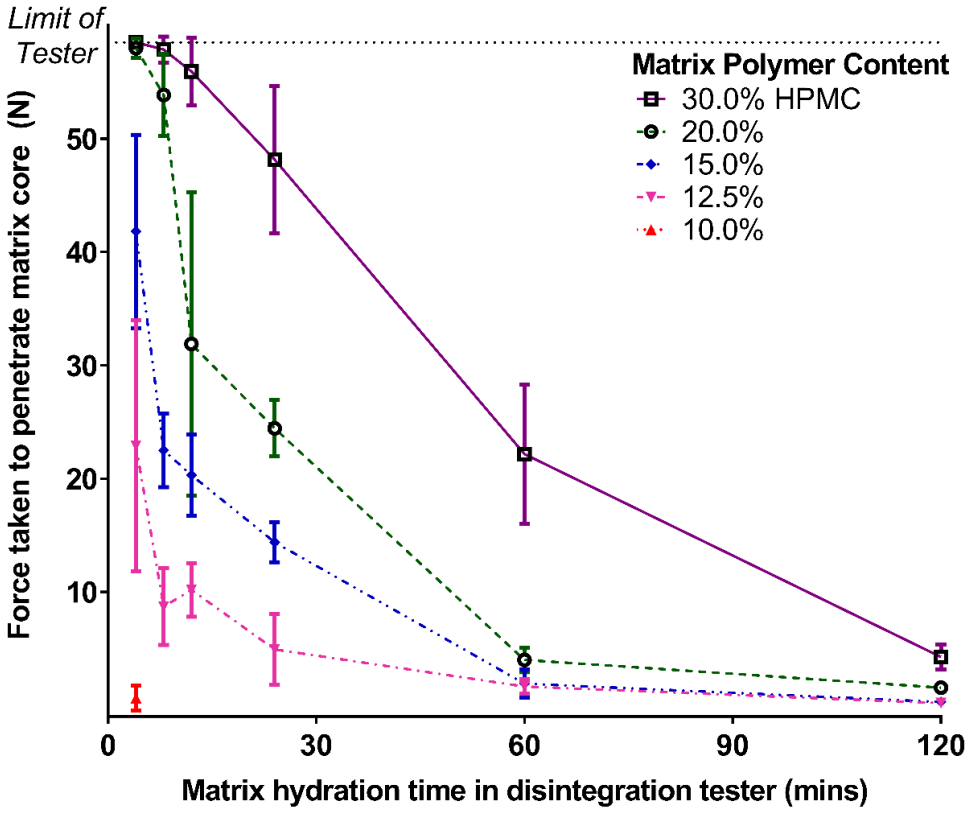


Figure 4.15: The force taken to penetrate the HPMC matrix core with respect to hydration time and polymer content. Matrix polymer content reported as % w/w HPMC. Tablets hydrated in disintegration apparatus (water, 37 °C, mean (n=3) ± 1 SD) for different times before removal and testing using texture analyser (2 mm Ø diameter probe)

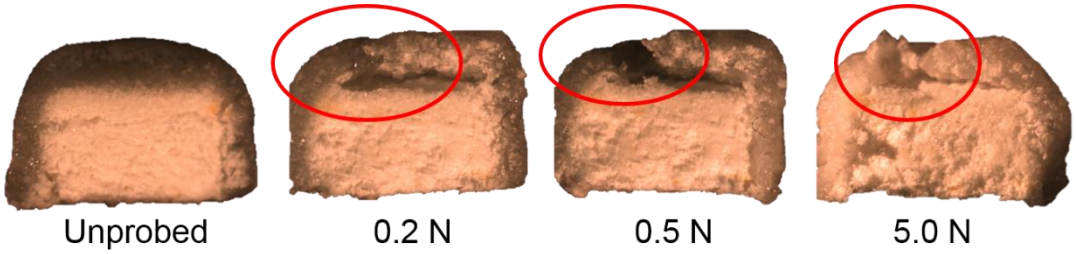


Figure 4.16: Photographs of 30% w/w HPMC matrices that have been probed using texture analysis with respect to probe force. Tablets hydrated in USP II dissolution apparatus (900 mL water, 37 °C, 50 RPM) for 90 minutes whilst fixed to a glass cover slip. Probed using texture analyser (2 mm Ø diameter probe) to different maximum forces (0.2 N, 0.5 N, 5.0 N). Red circles indicate indentation marks caused by probe.

4.4.3.2 The extended release properties of HPMC matrices exposed to different paddle speeds in the USP dissolution test

Figure 4.17 shows caffeine release with respect to HPMC content at five paddle rotation speeds. The sensitivity of drug release to the paddle speed was found to be dependent on the matrix polymer content. Drug release from the 30% w/w matrix formulation was broadly insensitive to paddle speed between 25 and 150 RPM. But as matrix polymer content was reduced, formulations became progressively more sensitive to the hydrodynamic conditions of the test, and at 10% w/w polymer, the matrix exhibited extended release at low paddle speeds and total drug release within 30 minutes at high speeds.

Dissolution parameters ($T_{80\%}$, DR10min, Higuchi and Korsmeyer-Peppas) are reported in Table 4.2. Where drug release was very fast (i.e. > 80% drug release within 10 minutes), there was an insufficient number of time points to enable a linear regression, so no Higuchi or Korsmeyer-Peppas analysis could be conducted. To allow the relationship between paddle speed and these kinetic outputs to be seen, $T_{80\%}$ and the release exponent *n* were plotted separately in Figure 4.18 and Figure 4.19.

Figure 4.18 shows how a change in the paddle rotational speed (from 25 – 150 RPM) affects the time for 80% drug to be released. As discussed in Section 3.4.1, matrices with higher polymer contents show longer $T_{80\%}$ values. It can be seen that the formulations remain in order of polymer content irrespective of the paddle rotational speed (up to 150 RPM). However, the figure shows that there is a general downward trend for each formulation, with shorter $T_{80\%}$ values as the paddle speed is sequentially increased. The percentage drop in $T_{80\%}$ value between 25 and 150 RPM was related to the matrix polymer content; 10% w/w HPMC formulations show an 89.1% drop, whereas formulations with 30% w/w HPMC show a reduced 24.6% drop between the means at 25 and 150 RPM.

As expected, release rate constants became faster as paddle speed increased for all formulations (Table 4.2). However, there is a difference in the trend for release exponent *n* values. This value, calculated from the Korsmeyer-Peppas equation, is considered to be broadly indicative of the drug release mechanism. In the case of a cylindrically shaped matrix tablet, values near 0.45 suggest a mechanism in which drug diffusion predominates, whereas values approaching 0.89 suggest erosion-dominated release.

Values between 0.45 and 0.89 indicate a mixed mechanism, often defined as ‘anomalous’ (Siepmann and Peppas, 2001).

Figure 4.19 shows how the *n* exponent for formulations containing 20% w/w or less HPMC decreases from around 0.75 to 0.4 as the paddle speed is increased up to 150 RPM. This suggests that the drug release mechanism is changing to a more diffusional release under the high-speed conditions. Whilst we would anticipate that higher shear rates would disrupt the gel layer to such an extent that more erosion occurs, it is possible that the gel layer becomes thinner / less coherent allowing the drug to easily diffuse through it, and this results in the smaller *n* exponent value. The decrease in *n* exponent with higher paddle speeds is in contrast to results of the 30% w/w HPMC formulation where the *n* exponent remains between 0.66 – 0.69 for all paddle speeds, despite observed changes in $T_{80\%}$ and rate constants.

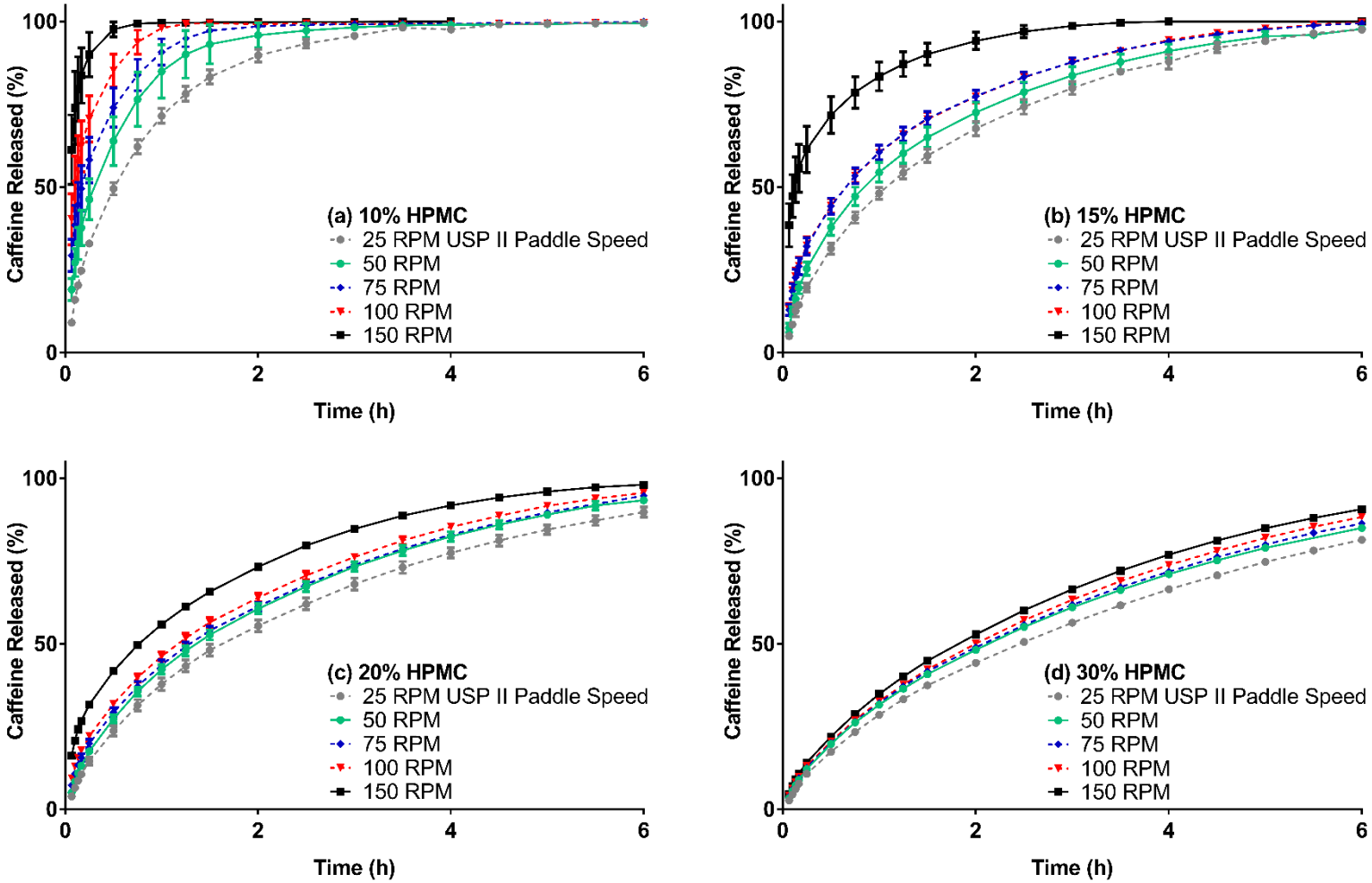


Figure 4.17: Release of caffeine from HPMC matrices as a function of USP II paddle speed for formulations containing different HPMC contents. HPMC contents, reported as % w/w, were (a) 10% HPMC, (b) 15% HPMC, (c) 20% HPMC and (d) 30% HPMC. USP apparatus II, 50 RPM, 900 mL water, 37 ± 0.5 °C. Mean (n=3) + 1 SD.

Polymer content (% w/w)	Paddle Speed (RPM)	$T_{80\%}$ (hours)	DR10min (%)	Higuchi		Korsmeyer-Peppas		
				k_h ($min^{-0.5}$)	r^2	K_{kp} ($mins^{-n}$)	*n*	r^2
10	25	1.34 ± 0.11	24.7 ± 1.0	11.07 ± 0.21	0.9933	3.90	0.75	0.9653
	50	0.88 ± 0.27	37.7 ± 5.4	12.60 ± 0.78	0.8860	9.11	0.59	0.8683
	75	0.64 ± 0.14	49.5 ± 6.9	15.24 ± 2.31	0.7707	14.7	0.52	0.7732
	100	0.40 ± 0.10	62.3 ± 7.7	18.91 ± 4.81	0.6074	20.6	0.49	0.6064
	150	0.15 ± 0.07	83.7 ± 8.4	*	*	*	*	*
15	25	3.01 ± 0.17	14.4 ± 1.1	7.11 ± 0.10	0.9942	2.40	0.73	0.9724
	50	2.54 ± 0.30	19.0 ± 1.9	7.91 ± 0.20	0.9820	3.32	0.69	0.9596
	75	2.22 ± 0.15	26.1 ± 2.6	7.82 ± 0.21	0.9830	7.11	0.53	0.9681
	100	2.22 ± 0.16	26.2 ± 2.6	7.77 ± 0.21	0.9825	7.21	0.53	0.9658
	150	0.83 ± 0.21	55.7 ± 7.2	11.94 ± 2.53	0.6317	24.2	0.35	0.6456
20	25	4.35 ± 0.23	10.6 ± 0.9	5.69 ± 0.07	0.9952	2.15	0.68	0.9889
	50	3.72 ± 0.17	13.1 ± 0.8	6.11 ± 0.05	0.9954	2.90	0.64	0.9905
	75	3.65 ± 0.10	15.6 ± 1.2	5.97 ± 0.06	0.9960	3.70	0.60	0.9879
	100	3.39 ± 0.12	17.8 ± 0.4	6.13 ± 0.06	0.9970	4.80	0.55	0.9949
	150	2.53 ± 0.05	26.7 ± 0.3	6.48 ± 0.08	0.9960	9.49	0.43	0.9958
30	25	5.79 ± 0.08	7.8 ± 0.4	4.79 ± 0.02	0.9992	1.60	0.69	0.9959
	50	5.17 ± 0.09	8.8 ± 0.2	5.07 ± 0.02	0.9996	1.81	0.68	0.9950
	75	5.06 ± 0.21	9.4 ± 0.1	5.12 ± 0.03	0.9990	1.95	0.67	0.9967
	100	4.75 ± 0.11	9.7 ± 0.2	5.22 ± 0.03	0.9987	2.08	0.66	0.9976
	150	4.36 ± 0.10	10.7 ± 0.3	5.42 ± 0.03	0.9990	2.11	0.68	0.9946

Table 4.2: The effect of USP apparatus II paddle speed and matrix HPMC content on drug release parameters ($T_{80\%}$, DR10min, Higuchi and Korsmeyer-Peppas). Mean (± 1 SD for $T_{80\%}$, DR10min and Higuchi:) (n=3). (*) For 10% HPMC at 150 RPM, drug release was too fast for linear regression.

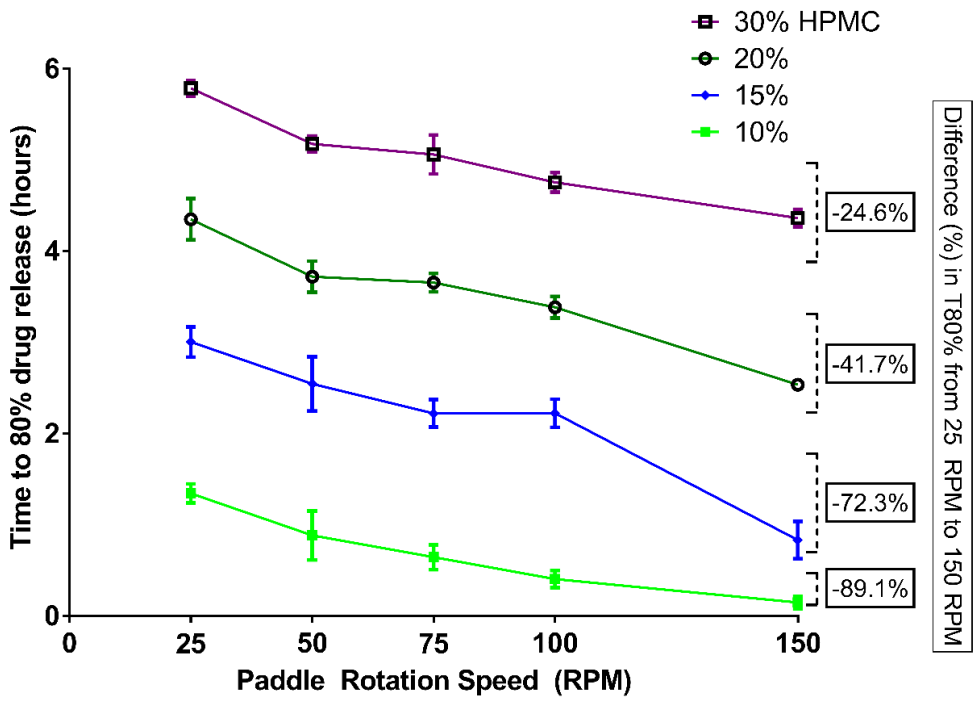


Figure 4.18: Time for 80% caffeine release from HPMC matrices as a function of USP II paddle rotational speed (RPM) and matrix HPMC content (% w/w). USP apparatus II, 25 - 150 RPM, 900 mL water, 37 ± 0.5 °C. Mean (n=3) + 1 SD

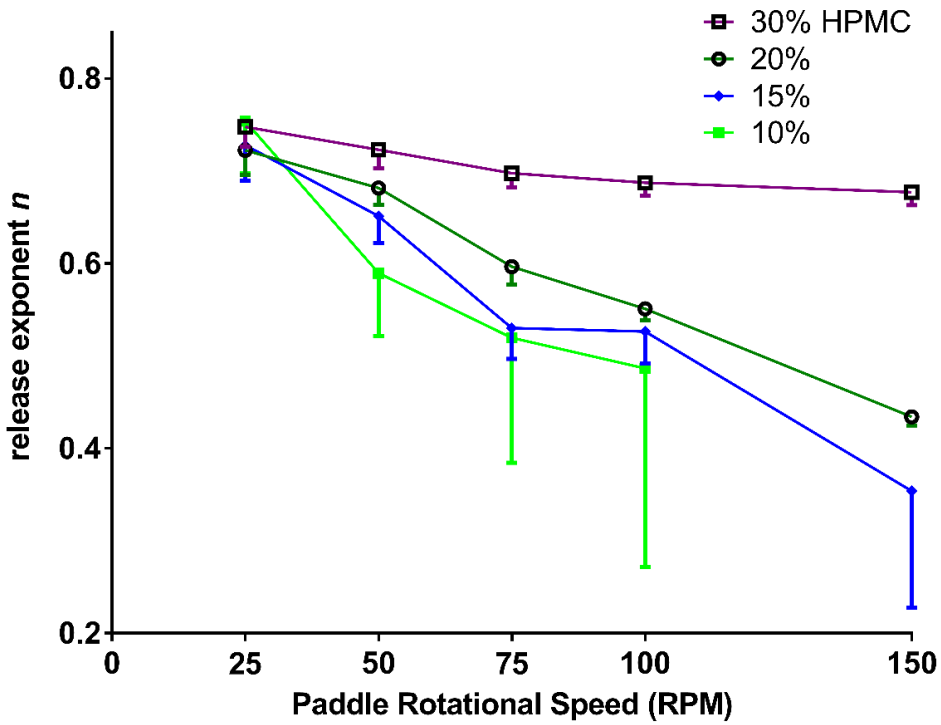


Figure 4.19: Change in release exponent *n* of HPMC matrices as a function of USP II paddle rotational speed (RPM) and matrix HPMC content (% w/w). USP apparatus II, 25 - 150 RPM, 900 mL water, 37 ± 0.5 °C. Mean (n=3) - 1 SEM.

4.4.4 Discussion: The impact of mechanical stress on HPMC matrices

In the previous section, we saw that lower forces were needed to penetrate the tablet core of a hydrated tablet as the polymer content was lowered. In addition, low polymer content matrices became progressively more sensitive to increasing paddle speed.

Whilst hardness of the core does not necessarily correlate to the rate of drug release through the gel layer, we would expect that tablets with a lower break force are more likely to be susceptible to hydrodynamic forces *in-vivo*. These forces have been reported as around 2.0 N in the stomach and 1.2 N in the small intestines of fed subjects (Kamba et al., 2002, Takieddin and Fassihi, 2014), Another study using agar beads reports lower forces of between 0.53 and 0.78 N (Marciani et al., 2001). These forces are considerably lower than the matrix breaking forces seen for the majority of our matrix formulations (Figure 4.15). However, we were testing the breaking force of the core, but not the outer gel layers which, it is believed, predominately control drug release. Photographs (Figure 4.16) showed that a probe force of 0.2 N and above can penetrate through the outermost layer of the gel, and therefore we conclude that forces akin to those found *in-vivo* may damage hydrophilic matrix formulations.

Several groups have varied USP II paddle speed in an attempt to predict or better match *in-vivo* drug release data. A paddle speed of 75 (fasted) or 125 RPM (fed) was suggested to generate an IVIVC of the dissolution of felodipine in dog studies, although it was also highlighted that the dissolution media was important (Scholz et al., 2003). In a similar study which attempted to adjust USP dissolution conditions to match *in-vivo* results, Abrahamsson et al (1998) suggested a paddle rate of 140 RPM and an ionic strength of 0.14 M NaCl to simulate prandial administration of two HPMC formulations. The authors also discussed how high paddle speeds may be necessary to represent the agitation intensity in the stomach after food (Abrahamsson et al., 1998b). In a follow-up study using a food sensitive and a food insensitive HPMC formulation, much larger increases in erosion rate with increases in paddle speed were observed for the formulation which was food sensitive. They suggested formulators should compare dissolution data at 50 and 100 RPM, with any formulations showing a difference under these two conditions being suggested to be at risk of a food sensitivity (Abrahamsson et al., 1999). All the HPMC formulations studied contained more than 40% w/w HPMC.

In the opinion of the author of this thesis, the use of USP tests to predict what may happen *in-vivo* is inherently problematic as the different USP apparatus were not designed with the *in-vivo* environment in mind. In addition, the hydrodynamic conditions can vary within the dissolution vessel itself (Kostewicz et al., 2014). However, our studies show that adjusting the paddle speed of USP II dissolution tests is likely to garner some useful information on the sensitivity of different formulations to variations in hydrodynamic forces.

Until the studies in this thesis, there appears to be no coherent information in the literature describing how USP II paddle speed influences matrices with respect to reductions in matrix polymer content. Ghimire et al. (2008) showed how matrices with 20% HPMC had a higher erosion rate and more variable release profiles than those formulated with 40% HPMC (Ghimire et al., 2010). We might, therefore, have expected to see larger effects of increased paddle speed on the low polymer formulations. Caffeine is a model soluble drug, released by both diffusion and polymer erosion mechanisms, and is generally released quite quickly from our formulations (all the $T_{80\%}$ values are lower than 6 hours). Larger differences might be observed if a poorly soluble drug is used, as a change in the integrity of the gel layer is expected to have a greater impact on release rates for drugs released predominantly by erosional mechanisms.

As the polymer content was lowered, matrices became more sensitive to changes in paddle speed with increased drug release rate and change in release mechanism. This may be because matrices containing lower HPMC content become softer quicker during hydration. The results suggest that a reducing matrix polymer content may result in deleterious changes in robustness to hydrodynamic forces.

Section C:

The impact of the combination of salts and mechanical stress on drug release from HPMC matrices

4.4.5 Results: The impact of the combination of salts and mechanical stress on drug release from HPMC matrices

4.4.5.1 Rationale

From the results in the previous sections, is clear that both rotational speed and ionic challenge can affect drug release from HPMC matrices. Salt affects matrices when the concentration goes above an *SCrit* value, which was 1.0 M for NaCl. Matrices of different HPMC content (7.5 – 30% w/w) had the same *SCrit* value. Therefore, the salt effect appears to be independent of matrix HPMC content. The *SCrit* of NaCl for these formulations (1.0 M) is far greater than anticipated concentrations *in-vivo* and therefore not a specific concern when developing formulations of lower polymer content.

In contrast, there is some evidence that the impact of paddle rotational speed is related to matrix tablet HPMC content. When formulations contain more HPMC, they become less sensitive to changes in USP II paddle speed. The paddle speeds studied (up to 150 RPM) have been used in other studies and shown good correlation with *in-vivo* results and therefore the observed difference between formulations is a result that may manifest *in-vivo*.

As discussed in Section 4.4.2, physical differences in the gel layer and overall matrix swelling were observed at salt concentrations below the *SCrit*, with greater swelling and gel layer thickness at these lower salt concentrations. If, as we hypothesised, paddle speed disrupts the forming gel layer causing it to be thinner and less of a diffusional barrier, then it should be considered that salt in dissolution media and an increase in USP II paddle speed could combine for an enhanced negative effect. This may lower the *SCrit* to a concentration that is more feasible *in-vivo*. The present section attempts to compare the effect of a combination of NaCl (0 – 0.6 M) and paddle speed (50 – 150 RPM) on HPMC matrices with different polymer contents.

4.4.5.2 The impact of a dual challenge (salt and mechanical stress) on drug release from HPMC matrices with respect to matrix polymer content

Figure 4.20 and Figure 4.21 show caffeine release as a function of salt concentration and paddle speed for matrices containing 10, 15, 20 and 30% w/w HPMC. Drug release from the 10% w/w matrices is always very fast ($T_{80\%}$ < 1 hour), making interpretation of any differences difficult and so these results are not discussed in detail. The results of dissolution data analysis are shown in Table 4.3 and Table 4.4.

At 50 RPM (column one), there is little difference in drug release over the range of 0 – 0.6 M NaCl with respect to matrix polymer content. Results discussing the impact of salt at a paddle speed of 50 RPM were discussed in Section 4.4.1.1.

At 100 RPM (column two), some changes in drug release rates are seen with respect to salt concentration and matrix polymer content. 15% w/w HPMC tablets (Figure 4.20e) show slowest drug release in water, faster release in 0.2 M and 0.4 M NaCl and a linear type profile in 0.6 M. In addition, larger error bars are observed than in water/50 RPM, which indicates greater variability. 20% w/w HPMC tablets (Figure 4.21e) have somewhat faster release in salt with larger error bars than in water, although the differences are smaller than for the 15% w/w formulations. Results of 20% w/w matrices in 0.6 M at 100 RPM show a similar release profile to 0.8 M NaCl and 50 RPM, whereby drug release is slow for 2 hours, before an acceleration in release rate (see Section 3.4.1). Matrix tablets containing 30% w/w HPMC (Figure 4.21k) show limited sensitivity to salt over the concentrations studied at 100 RPM.

At 150 RPM (column three), more substantial differences are seen with respect to salt concentration and matrix polymer content. Low concentrations of NaCl (0.2 M) cause the $T_{80\%}$ of 15% w/w matrices to drop from 0.83 hr (water) to 0.29 hr. 20% w/w matrix tablets show a similar drop in $T_{80\%}$ from 2.53 hr (water) to 1.32 hr (0.2 M NaCl). In contrast, 30% w/w HPMC matrices are able to withstand the combined challenge of 150 RPM paddle speed and NaCl concentration up to 0.4 M. 30% w/w matrices in 0.6 M NaCl, show slow drug release for 2 hours, before a slight acceleration in release rate. This is similar to the 20% w/w matrix in 0.6M at 100 RPM, and the 30% and 20% w/w matrices in 0.7 M and 0.8 M at 50 RPM.

There is an interesting similarity between results for the 20% w/w HPMC matrix at 150 RPM (Figure 4.21i) and the 15% w/w HPMC matrix at 100 RPM (Figure 4.20e). These

both show slowest release in water, similar release in 0.2 M and 0.4 M NaCl, and a bimodal release profile in 0.6 M.

Polymer content (% w/w)	Paddle Speed (RPM)	NaCl conc (M)	T80% (hours)	DR10min (%)	Higuchi		Korsmeyer-Peppas		
					k_h (mins$^{-0.5}$)	r^2	K_{kp} (mins^{-n})	*n*	r^2
10	50	0.0	0.88 ± 0.27	37.7 ± 5.4	12.60 ± 0.78	0.8860	9.11	0.59	0.8683
		0.2	0.93 ± 0.16	39.5 ± 5.6	11.95 ± 1.02	0.8948	10.3	0.55	0.8650
		0.4	0.94 ± 0.19	42.7 ± 8.6	11.43 ± 1.49	0.7871	12.5	0.50	0.7790
		0.6	1.23 ± 0.04	37.3 ± 1.8	9.14 ± 0.37	0.9705	12.2	0.46	0.9568
	100	0.0	0.40 ± 0.10	62.3 ± 7.7	18.91 ± 4.81	0.6074	20.6	0.49	0.6064
		0.2	0.38 ± 0.11	66.2 ± 6.2	22.60 ± 8.27	0.3183	24.0	0.49	0.3654
		0.4	0.27 ± 0.12	74.0 ± 6.6	24.27 ± 12.56	0.4826	28.6	0.46	0.4644
		0.6	0.14 ± 0.12	86.6 ± 13.7	*	*	*	*	*
	150	0.0	0.15 ± 0.07	83.7 ± 8.4	28.14 ± 19.60	0.3401	31.6	0.47	0.3331
		0.2	0.08 ± 0.02	95.6 ± 4.8	*	*	*	*	*
		0.4	0.06 ± 0.00	99.0 ± 0.9	*	*	*	*	*
		0.6	0.06 ± 0.00	99.4 ± 0.1	*	*	*	*	*
15	50	0.0	2.54 ± 0.30	19.0 ± 1.9	7.91 ± 0.20	0.9820	3.32	0.69	0.9596
		0.2	2.49 ± 0.26	20.4 ± 3.5	7.87 ± 0.23	0.9765	3.70	0.67	0.9350
		0.4	2.63 ± 0.35	23.6 ± 5.2	7.05 ± 0.32	0.9456	6.37	0.53	0.9184
		0.6	2.19 ± 0.24	18.7 ± 2.3	7.36 ± 0.16	0.9868	4.63	0.59	0.9789
	100	0.0	2.22 ± 0.16	26.2 ± 2.6	7.77 ± 0.21	0.9825	7.21	0.53	0.9658
		0.2	1.09 ± 0.83	51.4 ± 2.8	8.31 ± 1.59	0.4059	15.9	0.39	0.7385
		0.4	1.20 ± 0.38	45.3 ± 8.3	8.60 ± 1.51	0.6704	19.4	0.35	0.6338
		0.6	0.89 ± 0.39	41.2 ± 9.3	10.22 ± 1.99	0.6201	15.5	0.41	0.6393
	150	0.0	0.83 ± 0.21	55.7 ± 7.2	11.94 ± 2.53	0.6317	24.2	0.35	0.6456
		0.2	0.29 ± 0.34	77.1 ± 19.1	*	*	34.5	0.38	0.0753
		0.4	0.23 ± 0.28	81.3 ± 16.8	*	*	48.3	0.23	0.0792
		0.6	0.10 ± 0.04	90.9 ± 5.0	*	*	*	*	*

Table 4.3: The effect of paddle speed, salt concentration and matrix HPMC content on drug release parameters. USP apparatus II, 900 mL, 37 ± 0.5 °C. Mean (n=3) For $T_{80\%}$, DR10min and Higuchi ± 1 SD. (*) represents where drug release was too fast for linear regression analysis to be performed.

Polymer content (% w/w)	Paddle Speed (RPM)	NaCl conc (M)	T80% (hours)	DR 10min (%)	Higuchi		Korsmeyer-Peppas		
					($mins^{-0.5}$)	r^2	k_{kp} (min^{-n})	n	r^2
20	50	0.0	3.72 ± 0.17	13.1 ± 0.8	6.11 ± 0.05	0.9954	2.90	0.64	0.9905
		0.2	3.62 ± 0.28	15.7 ± 2.2	6.30 ± 0.14	0.9859	3.30	0.63	0.9699
		0.4	3.66 ± 0.17	16.3 ± 0.7	6.10 ± 0.08	0.9943	3.66	0.61	0.9818
		0.6	3.13 ± 0.30	19.0 ± 2.6	5.65 ± 0.12	0.9851	5.82	0.50	0.9710
	100	0.0	3.39 ± 0.12	17.8 ± 0.4	6.13 ± 0.06	0.9970	4.80	0.55	0.9949
		0.2	2.71 ± 0.47	27.9 ± 7.8	6.52 ± 0.23	0.9343	8.88	0.45	0.9138
		0.4	2.06 ± 0.43	37.6 ± 9.6	6.45 ± 0.62	0.8123	11.1	0.35	0.7832
		0.6	2.14 ± 0.43	27.4 ± 3.8	5.61 ± 0.21	0.9621	19.1	0.38	0.9465
	150	0.0	2.53 ± 0.05	26.7 ± 0.3	6.48 ± 0.08	0.9960	9.49	0.43	0.9958
		0.2	1.32 ± 0.29	45.8 ± 7.1	8.15 ± 0.85	0.8284	19.1	0.35	0.8275
		0.4	1.72 ± 0.16	45.0 ± 1.9	6.46 ± 0.29	0.9639	23.8	0.27	0.9755
		0.6	1.13 ± 0.24	47.4 ± 11.0	6.20 ± 1.28	0.5545	25.5	0.25	0.5237
30	50	0.0	5.17 ± 0.09	8.8 ± 0.2	5.07 ± 0.02	0.9996	1.81	0.68	0.9950
		0.2	5.62 ± 0.03	8.5 ± 0.6	4.87 ± 0.03	0.9985	1.76	0.68	0.9944
		0.4	5.93 ± 0.07	8.5 ± 0.3	4.69 ± 0.01	0.9996	1.80	0.67	0.9949
		0.6	6.08 ± 0.15	9.2 ± 0.5	4.49 ± 0.02	0.9995	2.14	0.63	0.9941
	100	0.0	4.75 ± 0.11	9.7 ± 0.2	5.22 ± 0.03	0.9987	2.08	0.66	0.9976
		0.2	5.33 ± 0.19	10.2 ± 1.0	5.00 ± 0.03	0.9966	2.31	0.64	0.9924
		0.4	5.31 ± 0.20	13.0 ± 0.3	4.85 ± 0.02	0.9990	3.31	0.57	0.9951
		0.6	4.40 ± 0.14	14.6 ± 0.6	4.87 ± 0.04	0.9978	4.17	0.53	0.9973
	150	0.0	4.36 ± 0.10	10.7 ± 0.3	5.42 ± 0.03	0.9990	2.11	0.68	0.9946
		0.2	4.50 ± 0.23	11.4 ± 0.1	5.33 ± 0.04	0.9982	2.39	0.65	0.9947
		0.4	4.76 ± 0.36	15.5 ± 1.6	5.02 ± 0.07	0.9933	4.62	0.52	0.9894
		0.6	3.22 ± 0.38	18.9 ± 3.6	5.07 ± 0.25	0.9322	6.22	0.46	0.9360

Table 4.4: The effect of paddle speed, salt concentration and matrix HPMC content on drug release parameters USP apparatus II, 900 mL, 37 ± 0.5 °C. Mean (n=3). For $T_{80\%}$, DR10min and Higuchi: ± 1 SD.

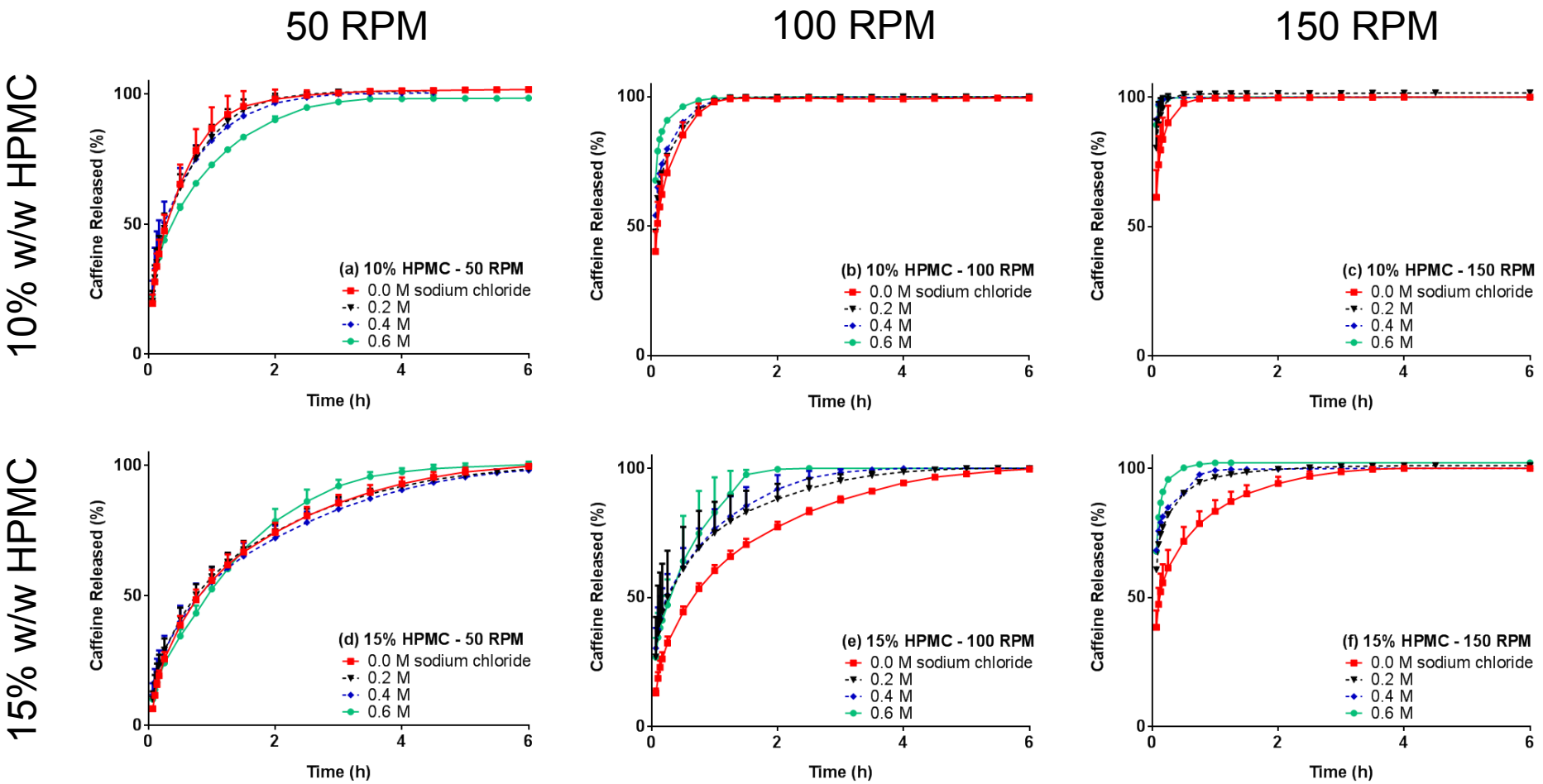


Figure 4.20: Release of caffeine from HPMC matrices as a function of sodium chloride content for formulations containing different HPMC contents and in different USP II paddle speeds. HPMC contents were (a-c) 10% w/w HPMC, (d-f) 15% w/w HPMC. USP apparatus II, 900 mL, 37 ± 0.5 °C. Mean (n=3) + 1 SD

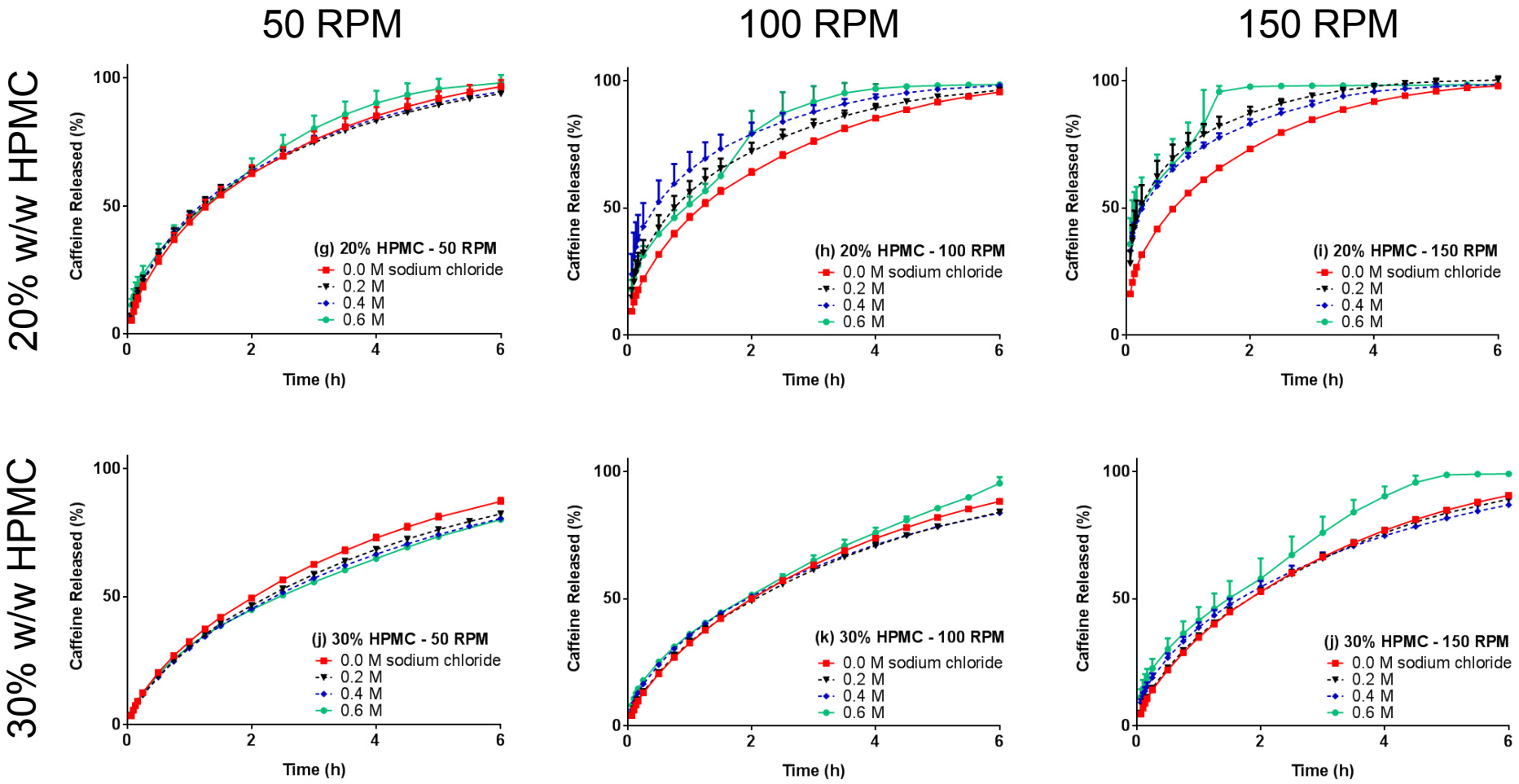


Figure 4.21: Release of caffeine from HPMC matrices as a function of sodium chloride content for formulations containing different HPMC contents and in different USP II paddle speeds. HPMC contents were (g-i) 20% w/w HPMC and (j-l) 30% w/w HPMC. USP apparatus II, 900 mL, 37 ± 0.5 °C. Mean (n=3) + 1 SD

4.4.6 Discussion: the impact of a dual challenge (salt and mechanical stress) on drug release from HPMC matrices with respect to matrix polymer content

This work has shown how matrices containing 30% w/w HPMC are better able to withstand the combined challenge of salt and paddle speed, than formulations containing 20% w/w HPMC or less. For 30% w/w matrices, release rates were similar with DR10min below 20% caffeine under any conditions. $T_{80\%}$ was always greater than 4.3 hours, with the exception of 0.6 M/150 RPM. In contrast, low salt concentrations (0.2 M NaCl) impacted upon drug release from matrices containing 15% and 20% w/w HPMC at paddle speeds of 100 and 150 RPM. Results suggested that increasing the polymer content of the formulation enhanced the tolerance of the formulation to an ionic and paddle challenge. 0.2 M is a feasible *in-vivo* gastric concentration of NaCl. In addition, paddle speeds of 100 RPM or higher have been shown to correlate with *in-vivo* results.

Section D:

Proposal of an *in-vitro* screening tool for assessing robustness of HPMC matrices

4.4.7 Proposal of an *in-vitro* screening tool for assessing robustness of HPMC matrices

As discussed in the thesis introduction, it can be necessary to lower the matrix polymer content. However, this chapter has consistently shown that drug release from matrices containing 20% w/w or less HPMC is more influenced by the dissolution environment, than matrices containing 30% w/w HPMC. This included the presence of salts and increased paddle speed. One of the aims of this thesis is to develop formulation strategies which enable lower polymer levels to be used, without compromising the reliability of drug release from the formulation.

To facilitate the development of low polymer formulations that are less sensitive to the dissolution environment, a discriminatory *in-vitro* dissolution test has been developed. Dissolution conditions of 0.2 M NaCl and 100 RPM were proposed as a suitable comparator to the more 'standard' dissolution conditions of water and 50 RPM paddle speed, based on results in Section 4.4.5. Dissolution kinetics in 0.2 M NaCl and 100 RPM, deemed as 'stress' conditions, have been compared to results in the 'standard' conditions in Table 4.5. Table 4.5 shows how there is a smaller difference in each of the calculated parameters for 30% w/w HPMC matrices than for formulations containing 20% HPMC or less; especially for $T_{80\%}$ and DR10min results. This suggests that the two dissolution environments can provide good discrimination. This will aid the development of formulations with reduced sensitivity to *in-vitro* dissolution conditions.

4.4.7.1 The discriminatory dissolution test

The following conditions were proposed as a discriminatory tool for formulation development using USP apparatus II.

- 'Standard' – water at 50 RPM paddle speed
- 'Stress' – 0.2 M NaCl at 100 RPM paddle speed

The drug release in the two dissolutions environments will be compared, with the following criteria used as tools to evaluate the success of each formulation strategy.

- Less than a 10% difference in Higuchi rate constant
- Less than a 10% difference in $T_{80\%}$ value
- No more than 30% drug release in the first 10 minutes.

Polymer Content (% w/w)	Dissolution Condition	DR10min		T80%		Higuchi		Korsmeyer-Peppas	
		DR10min (%)	Change (%)	$T_{80\%}$ (hours)	Change (%)	k_h ($min^{-0.5}$)	Change (%)	k_{kp} (min^{-n})	*n*
10%	Standard	37.7 ± 5.4	+75.6%	0.88 ± 0.27	-56.8%	12.60 ± 0.78	+79.4%	9.11	0.59
	Stress	66.2 ± 6.2		0.38 ± 0.11		22.60 ± 8.27		24.0	0.49
12.5%	Standard	29.6 ± 3.4	+114.2%	1.43 ± 0.13	-69.2%	9.86 ± 0.30	+135.5%	7.47	0.57
	Stress	63.4 ± 9.2		0.44 ± 0.16		23.22 ± 6.40		17.4	0.59
15%	Standard	19.0 ± 1.9	+170.5%	2.54 ± 0.30	-57.1%	7.91 ± 0.20	+5.1%	3.32	0.69
	Stress	51.4 ± 26.8		1.09 ± 0.83		8.31 ± 1.59		15.9	0.39
17.5%	Standard	18.6 ± 3.3	+96.8%	2.74 ± 0.33	-33.2%	7.40 ± 0.17	+0.3%	3.77	0.64
	Stress	36.6 ± 3.0		1.83 ± 0.15		7.42 ± 0.31		14.5	0.38
20%	Standard	13.1 ± 0.8	+113.0%	3.72 ± 0.17	-27.2%	6.11 ± 0.05	+6.7%	2.90	0.64
	Stress	27.9 ± 7.8		2.71 ± 0.47		6.52 ± 0.23		8.88	0.45
30%	Standard	8.8 ± 0.2	+15.9%	5.17 ± 0.09	+3.1%	5.07 ± 0.02	-1.4%	1.81	0.68
	Stress	10.2 ± 1.0		5.33 ± 0.19		5.00 ± 0.03		2.31	0.64

Table 4.5: A comparison of drug release kinetics for HPMC K4M matrices of varying polymer content in two different USP II dissolution conditions. USP apparatus II, 900 mL, 37 ± 0.5 °C. 'Standard' dissolution is water at 50 RPM. 'Stress' dissolution is 0.2 M NaCl at 100 RPM. Mean (for $T_{80\%}$, DR10min and Higuchi: ± 1 SD) (n=3). % values are the relative increase in mean of 'stress' dissolution compared to 'standard' conditions.

4.5 Conclusions

It has been shown that sodium chloride and trisodium citrate in solution can change the hydration and release of caffeine from HPMC-based matrix formulations. Above a critical threshold concentration (*SCrit*), HPMC matrices rapidly disintegrate and exhibit $T_{80\%}$ values of less than 1 hour. The effect appears to be independent of the matrix polymer content between 10 and 30% w/w HPMC. However, *SCrit* was dependent on the potency of the salt to impede the hydration of HPMC, with a multivalent salt (trisodium citrate) having 5-10 times the potency of a monovalent salt (sodium chloride) when measured by the cloud point in dilute solution (ΔCPT) and the threshold for disintegration in dissolution tests (*SCrit*).

In line with previous studies, the paddle rotational speed of the USP II dissolution test has been shown to affect drug release rates from HPMC matrices, with faster drug release as the paddle speed increases. The sensitivity to changes in paddle speed increases as the formulations contain less polymer, and a change in drug release mechanism is seen in formulations containing 20% w/w HPMC or less. This suggests that formulations containing 30% w/w HPMC are more resilient to increased hydrodynamic forces, as might be expected for a higher gel strength. A combined challenge of salt and paddle speed resulted in even greater discrimination between 30% w/w HPMC formulations and those containing 20% w/w HPMC or less. Formulations containing 20% w/w HPMC or less showed sensitivity to even lower salt concentrations, as the paddle speed was increased.

A discriminatory *in-vitro* dissolution test was developed to enable an assessment of the dissolution sensitivity of any given formulation. USP II dissolution test conditions of water and 50 RPM replicated ‘standard’ conditions, whilst 0.2 M NaCl and 100 RPM were used to replicate stress conditions. 30% w/w matrices showed less difference in drug release kinetics in the two environments than matrices containing 20% w/w HPMC or less. These tests will be used in Chapters 6 and 7 as a basis to develop lower polymer formulations which show reduced sensitivity to variable *in-vitro* dissolution conditions.

Chapter 5
Examining drug release using the Dynamic Gastric Model (DGM)

5.1 Introduction

The sensitivity of HPMC matrices to the dissolution conditions, with consideration of the matrix polymer content, has been discussed in the previous chapter (Chapter 4). We established that low polymer content matrices show greater sensitivity to increasing USP apparatus II paddle speeds. As the paddle speed increased, these lower polymer content matrices also showed greater sensitivity to the presence of sodium chloride in solution. This suggests that the drug release from lower polymer content matrices (i.e. less than 20% w/w HPMC) is more dependent on the dissolution environment. However, the USP dissolution apparatus are not designed to reflect the *in-vivo* dissolution conditions.

The emergence of biorelevant dissolution testers was discussed in Section 1.4.3. These methods are designed to better reflect the contents of the stomach, and/or the transient forces induced by the intake of food. HPMC based hydrophilic matrices have displayed an occasional food effect, where drug release rates vary under fed and fasted conditions, as discussed in Section 1.4.1. To investigate how the matrix polymer content may influence the susceptibility to a prandial effect, the formulations have been tested in the Dynamic Gastric Model (DGM). The DGM is one of the few models that attempts to replicate GI motility and can offer useful insights into the direct interaction between formulations and food or alcohol.

5.2 Aims

The aims of this chapter are:

- To understand how polymer content might influence the drug release kinetics of HPMC matrices in fasted DGM conditions.
- To compare drug release in the fasted DGM with conventional USP I and USP II compendial dissolution apparatus.
- To explore the influence of an FDA high fat breakfast on drug release using the Dynamic Gastric Model.
- To consider the effect of matrix polymer content on the sensitivity to prandial state.

5.3 Materials and Methods

5.3.1 Materials

Full details of the materials used are described in Appendix 1. The HPMC used was METHOCEL™ K4M CR premium (Colorcon, Dartford, UK).

5.3.2 Manufacture of HPMC matrices

The matrix tablet formulations are listed in Table 4.1. HPMC content was varied between 10% and 30% w/w. The manufacturing methods are described in Section 2.1.

5.3.3 USP apparatus I and II dissolution testing

The release kinetics of caffeine from HPMC matrices were determined in 900 mL de-gassed, de-ionised water at 37 ± 0.5 °C in both USP apparatus I (basket, 100 RPM) and USP apparatus II (paddle, 50 RPM). Caffeine was quantified by UV analysis at λ = 273 nm as fully described in Section 2.3.2. Dissolution data was characterised using the mathematical models discussed in Section 2.3.3.

	Quantity of excipient (% w/w)					
HPMC K4M	10	12.5	15	17.5	20	30
Caffeine	10	10	10	10	10	10
Lactose	53.0	51.3	49.7	48.0	46.3	39.7
MCC	26.5	25.7	24.8	24.0	23.2	19.8
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5

Table 5.1: HPMC matrix tablet formulations. Caffeine was sieved through a 125 µm sieve, other excipients as received. Materials were blended for 15 minutes with magnesium stearate added for the final 2-minute lubrication step. Tablets were 250 ± 5 mg (8 mm Ø, flat-faced, round) and manufactured using direct compression at 150 MPa.

5.3.4 The Dynamic Gastric Model

The DGM is schematically represented in Figure 5.1. The model has two main sections. The top half is a flexible main body which represents the fundal region of stomach. This area has a low mixing rate of 3 pulses per minute. The bottom half of the DGM is a piston and barrel which represents the higher shear antral region of the stomach. This region is responsible for greater processing of the stomach contents.

5.3.4.1 Operation of the Dynamic Gastric Model

The DGM is operated as below:

1. Before the start of the experiment, the DGM was primed with 20 mL of gastric priming acid (composition of solutions in Table 5.2), which simulates the fasting residual acid in the stomach. Food (already chewed or blended with artificial saliva) is added to the main body of the DGM, which represents the fundus. The whole system is jacketed to maintain a temperature of 37 °C.
2. The experiment starts when the tablet sample is added to the main body, this is typically with a glass of water to simulate the patient swallowing the tablet with a drink. Gastric acid and enzymes are added at rates commensurate to those *in-vivo*. These rates vary depending on the pH and volume changes in the contents of the DGM.
3. The main body contracts at a rate of 3 pulses per minute, to gently mix the contents of the fundus with gastric secretions. Some of the contents will transition down to the piston which represents the antral region of the stomach.
4. The up and downward movement of the piston forces the food to pass a flexible annulus during every stroke, which simulates the rhythmic peristaltic contractions of the human stomach, and exerts a shear stress on the antral contents.
5. At defined time points, calibrated to *in-vivo* data and according to the calorific content of the meal, a sample is ejected from the antrum less a dead volume which simulates gastric sieving and the retention of larger particles.

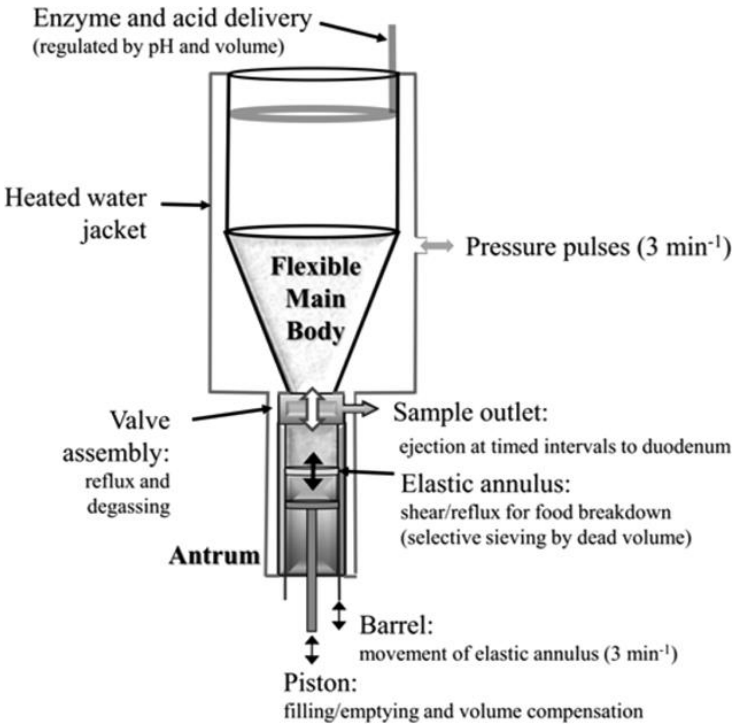


Figure 5.1: Schematic representation of the Dynamic Gastric Model. Reprinted with permission from Koziolek et al. (2013). Copyright 2013 American Chemical Society.

Solution	Component	Concentration
Artificial saliva (pH 6.9)	Salt (NaCl)	150 mM
	Urea	3 mM
	Salivary amylase (human)	36 U/mL
Gastric priming acid	Salts (NaCl, KCl, $CaCl_2$, NaH_2PO_4)	89 mM (total)
	HCl	10 mM
Gastric acid	Salts (NaCl, KCl, $CaCl_2$, NaH_2PO_4)	89 mM
	HCl	10 mM
Gastric enzyme	Salts (NaCl, KCl, $CaCl_2$, NaH_2PO_4)	89 mM (total)
	Egg lecithin	0.38 mM
	Lipase (fungal, DF15)	60 U/mL
	Gastric pepsin (porcine)	8.9 kU/mL

Table 5.2: Composition of solutions used in the Dynamic Gastric Model. Stated concentrations are for the stock solutions used. Final concentrations within the gastric compartment will be significantly lower due to dilution with food bolus and other solutions, bringing them within physiological ranges presented in literature. From: Thuenemann et al. (2015).

5.3.4.2 Gastric digestion in the simulated fasted state

A matrix tablet was added to the DGM containing 20 mL of gastric priming acid, along with 240 mL of water to simulate a patient taking their medication with a glass of water. The DGM was programmed to process for 30 minutes, with the pH dropping from a start reading around pH 2.7 to pH 2.0. Six samples were discharged approx. every 4 minutes Caffeine content in each sample was quantified by UV absorption at λ = 273 nm.

5.3.4.3 Gastric digestion in the simulated fed state

A high fat breakfast, containing fried egg, bacon, hash browns and toast (total of 620 g) with 260 mL full fat milk, was blended in a food processor until the particle size resembled, by eye, a meal chewed by humans. Care was taken not to over-process the mixture. Artificial saliva (pH 6.9) was added, and the meal added to the primed DGM. The tablet was placed on top of the food bolus, along with a simulated glass of water (240 mL). Gastric acid and enzymes were added throughout the experiment at rates that mimicked the pattern of secretions *in-vivo*. The pH readings of ejected samples dropped from pH 6.5 to pH 1.3. Eleven samples were discharged and collected from the DGM at 15 minute intervals, over a period of 2.5 hours. Samples were stored in the fridge until analysis.

5.3.4.4 Quantification of caffeine in the simulated fed state

For caffeine content analysis, each sample was centrifuged for 15 minutes at 4000 RPM (5 °C), and the supernatant recovered. 1 mL of supernatant was added to 1 mL acetonitrile, vortex-mixed, centrifuged for 15 minutes at 4000 RPM (5 °C), and filled into HPLC vials for analysis. HPLC analysis was performed on a Waters 2695 separations module with degasser, connected to a Waters 2487 dual absorbance uv-vis and 996 PDA detectors. Separation was performed on a Kromasil C-18 column (4.6 x 250 mm, Hichrom, UK), proceeded by an analytical security guard column equipped with a security guard C-18 cartridge (4 x 3 mm, Phenomenex, UK). The column temperature was kept at 40 °C by an Igloo-Cil (CIL Cluzeau Info Lab, France) column heater. The mobile phase was a mixture of 0.1M sodium phosphate buffer: HPLC grade acetonitrile (90:10) at pH 3.0, which was filtered through a 0.22 µm GS membrane (Millipore, UK) prior to use. The mobile phase was pumped isocratically at a flow rate of 1 mL/min. Absorbance was monitored at 273 nm. Retention time for caffeine was approximately 9 mins. Chromatograms were analysed using the inbuilt software (Empower 2 software, version 2154).

5.4 Results and Discussion

5.4.1 Drug release in compendial USP I and USP II dissolution tests

Drug release became progressively slower in USP apparatus II as the matrix polymer content increased, as shown in Section 3.4.1. To enable a comparison with the later fasted DGM tests, Figure 5.2 shows the first 0.5 h of the test for drug release in both USP I and USP II dissolution apparatus. It can be seen that even in these early stages, drug release rate is closely related to polymer content and differentiation between profiles can be seen very early (four minutes) into the test.

When drug release profiles were compared using the F_2 similarity model, drug release in USP I and USP II dissolution apparatus was found to be similar at each polymer content, with F_2 values greater than 50. This was true for results of the first 0.5 h, and for the full dissolution test (up to 85% drug release). F_2 values were 54 and 56 for 10% w/w HPMC matrices and between 69 and 90 for all other formulations).

The mechanism of drug release was found to be similar in both USP I and USP II apparatus, with Korsmeyer-Peppas exponent values (*n*) between 0.50 and 0.72 suggesting a mixture of diffusional and erosional release.

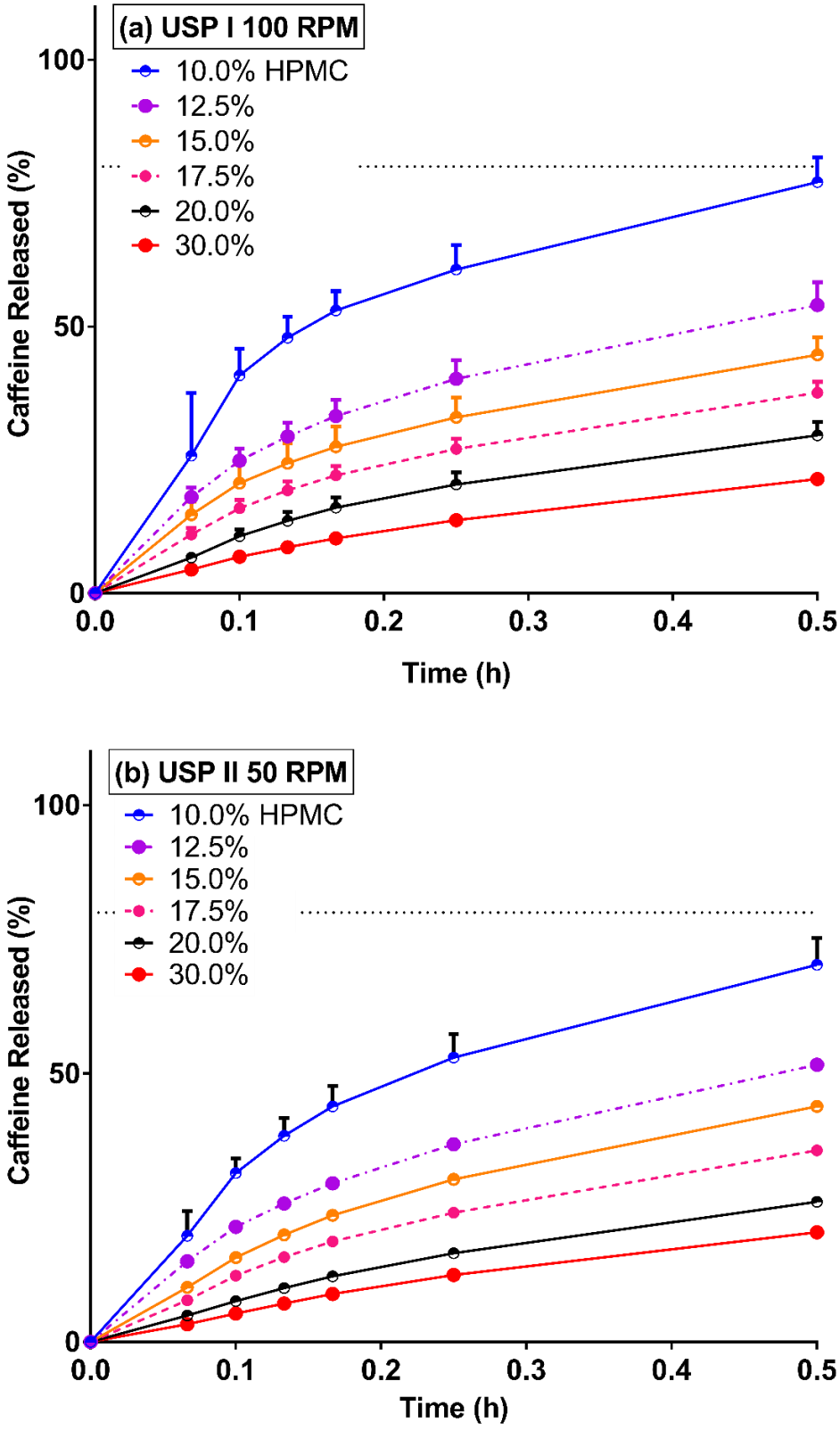


Figure 5.2: Release of caffeine over the first 30 minutes from HPMC matrices as a function of polymer content in compendial USP dissolution tests. Matrix polymer content reported as % w/w HPMC. a) USP I (basket) apparatus at 100 RPM, and b) USP II (paddle) apparatus at 50 RPM. 900 mL water at 37 + 0.5 °C). Mean (n=6) +1 SD. Dotted line represents 80% drug release.

Figure 5.2 is reproduced from International Journal of Pharmaceutics, Volume 510 (1), Mason LM et al, Use of the Dynamic Gastric Model as a tool for investigating fed and fasted sensitivities of low polymer content hydrophilic matrix formulations, 210-220., Copyright (2016), with permission from Elsevier.

5.4.2 Drug release under fasted conditions in the DGM

In the simulated fasted state the DGM was programmed to run for 30 min, ejecting a sample every 4 – 5 min, with six samples in total. Figure 5.3 shows drug release profiles in the fasted state and shows how the release of caffeine from matrices became slower as the matrix polymer content was increased. The release profiles were clearly grouped, with an apparent threshold of change between 15% and 17.5% w/w HPMC. Similar grouping was not apparent in USP compendial apparatus.

The drug release profiles appeared to be linear, suggesting that erosion was a dominant release mechanism in the fasted DGM. Kinetic parameters are detailed in Table 5.3. The release exponent value (*n*) in the fasted DGM increased from 0.69 to 1.02 as the polymer content was increased, suggesting that drug release became more dependent on the erosion of HPMC. A delay or a burst in drug release in the first few minutes of the dissolution test can dramatically change Korsmeyer-Peppas results, and therefore a fit for lag-adjusted values was also calculated. Lag times were calculated from the intercept of zero order fitting, as this showed a better fit for most formulations than Higuchi modelling.

For the majority of formulations (10–20% w/w, with 10–15% w/w being the greatest) there was an initial burst release in drug release, with only the 30% w/w formulation exhibiting a lag time, of about 40 s. After adjusting for the initial burst or lag of drug release, Korsmeyer-Peppas *n* values were found to be very similar (approx. 0.94) for all formulations. This suggests that erosion dominates as the drug release mechanism in the fasted DGM.

This is in contrast to results for the same formulations in USP I or USP II dissolution tests (Section 5.4.1 and Section 3.5.3), where the drug release mechanism was found to be anomalous (mixed diffusion and erosion). The linear DGM profiles suggest that the gel layer is being constantly eroded by the high shear forces. This is supported by photographs of tablets that had been tested in USP I and the DGM for 24 minutes (Figure 5.4). The more rounded gel layers of matrices tested in USP apparatus contrasts with the flatter and more irregular tablets tested in the DGM. This suggests the latter have been subject to much greater erosional forces.

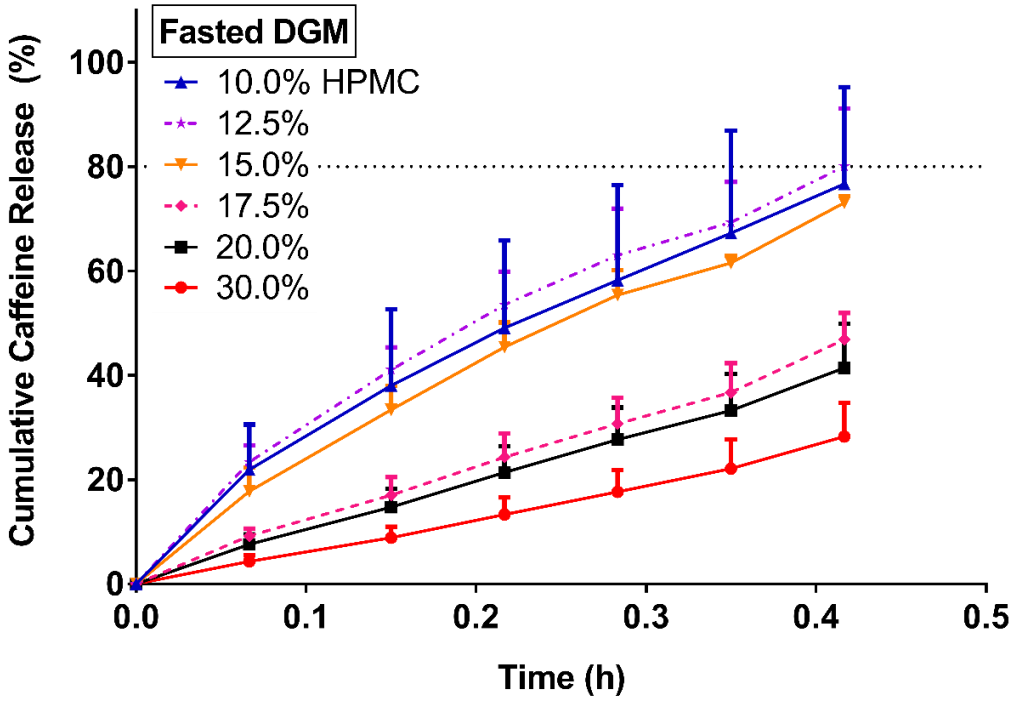


Figure 5.3: Release of caffeine from HPMC matrices in the Dynamic Gastric Model under fasted conditions as a function of polymer content. Matrix polymer content reported as % w/w HPMC. Mean (n=3 + 1 SD). Dotted line represents $T_{80\%}$.

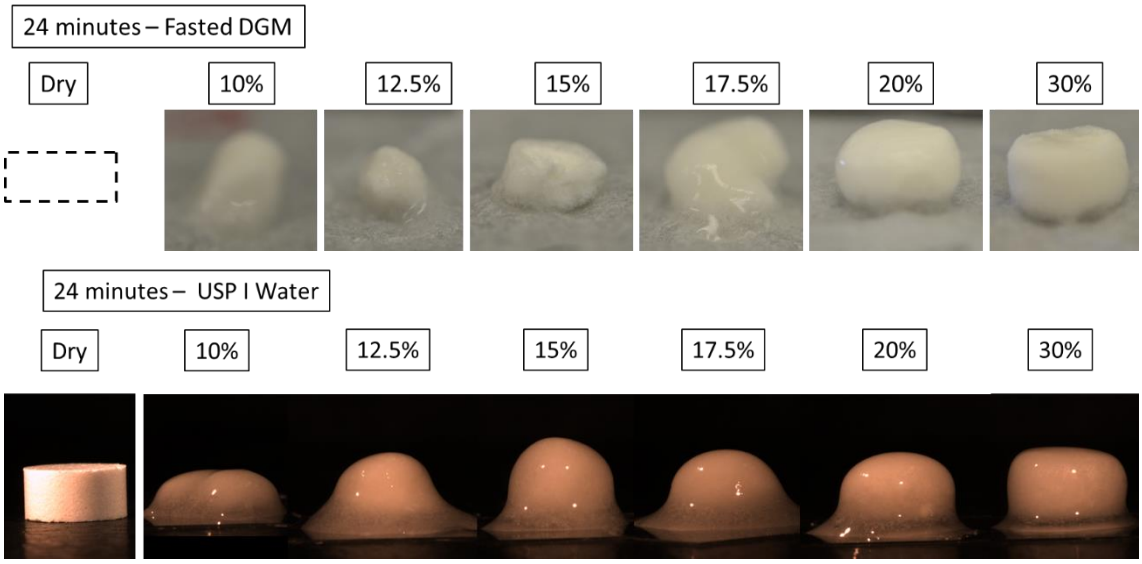


Figure 5.4: Images of HPMC matrices with respect to matrix polymer content and dissolution test. Matrix polymer content reported as % w/w HPMC. (Top) The fasted DGM and (Bottom) USP I basket 100 RPM water. Removed from test after 24 minutes.

Figure 5.3 *and* Figure 5.4 *are reproduced from the International Journal of Pharmaceutics, Volume 510 (1), Mason LM et al, Use of the Dynamic Gastric Model as a tool for investigating fed and fasted sensitivities of low polymer content hydrophilic matrix formulations, 210-220., Copyright (2016), with permission from Elsevier.*

		Zero Order		Korsmeyer-Peppas			Peppas-Sahlin				Lag Time	Korsmeyer-Peppas (Lag Adjusted)		
HPMC content (% w/w)	**T80% (hours)**	**k_{zero} (%/min)**	**Mins**	**K_{kp} ($mins^{-n}$)**	**Mins**	**r^2**	**K_d ($mins^{-0.44}$)**	**K_r ($mins^{-0.88}$)**	**R/F**	**r^2**	**Mins**	**K_{kp} ($mins^{-n}$)**	**n**	**r^2**
10	0.441	2.80	-2.78	8.01	0.69	0.6517	6.73	2.91	0.43	0.5487	-2.78	3.51	0.94	0.6502
12.5	0.43	3.07	-2.66	8.93	0.69	0.9265	6.96	3.26	0.47	0.8971	-2.66	4.07	0.93	0.9230
15	0.62	2.62	-2.55	5.99	0.78	0.9346	4.40	3.19	0.73	0.9470	-2.55	2.72	1.01	0.9285
17.5	0.79	1.75	-0.67	2.59	0.88	0.9387	1E-11	2.90	relaxational	0.9111	-0.67	2.06	0.94	0.9408
20	0.87	1.59	-0.36	1.98	0.92	0.8844	2E-16	2.70	relaxational	0.8422	-0.36	1.74	0.96	0.8852
30	1.32	1.13	0.65	1.00	1.02	0.8854	2E-12	1.53	relaxational	0.8167	0.65	1.28	0.94	0.8828

Table 5.3: Kinetic parameters as a function of polymer content under fasted DGM conditions as calculated from dissolution profiles using three standard models
Calculated from mean dissolution profiles (n=3) using the Korsmeyer-Peppas equation (data between 5% and 70% drug release) and the Peppas-Sahlin model (between 5% and 60%). Lag time was calculated using the zero order equation.

5.4.3 Drug release under fed conditions in the DGM

HPMC matrix formulations were dosed into the DGM along with a high fat, FDA breakfast that had been mechanically blended to resemble food that had been chewed to the point of swallowing. Figure 5.5 shows caffeine release with respect to matrix polymer content under these fed DGM conditions. The profiles all show a substantial delay before the initial release of drug, ranging from 30 to 75 minutes (mean 62.5 minutes). This was followed by slow release of the remaining drug over the following two hours. Lag times were similar, irrespective of the matrix polymer content, and therefore appears to be a general factor associated with the processing of matrices in the fed state.

A number of matrices were ejected prior to the end of gastric processing, as shown in Figure 5.6. Where the time for tablet ejection is recorded as 150 min, this shows either (a) an intact tablet recovered in the final sample, nor during machine dismantling or (b) no fragment remaining. 44% of tablets tested in the fed state study were ejected from the DGM before complete tablet dissolution had occurred. Results seem to suggest that matrices containing higher HPMC content were more likely to eject prematurely, however, given that no intact fragments were found for 7 out of 18 matrices (39%), either in ejected samples or when the machine was dismantled, it is more likely that the lower polymer content tablets had fully eroded over the 2.5 h in the DGM. This could be expected for the lower polymer content formulations. The ejection of tablets from the DGM occurred as a random, unpredictable event, similar to fed state physiological studies, in which gastric emptying time has been found to vary between 2 h to >8 h in subjects fed with a heavy breakfast (Davis et al., 1986) although a recent study found a more consistent gastric emptying time of 3.5 h (± 35 mins) for 11 mm diameter hydrophilic matrix tablets (Weitschies et al., 2005). The average gastric emptying time was faster in our study, which may be due to a smaller tablet size. When the tablet was ejected, the experiment was halted, and data up to this point was used for drug release analysis. This enabled a comparison of the drug release between formulations under fed conditions.

Under fed state conditions, there was little apparent difference in the rate of drug release between formulations that contain different HPMC contents. Whilst some differences could be masked by the greater sample variability, the results suggest that drug release rates may be driven by the fed conditions of the stomach, rather than the polymer content of the tablet. The rate of drug release, calculated by a zero order equation (with data offset so that drug was first detected at 15 minutes) was around 0.9%/min for all formulations.

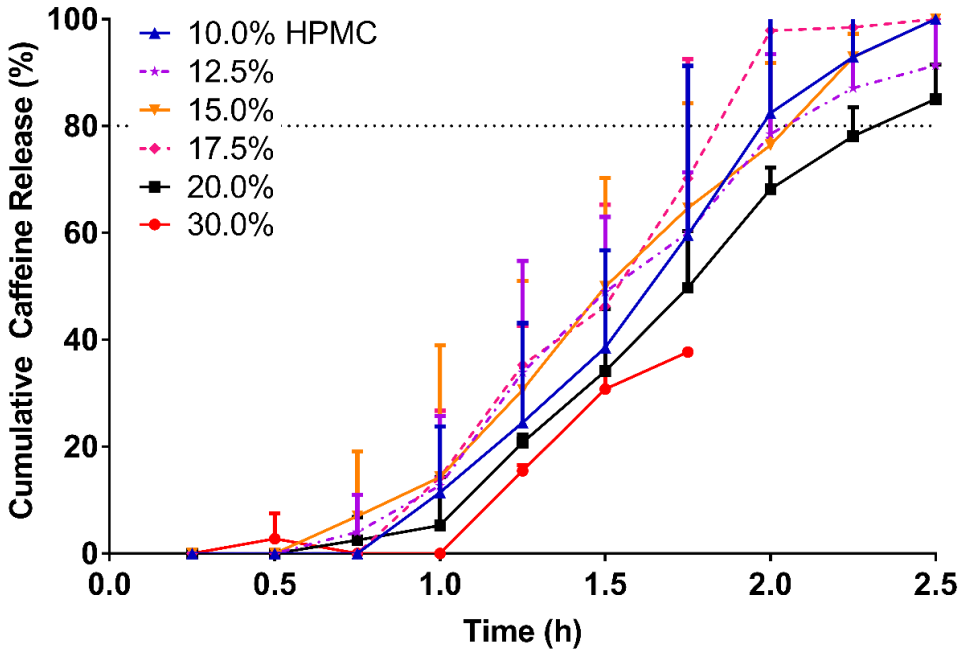


Figure 5.5: Release of caffeine from HPMC matrices in the Dynamic Gastric Model under fed conditions as a function of polymer content. Matrix polymer content reported as % w/w HPMC. Meal was FDA breakfast with gastric acid addition. Mean (n=3) + 1 SD. Dotted line represents T80%.

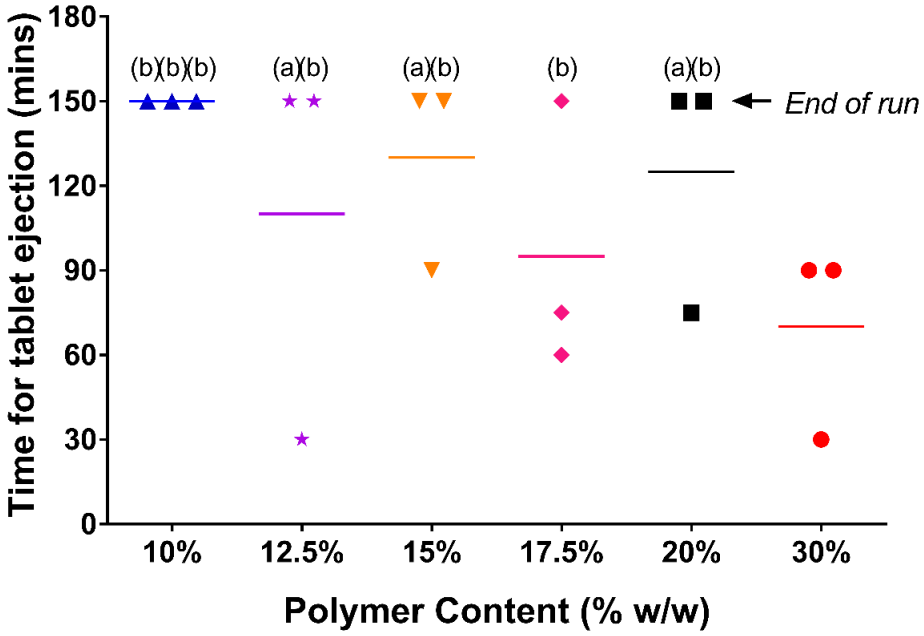


Figure 5.6: Time point at which fragments or whole tablets were ejected from the fed DGM Each replicate with mean. Colours represent polymer concentration as in previous figures. (a) Intact tablet recovered in final sample/during machine dismantling and (b) no tablet fragment recovered.

5.4.4 Comparing drug release under fasted and fed conditions in the DGM, with respect to matrix polymer content

Under fed conditions there was a mean lag time of 62.5 minute, whereas no significant lag time was observed under fasted conditions. The initial delay could be the result of the slower movement of the tablet through the food bolus, which would be related to the viscosity of the meal, and buoyancy of the hydrated matrix (Davis et al., 1986). Another potential factor is that the DGM contents are likely to be less uniformly mixed under fed conditions, than under fasted conditions. Therefore, caffeine released in the upper part of the DGM may not appear in the ejected samples until sufficient gastric processing has occurred. Nonetheless, several *in-vivo* studies have reported a similar delay. This has been attributed to the formation of a film on the surface of the tablet, which impedes water ingress (Abrahamsson et al., 1998a, Weitschies et al., 2005, Davis et al., 2009, Brouwers et al., 2011). Williams et al. have shown that fat can accumulate this way on the surface of a hydrated HPMC matrix (Williams et al., 2011).

Figure 5.7 compares drug release profiles for 10%, 20% and 30% w/w matrices in fasted and fed DGM conditions. Results from the fed DGM have been adjusted so that initial detection of caffeine occurs at 15 minutes. This allows a direct comparison of the rate of caffeine release. It can be seen that the drug release from matrices containing 30% w/w HPMC was similar in the fasted and fed DGM conditions. However, in the case of matrices containing a lower polymer content (20% or 10% w/w), drug release was faster under fasted conditions than under fed conditions. This may suggest that it is the deposition of fat on the matrix surface that is slowing drug release under fed conditions. 30% w/w matrices may be less affected as the gel layer is already an effective retarder of drug release, and therefore addition of fat to this layer has minimal impact. The importance of matrix polymer content is in agreement with a previous study where formulations with a polymer content above the percolation threshold (40% w/w) showed less sensitivity to *in-vivo* conditions, compared to a matrix with a polymer content below the threshold (20% w/w) (Ghimire et al., 2010).

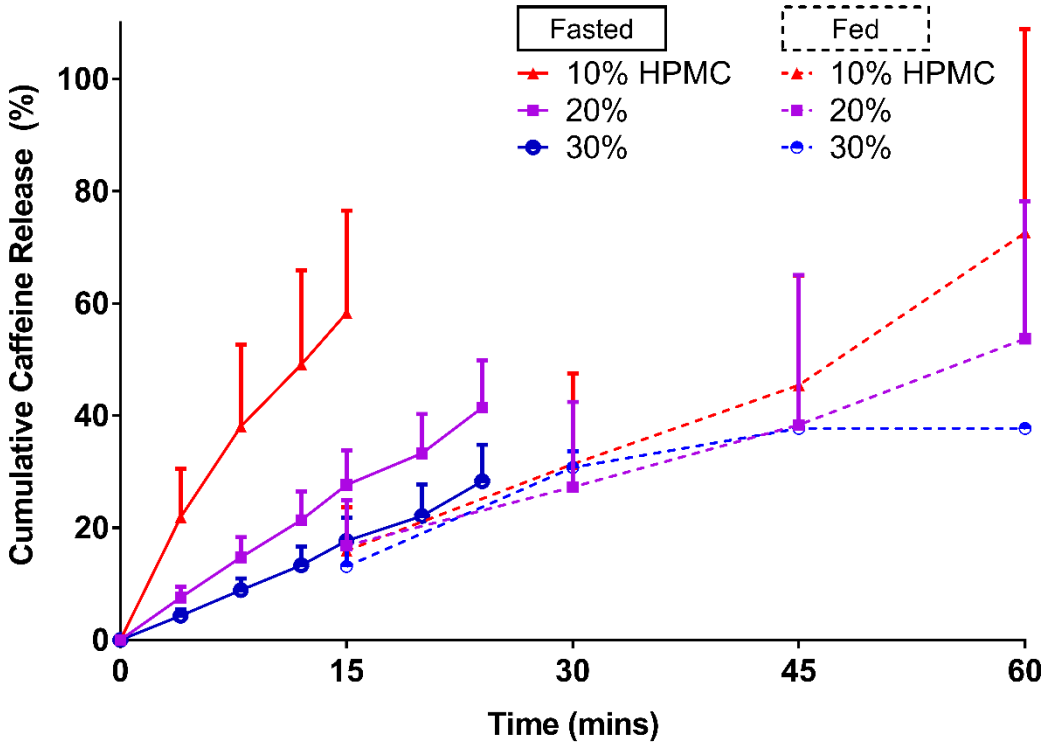


Figure 5.7: Release of caffeine from 10%, 20% and 30% w/w HPMC matrices in the Dynamic Gastric Model under fasted and fed conditions.. Fasted (solid line) and fed (dashed line) with fed data adjusted so first caffeine release at 15 minutes. Mean (n=3) + 1 SD

5.4.5 A comparison of presented DGM data with other published *in-vivo*/biorelevant *in-vitro* dissolution data

HPMC matrices have often been studied in biorelevant / *in-vivo* studies owing to their occasional food effect. It is unclear how the formulation of HPMC matrices may influence the propensity to food effects; whilst Ghimire et al. (2007) found post-prandial effects occurred only when polymer content was lowered below the percolation threshold, Abrahamsson et al. (1999) reported two formulations both containing approximately 50% w/w HPMC, where one showed *in-vivo* food effects whilst the other was insensitive. Direct comparisons between studies is difficult as several properties of the studied formulations differ, which could also influence the sensitivity of such formulations to food.

Unlike the results from our study, where slower drug release was observed from formulations under fed conditions, several *in-vivo* studies have reported faster drug release from HPMC matrices under similar fed conditions (Abrahamsson et al., 1998a, Davis et al., 2009, Jain et al., 2014). Results from different studies are not always directly comparable due to the different formulations that are used, resulting in different drug release mechanisms. For example, Jain et al. (2014) used formulations containing low molecular weight HPMC and high contents of dicalcium phosphate, both factors encouraging erosional drug release, as they highlighted with their mention of linear drug release profiles. The formulations used in this study exhibit diffusional drug release under USP conditions, which may make them especially susceptible to the reduced matrix hydration under fed conditions. Mercuri et al. (2011) suggest that the DGM is able to mimic fat processing (lipolysis) that is reported as important to ensure reliable conclusions on fat effects are drawn (Diakidou et al., 2009), and therefore we don't anticipate that the DGM will draw erroneous conclusions on the impact of fats on the matrix surface. It is worth noting that for some HPMC formulations, fed versus fasted conditions have little impact on *in-vivo* drug release (Abrahamsson et al., 1993, Gai et al., 1999, Delrat et al., 2002). Weitschies et al. (2005) discuss that plasma peaks, caused by excess matrix erosion may be due to poor mixing under fed conditions rather than failure of the formulation. Poor mixing could also result in seemingly slower drug release profiles.

5.4.6 Comparing drug release profiles obtained in the DGM with the modified USP dissolution apparatus

In Chapter 4, Section 4.4.5, the impact of the combination of salts and increased paddle rotational speed on drug dissolution from matrices was discussed. Following these results, a 'stress' dissolution test of 0.2 M NaCl and 100 RPM paddle speed was developed to allow formulations to be screened for potential dissolution sensitivities (as described in Section 4.4.7.1). Formulations showing a different drug release profile in 0.2 M / 100 RPM to that seen in water / 50 RPM were predicted to be at a greater risk of *in-vivo* dissolution variability. The 'stress' test conditions were also similar to the conditions reported by Abrahamsson to be necessary for *in-vitro*, *in-vivo* correlations (0.14 M NaCl/140 RPM) (Abrahamsson et al., 1998b). Our stress test suggested that HPMC matrices containing 7.5 – 20% w/w HPMC would be more likely to show *in-vivo* dissolution sensitivity than one containing 30% w/w HPMC.

Figure 5.8 shows the release of caffeine from formulations containing 10%, 20% and 30% w/w HPMC, in different DGM and USP conditions. In the case of 10% w/w HPMC matrices, drug release under fed DGM conditions was much slower than in any of the USP conditions or the fasted DGM. Fasted DGM results were most similar to the "standard" USP II conditions (water, 50 RPM).

In the case of 20% w/w HPMC matrices (Figure 5.8b), drug release under fed DGM conditions was most similar to the rate in "standard" USP II conditions during the first 30 minutes. However, the rate under fed conditions was faster over the remainder of the dissolution test. The shape of the curves is noticeably different depending on the apparatus used, being linear for tests in the DGM and more rounded for those in USP apparatus. As discussed in Section 5.4.2, this is thought to be due to the greater shear and erosional forces that the dosage form is exposed to in the Dynamic Gastric Model.

Results for 30% w/w HPMC matrices are much more similar to each other, with respect to the dissolution conditions. Results in the different DGM conditions are similar to each other, as are results from different USP II conditions; albeit DGM results are only over a 1 hour time frame.

None of the USP II dissolution conditions produced a linear, extended release curve as seen in the DGM. This suggests that even at high paddle speeds, the shear rates generated in USP II apparatus do not match those generated in the DGM.

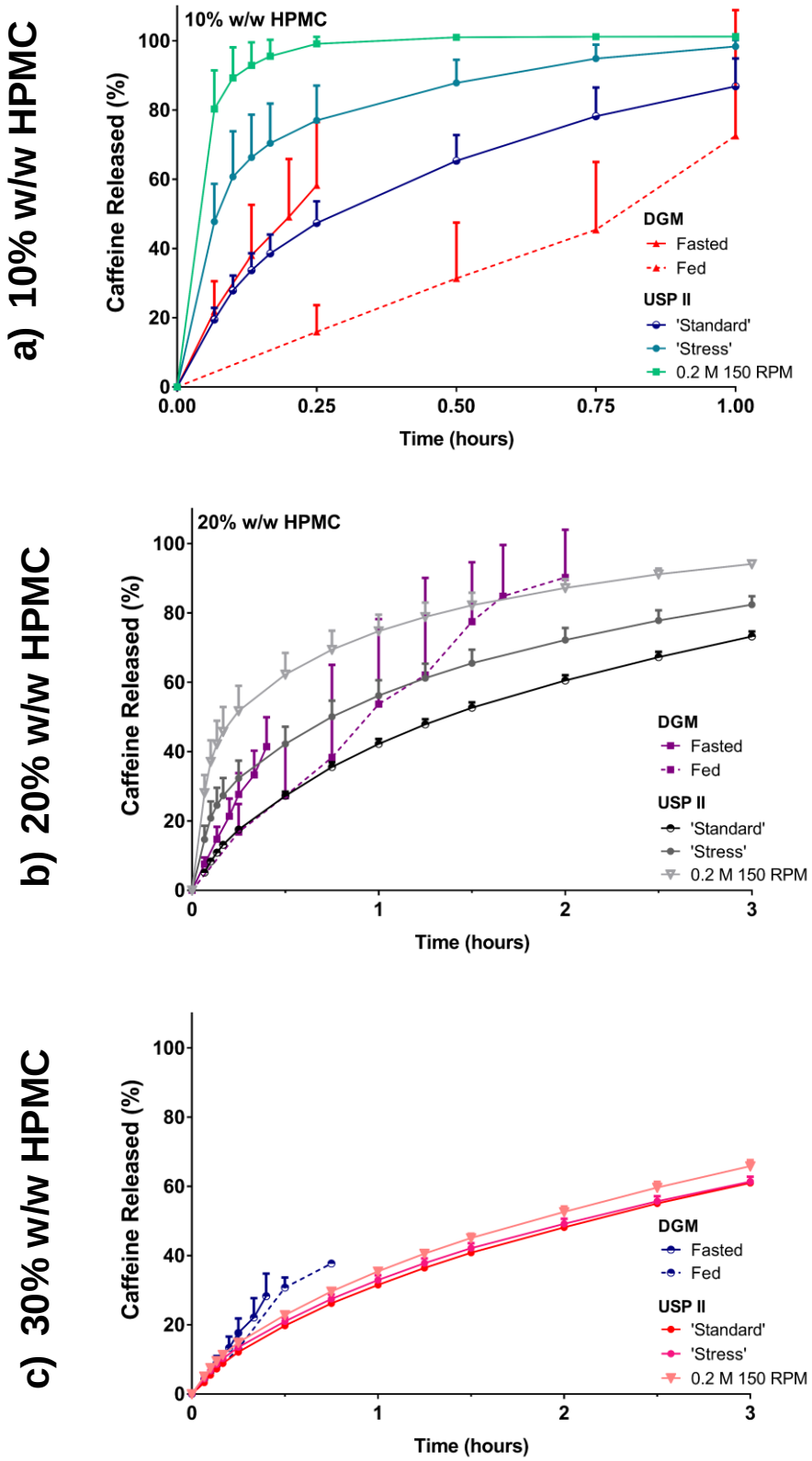


Figure 5.8: Release of caffeine from HPMC matrices in different DGM and USP conditions. Matrix tablet polymer content of a) 10% w/w, b) 20% w/w and c) 30% w/w HPMC. Dynamic gastric model (DGM) under fasted or fed (FDA breakfast) conditions, described in Section 5.3.4. USP tests were USP apparatus II, 900 mL media at 37 ± 0.5 °C. “Standard” conditions were in water at 50 RPM. “Stress” conditions were in 0.2 M NaCl at 100 RPM, 0.2 M 150 RPM means conditions of 0.2 M NaCl at 150 RPM paddle speed. All results mean (n=3) ± 1 SD.

5.5 Conclusions

The Dynamic Gastric Model has been used to evaluate drug release from extended release (ER) formulations, allowing *in-vitro* predictions of the possible impact of formulation changes on drug release under bio-relevant conditions.

When hydrophilic matrix tablets were tested under fasted conditions, polymer content had a clear effect on drug release rates, with faster drug release as the polymer content was lowered. In compendial USP apparatus, there was clear, stepwise discrimination between matrix formulations containing different polymer contents. However, in the fasted DGM apparatus, formulations with polymer content between 10 and 15% w/w, and 17.5% and 20% w/w, behaved more similarly to one another, which could suggest that formulation changes which seem significant in USP apparatus may not necessarily manifest into differences under more biorelevant conditions. The environment of the fasted DGM was found to be more erosional than that of the USP apparatus, with the gel layer being constantly eroded, resulting in linear, first order kinetics.

In the fed state, drug release was heavily influenced by the presence of a high fat meal, with a significant delay being apparent before drug was present in ejected samples. This may be due to the physical impedance by food on the transit of the dosage form into the high shear, antral region, or alternatively a reduced availability of water. Remarkably, under fed conditions in the DGM, all formulations released drug at similar rates despite the large differences in polymer content.

Once data was adjusted for the lag time, it was observed that for formulations containing 20% w/w polymer or less, drug release was faster under fasted conditions than in fed conditions. This could be due to the deposition of fat onto the matrix surface, providing a greater diffusional barrier. For matrices containing 30% w/w HPMC, the drug release rate was similar in fasted and fed DGM studies, which suggests that formulations with higher polymer content may be less sensitive to changes in the dissolution environment.

In this study, we were able to determine that HPMC formulations with reduced polymer content (20% w/w or lower) show sensitivity to prandial state, that was not apparent when the matrix contained 30% w/w HPMC. Results from USP apparatus showed greater discrimination between formulations than was seen under the more biorelevant conditions of the fasted DGM.

Chapter 6
Strategies for improving low polymer content matrices: (1) Changing HPMC properties

6.1 Introduction

The results of Chapter 4 showed how reducing the matrix polymer content from the recommended 30% w/w to 10 – 15% w/w HPMC resulted in drug release becoming more sensitive to salts in the dissolution environment. The sensitivity of matrices to the presence of ionic salts in the dissolution medium was similar irrespective of the matrix polymer content. However, lowering the matrix polymer content resulted in greater sensitivity to increased hydrodynamic forces, as drug release became faster as the USP II paddle speed was increased from 25 to 150 RPM. A combination of NaCl and increased paddle speed resulted in even greater increases in drug release rate. The Dynamic Gastric Model studies reported in Chapter 5 showed that only matrices with 30% w/w HPMC could provide drug release rates that were similar in 'fasted' and 'fed' dissolution environments. Matrices containing 20% w/w HPMC or less released their drug content 1.5 to 3 times faster under 'fasted' conditions. The fastest release rates were shown by matrices with the lowest polymer content.

These results suggest that the low polymer content formulations may exhibit more variable drug release rates *in-vivo,* which may be a function of the prandial state, whereas this is less likely in matrices containing 30% HPMC. Any variability in drug release according to prandial state is undesirable, because it may lead to inconsistent clinical efficacy.

As discussed in Section 1.3.1, the physical properties of HPMC can markedly influence drug release rates. In particular, HPMC particle size and viscosity grade can have profound effects. It is presently unclear how these parameters might influence the drug release rate variability in low polymer content matrices.

6.2 Aims

The overall aims of chapter 6 and 7 are:

- To develop formulation strategies to reduce the amount of rate controlling excipient necessary in a HPMC matrix formulation, with the aim of reducing polymer content to below 30%.
- To develop formulation strategies that reduce how sensitive HPMC matrix formulations are to the dissolution environment, at low polymer content.

The objectives of this chapter are to:

- Investigate how changing the molecular weight grade of HPMC influences drug release as a function of matrix tablet polymer content and dissolution environment
- Investigate how changing the particle size of HPMC influences drug release as a function of matrix tablet polymer content and dissolution environment

6.3 Materials and Methods

6.3.1 Materials

Full details of the materials used are described in Appendix 1.

6.3.1.1 HPMC viscosity grades

Four viscosity grades of HPMC were used in this study: METHOCEL™ 100LV CR Premium, METHOCEL™ K4M CR Premium, METHOCEL™ K100M CR Premium and METHOCEL™ K200M CR Premium (Colorcon, Dartford, UK). The viscosities of each HPMC grade, as taken from the certificate of analysis, are listed in Table 6.1. Other polymer characteristics are listed in Section 2.1.1.

6.3.1.2 METHOCEL K4M particle size fractions

Particle size fractions of METHOCEL K4M were obtained using sieves of mesh size 125 µm, 90 µm, 63 µm and 45 µm (Endecott, UK).

6.3.2 Formulation and manufacture of HPMC matrices

A number of different matrices were manufactured, with the basic formulations listed in Table 6.2. Included within formulations, in accordance to the objectives of each section, were HPMC viscosity grades METHOCEL K100LV, K4M, K100M and K200M, and the HPMC K4M particle size fractions of > 125 µm, 90 - 125 µm, < 90 µm, 63 - 90 µm, < 63 µm, 45 - 63 µm and < 45 µm. The manufacturing methods are described in Section 2.1.

6.3.3 USP apparatus II (paddle) dissolution testing

Drug release kinetics were determined in 900 mL de-gassed, de-ionised media 37 ± 0.5 °C in USP apparatus II (paddle). ‘Standard’ (50 RPM paddle speed and water) and ‘stressed’ (100 RPM paddle speed and 0.2 M NaCl) dissolution conditions were used.

Caffeine was quantified at a UV absorbance of λ = 273 nm as fully described in Section 2.3.2. Dissolution data was characterised using the mathematical models discussed in Section 2.3.3.

	K100LV	K4M	K100M	K200M
Viscosity (cP)	95	3,990	102,634	218,953

Table 6.1: Viscosity of HPMC grades. Data from certificate of analysis (Colorcon, UK) Viscosity of 2% w/v solution at 20 °C

	Quantity of excipient (% w/w)									
HPMC	5	7.5	10	12.5	15	17.5	20	30	40	50
Caffeine	10	10	10	10	10	10	10	10	10	10
Lactose	56.3	54.7	53.0	51.3	49.7	48.0	46.3	39.7	33.0	26.3
MCC	28.2	27.3	26.5	25.7	24.8	24.0	23.2	19.8	16.5	13.2
MgSt	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Table 6.2: HPMC matrix tablet formulations. Caffeine was sieved through a 125 µm sieve, other excipients as received. Materials were blended for 15 minutes with magnesium stearate added for the final 2-minute lubrication step. Tablets were 250 ± 5 mg (8 mm Ø, flat-faced, round) and manufactured using direct compression at 150 MPa. MCC is Avicel PH102. MgSt is magnesium stearate.
The HPMC grades used were: METHOCEL K100LV, K4M, K100M and K200M. In the particle size experiments, particle size fractions of METHOCEL K4M were > 125 µm, 90 - 125 µm, < 90 µm, 63 - 90 µm, < 63 µm, 45 - 63 µm and < 45 µm.

6.3.4 Determination of excipient true density using helium pycnometry

The solid volume fraction of matrices was determined using true density measurements of the powders, obtained by helium pycnometry, using the method in Section 2.4.2.

6.3.5 Estimation of the percolation threshold from dissolution kinetic parameters

Percolation threshold estimates were made using linear regression of the Higuchi rate constants against the matrix HPMC content, as fully described in Section 2.3.4.

6.3.6 Confocal microscopy imaging of early gel layer formation

Imaging of early gel formation was undertaken in 0.008% w/v Congo red using a Bio-Rad MRC-600 confocal microscope (Bio-Rad, Hemel Hempstead, UK) and using the methods described in Section 2.3.5. The tablet was held between two Perspex® discs allowing imaging of the matrix from overhead, to capture the processes of gel layer formation at the radial edge of the tablet.

6.3.7 Time lapse photography of hydrating matrices

Matrices, fixed to a Perspex® stand and held in a water-jacketed beaker, were photographed every 30 seconds from the addition of media at 37 ± 1 °C. A series of images were obtained for the first 30 minutes of hydration. Full methods are described in Section 2.3.6.

6.3.8 Sieve analysis to determine HPMC particle size distribution

The particle size distribution of HPMC was determined using sieve analysis according to USP methods, and as fully described in 2.4.1.

6.4 Results and Discussions

The chapter is formatted into 2 sections.

Section A	The effect of **HPMC viscosity grade**	6.4.1 - 6.4.2
Section B	The effect of **HPMC particle size**	6.4.3 - 6.4.4

Section A:

The effect of HPMC viscosity grade on drug release from low polymer content matrices

6.4.1 Result: Effect of HPMC viscosity

6.4.1.1 Extended release properties of matrices with respect to HPMC viscosity grade

Figure 6.1 shows caffeine release from matrices of different polymer contents as a function of the HPMC viscosity grade. Viscosities ranged from the low viscosity K100LV to the high viscosity grade K200M. Dissolution data were characterised by their $T_{80\%}$ and DR10min values, and the Higuchi and Korsmeyer-Peppas equations were fitted to the data. The results are shown in Table 6.3.

For each of the HPMC viscosity grades studied, drug release became slower as the matrix polymer content was increased. The drug release curve was similar in shape, irrespective of the viscosity grade used, which suggests that all formulations have a similar drug release mechanism. This is supported by Korsmeyer-Peppas (*n*) between 0.50 and 0.78 which signifies an anomalous release mechanism. Formulations containing lower HPMC contents, below 15% w/w, typically exhibited more variability than those containing 30% w/w HPMC. This is seen from the larger error bars.

$T_{80\%}$ values and Higuchi rate constants for each formulation are plotted with respect to the viscosity grade in Figure 6.2 and Figure 6.3. As previously observed with K4M matrices (Section 3.4.1), $T_{80\%}$ decreased and Higuchi rate constants increased as the matrix polymer content was lowered. This was the same with all viscosity grades. For any particular matrix polymer content, the drug release rate was faster as the polymer viscosity was decreased.

The dotted lines in Figure 6.2 and Figure 6.3 show the mean $T_{80\%}$ and Higuchi rate constant values for 15% w/w K4M and 30% w/w K4M matrices, which had $T_{80\%}$ values of 2.5 and 5 hours respectively. Approximations of equivalent matrix polymer contents (% w/w) were;

- 17.5% K100LV = 15% K4M = 15% K100M = 10% K200M
- 50% K100LV = 30% K4M = 25% K100M = 20% K200M

The approximations showed that when a lower viscosity grade of HPMC is used, a higher matrix content was necessary to obtain equivalent drug release profiles, all other factors remaining constant.

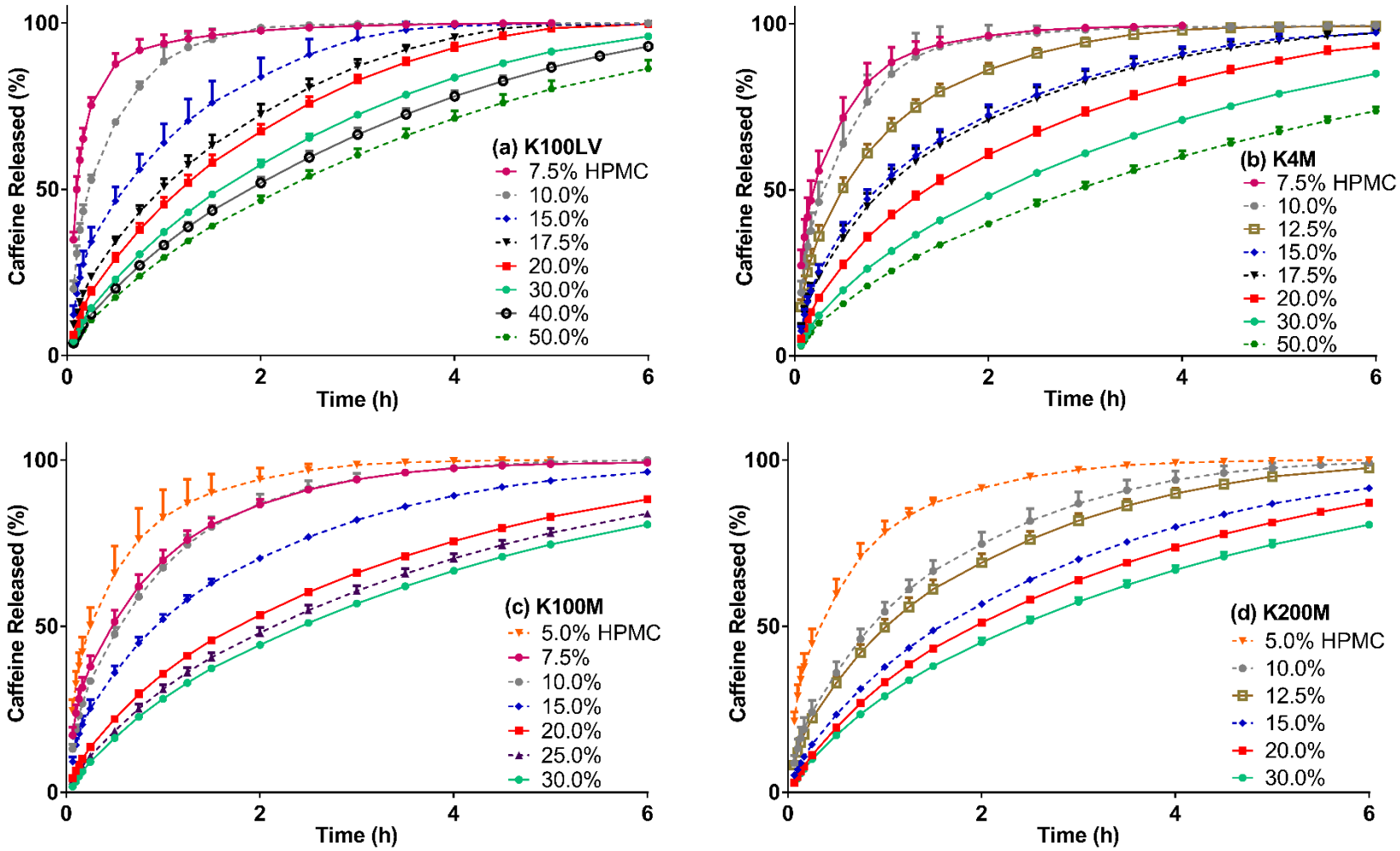


Figure 6.1: Release of caffeine from HPMC matrices as a function of polymer content for formulations containing different HPMC viscosity grades Polymer content reported as % w/w HPMC. HPMC grades were (a) K100LV, (b) K4M, (c) K100M and (d) K200M. USP apparatus II, 50 RPM, 900 mL water, 37 ± 0.5 °C. Mean (n=3) ± 1 SD.

Polymer Grade	Polymer Content (% w/w)	T80% (hours)	DR10min (%)	Higuchi		Korsmeyer-Peppas		
				k_h (mins$^{-0.5}$)	r^2	K_{kp} (mins^{-n})	*n*	r^2
K100LV	7.5%	0.35 ± 0.04	65.2 ± 3.2	26.10 ± 2.25	0.9306	13.8	0.69	0.9332
	10%	0.74 ± 0.04	43.4 ± 2.0	13.93 ± 0.68	0.9633	9.98	0.60	0.9353
	15%	1.74 ± 0.38	27.4 ± 4.0	8.67 ± 0.41	0.9528	6.52	0.58	0.9276
	17.5%	2.47 ± 0.18	18.6 ± 0.9	7.11 ± 0.11	0.9932	4.49	0.59	0.9910
	20%	2.80 ± 0.13	14.6 ± 1.2	6.83 ± 0.09	0.9949	2.85	0.67	0.9885
	30%	3.65 ± 0.08	10.6 ± 0.4	6.00 ± 0.04	0.9975	2.05	0.70	0.9968
	40%	4.22 ± 0.17	9.2 ± 0.4	5.54 ± 0.06	0.9960	1.77	0.71	0.9968
	50%	5.02 ± 0.37	7.8 ± 0.2	5.17 ± 0.06	0.9957	1.51	0.72	0.9974
K4M	7.5%	0.71 ± 0.14	46.8 ± 6.0	15.12 ± 1.54	0.7742	13.0	0.55	0.7858
	10%	0.88 ± 0.27	37.7 ± 5.4	12.60 ± 0.78	0.8860	9.11	0.59	0.8683
	12.5%	1.49 ± 0.20	28.9 ± 3.4	9.86 ± 0.30	0.9633	7.47	0.57	0.9397
	15%	2.63 ± 0.27	19.5 ± 1.7	7.91 ± 0.20	0.9820	3.32	0.69	0.9596
	17.5%	2.74 ± 0.33	18.6 ± 3.3	7.40 ± 0.17	0.9716	3.77	0.64	0.9503
	20%	3.72 ± 0.17	13.1 ± 0.8	6.11 ± 0.05	0.9954	2.90	0.64	0.9905
	30%	5.17 ± 0.09	8.8 ± 0.2	5.07 ± 0.02	0.9996	1.81	0.68	0.9950
	50%	7.27 ± 0.25	7.2 ± 0.2	4.28 ± 0.03	0.9983	1.08	0.75	0.9932
K100M	5%	0.94 ± 0.29	42.2 ± 4.4	13.58 ± 1.60	0.8471	11.8	0.54	0.8464
	7.5%	1.47 ± 0.14	31.5 ± 2.9	9.17 ± 0.40	0.9654	9.30	0.51	0.9480
	10%	1.53 ± 0.16	26.7 ± 1.0	9.31 ± 0.19	0.9912	6.57	0.58	0.9802
	15%	2.81 ± 0.08	20.3 ± 2.7	7.03 ± 0.13	0.9903	4.90	0.58	0.9704
	20%	4.58 ± 0.06	10.1 ± 0.6	5.52 ± 0.04	0.9983	2.08	0.68	0.9945
	25%	5.33 ± 0.22	7.9 ± 0.9	5.14 ± 0.05	0.9968	1.47	0.73	0.9917
	30%	5.90 ± 0.10	6.2 ± 0.2	4.98 ± 0.03	0.9991	1.28	0.74	0.9925
K200M	5%	1.08 ± 0.14	37.7 ± 4.1	10.63 ± 0.78	0.9212	11.5	0.50	0.9141
	10%	2.40 ± 0.29	19.0 ± 3.4	7.70 ± 0.18	0.9847	4.14	0.63	0.9574
	12.5%	2.84 ± 0.21	17.5 ± 1.2	7.03 ± 0.12	0.9920	3.92	0.62	0.9855
	15%	4.02 ± 0.01	10.7 ± 0.3	5.84 ± 0.03	0.9989	2.08	0.70	0.9948
	20%	4.83 ± 0.07	7.9 ± 0.3	5.44 ± 0.03	0.9990	1.23	0.78	0.9903
	30%	5.91 ± 0.20	7.0 ± 0.5	4.86 ± 0.03	0.9981	1.15	0.77	0.9910

Table 6.3 The effect of HPMC viscosity grade and matrix HPMC content on drug release kinetics. Measured as $T_{80\%}$, DR10min, Higuchi and Korsmeyer-Peppas dissolution parameters. Mean (n=3). (For $T_{80\%}$, DR10min and Higuchi: ± 1 SD)

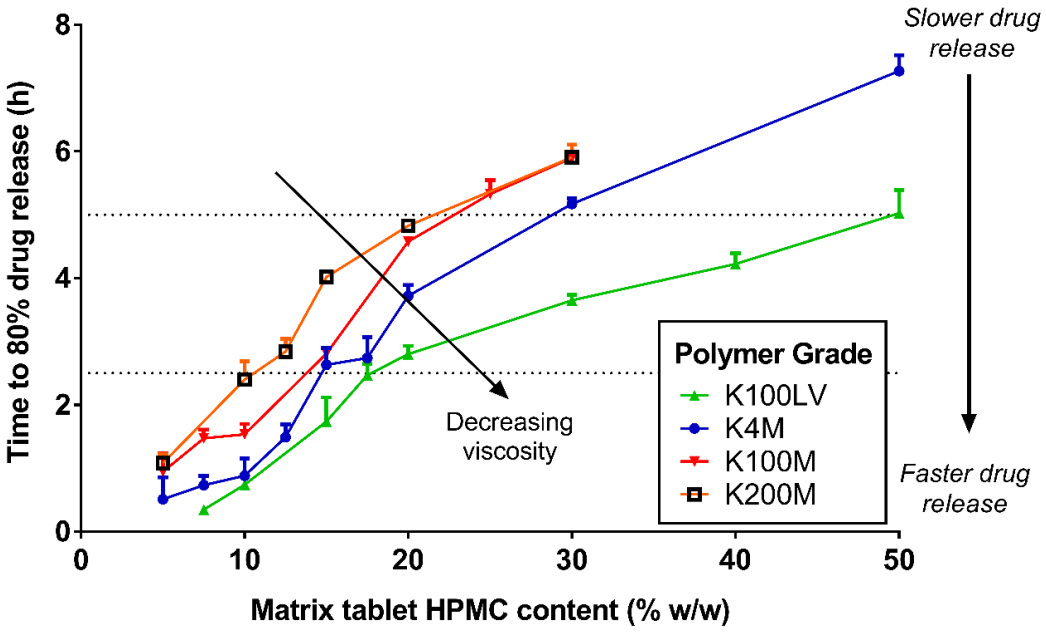


Figure 6.2: Time for 80% caffeine release ($T_{80\%}$) from HPMC matrices as a function of matrix HPMC content and HPMC grade. USP apparatus II, 50 RPM, 900 mL, 37 ± 0.5 °C. Mean (n=3) + 1 SD. Dotted lines are $T_{80\%}$ = 2.5 hours and $T_{80\%}$ = 5 hours

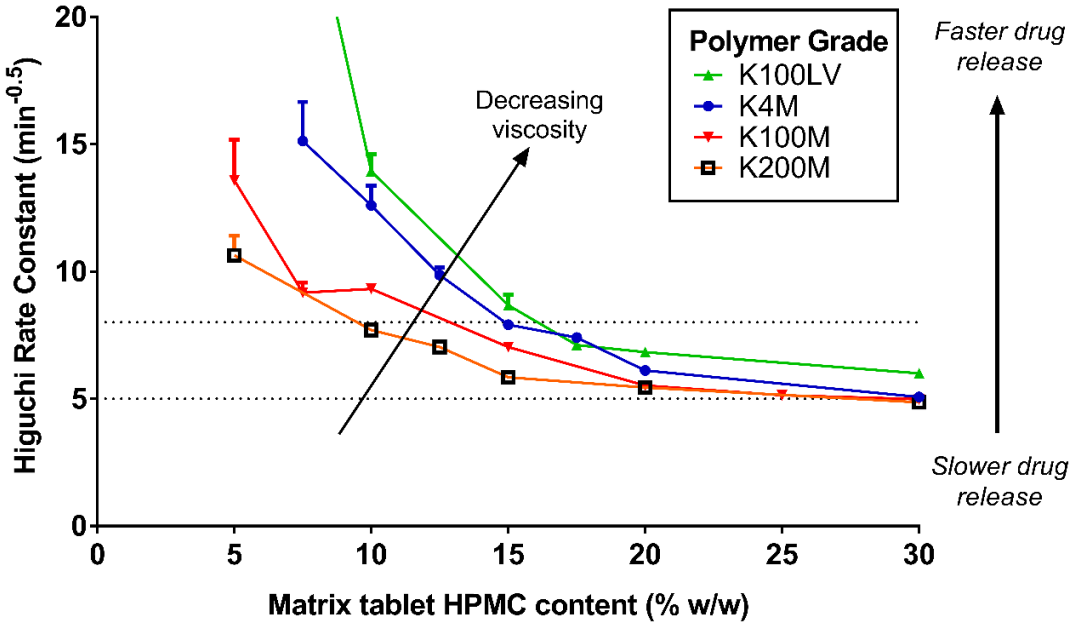


Figure 6.3: Higuchi rate constant of HPMC matrices as a function of matrix HPMC content and HPMC grade. USP apparatus II, 50 RPM, 900 mL, 37 ± 0.5 °C. Mean (n=3) + 1 SD. Dotted lines are Higuchi rate constants of 5 $min^{-0.5}$ and 8 $min^{-0.5}$

6.4.1.2 Effect of HPMC viscosity on matrix percolation threshold

As concluded from the results in Chapter 3 and 4, HPMC matrices should include a polymer content higher than the percolation threshold, in order to minimise variability in drug release. Percolation threshold values were estimated for each of the different viscosity grades.

The true density values determined by helium pycnometry for the different HPMC viscosity grades are compared in Table 6.4. HPMC viscosity grade appeared to have minimal effect on particle true density, with all values being between 1.31 and 1.33 gcm^{-3}. For comparison, the true density values determined previously for caffeine was 1.45, lactose 1.54, MCC 1.55 and magnesium stearate 1.08 gcm^{-3}.

Due to the low number of formulations manufactured, it was felt inappropriate to attempt to generate two linear regression lines in order to estimate the percolation threshold. Therefore, estimation was made by eye based on Figure 6.4. For all formulations, the apparent region of change was between 12 and 17% v/v HPMC content. K200M appeared to have a slightly lower percolation threshold than the other grades.

HPMC Grade	True Density (g/cm^3)		
	Run 1	Run 2	Average
K100LV	1.3256 ± 0.0007	1.3245 ± 0.0005	1.3251
K4M	1.3252 ± 0.0011	1.3216 ± 0.0002	1.3234
K100M	1.3134 ± 0.0008	1.3117 ± 0.0007	1.3126
K200M	1.3146 ± 0.0011	1.3122 ± 0.0005	1.3134

Table 6.4: True densities of HPMC powders Measured by helium pycnometry.

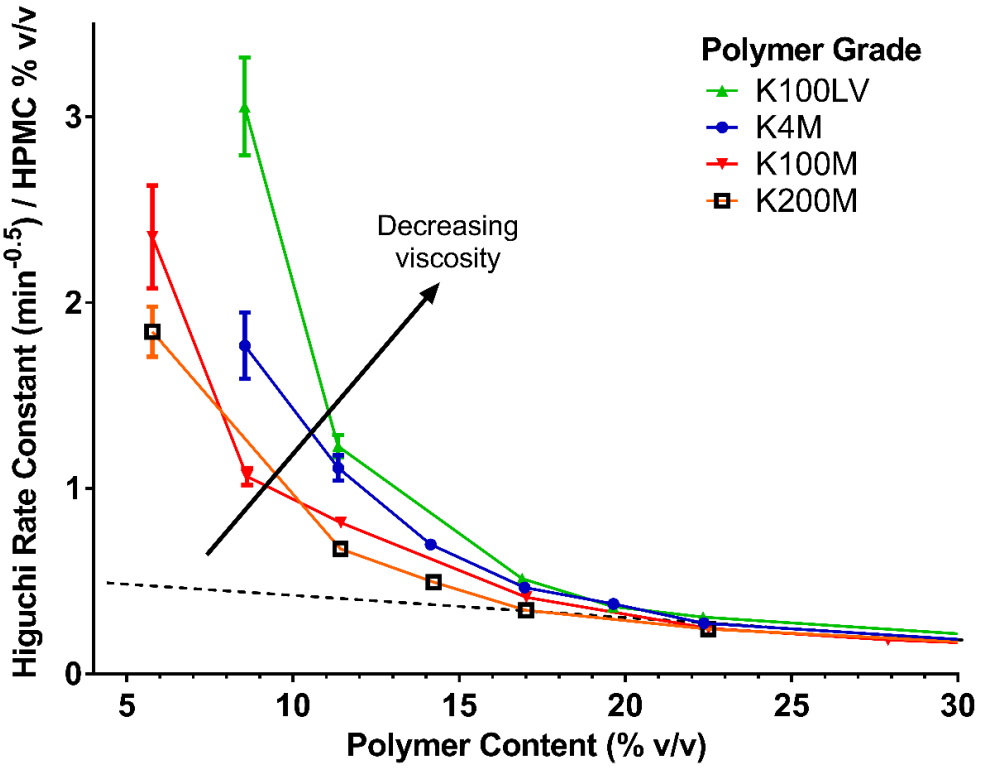


Figure 6.4: Estimation of the percolation threshold in matrix formulations containing different viscosity grades of HPMC. Higuchi rate constants (mean ± 1 SD) calculated from dissolution data (n=3, USP II, 50 RPM paddle, water 37 °C).

6.4.1.3 Early gel layer formation with respect to HPMC viscosity

Figure 6.5, Figure 6.6 and Figure 6.7 show images of early gel layer formation visualised by confocal microscopy. Matrices containing 30% w/w HPMC were examined, as well as those containing sufficient polymer to result in $T_{80\%}$ values of approx. 5 hours or 2.5 hours. This equates to the release from K4M matrices containing 30% and 15% w/w HPMC respectively. In addition to a $T_{80\%}$ of 5 hours that might be necessary for a twice daily extended release matrix, a $T_{80\%}$ of 2.5 hours was also selected as a target for our formulations. Although this may appear relatively quick for an ER dosage form, if drug absorption is slow, a faster $T_{80\%}$ target may be necessary to achieve the desired *in-vivo* pharmacokinetics. In addition, some extended release dosage forms are intended to lower the peak plasma concentration of drug, and may not require drug release to be extended over a long period.

The initial dry matrix edge is denoted in the figures by the dashed, white lines. Fluorescence is recorded in grayscale, with white areas showing highly fluorescent regions where Congo red has bound to cellulose sequences. This indicates the location of hydrated HPMC, which is interpreted as the emerging gel layer, although sometimes particle of MCC are also visualised.

Figure 6.5 shows matrices containing 30% w/w HPMC (of different viscosity grades). Differences between each polymer grade are less apparent. After hydration for 1 minute, the fluorescent regions are similar in size. After 15 minutes, all formulations show outward swelling of the gel layer, although in the case of K100LV, the fluorescent region appears to be less bright than for matrices containing higher viscosity polymers, with a narrow fluorescent band at the edge of the gel layer. The gel layer is also somewhat smaller for K100LV than the higher viscosity grades of HPMC after 15 minutes. In all cases, no ingress of water (visualised as white regions to the right of the dry boundary) or HPMC erosion (visualised by white regions to the left and detached from the surface gel layer) is seen.

Figure 6.6 shows formulations with $T_{80\%}$ values of 5 hours, and matrices contain different viscosity grades required different HPMC contents to achieve this $T_{80\%}$. All formulations show fluorescent regions to the left of the initial dry boundary, indicating the outward swelling of the gel layer over time. The pattern of gel layer formation was similar as described above for formulations containing 30% w/w, with a seemingly coherent gel layer formed by 15 minutes. The only clear difference between formulations was a

slightly thicker gel layer when the matrix polymer content was lower than 30% w/w, which was necessary for K100M and K200M to achieve a $T_{80\%}$ of 5 hours. The increased thickness is apparent after hydration for one minute.

The gel layer development in formulations with $T_{80\%}$ values of 2.5 hours are shown in Figure 6.7. Once again the matrix polymer content was lowered from 17.5% to 10% w/w as the HPMC viscosity grade increased. There are more differences in the appearance of the gel layer over time, compared to formulations containing 30% w/w HPMC. The gel layer is thicker when the matrix contains K100M and K200M, and this thickness is clear after hydration for one minute. This is likely to be a result of the lower matrix polymer content of 15% and 10% w/w respectively, as described in Section 3.5.4. Matrices containing K4M or K100LV have similar swelling after one minute to that observed for the 30% w/w matrices. However, the gel layer does not expand in thickness over the 15 minutes to the same extent. This may suggest that the rates of matrix swelling and erosion are similar.

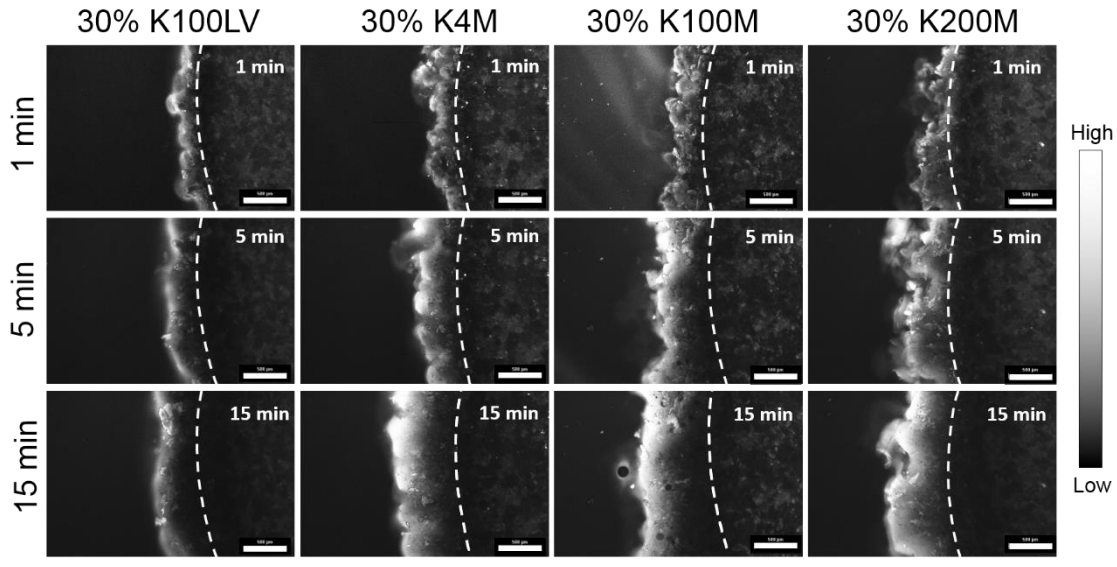


Figure 6.5: Early gel layer formation at the boundary of hydrating matrices as a function of time and viscosity grade. All matrices contain 30% w/w HPMC. Confocal fluorescence imaging at Ex 488/Em >510 nm. Experiments conducted at 37 ± 1 °C using 0.008% w/v Congo red as a visualisation aid. Dotted white lines represent the dry matrix boundary at t=0 minutes. Scale bar = 500 µm.

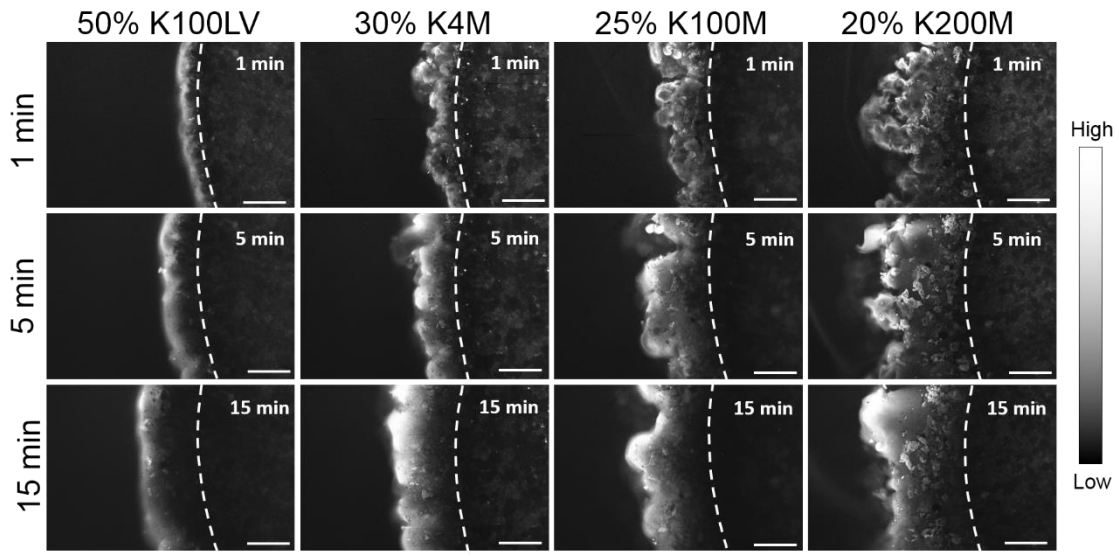


Figure 6.6: Early gel layer formation at the boundary of hydrating HPMC matrices as a function of time and polymer content and viscosity grade. Matrix polymer content reported as % w/w HPMC. Confocal fluorescence imaging at Ex 488/Em >510 nm. Experiments conducted at 37 ± 1 °C using 0.008% w/v Congo red as a visualisation aid. Dotted white lines represent the dry matrix boundary at t = 0 minutes. Scale bar = 500 µm.

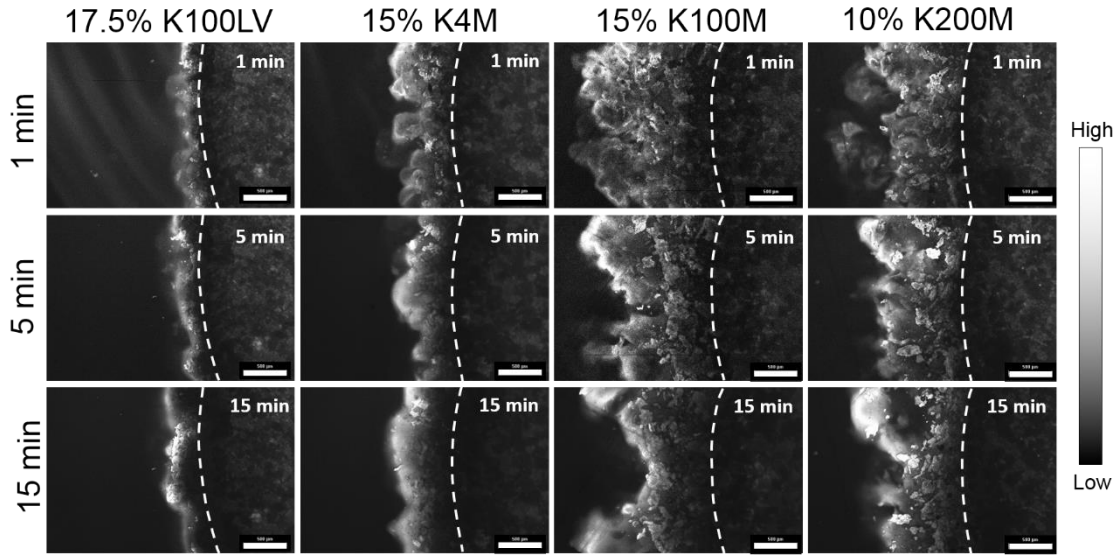


Figure 6.7: Early gel layer formation at the boundary of hydrating HPMC matrices as a function of time and polymer content and viscosity grade. Matrix polymer content reported as % w/w HPMC. Confocal fluorescence imaging at Ex 488/Em >510 nm. Experiments conducted at 37 ± 1 °C using 0.008% w/v Congo red as a visualisation aid. Dotted white lines represent the dry matrix boundary at t = 0 minutes. Scale bar = 500 µm**.**

6.4.1.4 Extended release properties of matrices with respect to dissolution conditions

As described in Chapter 4, a "discriminatory" dissolution test was developed in order to probe the sensitivity of matrix tablets to *in-vitro* dissolution conditions. Drug release under the 'standard conditions' of water and 50 RPM paddle speed was compared to drug release under the 'stress conditions' of 0.2 M NaCl and 100 RPM. Figure 6.8 and Figure 6.9 show the drug release profiles of matrices containing different viscosity grades of HPMC under these conditions. Once again, the polymer content of formulations was chosen to obtain $T_{80\%}$ values of approx. 5 hours (Figure 6.8) or 2.5 hours (Figure 6.9). This equates to release from K4M matrices containing 30% w/w and 15% w/w HPMC respectively.

Stress sensitivity was evaluated according to the test conditions established in Section 4.4.7. A successful formulation would show:

- Less than 10% difference in $T_{80\%}$ value
- Less than 10% difference in Higuchi rate constant
- Less than 30% drug release in 10 minutes (DR10min),

Between drug release data in "standard" and "stress" dissolution conditions. Green boxes show that the formulation has passed the criteria above, orange boxes show $T_{80\%}$ between 10 and 20% different, and red boxes denote a fail according to the criteria above.

Figure 6.8 shows the drug release of matrices with a $T_{80\%}$ of around 5 hours. Similar drug release is seen under both dissolution conditions. In Table 6.5, the mean dissolution parameters under the two dissolution conditions have been compared. It can be seen that for the '5 hour' formulations, all parameters fall within the desired criteria. In addition, the *n* exponent ranges between 0.60 and 0.78, suggesting that the drug release mechanism is similar under both 'standard' and 'stress' dissolution conditions.

Figure 6.9 shows drug release from matrices with a $T_{80\%}$ of around 2.5 hours. All formulations are faster under 'stress conditions' compared to 'standard conditions'. Table 6.6 compares the dissolution parameters. In all formulations, the $T_{80\%}$ is over 25% shorter under stress conditions. The matrices exhibit nearly double the amount of drug release (%) in the first 10 minutes. Matrices containing K100LV and K100M show a smaller drop in $T_{80\%}$ than K4M and K200M matrices.

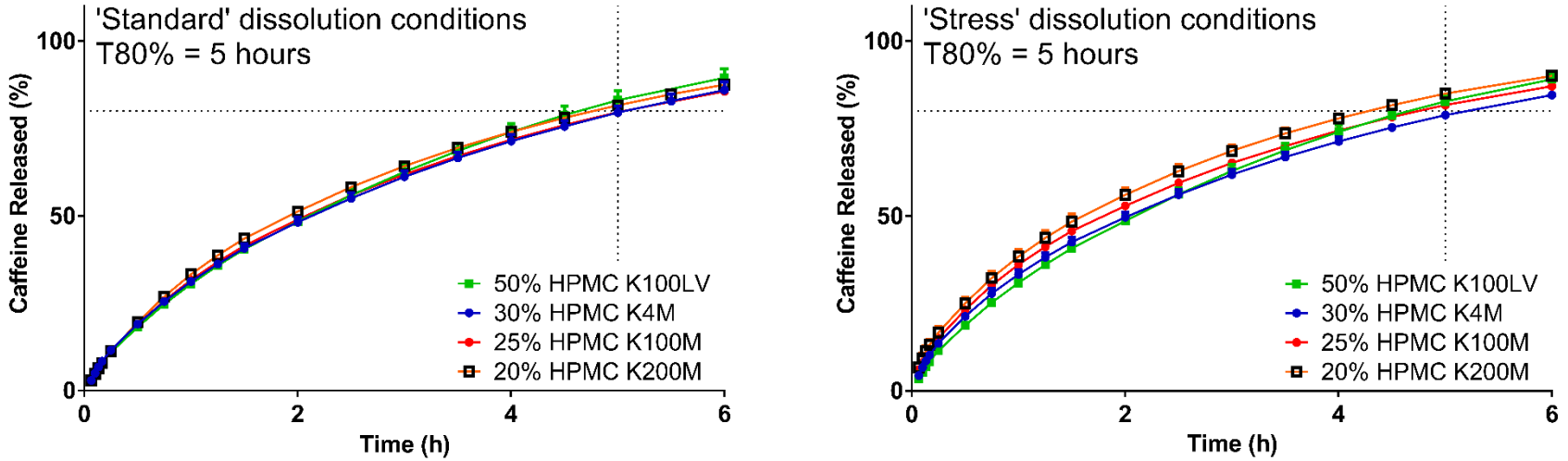


Figure 6.8: Release of caffeine from HPMC matrices under 'standard' and 'stress' dissolution conditions. Matrices contain amounts of different HPMC, sufficient to provide a $T_{80\%}$ of 5 hours.Matrix polymer content reported as % w/w HPMC. USP apparatus II, 900 mL, 37 ± 0.5 °C. Mean (n=3) + 1 SD. 'Standard' dissolution = 50 RPM paddle speed and water, 'Stress' dissolution = 100 RPM and 0.2M NaCl

Formulation (% w/w)	Dissolution Condition	T80%		DR10min		Higuchi		Korsmeyer-Peppas	
		$T_{80\%}$ (h)	Change (%)	DR10min	Change (%)	k_h ($min^{-0.5}$)	Change (%)	k_{kp} (min^{-n})	n
50% K100LV	Standard	5.02 ± 0.37	-4.8	7.8 ± 0.2	< 30%	5.17 ± 0.06	+1.2	1.51	0.72
	Stress	4.78 ± 0.16		8.3 ± 0.2	< 30%	5.23 ± 0.05		1.59	0.71
30% K4M	Standard	5.17 ± 0.09	+3.1	8.8 ± 0.2	< 30%	5.07 ± 0.02	-1.4	1.81	0.68
	Stress	5.33 ± 0.19		10.2 ± 1.0	< 30%	5.00 ± 0.03		2.31	0.64
25% K100M	Standard	5.33 ± 0.22	-9.9	7.9 ± 0.9	< 30%	5.14 ± 0.05	+1.2	1.47	0.73
	Stress	4.80 ± 0.08		11.5 ± 0.8	< 30%	5.20 ± 0.03		2.72	0.62
20% K200M	Standard	4.83 ± 0.07	-7.2	7.9 ± 0.3	< 30%	5.44 ± 0.03	-1.1	1.23	0.78
	Stress	4.48 ± 0.28		12.9 ± 1.8	< 30%	5.38 ± 0.08		3.10	0.60

Table 6.5: A comparison of drug release kinetics for HPMC matrices under 'standard' and 'stress' dissolution conditions. Matrices contain amounts of different HPMC, sufficient to provide a $T_{80\%}$ of 5 hours USP apparatus II, 900 mL, 37 ± 0.5 °C. 'Standard' dissolution is 0.0 M (water) at 50 RPM. 'Stress' dissolution is 0.2 M NaCl at 100 RPM. Mean (for $T_{80\%}$, DR10min and Higuchi: ± 1 SD) (n=3). % values for $T_{80\%}$ and Higuchi are the relative increase in mean of 'stress' dissolution compared to 'standard' conditions.

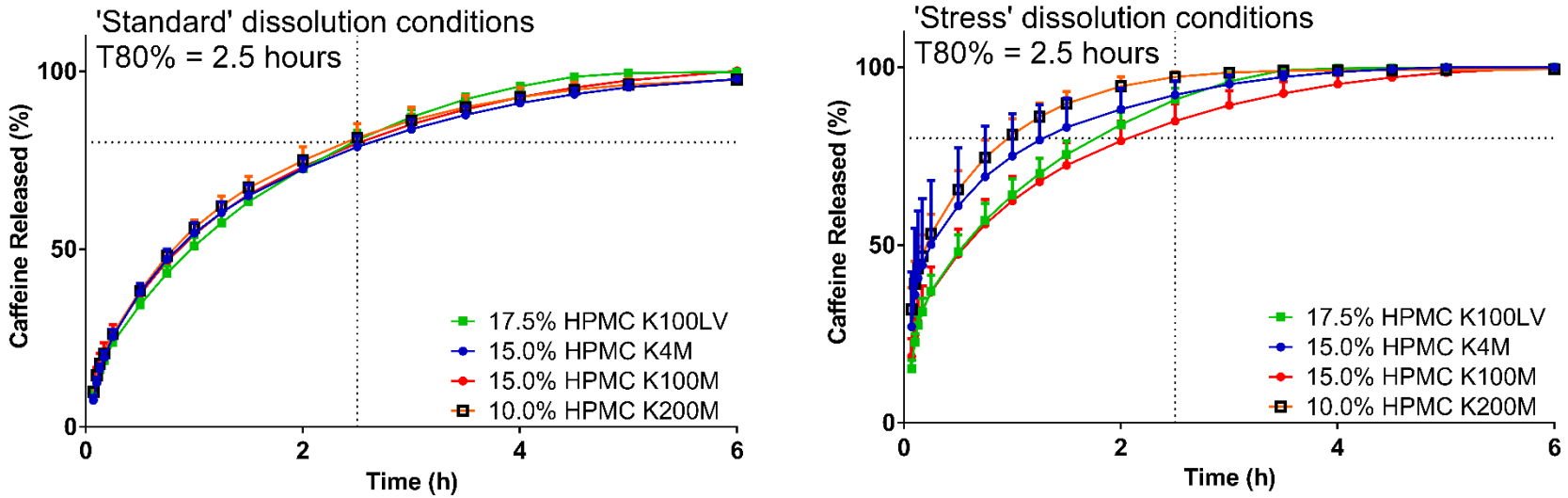


Figure 6.9: Release of caffeine from HPMC matrices under 'standard' and 'stress' dissolution conditions. Matrices contain amounts of different HPMC, sufficient to provide a $T_{80\%}$ of 2.5 hours. Matrix polymer content reported as % w/w HPMC. USP apparatus II, 900 mL 37 ± 0.5 °C. Mean (n=3) + 1 SD. 'Standard' dissolution = 50 RPM paddle speed and water, 'Stress' dissolution = 100 RPM and 0.2M NaCl

		T80%		DR10min		Higuchi		Korsmeyer-Peppas	
Formulation (% w/w)	**Dissolution Condition**	**$T_{80\%}$ (h)**	**Change (%)**	**DR10min**	**Change (%)**	**$T_{80\%}$ (h)**	**Change (%)**	**DR10min**	**Change (%)**
17.5% K100LV	Standard	2.47 ± 0.18	-28.3	18.6 ± 0.9	<30%	7.11 ± 0.11	+12.5	4.49	0.59
	Stress	1.77 ± 0.22		31.2 ± 3.8	>30%	8.00 ± 0.41		9.17	0.49
15% K4M	Standard	2.63 ± 0.27	-50.6	19.5 ± 1.7	<30%	7.91 ± 0.20	+5.1	3.32	0.69
	Stress	1.30 ± 0.58		44.3 ± 18.7	>30%	8.31 ± 1.59		15.9	0.39
15% K100M	Standard	2.81 ± 0.08	-26.7	20.3 ± 2.7	<30%	7.03 ± 0.13	+3.8	4.90	0.58
	Stress	2.06 ± 0.46		31.6 ± 6.9	>30%	7.30 ± 0.60		11.02	0.43
10% K200M	Standard	2.40 ± 0.29	-60.0	19.0 ± 3.4	<30%	7.70 ± 0.18	+44.8	4.14	0.63
	Stress	0.96 ± 0.19		46.8 ± 6.0	>30%	11.15 ± 2.20		18.79	0.39

Table 6.6: A comparison of drug release kinetics for HPMC matrices under 'standard' and 'stress' dissolution conditions. Matrices contain amounts of different HPMC, sufficient to provide a $T_{80\%}$ of 2.5 hours USP apparatus II, 900 mL, 37 ± 0.5 °C. 'Standard' dissolution is 0.0 M (water) at 50 RPM. 'Stress' dissolution is 0.2 M NaCl at 100 RPM. Mean (for $T_{80\%}$, DR10min and Higuchi: ± 1 SD) (n=3). % values for $T_{80\%}$ and Higuchi are the relative increase in mean of 'stress' dissolution compared to 'standard' conditions.

6.4.2 Discussion

6.4.2.1 Effect of HPMC viscosity grade on drug release rates and mechanisms

Our results showed that the viscosity grade of HPMC influenced drug release rate, with slower drug release when higher viscosity grades were used. Larger differences in release rate and $T_{80\%}$ were seen as the matrix polymer content was lowered below 30% HPMC. The effect of HPMC viscosity grade on drug release has previously been reported in the literature (Alderman, 1984), and there has been some previous suggestion that the effect of viscosity is less dramatic at higher matrix polymer contents (Nellore et al., 1998). Campos-Aldrete and Villafuerte-Robles (1997) described how at a matrix HPMC content of 20% or higher, viscosity grade no longer impacted on dissolution rate (Campos-Aldrete and Villafuerte-Robles, 1997). They studied viscosity grades from 30000 cP down to 15 cP, however the tablet manufacturing process included wet granulation, which may limit the effect of formulation variables on HPMC matrix tablets (unpublished results, MSD UK Ltd). In our study we found that release from matrices containing K100LV was faster than other grades, at all the polymer contents studied, and this has also been reported in the literature (Ford et al., 1985a, Ford et al., 1985b, Gao et al., 1996, Nellore et al., 1998).

Confocal images showed that formulations containing K4M, K15M and K100M had similar gel layer thicknesses and growth rates. This corresponds with the results of earlier studies (Pham and Lee, 1994, Gao et al., 1996). Gao et al. (1996) have remarked on how a thinner gel layer was formed for K100LV matrices, in contrast with matrices containing higher viscosity grades (Gao et al., 1996). Our studies confirm this. It has been reported that using higher viscosity HPMC gives rise to a greater percentage swelling of matrices due to a greater and faster water absorption capacity of the higher viscosity grades (Katzhendler et al., 2000, Ravi et al., 2007). Dahl et al (1990) have similarly reported increased water uptake with higher viscosity grade HPMCs. They evaluated HPMC viscosities in the range of K4M (4380 cP) to K50M (44400 cP) (Dahl et al., 1990), a narrower range than we have studied. The purported increase in water uptake may be one reason for the differences in gel layer thickness between matrices containing 30% w/w K100LV and those of higher viscosity (Figure 6.5). Differences in the appearance of the gel layer were clearer in Figure 6.6 and Figure 6.7, however, the different polymer content of each matrix is likely to have also influenced the gel layer thickness.

Differences in drug release behaviour have been attributed to different rates of polymer erosion for the viscosity grades, with faster erosion for lower viscosity grades (Reynolds et al., 1998). Meanwhile, studies have reported that the drug dissolution rate depends only on the concentration of the viscosity-inducing agent and not on the polymer molecular weight (Gao et al., 1996, Reynolds et al., 1998). Gao et al. (1996) found that viscosity grade only impacted on the drug dissolution rate when the molecular weight was below a critical value, which included K100LV (Gao and Fagerness, 1995, Gao et al., 1996). This may also explain why we found faster drug release from matrices containing K100LV compared to higher viscosity grades.

If viscosity influences the rate of erosion more than the rate of diffusion, greater differences in drug release rate with respect to polymer viscosity grade might ensue if a poorly soluble drug is used (Tahara et al., 1995). One such example is Kim and Fassihi (1997) who saw differences in prednisolone release from K4M, K15M and K100M matrix tablets which contained 60% polymer (Kim and Fassihi, 1997).

6.4.2.2 Effect of viscosity grade on the sensitivity to dissolution conditions

Relatively few studies have investigated how the HPMC viscosity grade may influence susceptibility of an HPMC matrix to different dissolution conditions. It has been reported that matrices containing around 20% w/w K100LV showed a greater sensitivity to USP dissolution apparatus III (BIO-DIS) than formulations with the same content of K4M, K15M or K100M (Asare-Addo et al., 2010). K100LV formulations were also reported to show greater sensitivity to increasing NaCl concentration (up to 0.4 M NaCl) (Asare-Addo et al., 2011). In addition, slower erosion rates have been seen both *in-vivo* and *in-vitro* for formulations containing 40% w/w K100LV rather than 20% w/w K100LV (Jain et al., 2014).

In our work, the percolation threshold estimations (section 6.4.1.2) suggested that all the viscosity grades had a similar minimum necessary polymer content of HPMC of between 14 and 19% v/v (12.5 – 17.5% w/w). When formulations contained a HPMC content above the threshold, i.e. between 20 and 50% w/w HPMC, no difference was observed in the drug release rate with respect to the dissolution environment.

To achieve a $T_{80\%}$ of 2.5 hours using HPMC K4M, the matrix polymer content required lowering to 15% w/w. As seen in Section 4.5, matrices containing 15% w/w K4M had *in-*

vitro sensitivities to increasing paddle speed and sodium chloride in solution. These sensitivities were not observed when the matrix contained more typical polymer contents of 30% w/w HPMC. Therefore, we intended to see if a $T_{80\%}$ value of 2.5 hours could be achieved through the judicious selection of HPMC viscosity grade, without the appearance of these dissolution sensitivities.

In order to obtain a $T_{80\%}$ of 2.5 hours, a matrix polymer content between 10 and 17.5% w/w was required, depending on the HPMC viscosity grade used. All 2.5 hour formulations showed a sensitivity when exposed to stress dissolution conditions, with decreases in $T_{80\%}$ of between 26 and 60%. The 2.5 hour formulations had a polymer content in the region of the percolation threshold, which may be why significant differences in the $T_{80\%}$ were observed under stress dissolution conditions. This supports the manufacturer's recommendations that matrices are manufactured with a HPMC content at least 10% w/w greater than the percolation threshold, in order to avoid variability in release (Hughes, 2013).

The use of a higher viscosity HPMC grade was found to facilitate the lowering of the matrix HPMC content (6.4.1.1), which can be advantageous when a high drug loading is required. However, care must be taken not to reduce the matrix polymer content excessively, and stray into the region of the percolation threshold. This study also showed that within the formulations studied, the HPMC percolation threshold was similar irrespective of the HPMC viscosity grade. Our studies utilised a soluble model drug. It is possible that different trends would be seen when drugs of poor solubility are used.

Reducing the matrix polymer content of a formulation appears to be, at first glance, a straightforward means for formulators to increase drug release rate. However, the work of this section has shown that is vital to consider the matrix polymer content with respect to the percolation threshold. In some instances, the polymer content may need lowering to a level that is close the percolation threshold but we have found that an alternative possibility is to use a lower viscosity HPMC grade instead. The lower viscosity HPMC grade (K100LV) has been shown to have faster drug release rate at equivalent HPMC contents. Therefore, the content of HPMC in the matrix can be increased, without excessively slowing drug release. This matrix polymer content may then be sufficiently higher than the percolation threshold to ensure consistent drug release, irrespective of the dissolution conditions.

Section B:

The effect of HPMC particle size on drug release from low polymer content matrices

6.4.3 Results: Effect of HPMC particle size

6.4.3.1 Particle size distribution of HPMC K4M CR

The particle size distribution of METHOCEL K4M CR was determined using sieve analysis as described in Section 2.4.1. The relative amounts collected at each sieve designation is shown in Figure 6.10. Results show that all particles passed through the 355 µm and 180 µm sieves, and the majority of HPMC particles had a particle size of 90 µm or less (84.85% of the sample). The manufacturer's designation of the different types of METHOCEL K4M are important here. The CR grades of METHOCEL have tighter particle size specifications compared to METHOCEL Premium, in which require that 90% of particles must pass through a 149 µm sieve. Premium grades only specify that 99% of particles must pass through a 420 µm sieve, therefore may contain a greater content of larger HPMC particles. The CR grade has been available since 1997.

The certificate of analysis for the K4M batch used reported that 96.9% passed through a 149 µm sieve, which is in similar to our analysis (93.4% through 125 µm sieve). Based on the particle size analysis, five different particle size fractions were selected for tabletting in order to compare the effect of particle size and polymer content on drug release. Formulations were prepared according to Table 6.2.

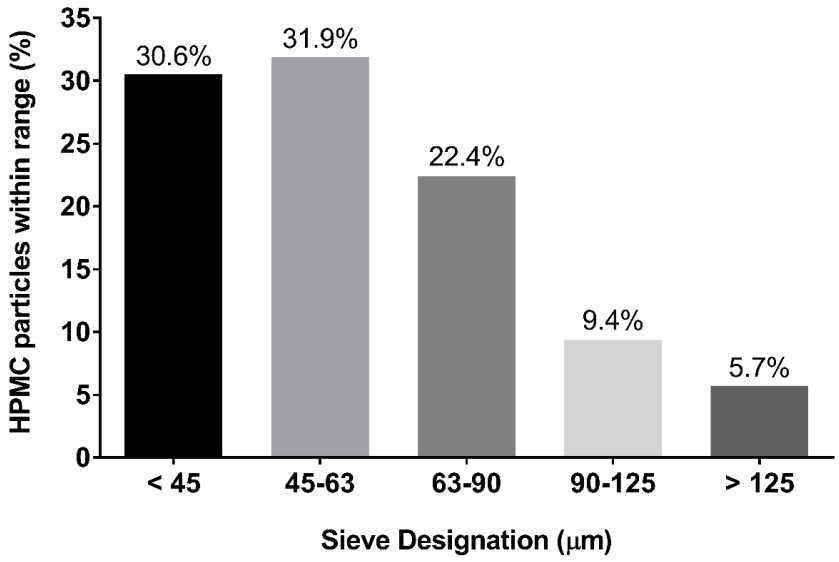


Figure 6.10: Size distribution for METHOCEL K4M CR Premium Determined using sieve analysis, sample of 29.98 g (sieved to within 5% weight change as per USP).

6.4.3.2 Extended release properties of matrices with respect to HPMC particle size

Figure 6.11 shows how caffeine was released from 15% and 30% w/w HPMC matrices as a function of particle size fraction. For formulations containing 30% w/w HPMC (Figure 6.11a), drug release from matrices containing HPMC particle size fractions smaller than 90 µm was similar to those made with unfractionated HPMC. All had a mean $T_{80\%}$ around 5 hours. Faster drug release was seen when larger HPMC particle size fractions (90-125 µm or >125 µm) were used, with a mean $T_{80\%}$ of 2.8 hours and 1.1 hours respectively.

15% w/w HPMC matrices showed a greater sensitivity to HPMC particle size (Figure 6.11b). Drug release became increasingly faster as the particle size increased. Matrices that contained the 45-63 µm HPMC fraction had drug release profiles most similar to formulations containing the unfractionated HPMC. This results is perhaps unsurprising given that the largest proportion of HPMC particles fell within this size range (Figure 6.10).

Dissolution parameters were calculated and are shown in Table 6.8. The Korsmeyer-Peppas *n* exponent varied between 0.65 and 0.70 for the 30% w/w HPMC matrices which suggested a mixed drug release mechanism. In the case of 15% w/w matrices, the *n* exponent varied from 0.69 to 0.42 as the particle size was increased. This suggested a change in the drug release to more diffusional release mechanism.

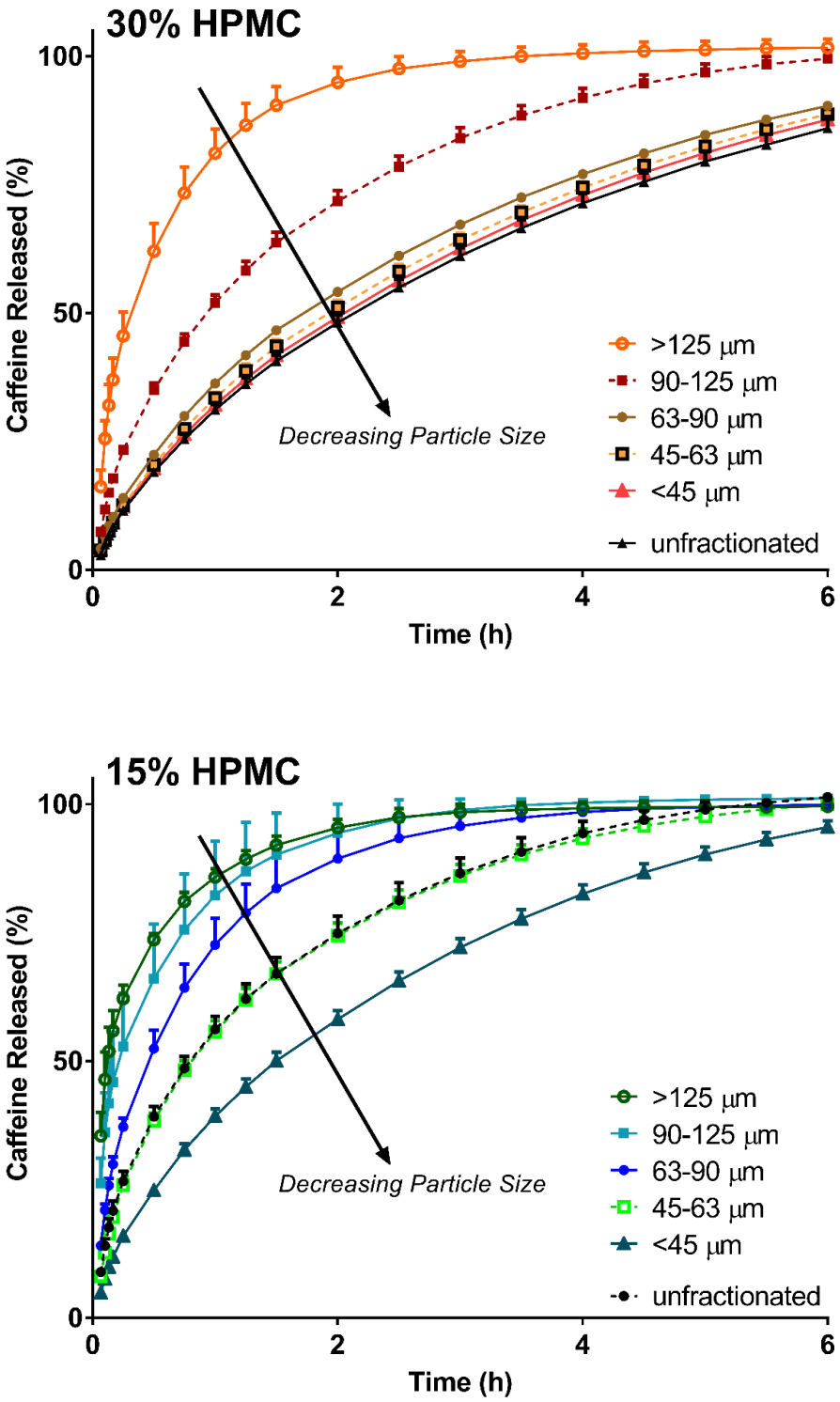


Figure 6.11: Release of caffeine from HPMC matrices in formulations containing different HPMC particle size fractions. Matrix tablet polymer content of (top) 30% w/w HPMC and (bottom) 15% w/w HPMC. USP apparatus II, 50 RPM, 900 mL water, 37 ± 0.5 °C. Mean (n=3) + 1 SD.

6.4.3.3 Early gel layer formation in HPMC matrices containing different HPMC particle size fractions

Figure 6.12 shows confocal images of matrices containing 30% and 15% w/w of different particle size fractions of HPMC. The gel layer development of the unfractionated HPMC is also shown.

After one minute hydration, matrix tablets which contained 30% w/w of unfractionated HPMC or a particle size fraction of 63-90 µm or smaller exhibited a narrow fluorescent region, which suggests rapid establishment of the gel layer. This is the classical matrix pattern of gel layer formation which was previously described in Section 3.4.5 and elsewhere (Bajwa et al., 2006). In 30% w/w HPMC matrices containing the larger 90-125 µm or > 125 µm sieve fractions, the fluorescent region is thicker, and the outer edge appears to be lumpier. All 30% w/w HPMC formulations appeared to have developed a well-established gel layer after 15 minutes, with fluorescence being limited to the gel layer and no sign of water ingress into the core or erosion of the outer gel layer.

In matrices containing 15% w/w HPMC, greater differences were observed in the fluorescence pattern. Images of the gel formation in matrices containing the unfractionated HPMC showed a gel layer was initially lumpy and irregular, but that a smooth gel layer formed within 15 minutes. A similar fluorescence pattern is seen in matrices containing the sieve fractions < 45 µm or 45-63 µm. This suggests that water penetration is limited and a rate limiting gel layer is formed. When the matrix contains larger HPMC sieve fractions (63-90 µm, 90-125 µm or > 125 µm), the fluorescent band was much thicker at one minute and little change was seen over 15 minutes, which suggests that the hydrated HPMC gel layer was more extensive, but stable over this time.

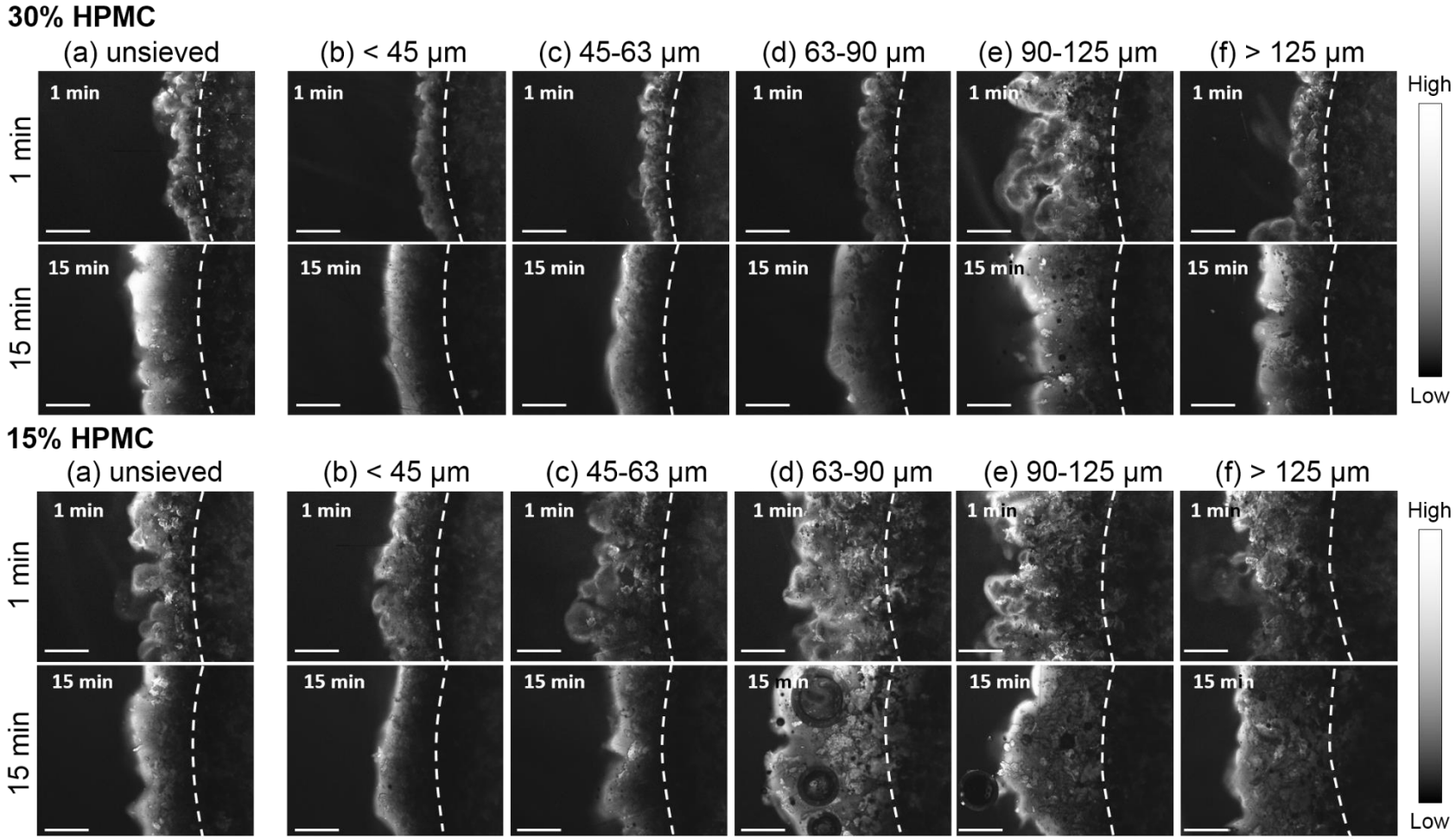


Figure 6.12: Early gel layer formation at the boundary of hydrating HPMC matrices as a function of time, polymer content and HPMC particle size fraction. Matrix polymer content reported as % w/w HPMC. Confocal fluorescence imaging at Ex 488/Em >510 nm. Experiments conducted at 37 ± 1 °C using 0.008% w/v Congo red as a visualisation aid. Dotted white lines represent the dry matrix boundary at t=0 minutes. Scale bar = 500 µm.

6.4.3.4 The effect of HPMC particle size on the percolation threshold

Additional formulations were manufactured to enable an approximation of the HPMC percolation threshold for each HPMC particle size fraction to be obtained. Again, there was an insufficient number of data points for two linear regression lines, but percolation thresholds could be estimated by eye. Figure 6.13 shows how the Higuchi rate constant varied with matrix polymer content. The dashed lines at Higuchi rate constant of 8 and 5 $mins^{-0.5}$ pertain to the rate constants for matrices containing 15% and 30% w/w of unfractionated HPMC. These were used to estimate the "equivalent concentrations" of each particle size fraction, which are shown in Table 6.7. It can be seen that typically as the particle size decreases, less HPMC is needed in the matrix to achieve the same drug release rate.

The effect of changing particle size fraction on drug release rate becomes less significant as the matrix polymer content is increased. To achieve similar drug release to the unfractionated 30% w/w HPMC matrix, a 25% reduction in polymer content is necessary when the HPMC particle size fraction changes from > 125 µm to < 45 µm. However, the same particle size change for the faster formulation (un-sieved 15% w/w HPMC) necessitates a 75% reduction in polymer content.

The percolation threshold was found to lower as the particle size fraction decreased, from 40% to 12% w/w HPMC (Figure 6.13 and Table 6.7).

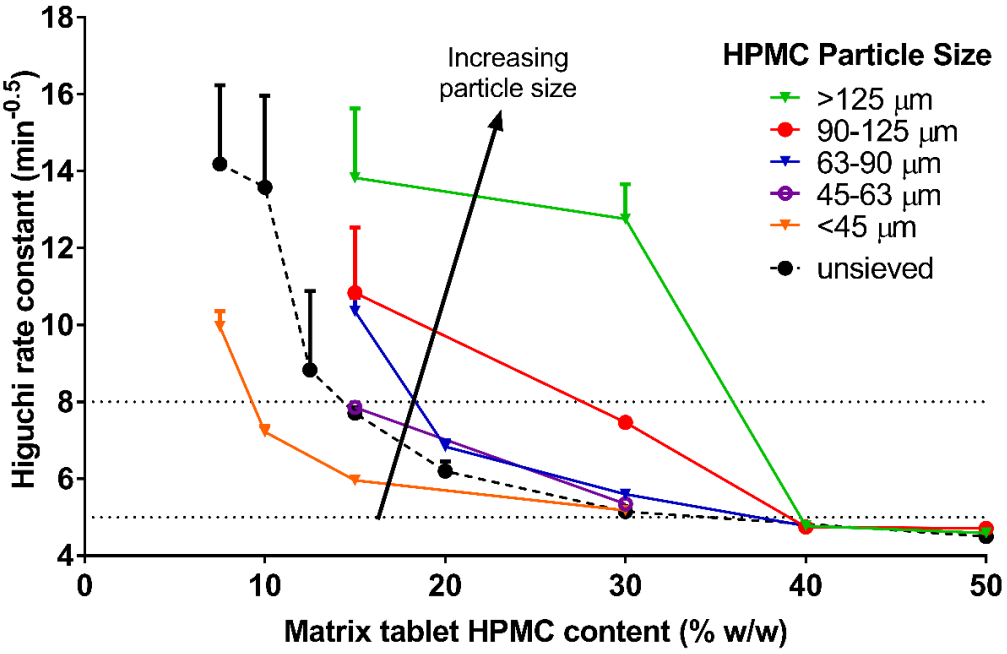


Figure 6.13: Higuchi rate constant as a function of matrix HPMC content and HPMC particle size. USP apparatus II, 50 RPM, 900 mL, 37 ± 0.5 °C. Mean (n=3) + 1 SD. Dotted lines are Higuchi rate constants of 5 $mins^{-0.5}$ and 8 $min^{-0.5}$

	HPMC Particle Size Fraction (µm)					
	Unfractionated HPMC	**< 45**	**45-63**	**63-90**	**90-125**	**> 125**
	30%	30%	30%	37%	39%	40%
	15%	9%	15%	18%	28%	36%
Estimation of Percolation Threshold (% w/w)	**12%**	**12%**	**20%**	**20%**	**40%**	**40%**

Table 6.7: Equivalent contents of HPMC particle size fractions and estimation of matrix percolation threshold. Equivalent based on having similar Higuchi rate constant values to 30% and 15% w/w un-sieved K4M matrices

6.4.3.5 Extended release properties of matrices with respect to dissolution conditions

The $T_{80\%,}$ DR10min and Higuchi rate constants were compared when formulations were tested under 'standard' and 'stress' dissolution conditions. The kinetic analysis results can be seen in Figure 6.8. Stress sensitivity was evaluated according to the test conditions established in Section 4.4.7, which specified that a successful formulation would show:

- Less than 10% difference in $T_{80\%}$ value
- Less than 10% difference in Higuchi rate constant
- Less than 30% drug release in 10 minutes (DR10min),

Between drug release data in "standard" and "stress" dissolution conditions.

The differences in the dissolution parameters between test conditions are shown in Figure 6.14. Green boxes show that the formulation has passed the criteria above and red boxes denote a fail. In cases where the difference in $T_{80\%}$ or Higuchi was between 10 and 20%, the box is coloured orange.

Figure 6.14 is therefore a summary of the stress sensitivity of formulations, with respect to their matrix polymer content and HPMC particle size. As HPMC particle size was increased, the matrices failed the given criteria at higher matrix polymer contents. For example, 40% w/w HPMC matrices containing > 125 µm failed, whereas 15% matrices containing < 45 µm passed. Matrices containing the larger particle size fractions (> 125 µm, 90-125 µm and 63-90 µm) also showed a sensitivity to dissolution conditions at the previously 'safe' level of 30% w/w HPMC.

Further work also evaluated matrices which contained two extra particle size fractions: < 90 µm and < 63 µm. The rationale was that it was illogical to remove the smaller sieve cuts when these clearly improved the performance of the matrices. In addition, the ideal sieve specification would be as wide as possible to minimise material wastage. Both < 90 µm and < 63 µm sieve cuts showed a similar stress sensitivity to matrices containing the unfractionated HPMC.

The percolation thresholds for each formulation, as estimated in Table 6.7, are also marked on Figure 6.14. In the case of each HPMC particle size fraction, dissolution sensitivity is first observed within ± 10% w/w of the percolation threshold. This adds

weight to the commonly-held opinion that formulations should be manufactured with at least 10% more polymer than the percolation threshold to ensure reliable drug release.

Particle Size	Polymer Content (% w/w)	Dissolution conditions	$T_{80\%}$		DR10min		Higuchi		Korsmeyer-Peppas	
			$T_{80\%}$ (hours)	%	DR10min (%)		k_h ($mins^{-0.5}$)	%	K_{kp} ($mins^{-n}$)	n
<45 µm	7.5%	Standard	1.46 ± 0.28	-33.6%	30.5 ± 2.2		9.96 ± 0.40	-1.8	7.56	0.57
		Stress	0.97 ± 0.17		48.1 ± 4.9		9.78 ± 0.95		19.5	0.37
	10.0%	Standard	2.59 ± 0.18	-17.0	20.0 ± 2.5		7.22 ± 0.16	-1.7	4.70	0.59
		Stress	2.15 ± 0.06		29.9 ± 1.0		7.10 ± 0.13		10.57	0.43
	15.0%	Standard	3.96 ± 0.22	-7.1	11.6 ± 0.7		5.96 ± 0.05	+1.0	2.23	0.69
		Stress	3.64 ± 0.04		14.3 ± 0.3		6.02 ± 0.03		3.12	0.63
	30.0%	Standard	5.09 ± 0.05	-0.4	9.0 ± 0.1		5.18 ± 0.03	-0.6	1.74	0.70
		Stress	5.07 ± 0.04		9.6 ± 0.1		5.15 ± 0.02		2.06	0.66
45-63 µm	15.0%	Standard	2.52 ± 0.17	-57.5	19.4 ± 0.5		7.86 ± 0.12	+48.1	4.03	0.64
		Stress	1.07 ± 0.49		48.3 ± 14.3		11.64 ± 5.21		19.72	0.39
	30.0%	Standard	5.07 ± 0.15	-4.5	8.9 ± 0.6		5.35 ± 0.04	-0.4	1.67	0.72
		Stress	4.84 ± 0.08		11.8 ± 0.6		5.33 ± 0.02		2.76	0.62
63-90 µm	15.0%	Standard	1.41 ± 0.06	-85.8	29.5 ± 1.0		10.36 ± 0.35	fast	7.01	0.60
		Stress	0.20 ± 0.18		81.1 ± 12.7		fast		fast	fast
	20.0%	Standard	3.14 ± 0.25	-52.2	15.4 ± 2.3		6.84 ± 0.16	+23.2	3.07	0.66
		Stress	1.50 ± 0.43		39.4 ± 8.4		8.43 ± 1.03		13.9	0.42
	30.0%	Standard	4.49 ± 0.06	-23.4	10.2 ± 0.5		5.60 ± 0.03	+16.3	1.89	0.71
		Stress	3.44 ± 0.50		18.2 ± 3.3		6.51 ± 0.22		4.47	0.58
	40.0%	Standard	5.94 ± 0.27	+7.1	7.6 ± 0.2		4.78 ± 0.06	-3.8	1.57	0.69
		Stress	6.36 ± 0.38		7.5 ± 0.3		4.60 ± 0.04		1.61	0.68
90-125 µm	15.0%	Standard	0.99 ± 0.46	-92.9	45.4 ± 9.5		10.84 ± 1.70	fast	15.56	0.44
		Stress	0.07 ± 0.01		98.4 ± 0.4		fast		fast	fast
	30.0%	Standard	2.78 ± 0.11	-76.6	18.0 ± 0.5		7.47 ± 0.08	+174.2	3.64	0.65
		Stress	0.65 ± 0.09		53.7 ± 4.3		20.48 ± 2.03		9.59	0.74
	40.0%	Standard	6.00 ± 0.28	-4.0	7.4 ± 0.6		4.75 ± 0.04	-1.3	1.53	0.70
		Stress	5.76 ± 0.26		10.7 ± 1.2		4.69 ± 0.04		2.49	0.61
	50.0%	Standard	6.75 ± 0.10	+6.8	6.7 ± 0.1		4.71 ± 0.02	-0.4	1.45	0.70
		Stress	7.21 ± 0.39		7.7 ± 0.3		4.69 ± 0.04		1.66	0.67

>125 µm	15.0%	Standard	0.70 ± 0.01	-91.4	56.1 ± 4.2		13.83 ± 1.80	fast	20.75	0.42
		Stress	0.06 ± 0.00		98.8 ± 0.2		fast		fast	fast
	30.0%	Standard	1.08 ± 0.17	-89.8	36.2 ± 3.5		12.76 ± 0.91	fast	7.63	0.65
		Stress	0.11 ± 0.02		90.6 ± 2.6		fast		fast	fast
	40.0%	Standard	5.95 ± 0.26	-56.3	7.9 ± 1.1		4.78 ± 0.06	+43.5	1.66	0.69
		Stress	2.60 ± 1.52		32.8 ± 14.3		6.86 ± 0.04		9.07	0.47
	50.0%	Standard	6.62 ± 0.03	-0.8	7.0 ± 0.1		4.59 ± 0.02	-3.5	1.48	0.69
		Stress	6.57 ± 0.43		10.5 ± 1.8		4.43 ± 0.05		2.71	0.58
< 63 µm	10.0%	Standard	1.50 ± 0.10	-34.0	30.2 ± 2.9		9.99 ± 0.39	+306.4	7.10	0.59
		Stress	0.99 ± 0.26		44.2 ± 3.7		40.60 ± 0.85		15.5	0.43
	15.0%	Standard	3.16 ± 0.20	-26.6	16.2 ± 1.3		6.66 ± 0.11	+1.5	3.57	0.63
		Stress	2.32 ± 0.02		30.4 ± 1.9		6.76 ± 0.15		10.9	0.42
	30.0%	Standard	5.30 ± 0.19	+0.2	8.4 ± 0.5		5.07 ± 0.04	-2.4	1.74	0.69
		Stress	5.31 ± 0.07		9.3 ± 0.2		4.95 ± 0.01		2.03	0.66
< 90 µm	15.0%	Standard	2.21 ± 0.20	-39.8	21.7 ± 2.1		8.47 ± 0.18	+1.5	4.99	0.62
		Stress	1.33 ± 0.14		40.8 ± 1.1		8.60 ± 0.33		15.8	0.39
	20.0%	Standard	4.00 ± 0.19	-12.0	12.2 ± 0.7		5.83 ± 0.06	+1.0	2.66	0.65
		Stress	3.52 ± 0.13		17.9 ± 1.4		5.89 ± 0.07		4.97	0.54
	30.0%	Standard	5.43 ± 0.11	-1.7	8.3 ± 0.3		4.96 ± 0.02	-0.4	1.64	0.70
		Stress	5.34 ± 0.07		9.7 ± 0.3		4.94 ± 0.02		2.14	0.65
Particle Size	**Polymer Content (% w/w)**	**Dissolution conditions**	**$T_{80\%}$**		**DR10min**		**Higuchi**		**Korsmeyer-Peppas**	
			$T_{80\%}$ (hours)	%	DR10min (%)		k_h (mins$^{-0.5}$)	%	K_{kp} (mins^{-n})	n

Table 6.8: The effect of HPMC particle size and matrix HPMC content on drug release kinetics in two dissolution conditions. ($T_{80\%}$, DR10min, Higuchi and Korsmeyer-Peppas dissolution parameters). Standard dissolution is 0.0 M (water) at 50 RPM. Stress dissolution is 0.2 M NaCl at 100 RPM. Mean (for $T_{80\%}$, DR10min and Higuchi: ± 1 SD) (n=3). % values for $T_{80\%}$ and Higuchi are the relative increase in mean of stress dissolution compared to standard conditions. Where row says 'fast', drug release was too fast for linear regression.

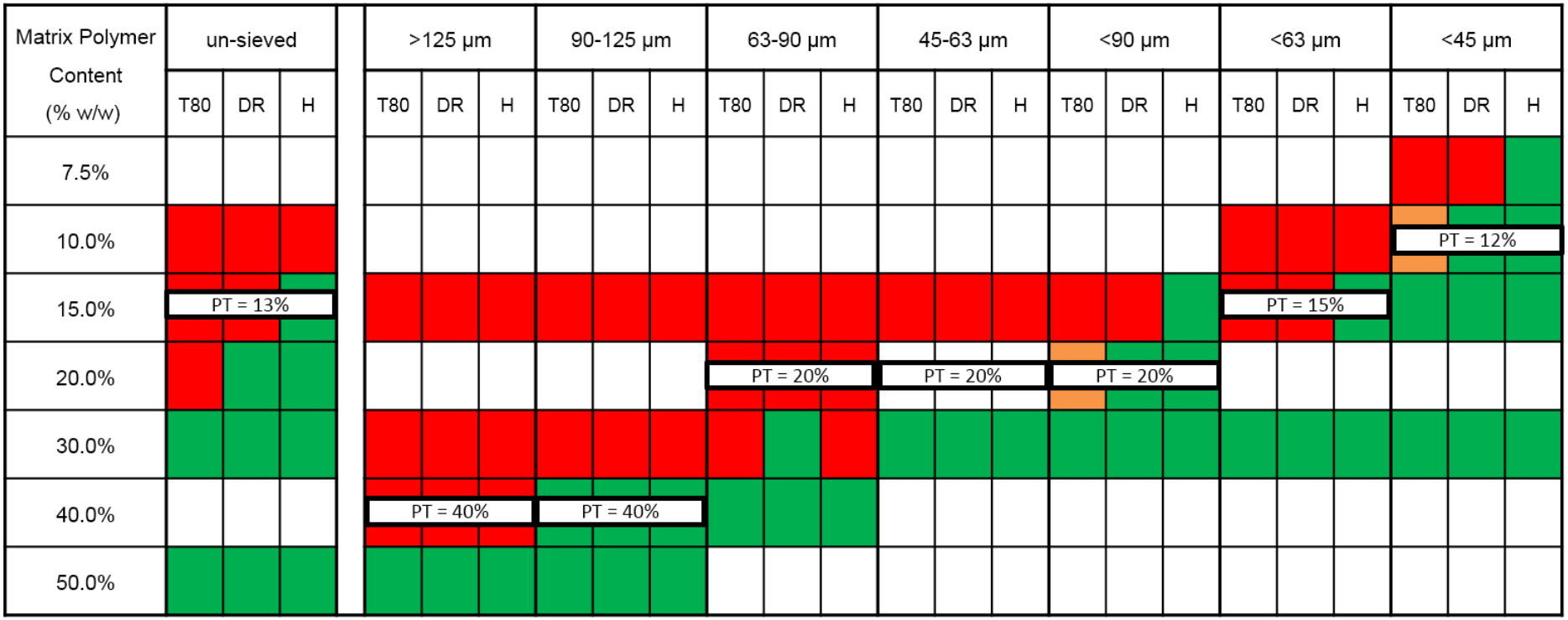


Figure 6.14: Comparison of $T_{80\%}$, DR10min and Higuchi rate constant in standard and stress dissolution conditions for HPMC matrix tablets containing different HPMC particle size fractions and variable polymer content. Green boxes show that $T_{80\%}$ < 10% difference, DR10min < 30% in both conditions and < 10% difference in Higuchi rate constant. Orange boxes depict $T_{80\%}$ with10-20% differences. Red boxes are where parameter is outside the target criteria. Standard dissolution of water/50 RPM paddle speed, Stress dissolution of 0.2M NaCl/100 RPM paddle speed.

6.4.4 Discussion: The effect of HPMC particle size

6.4.4.1 Effect of HPMC particle size on drug release rates and mechanisms

The results presented above have shown that, as the HPMC particle size decreases, drug release can become slower. Other groups have stated that this effect is due to the impact of HPMC particle size on the hydration time, with smaller particles hydrating faster as a result of their high surface to volume ratio (Alderman, 1984, Johnson et al., 1993, Dabbagh et al., 1996, Campos-Aldrete and Villafuerte-Robles, 1997). In some cases, drug release rate has been shown to be less sensitive to further reductions in particle size below a thresholds of < 113 µm (Heng et al., 2001) and < 150 µm (Mitchell et al., 1993c). It is worth nothing that the fractional ranges studied by Heng (2001) and Mitchell (1993c) were larger than those in our study as the Methocel™ Premium grade was used, which has a wider particle size distribution than the CR grade used in our study. In our study we found that the drug release rate consistently decreased as the polymer particle size fraction decreased to < 45 µm.

In parallel with the findings of the viscosity grade studies, our particle size study showed that the effect of HPMC particle size is typically reduced as the polymer content is increased. Other studies have similarly reported that the effect of HPMC particle size is minimised by increasing the HPMC content (Mitchell et al., 1993c). However, we also found that the use of large HPMC particle size fractions (>125 µm and 90-125 µm) resulted in faster drug release at the previously 'safe' content of 30% HPMC.

The HPMC particle size influenced the excipient percolation threshold, with matrices containing the smaller HPMC fractions having a lower polymer percolation threshold. This is in agreement with other studies (Caraballo et al., 1993, Millán et al., 1998). We attribute this effect to the increased surface area and smaller inter-particle distances when HPMC particle size is reduced. The smaller distances between adjacent particles, means that a continuous cluster of HPMC can be formed more rapidly, more uniformly and at a lower polymer content.

6.4.4.2 Effect of HPMC particle size on matrix sensitivity to dissolution conditions

Matrix dissolution sensitivity depended both on the polymer content and HPMC particle size. In general, smaller HPMC particle size fractions were less sensitive to the dissolution conditions at lower polymer contents, than the larger particle size fractions. However, when the matrix polymer content was lowered, all formulations showed sensitivity to 'stress' dissolution conditions. The HPMC content where inter-dissolution differences were observed was close to the percolation threshold (within ± 10%) for each HPMC particle size. We envisage there to be a close relationship between the rapid formation of a gel layer and lack of sensitivity to the stress dissolution test.

The few previous studies reported have shown similar trends. Fine particle size hydroxypropyl cellulose (HPC) has been found to be more resistant to ionic salt influence (Johnson et al., 1993) and fine HPMC fractions (< 63 µm) have been shown to reduce the sensitivity of formulations to high sucrose challenge (Williams et al., 2010a). It is therefore apparent that excipient particle size can be used as a formulation strategy to improve the robustness of HPMC matrices.

Reducing the overall content of HPMC in a matrix is possible by using a smaller particle size fraction. This could be advantageous when there is a high drug load. Similar to the results of the HPMC viscosity study, care must be taken not to reduce the polymer content excessively so that the matrix HPMC content becomes too close to the percolation threshold. However, our work has found that a reduction in HPMC particle size also lowered the matrix percolation threshold. It is a fine balance between drug release rate, sensitivity to dissolution conditions and overall polymer content; however the judicious selection of HPMC particle size seems to improve the robustness of HPMC matrix formulations, and should be considered during formulation development.

6.5 Conclusions

The work in this chapter has investigated the potential for HPMC viscosity and particle size to influence drug release rate, the necessary amount of polymer and sensitivity of the matrix to the dissolution environment.

Key conclusions are that for low polymer matrices:

1. The percolation threshold should be calculated for all systems, as this has an overriding influence on matrix sensitivity to the dissolution conditions. In all the systems we studied, dissolution sensitivity was only observed in matrices with a polymer content of less than 10% above the percolation threshold.
2. HPMC particle size had a clear impact on drug release rate. Using a smaller HPMC particle size fraction (< 45 µm) can enable the matrix polymer content to be lowered.
3. HPMC particle size impacted upon dissolution sensitivity, with less sensitivity as the HPMC particle size decreased.
4. HPMC viscosity grade influences drug release rate, with slower drug release as polymer viscosity is increased.
5. HPMC viscosity had little influence on the percolation threshold.
6. A high matrix content of lower viscosity grade HPMC is preferable to lowering the overall HPMC content of a higher viscosity grade, to below the percolation threshold.

The chapter provides good evidence that the judicious selection of HPMC properties can enable matrices containing low polymer contents to have extended release properties and drug release that can be independent of the dissolution environment. In the next chapter, non HPMC based formulation strategies will be tested.

Chapter 7
Strategies for improving low polymer content matrices. (2) non-HPMC properties

7.1 Introduction

The results of Chapters 4 and 5 showed that when the polymer content of HPMC hydrophilic matrices was reduced below the typical 30% w/w, drug release rates became more sensitive to the dissolution environment. In Chapter 6, we explored how HPMC viscosity and HPMC particle size influenced matrix sensitivity to dissolution conditions, at different matrix polymer contents. From this, we concluded that low polymer matrices could be improved by judicious choices of HPMC viscosity grade and particle size fraction.

In this chapter, we explore approaches that do not involve modifying the HPMC component. In the thesis introduction (Section 1.3.2) we discussed how other excipients in HPMC matrices can influence the drug release mechanism and matrix behaviour. There is some suggestion that excipients can have a greater influence on drug release when the matrix polymer content is lower (Alderman, 1984, Ford et al., 1987). However, there is to date a lack of studies that focus on the impact of excipients, across a range of matrix polymer contents. In these studies, we investigate various excipients that are commonly used in tabletting. In addition, we study the inclusion of other polymers (i.e. xanthan gum, polyethylene oxide and sodium carboxymethyl cellulose), in a supporting role to HPMC as rate controlling excipients.

7.2 Chapter Aims

The aims of this chapter are to:

- Investigate how tabletting excipients influence drug release as a function of matrix tablet polymer content and dissolution environment
- Investigate how combining complementary polymers with HPMC influences drug release as a function of matrix tablet polymer content and dissolution environment

7.3 Materials and Methods

7.3.1 Materials

Full details of the materials used are described in Appendix 1. The HPMC used was METHOCEL™ K4M CR Premium (Colorcon, Dartford, UK).

7.3.1.1 Tabletting excipient effects

Five excipients were used in the tablet excipient study.

- Lactose – Foremost NF Fast Flo™ Lactose 316 (Foremost Farms, USA)
- Mannitol – Pearlitol™ 100 SD (Roquette, France)
- Dicalcium phosphate (DCP) – Emcompress™ (JRS Pharma, Germany)
- Starch – Starch 1500™ (Colorcon, UK)
- Microcrystalline cellulose (MCC) – Avicel PH-102™ (FMC Biopolymer, Ireland)

7.3.1.2 Polymer combination systems

Eight polymers were studied in this section of work.

- Poloxamer 407 – Kolliphor® P 407 micro (BTC, Germany)
- NaCMC 7M31F – Blanose® 7M31F (Ashland, France)
- λ-carrageenan GP 209 – Viscarin® GP-209NF
- PEO N-60K – Polyox™ WSR N60K (Colorcon, UK)
- Xanthan 200 – Grindsted Xanthan 200 (Danisco, France)
- Xanthan Ultra – Grindsted Xanthan Ultra (Danisco, France)
- Xanthan 80 – Grindstead Xanthan 80 (Danisco, France)
- Polyacrylic acid 971P – Carbopol® 971P NF (Lubrizol, USA)

7.3.2 Manufacture of HPMC matrices

A number of different matrices were manufactured, and the base formulations are listed in Table 7.1 and Table 7.2. The manufacturing methods are described in Section 2.1. Determination of tablet tensile strength was according to the method of Section 2.3.1.

Formulations for Section A: Diluent Effects

	Quantity of excipient (% w/w)	
METHOCEL K4M	15%	30%
Tabletting excipients One of mannitol, lactose, dicalcium phosphate, MCC or starch, as listed in Section 7.3.1.1.	59.5%	59.5%
MCC	15%	0%
Caffeine	10%	
MgSt	0.5%	

Table 7.1. HPMC matrix tablet formulations for studying the effect of tabletting excipients For all formulations, caffeine was sieved through a 125 µm sieve, other excipients were used as received. Tablets were manufactured using direct compression at 150 MPa (250 ± 5 mg, 8 mm Ø, flat-faced, round) MCC is Avicel PH102. MgSt is magnesium stearate.

Formulations for Section B: Complementary Polymers

	Quantity of excipient (% w/w)	
Complementary Polymer One of METHOCEL K4M, Poloxamer 407, NaCMC, λ-carrageenan, PEO, Xanthan or Polyacrylic acid, as detailed in Section 7.3.1.2.	15%	7.5%
METHOCEL K4M	0%	7.5%
Diluents	49.7% Lactose 27.8% MCC	
Caffeine	10%	
MgSt	0.5%	

Table 7.2: HPMC matrix tablet formulations for complementary polymer experiments For all formulations, caffeine was sieved through a 125 µm sieve, other excipients were used as received. Tablets were manufactured using direct compression at 150 MPa (250 ± 5 mg, 8 mm Ø, flat-faced, round) MCC is Avicel PH102. MgSt is magnesium stearate.

7.3.3 USP apparatus II (paddle) dissolution testing

Drug release kinetics were determined in 900 mL degassed, de-ionised media (37 ± 0.5 °C) in USP apparatus II (paddle). 'Standard' (50 RPM paddle speed and water) and 'stress' (100 RPM paddle speed and 0.2 M NaCl) dissolution conditions were used.

Caffeine was quantified at a UV absorbance of λ = 273 nm as fully described in Section 2.3.2. Dissolution data was characterised using the mathematical models discussed in Section 2.3.3.

7.3.4 Confocal microscopy imaging of nascent gel layer formation

Imaging of early gel formation was undertaken in 0.008% w/v Congo red using the methods described in Section 2.3.5.

7.3.5 Time lapse photography of hydrating matrices

A series of photographs were taken every 30 seconds for the first 30 minutes of hydration as described in Section 2.3.6.

7.3.6 Manufacture of HPMC solutions for viscosity measurements

HPMC solutions were manufactured by high shear mixing as described in Section 2.5.1.

7.3.7 Determination of solution viscosity

The viscosity of solutions was measured at a shear rate of 6.81 Hz (37 °C) on an MCR302 Rheometer fitted with a 2° cone and plate (Anton Paar, Austria), as detailed in the full methods in Section 2.5.3.

7.4 Results and Discussions

The chapter is formatted into 2 sections.

Section A	The effect of **matrix excipients**	(7.4.1 - 7.4.2)
Section B	The effect of **complementary polymers**	(7.4.3 - 7.4.6)

Section A:

The effect of changing the tabletting excipients on drug release from low polymer content matrices

7.4.1 Results: The effect of tabletting excipients

7.4.1.1 The effect of matrix excipient on tablet tensile strength

Some of the excipients included in the formulation had functional properties, for example, MCC is usually included in formulations to improve tablet hardness. Therefore, the tensile strengths of matrices manufactured with different tabletting excipients were compared. Figure 7.1 shows the tensile strength of tablets with respect to their diluent and HPMC content. Matrices containing microcrystalline cellulose (MCC) matrices were hardest, followed by mannitol. Di-calcium phosphate (DCP), starch and lactose tablets were softer. When the matrix HPMC content was lowered from 30% to 15% w/w, more MCC was added to the formulation to compensate. As a result, we would expect a consistent difference in tensile strength between the 30% and 15% w/w HPMC formulations. In the case of matrices containing lactose, mannitol or DCP, the tensile strength was higher as the HPMC content was lowered from 30% to 15% w/w. This was expected due to the binder properties of MCC. Surprisingly, for two excipients (MCC and starch), the tensile strength decreased as the HPMC content was reduced.

Although not a clear relationship, it is generally held that tensile strength has little impact on drug release from hydrophilic matrices (Velasco et al., 1999, Viriden et al., 2009c), as discussed in Sections 1.3.3.1 and 2.6.2. However, there is some evidence that the applied compression force can influence drug release rate, the extent of which has been found to depend on the type of excipient used (Levina and Rajabi-Siahboomi, 2004).

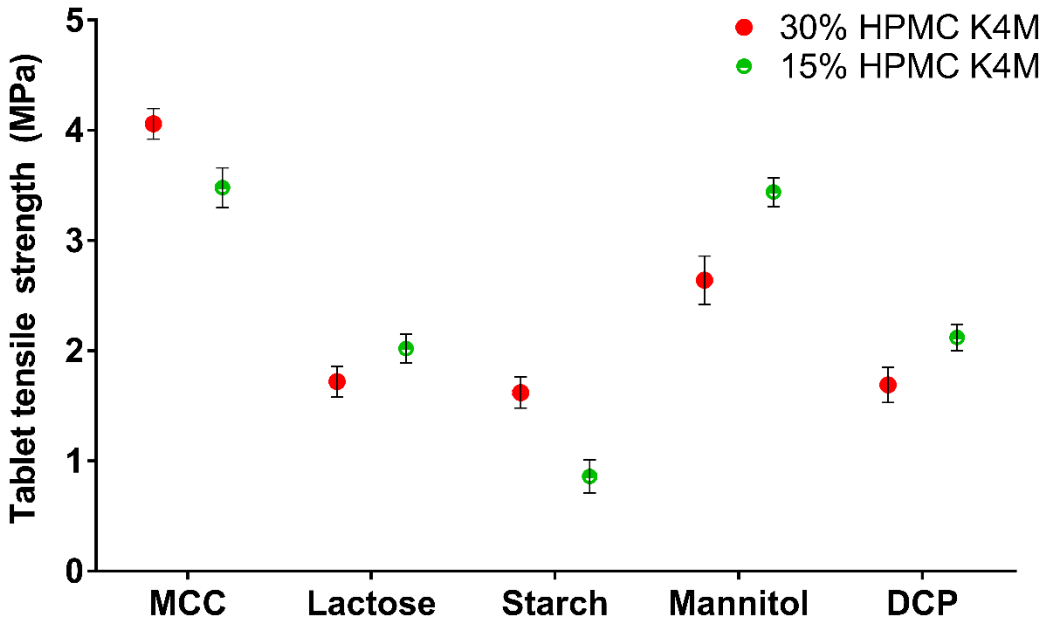


Figure 7.1: Tensile strength of HPMC matrices calculated from diametral breaking force. (n=6 ± 1 SD). All excipient contents reported as % w/w. HPMC Formulations contain 59.5% of the tabletting excipient in addition to 0.5% MgSt, 10% caffeine and either 30% HPMC K4M or 15% HPMC K4M and 15% MCC. All matrices were manufactured at a compression pressure of 158 MPa. Tensile strength calculation listed in Section 2.3.1.

7.4.1.2 Extended release properties of HPMC matrices which contain different tabletting excipients

Figure 7.2 shows how caffeine is released from HPMC matrices as a function of the excipient and HPMC polymer content. Dissolution parameters for the formulations are shown in Table 7.3. When the matrix tablet contained 30% w/w HPMC (Figure 7.2a), only small differences in the $T_{80\%}$ values were seen. Drug release was faster from formulations containing the water soluble excipients mannitol and lactose ($T_{80\%}$ = 4.3 and 4.8 h), than from formulations containing MCC (poorly soluble) and starch (swellable) ($T_{80\%}$ = 6.98 and 7.12 h). DCP, which is virtually insoluble, resulted in an intermediate $T_{80\%}$ of 5.4 hours. In general, the more soluble the diluent, the faster the drug release. No substantial initial burst or uncontrolled release was observed in any formulations containing 30% w/w HPMC. DR10min remained below 11% for all formulations. Korsmeyer-Peppas *n* exponent values of 0.63 - 0.74 suggested an anomalous (mixed) release mechanism for all 30% w/w HPMC formulations.

In matrices with a polymer content of 15% w/w HPMC (Figure 7.2 b), there were greater differences between formulations. Values of $T_{80\%}$ and DR10min varied substantially between the different diluents. Release was fastest for the mannitol containing formulations ($T_{80\%}$ = 1.2 h), followed by lactose ($T_{80\%}$ = 2.1 hr) and DCP ($T_{80\%}$ = 3.8 hr) with MCC and starch exhibiting the slowest release ($T_{80\%}$ = 6.1 and 6.2 hrs respectively).

The Higuchi drug release rate from MCC and starch based matrices was similar, irrespective of the matrix polymer content. In contrast, drug release from DCP, mannitol and lactose based formulations was faster when the polymer content was lowered from 30% to 15% w/w. The Korsmeyer-Peppas *n* exponent values showed greater variation in 15% w/w HPMC matrices than 30% w/w HPMC matrices, with values between n = 0.89 and 0.59. These results suggest that although the drug release mechanism is still anomalous, the excipients appear to be influencing the release mechanism to some degree.

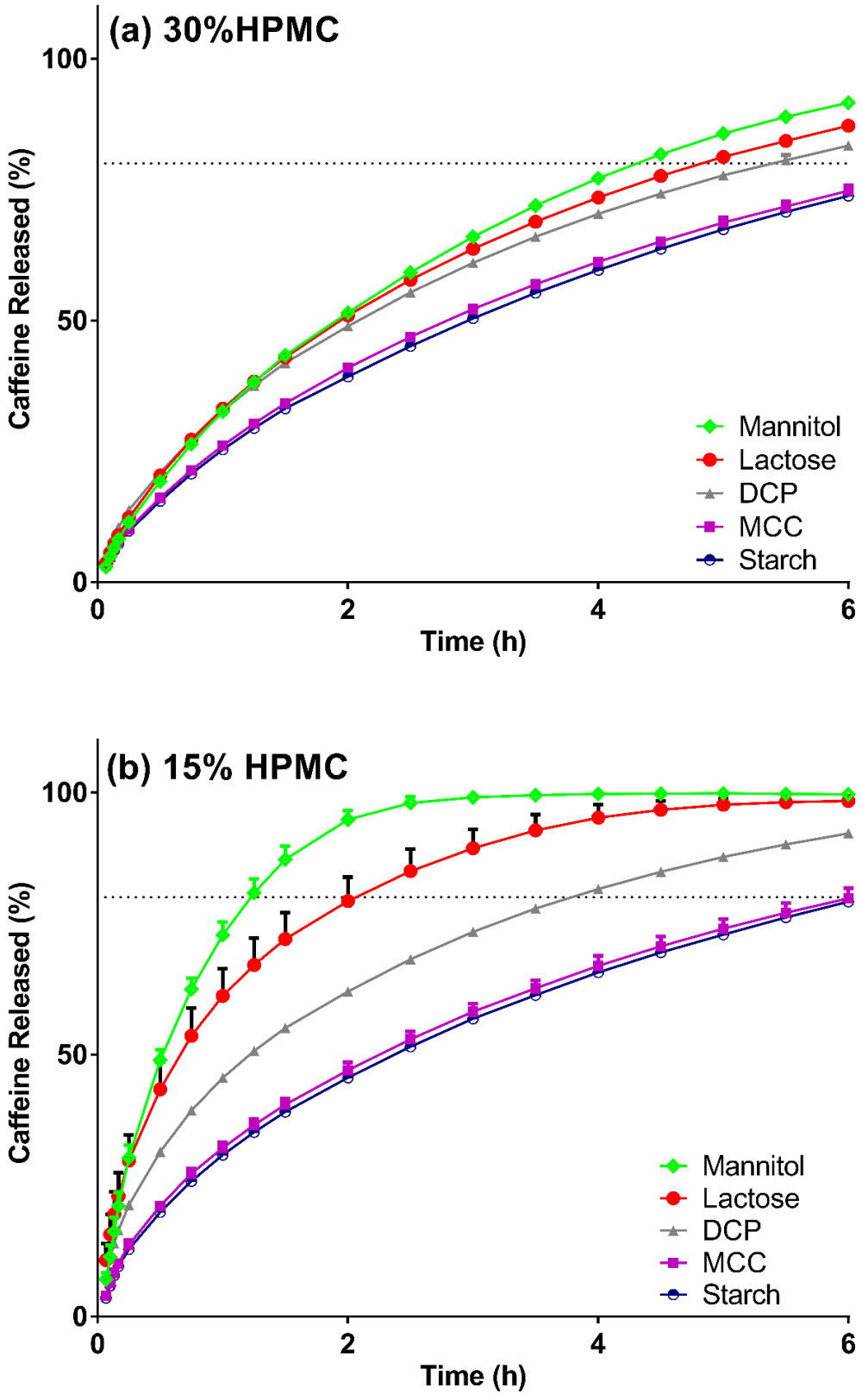


Figure 7.2: Release of caffeine from HPMC matrices containing different tabletting excipients. Matrix tablet polymer content of (a) 30% w/w HPMC K4M or (b) 15% w/w HPMC K4M. USP apparatus II, 50 RPM, 900 mL water, 37 ± 0.5 °C. Mean (n=3) + 1 SD. Black dashed lines show $T_{80\%}$

Tabletting excipient	HPMC Content (% w/w)	T80% (hours)	DR10min (%)	Higuchi		Korsmeyer-Peppas		
				k_h ($min^{-0.5}$)	r^2	k_{kp} (min^{-n})	n	r^2
Mannitol	30	4.31 ± 0.05	8.2 ± 0.1	5.66 ± 0.04	0.9986	1.52	0.74	0.9972
Lactose		4.83 ± 0.03	9.0 ± 0.7	5.34 ± 0.03	0.9991	1.77	0.70	0.9931
DCP		5.40 ± 0.17	10.5 ± 0.2	4.95 ± 0.02	0.9994	2.37	0.63	0.9965
MCC		6.98 ± 0.20	7.6 ± 0.0	4.39 ± 0.03	0.9986	1.70	0.66	0.9980
Starch		7.12 ± 0.05	7.3 ± 0.1	4.29 ± 0.03	0.9986	1.62	0.66	0.9984
Mannitol	15	1.23 ± 0.09	21.1 ± 2.7	11.95 ± 0.28	0.9897	2.36	0.89	0.9574
Lactose		2.07 ± 0.37	23.0 ± 4.5	8.47 ± 0.34	0.9602	5.17	0.61	0.9379
DCP		3.79 ± 0.02	16.5 ± 0.5	5.98 ± 0.07	0.9952	3.97	0.59	0.9878
MCC		6.05 ± 0.36	10.1 ± 0.9	4.66 ± 0.04	0.9969	2.37	0.62	0.9898
Starch		6.16 ± 0.17	9.6 ± 0.3	4.58 ± 0.02	0.9995	2.18	0.63	0.9938

Table 7.3: The effect of tabletting excipient and matrix HPMC content on drug release kinetics ($T_{80\%}$, DR10min, Higuchi and Korsmeyer-Peppas dissolution parameters**.** Mean (n=3). (For $T_{80\%}$, DR10min and Higuchi: ± 1 SD)

7.4.1.3 Early gel layer formation with respect to matrix tabletting excipient

Figure 7.3 shows matrices containing 15% w/w HPMC and the five test excipients hydrating for 15 minutes and visualised using confocal fluorescence microscopy. The initial dry matrix edge is shown in each image by the dashed, white line. Fluorescence is recorded in grayscale, with the white areas showing highly fluorescent regions where Congo red has bound. This indicates the location of hydrated HPMC, which we can interpret as the emerging gel layer.

After one minute of hydration, all images show a fluorescent region to the left of the initial dry boundary, which indicates that significant swelling has occurred in all formulations in this time. The fluorescent region is widest for matrices containing lactose, followed by starch, with mannitol, DCP and MCC being similar. There is no significant fluorescence right of the initial dry boundary, suggesting no significant penetration of media into the matrix. After 5 minutes, the fluorescent hydrated regions are more similar in appearance and of a similar size. As this represents a thinning of the gel layer in lactose-based matrices, it suggests an erosion of the outer edge of the gel layer has occurred.

After 15 minutes of hydration, the fluorescence pattern is similar in appearance for all formulations, suggesting that a rate limiting gel layer is formed in all cases. There is no indication of extensive surface erosion in any formulations.

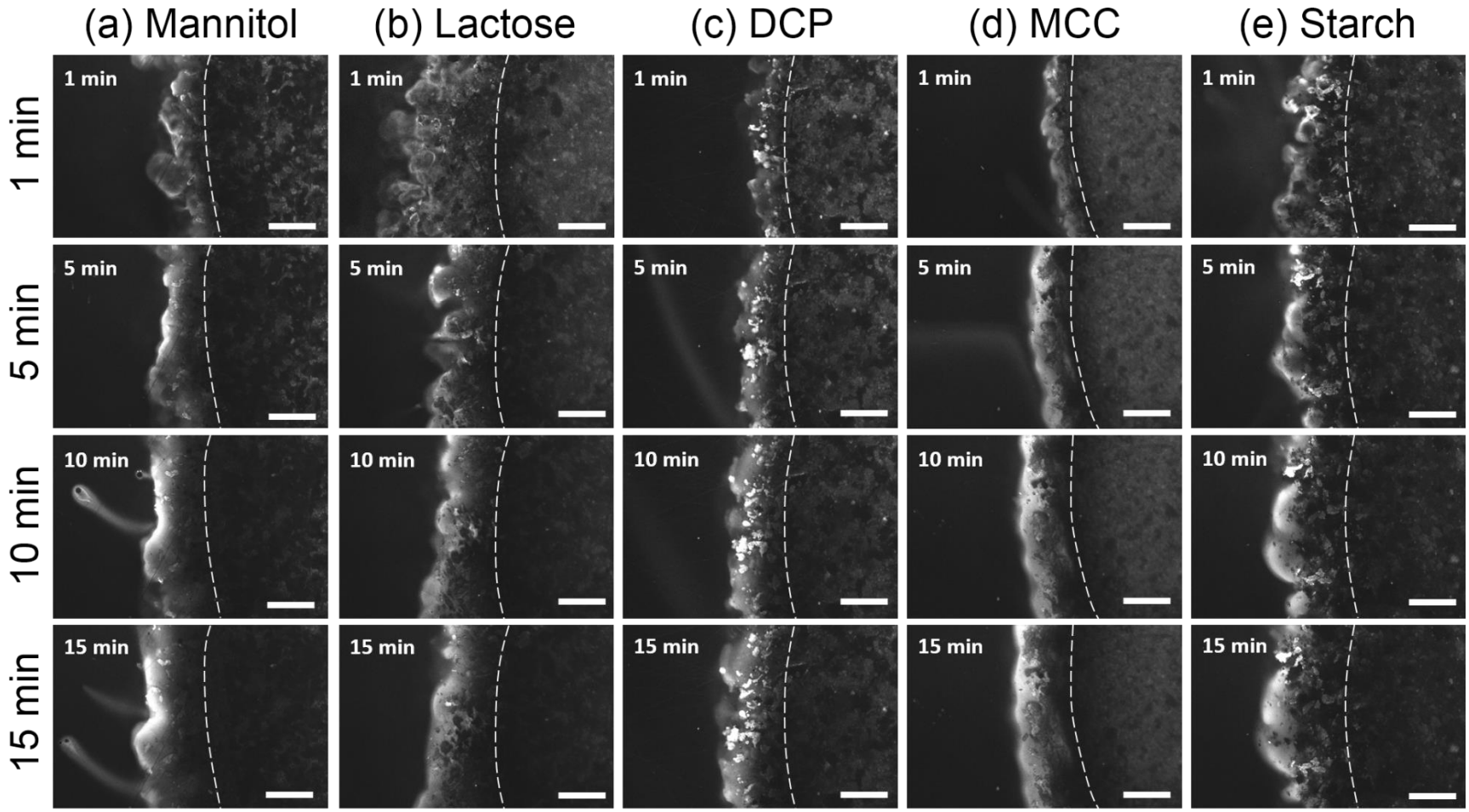


Figure 7.3: Early gel layer formation at the boundary of hydrating 15% w/w HPMC matrices as a function of time and tabletting excipient. Confocal fluorescence imaging at Ex 488/Em >510 nm. Experiments conducted at 37 ± 1 °C using 0.008% w/v Congo red in water as a visualisation aid. Dotted white lines represent the dry matrix boundary at t=0 minutes. Scale bar = 500 µm. All images brightened by 15% in Microsoft PowerPoint to allow better visualisation in the printed copy.

7.4.1.4 The extended release properties of matrices containing different excipients under "standard" and "stressed" dissolution conditions

The drug release profiles of matrices containing different excipients are shown in Figure 7.4 (30% w/w HPMC formulations) and Figure 7.5 (15% w/w HPMC formulations). The $T_{80\%}$, DR10min and Higuchi rate constants are compared in Table 7.4 and Table 7.5. Stress sensitivity was evaluated according to the criteria established in Chapter 4 (Section 4.4.7.1) in which a successful formulation would show:

- Less than a 10% difference in $T_{80\%}$ value between "standard" and "stress" conditions
- Less than a 10% difference in Higuchi rate constant.
- Less than a 30% drug release in 10 minutes (DR10min).

In Table 7.4 and Table 7.5, the green boxes indicate that the formulation did not exceed the criteria above, the orange boxes show a $T_{80\%}$ value between 10 and 20% different, and red boxes denote values that exceed the criteria above.

In matrices containing 30% w/w HPMC, there was little evidence of stress sensitivity, as the dissolution profiles were broadly similar irrespective of the type of excipient it contained. $T_{80\%}$ values ranged from 4.05 to 8.07 h under stress conditions, compared to between 4.31 to 7.12 h under standard conditions. The $T_{80\%}$ values were in a similar rank order (in terms of the excipient being used) under both standard and stress dissolution conditions. Similarly, values for DR10min and Higuchi rate were within the criteria, for all formulations that contained 30% w/w HPMC.

In contrast, 15% w/w HPMC formulations showed dissolution sensitivity. Matrices containing mannitol or lactose exhibited much faster drug release under stress dissolution conditions, than typical conditions, with twice as much caffeine being released as an initial burst (DR10min). When MCC, starch or di-calcium phosphate were included, limited sensitivity to dissolution conditions was observed.

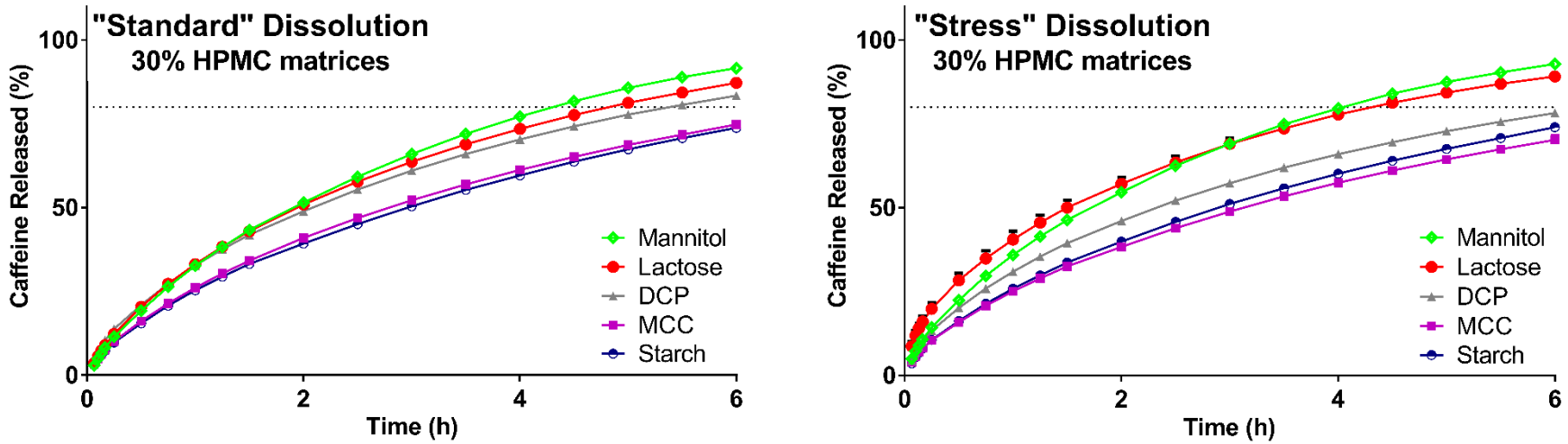


Figure 7.4: Release of caffeine from 30% w/w HPMC matrices containing different tabletting excipients in two dissolution conditions. USP apparatus II, 900 mL, 37 ± 0.5 °C. Mean (n=3) + 1 SD. Standard dissolution = 50 RPM paddle speed and water, Stress dissolution = 100 RPM and 0.2M NaCl.

HPMC Content (% w/w)	Diluent	Dissolution conditions	T80% (hours)	%	DR10min (%)		Higuchi	%	Korsmeyer-Peppas	
							k_h (min$^{-0.5}$)		k_{kp} (min^{-n})	n
30%	Mannitol	Standard	4.31 ± 0.05	-3.7	8.2 ± 0.1		5.66 ± 0.04	-0.2	1.52	0.74
		Stress	4.05 ± 0.10		10.8 ± 0.5		5.65 ± 0.03		2.15	0.68
	Lactose	Standard	4.83 ± 0.03	-10.8	9.0 ± 0.7		5.34 ± 0.03	-1.1	1.77	0.70
		Stress	4.31 ± 0.20		16.1 ± 1.7		5.28 ± 0.07		4.54	0.53
	DCP	Standard	5.40 ± 0.17	+18.1	10.5 ± 0.2		4.95 ± 0.02	-8.1	2.37	0.63
		Stress	6.38 ± 0.11		10.3 ± 0.2		4.55 ± 0.02		2.54	0.60
	MCC	Standard	6.98 ± 0.20	+16.6	7.6 ± 0.0		4.39 ± 0.03	-8.7	1.70	0.66
		Stress	8.07 ± 0.29		8.1 ± 0.2		4.01 ± 0.02		1.95	0.62
	Starch	Standard	7.12 ± 0.05	-0.8	7.3 ± 0.1		4.29 ± 0.03	-1.2	1.62	0.66
		Stress	7.06 ± 0.11		8.1 ± 0.2		4.24 ± 0.02		1.82	0.64

Table 7.4: A comparison of drug release kinetics for 30% w/w HPMC matrices containing different tabletting excipients in two dissolution conditions. USP apparatus II, 900 mL, 37 ± 0.5 °C. Standard dissolution is 0.0 M (water) at 50 RPM. Stress dissolution is 0.2 M NaCl at 100 RPM. Mean (for $T_{80\%}$, DR10min and Higuchi: ± 1 SD) (n=3). % values for $T_{80\%}$ and Higuchi are the relative increase in the mean of stress dissolution compared to standard conditions.

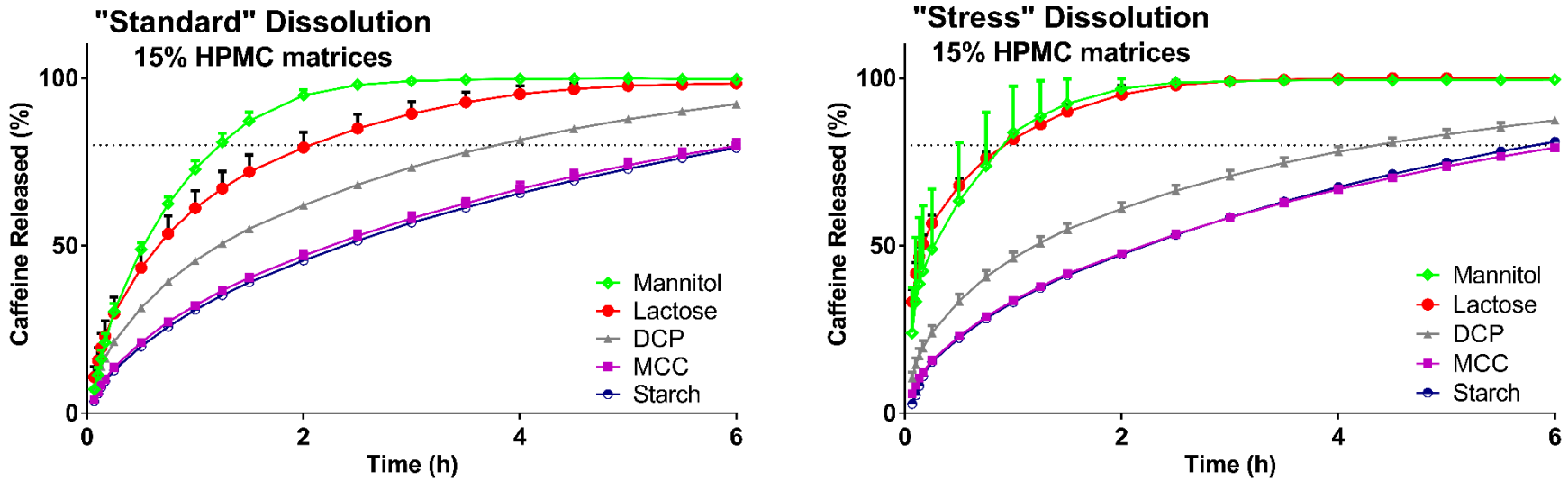


Figure 7.5: Release of caffeine from 15% w/w HPMC matrices containing different tabletting excipients in two dissolution conditions. USP apparatus II, 900 mL, 37 ± 0.5 °C. Mean (n=3) + 1 SD. Standard dissolution = 50 RPM paddle speed and water, Stress dissolution = 100 RPM and 0.2M NaCl

HPMC Content (% w/w)	Diluent	Dissolution conditions	T80% (hours)	%	DR10min (%)		Higuchi	%	Korsmeyer-Peppas	
							k_h ($min^{-0.5}$)		k_{kp} (min^{-n})	n
15%	Mannitol	Standard	1.23 ± 0.09	-26.0	21.1 ± 2.7		11.95 ± 0.28	-17.1	2.36	0.89
		Stress	0.91 ± 0.45		42.4 ± 19.4		9.97 ± 2.12		12.55	0.47
	Lactose	Standard	2.07 ± 0.37	-55.6	23.0 ± 4.5		8.47 ± 0.34	11.9	5.17	0.61
		Stress	0.92 ± 0.09		50.5 ± 2.7		9.48 ± 0.73		21.95	0.34
	DCP	Standard	3.79 ± 0.02	15.0	16.5 ± 0.5		5.98 ± 0.07	-8.4	3.97	0.59
		Stress	4.36 ± 0.27		19.5 ± 2.2		5.48 ± 0.11		5.93	0.50
	MCC	Standard	6.05 ± 0.36	2.0	10.1 ± 0.9		4.66 ± 0.04	-4.1	2.37	0.62
		Stress	6.17 ± 0.02		12.3 ± 0.3		4.47 ± 0.02		3.14	0.57
	Starch	Standard	6.16 ± 0.17	-5.0	9.6 ± 0.3		4.58 ± 0.02	0.4	2.18	0.63
		Stress	5.85 ± 0.09		11.0 ± 1.0		4.60 ± 0.04		2.84	0.59

Table 7.5: A comparison of drug release kinetics for 15% w/w HPMC matrices containing different tabletting excipients in two dissolution conditions. USP apparatus II, 900 mL, 37 ± 0.5 °C. Standard dissolution is 0.0 M (water) at 50 RPM. Stress dissolution is 0.2 M NaCl at 100 RPM. Mean (for $T_{80\%}$, DR10min and Higuchi: ± 1 SD) (n=3). % values for $T_{80\%}$ and Higuchi are the relative increase in the mean of stress dissolution compared to standard conditions.

7.4.2 Discussion: Effect of Tabletting Excipient

7.4.2.1 The effect of tabletting excipients on drug release rates and mechanisms

It has been reported previously that the diluent must be present at a high content in the matrix to have an impact on release, and that the higher the level of excipient, the greater the impact on release rate (Ford et al., 1987, Williams III et al., 2002, Lotfipour et al., 2004). In this study, all formulations contained 59.5% w/w of the test diluent and so we would expect excipient effects to be pronounced. Previous studies, such as those by Ford et al. (1987), Lotfipour et al. (2004) and Sako et al. (2002) have replaced HPMC with tabletting excipients, or changed the final tablet weight, and therefore determining which change is affecting drug release can be problematic as commented by Li et al. (2005). Therefore, to try to control this, 15% w/w MCC was added to all formulations as the polymer content was lowered from 30% to 15% w/w HPMC.

Greater differences were apparent when the matrix polymer content was 15% w/w, and therefore the effect of tabletting excipients is discussed for matrices containing 15% w/w HPMC. The impact of matrix polymer content is discussed in the subsequent section (7.4.2.2).

In the case of 15% w/w HPMC matrices, drug release was faster when soluble tabletting excipients (mannitol or lactose) were used, compared to the use of poorly soluble excipients (DCP, MCC or starch). The $T_{80\%}$ values ranged from 1.23 h to 6.16 h. In addition, there was a larger burst release of drug in the first 10 minutes when soluble tabletting excipients were included, with DR10min = 21.1% for mannitol, compared with DR10min = 9.6% for starch.

The inclusion of soluble diluents within matrix tablets is known to increase drug release rate, and is thought due to solubility effects (Lapidus and Lordi, 1966, Holgado et al., 1995, Levina and Rajabi-Siahboomi, 2004). Lactose and mannitol are both readily soluble in water, which can result in increased water uptake during early dissolution (Jamzad et al., 2005). Lactose and mannitol may also induce higher water transport rates into the matrices as they drive an increased osmotic pressure gradient (Tajarobi et al., 2009b). Increased water uptake can result in a lower gel strength, increased matrix porosity and increased tablet erosion rate (Williams III et al., 2002). Sako et al. (2002)

showed that a larger portion of the matrix gelated on contact with water when water soluble excipients were included, with the first measurement taken after one hour.

In our study, we used confocal microscopy to image the emerging gel layer over the first 15 minutes of hydration (Figure 7.3). The results showed marginal differences in gel layer formation, with respect to the tabletting excipient included. The only apparent difference was that formulations containing lactose showed a greater degree of initial swelling at t =1 min, but after 15 minutes the gel layer was a similar size for all formulations. Our work, which contrasts with Sako et al. (2002), suggests that the tabletting diluent has little impact on the size of the gel layer, albeit our study was over a shorter time frame. Confocal microscopy is unable to estimate the tortuosity or strength of the gel layer.

Based on how soluble tabletting excipients influence drug release, it would be expected that drug release would be slower when poorly soluble excipients are used. It has been shown in the literature that DCP/HPMC matrices have slower water uptake than mannitol/HPMC formulations, due to the decreased solubility of the excipient (Tajarobi et al., 2009a). In our study, the inclusion of starch, MCC or DCP resulted in drug release that was slower than for matrices containing lactose or mannitol. However, formulations containing DCP had a faster drug release than those containing MCC or starch.

Insoluble diluents can be further classified as insoluble but swellable, or non-swelling (Alderman, 1984). DCP is non-swelling, starch is swellable and MCC is known to wick water, which would put it into the swellable category (Alderman, 1984). MCC and starch are therefore excipients that can imbibe water into the formulation (Rane et al., 2010), but without rapidly dissolving. MCC and starch are therefore likely to limit rapid drug diffusion as the gel layer forms. They may contribute to the sum of extended release excipients in the matrix. This may be in contrast to the behaviour of DCP on initial matrix hydration. DCP, being insoluble and non-swelling, may act as a physical obstruction to water uptake. There is some evidence of this in our confocal study, where we can observe particulate matter in the gel layer of the hydrating DCP/HPMC matrices (Figure 7.3). The presence of insoluble material within the gel layer has been reported to result in a weakened gel with less swelling, and a gel which is no longer homogenous (Zuleger et al., 2002). These materials have been reported to create ‘stress cracks’ during gelling, which may result in failure of the matrix (Alderman, 1984), however such ‘dose-dumping’ was not observed in our study nor in several other published studies (Ford et al., 1987, Rekhi et al., 1999).

7.4.2.2 The impact of matrix polymer content on sensitivity to tabletting excipient

As mentioned in the previous section, the impact of the tabletting excipient was greater when the matrix polymer content was 15% instead of 30% w/w HPMC.

In the case of 30% w/w HPMC matrices, a change in the tabletting excipient had little impact on the drug release in the first 10 minutes (DR10min), which was between 7.3 and 10.5% for all formulations. All 30% w/w HPMC formulations were found to have similar Korsmeyer-Peppas *n* values between *n* = 0.63 and *n* = 0.74, suggesting anomalous release mechanisms. The $T_{80\%}$ values for 30% w/w HPMC formulations varied from 4.31 h to 7.12 h, a 65% difference. In the case of 15% w/w HPMC matrices, the $T_{80\%}$ varied from 1.23 h to 6.16 h, a 400% increase.

The importance of matrix polymer content in determining the sensitivity to changes in tabletting excipient has been reported previously in the literature (Vargas and Ghaly, 1999). It has been suggested that insoluble DCP can increase the mechanical strength of the hydrated matrix and, in addition, contribute to the viscosity of the erosion front. DCP permitted controlled drug dissolution at lower matrix polymer contents than was possible when the formulation contained a soluble diluent (mannitol) (Tajarobi et al., 2009b). Starch 1500, the partially pregelatinized grade used in this study, has also been shown to slow water uptake and increase gel tortuosity, thereby decreasing diffusion rate. It was suggested by the authors that starch itself may act as an extended release polymer (Levina and Rajabi-Siahboomi, 2004). We saw evidence that insoluble diluents contribute towards extended drug release, as in the case of matrices containing MCC or starch, there was little change in drug release when the matrix polymer content was lowered from 30% to 15% w/w HPMC.

7.4.2.3 The effect of the tabletting diluent on matrix sensitivity to dissolution conditions

Matrix dissolution sensitivity was shown to primarily depend on the matrix polymer content. When the matrix contained 30% w/w HPMC, limited sensitivity to ‘stress’ dissolution conditions was observed. For all formulations, the DR10mins was less than 20%, Higuchi rate constants remained similar under both dissolution conditions and drug release was driven by anomalous mechanisms (Korsmeyer-Peppas *n* exponent between n = 0.53 and 0.74).

However, when the matrix polymer content was lowered to 15% w/w, stress sensitivity was dependent on which tabletting excipient was included. In the case of MCC or starch matrices, no stress sensitivity was seen; the inclusion of DCP resulted in slightly slower drug release under 'stress' dissolution conditions, whereas drug release was much faster under 'stress' conditions than 'standard' dissolution conditions for mannitol or lactose-containing formulations. We know from the work in Chapter 4, that the original formulations containing 15% w/w HPMC (which contained a 2:1 mixture of lactose:MCC) were sensitive to 'stress' dissolution conditions (Section 4.4.6). We have also seen in Chapter 6 that the sensitivity to dissolution conditions can be related to the percolation threshold (Section 6.4.4.2), with dissolution sensitivity apparent when the matrix polymer content is less than or close to the percolation threshold. Therefore, it may be that the tabletting diluent influences the matrix percolation threshold, although no such correlation has been reported when drugs of different solubilities are included (Fuertes et al., 2010). However starch and MCC could contribute to the formation of a gel layer, as discussed in Section 7.4.2.2, and therefore the necessary HPMC content may be lower.

7.4.2.4 Summary of the effect of tabletting diluent

Whilst using insoluble excipients seemed to limit matrix dissolution sensitivity, the formulation change did not result in faster drug release. There seems to be little advantage in substituting HPMC for a poorly soluble diluent, as the overall excipient load on the formulation would be unchanged. Drug release rates increased when the matrix polymer content was lowered to 15% w/w if a soluble diluent was included. However, these formulations became sensitive to the dissolution conditions. Lactose formulations showed greater dissolution sensitivity than those containing mannitol. When the formulation contained 30% w/w HPMC, drug release rates were only slightly faster when the matrix contained soluble diluents rather than insoluble diluents. The increase in rate was not sufficient to achieve the target $T_{80\%}$ of around 2.5 hours. The right balance between release rate increase and dissolution sensitivity may be achievable at intermediate HPMC contents.

In conclusion, in our study, diluent selection did not offer any clear improvements in the robustness of low polymer formulations, especially when considering that often these systems require the overall excipient load to be low. However, we have noted that changing the excipient of matrices containing low polymer contents can alter both the rate and mechanism of drug release.

Section B:

The effect of complementary polymers on drug release from low polymer content matrices

7.4.3 Results: Non-HPMC polymers

7.4.3.1 Extended release properties of non-HPMC polymer matrices

Figure 7.6 shows the release of drug from matrices containing 15% w/w polymer under standard dissolution conditions. Four of the polymers tested were anionic (NaCMC, polyacrylic acid 971P, xanthan gum and λ-carrageenan) and the remaining two were non-ionic (PEO N-60K and poloxamer 407). Dissolution data were characterised by their $T_{80\%}$ and DR10min values, and by the fitting of Higuchi and Korsmeyer-Peppas equations. The results are shown in Table 7.6.

Drug release profiles varied depending on the polymer used, with $T_{80\%}$ values ranging from 0.68 h for poloxamer 407 to 4.94 h for polyacrylic acid 971P. The HPMC (METHOCEL K4M) formulations had a mean $T_{80\%}$ of 2.41 hours. Formulations containing xanthan gum (all three grades) and polyacrylic acid exhibited slower drug release than HPMC matrices with $T_{80\%}$ values of 3.82, 3.84, 3.78 and 4.94 h). This suggests that these polymers are more potent than HPMC as rate extending polymers. Xanthan Ultra is designed for faster dispersion and hydration through the addition of 1% w/w polysorbate 60, but this made no difference to drug release profiles compared to the other xanthan grades.

The DR10min value can highlight whether there has been any burst release of the drug. The HPMC formulations had a mean DR10min of 20.9%. Only two polymers showed a higher burst release of the drug; poloxamer 407 (DR10min = 25.9%) and PEO N-60K (DR10min = 25.1%). For the remaining polymers, DR10min was below 10.2%.

The shape of the drug release curve was almost linear for matrices containing 15% w/w poloxamer 407, NaCMC 7M31F, λ-carrageenan GP209 and xanthan gum. In these cases, the Korsmeyer-Peppas *n* exponent value was close to or more than 1, which suggests erosion was the predominant release mechanism. In contrast, the drug release curve for PEO N-60K was similar in shape to that of HPMC, with a Korsmeyer-Peppas *n* exponent of 0.49, indicating an anomalous drug release mechanism.

Figure 7.7 shows the release of drug from matrices containing 15% w/w polymer under ‘stress’ dissolution conditions. Drug release, with respect to dissolution conditions, is compared in the next section (7.4.3.2),

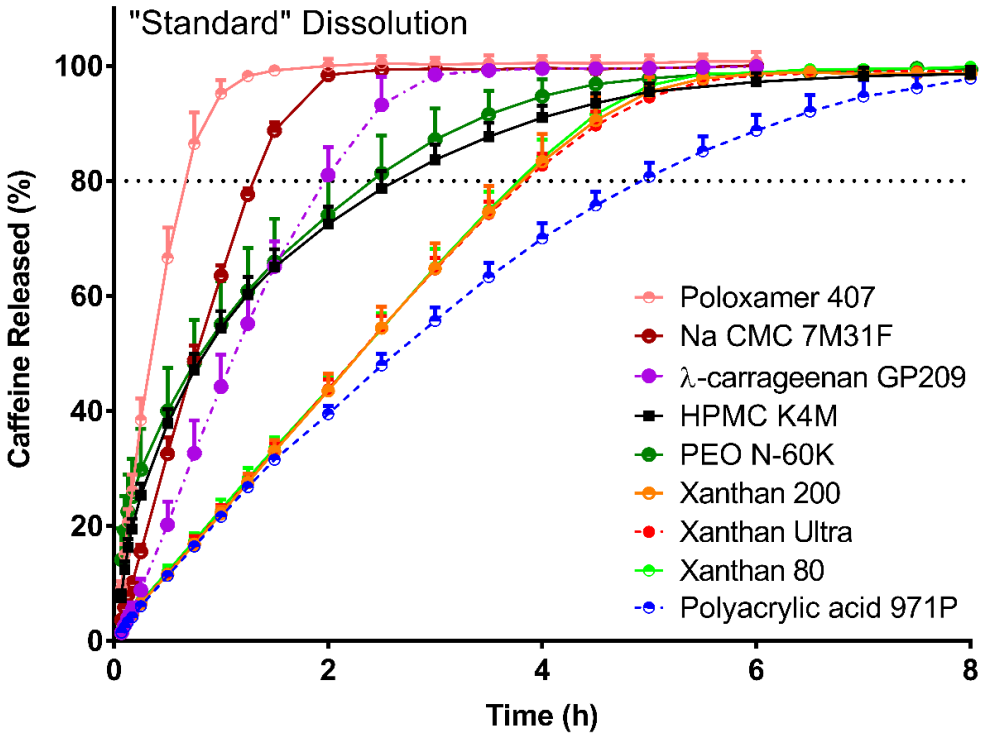


Figure 7.6: Release of caffeine from matrices containing 15% w/w of different polymers under 'standard' dissolution conditions. USP apparatus II (50 RPM), 900 mL water at 37 ± 0.5 °C. Mean (n=3) + 1 SD. Dashed line denotes $T_{80\%}$. Release curve for xanthan ultra is obscured by xanthan 200 and xanthan 80.

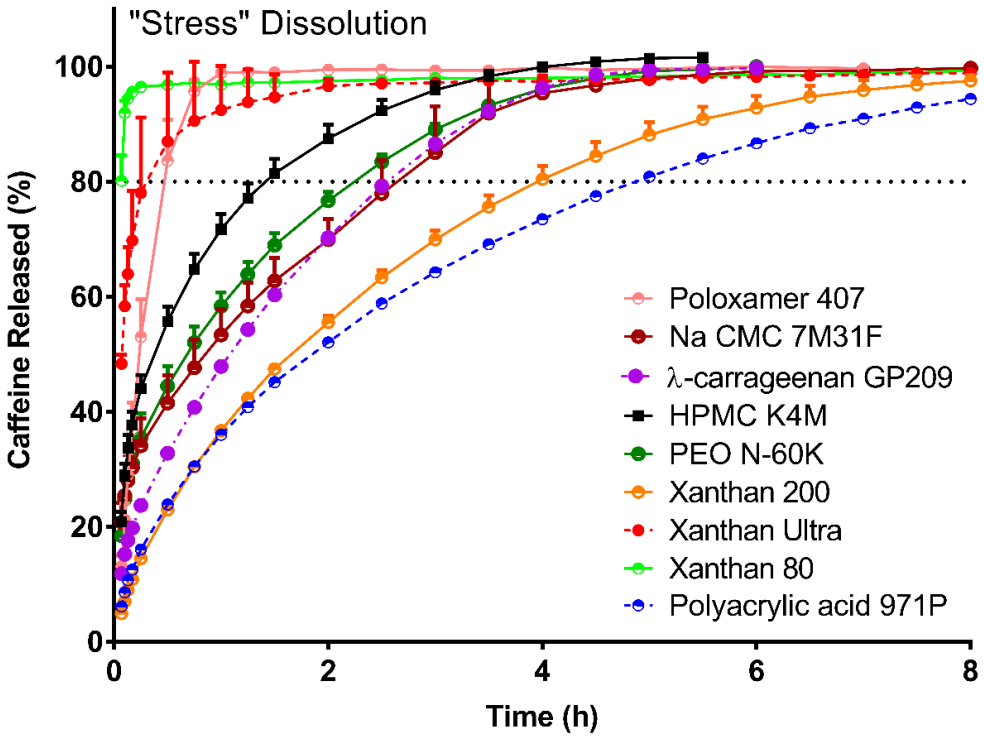


Figure 7.7: Release of caffeine from matrices containing 15% w/w of different polymers under 'stress' dissolution conditions. USP apparatus II (100 RPM), 900 mL of 0.2 M NaCl (37 ± 0.5 °C). Mean (n=3) + 1 SD. Dashed line denotes T80%.

7.4.3.2 A comparison of drug release under 'standard' and 'stress' dissolution conditions

Figure 7.6 and Figure 7.7 show drug release from matrices under 'standard' and 'stress' dissolution conditions. Calculated dissolution parameters of the drug release in both conditions were compared in Table 7.6. Stress sensitivity was evaluated according to the criteria established in Section 4.4.7, in which a successful formulation would show:

- Less than a 10% difference in $T_{80\%}$ value between 'standard' and 'stress' conditions
- Less than a 10% difference in Higuchi rate constant
- Less than a 30% drug release in 10 minutes (DR10min).

In Table 7.6, green boxes indicate that the formulation did not exceed the criteria above, the orange boxes show $T_{80\%}$ between 10 and 20% different, and red boxes denoting values that exceed the criteria above.

Drug release was similar under both dissolution conditions for matrices containing either PEO N-60K, xanthan 200 or polyacrylic acid 971P, according to the results in Table 7.6. From Figure 7.6 and Figure 7.7, it can be seen that the drug release curve has changed shape for formulations containing xanthan 200 or polyacrylic acid 971P. Unlike the dissolution tests undertaken in 'standard' conditions, under stress conditions the shape of the dissolution curve was non-linear. A similar change in the shape of the dissolution curve was apparent for all formulations, except for poloxamer 407, which remained linear, with a Korsmeyer-Peppas *n* value of 1.06. In the case of the other polymers, the *n* exponent values were between 0.39 and 0.69, suggesting that drug release under stress dissolution conditions was predominantly driven by diffusional to mixed mechanisms. The mechanism of drug release from PEO N-60K and HPMC-based formulations was mixed under both 'standard' and 'stress' dissolution conditions.

Table 7.6 shows that the drug release from formulations containing poloxamer 407, xanthan ultra and xanthan 80 was faster under 'stress' conditions than 'standard' dissolution conditions. This is similar to the case of the 15% w/w HPMC matrices, where the $T_{80\%}$ was 40% faster under stress conditions than under standard dissolution conditions. In particular, xanthan ultra and xanthan 80 formulations showed extreme sensitivity to 'stress' dissolution conditions, with $T_{80\%}$ values more than 88% quicker than under 'standard' conditions.

Drug release from matrices containing λ-carrageenan or NaCMC 7M31F was slower in 'stress' conditions, than under 'standard' dissolution conditions. In both cases, twice as

much drug was released in the first 10 mins (DR10min) under stress conditions as compared to standard conditions. However, Figure 7.6 and Figure 7.7 show that the drug release then slowed to such an extent that the overall drug release profile was slower than under standard dissolution conditions.

Polymer (% w/w)	Dissolution conditions	T80% (h)	Change %	DR10min (%)		Higuchi	Change %	Korsmeyer-Peppas	
						k_h ($min^{-0.5}$)		k_{kp} (min^{-n})	n
15% HPMC K4M	Standard	2.41 ± 0.27	-41.1	20.9 ± 1.9		7.71 ± 0.15	14.3	4.62	0.61
	Stress	1.42 ± 0.16		37.7 ± 2.3		8.81 ± 0.42		12.76	0.44
15% poloxamer 407	Standard	0.68 ± 0.08	-30.9	25.9 ± 3.2		16.59 ± 0.68	29.2	2.53	0.98
	Stress	0.47 ± 0.06		36.9 ± 4.8		21.44 ± 1.56		3.11	1.06
15% NaCMC 7M31F	Standard	1.31 ± 0.03	+108.4	10.1 ± 0.8		10.88 ± 0.33	-51.3	0.92	1.04
	Stress	2.73 ± 0.40		30.3 ± 4.6		5.32 ± 0.27		13.46	0.34
15% λ-carrageenan	Standard	1.98 ± 0.17	+28.8	5.5 ± 1.3		9.53 ± 0.46	-32.7	0.39	1.15
	Stress	2.55 ± 0.01		19.8 ± 0.6		6.41 ± 0.05		5.97	0.51
15% PEO N-60K	Standard	2.40 ± 0.48	-6.7	25.1 ± 6.6		6.79 ± 0.49	-5.7	7.55	0.49
	Stress	2.24 ± 0.11		31.1 ± 4.6		6.40 ± 0.28		11.78	0.39
15% Xanthan 200	Standard	3.82 ± 0.27	4.2	4.6 ± 0.3		6.19 ± 0.25	-7.4	0.49	0.93
	Stress	3.98 ± 0.24		10.9 ± 0.3		5.73 ± 0.04		2.08	0.69
15% Xanthan Ultra	Standard	3.84 ± 0.13	-88.8	4.6 ± 0.3		6.18 ± 0.22	206.0	0.50	0.93
	Stress	0.43 ± 0.33		67.8 ± 8.7		18.91 ± 3.35		27.80	0.40
15% Xanthan 80	Standard	3.78 ± 0.18	-98.1	4.9 ± 0.6		6.15 ± 0.23	*	0.55	0.91
	Stress	0.07 ± 0.01		95.7 ± 0.8		*		*	*
15% polyacrylic acid 971P	Standard	4.94 ± 0.25	-1.4	4.1 ± 0.0		5.50 ± 0.13	-7.8	0.55	0.89
	Stress	4.87 ± 0.04		12.6 ± 0.3		5.07 ± 0.02		3.03	0.60

Table 7.6: A comparison of drug release kinetics for matrices containing 15% w/w polymer in two different USP II dissolution conditions USP apparatus II, 900 mL, 37 ± 0.5 °C. Standard dissolution is 0.0 M (water) at 50 RPM. Stress dissolution is 0.2 M NaCl at 100 RPM. Mean (for $T_{80\%}$, DR10min and Higuchi: ± 1 SD) (n=3). % values for $T_{80\%}$ and Higuchi are the relative increase in the mean of stress dissolution compared to standard conditions. (*) indicates that drug release was too fast for calculation of parameters.

7.4.3.3 Time-lapse photography imaging of hydrating matrices in water and salt solutions

Figure 7.8 shows time-lapse photographs of matrices containing 15% w/w test polymer, hydrating in either water or 0.2 M sodium chloride under static conditions. The images are in order of their $T_{80\%}$, from the slowest to the quickest formulation.

In water, formulations containing xanthan ultra, xanthan 80, HPMC K4M and PEO N-60K exhibited more swelling after 1 minute of hydration than the other formulations. After 30 minutes, matrices containing xanthan gum retained the same geometry but had become larger in height and width. Matrices with faster $T_{80\%}$ values (the right-hand side of Figure 7.8) appear more rounded at the edges, suggesting some degree of erosion. Matrices containing poloxamer 407 and HPMC K4M had a build-up of eroded material at the base of the matrix, suggesting that some disintegration had occurred.

In 0.2 M NaCl, the behaviour of some matrices was different to that in water. More swelling was apparent in matrices containing xanthan ultra, xanthan 80 and NaCMC. These three formulations had $T_{80\%}$ values of less than one hour under stress dissolution, and the photographs suggest that NaCl induces a greater initial swelling in these formulations. The remaining formulations, including xanthan 200, do not show the same extensive swelling, and the appearance of matrices after 30 minutes is similar to the appearance in water.

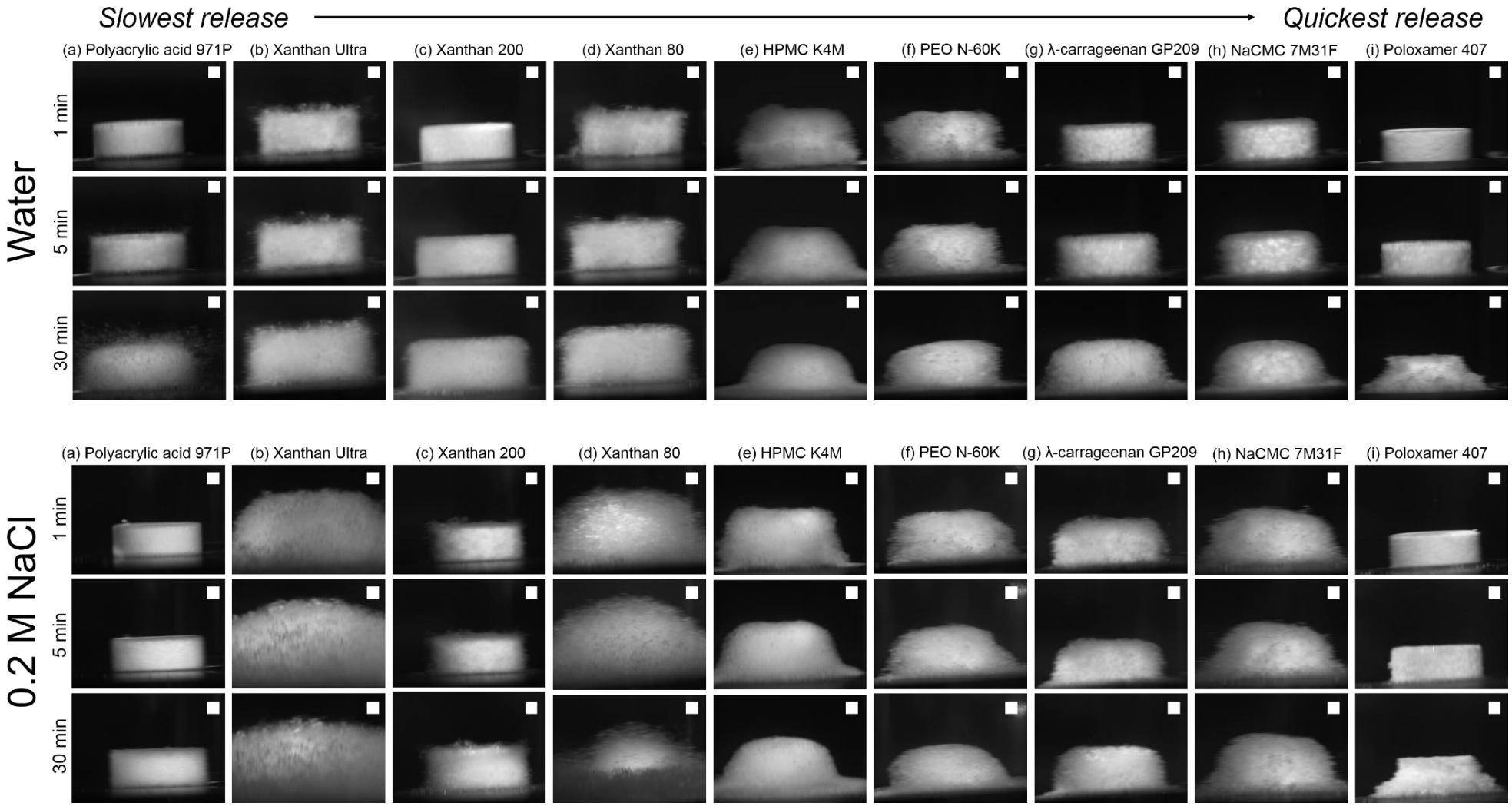


Figure 7.8: Time-lapse photography of hydrating matrix tablets with respect to polymer in Water and 0.2 M sodium chloride. Matrices contain 15% w/w polymer. 600 mL water or 0.2 M sodium chloride at 37 ± 1 °C under static conditions. White square is 1 x 1 mm. Images are ordered according to their $T_{80\%}$ value in 'standard' dissolution conditions, slowest to quickest.

7.4.3.4 Relationship between matrix $T_{80\%}$ and solution viscosity

The slow drug release and erosion-dominated mechanism, discussed in Section 7.4.3.1, suggests that the polymers are forming particularly strong gel layers. This can arise from a high polymer molecular weight or the formation of crosslinking and ordered structures within the gel layer.

The viscosities of 2% w/v polymer solutions, at a shear rate of 6.81 Hz, were measured and compared to the $T_{80\%}$ of drug release for each polymer. Results are shown in Figure 7.9. Results show a general correlation where the $T_{80\%}$ became longer as the solution viscosity increased (r^2 = 0.812). A similar relationship has been reported on the basis of molecular weight for HPMC systems (Wan et al., 1992). However, there is some significant deviation from a linear relationship, suggesting that viscosity of the gel layer is not the only factor governing extended drug release.

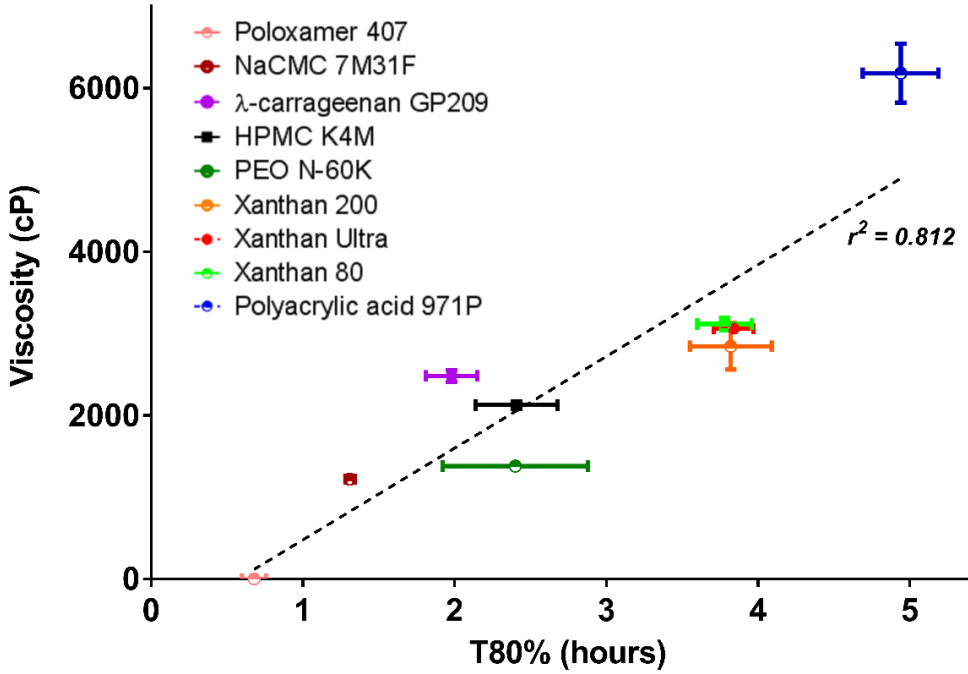


Figure 7.9: Comparison of the time for 80% caffeine release (h) from 15% w/w matrix tablets with viscosity (cP) for 2% w/v polymer solution. USP apparatus II, 50 RPM, 900 mL water at 37 ± 0.5 °C. Mean (n=3) + 1 SD. Viscosity measured using rheometer plate and 2° cone at a shear rate of 6.81 Hz

7.4.4 Results: HPMC and Complementary polymers

In this section, combination formulations were developed that contained 7.5% w/w HPMC and 7.5% w/w of the complementary polymer. The formulations are outlined in Table 7.1 and Table 7.2. Drug release under the 'standard conditions' of water and 50 RPM paddle speed was compared to drug release under the 'stress conditions' of 0.2 M NaCl and 100 RPM.

Firstly, section 0 shows dissolution results for matrices containing polyacrylic acid, xanthan 200 or polyethylene oxide as a complementary polymer to HPMC. Individually, these polymers had slower or similar $T_{80\%}$ to HPMC (Section 7.4.3.1). Xanthan ultra and xanthan 80 were not tested as complementary polymers, based on the clear dissolution sensitivity described in Section 7.4.3.2.

Secondly, Section 7.4.4.2 shows the results of dissolution testing for matrices containing λ-carrageenan, NaCMC or poloxamer P407 as a complementary polymer.

Stress sensitivity was evaluated according to the criteria established in Section 4.4.7, in which a successful formulation would show:

- Less than a 10% difference in $T_{80\%}$ value between 'standard' and 'stress' conditions
- Less than a 10% difference in Higuchi rate constant
- Less than 30% drug release in 10 minutes (DR10min).

In Table 7.6, green boxes indicate that the formulation did not exceed the criteria above, the orange boxes show that $T_{80\%}$ was between 10 and 20% different, and red boxes denoting values that exceed the criteria above.

7.4.4.1 Extended release properties of combination matrices: xanthan, polyacrylic acid or polyethylene oxide

Figure 7.10 shows the drug release from matrices containing either polyacrylic acid, xanthan 200, or polyethylene oxide under 'standard' and 'stress' dissolution conditions. In Table 7.7 the mean dissolution parameters under the two dissolution conditions have been reported and compared.

Under standard dissolution conditions, matrices containing PEO had $T_{80\%}$ values, DR10min, drug release rates and Korsmeyer-Peppas exponent *n* values that were similar to the original 15% HPMC matrices. This suggests that the drug release mechanism was similar for both formulations. $T_{80\%}$ values became slower when either polyacrylic acid or xanthan were included in the formulation ($T_{80\%}$ = 5.10 and 3.74 h, compared to 2.41 h for HPMC). When these polymers were included in the formulations, the Korsmeyer-Peppas exponent values shifted from n = 0.61 to *n* = 0.84 and 0.85. This is a shift towards erosional release, however, these values suggest that an anomalous drug release mechanism predominates overall.

In Table 7.7, the dissolution parameters under both dissolution conditions have been compared. HPMC matrices containing polyacrylic acid or xanthan no longer showed any dissolution sensitivity, as all the parameters fell within the desired criteria. Whilst both formulations showed a slight increase in the drug release within the first 10 minutes (DR10min) under stress conditions, the burst release of drug was low (less than 20%). In contrast, the formulations containing PEO showed greater sensitivity to dissolution conditions than matrices containing HPMC alone, and 'failed' on all three criteria.

7.4.4.2 Extended release properties of combination matrices: λ-carrageenan, NaCMC or poloxamer.

Figure 7.11 shows the drug release from matrices containing either λ-carrageenan, NaCMC or poloxamer under 'standard' and 'stress' dissolution conditions. In Table 7.8 the mean dissolution parameters under the two dissolution conditions have been reported and compared.

Under standard dissolution conditions, the $T_{80\%}$ was similar in all formulations ($T_{80\%}$ between 1.94 and 2.77 h). In all cases, the inclusion of a complementary polymer resulted in a smaller burst release of the drug (DR10min) than for HPMC matrices, with formulations containing λ-carrageenan having a mean DR10min of just 6.5%. The Korsmeyer-Peppas exponent value for matrices containing poloxamer was most similar

to that of HPMC matrices (*n* = 0.71 compared to 0.61). In contrast, matrices containing NaCMC or λ-carrageenan had *n* values of 0.91 and 1.00 respectively. This suggests that drug release from these formulations was predominantly attributable to erosional processes, and the shape of the dissolution profiles in Figure 7.11 was linear.

In Table 7.8, the dissolution parameters under both dissolution conditions have been compared. All formulations showed differing degrees of sensitivity to the dissolution conditions. For all three combination formulations, the burst release of the drug (DR10min) was lower than for HPMC matrices. When poloxamer was included, the DR10min was similar under both 'standard' and 'stress' conditions (13.0% and 15.4%). In addition, poloxamer formulations showed little change in drug release mechanism according to the Korsmeyer-Peppas *n* exponent. In contrast, the mechanism of drug release from matrices containing NaCMC or λ-carrageenan shifted to a more diffusional based mechanism (*n* = 0.91 to *n* = 0.38, and *n* = 1.00 to *n* = 0.43). Although dissolution conditions caused a change in the shape of the dissolution curve when the formulation contained λ-carrageenan, the $T_{80\%}$ value was unaffected by dissolution conditions and remained around 2.3 h.

Matrices containing NaCMC showed an opposite sensitivity to dissolution conditions than had previously been observed throughout the studies. Drug release was slower under stress conditions than standard conditions, with $T_{80\%}$ values changing from 1.94 h under standard dissolution conditions to 2.65 h under stress conditions.

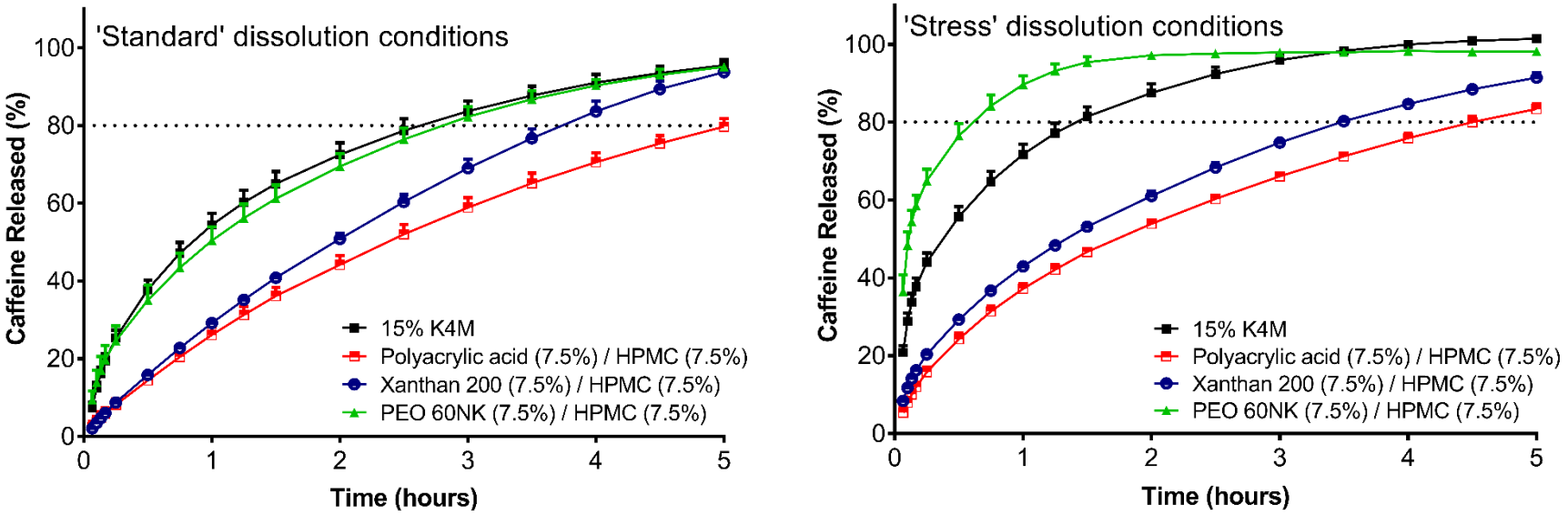


Figure 7.10: Release of caffeine from matrices containing HPMC K4M and a complementary polymer under 'standard' and 'stress' dissolution conditions. Polymer as % w/w. USP apparatus II, 900 mL, 37 ± 0.5 °C. Mean (n=3) + 1 SD. 'Standard' dissolution = 50 RPM paddle speed & water, 'Stress' dissolution = 100 RPM and 0.2M NaCl

Complementary polymer (% w/w)	HPMC K4M (% w/w)	Dissolution conditions	T80%		DR10min		Higuchi		Korsmeyer-Peppas	
			T80% (hours)	Change (%)	DR10min (%)	<30%?	k_h ($min^{-0.5}$)	Change (%)	K_{kp} (min^{-n})	n
-	15%	Standard	2.41 ± 0.27	-41.1	20.9 ± 1.9		7.71 ± 0.15	+14.3	4.62	0.61
		Stress	1.42 ± 0.16		37.7 ± 2.3		8.81 ± 0.42		12.76	0.44
7.5% polyacrylic acid 971P	7.5%	Standard	5.10 ± 0.22	-11.6	5.0 ± 1.1		5.62 ± 0.12	-4.8	0.75	0.84
		Stress	4.51 ± 0.19		12.0 ± 1.2		5.35 ± 0.05		2.82	0.62
7.5% Xanthan 200	7.5%	Standard	3.74 ± 0.18	-7.5	6.0 ± 0.1		6.20 ± 0.12	-5.8	0.89	0.85
		Stress	3.46 ± 0.11		16.0 ± 0.8		5.84 ± 0.04		4.18	0.57
7.5% PEO N-60K	7.5%	Standard	2.80 ± 0.24	-78.2	19.8 ± 3.7		6.79 ± 0.21	+116.8	4.85	0.57
		Stress	0.61 ± 0.10		58.6 ± 2.6		14.72 ± 1.58		21.23	0.43

Table 7.7: A comparison of drug release kinetics for matrices containing HPMC K4M and a complementary polymer under 'standard' and 'stress' conditions. USP apparatus II, 900 mL, 37 ± 0.5 °C. Standard dissolution is water at 50 RPM. Stress dissolution is 0.2 M NaCl at 100 RPM. Mean (for $T_{80\%}$, DR10min and Higuchi: ± 1 SD) (n=3). % values for $T_{80\%}$ and Higuchi are the relative increase in the mean of stress dissolution compared to standard conditions.

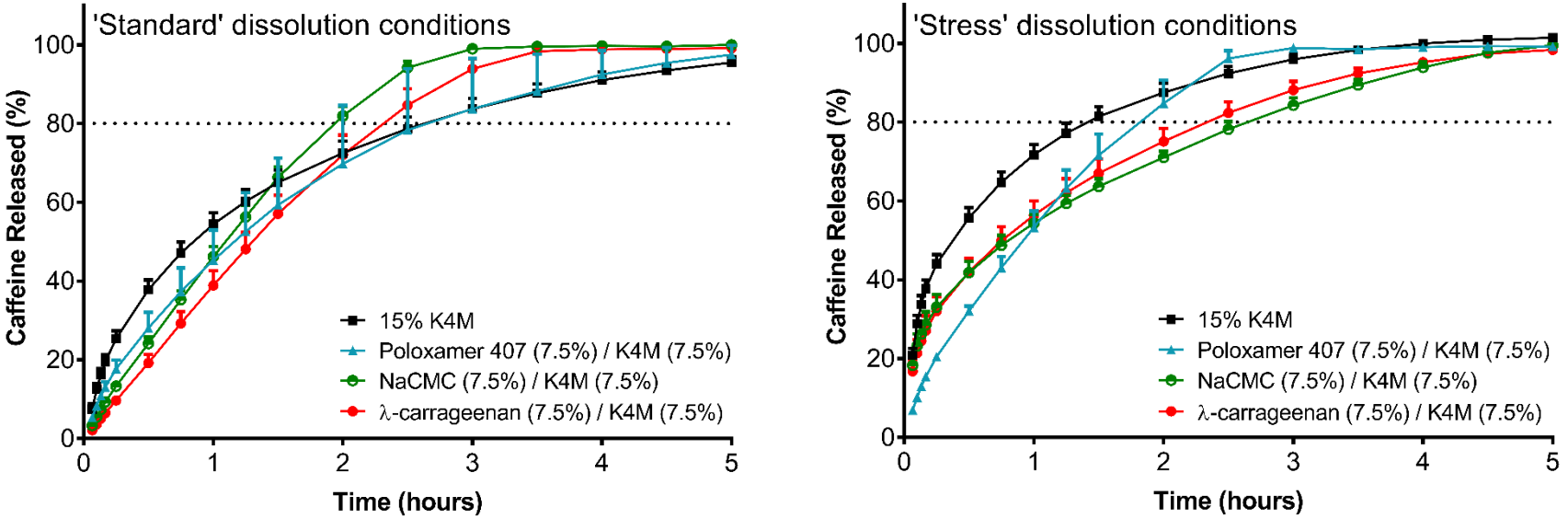


Figure 7.11: Release of caffeine from matrices containing HPMC K4M and a complementary polymer under 'standard' and 'stress' dissolution conditions. Polymer as % w/w. USP apparatus II, 900 mL, 37 ± 0.5 °C. Mean (n=3) + 1 SD. 'Standard' dissolution = 50 RPM paddle speed & water, 'Stress' dissolution = 100 RPM and 0.2M NaCl

Complementary polymer (% w/w)	HPMC K4M (% w/w)	Dissolution conditions	T80%		DR10min		Higuchi		Korsmeyer-Peppas	
			T80% (hours)	Change (%)	DR10min (%)	<30%?	k_h ($min^{-0.5}$)	Change (%)	K_{kp} (min^{-n})	n
-	15%	Standard	2.41 ± 0.27	- 41.1	20.9 ± 1.9		7.71 ± 0.15	+ 14.3	4.62	0.61
		Stress	1.42 ± 0.16		37.7 ± 2.3		8.81 ± 0.42		12.76	0.44
7.5% poloxamer 407	7.5%	Standard	2.77 ± 0.89	- 33.9	13.0 ± 1.4		7.18 ± 0.42	+ 15.0	2.48	0.71
		Stress	1.83 ± 0.21		15.4 ± 0.3		8.26 ± 0.20		2.74	0.73
7.5% NaCMC 7M31F	7.5%	Standard	1.94 ± 0.07	+ 36.6	9.3 ± 0.5		8.49 ± 0.24	- 31.2	1.11	0.91
		Stress	2.65 ± 0.16		28.6 ± 3.4		5.84 ± 0.22		11.43	0.38
7.5% λ-carrageenan GP209	7.5%	Standard	2.31 ± 0.17	+ 0.9	6.5 ± 0.8		7.71 ± 0.31	- 15.0	0.64	1.00
		Stress	2.33 ± 0.22		27.1 ± 3.8		6.55 ± 0.22		9.69	0.43

Table 7.8: A comparison of drug release kinetics for matrices containing HPMC K4M and a complementary polymer under 'standard' and 'stress' conditions USP apparatus II, 900 mL, 37 ± 0.5 °C. Standard dissolution is water at 50 RPM. Stress dissolution is 0.2 M NaCl at 100 RPM. Mean (for $T_{80\%}$, DR10min and Higuchi: ± 1 SD) (n=3). % values for $T_{80\%}$ and Higuchi are the relative increase in the mean of stress dissolution compared to standard conditions.

7.4.4.3 Relationship between solution viscosity and $T_{80\%}$ to investigate synergistic effects

As described in Sections 0 and 7.4.4.2, the inclusion of complementary polymers within HPMC matrices could influence the $T_{80\%}$, any burst release of the drug, the mechanism of drug release as well as the sensitivity of drug release to dissolution conditions. These changes could be a simple additive effect of the properties of each polymer in isolation, or could be due to a direct interaction between HPMC and the polymer. To gain a greater understanding of possible mechanisms, the viscosities of polymer solutions were compared to the $T_{80\%}$ of matrices. Different ratios of HPMC and the complementary polymer were evaluated, both for solution and matrix tests.

Figure 7.12 shows how the solution viscosity is related to the loading of complementary polymer in the system. In this figure, 0% test polymer represents a solution containing 2% w/v HPMC K4M. A proportion of test polymer of 100% means a solution containing 2% w/v of the complementary polymer. A similar representation based on the $T_{80\%}$ of 15% matrix tablets is shown in Figure 7.13. The graphs aim to indicate whether there is any interaction between the polymers, which would be apparent as a value above a straight line between values at 0 and 100% test polymer.

Figure 7.12 shows the viscosity of 2% w/v solutions containing different ratios of HPMC to the complementary polymer. As the proportion of NaCMC or PEO in the solution was increased, the viscosity of the solution decreased, in a linear manner throughout. This suggests that there was no viscosity-affecting interaction between either NaCMC and HPMC or PEO and HPMC. This differs from results with the four other polymers where the relationship between viscosity and proportion of complementary polymer is not linear throughout all polymer ratios.

In the case of xanthan 200 or λ-carrageenan, the viscosity for combination mixtures (25:75, 50:50 or 75:25) is higher than might be expected for a simple mixture of either polymer with HPMC. In the case of the polyacrylic acid and poloxamer solutions, the viscosity of a 50:50 mixture with HPMC is lower than expected.

Figure 7.13 shows the $T_{80\%}$ of 15% matrix tablets containing different ratios of complementary polymer and HPMC. In the case of matrices containing λ-carrageenan, or NaCMC, the $T_{80\%}$ decreases linearly as the ratio of complementary polymer increases. Matrices containing PEO show a slight increase in the $T_{80\%}$ value for a matrix containing

a 50:50 mixture with HPMC, but PEO matrices showed high variability as seen by the larger error bars.

Matrices that contained either xanthan 200 or polyacrylic acid had slower drug release than 15% w/w HPMC matrices, as described in Section 7.4.3.1. Figure 7.13 shows us that the drug release for 33:66 or 50:50 mixtures of polymer with HPMC was slower than expected for a simple mixture of the two. In both cases, the $T_{80\%}$ of a 33:66 matrix tablet was similar to that which contained just the complementary polymer.

Poloxamer, when used alone as an extended release polymer, was shown in Section 7.4.3.1 to have limited extended release properties, with a $T_{80\%}$ of only 0.68 h. However the $T_{80\%}$ of a 33:66 mixture of poloxamer and HPMC was found to be slower than that of a matrix containing just 15% w/w HPMC ($T_{80\%}$ = 3.06 h v. 2.41 h).

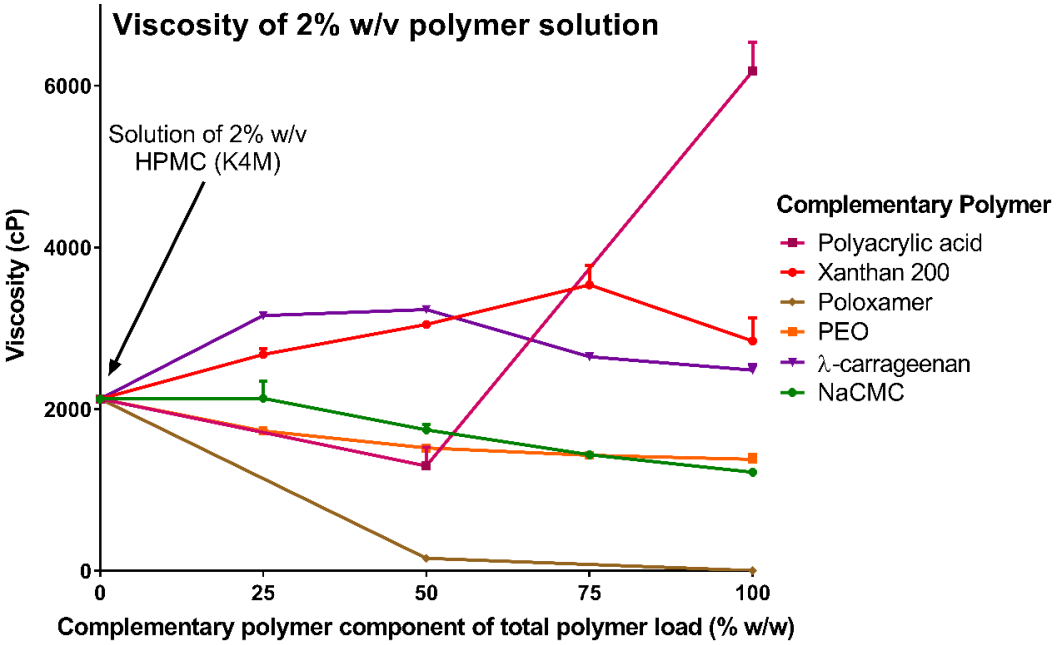


Figure 7.12: Viscosity (cP) of 2% w/v polymer solutions as a function of complementary polymer load Loadings where 0 is HPMC K4M only, and 100% is complementary polymer only. Viscosity measured at 37°C using rheometer (2° cone and plate) at a shear rate of 6.81 Hz. Mean (n=3) + 1 SD

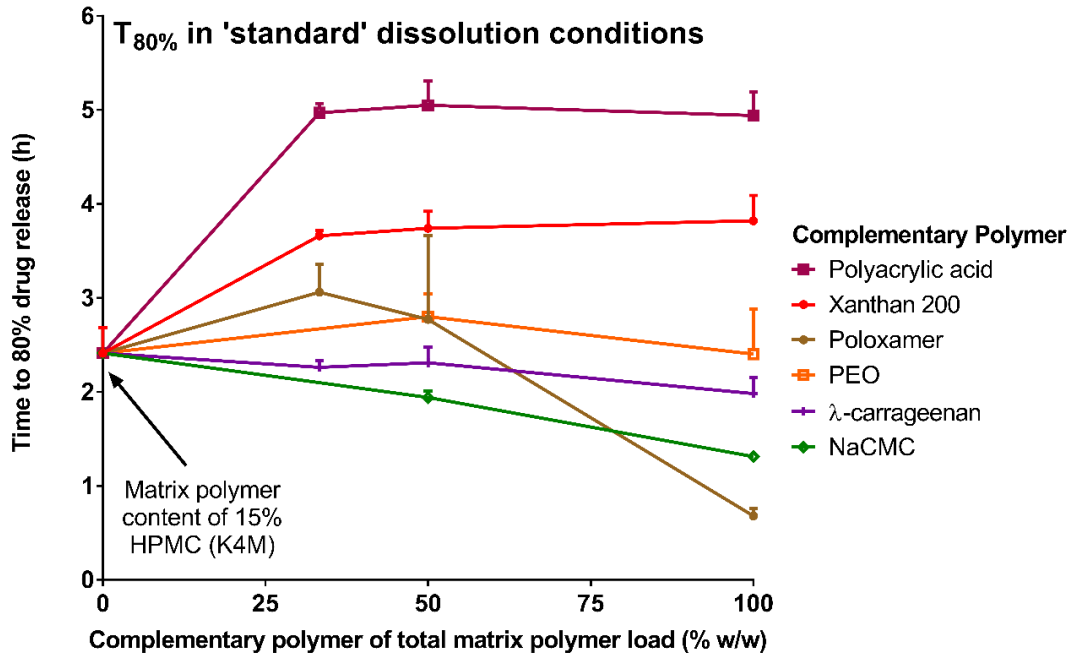


Figure 7.13: Time for 80% caffeine release from 15% w/w matrix tablets as a function of complementary polymer load, Loadings where 0 is HPMC K4M only, and 100% is complementary polymer only. Drug release measured in USP apparatus II, 50 RPM, 900 mL water at 37 ± 0.5 °C. Mean (n=3) + 1 SD.

7.4.5 Discussion: The use of complementary polymers in hydrophilic matrices

7.4.5.1 Comparison of the polymers as extended release excipients

The properties of individual polymers varies according to factors such as pH, temperature, molecular weight, ionic strength and concentration. Our results showed that the drug release rate changed when different polymers were included in the matrix. We found as a general trend that the more viscous the polymer in solution, the slower the drug release rate. For the polymer grades studied, the $T_{80\%}$ values varied from 0.68 h to 4.9 h.

The polymer structures are detailed in Table 7.9. Hydrated polymer chains interact with each other in a 3D fashion, with entanglement of polymer chains, as discussed in Section 1.1.3. Non covalent bonding, such as hydrogen, dipole-dipole or van der Waals, can occur between the adjacent chains, the strength of which depend on the substituents. The number of entanglements may also depend on the molecular size and conformation. Upon hydration, polymers do not dissolve instantaneously. The polymer chains must disentangle before chain diffusion can occur. When a good solvent for the polymer is introduced, such as water, the polymer will expand and swell. This process can break some of the bonds between adjacent polymer chains, and water can plasticise the polymer. This process takes longer when the polymer has a longer chain length, hence polymer dissolution rate tends to decrease as the molecular weight increases (Florence and Attwood, 1998, Miller-Chou and Koenig, 2003).

Xanthan gum and polyacrylic acid were found to extend drug release at a lower matrix content than HPMC. Xanthan gum and polyacrylic acid are both large molecules, with molecular weights higher than 1×10^6 Da. The literature similarly reports that xanthan gum and polyacrylic acid are more effective at extending drug release at lower matrix content than HPMC. Xanthan gum has been reported to be 3 times more powerful than HPMC due to its rapid swelling properties, which may be due to the presence of carboxyl substituents (Dhopeshwarkar and Zatz, 1993). The study found that 5% w/w xanthan gum could extend drug release to the same extent as 15% HPMC K4M. The manufacturers of polyacrylic acid 971P, Lubritzol, suggest the excipient can work to extend drug release at concentrations down to 3% w/w, although they often use aqueous granulation methods due to high drug loading as a means to improve powder flow (Lubrizol Advanced Materials, 2007).

The three alternative polysaccharides investigated, NaCMC, λ-carrageenan and xanthan gum, are anionic due to the nature of side groups (carboxylic and sulfonate), unlike HPMC which is non-ionic. Carboxylate and sulfonate substituents are strongly solvated in water, and therefore it would be expected that these polymers would hydrate faster than HPMC. This may result in faster gel layer formation, and therefore a smaller burst release of the drug. Accordingly, we found that under 'standard' dissolution conditions, the DR10min was reduced in comparison to HPMC, when an ionic polysaccharide was used (with DR10min between 4.6 and 10.1% compared to a DR10min = 20.9% for HPMC). It would also be expected that the gel strength of ionic polysaccharides would be higher than HPMC, due to stronger associations between the polymer chains. This would make the molecule more rigid. The drug release from matrices containing NaCMC or λ-carrageenan was faster than from HPMC matrices and both polymers had a lower 2% w/v solution viscosity (measured at 6.81 Hz) than HPMC. This may suggest there were fewer chain entanglements, thus more water can infiltrate the system, and therefore drug diffusivity may be higher.

In the case of matrices containing poloxamer, fast drug release was seen ($T_{80\%}$ = 0.68 h). Poloxamer 407 is typically used as a surfactant and is water soluble. Gelation of poloxamer solutions is thought to be a result of the association of poloxamer surfactant micelles, and therefore gels have weak mechanical strength and are easily diluted (Florence and Attwood, 1998, Ruel-Gariepy and Leroux, 2004). Therefore, poloxamer 407 would not be expected to have good extended release properties in isolation, and this holds in our study.

Polyethylene oxide (PEO) is another high molecular weight polymer that was studied in addition to polyacrylic acid. The weight average molecular weight of the specific PEO studied is much larger than HPMC ($M_w = 2x10^6$ compared with $M_w = 4x10^5$). However, the viscosity of a 2% w/v PEO solution was slightly lower, according to the certificate of analysis (3300 cP v. 3990 cP), and as found in our studies (1380 cP v 2127 cP). The drug release from matrices of either polymer was similar, with a $T_{80\%}$ = 2.4 h. In addition, both formulations had a similar, anomalous drug release mechanism, as determined using the Korsmeyer-Peppas *n* exponent.

In the case of the formulations containing other polymers to PEO or HPMC, drug release was found to be due to erosional release mechanisms, with Korsmeyer-Peppas *n* exponent values between *n* = 0.89 and *n* = 1.15. Linear drug release profiles have been

attributed to the attrition/erosion of the surface gel layer which prevents an increase in the diffusional path length (Bonferoni et al., 1993). In our study, time-lapse photography (Section 7.4.3.3) did not show much difference in the swelling of matrices with respect to the drug release mechanism. Formulations containing PEO and HPMC, with *n* values between 0.39 and 0.61, had marginally more rounded edges after t = 1 min, than those formulations which had linear drug release profiles. This may indicate that more swelling and/or erosion has occurred.

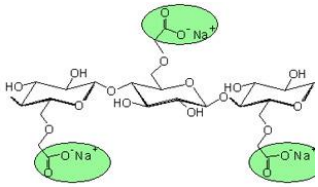
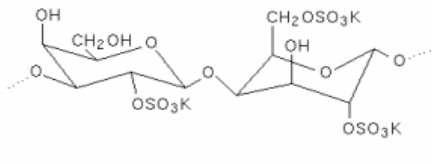
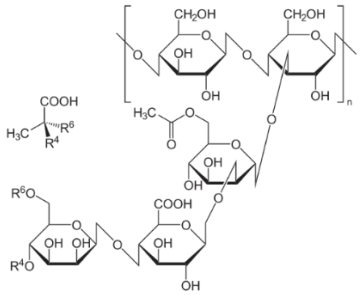
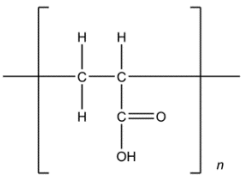
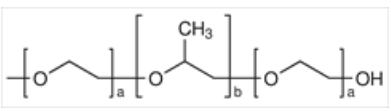
Test Polymer	Chemical structure	Mechanism of extended release
Ionic polysaccharide: polymers gel when the intra and inter-molecular bonding is favoured over H-bonding. Physical gelation		
NaCMC	 substitution with: H or CH_2COONa	Cellulose ether like HPMC, but contains anionic side chains. Hydrophilic polymer that hydrates to form a gel layer
λ-carrageenan		Sulphated polysaccharide. Doesn't gel, but chain entanglements occur.
Xanthan gum		Cellulose ether substituted with tri-saccharide side chain, with carboxyl groups, meaning gum is anionic.
High molecular weight polymer chains		
Polyacrylic acid		Polyelectrolyte that can absorb and retain water, swelling to many times original volume, forming a 3D structure.
Polyethylene oxide	$-[-O-CH_2-CH_2-]_n-OH$	Hydrophilic polymer that crosslinks with water and hydrates to form a gel layer.
Surfactants		
Poloxamer	 Synthetic block copolymer of ethylene oxide and propylene oxide	Not designed for extended release. Act as surfactants due to amphiphilic structure

Table 7.9: Chemical structures and mechanisms of complementary polymers. Sweetman (2013), The U.S. Pharmacopeial Convention (2016)

7.4.5.2 Sensitivity of the polymers to dissolution conditions

Matrix dissolution sensitivity was found to depend on which polymer was included. Matrices containing PEO, xanthan 200 and polyacrylic acid showed the least sensitivity to the dissolution conditions in terms of $T_{80\%}$ values and Higuchi rate constants, although in the case of PEO matrices, the DR10min was 31% under stress conditions and therefore just outside our test criteria of less than 30%.

The dissolution sensitivity differed for the three xanthan gum grades. The drug release was faster under stress conditions for xanthan ultra and xanthan 80 matrices. In contrast, xanthan 200 matrices showed no stress sensitivity. Xanthan 80 and xanthan ultra had a similar particle size (d(4,3) = 126.6 µm and 128.0 µm), which was larger than the measured particle size of xanthan 200 (d(4,3) = 43.3 µm). In our time-lapse photography, we observed that matrices containing xanthan 80 and xanthan ultra swelled to a greater extent than xanthan 200, in the presence of 0.2 M NaCl.

A direct interaction between NaCl and xanthan gum has been reported in the literature. The addition of at least 0.01 M NaCl to xanthan gum can cause a transformational change from a random coil to a rigid, ordered state (Rochefort and Middleman, 1987). This is reportedly due to charge screening effects which stabilises the polymer backbone, and results in a higher solution viscosity as the molecules can align and strongly associate with one another (Rochefort and Middleman, 1987, Talukdar and Kinget, 1995). However, the degree or volume of swelling, and thus gel layer thickness, has been found to decrease as the salt concentration increases, which may be due to intramolecular polymer interactions condensing the molecule (Talukdar and Kinget, 1995, Mikac et al., 2010). The effect is dependent both on the ionic strength and xanthan gum concentration (Talukdar and Kinget, 1995). It seems unlikely that a higher solution viscosity would result in the failure of xanthan ultra and xanthan 80 matrices under stress conditions. However, changes in the degree of swelling may be significant, especially when considering the impact of xanthan gum particle size. The combination of reduced swelling and large particle size may result in the formation of a non-homogenous gel layer (as was discussed in Section 6.4.4 in relation to HPMC particle size). It has also been reported that NaCl can slow the rate of hydration of xanthan gum at a salt concentration greater than 1 - 2% w/v (Sworn, 2009). This effect, in combination with the aforementioned slower hydration of particles of a larger size, may account for the difference in stress sensitivity.

Drug release from matrices containing NaCMC or λ-carrageenan was slower in 'stress' dissolution conditions than in 'standard' dissolution conditions, with mean $T_{80\%}$ values being 108.4% and 28.8% slower respectively. However, a larger amount of drug was released in the first 10 minutes of dissolution (DR10min) under stress conditions in both formulations. This suggests that the formation of the gel layer is not faster in the presence of salt, although the increase in paddle speed from 50 to 100 RPM under stress dissolution may be confounding this as this may increase polymer erosion (Miller-Chou and Koenig, 2003). Both NaCMC and λ-carrageenan are polyelectrolytes, due to ionic substitution onto the cellulose backbone. The polymer conformation can change in the presence of ions in solution, due to charge repulsion (Florence and Attwood, 1998). A change in polymer conformation has been found to decrease the elastic and viscous moduli, which may indicate that the polymer network becomes tighter at higher ionic strengths. This may influence the gel layer properties (Schneider and Doty, 1954, Bonferoni et al., 1995, Michailova et al., 1999). λ-carrageenan solutions and matrices have been shown to have similar ionic sensitivity, with higher solution viscosity and slower drug release when the buffer has an ionic strength, which was attributed to decreased polymer solubility (Bonferoni et al., 2000).

The shape of the drug release profiles was found to be more linear under 'standard' dissolution conditions than under 'stress' conditions, for formulations that contained NaCMC, λ-carrageenan, xanthan gum or polyacrylic acid. When the matrices contained non-ionic polymers, namely HPMC, PEO and poloxamer, the mechanism of drug release did not change with respect to the dissolution conditions. The mechanism may change when ionic polymers are included due to changes in polymer conformation in the presence of ionic charges. This may result in decreased polymer solubility.

7.4.6 Discussion: The addition of complementary polymers to HPMC matrices

7.4.6.1 The addition of complementary polymers to HPMC matrices

In Section 7.4.4, the combination of HPMC with various complementary polymers has been investigated. Figure 7.13 compares the extended release properties of matrices containing HPMC/complementary polymer mixtures, to those containing each polymer in isolation. Drug release from matrices containing HPMC with either PEO, λ-carrageenan or NaCMC, evaluated by $T_{80\%}$, exhibited an additive effect only. However, the viscosity of HPMC:λ-carrageenan solutions was higher than expected, suggesting there may be some rheological synergy between the two. In contrast, solutions of HPMC with NaCMC or PEO showed no sign of an unexpected increase in viscosity.

PEO and HPMC are both non-ionic, and it has previously been suggested that combining the two, results in additive effects rather than an interaction of the two (Hu, 2016). NaCMC and λ-carrageenan are both anionic polymers, containing carboxyl and sulphate groups respectively. These groups have the potential to strongly interact through hydrogen bonding with the substituted groups on the HPMC chain, and combinations have shown increased gel viscosity (Walker and Wells, 1982, Nerurkar et al., 2005). In the case of HPMC:NaCMC matrices, a previous study has seen an increase in $T_{80\%}$ values beyond that expected for a simple additive effect. NaCMC:HPMC matrices (Conti et al., 2007). Association between polymers has been attributed to many factors, including the molecular weight, conformation and side chain substitution of both polymers. The grades of each polymer used in our work may not be comparable to Conti et al. (2007), and this may mean a similar increase in $T_{80\%}$ was not observed.

In our study, we saw synergy between HPMC and λ-carrageenan in terms of solution viscosity, but not in $T_{80\%}$ value. It would be expected that synergy would be more apparent in viscosity studies, as in solution the polymers are intimately mixed. In a matrix tablet, polymers may hydrate independently and there are other components in the formulation which may affect the rate of hydration of either polymer. A previous study has reported that formulations containing a combination of λ-carrageenan and HPMC have a smaller burst release of drug than HPMC matrices alone, which we have also reported in our study (DR10min = 6.5% compared to DR10min = 20.9%). As discussed in the previous section (7.4.5.1), this is thought to be due to faster hydration of λ-

carrageenan than HPMC, as a result of the carrageenans strongly hydrophilic sulphate groups.

Drug release from matrices containing HPMC with either polyacrylic acid, xanthan 200 or poloxamer 407 was slower than expected, based on a simple mixture of the two. Viscosity results suggested that HPMC and xanthan 200 showed a synergistic interaction, with increased viscosity for mixtures than expected. In contrast, poloxamer 407 and polyacrylic acid solution viscosities were lower than expected, and therefore there was no indication of viscosity-inducing interactions with HPMC.

Xanthan gum is an anionic polysaccharide and, as in the case of λ-carrageenan and NaCMC, ionic groups (carboxyl) on the side chains could hydrogen bond with hydroxyl groups on the HPMC backbone. Whilst xanthan gum and HPMC have been compared as extended release polymers many times (Talukdar et al., 1996, Talukdar and Kinget, 1997, Oni, 2014), only a few studies look at the performance of matrices containing a combination of the two. Gohel et al. (2009) and Varshosaz et al. (2006) both showed that a combination of xanthan gum and HPMC could generate a target drug release profile, with xanthan gum limiting the initial burst release of the drug. Neither paper discussed any chemical interactions between the two.

In the case of polyacrylic acid, a lack of rheological synergy suggests that longer $T_{80\%}$ values are more likely to be the result of polyacrylic acid exerting control over the drug release kinetics, even at a low matrix content. HPMC:polyacrylic acid matrices showed a much smaller burst release of the drug than HPMC only matrices (DR10min = 5.0% compared to DR10min = 20.9%). This suggests that polyacrylic acid is able to quickly limit the burst release of drug from hydrophilic matrix systems. This potency and burst limiting effect of polyacrylic acid has been reported previous studies (Samani et al., 2003).

In isolation, poloxamer 407 had little ability to extend the drug release, with a mean $T_{80\%}$ value of 0.68 hr. However, in combination with K4M, the $T_{80\%}$ value was larger than for K4M alone (2.77 h versus. 2.41 h). There was no indication of viscosity based synergy between HPMC and poloxamer. The addition of poloxamer to HPMC matrices decreased the burst release of drug from a DR10min = 20.9% to a DR10min = 13.0%. This may indicate that poloxamer can result in the faster hydration of HPMC.

The poloxamer 407 grade is used as a solubilisation aid (surfactant) due to its amphiphilic, block co-polymer structure. It has been used in tablets as a drug dissolution enhancer. The use of surfactants within HPMC matrices has been explored, although typically studies have used anionic surfactants such as SLS and SDS (Daly et al., 1984, Feely and Davis, 1988, Nokhodchi et al., 2002). Although surfactants in solution have been found to increase the viscosity of HPMC solutions (Kulicke et al., 1998), it is generally held that surfactants influence drug release from HPMC-based dosage forms due to drug complexation or changes in drug solubility. Joshi (2009) found that Triton X, a non-ionic surfactant, had a weak interaction with HPMC, with a minor 'salting-out' effect and a lowering of the HPMC gelation temperature. They attributed this to disruption of water cages that solubilise the hydrophobic regions of the polymer chain, thus these regions become more polar (Joshi and Chen, 2009). Studies between polymers and surfactants have been undertaken to explore solid dispersions, reporting that surfactants can lower the glass transition temperature (T_g) of polymers, such as HPMC, due to an increase in chain mobility (Ghebremeskel et al., 2007). This may be because the surfactant can interact with the hydrophobic regions of the HPMC backbone, and as a result of the surfactants amphiphilic nature, make these regions of HPMC more hydrophilic at the surface.

7.4.6.2 Sensitivity of matrices containing HPMC and a complementary polymer to stress conditions

It was found that the inclusion of 7.5% w/w of (i) polyacrylic acid, (ii) xanthan 200, or (iii) λ-carrageenan could prevent faster drug release from a 15% w/w polymer matrix under 'stress' dissolution conditions. In the case of λ-carrageenan containing matrices, the drug release mechanism changed from erosional (n = 1.0) to diffusional (n = 0.43) when the dissolution conditions changed from 'standard' to 'stress'. This suggests that the formulation is still sensitive to the conditions, with changes in λ-carrageenan solubility in the presence of sodium chloride driving a change in drug release mechanism, as discussed in Section 7.4.5.2. Similarly, in the case of HPMC and NaCMC matrices, drug release was slower under stress conditions, with a change in drug release mechanism from erosional to diffusional according to Korsmeyer-Peppas modelling. It could be that including a lower ratio of either λ-carrageenan or NaCMC may offer the benefits of more rapid hydration, without affecting the mechanism of drug release.

As no stress sensitivity was observed, and drug release was extended, xanthan 200 or polyacrylic acid could be included as polymer sparing excipients. The thesis of Oni

(2014) reported that Xanthan gum extended drug release in matrices in NaCl solutions up to 2.0 M, which is much greater than the 1.0 M NaCl tolerated by HPMC matrices in this thesis (Section 4.4.1). The inclusion of xanthan 200 or polyacrylic acid offered promising advantages over HPMC in potency at low polymer content and seeming lack of sensitivity to ionic challenge, although it is important to consider excipient particle size. It is also important to consider that including ionic polymers may make drug release from polyacrylic acid matrices pH dependent, with the pKa of polyacrylic acid being 6 ± 0.5 (Lubrizol Advanced Materials, 2007).

In our study, we found no clear benefit of using PEO N-60K within the matrices, as drug release from HPMC:PEO matrices was even more 'stress' dissolution sensitive than the original 15% w/w HPMC matrices. In the thesis of Hu, a higher viscosity grade of PEO (WSR-303) has been found to be beneficial in reducing the sensitivity of HPMC matrices to high sodium chloride concentrations, although the two polymers were shown by confocal microscopy to work independently to extend drug release (Hu, 2016, Hu et al., 2016)

The inclusion of poloxamer also failed to prevent matrix sensitivity, although including poloxamer in HPMC matrices lowered the burst release of the drug, even under 'stress' conditions (DR10min = 13.0% under 'standard' and DR10min = 15.4% under 'stress' dissolution conditions).

Test Polymer	Effect on drug release in isolation (15% w/w)	Effect on drug release in combination	Stress sensitivity in combination?	Tablet synergy	Viscosity synergy	Mechanism of effect
HPMC K4M	$T_{80\%}$ = 2.41hr	$T_{80\%}$ = 2.41hr	Yes - faster ($T_{80\%}$ = 1.42 hr)	N/A	N/A	N/A
Poloxamer 407	Faster drug release (0.68 hr)	Slightly slower than HPMC (2.77hr)	Yes - faster (1.83 hr)	Yes	No	Tablet synergy may be drug complexation or drug solubility changes. May be a plasticising effect on the HPMC polymer chains.
NaCMC 7M31F	Faster than HPMC (1.31 hr)	Faster than HPMC (1.94 hr)	Yes - slower (2.65 hr)	No	No	Carboxyl groups may H-bond with HPMC chains, but no evidence in our work
λ-carrageenan GP209	Faster than HPMC (1.98 hr)	Similar to HPMC (2.31 hr)	Mixed – change in mechanism (2.33 hr)	No	Yes	H-bonding between sulphated groups and HPMC side chains
PEO N-60K	Similar to HPMC (2.40 hr)	Slightly slower to HPMC (2.80 hr)	Yes - faster (0.61 hr)	No	No	Both non-ionic. Any effects seem additive not synergistic
Xanthan 200	Slower than HPMC (3.82 hr)	Slower than HPMC (3.74 hr)	No (3.46 hr)	Yes	Yes	Carboxyl groups may H-bond with HPMC chains to form enhanced gel, synergy apparent in our studies.
Polyacrylic acid 971P	Slower than HPMC (4.94 hr)	Slower than HPMC (5.10 hr)	No (4.5 hr)	Yes	No	Carboxyl groups may H-bond with HPMC chains, but no evidence in our work. Effect more likely to be additive and not synergy

Figure 7.14: Summary of the use of polymer combinations to improve the robustness of low polymer content HPMC matrices

7.5 Conclusions

The work in this chapter has investigated the potential for common matrix excipients and complementary polymers to influence (i) drug release rate and (ii) matrix sensitivity to the dissolution environment, at the low polymer content of 15% w/w.

The key conclusions from the diluent effect study are:

1. Matrices containing 15% w/w HPMC are more sensitive to changes in diluent than those containing 30% w/w HPMC.
2. Changing the excipient within low polymer matrices can alter both the rate and mechanism of drug release.
3. The diluent section did not offer any clear improvements in the robustness of low polymer formulations, and we must also bear in mind that commercial requirements often require the overall excipient load to be low.

The key conclusions from the complementary polymer study are:

1. Xanthan gum particle size dramatically influenced the stress sensitivity of the matrix and reinforces the importance of choosing an appropriate polymer particle size in order to assure extended release from these dosage forms.
2. The inclusion of other polymers within HPMC-based matrices can retard the drug release rate and change the release mechanism, although some polymers (poloxamer 407, NaCMC, PEO N-60K) suffered the same stress sensitivity as METHOCEL K4M matrices alone.
3. There are numerous grades of all polymers, and we anticipated that some grades of the above polymers may show reduced stress sensitivity, but we has not extensively tested this.
4. Xanthan gum and polyacrylic acid were both shown to be more potent than HPMC at extending drug release. This may allow reductions in the overall matrix polymer content.
5. Using solution viscosity as a surrogate for drug release rates proved a poor strategy for shortlisting successful polymers. It showed that polymer viscosity was just one factor that influences drug release from matrices.

This chapter has shown that tabletting excipients and other, non-HPMC polymers, can change the drug release rate and mechanism from HPMC-based hydrophilic matrices. Certain other polymers could also allow a reduction in the overall polymer load of the tablet, offering benefits when high drug loads are to be included.

Chapter 8
Summary, Conclusions and Future Work

8.1 Summary

The aim of the work in this thesis was to evaluate the feasibility of hydrophilic matrices containing less than 30% w/w HPMC. A 30% minimum polymer content is recommended by the manufacturers due to concerns that lower polymer contents would result in increased sensitivity to formulation parameters, manufacturing properties and external dissolution factors. However, these concerns have not yet been evaluated in the literature. The principal aim of this thesis was to determine what issues may arise when the matrix polymer content is lowered. A formulation was chosen that was typical of a commercial matrix containing a soluble drug and tabletting excipients, and not just a simple drug:polymer mixture as had been used in previous studies.

In this thesis we have:

- Found that the polymer percolation threshold, and not the actual matrix polymer content, is the key consideration. Formulations with a polymer content close to or less than the percolation threshold were shown to be more sensitive to challenging dissolution conditions.
- Shown that HPMC particle size, HPMC viscosity grade, tabletting excipients and complementary polymers can influence the drug release rate, mechanism and dissolution sensitivity. Formulations have been manufactured that contain just 15% w/w polymer with limited sensitivity to dissolution conditions.
- Determined that matrix polymer content influences the sensitivity of the formulation to paddle rotational speed, but not to the presence of ionic salts.
- Used confocal laser scanning microscopy to provide first-time physical evidence for the method and conclusions drawn from percolation theory.
- Used the Dynamic Gastric Model as a formulation development tool. The use of the DGM on a series of formulations has not been reported previously. We found that lowering the matrix polymer content made the formulations more sensitive to food.

The key findings of this thesis are now further discussed

In **Chapter 3**, the impact of matrix polymer content on drug release was explored. The rate and mechanism of drug release were interpreted by fitting dissolution data to established mathematical models. From this, we estimated a polymer percolation threshold. Confocal laser scanning microscopy, time-lapse photography, texture analysis and erosion measurements were used to evaluate the properties and performance of the matrix, with respect to the polymer percolation threshold.

It was found that:

- As the matrix polymer content was decreased (from 30% w/w), drug release became faster, and a greater quantity of drug was released as a burst in the first 10 minutes of dissolution. However, the mechanism of drug release, derived from mathematical modelling of the release curves was similar, irrespective of the matrix polymer content. Korsmeyer-Peppas exponent values suggested it was a mixture of diffusion and erosion. The percolation threshold was estimated at 11% w/w by plotting Higuchi rate constants against matrix polymer content. However the Higuchi model used to generate this plot showed a poorer fit to drug release data when matrices contained less than 15% w/w HPMC. This reinforces the concern of relying solely on dissolution data to estimate the percolation threshold.

- Time-lapse photography, texture analysis and erosional measurements showed clear differences between matrices either side of the percolation threshold (containing 10% and 15% w/w HPMC). In the case of matrices containing 10% w/w HPMC, there was substantial matrix erosion and minimal swelling, compared to the greater swelling of the 15% w/w matrices.

- Confocal laser scanning microscopy (CLSM) showed differences in early gel layer formation with respect to polymer content, with a discontinuous gel being formed in the case of matrices containing 5% or 10% w/w HPMC.

These confocal studies provide, for the first time, the visual evidence to support the application of percolation theory to HPMC matrices. Clear, distinct differences could be seen in the formation of the gel layer above and below the percolation threshold that was estimated from dissolution data. This suggests that, despite limitations, percolation theory can be estimated from dissolution data. This provides a simple method of establishing the necessary HPMC content for extended release of the drug.

In **Chapter 4**, the effect of exposing low polymer content matrices to challenging dissolution conditions was studied. The aim was to explore the potential *in-vivo* sensitivity of matrices that contained lower than recommended amounts of HPMC. Specifically, the effect of salts and/or hydrodynamic forces were investigated.

It was found that:

- Drug release was accelerated, to a $T_{80\%}$ value of less than 1 hour, in the presence of highly concentrated salt solutions (0.2 M for trisodium citrate, and 1.0 M for sodium chloride). For these salts, there was a relationship between the potency of a salt to depress the cloud point and the concentration of that salt which caused failure of HPMC matrices. However, matrix polymer content had no apparent impact on matrix salt sensitivity in our formulations.

- In contrast, we found that matrix polymer content did influence the release rate sensitivity to hydrodynamic forces, when USP II paddle speed was increased from 25 to 150 RPM. 30% w/w HPMC matrices were the least affected, and 10% w/w HPMC matrices showed the greatest variability in drug release rate at different paddle speeds.

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- Experiments were conducted to investigate the combined effect of salt and hydrodynamic stress. The drug release rate became faster at lower NaCl concentrations when the paddle speed was increased from 50 to 100 RPM. At 100 RPM, a more likely *in-vivo* NaCl concentration of 0.2 or 0.4 M resulted in increased drug release rates for 15 and 20% w/w HPMC matrices, compared to studies in water. Drug release from 30% w/w HPMC matrices showed little sensitive to 0.2 M or 0.4 M NaCl at increased paddle speeds.

This chapter identified the sensitives of lower polymer matrices to dissolution conditions in the standard USP test. It was found that, in our formulations, the ionic sensitivity of matrices was independent of the matrix polymer content. In contrast, the drug release differed with changes in the paddle speed, when the matrix polymer content was lowered to 15% w/w or less. This suggests that drug release from matrices containing lower polymer content is sensitive to any changes in the *in-vitro* dissolution conditions. One such example could be variation in drug release according to whether the matrix is taken when the stomach is empty or fed.

In **Chapter 5**, the behaviour of our low polymer formulations were studied using the Institute for Food Research's Dynamic Gastric Model (DGM). The DGM apparatus is designed to resemble the stomach, and it can be programmed to reflect either the fasted or fed state. The drug release from our formulations was measured under both conditions, and subsequently compared. This was one of the first reported studies in which a complete formulation series had been tested in the DGM.

It was found that:

- Greater matrix erosion occurred in the DGM than in the compendial USP dissolution test and the primary mechanism of drug release in the DGM was through erosional processes. This could be a result of the cyclical and transient, rather than continual, shear forces being applied to the dosage form in the DGM. The DGM is designed to produce shear forces that are akin to those found *in-vivo*, with forces matched based on the breaking of agar beads. In contrast, the USP apparatus was designed to provide a reproducible quality control test to compare formulations.
- There was a clear difference in drug release between 15 and 17.5% w/w HPMC matrices, and formulations at either side of this threshold behaved similarly to one another. We did not see an obvious rank ordering of formulations according to matrix polymer content, as had occurred in the USP dissolution tests.
- The presence of food resulted in a lag time of over 30 minutes before the drug was released. Based on the literature, this could be a result of fats on the matrix surface inhibiting water diffusivity.
- Under 'fed' DGM conditions, the rate of drug release from matrices with different polymer contents was similar. This suggested that drug release in the fed state was no longer driven by the matrix polymer content, but is a response to the dissolution environment.
- Most significantly, we found that matrices containing 30% w/w HPMC had similar drug release under fed and fasted conditions (once the results were adjusted for the lag time). In contrast, the drug release from matrices containing 20% w/w HPMC or lower was more rapid under fasted conditions than under fed conditions.

Chapter 5 highlighted that drug release from matrices that contained less than 30% w/w HPMC were more dependent on the dissolution environment, whereas 30% w/w HPMC matrices showed little change in drug release with dissolution conditions. This correlates

with the *in-vitro* USP dissolution testing undertaken in Chapter 4 where the lower the matrix polymer content, the greater was the sensitivity to changing hydrodynamic forces.

In **Chapter 6**, the influence of HPMC viscosity grade and HPMC particle size on drug release and dissolution sensitivity was investigated.

It was found that:

- The choice of HPMC viscosity grade influenced the drug release rate, with slower drug release as the viscosity was increased. This has been observed in many previous studies, and is thought to be due to the higher water absorption capacities of the higher viscosity grades, in addition to their viscosity being reflected in their gel strength and diffusion barrier properties. We showed that changing the viscosity grade had little impact on the percolation threshold.
- As the HPMC particle size was decreased, the drug release rate also decreased. The percolation threshold was lowered as the particle size decreased. Particle size effects are thought to be due to faster hydration as a result of larger polymer surface area and quicker gel layer formation.
- The polymer percolation threshold had an overriding influence on the matrix sensitivity to dissolution conditions. Sensitivity was only observed when the matrix polymer content was below ± 5% w/w of the percolation threshold.

In **Chapter 7**, we studied how the diluents within the formulation and the addition of a second polymer influenced drug release characteristics and the matrix sensitivity to *in-vitro* dissolution conditions.

It was found that:

- The diluent used can influence both the drug release rate and the release mechanism. This appeared to be due to the changes in matrix solubility. However, there was no clear benefit of using one diluent over another for low polymer content systems.
- Xanthan gum and polyacrylic acid were individually more effective at a lower content than HPMC at extending drug release, and either polymer could be used a polymer sparing strategy. The reduced burst release of drug in the first 10 minutes of dissolution suggests that this is due to faster hydration of these polymers compared to HPMC and therefore burst release of the drug is reduced.

- The inclusion of other polymers in HPMC matrices can dramatically change the rate and mechanism of drug release, with the drug release generally being more erosion based. However, non-HPMC polymers can show pH sensitivity.

Chapter 6 and **Chapter 7** suggested some formulation strategies for modulating the drug release rate, release mechanism and dissolution stress sensitivity of low polymer matrices. It was found that one of the most importance parameters of an HPMC-based formulation is the polymer percolation threshold. In our formulations, it was found that when the matrix polymer content was higher than the percolation threshold, variability in drug release according to the dissolution conditions was minimal. However, 15% w/w polymer matrices were feasible with minimal variability if they contained either (i) a small HPMC particle size fraction (< 45 µm), or (ii) a combination of HPMC with either xanthan 200 or polyacrylic acid 971P. The optimum formulation strategy may vary depending on the specific requirements of the formulation, and the total polymer loading that can be included, but this work has provided some ideas on how dissolution variability in low polymer matrices can be avoided.

8.2 Overall conclusions and implications for the formulation of HPMC matrices in the pharmaceutical industry

This project was based on a desire to understand the key considerations for matrices that contain a content of HPMC that is lower than recommended. In this thesis, “low polymer content” was initially defined as a matrix having less than the manufacturers’ recommended 30% w/w METHOCEL K4M. There was an expectation that low polymer content matrices might be more sensitive to the dissolution environment. From the perspective of the pharmaceutical industry however, there are clear advantages in being able to develop low polymer content hydrophilic matrices. This would enable the formulation of dosage forms for drugs which would otherwise show *in-vivo* release characteristics that were too slow, or where the drug load needs to be very high.

This thesis has provided confocal images which support the application of percolation theory to swellable matrices (Chapter 3) and whilst percolation theory has been applied to HPMC-based swellable matrices for a number of years (Miranda et al., 2006a), there has been a lack of supporting evidence beyond simple dissolution data. This work has also highlighted some issues with the method by which the percolation threshold is estimated. The method requires at least 8, and ideally more, batches of tablets containing different HPMC contents, in order to plot reasonable regression lines. There is also an argument that the identification of the percolation threshold in hydrophilic matrices is not clear cut as determining the intercept between two linear regression lines suggests, as the data may better fit a reciprocal curve. This is probably a more realistic relationship, because as the matrix polymer content is lowered, increasing numbers of localised areas within the matrix become “HPMC-deficient”. The overall result is that the drug release becomes faster overall. In addition, the confocal imaging studies have shown how the gel layer becomes increasingly poorly formed as the matrix polymer content is lowered below the percolation threshold (Section 3.4.5). The confocal microscopy results support the underpinning theory of why matrices have a percolation threshold, and thus supports applying percolation theory to swellable matrices.

We have also considered the role of percolation theory in developing formulations of HPMC matrices. The results have shown that estimating the HPMC percolation threshold is an important step when developing HPMC matrices. Greater sensitivity to challenging dissolution conditions is observed as the matrix polymer content approaches or is lower than the percolation threshold (Chapter 4 and Chapter 5). Therefore, it appears important

to establish how the matrix polymer content compares to the percolation threshold for that particular drug and formulation base. Our *in-vitro* dissolution testing and Dynamic Gastric Model studies agreed with the commonly-held consensus that to avoid problems, it is necessary to formulate matrices with a polymer content at least 10% w/w above the percolation threshold. Doing so helps to ensure reliable drug release that is less sensitive to dissolution conditions.

In-vitro dissolution testing is, rightly or wrongly, often used as a screen for detecting possible *in-vivo* sensitivities. Abrahamsson (1998) has discussed how compendial dissolution tests require modification to correlate with *in-vivo* results (Abrahamsson et al., 1998b). They generated the best *in-vivo/in-vitro* correlation at a paddle stirring rate of 140 RPM and an ionic strength of 0.14 M (NaCl). This is very different to the USP recommended 50 RPM in SGF media. Although it can be (and is) debated how biorelevant USP dissolution testing can ever be, it seems reasonable to suggest that differences in drug release between two *in-vitro* conditions can allow you to compare the sensitivities of different formulations. This hypothesis is supported by the work in this thesis.

Studies using the Dynamic Gastric Model found that matrices containing 30% w/w HPMC had similar drug release with variable dissolution conditions. This is a similar polymer content to that found in our *in-vitro* dissolution screening. However, we predicted that the mechanism of sensitivity in USP dissolution testing was different to that in the DGM. For example, the fats in the DGM meal may be responsible for slowing drug release under fed conditions. Previous studies using the DGM have typically focussed on one formulation (Chessa et al., 2014), or the DGM has been used to explain differences between *in-vitro* and *in-vivo* drug release profiles (Mann and Pygall, 2012). Our study was one of the first to use the DGM as a formulation screening tool, and we observed differences between matrices that could be attributed to differences in the formulation. The DGM could therefore potentially be used for formulation development in the future, although at the time of writing, there are only two built versions.

In Chapter 6 and Chapter 7, we saw that adjustments to the matrix formulation can change the drug release rate, percolation threshold and the sensitivity of the matrix to *in-vitro* dissolution conditions. Of particular note was the dramatic effect of HPMC particle size, where the use of increasing particle size fractions raised the matrix percolation threshold from 11% to approx. 40% w/w. Formulations containing 15% w/w of the smallest HPMC particle size fraction (< 45 µm) were no longer sensitive to the stress

dissolution conditions. A formulation containing 15% w/w of a combination of HPMC with either xanthan 200 or polyacrylic acid 971P also showed no sensitivity to our challenging dissolution conditions. These results suggest that matrices containing a low HPMC content are feasible.

We cannot be certain of the applicability of these formulation strategies to systems containing different drug loadings or drugs of different solubilities. However, it seems that judicious selection of formulation properties is important and that reliable low polymer content matrices are achievable in practice.

8.3 Potential future work

Despite the extensive wealth of literature in the HPMC matrix field, there are still major areas of uncertainty as highlighted by this project. Whilst it offers novel insights into the behaviour and mechanistic understanding of low polymer content matrices, this work has only used a narrow range of formulations.

Possible future work could include;

- Using drugs of different solubility and higher drug loading. In this thesis, we only studied caffeine as a model soluble drug at a matrix content of 10% w/w.

- Using animal and/or human studies to generate *in-vivo* PK data on drug release rate with respect to HPMC content. A comparison between fasted and fed *in-vivo* data should enable more substantial conclusions to be drawn from our Dynamic Gastric Model and *in-vitro* dissolution studies.

- The use of computer-aided design (CAD) and particle swelling experiments to better describe early gel layer formation. Whilst confocal imaging showed the effects of HPMC content on gel layer formation, the technique cannot precisely describe the underlying particle interactions. Modelling early hydration of the matrix using CAD may provide an understanding of the impact of inter-particle distance and polymer hydration rate on the time taken for the gel layer to form. Our studies have shown that limiting the burst release of drug during early dissolution is important in generating ER drug release kinetics.

- Using a combination of the formulation strategies studied to develop matrices with maximal resistance to challenging dissolution conditions. Refining the formulation may enable stress sensitivity to be limited, without such a tight specification on HPMC properties such as particle size. This would be industrially advantageous for reasons of cost and time economy.

Chapter 9
Appendix

9.1 General lab materials

Material	Brand name /Grade	Manufacturer	Batch Number	Purpose
Congo Red		Fisher	1137790	Imaging Contrast
Sodium chloride		Sigma Aldrich	SZBD2480V	Dissolution Media
Trisodium citrate		Fisher	1228939	Dissolution Media

9.2 Tabletting excipients

Material	Brand name /Grade	Manufacturer	Batch Number	Purpose
Hydroxypropyl methylcellulose	Methocel™ K100LV	Colorcon, UK	2E14012N24	Tablet Polymer
Hydroxypropyl methylcellulose	Methocel™ K4M	Colorcon, UK	1H27012N01	Tablet Polymer
Hydroxypropyl methylcellulose	Methocel™ K100M	Colorcon, UK	2B11012N01	Tablet Polymer
Hydroxypropyl methylcellulose	Methocel™ K200M	Colorcon, UK	3A19012NEA	Tablet Polymer
Caffeine Anhydrous		Sigma Aldrich, Dorset, UK	0001428211	API
Lactose (spray dried)	316 NF Fast Flo™	Foremost Farms, USA	51107	Tablet Excipient
Microcrystalline cellulose	Avicel PH-102™	FMC Biopolymer, Ireland	C283521	Tablet Excipient
Magnesium stearate		Sigma Aldrich, UK	SZBA2440	Tablet Excipient
Starch	Starch 1500™	Colorcon, UK	IN506125	Tablet Excipient
Mannitol	Pearlitol™ 100 SD	Roquette, France	450310H	Tablet Excipient
Dicalcium phosphate	Emcompress®	JRS Pharma, Chicago Heights, US	356655	Tablet Excipient
Poloxamer	Kolliphor® P 407 micro	BTC, Germany	WPWJ587T	Test polymer
Sodium carboxymethyl cellulose (NaCMC)	Blanose® 7M31F	Ashland, France	C150908	Test polymer

λ-carrageenan	Viscarin® GP-209NF	FMC Corporation, USA	20902051	Test polymer
Polyethylene oxide	Polyox™ WSR N60K	Dow Chemicals, UK	2J0155S5M6	Test polymer
Xanthan gum	Grindsted Xanthan 200	Danisco, France	4452602947	Test polymer
Xanthan gum	Grindsted Xanthan Ultra	Danisco, France	4452496681	Test polymer
Xanthan gum	Grindstead Xanthan 80	Danisco, France	4452604102	Test polymer
Polyacrylic acid	Carbopol® 971P NF	Lubrizol, USA	0101637652 –W1	Test polymer

Chapter 10
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