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Mechanisms of drug release in citrate buffered HPMC matrices

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ABSTRACT

Few studies report the effects of alkalizing buffers in HPMC matrices. These agents are incorporated to provide micro-environmental buffering, protection of acid-labile ingredients, or pH-independent release of weak acid drugs. In this study, the influence of sodium citrate on the release kinetics, gel layer formation, internal gel pH and drug release mechanism was investigated in HPMC 2910 and 2208 (Methocel E4M and K4M) matrices containing 10% felbinac 39% HPMC, dextrose and sodium citrate. Matrix dissolution at pH 1.2 and pH 7.5 resulted in complex release profiles. HPMC 2910 matrices exhibited biphasic release, with citrate increasing the immediate release phase (<60 min) and reducing the extended release. HPMC 2208 matrices were accelerated, but without the loss of extended release characteristics. Studies of early gel layer formation suggested gel barrier disruption and enhanced liquid penetration. pH modification of the gel layer was transitory (<2 h) and corresponded temporally with the immediate release phase. Results suggest that in HPMC 2910 matrices, high initial citrate concentrations within the gel layer suppress particle swelling, interfere with diffusion barrier integrity, but are lost rapidly whereupon drug solubility reduces and the diffusion barrier recovers. These Hofmeister or osmotic-mediated effects are better resisted by the less methoxylated HPMC 2208.

1. Introduction

Hydrophilic matrices based on hypromellose or hydroxypropyl methylcellulose (HPMC) are widely used within the pharmaceutical industry (Melia, 1991; Li et al., 2005). Drug solubility is a key determinant of release in these dosage forms and, when drug solubility is pH-dependent, the changing pH environment in the gastro-intestinal tract can give rise to changes in drug solubility and a change in the drug release mechanism (Badawy and Hussain, 2007). The most common examples are weakly basic drugs, which have a high solubility in the stomach but are poorly soluble at the higher pH of the duodenum. In an HPMC matrix tablet, this would result in a switch from diffusion to erosion-controlled release at around the time of gastric emptying and, as a consequence, we can envisage that drug bioavailability may become highly dependent on patient variables and the fed state. A common approach to this problem is to maintain the drug in its soluble form by incorporating pH-modifying excipients in the matrix.

The release of weakly basic drugs is commonly improved by the inclusion of weak acids or acidic polymers (Gabr, 1992; Thoma and Ziegler, 1998; Streubel et al., 2000; Espinoza et al., 2000; Varma et al., 2005; Kranz et al., 2005; Siepe et al., 2006). In contrast, neutral or high pH buffering excipients for HPMC matrices containing weak acid drugs have received relatively little attention. Phosphates, citrates, carbonates, magnesium oxide/hydroxide and Eudragit E have all been proposed as buffering agents for extended release dosage forms (Doherty and York, 1989; Akiyama et al., 1994; Rao et al., 2003; Li and Schwendeman, 2005; Riis et al., 2007) but few of these examples have been used in hydrophilic matrix systems.

Critically, an issue yet to be fully explored is the influence of these pH modifying agents on the drug release mechanism. For example, buffers are ionic in nature, and dissolved ions can modulate polymer: water interactions in non-ionic hydrophobically modified cellulose ethers such as HPMC. This can be conveniently monitored by the temperature dependency of the sol: gel phase transition (Touitou and Donbrow, 1982). Highly ionic electrolytes depress the temperature of this transition by competing for water molecules in the polymer hydration sheath. This increases molecular dehydration and results in the clustering of hydrophobically substituted regions and the eventual formation of a 3D network stabilized by hydrophobic interactions (Sarkar, 1979; Doelker, 1993; Haque and Morris, 1993). The observed effect is gel formation or turbid precipitation of the polymer ("salting out"). The potency of different electrolytes to do this follows a Hofmeister-like series, and the effects are greatest with multivalent anions (Nakano et al., 1999). This effect can be valuable. The suppression of polymer swelling and solubility has been used to aid polymer dispersion (Yuasa et al., 1997) and ions high in the Hofmeister series have been used to inhibit agglomeration during HPMC film coating (Nakano et al., 1999). This can be attributed to a reduction in film tacki-

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ness resulting from the inhibition of polymer solubility. Sodium citrate was found to be a particularly potent agent in inhibiting agglomeration, but it also resulted in more brittle, porous films with a low tensile strength (Nakano and Yuasa, 2001). This suggests HPMC molecules are adopting a more compact globular conformation in the presence of trivalent citrate, as might be expected if water interactions were reduced and intra-molecular hydrophobic interactions were promoted. The reduction in polymer solubility may also result in a some polymer being unable to contribute to the polymer film network.

Multivalent ions are known to influence drug release in HPMC matrices (Alderman, 1984; Touitou and Donbrow, 1982; Mitchell et al., 1990). Lapidus and Lordi (1966) first reported that the presence of electrolytes in the dissolution medium could influence drug release and Fagan et al. (1989) showed how disintegration of HPMC, HPC and HEC matrices can occur as the chloride or phosphate concentration in the medium approached the cloud point of the polymer. Mitchell et al. (1990) demonstrated that salt-induced changes can markedly affect HPMC viscosity and reported how higher sodium phosphate concentrations in the test medium resulted in a rapid 'burst' of drug release. Hodsdon et al. (1993) showed how increasing phosphate ion concentration decreased the disintegration time of HPMC matrices. Incorporation of ionic salts into HPMC matrices has also been used to influence drug release kinetics although only speculative reasons for the underlying mechanism have been advanced. For example, sodium dihydrogen phosphate (NaH_2PO_4) has been used to modulate the release of acetaminophen in HPMC matrices (Cao et al., 2005) whilst sodium carbonate and pentasodium tripolyphosphate modulate the release of metoprolol tartrate in polyethylene oxide matrices (Pillay and Fassihi, 2000). Alderman (1984) has reported the highly adverse effects on extended release when high valency salts such as aluminium sulphate ($Al_2(SO_4)_3$), sodium sulphate (Na_2SO_4) and sodium carbonate (Na_2CO_3) are incorporated into a HPMC hydrophilic matrix. Changes in release rate may also occur when incorporated salts influence drug solubility through *in situ* salt formation or common-ion effects, for example when sodium chloride is incorporated into diclofenac matrices (Sheu et al., 1992).

Overall, the literature suggests that incorporated ionic substances have the potential to substantially alter drug release kinetics in HPMC matrices, and that multivalent buffers might have potent Hofmeister effects on the interaction of HPMC with water. As a result, in addition to increasing drug solubility, a buffering agent may also influence polymer swelling, dissolution and the structure of the hydrated polymer network, which are key factors in HPMC matrix gel layer retardation of drug release. The increasing use in recent years of hydrophilic matrix technology to develop floating gastro-retentive dosage forms has made buffering against prolonged exposure to acidic conditions an increasingly important area, and using citrate buffers in the trivalent state would maximize buffering capacity and be an obvious choice. A higher bioavailability of weakly acidic drugs such as NSAIDS has been demonstrated in the presence of alkalizing agents, and citrate buffers can be used to improve drug solubility in these circumstances (Fuder et al., 1997; Neuvonen, 1991). In this work, we investigate how incorporated trivalent sodium citrate influences the behaviour of HPMC matrices containing the weak acid NSAID drug felbinac, with respect to the underlying drug release mechanisms.

2. Materials and methods

2.1. Materials

Methocel E4M (Hypromellose USP 2910) and K4M (Hypromellose USP 2208) HPMC CR premium EP were kind gifts from Colorcon Ltd. (Orpington, Kent). Felbinac (4-biphenylacetic acid) was obtained from Sigma (Poole, Dorset). Monobasic, dibasic and tribasic sodium citrate dihydrate were obtained from Acros Organics (New Jersey, USA). Tris(hydroxymethyl)aminomethane was obtained from Sigma–Aldrich (Poole, Dorset). Universal pH indicator was obtained from Fisher Scientific (Leicestershire, UK). Compression grade dextrose was a gift from Cerestar (Manchester, UK). Magnesium stearate was obtained from BDH Laboratory Supplies, (Dorset, UK). Water used for solution preparation was Maxima HPLC grade (USF Elga, Buckinghamshire) with a maximum conductance of 18 MΩ cm.

2.2. Preparation of HPMC solutions

HPMC solutions were manufactured using an adaptation of the hot dispersion method (Dow Chemical Company). One-third of the required volume of water was heated to 80–90 °C in a beaker, weighed HPMC powder was added, the solution mixed for 10 min on maximum speed using a high velocity laboratory emulsifier (Silverson Machines Ltd., Buckinghamshire, UK) and the remainder of the water was added at room temperature with continued mixing until a good dispersion was obtained. Once cooled, the solution was held refrigerated at 2–8 °C for 24 h prior to use, to allow complete hydration of the polymer and clearance of air bubbles. HPMC: citrate mixtures were prepared by mixing double strength solutions.

2.3. Cloud point temperature determination by turbidimetry

Cloud point temperature measurements were made in a temperature-ramped white light turbidimeter (C. Washington, Nottingham, UK) in 10 mm pathlength cells. The cloud point temperature was defined as the temperature at which light transmission was reduced by 50% (Sarkar, 1979). Measurements were undertaken in triplicate.

2.4. Tablet manufacture

The matrix compositions used in this study are shown in Table 1. Tablet ingredients were blended in a Y cone blender (Neco, London, UK) without lubricant for 10 min. Magnesium stearate was added, and blending continued for a further 5 min. The powder blends were compressed on an instrumented Manesty F3 single punch tabletting machine (Manesty, Liverpool, UK) at a 590 ± 20 MPa to produce round, flat-faced 5 mm diameter tablets with a mean weight of 70 ± 10% mg.

2.5. Dissolution testing

Dissolution testing of matrix tablets was undertaken using a USP apparatus I dissolution tester (Prolabo, France) at 100 rpm. Experiments were undertaken at 37 ± 1 °C in 900 ml degassed 0.1 M HCl adjusted to pH 1.2 or 0.05 M Tris buffer adjusted to pH 7.5. Drug was quantified by UV spectrometry in 10 mm quartz cells at λ = 252 nm (pH 1.2) or 255 nm (pH 7.5).

Table 1
Formulations used in the manufacture of sodium citrate buffered HPMC 2208 and 2910 matrices.

HPMC	Felbinac	Sodium citrate	Dextrose	Magnesium stearate
Content in tablet (%, w/w)				
39	10	0	50	1
39	10	10	40	1
39	10	20	30	1
39	10	30	20	1
39	10	40	10	1
39	10	50	0	1

2.6. Formulation design

The matrix formulation was designed to isolate the effect of the incorporated buffers, and to limit or standardise the effects of other ingredients or variables that might otherwise impact on drug release. Methocel K4M (22.5% methoxy, 9.2% hydroxylpropyl) and E4M (29.5% methoxy and 9.3% hydroxypropyl) were chosen as typical representatives of USP 2208 and USP 2910 controlled release grades of HPMC and particle size was maintained between 35–425 μm, to match the particle size distribution of the soluble diluents. All matrix tablets comprised 39% (w/w) HPMC, 10% (w/w) drug and 50% (w/w) soluble material. Dextrose was chosen as the diluent as it has a negligible effect on the HPMC sol:gel transition temperature in comparison with other sugars (Williams et al., 2008). The particle size range of buffer and diluent were matched to minimise differences in matrix dissolution behaviour as a result of differential excipient loss.

The chosen model drug, felbinac (pK_a ~4.3) had the solubility characteristics typical of a weak acid drug. Drug solubility at 37 °C was determined to be 10 mg L^{-1} at pH 1.2 and 5 g L^{-1} at pH 7.5. This weak acid therefore appears to be a good candidate for improving drug release by incorporation of an alkalizing buffer. The drug was found to have a negligible effect on the sol:gel transition temperature of both grades of HPMC.

2.7. Measurement of HPMC single particle swelling

Individual HPMC particles were placed between a microscope slide and a fixed cover slip on the stage of a fluorescent microscope (Nikon Instruments, Japan). The swelling of the particles were monitored in the presence of 0.1% (w/v) aqueous Congo red solution as a visualisation aid, using a video camera (Cohu Instruments, San Diego, California). A time-series of images were collected immediately after the hydration solution came into contact with the particle under investigation, using the "snapper" function in Image Pro Plus (Version 3.0 Media Cybernetics, Maryland, USA). The microscope slide was placed on a heating/cooling plate (Linkam MS100, Wishart Scientific, Ballyclare, UK) to maintain the temperature of the experiment at $T \pm 1$ °C.

The area occupied by a HPMC particle before and after hydration at each time point was calculated using a measurements function in Image Pro Plus Version 3.0, and the normalised cross sectional area of the particle was calculated to show the increase in particle swelling with time.

2.8. Confocal laser microscopy imaging of the nascent gel layer

The Confocal microscopy imaging was undertaken using the method of Bajwa (Bajwa et al., 2006). In summary, fluorescence images were obtained using a Bio-Rad MRC-600 confocal microscope (Bio-Rad, Hemel Hempstead, UK) equipped with a 15 mW Krypton Argon laser and a Nikon Optiphot upright microscope through a 4/0.13NA air lens (Nikon, London, UK) at Ex 488/Em 510 nm using a BHS filter block Matrices held between Perspex discs in a Fixed Observational Geometry (FOG) apparatus were hydrated in a degassed 0.05% (w/v) aqueous solution of Congo red, a fluorophore which provides a marker for hydrated HPMC (Bajwa et al., 2006).

Images of radial gel layer growth were obtained up to 10 min after the initial hydration. The average (mean $n = 10$) thickness of gel from the inner boundary of the brightest region of the gel layer (>200 pixel intensity), which represents the region of free fluorophore penetration, was measured by image analysis using a fixed scaled grid fitted across the image.

2.9. Determination of gel layer pH using a pH microelectrode

The pH micro-environment within the gel layer of hydrating HPMC matrices was measured using a 100 μm diameter Beetrode pH microelectrode (NMPH1, World Precision Instruments, Inc., Sarasota, FL, USA) and a separate 450 μm diameter reference electrode (DriRef450, World Precision Instruments, Inc., Sarasota, FL, USA) attached to a pH meter (H18424, Hanna Instruments, Inc., Woonsocket, RI, USA). Prior to use, the pH microelectrode was held in distilled water, and calibrated using pH 4 and 7 buffer solutions before and after measurement. Matrices were hydrated in 900 ml degassed 0.1 M HCl at 37 ± 1 °C in a beaker and at periodic intervals, the pH microprobe tip and reference electrode were carefully inserted into the gel layer of the matrix to a depth of 1 mm and the pH recorded. Measuring the pH at this depth avoided measuring the external fluid, gave good reproducibility for comparative purposes and prevented damage to the probe by forcing it into the core. Measurements were made on hydrated matrices *in situ*, to minimise the disruption of the gel layer. However, the technique remains invasive and it is recognised that some disruption to the emerging gel layer will occur in the vicinity of the probe. This is especially true in the very early phases of gel formation, when the gel is thin and gel growth is rapid, and for this reason measurements are not shown before 10 min.

2.10. pH determination using halved tablets and Universal pH indicator

Dry matrices were sectioned through the flat face to provide approximately equal halves and were clamped between two microscope slides. This assembly was placed in a USP apparatus II containing 450 ml degassed 0.1 M HCl with 0.5% (v/v) Universal pH indicator at 37 ± 1 °C, and agitated at 100 rpm for an initial period of 2 min. The clamps and top microscope slide were then removed as gel layer formation led to matrix adhesion to the lower slide. The halved matrix and slide were re-introduced into the dissolution vessel with the matrix facing upwards (to expose it to agitation) and

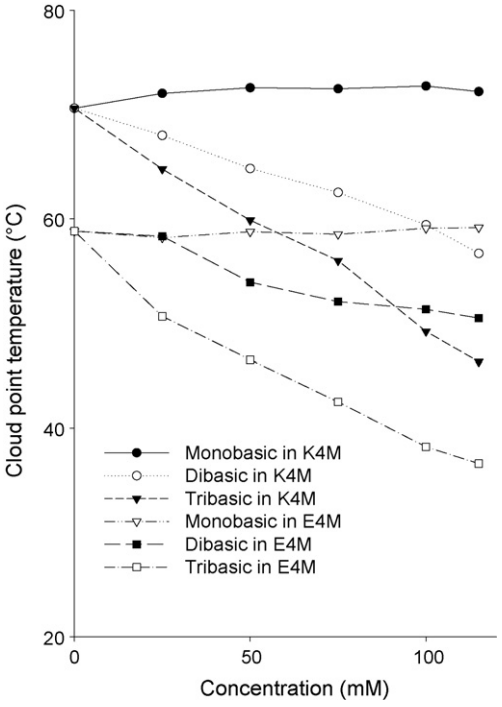

Fig. 1. The effect of sodium citrate valency on the cloud point temperature of 1% (w/w) solutions of HPMC 2208 and 2910. Mean ($n = 3$) ± 1S.D.

the experiment continued. At intervals, the slide was removed from the vessel, placed onto an upright Petri dish, and photographed through the microscope slide, to reveal an image showing the dry core and a gel layer colour with pH indicator. Photography was undertaken under fixed lighting intensity using a Nikon FM2 camera fitted with a 600 mm macro lens F/2.8D (Nikon instruments, Tokyo, Japan).

3. Results and discussion

3.1. The effect of citrate ion valency on the cloud point temperature of HPMC solutions

Fig. 1 shows the effect of buffer concentration on the cloud point temperature (CPT) of HPMC solutions containing different citrate salts. Whilst monovalent ions had little influence, multivalent citrate salts lowered CPT to an extent approximately proportional to the charge on the anion. The tribasic citrate salt had the most potent effect on cloud point (HPMC 2910 Methocel E4M $\Delta CPT = -186.05\,^{\circ}C\,M^{-1}$, HPMC 2208 Methocel K4M $\Delta CPT = -208.1\,^{\circ}C\,M^{-1}$). This is typical of Hofmeister behaviour, in which a lowering of the CPT value represents the increasing tendency of this thermo-sensitive polymer to undergo salting-out through ionic disruption and dehydration of the polymer water sheath (Chen et al., 2007; Zhang and Cremer, 2006; Richardson et al., 2006). The effect of increasing valency is consistent with the position of each salt in the previously observed Hofmeister series for HPMC (Zhang et al., 2005; Zhang and Cremer, 2006). Trivalent citrate had the same overall effect on both grades of HPMC but results were shifted downwards (Fig. 1). This reflects the higher degree of methoxyl substitution and the greater hydrophobicity of the HPMC 2910 grade.

3.2. Drug release from citrate-buffered HPMC matrices

3.2.1. General observations

Fig. 2a–d shows dissolution testing of HPMC 2910 (E4M) and HPMC 2208 (K4M) matrices at pH 1.2 and 7.5. The release profile in

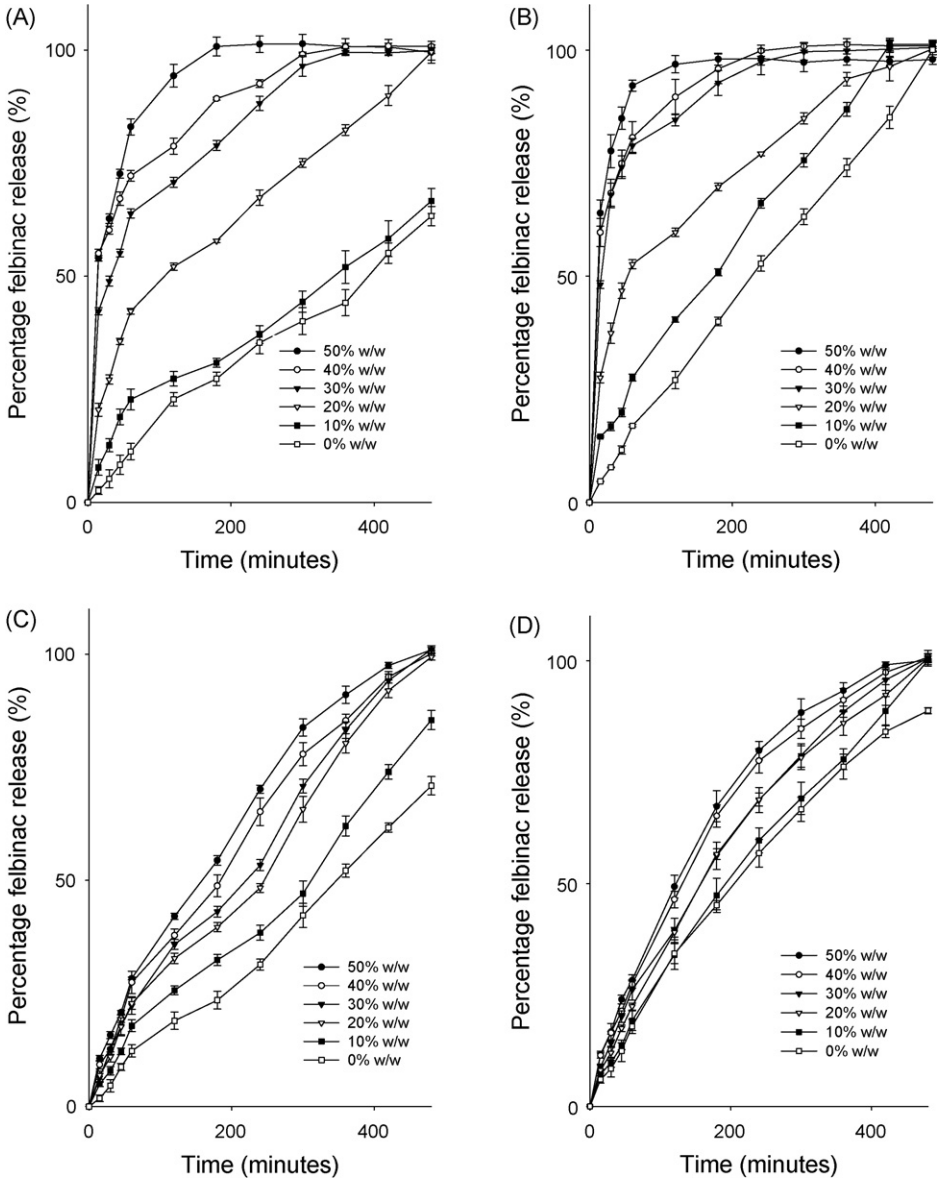

Fig. 2. Release of felbinac from HPMC matrices as a function of sodium citrate content—(A) HPMC 2910 matrices at pH 1.2, (B) HPMC 2910 matrices at pH 7.5, (C) HPMC 2208 at pH 1.2 and (D) HPMC 2208 at pH 7.5. The percentage w/w sodium citrate in the matrix is shown in the figure legend. USP I @ 100 rpm, 37 °C ± 1, mean ($n = 5$) ± 1S.D.

the absence of buffer is typical for HPMC matrices containing a low content of an intermediate solubility drug: a non-Fickian and often prolonged linear phase which suggests a drug release mechanism in which erosion plays a significant role. In each case, increasing the content of sodium citrate in the matrix resulted in a progressive acceleration of drug release, but with clear differences in profile shape between the two HPMC grades and media. The effect of incorporating sodium citrate into HPMC 2910 matrices was dramatic. At pH 1.2 the time for 60% drug release was reduced from 8 h in the absence of buffer, to only 20 min in a matrix containing 50% (w/w) sodium citrate. A 20% (w/w) citrate loading was sufficient to facilitate 100% drug release within 8 h, and at higher citrate levels the extended release characteristics of the matrix progressively deteriorated, as more drug was released during the early stages of dissolution. At pH 7.5, the faster drug release of the control matrix (containing 0% citrate) reflects the increased drug solubility and the change from non-sink to sink conditions in the dissolution test. However, the effect of sodium citrate on the extended release characteristics of these matrices was as deleterious in pH 7.5 as in pH 1.2 medium.

HPMC 2208 matrices also exhibited faster drug release with increasing citrate content. However, the shape of the release profiles were markedly different to those of HPMC 2910 matrices (Fig. 2c and d). Although drug release was accelerated overall, there was no loss of extended release characteristics even at the highest levels of sodium citrate incorporation. There was a change from a sigmoidal to a more curved Fickian profile when the dissolution medium was changed from pH 1.2 to 7.5 which reflects the increased drug solubility at the higher pH.

These complex dissolution curves are difficult to interpret in terms of the underlying drug release mechanisms, but (i) the extent of the acceleration, (ii) the changing shape of the release profiles, and (iii) the apparent dependence on polymer substitution strongly suggest that in addition to the internal enhancement of drug solubility, the inclusion of sodium citrate resulted in other mechanisms contributing substantially to the drug release process.

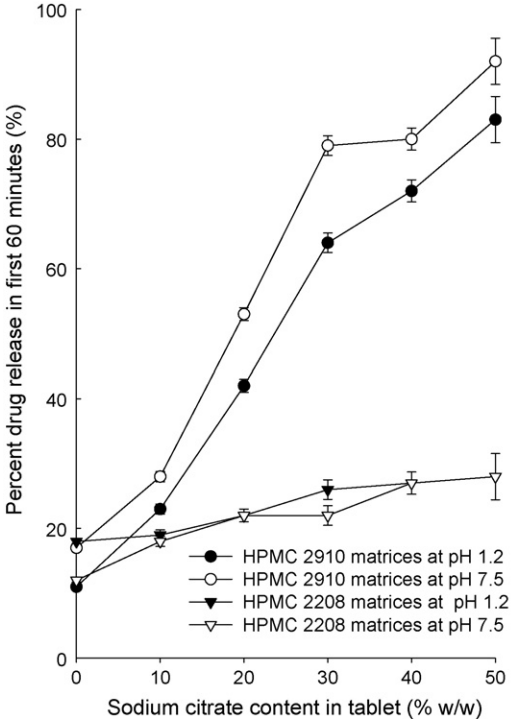

Fig. 3. The effect of sodium citrate content on the percentage of drug released in the first 60 min of dissolution testing. Mean ($n = 5$) ± 1S.D.

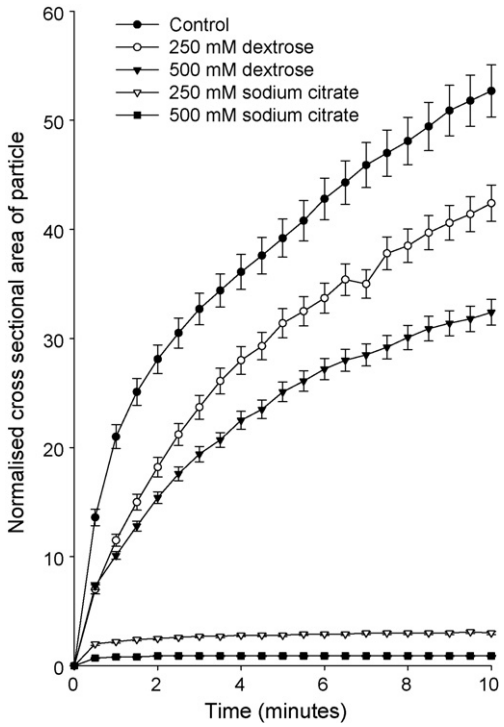

Fig. 4. A comparison of HPMC 2910 particle swelling in dextrose and sodium citrate solutions. Visualising agent 0.1% (w/v) Congo red. Tests conducted at 20 ± 1 °C, mean ($n = 10$) ± 1S.E.M.

Identifying drug release mechanisms through a mathematical interpretation of these release profiles is problematic. Power law analysis (Peppas, 1985) would be inappropriate in many of these systems because there is strong evidence of matrix disrup-

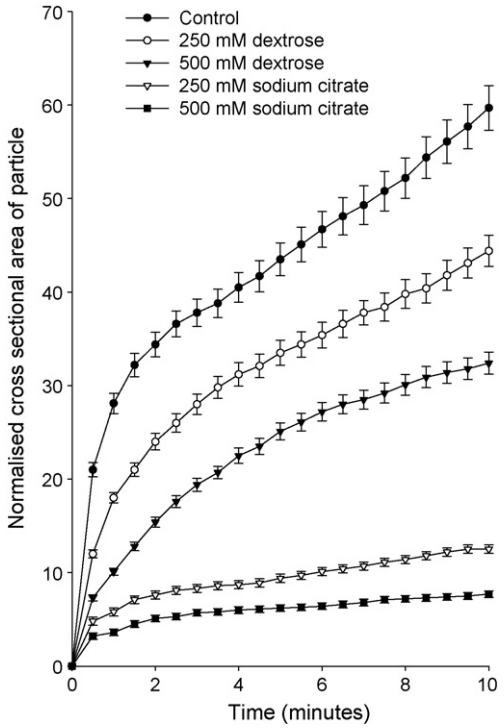

Fig. 5. A comparison of HPMC 2208 particle swelling in dextrose and sodium citrate solutions. Visualising agent 0.1% (w/v) Congo red. Tests conducted at 20 ± 1 °C, mean ($n = 10$) ± 1S.E.M.

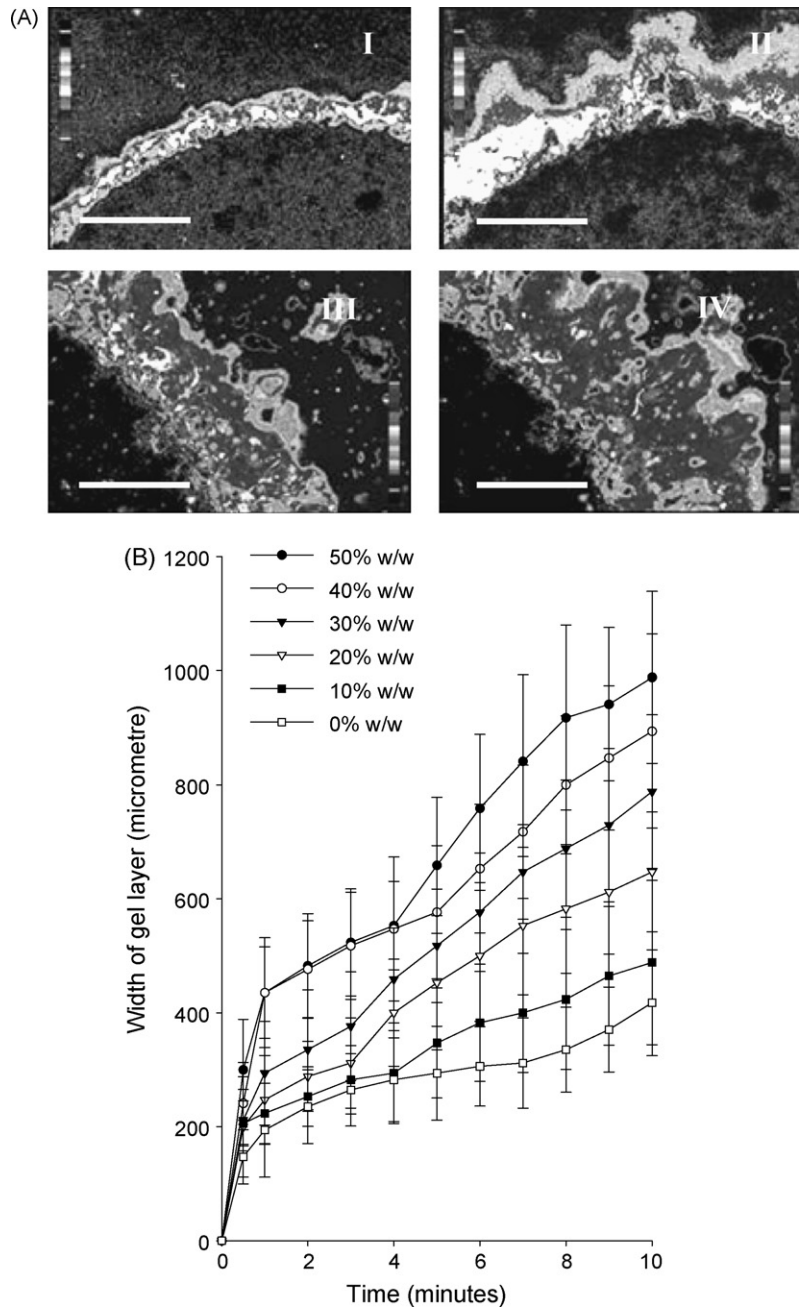

Fig. 6. Early gel layer growth and liquid penetration in HPMC 2910 matrices as a function of their sodium citrate content (A) HPMC 2910 example images: (I) HPMC 2910 with 0% citrate at 1 min, (II) HPMC 2910 with 0% citrate at 10 min, (III) HPMC 2910 with 50% citrate at 1 min and (IV) HPMC 2910 with 50% citrate at 10 min; (B) gel layer growth in HPMC 2910 matrices. Tests conducted at 37 ± 1 °C, mean (n = 3) ± 1S.D. Scale bar (white line) = 500 μm.

tion in the early stages of dissolution, and because in acid media, drug dissolution is probably taking place under non-sink conditions. It is clear from the shape of these dissolution curves that the drug release mechanism does not follow the usual diffusion or erosion-controlled release model, except in the case of the matrices undergoing dissolution at pH 7.5. A power law analysis of the HPMC 2208 dissolution curves at pH 7.5 show a progressive shift in exponent value (n) from 0.77 to 0.6, indicating a small shift towards diffusional controlled release as the citrate content of the matrix is increased. This can be attributed to improved internal drug solubility. HPMC 2910 matrices at pH 7.5 exhibit the linear release (exponent value $\sim n = 1$) characteristic of a Case II mechanism in which polymer relaxation and erosion are rate-controlling. At this pH the drug is soluble, and so this result suggests that the gel layer has weakened and become more fragile in the presence of citrate.

3.2.2. The mechanism of drug release in HPMC 2910 matrices

The dissolution profiles of HPMC 2910 matrices show increasing curvature with greater sodium citrate content. This could be interpreted as a shift towards a more diffusion-based drug release mechanism as a result of gel layer buffering and improved drug solubility. However, closer examination reveals that these profiles are biphasic, and that the profile changes as a result of a greater proportion of drug undergoing immediate release within the first hour of dissolution. After 60 min, the remaining drug is released almost linearly, and at a similar rate at all citrate contents. Fig. 3 also shows how the drug released in the first 60 min is closely related to the citrate content of the matrix.

HPMC matrices often show immediate release (often termed an 'initial burst') at the start of a dissolution test. This has been attributed to the liberation of drug residing in the gel layer and

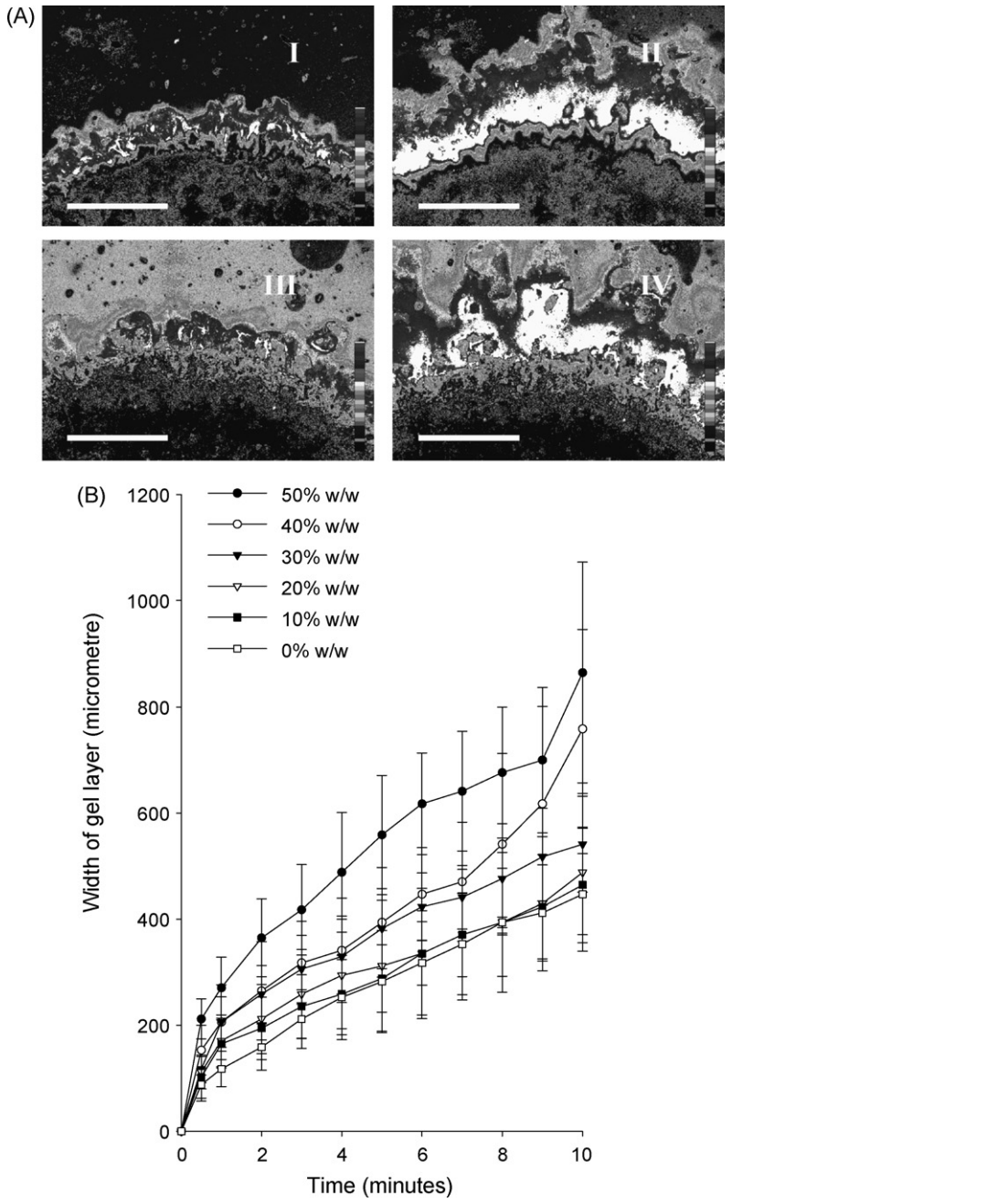

Fig. 7. Early gel layer growth and liquid penetration in HPMC 2208 matrices as a function of their sodium citrate content (A) HPMC 2208 example images: (I) HPMC 2208 with 0% citrate at 1 min, (II) HPMC 2208 with 0% citrate at 10 min, (III) HPMC 2208 with 50% citrate at 1 min and (IV) HPMC 2208 with 50% citrate at 10 min; (B) gel layer growth in HPMC 2208 matrices. Tests conducted at 37 ± 1 °C, mean (n = 3) ± 1S.D. Scale bar (white line) = 500 μm.

before the establishment of stable internal concentration gradients within the gel. The amount of drug available is proportional to the depth of liquid penetration into the matrix, and therefore the increased drug release suggests that sodium citrate is promoting liquid ingress before gel barrier properties are fully established.

Other multivalent salts accelerate drug release in HPMC matrix formulations and it has been suggested that this is a consequence of the polymer 'salting out' (Alderman, 1984; Mitchell et al., 1990). More recent evidence suggests that dissolved ions at low concentrations slow HPMC particle swelling and gel layer growth, but at higher concentrations they inhibit the coalescence of HPMC particles and disrupt the development of an effective gel layer diffusion barrier (Bajwa et al., 2006).

Several mechanisms might explain the changes in dissolution profile seen in citrate-buffered matrices. Sodium citrate might for example (i) disrupt or delay the development of diffusion barrier properties through the mechanisms described above, (ii) reduce polymer solubility, resulting in a more diluted polymer network which is a poorer diffusion barrier or (iii) inhibit HPMC solubility and particle coalescence, resulting in a physically weaker gel less able to resist erosion. A fourth potential mechanism arises from the replacement of the dextrose diluent in the tablet with sodium citrate. Although they have similar solubilities, the osmotic potential of the trivalent sodium citrate is much greater than the dextrose it is replacing and therefore (iv) substituting sodium citrate for dextrose may cause the matrix to imbibe external fluid more extensively as a result of the osmotic pressure exerted by the dissolving salt.

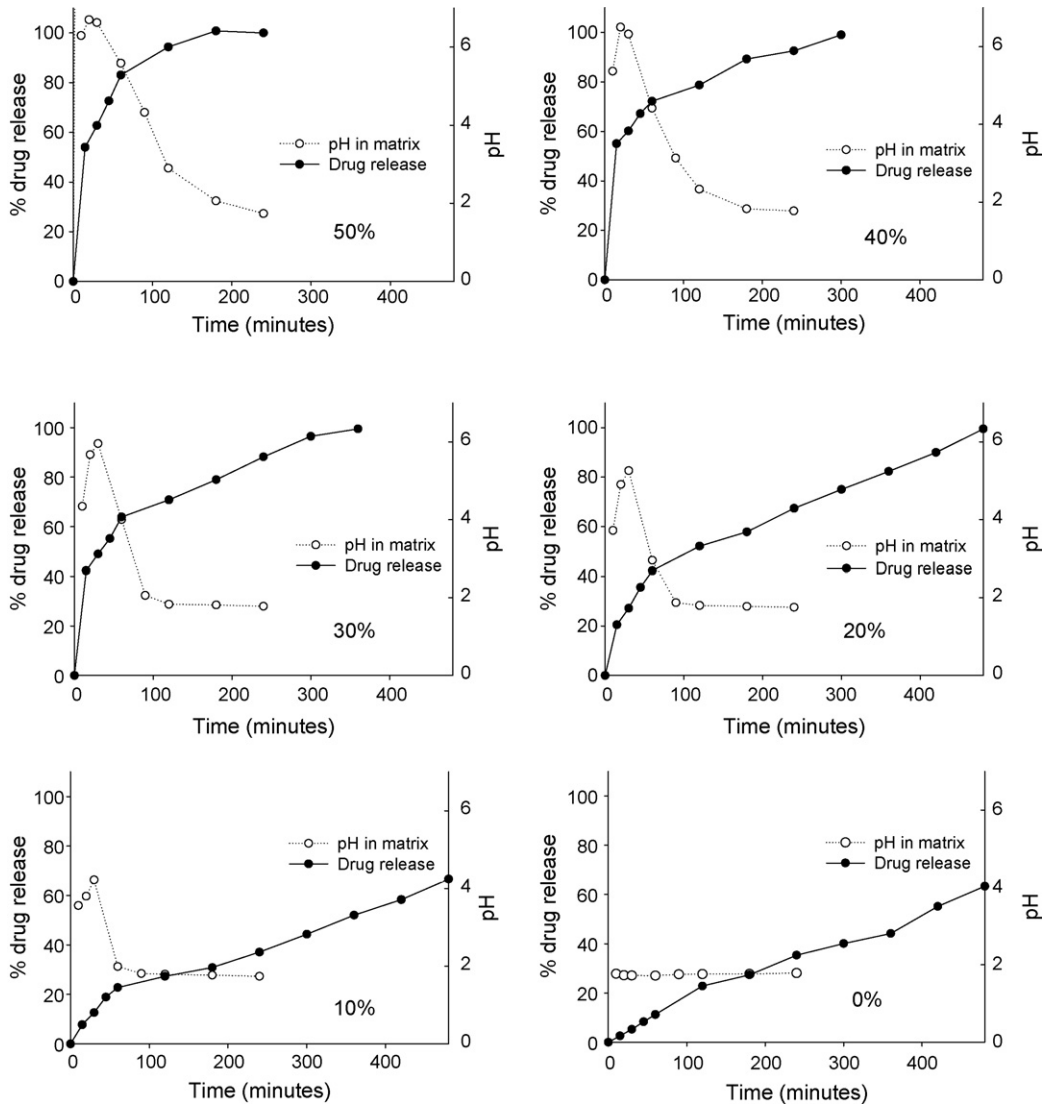

Fig. 8. The relationship between gel layer pH and drug release in HPMC 2910 matrices containing between 0 and 50% (w/w) sodium citrate. pH measurements by micro-probe.

Each of these mechanisms (i–iv) would promote more extensive liquid penetration in the early stages of matrix hydration, and would result in the greater drug release in the initial phase of dissolution and the effect of sodium citrate could arise from any combination of these mechanisms. Particle swelling data (Fig. 4) clearly shows that sodium citrate profoundly suppresses the swelling of HPMC 2910 particles, in comparison with dextrose and the disruption of gel layer formation through inhibition of particle swelling is therefore a realistic proposition, especially if high local concentrations of dissolved citrate are present in the emerging gel layer.

3.2.3. *The mechanism of drug release in HPMC 2208 matrices*

In contrast, HPMC 2208 matrices showed accelerated drug release in the dissolution tests, without the loss of extended release characteristics at high citrate concentrations (Fig. 2c and d). Most strikingly, they also show no initial burst effect. The lower methoxyl substitution makes this grade less susceptible to 'salting out' (Mitchell et al., 1993a,b). This is seen in Fig. 1, where the higher sol:gel transition temperatures show HPMC 2208 to be more tolerant to the presence of citrate than HPMC 2910. As a result, HPMC 2208 particles will be more capable of swelling, coalescence and forming an effective gel diffusion barrier at citrate concentrations where HPMC 2910 particles cannot. Therefore the observed differences in citrate sensitivity, and in particular the initial burst release, can be explained by the formation of an effective gel diffusion properties in the HPMC 2208 matrix whereas in the more citrate-sensitive HPMC 2910 matrix, the gel layer formation is disrupted. If the initial burst also has an osmotic driver, then gel layer development in the HPMC 2208 matrix has clearly advanced sufficiently far to resist the disruption from the osmotic pressures generated by incorporated citrate. Fig. 5 shows the effect of sodium citrate on the swelling of HPMC 2208 particles. Swelling is suppressed, but in comparison with Fig. 4, the influence of sodium citrate is considerably less on HPMC 2208 particles. It is worth noting that the high concentrations of sodium citrate in this study (0.25–0.5 M) were chosen for comparison purposes to represent an extreme case in which the sol:gel transition was highly depressed (Fig. 1). The swelling of HPMC 2208 under these conditions is therefore remarkable and we would expect this swelling behaviour to be more pronounced at lower buffer concentrations.

3.3. *Early gel layer development*

Figs. 6 and 7 show gel layer growth during the early stages of gel layer formation. This is a critical period in the creation of gel diffusion barrier properties and interference with particle swelling and

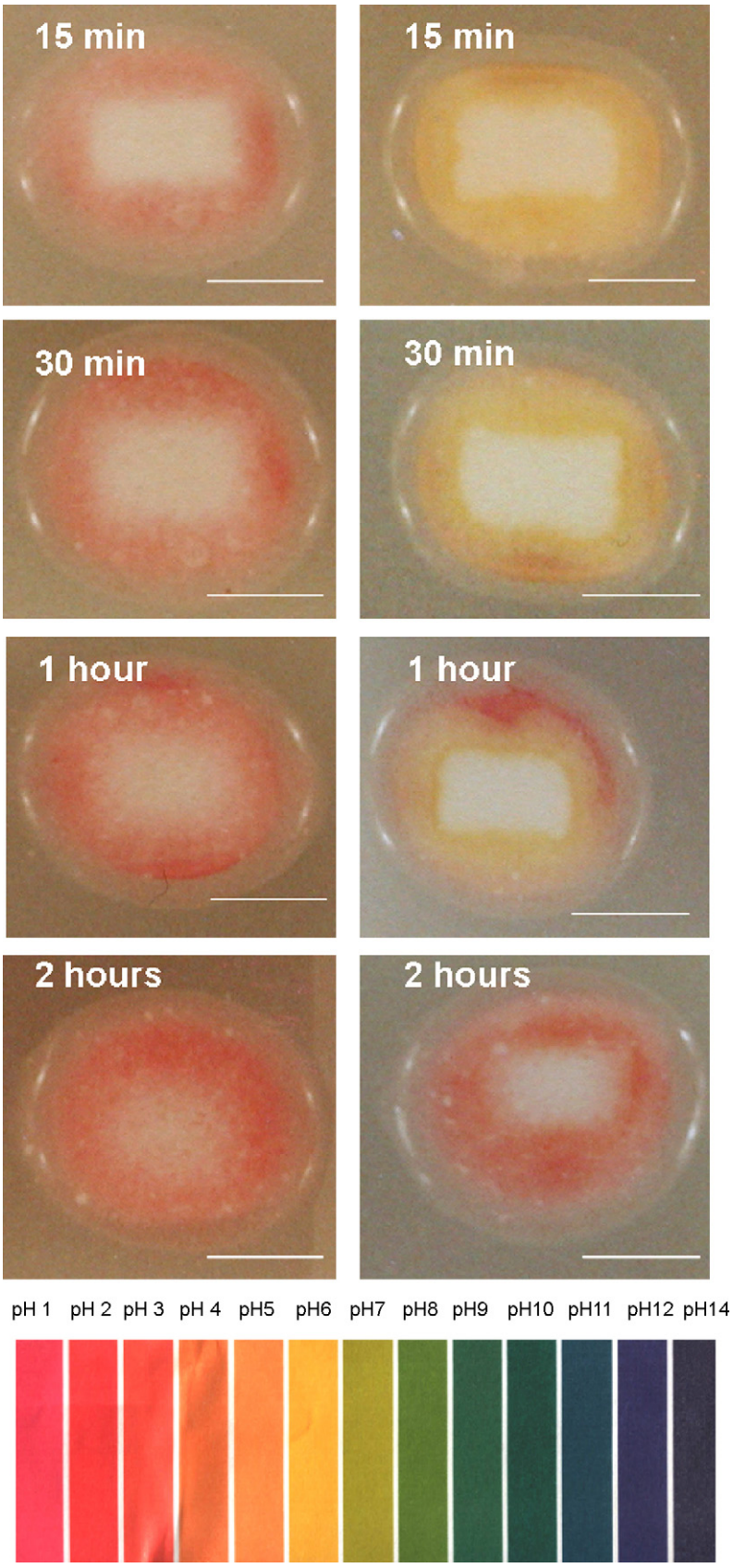

Fig. 9. Images of halved HPMC 2910 matrices containing 0% sodium citrate (left column) and 50% sodium citrate (right column) after hydration in 0.1 M HCl containing 0.05% (v/v) universal indicator. Scale bar = 2 mm.

coalescence at this stage results in greater liquid penetration into the matrix (Bajwa et al., 2006). Measurements of gel layer thickness were made from the brightest areas of the fluorescence images, as these represent regions that can be freely penetrated by fluorophore (region B1 in Bajwa et al. 2006). This measurement therefore indirectly provides evidence of the rate of development, or inhibition, of gel diffusion barrier properties. In the case of HPMC 2910 matrices (Fig. 6) an increase in citrate content elicits an almost proportional enhancement of matrix hydration. In contrast, the HPMC 2208 matrices (Fig. 7) exhibited no change in fluorophore penetration at the lower citrate levels (10–20%), and enhanced fluorophore penetration is seen only at high (30–50%) citrate levels. This is further evidence that the diffusion barrier formed in HPMC 2208 matrices is more resistant to the effects of incorporated sodium citrate.

3.4. Gel layer pH

In addition to releasing the drug, HPMC matrices simultaneously release other soluble components into the dissolution medium. High solubility, low molecular weight materials such as sodium citrate may be released rapidly, and if this occurs at a rate faster than buffering capacity can be replenished from the core, then pH control may be compromised. If the pH environment in the gel layer becomes insufficient to maintain drug solubility, then there is a clear possibility of drug precipitation, and a consequential change from diffusion to erosion-controlled release.

Experiments were therefore undertaken to estimate the longevity of internal pH control. A pH microprobe (100 μm diameter) was inserted to a depth of 1 mm into the gel layer. Results should be interpreted with this fixed position in mind. As the gel layer thickens with time, the distance of the probe from the hydration front (gel/core interface) will increase with time, and the fixed position of the probe means that increasingly the outer part of the gel layer is being monitored. However, it is precisely this region of the gel that may be important in pH control, because if the pH drops in this region, then the drug has to potential to precipitate within the gel and only be released by erosion processes. This phenomenon was observed in the subsequent pH imaging studies where white specs appeared in the outer gel layer when the pH in this region became acidic after 2 h.

Fig. 8 shows gel layer pH measurements in HPMC 2910 matrices plotted as a function of hydration time and sodium citrate content, and with the results superimposed on the corresponding drug release profiles. The control matrices (0% citrate content) had little intrinsic buffering capacity and remained at approximately pH 1.7 throughout the experiment. In matrices containing sodium citrate, gel layer pH values rapidly increased to a maximum value after approximately 20–30 min, but then declined rapidly thereafter. The pH maximum reached increased with the citrate content of the matrix, but in all cases a micro-environment greater than pH 5 (a nominal pH above which drug solubility should be enhanced), was achieved only transiently. This shows that after an initial phase of high citrate concentration in the gel, there is rapid loss of sodium citrate at a rate that cannot be replenished from the core. This would arise both from the high water solubility of the buffer and the propensity of sodium citrate to damage the diffusion barrier properties of the gel layer. It should be noted that these pH measurements were carried out under static conditions. Under the more agitated conditions of a dissolution test, we can predict a faster rate of buffer egress as a result of gel erosion. However, there is a clear correlation between the period of pH elevation and the accelerated phase of drug release during the early stages of the dissolution test (Fig. 8). The higher the maximum pH attained, the greater was the amount of drug released in the first 15 min after hydration. This result links the immediate release 'burst' in the dissolution test to the citrate concentration in the gel layer. Significantly, this effect is also seen in the matrix containing 10% citrate, where the pH rise is too low to aid drug solubility. This is further evidence that enhanced drug release is not solely through enhancement of drug solubility but also occurs as a result of gel barrier disruption or osmotic effects.

After the pH maximum, gel layer pH reverted to a low value and in parallel, the drug release profiles in the dissolution test adopted the slower linear profile characteristic of a Case II mechanism. This suggests that once citrate levels had reduced, the gel had recovered diffusion barrier properties to water ingress and, with the drug in a less soluble environment the matrix then changed to a more erosion-based drug release mechanism.

Further evidence for the loss of micro-environmental pH control in the gel layer can seen in the pH indicator experiments. Fig. 9 shows the appearance of a sectioned HPMC 2910 matrix hydrated in 0.1 M HCl in the presence of Universal pH indicator. When the buffer was absent from the matrix, the pH in the gel layer reflected that of the hydrating medium, showing that without sodium citrate, the formulation had little intrinsic buffering capacity. In the matrix containing 50% sodium citrate, the pH reached a value of 6 throughout the gel layer within 15 min. However after 1 h, there is clear evidence of a lowering of pH in the outer regions of the gel, and after 2 h the gel layer had almost entirely reverted to low pH. Although crude, these experiments confirm the microelectrode results. White specks were observed in the gel layer of the unbuffered tablets, suggesting the presence of undissolved drug. These were not seen in citrate-buffered matrices in the early stages of hydration, when the gel layer was pH 6, but they became visible in outer parts of the gel layer after 2 h when the gel layer had reverted to low pH. This observation suggests that undissolved drug reappears once the pH buffering is exhausted, and this further supports the change from a diffusion-dominated to an erosion-based drug release mechanism, as proposed above.

Overall, these drug release and physico-chemical characterization studies show that a relatively high content (10–20%, w/w) of sodium citrate is required to modify drug release and gel layer formation. The results also suggest that a threshold concentration is required within the gel layer in order for these changes to take effect.

4. Conclusions

The inclusion of sodium citrate in HPMC matrix tablets accelerated the release of the weak acid model drug felbinac, but the mechanism for this effect was clearly more complex than simple improvement of drug solubility. The effect was more profound in HPMC 2910 matrices where faster drug release was accompanied by a loss of extended release characteristics. In HPMC 2208 matrices there was no loss of extended release control. The increased immediate 'burst' release observed in the HPMC 2910 matrices, and the studies of early gel layer formation both suggest a citrate-dependent enhancement of liquid penetration into the matrix. Whilst this may be an osmotic effect from the dissolving salt, the results of this study suggest an interference with the barrier properties of the gel layer. The lowering of sol:gel transition temperature, dependence on polymer substitution, the suppression of particle swelling and literature evidence of the effects of multivalent ions on HPMC, all suggest a Hofmeister effect in which the polymer: water interaction is suppressed by the citrate ion. The reduced polymer affinity for water then reduces HPMC particle swelling and gel layer coalescence, disrupting the establishment of the diffusion barrier properties of the gel layer, and leading to an increased penetration of hydration media in the early stages of matrix hydration. There was also some evidence in these studies for an increased gel layer fragility and increased susceptibility to erosion. The pH modification of the gel layer by sodium citrate was only transitory: the conditions for enhanced drug solubility existed for only 2 h at best

in this static study. It should also be noted that the effects reported with HPMC 2910 occur at significant levels of buffer incorporation (10–20%, w/w), and that HPMC 2208 conferred a greater degree of resistance to the disruptive effects of incorporated citrate ions, even at the highest (50%) buffer levels incorporated. Nonetheless, this study shows how the use of buffering co-excipients can increase the complexity and temporal dependence of the processes that contribute to drug release in HPMC matrices. This has consequences for the formulation of pH-dependent drugs, since the physicochemical influence of the buffering agent on the formulation, as well as on the drug, needs to be considered when designing these dosage forms.

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