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The suitability of tris(hydroxylmethyl) aminomethane (THAM) as a buffering system for hydroxypropyl methylcellulose (HPMC) hydrophilic matrices containing a weak acid drug

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ABSTRACT

There are few studies of alkalising pH-modifiers in HPMC hydrophilic matrices. These agents may be incorporated to provide microenvironmental buffering and facilitate pH-independent release of weak acid drugs. This study compared tris(hydroxylmethyl) aminomethane (THAM, TRIS, tromethamine, trometamol) with sodium citrate as internal buffering agents for HPMC (4000 cps) 2208 and 2910 matrices containing felbinac, a weak acid drug which exhibits pH-dependent solubility. Drug release at pH 1.2 and 7.5 was accelerated by both buffers, but THAM-buffered matrices provided extended, diffusion-based release kinetics, without loss of matrix integrity at high buffer concentrations. Release kinetics appeared to be independent of media pH. THAM did not depress the sol–gel transition temperature or suppress HPMC particle swelling, and had minimal effects on gel layer formation. Sodium citrate promoted greater thickness of the early gel layer than THAM. Measurements of internal gel layer pH showed that both buffers produced a rapid alkalisation of the gel layer which was progressively lost. As result of its higher pK_a and molar ratio on a percent weight basis, THAM provided a higher internal pH and a greater longevity of pH modification. It is concluded that THAM offers a useful buffering option for weak acid drugs in HPMC-based systems.

1. Introduction

Hydroxypropyl methylcellulose (HPMC) hydrophilic matrices are an approach to oral extended release dosage forms with a knowledge base that spans many decades (Alderman, 1984; Melia, 1991; Li et al., 2005). However, in common with other oral extended release technologies, matrices that contain weakly acidic or weakly basic drugs, may exhibit poor or variable bioavailability when traversing regions of the gastrointestinal tract where pH adversely affects drug ionisation and solubility (Badawy and Hussain, 2007; McConnell et al., 2008). In hydrophilic matrices, an additional consideration is that changes in environmental pH may also influence the drug release mechanism. Whilst polymer properties remain generally unchanged in the physiological range of pH, an HPMC matrix moving from a high drug solubility to a low drug solubility environment may experience a change from diffusion to erosion-dominated release if drug is precipitated within the rate-controlling surface 'gel' layer (Pygall et al., 2009). The result is often a change in the release profile and a marked slowing of drug release. To overcome this problem, buffering excipients are often incorporated in HPMC matrices to stabilise the gel layer pH, and maintain drug ionisation and diffusional release irrespective of the external pH environment (Badawy and Hussain, 2007). There are numerous studies which describe improvements in the release of weakly basic drugs following the incorporation of organic acids or acidifying polymers (Gabr, 1992; Timmins et al., 1997; Streubel et al., 2000; Varma et al., 2005; Siepe et al., 2006) but few studies describe buffering systems suitable for HPMC matrices that contain weak acid drugs. Magnesium hydroxide (Fuder et al., 1997), magnesium oxide (Riis et al., 2007), and basic methacrylic acids polymers (Rao et al., 2003) have been used with varying degrees of success.

There is a need for judicious selection of buffering systems that are compatible with all components of an HPMC matrix formulation. Ionic species for example, may form poor solubility salts with oppositely-charged drugs *in situ* (Feely and Davis, 1988). High valency anions such as phosphates and citrates, and even monovalent cations in high concentration, can dehydrate the polymer hydration sheath and 'salting out' of the HPMC polymer (Mitchell et al., 1990; Alderman, 1984; Zheng et al., 2004; Bajwa et al., 2006). The mechanism is thought to involve dehydration of methoxyl-rich regions of the polymer chain, leading to the formation of an insol-

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uble 3D network stabilized by hydrophobic interactions (Sarkar, 1979; Haque and Morris, 1993; Kobayashi et al., 1999; Hussain et al., 2002). The critical importance of methoxyl regional interactions has been highlighted by the recent work of Viriden et al. (2009a,b,c) who provide evidence that drug release in HPMC matrix formulations may be sensitive not only to changes in overall methoxyl substitution, but also to differences in regional polymer chain heterogeneity. In HPMC solutions there is a considerable evidence for a Hofmeister rank-order effect within a series of simple ions (Xu et al., 2006; Liu et al., 2008), but the influence of salts on HPMC matrices appears to be through their effects on polymer hydration during gel layer formation (Bajwa et al., 2006). HPMC matrices rely on rapid polymer swelling and particle coalescence to develop an effective 'gel layer' diffusion barrier, and the influence of excipients which slow or inhibit polymer swelling can be profound. For example, sucrose or sodium chloride in high concentration disrupts gel layer formation in this way (Bajwa et al., 2006; Williams et al., 2009), and multivalent ions such as citrate are considerably more potent (Pygall et al., 2009). This effect explains the observations of Kajiyama et al. (2008) who showed how incorporation of alkali metal carbonates, chlorides, sulphates and phosphates all reduced the disintegration times of HPMC matrices.

A previous study investigated sodium citrate as a pH-modifying agent for HPMC matrices containing weak acid drugs (Pygall et al., 2009). It was found that high levels of incorporation were required as a result of the high solubility and relatively low pK_a (6.4) of this buffer. In simulated gastric fluid, it provided only a transitory alkalisation of the gel layer and, at the high levels of incorporation required, this buffer accelerated drug release markedly. This appeared to result from disruption of the diffusion barrier properties of the gel layer, and was attributed to suppression of swelling during gel formation by this multivalent ion.

It was concluded that there was a need to identify alternative buffering systems for weak acid drugs and in this study we investigate the suitability of tris(hydroxylmethyl) aminomethane (THAM, TRIS or tromethamine) for pH control in HPMC matrices containing a weak acid drug, felbinac. THAM has a higher pK_a (8.06) than sodium citrate and as it is monovalent may have less effect on HPMC hydration than sodium citrate. Previous studies suggest THAM has good compatibility with HPMC. It has been used to internally buffer gastroretentive HPMC matrices (Gabr and Borg, 2000), extended release osmotic tablets (Shivanand et al., 2000) and buccoadhesive HPMC films (Alanazi et al., 2007). As kerotolac tromethamine, it has also been formulated into HPMC matrices (Genc and Jalvand, 2008) and many HPMC-based nasal, ophthalmic and transdermal aqueous systems (El-Aleem et al., 2007; Chelladurai et al., 2008; Amrish and Kumar, 2009).

2. Materials and methods

2.1. Materials

Hydroxypropyl methylcellulose (HPMC) Methocel E4M CR premium EP (Hypromellose USP 2910) and K4M CR premium EP (Hypromellose USP 2208) were kind gifts from Colorcon Ltd. (Dartford, Kent). Felbinac (4-biphenylacetic acid) was obtained from Sigma (Poole, Dorset). Tris(hydroxylmethyl) aminomethane (THAM) was obtained from Aldrich Chemical Co. (Milwaukee, WI, USA), sodium citrate dihydrate from Acros Organics (New Jersey, USA) and Congo Red from Sigma (Poole, Dorset, UK). Universal pH indicator was obtained from Fisher Scientific UK Ltd. (Leicestershire, UK), compression grade dextrose was a kind gift from Cerestar UK Ltd. (Manchester, UK) and magnesium stearate was obtained from BDH Laboratory Supplies (Dorset, UK). Solutions were prepared using Maxima HPLC grade water (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, an accurately weighed amount of HPMC powder was added, and the solution was mixed for 10 min on maximum speed using a high velocity laboratory emulsifier (Silverson Machines Ltd., Buckinghamshire, UK). The remainder of the water was added at room temperature and mixing continued until a visually uniform dispersion was obtained. Once cooled, the solution was refrigerated at 2–8 °C for 24 h prior to use, to allow complete hydration of the polymer and the clearance of air bubbles. HPMC:drug and HPMC:THAM mixtures were prepared by mixing double strength solutions.

2.3. Determination of HPMC sol:gel phase transition temperatures by turbidimetry

Sol:gel phase transition temperatures were determined by cloud point determinations in a temperature-ramped white light turbidimeter (C. Washington, Nottingham, UK), on 1% (w/w) HPMC solutions containing varying concentrations of felbinac or THAM, in 10 mm cuvettes. The cloud point was taken as the temperature at which there was a 50% reduction in light transmission through the sample (Sarkar, 1979). The temperature at HPMC solutions become turbid is associated with the thermo-reversible sol:gel phase transition, and can be a sensitive indicator of the molecular hydration of the HPMC molecule and its propensity to be 'salted out'. Measurements were undertaken in triplicate.

2.4. Determination of drug pH solubility profile

An excess of felbinac was added to 10 ml water in a scintillation vial, and shaken in a water bath at 37 ± 1 °C for 48 h. Solution pH was adjusted using 0.1 M HCl and 0.1 M NaOH to produce solutions ranging from pH 1 to 8 at increments of 1 pH unit, measured using a calibrated pH meter (model number H18424, Hanna Instruments, Inc., Woonsocket, Rhode Island, USA). The vials were returned to the water bath for a further 48 h, and drug concentration in the supernatant quantified by UV spectrometry at 255 nm.

2.5. Matrix tablet manufacture

Table 1 shows the composition of the matrices used in this study. To minimise effects from extremes of particle size, the particle size ranges of the THAM, sodium citrate and dextrose were sieve-fractionated to match the particle size range (35–425 μm) of the HPMC 2910 and HPMC 2208. The particle sizes of the drug and lubricant could not be controlled owing to their static nature

Table 1
The composition of HPMC matrices used in this study.

Content in tablet (%, w/w)				
HPMC	Felbinac	THAM	Dextrose	Magnesium stearate
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

HPMC grades were HPMC 2910 (Methocel E4M CR) or HPMC 2208 (K4M CR). The buffer was THAM or sodium citrate.

and these ingredients were used as supplied. Powder blends without lubricant were prepared by mixing for 10 min in a Y cone blender (Neco, London, UK). Magnesium stearate was added and blending continued for a further 5 min. These powder blends were then compressed using an instrumented Manesty F3 single punch machine (Manesty, Liverpool, UK) at a compression pressure of 590 ± 20 MPa, to produce flat-faced 5 mm diameter tablets with a mean weight of 70 ± 10% mg.

2.6. Determination and analysis of drug release behaviour

Drug release kinetics were determined in a USP I dissolution apparatus (Prolabo, France) at 100 rpm and 37 ± 1 °C. Tests were undertaken in 900 ml degassed 0.1 M HCl adjusted to pH 1.2, or 900 ml degassed 0.05 M THAM adjusted to pH 7.5. Drug concentration was quantified by UV spectrometry in 10 mm quartz cells at 252 nm (pH 1.2) or 255 nm (pH 7.5), within the linear regions of the Beer–Lambert plots.

Release data from the matrix tablets was analysed using the power law (Eq. (1)) (Peppas, 1985):

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

where M_t/M_∞ is the fractional release of drug after time t, k is a constant that incorporates the geometric characteristics of the release device and n is the release exponent. The value of n is a parameter that is descriptive of the shape of the curve.

In the past this has been interpreted as drug release by Fickian diffusion ($n = 0.5$), Case II ($n = 1$) or a mechanism in which both diffusion and erosion play significant roles ($n = 0.5 < n < 1.0$) (Peppas, 1985). In reality, drug release is more complex than this simple model, however significant changes in this parameter signal a change in curve shape, which will itself indicate a significant shift in the drug release mechanism.

2.7. Measurement of matrix integrity

Comparative measurements of matrix susceptibility to erosion were made using an Erweka BP/USP Disintegration Tester (Copley Instruments, Nottingham, UK) without discs. Tests were conducted in water, pH 1.2 and 7.5 dissolution media at 37 ± 1 °C. Observations of matrix integrity were made visually at 5 min intervals, up to a maximum of 30 min. The end point was taken as the next 5 min interval after the matrix had disintegrated sufficiently to pass through the mesh.

2.8. Confocal laser microscopy imaging of the nascent gel layer

Confocal microscopy imaging of early gel layer formation was undertaken using the method of Bajwa et al. (2006). 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 were viewed from above, held between Perspex discs in a Fixed Observational Geometry (FOG) apparatus, whilst undergoing hydration in degassed 0.05% (w/v) aqueous Congo red, a fluorophore which provides a marker for hydrated HPMC (Bajwa et al., 2006). Images of radial gel layer growth were obtained at intervals up to 10 min after the initial hydration. The average (mean $n = 10$) thickness of gel, measured from the inner to the outer 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. Measurement of HPMC single particle swelling

A small amount of HPMC powder was placed on a microscope slide, distributed to allow visualisation of individual particles and covered with a cover slip and placed on the stage of a fluorescence microscope (Nikon Instruments, Japan). The swelling of the particles were monitored following the addition 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 held on a heating/cooling plate (Linkam MS100, Wishart Scientific, Ballyclare, UK) to maintain the temperature of the experiment at T ±1 °C. The 2D 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 as a measure of the increase in particle swelling with time.

2.10. Determination of gel layer pH using a pH microelectrode

The pH microenvironment within the gel layer of hydrating HPMC matrices was measured using a 100 μm diameter Beetrode pH microelectrode (NMPH1, World Precision Instruments, Inc., Sarasota, Florida, USA) and a separate 450 μm diameter reference electrode (DriRef450, World Precision Instruments, Inc., Sarasota, Florida, USA) attached to a pH meter (H18424, Hanna Instruments, Inc., Woonsocket, Rhode Island, USA). The pH microelectrode was maintained in Maxima grade 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. 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 avoided 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, it is recognised that the technique is invasive and that some disruption to the emerging gel layer will occur in the vicinity of the probe. This will be especially true in the very early phases of gel formation, when the gel is thin and gel growth is rapid, and for this reason pH measurements made in this way are not shown before 10 min.

3. Results and discussion

3.1. The pH solubility profile of felbinac

Fig. 1 shows how felbinac exhibits the pH-dependent solubility profile typical of a weak acid drug. The potential consequences for GI bioavailability and matrix drug release kinetics are profound. The poor drug solubility (~0.01 to 0.05 g l^{-1}) at pH 1–3 will result in erosion-dominated release behaviour typical of an HPMC matrix that contains a low solubility drug, at least when gastric conditions are highly acidic. At neutral pH, drug solubility is at least two orders of magnitude greater, and we can anticipate a change in drug release kinetics that indicate a switch to the more diffusion-controlled kinetics typical for water soluble drugs (Siepmann and Peppas, 2001).

3.2. The effect of THAM and sodium citrate on the sol:gel transition temperatures of 1% (w/w) HPMC solutions

Fig. 2 shows that THAM has much less influence on the sol:gel phase transition temperature of 1% HPMC solutions than sodium

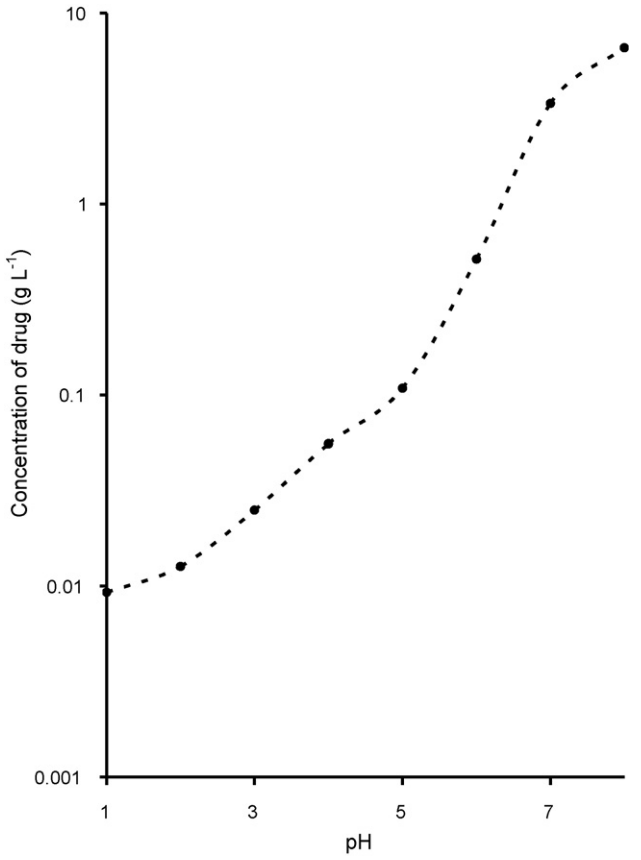

Fig. 1. The pH solubility profile of felbinac. Solubility determined at 37 ± 1 °C. Mean values (n = 3) ± 1 SD.

citrate. In the presence of 115 mM THAM (the maximum concentration investigated) mean cloud point values were shifted by +1.5 °C in HPMC 2208 solutions and −0.7 °C in HPMC 2910 solutions. These changes were statistically indistinguishable from HPMC solutions containing no buffer (paired t-test, $p > 0.05$). At the same concentration, sodium citrate induced significant depression of cloud point:

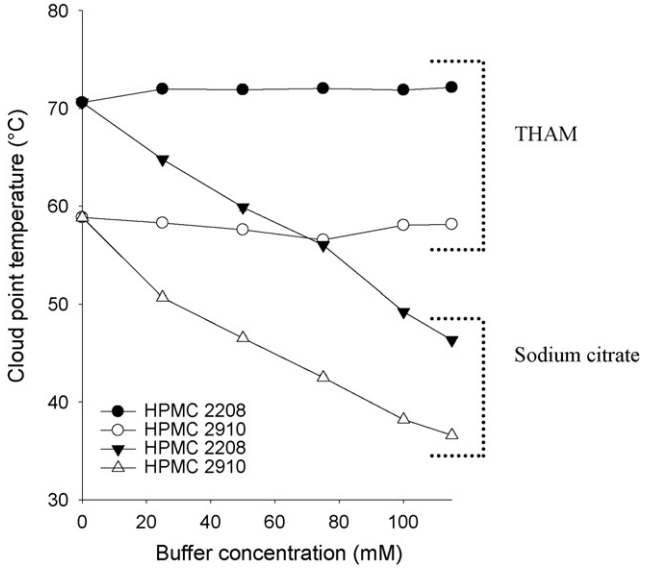

Fig. 2. The effect of THAM (circles) and sodium citrate (triangles) on the cloud point temperature of 1% (w/w) HPMC 2910 (open figures) and HPMC 2208 (closed figures) solutions. Mean values (n = 3) ± 1 SD.

−16 °C in HPMC 2208 solutions and −22 °C in HPMC 2910 solutions. The lowering of cloud point with increasing sodium citrate concentration is a typical of the ionic 'salting out' that commonly occurs when multivalent ions are added to HPMC solutions. With HPMC, this occurs through ionic disruption of the polymer water sheath and hydrophobic association of polymer chains, and the rank order of these effects, reflects the differences in methoxyl substitution in 2208 and 2910 grades (Chen et al., 2007; Zhang and Cremer, 2006; Richardson et al., 2006). Fig. 2 clearly shows THAM has much less propensity to 'salt out' HPMC, and suggests this buffer will have better compatibility than sodium citrate in HPMC matrix formulations. Felbinac, the model drug, also had no significant effect on the cloud point of 1% (w/w) HPMC 2910 and HPMC 2208 solutions.

3.3. The effect of THAM on drug release from HPMC matrices containing felbinac

Fig. 3 shows felbinac release as a function of buffer content for HPMC 2910 matrices in pH 1.2 and 7.5 media. Matrices containing THAM are represented by closed symbols and matrices containing sodium citrate are represented by open symbols. Drug release in unbuffered matrices was considerably slower at pH 1.2 than at pH 7.5, reflecting the difference in drug solubility in these media. The incorporation of THAM (10%, 20%, 50%, w/w) resulted in a signifi-

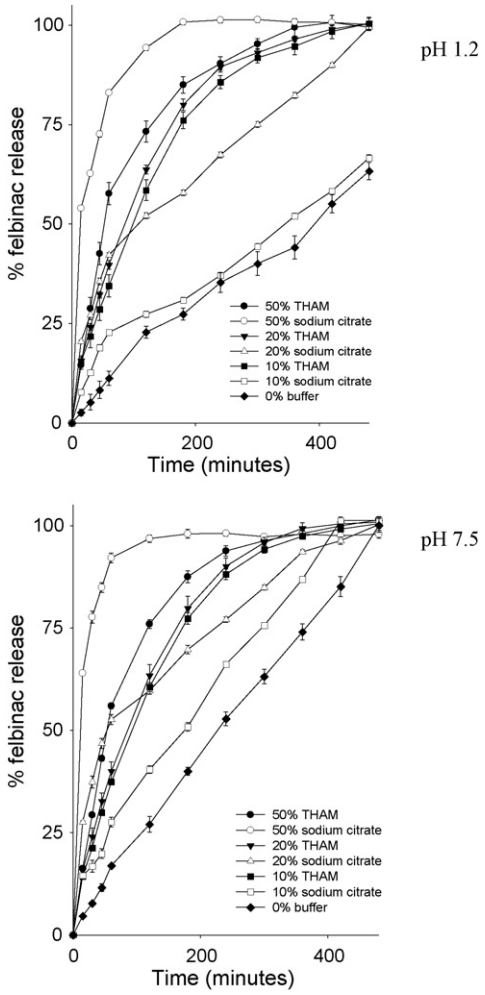

Fig. 3. Release of felbinac from HPMC 2910 matrices as a function of THAM or sodium citrate content. USP apparatus 1, 100 rpm 37 ± 1 °C. 900 ml dissolution medium at (A) pH 1.2 and (B) pH 7.5. Closed symbols represent matrices containing THAM and open symbols represent matrices containing sodium citrate. Mean (n = 5) ± SD.

Table 2
Power law analysis of release profiles for (a) HPMC 2910 and (b) HPMC 2208 matrices as function of THAM content.

Buffer content in tablet (w/w)	pH 1.2			pH 7.5		
	n	k	r^2	n	k	r^2
(a)						
0% THAM	0.885	0.0072	0.992	0.885	0.0108	0.9981
10% THAM	0.5768	0.310	0.983	0.5884	0.2839	0.9768
20% THAM	0.5518	0.4099	0.974	0.5519	0.3984	0.9755
50% THAM	0.5109	0.6485	0.9761	0.4954	0.7594	0.9171
(b)						
0% THAM	0.9796	0.00307	0.9814	0.8247	0.00202	0.9937
10% THAM	0.6049	0.23207	0.9887	0.6275	0.1832	0.9859
20% THAM	0.5631	0.367	0.9759	0.552	0.4074	0.9787
50% THAM	0.4363	1.329	0.9675	0.4496	1.166	0.9667

USP disintegration test without discs at 37 ± 1 °C. Mean values (n = 6).

cant shift in drug release kinetics in both media. Drug release was accelerated and there was a significant change in the curvature of the dissolution profile. Fitted to the power law, these dissolution curves showed a change in the release exponent n from 0.9 in the unbuffered, to 0.55 in the THAM-buffered matrix (Table 2). This is consistent with the drug becoming more freely soluble in the gel layer of the matrix and indicates a significant shift from erosion-dominated to diffusion-dominated drug release (Siepmann and Peppas, 2001).

Intriguingly, the incorporation of THAM accelerated drug release and changed the exponent in pH 1.2 and in pH 7.5 media. At pH 1.2, accelerated release would be an obvious consequence of effective internal buffering, but the same changes observed at pH 7.5 require a further explanation. At pH 7.5, felbinac solubility is almost 10 g l^{-1} (Fig. 1). Correspondingly, the unbuffered matrix exhibits faster release, but retains the linear dissolution profile (n = 0.98) typical of a drug of low solubility. A pragmatic explanation is that felbinac, a weak acid, acidifies the gel layer and as a result drug concentration gradients within the gel consequently limit the rate of drug dissolution. The ingressing pH 7.5 medium appears to have insufficient buffering capacity to overcome this, but the inclusion of THAM provides sufficient concentrations of buffer within the gel layer to allow significant drug dissolution, and a faster, more diffusion-based, release profile results. Therefore, the inclusion of THAM accelerates felbinac release even in dissolution media in which the drug is ostensibly soluble.

Fig. 3 shows how buffering HPMC 2910 matrices with sodium citrate or THAM resulted in faster drug release. There were marked differences between the two buffers over the range of buffer contents examined (10–50%). Drug release profiles of THAM-buffered matrices were more closely grouped than those of the sodium citrate matrices. THAM-buffered profiles at pH 1.2 and 7.5 were virtually superimposable (up to 85% drug release) at all levels of buffer incorporation, showing that pH-independent release had been achieved, and in contrast to sodium citrate, a buffer content of 10% THAM was effective at pH 1.2. There was also a clear difference in the shape of the release profiles. Sodium citrate matrices showed accelerated release, followed by an inflexion and slower release thereafter. Previous work (Pygall et al., 2009) has shown that this inflexion is associated with the short duration of pH control. THAM matrices however, exhibited the continuous diffusion-based profile typical of a soluble drug, suggesting that the alkalising effect allows dissolution of felbinac to be maintained for a longer period in the gel layer. Finally, there appears to be no evidence of release control failure with THAM. Even at the extreme of 50% buffer content, THAM-buffered matrices maintained an extended release profile. In contrast, sodium citrate matrices exhibited immediate release. This has been attributed to the disruptive influence of multivalent citrate ions on HPMC swelling, gel layer formation and the diffusion barrier properties of the gel layer (Pygall et al., 2009). This explanation is further supported by the erosion results (Table 3) which show how THAM-buffered matrices maintained their integrity even at the highest levels of buffer incorporation (50%, w/w), whilst the same matrices buffered with 10% sodium citrate failed within 30 min. In control experiments, all matrices exhibited the same characteristics in water as in the dissolution media, demonstrating that this effect was not a consequence of pH or the components of media.

Overall, these results suggest that THAM-buffered matrices do not suffer the interference with gel layer formation previously described in sodium citrate buffered matrices (Pygall et al., 2009). This supports the hypothesis that THAM, a monovalent ion with little effect on the HPMC sol:gel transition, does not have the effect on HPMC swelling and the development of an effective diffusion barrier, as trivalent ions such as citrate.

Table 3
Observations of matrix integrity during disintegration testing of (a) HPMC 2910 and (b) HPMC 2208 matrices buffered with THAM or sodium citrate.

Buffer type	Buffer content in tablet (w/w)	Disintegration time (min)			Matrix behaviour
		0.1 M	pH 7.5	Water	
(a)					
None	0	>30	>30	>30	Swelled and maintained integrity
THAM	50%	>30	>30	>30	Swelled and maintained integrity
Sodium citrate	10%	25	25	25	Disintegrated
Sodium citrate	20%	20	20	20	Disintegrated
Sodium citrate	50%	15	10	10	Disintegrated
(b)					
None	0	>30	>30	>30	Swelled and maintained integrity
THAM	50%	>30	>30	>30	Swelled and maintained integrity
Sodium citrate	10%	>30	>30	>30	Swelled and maintained integrity
Sodium citrate	20%	>30	>30	>30	Showed attrition and decreased diameter
Sodium citrate	50%	20	20	20	Disintegrated

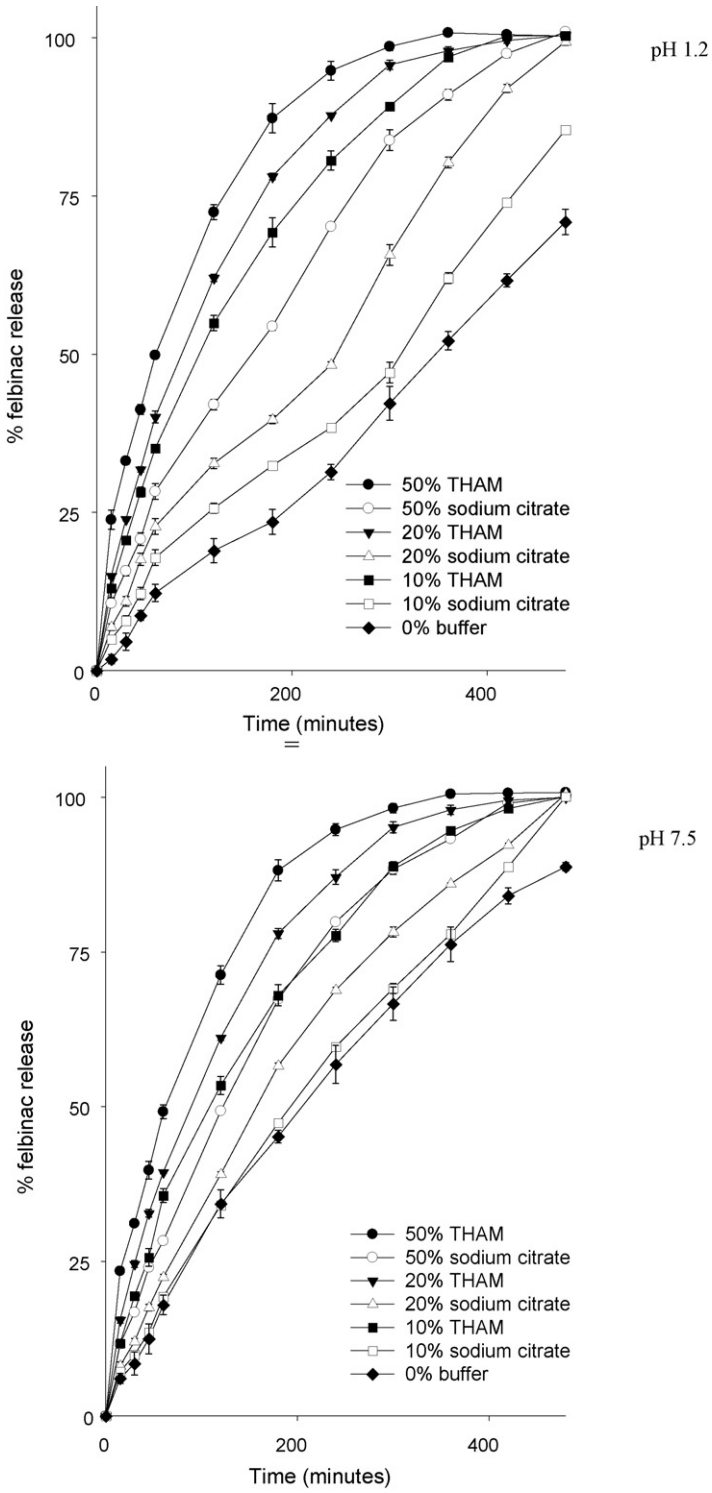

Fig. 4. Release of felbinac from HPMC 2208 matrices as a function of THAM or sodium citrate content. USP apparatus 1, 100 rpm 37 ± 1 °C. 900 ml dissolution medium at (A) pH 1.2 and (B) pH 7.5. Closed symbols represent matrices containing THAM and open symbols represent matrices containing sodium citrate. Mean (n = 5) ± SD.

Fig. 4a and b shows the corresponding drug release profiles for matrices containing HPMC 2208. Once again matrices containing THAM exhibited closely similar release kinetics at pH 1.2 and 7.5 (the curves were superimposable at 20% and 50% THAM content) whereas under the same conditions, matrices containing sodium citrate showed a clear shift in response to the pH of the medium. HPMC 2208 matrices were more robust in the erosion test than HPMC 2910 matrices (Table 3b) and this reflects the lower methoxyl substitution of the 2208 grade which renders it less susceptible to the effects of salts. Even so, 20% citrate matrices exhibited significant erosion and, at 50% buffer content, citrate buffered matrices disintegrated whereas their THAM-buffered counterparts did not.

3.4. The effect of THAM on early gel layer development

Fig. 5a shows typical confocal microscopy images of the early stages of gel layer development in HPMC 2910 matrices. Fig. 5b shows the kinetics of gel growth with respect to THAM content cal-

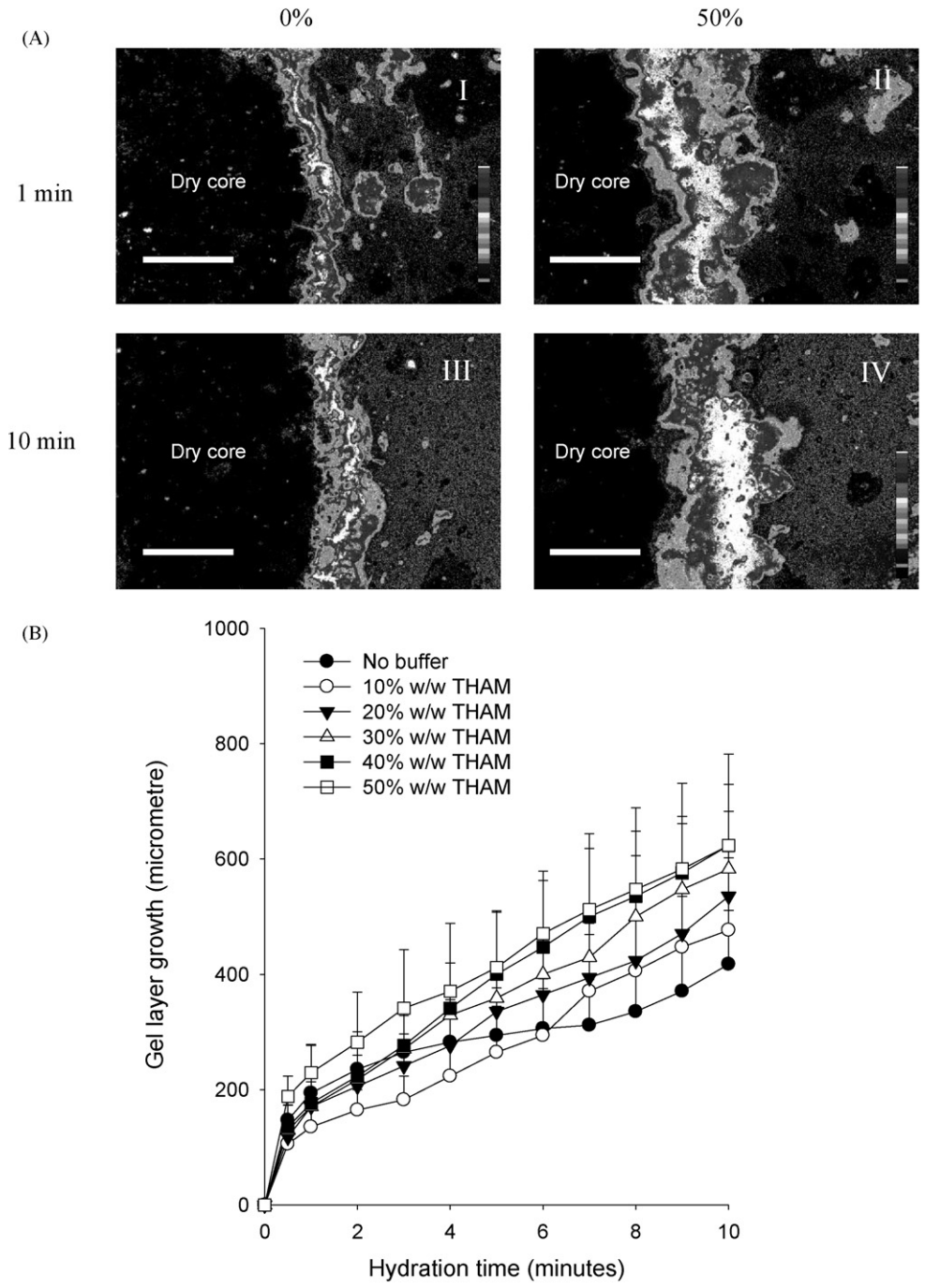

Fig. 5. Confocal microscopy images of early gel layer growth in HPMC 2910 matrices as a function of THAM content (A) Example images of matrices containing (I) 0% THAM after 1 min, (II) 0% THAM after 10 min, (III) 50% THAM after 1 min and (IV) 50% THAM after 10 min. Scale bar = 500 μm. (B) Gel thickness as a function of hydration time calculated from the entire image sequence. Mean values ($n = 3$) ± SD. Experiments conducted at 37 ± 1 °C.

culated from the confocal images. It shows how gel layer growth in the initial 30–120 s was critical in determining the eventual thickness of this early gel layer and resulted in a clear rank-order correlation between gel thickness and THAM content. After the initial period, the kinetics of gel growth was similar at all buffer contents. These early differences in gel growth show how increasing amounts of THAM cause expansion of the gel or otherwise enhance liquid penetration during the earliest stages of gel formation. The most likely explanation is an osmotic effect that promotes liquid penetration and a similar concentration-related expansion of the early gel layer has been reported previously with sodium citrate (Pygall et al., 2009). Fig. 6 compares these buffers in the same formulations, and it can be seen that gel layer expansion in sodium citrate matrices is almost double those of THAM, independent of the grade of HPMC in the matrix. After 10 min, in HPMC 2910 matrices the mean gel thickness was ~420 μm (unbuffered), ~620 μm (THAM) and ~990 μm (sodium citrate). In HPMC 2208 matrices the corresponding values were ~465, ~620 and ~865 μm. The differences between buffers might be from the differences in the osmotic potential between THAM and sodium citrate, or it could result from the suppression of swelling and coalescence of HPMC particles in forming the early gel layer by sodium citrate reported previously (Pygall et al., 2009). Evidence for disruption of gel layer integrity was provided on removal of the hydrated matrices from the sam-

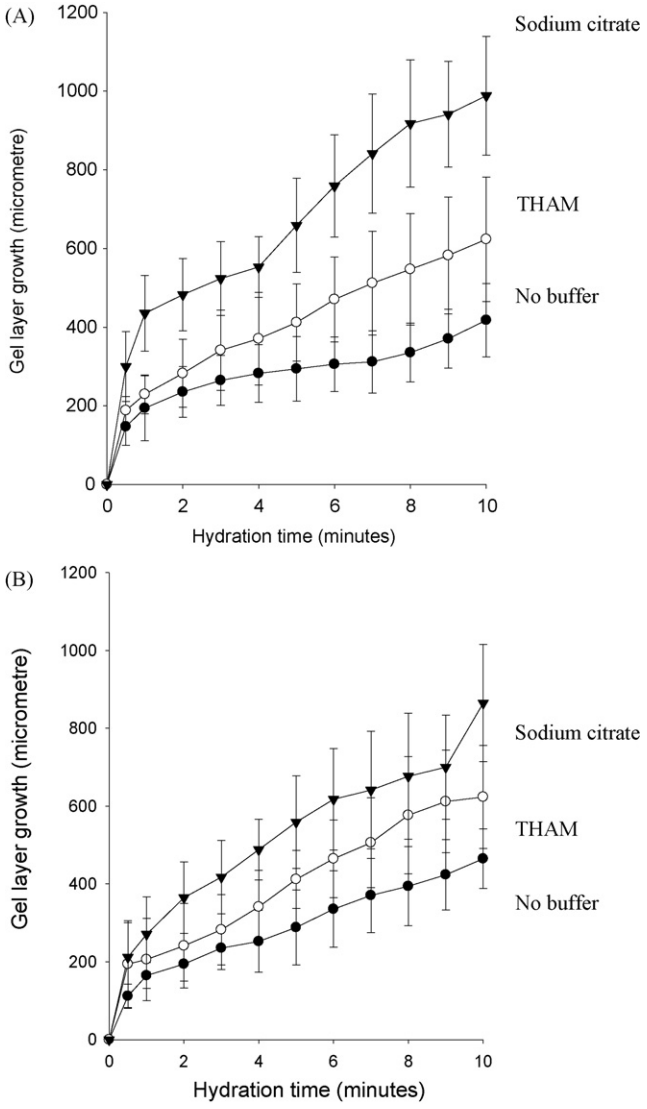

Fig. 6. A comparison of early gel layer growth in (A) HPMC 2910 and (B) HPMC 2208 matrices containing 50% THAM, 50% sodium citrate or no buffer. Mean values ($n = 3$) ± SD.

ple cell: THAM matrices remained intact whereas sodium citrate matrices were fragile and disintegrated.

3.5. The effects of buffers on the HPMC particle swelling

The effect of these buffers on HPMC swelling during the earliest phase of gel formation is tested by the single particle experiments shown in Fig. 7. It shows how the swelling of HPMC particles was almost unaffected by the presence of THAM, but was suppressed in sodium citrate solutions. Buffer concentrations within the nascent gel layer are unknown, and would be extremely difficult to determine during the first minute of swelling. However we might expect transient saturation concentrations in the microenvironment surrounding a dissolving buffer particle, and therefore the 0.5 and 0.25 M concentrations tested are unlikely to be unrealistic. The result suggests that the presence of THAM will allow normal particle swelling and coalescence allow formation of a coherent and effective gel diffusion barrier at the matrix surface. In contrast, sodium citrate may inhibit this process and allow further water ingress into the matrix.

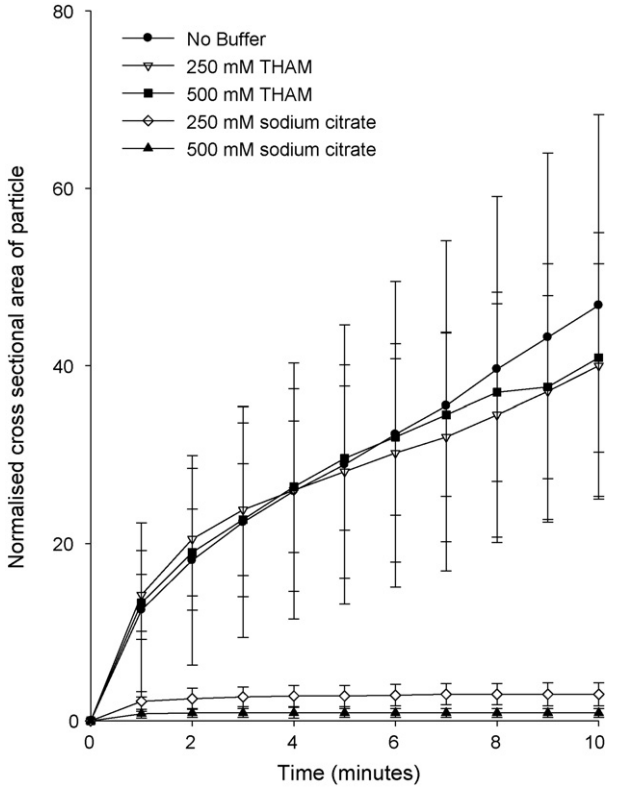

Fig. 7. A comparison of HPMC 2910 particle swelling in solutions of THAM and sodium citrate. 37 ± 1 °C. Mean values ($n = 10$) ± 1 SEM.

3.6. pH and buffering longevity in the gel layer

Fig. 8 shows the measured internal gel layer pH in HPMC 2910 matrices hydrated at pH 1.2, with respect to the type and amount of incorporated buffer. The horizontal line provides an arbitrary reference point at pH 5. This pH is above the published pK_a value of 4.3 for felbinac (Hadgraft et al., 2000) and which (Fig. 1) shows will provide an approximately 10-fold increase in drug solubility, in comparison with the hydrating medium at pH 1.2. Fig. 8 shows how both buffers afforded a rapid rise in gel layer pH, reaching a maximum at 20–30 min and thereafter, the pH progressively declined. This suggests that these freely soluble buffers rapidly dissolve, but then undergo slow diffusional loss from the dosage form, with a gradual loss of pH control. Similar pH-modifying behaviour has been shown in other extended release systems with highly soluble organic acid buffers (Cope et al., 2002). The maximum value of pH 9–10 achieved in THAM-buffered matrices contrasts markedly with the maximum pH of 6.5 measured in sodium citrate matrices. It reflects published measurements of the pH of solutions: a 5% THAM solution is reported to be pH 10.0–11.5 whereas 5% sodium citrate should be no more than pH 8.6 (Martindale, 2002) and the maxima can be partially explained through the characteristics of the buffers. Firstly, the solution pH and maximum pH observed differences in buffer pK_a (THAM $pK_a = 8.3$, sodium citrate $pK_a = 6.4$). Sodium citrate will also provide significant buffering around $pK_a = 3.15$ and $pK_a = 4.78$, which may explain the flatter peak shape observed. Secondly, on a gram molecular basis THAM ($C_4H_{11}NO_3 = 121.1$) is more potent for a given percentage weight than sodium citrate ($C_6H_5Na_3O_7 \cdot 2H_2O = 294.1$) although the actual concentrations will depend on the rate of solution versus the rate of loss. Thirdly, high concentrations of multivalent sodium citrate ions may damage gel layer diffusion barrier properties (Pygall et al., 2009) and therefore this buffer may accelerate its own loss from

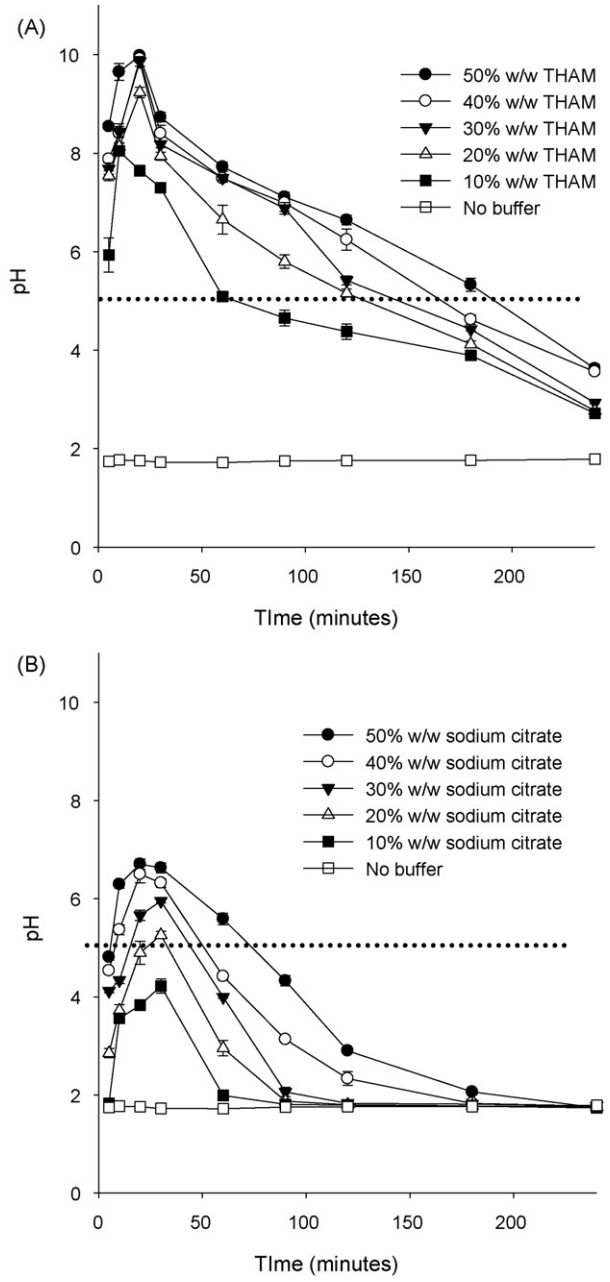

Fig. 8. Gel layer pH as a function of buffer content and hydration time in HPMC 2910 matrices. Matrices containing (A) THAM or (B) sodium citrate. Hydration medium 900 ml degassed 0.1 M HCl. 37 ± 1 °C. Mean values ($n = 3$) ± SD. Dotted line represents pH 5.0.

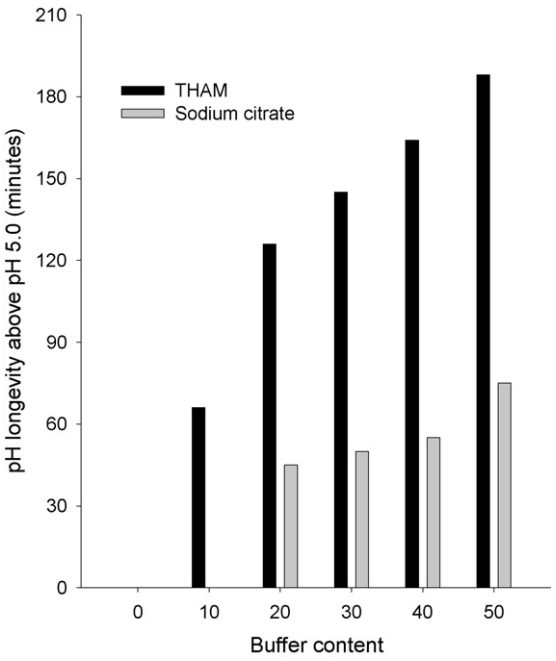

Fig. 9. The duration of gel layer microenvironmental above pH 5.0 with respect to THAM and sodium citrate content.

the system. This overall analysis is undoubtedly simplistic, and it makes various assumptions about the equivalence of solubility and concentration gradients, but it perhaps indicates the main drivers of pH change within the gel layer.

The longevity of pH control is a critical factor in determining how long drug solubility and diffusional release from the dosage form can be maintained. A previous study has shown how a drop in gel layer pH, was associated with the appearance of precipitated drug in the gel layer and an inflexion in the drug release profile. Modelling of the release profiles suggested a change from diffusion-dominated to erosion-dominated drug release kinetics, providing further evidence for a transition from soluble to a poorly soluble drug state (Pygall et al., 2009). Fig. 8 shows that, in THAM matrices, the pH declines at rate dependent on buffer loading, whereas with sodium citrate the longevity of pH control appears to be more a function of the maximum pH achieved. Sodium citrate matrices also undergo a faster rate of pH decline. We can postulate this occurs as a result of accelerated erosion of these matrices by the mechanism multivalent ion interference with gel layer formation as described previously (Pygall et al., 2009).

Fig. 9 summarises the time period that gel layer pH is maintained above pH 5. It illustrates that THAM provided over twice the duration of internal buffering obtained from the same amount of sodium citrate. This marked difference aids our understanding of matrix drug release characteristics, even though pH and dissolution tests were undertaken in different dynamic conditions. Fig. 3(a) shows that THAM matrices containing 10% and 20% buffer exhibit a curved profile typical for a soluble drug undergoing diffusional release. In contrast, their sodium citrate counterparts after a short period of acceleration, exhibit a change in release kinetics, marking the time when internal buffering has been lost.

4. Conclusions

The purpose of this work was to compare THAM and sodium citrate as buffering systems for the weak acid felbinac when formulated in an HPMC hydrophilic matrix. The inclusion of THAM and sodium citrate in HPMC matrices both improved the release of felbinac in alkaline and acidic media. Drug release was sufficiently enhanced to the extent that it was independent of pH, when THAM was at least 20% (w/w). Drug release occurred without the matrix attrition observed previously when sodium citrate was used as a buffering system. In comparison with sodium citrate, THAM was shown to maintain pH elevation for greater periods and was found to have a minimal effect on HPMC particle swelling and gel layer formation.

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