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Designing HPMC matrices with improved resistance to dissolved sugar

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ABSTRACT

High concentrations of dissolved sugars can accelerate *in vitro* drug release in certain hydroxypropyl methylcellulose (HPMC) matrices (Williams et al., 2009). This study investigated the potential for common formulation variables to modulate sucrose sensitivity, and explored if more resistant formulations could be designed. In a model matrix containing 30% HPMC (Methocel™ K4M), the inclusion of sugar as a tablet diluent was a key factor. Lactose:microcrystalline cellulose mixtures, dextrose and D-xylose all produced highly swollen, erodible matrices in 0.7 M sucrose (37 °C), which collapsed and rapidly released remaining drug after 1–4 h. This suggests internal and external sugars combine to disrupt the diffusion barrier properties of the gel layer. In contrast, matrices containing microcrystalline cellulose as the sole diluent provided extended release for 10 h. Small particle size (<63 μm) and high or low viscosity HPMC (Methocel™ K100M or K100LV) also improved sugar resistance. Knowledge of these variables allowed a significantly more resistant HPMC matrix to be designed which provided extended release for >16 h in 0.9 M sucrose. By judicious selection of excipient properties, the tolerance of HPMC matrices to high sucrose environments can be significantly improved.

1. Introduction

Previous studies have demonstrated how drug release from a hydroxypropyl methylcellulose (HPMC) matrix formulation can be accelerated by high concentrations of dissolved sugars in the dissolution medium. A threshold molar concentration of sugar (S_{CRIT}) was identified below which there was normal extended drug release behaviour, but above which the matrices exhibited only a short period of extended release, before disintegrating and releasing their remaining drug content in a rapid burst. Imaging studies suggested this behaviour arose from sugar-induced suppression of polymer hydration and a subsequent loss of gel layer diffusion-barrier function (Williams et al., 2009). The threshold concentration, S_{CRIT} varied between sugars, and correlated with their ability to disrupt water structure and to suppress the polymer sol:gel transition temperature in a manner analogous to the Hofmeister effects seen with inorganic salts (Alderman, 1984; Liu et al., 2008; Pygall et al., 2009). The concentrations of sugar required to achieve S_{CRIT} (0.5 M–1.15 M) were commonly higher than concentrations found in foods, and were considered unlikely to be encountered in the fed stomach. However, more recently it has become clear that the presence of food salts such as sodium chloride and sodium citrate can significantly lower the threshold concentration of sucrose required to accelerate release (Williams et al., 2010). It therefore seems appropriate that new HPMC matrix formulations should be designed to possess a high level of resistance to a sugar-laden environment in order to avoid the potential for fed state effects,

These effects are dependent on polymer substitution. For example, Levy and Schwarz (1958) showed that USP HPMC type 2208 (Methocel™ K) was generally less susceptible to "salting out" by sucrose and sorbitol than HPMC 2910 (Methocel™ K) grades. This is a result of the lower methoxyl content and higher sol:gel transition temperature of the 2208 grades (Alderman, 1984). Within a given substitution grade however, the key question is whether S_{CRIT} reflects an unchangeable intrinsic characteristic of the polymer carrier, or if it can be assuaged by manipulating matrix formulation variables. If S_{CRIT} depends on matrix properties, well-known formulation variables that influence HPMC matrix behaviour, might provide strategies to control sugar effects. The principal (non-drug) variables that influence drug release from HPMC matrices have been variously identified as, polymer content, drug:polymer ratio (Velasco et al., 1999), diluent type and solubility (Alderman, 1984; Furlanetto et al., 2006), polymer particle size (Sung et al., 1996), polymer substitution and viscosity grade (Mitchell et al.,

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

Ingredients (%, w/w)	Pure lactose	Lactose: MCC ratio			Pure MCC	Other sugars
		2:1	1:1	1:2		
Caffeine anhydrous	10.0	10.0	10.0	10.0	10.0	10.0
HPMC	30.0	30.0	30.0	30.0	30.0	30.0
Lactose	59.0	39.3	29.5	19.7	–	–
Microcrystalline cellulose	–	19.7	29.5	39.3	59.0	–
Dextrose, xylose or lactose	–	–	–	–	–	59.0
Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0

1993; Mitchell and Balwinski, 2008) and on occasion (especially in problematic formulations) matrix compression pressure (Rekhi et al., 1999). The hydration media used in these studies are typically water or simulated gastric fluid, and there is little literature in which formulation variables have been investigated in more challenging hydration environments.

This present study investigates how these factors influence the performance of HPMC matrices in a sugar-rich environment with a focus on the key variables of diluent solubility, HPMC particle size and polymer viscosity. A realistic, model formulation containing 30%, w/w polymer and a drug:polymer ratio of 3:1 HPMC:caffeine) is used to allow comparison with previous studies. USP HPMC type 2208 grades (Methocel K) are used throughout, as previous studies have shown this substitution grade to be the least susceptible to dissolved solutes. The sugar is sucrose, the most common sugar in Western diets. From the investigations of how the variables affect the behaviour of the matrix in sucrose concentrations close to S_{CRIT} (0.7 M), we then explore if this understanding can be used to design a more sugar-resistant matrix.

2. Materials and methods

2.1. Materials

USP 2208 grades of hydroxypropyl methylcellulose (Methocel™ Premium CR) were used in this study: Methocel™ K100LV (22.4% methoxyl, 10.1% hydroxypropyl, batch #O121012N21), Methocel™ K4M (23.2% methoxyl, 8.2% hydroxypropyl, batch #UH22012N11) and Methocel™ K100M (22.9% methoxyl, 10.5% hydroxypropyl batch #UG18012N11). All HPMC grades were kind gifts from Colorcon Ltd (Dartford, UK). Certificates of analyses showed their viscosities were 90 mPa s (K100LV), 4386 mPa s (K4M) and 82,404 mPa s (K100M) as 2% w/v solutions at 20 °C. Sucrose (analytical grade) was obtained from Fisher-Scientific (Leicestershire, UK), caffeine anhydrous, D-xylose, Congo red and magnesium stearate were from Sigma–Aldrich (Poole, Dorset, UK), dextrose (Meritab®) was from Tate & Lyle PLC (Aalst, Belgium) lactose Fast-flo NF was from Foremost Farms (Baraboo, USA) and microcrystalline cellulose (Avicel PH102) was from the FMC Corporation (Philadelphia, USA). Maxima HPLC grade water (USF Elga, Buckinghamshire, UK) with a minimum resistivity of 18.2 MΩ cm was used throughout the work.

2.2. HPMC fractionation

An accurately weighed 40 g portion of HPMC powder was size-fractionated on a sieve stack comprising 125 μm, 90 μm, and 63 μm aperture USP stainless-steel sieves (Endicotts, London, UK). The sieves were agitated for 30 min using a sieve shaker (Copley Scientific, Nottingham, UK) and weighed at 10 min intervals until there was a weight change of less than 1%. The sieve fractions were stored in amber glass bottles at room temperature prior to use.

2.3. Formulation design

The matrix composition used in previous studies (Williams et al., 2009, 2010) was used as a template: caffeine (10%, w/w), HPMC K4M 63–90 μm (30%, w/w), diluent (59%, w/w) and magnesium stearate (1%, w/w). The same tablet weight and fixed content of drug, polymer and lubricant was maintained throughout all the formulations used in this work. In the first experiments, the diluent composition was varied, as shown in Table 1. The second experiments used a fixed diluent ratio of 2:1 lactose:MCC, but varied the HPMC particle size using the <63 μm, 63–90 μm, 90–125 μm, >125 μm sieve fractions of HPMC K4M in comparison with the unfractionated material. A third set of experiments used the same 2:1 diluent ratio, but compared three viscosity grades of HPMC: Methocel™ K100LV, K4M and K100M. The 63–90 μm sieve fraction and the unfractionated form of these polymers were investigated.

2.4. Manufacture of HPMC matrices

Matrices were manufactured by direct compression of powder blends as described previously (Williams et al., 2009). 8 mm diameter, round flat-faced tablets (250 ± 5 mg) were prepared at ~240 MPa using a Manesty F3 instrumented tablet press (Manesty, Liverpool, UK).

2.5. Determination of drug release kinetics

Matrix drug release was studied in 900 ml deaerated medium at 37 ± 0.5 °C using USP apparatus 1 (Dissolutest, Prolabo, France) at a basket rotation speed of 100 rpm. Sampling was by a closed-loop Agilent automated dissolution system (Agilent 8453, Agilent Technologies, Stockport, UK) with caffeine quantification at 273 nm in 10 mm quartz flow-through cells. The time for 80% cumulative drug release (T_{80}%) was estimated from the dissolution profiles by linear interpolation between the two nearest time points.

When dissolution profiles showing extended release for >4 h were fitted, up to 80% cumulative release, to the modified power law ($M_t/M_\infty = k(t-\mathrm{l})^n$) (Ford et al., 1987), it was found the that the release exponent n, was always in the range 0.45–0.55. This suggested that all formulations released caffeine via predominantly a diffusion-based release mechanism, and provides evidence that the there was no change in release mechanism or drug solubility, as a result of formulation or dissolution media changes.

2.6. Confocal microscopy of nascent gel layer formation

Gel layer formation was examined by the method of Bajwa et al. (2006). Matrices were securely held in a fixed observational geometry holder (FOG) between two Perspex® discs, treated with Sigmacote® (Sigma–Aldrich, Poole, Dorset, UK) to make the surfaces water-repellent. The FOG was immersed in deaereated sucrose solutions containing Congo red 0.008%, w/v previously equilibrated to 37 ± 1 °C, and images of radial gel layer formation captured at Ex 488 nm/Em > 510 nm, using a Bio-Rad MRC-600 con-

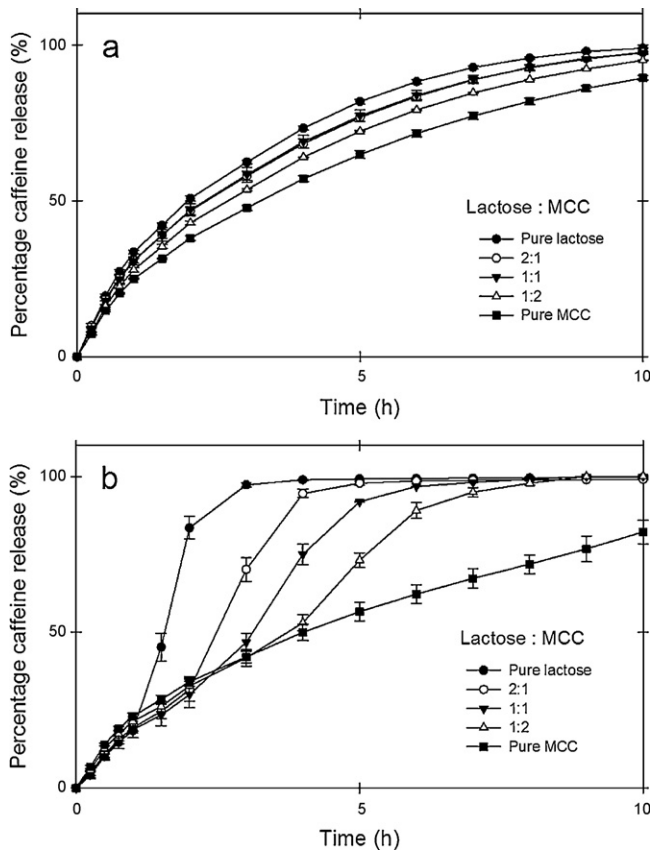

Fig. 1. Release of caffeine in water and sucrose as a function of diluent composition (lactose:MCC ratio). Dissolution medium (a) water (b) 0.7 M sucrose. All matrices contained 59%, w/w of diluent, with the legend indicating the weight ratio of lactose:MCC. USP apparatus 1, 100 rpm, 900 ml, 37 ± 0.5 °C. Mean (n = 3), ±1s.d.

focal laser scanning microscope (Hemel Hempstead, UK) equipped with a 15 mW Krypton Argon laser, a Nikon Optiphot upright microscope and a plan 4×/0.13NA air objective. The black level, aperture settings and gain levels on the confocal microscope were optimised to achieve images at maximum resolution and these settings remained unaltered for all the confocal studies undertaken. Images were captured every 60 s for 15 min and processed using Image Pro Plus v6.2 software (Media Cybernetics, USA).

2.7. Scanning electron microscopy imaging of HPMC particle morphology

A Jeol 6060LV variable pressure scanning electron microscope (Jeol Ltd., Welwyn Garden City, UK) was used to obtain images of particles of the unfractionated and 63–90 μm sieve fractions of Methocel™ K100LV, K4M and K100M. Polymer powder was mounted on carbon discs on aluminium stubs, sputter-coated with gold for 15 min using a Balzers SCD 030 gold sputter coater (Balzers Union Ltd., Liechtenstein) and images obtained under vacuum using an acceleration voltage of 12 kV.

3. Results and discussion

3.1. The effect of diluent selection on the sensitivity of the matrix to dissolved sucrose

3.1.1. Varying the lactose:MCC ratio in the diluent

Fig. 1 shows how changing the ratio of lactose and MCC affected drug release kinetics in water and 0.7 M sucrose. In water (Fig. 1a) all matrix compositions gave extended release for at least 10 h, with drug release rate becoming progressively slower as the proportion of MCC in the diluent was increased. The matrix containing only lactose as a diluent, had a T_{80}% value (the time for 80% drug release) of 4.8 h, whereas T_{80}% was extended to 7.6 h when the diluent was entirely MCC. This substantial change can be ascribed to differences in diluent solubility. Alderman (1984) has proposed that lactose accelerates drug release by increasing the gel layer porosity as it dissolves whereas MCC remains as inclusions in the gel layer (Pygall et al., 2008). Lactose may therefore facilitate drug transport through the gel layer, whereas MCC provides an additional barrier by increasing the tortuosity of the diffusion path.

Fig. 1b shows the same dissolution tests conducted in 0.7 M sucrose. This concentration of sucrose was the threshold concentration for accelerated release in a previous study using HPMC matrices of closely similar composition (Williams et al., 2009). The release profiles show that in this medium, all the matrices containing lactose exhibited short periods of extended release, followed by an acceleration in release after a few hours. The onset of acceleration appeared to be directly related to the content of lactose in the matrix: at a lactose:MCC ratio of 1:2, the extended release period was 4 h whereas without MCC, there was extended release for only 1 h. Some evidence of the mechanism underlying this behaviour was provided by the visual behaviour of the matrix in the dissolution basket. All matrices containing lactose extensively swelled, forming large, highly-swollen masses before disintegrating. This suggests extensive water penetration into the core and dissolution of soluble components with partial polymer swelling, leading to the collapse of matrix integrity on reaching a critical fragility. Increasing the lactose content of the diluent accelerated this effect. Previous work has shown that both lactose and sucrose can induce matrix failure when present as individual sugars in solution, and at 0.8 M sucrose (only a slightly higher concentration than used here), it prevents gel layer formation by almost entirely suppressing HPMC particle swelling (Williams et al., 2009). We therefore propose that the effect of sucrose is enhanced by the lactose diluent dissolving within the gel layer, and in combination, this provides a sufficient local concentration of sugars to suppress polymer swelling and reduce the effectiveness of the gel layer as a diffusion barrier. An alternative explanation is that increasing the ratio of MCC reduces the soluble content of the matrix, decreases the porosity of the gel layer and the osmotic pressure within the matrix, and thereby offers better protection against the effects of sucrose by reducing the rate of medium ingress into the matrix (Alderman, 1984; Tajarobi et al., 2009). Fig. 1b shows that all matrices with lactose in the diluents exhibited accelerated drug release, and only the matrices containing MCC as the sole diluent were capable of maintaining extended release for 10 h or more.

3.1.2. The use of alternative sugars as diluents

Different sugars exhibit different potencies in their ability to elicit accelerated release when present in a dissolution medium, and this effect has been related to their molecular ability to disrupt water structure and the associated polymer hydration sheath. This can be measured as a lowering of the sol:gel transition temperature of HPMC in aqueous solution (Williams et al., 2009). In a study which used the parameter Δ_{CPT} as a descriptor of a sugar's ability to lower the sol:gel transition temperature of HPMC lactose was found to be the most potent sugar (Δ_{CPT} = −25.23 °C mol^{-1} kg), dextrose was intermediate (−9.864 °C mol^{-1} kg) and xylose was the least potent sugar examined (−0.83 °C mol^{-1} kg) (Williams et al., 2009). Therefore, we can predict that when present as internal diluents, different sugars may vary in their ability to affect polymer hydration. Fig. 2 shows the dissolution of matrices containing these alternative sugar diluents in sucrose dissolution media. At lower sucrose concentrations, increasing the sucrose in the dissolution medium progressively retarded drug release rates in all the

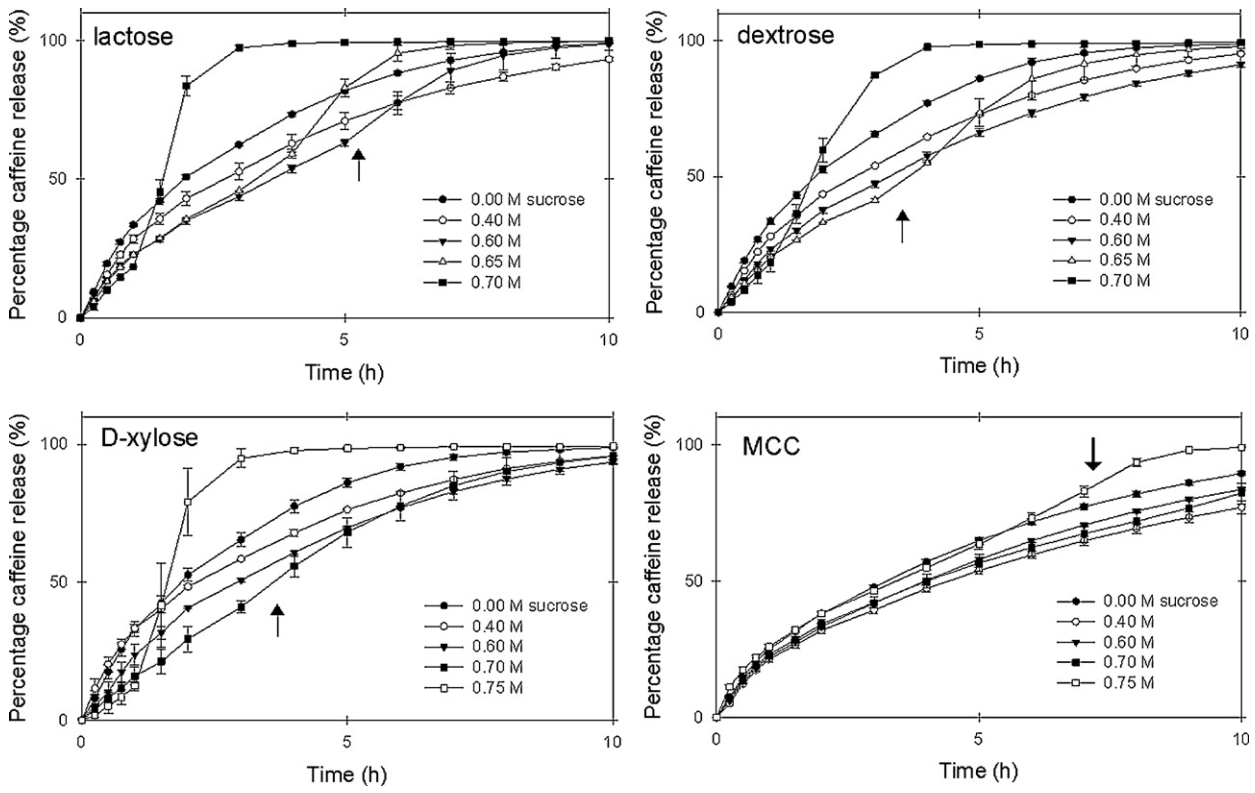

Fig. 2. Release of caffeine with respect to sucrose concentration in matrices containing alternative sugar diluents. The legend shows the sucrose concentration in the dissolution medium. Matrices contained 59%, w/w lactose, dextrose, D-xylose or MCC (for comparison). Arrows show inflexions in the release profiles that were the initial sign of matrix sensitivity to sucrose. USP apparatus 1, 100 rpm, 900 ml, 37 ± 0.5 °C. Mean (n = 3), ±1s.d.

matrix formulations tested. This phenomenon has been observed previously, and has been attributed to the formation of thicker gel layers and an increase in diffusional pathlength for dissolved drug molecules. (Williams et al., 2009). At high sucrose concentrations, there was evidence of a switch to accelerated drug release. The threshold concentration at which the profile changed from retarded to an accelerated drug release, was dependent on the type of sugar incorporated into the matrix (Fig. 2). Matrices containing lactose as a diluent required 0.6 M sucrose to accelerate release, matrices containing dextrose required 0.65 M and matrices containing D-xylose required 0.7 M. Whilst this rank order reflects their position in the lyophilic series (Williams et al., 2009) these differences are small in comparison to their marked influence on dilute solution sol:gel transition temperatures. Matrices incorporating MCC provided the best resistance to external sucrose solution: dissolution tests showing only a modest increase in release rate after ~8 h in 0.75 M sucrose (Fig. 2). Therefore, this diluent was chosen for use in the "more resistant" formulation described in Section 3.4.

3.2. The effect of HPMC particle size on matrix sensitivity to dissolved sucrose

Fig. 3a shows the effect of changing the particle size fraction of HPMC on drug release in water. Matrices containing the <63 μm and 63–90 μm sieve fractions gave extended release profiles comparable with unfractionated HPMC, whereas matrices containing the larger 90–125 μm and >125 μm particle size fractions exhibited faster release. This relationship has been reported before and has been variously explained through differences in (i) particle water uptake and solubility (Alderman, 1984), (ii) gel layer viscosity (Rajabi-Siahboomi, 1993), (iii) a slower rate of gel layer formation (Velasco et al., 1999) or (iv) differences in compressibility during tablet manufacture (Nokhodchi et al., 1996).

In 0.7 M sucrose, this pattern was changed, and in general the dissolution times were shorter (the maximum $T_{80\%}$ was ~8 h) (Fig. 3b). Matrices containing unfractionated HPMC displayed the typical pattern seen previously, with extended release for ~2 h, followed by a phase of accelerated release. A similar profile occurred with the 63–90 μm fraction, confirming the comparability of these two materials. Surprisingly, the larger polymer fractions (90–125 μm and >125 μm) provided extended release, but with a completely different shape of dissolution profile. There was an initial burst of accelerated release at the beginning of the dissolution test, followed by an extended release phase. This suggests that the gel layer barrier was at first, slow to develop, but once it had formed it provided a good barrier properties to drug release. The mechanisms underlying this change in behaviour are not obvious, but it may reflect the reduced rate of particle swelling in sugar, which may reduce the rate of surface disintegration.

Matrices containing the smallest particle size fraction (<63 μm) exhibited the longest extended release, and this particle size fraction of HPMC was selected for inclusion in the "more resistant" formulation in Section 3.4. A similar effect has been reported by Johnson et al. (1993), who observed that better extended release was achieved using a fine particle size of hydroxypropyl cellulose (HPC) in matrices releasing in high salt media.

3.3. The effect of HPMC viscosity grade on matrix sensitivity to dissolved sucrose

3.3.1. Drug release

Three different viscosity grades of HPMC were used in these studies: Methocel™ K100LV, K4M and K100M. Table 2 shows there were differences in particle size distribution between these grades, and therefore to allow a comparison free from particle size effects, a 63–90 μm sieve fraction was used in this study. Fig. 4 shows

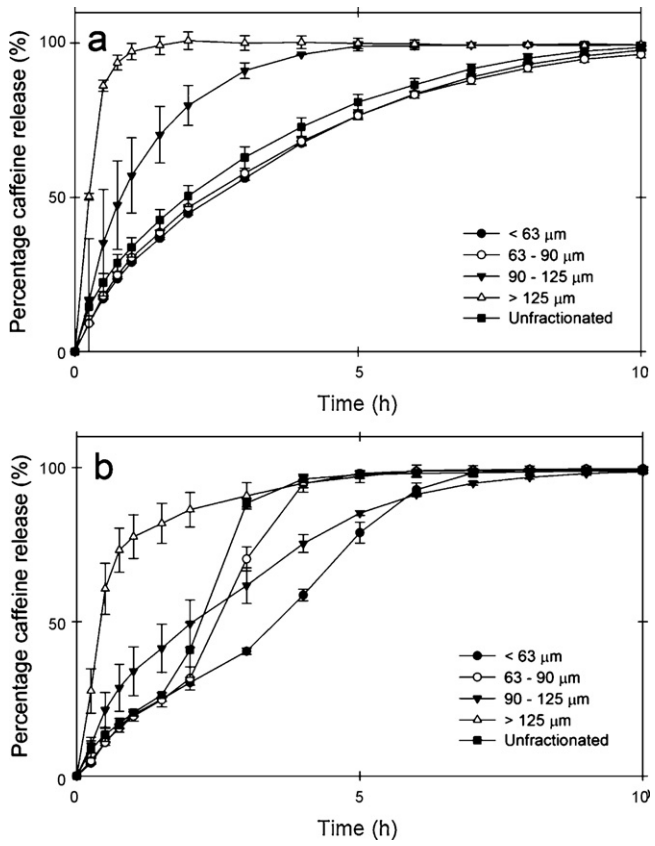

Fig. 3. Release of caffeine in water and sucrose with respect to polymer particle size. Dissolution medium (a) water (b) 0.7 M sucrose. Legend indicates the sieve fraction of HPMC K4M in the matrix. USP apparatus 1, 100 rpm, 900 ml, 37 ± 0.5 °C. Mean (n = 3), ±1s.d.

how polymer viscosity grade affected the matrix release kinetics in water and 0.7 M sucrose. In water, the low viscosity grade (K100LV) provided the fastest drug release (T_{80}% = 3.6 h), but differences between the two higher viscosity grades (K4M and K100M) were small (T_{80}% = 5.5–5.9 h). This is in agreement with the literature (Gao et al., 1996; Kavanagh and Corrigan, 2004; Reynolds et al., 1998; Sung et al., 1996). The K4M matrices disintegrated in 0.7 M sucrose after ~2 h, but surprisingly both the lower viscosity (K100LV) and the higher viscosity (K100M) HPMC matrices exhibited extended release throughout the entire test (T_{80}% >5 h). To challenge these matrices further, the same experiments were therefore undertaken in 0.8 M sucrose and in this environment, only the K100M matrices could provide extended release for longer than 2 h. The K100M grade was therefore selected for use in the "more resistant" formulation in Section 3.4.

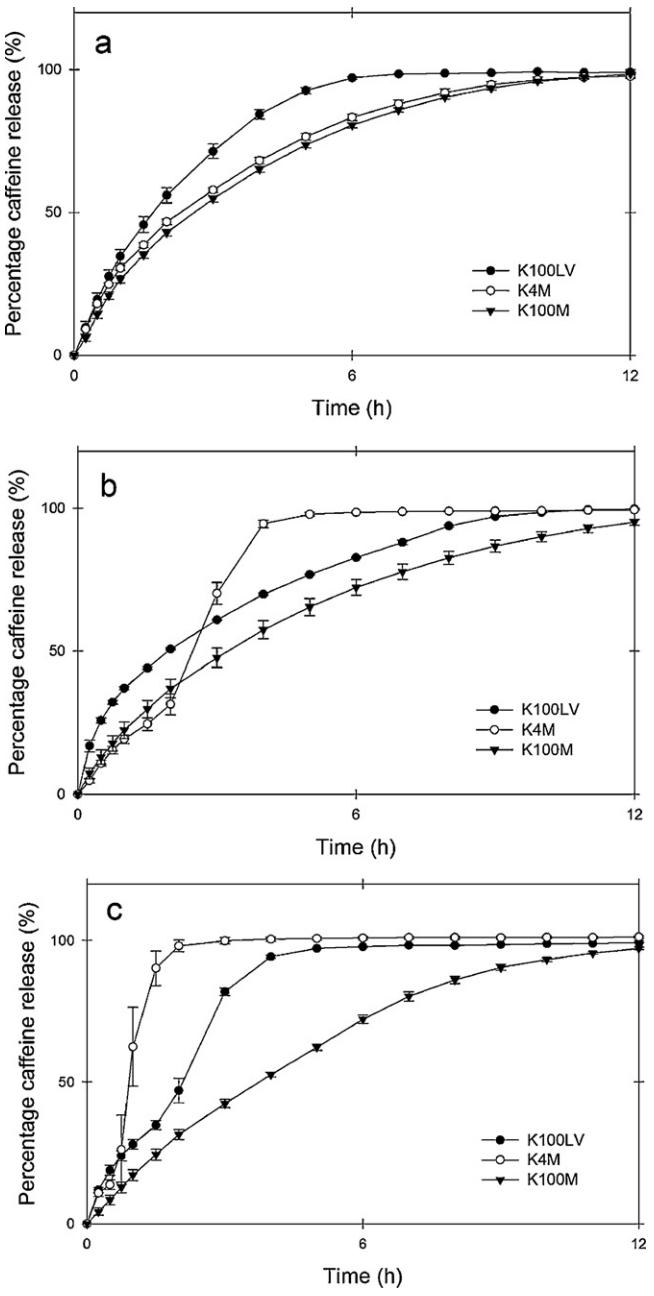

Fig. 4. Release of caffeine in water and sucrose with respect to polymer viscosity grade. Dissolution medium (a) water (b) 0.7 M sucrose (c) 0.8 M sucrose. Legend indicates the grade of Methocel™ HPMC in the matrix. USP apparatus 1100 prm, 900 ml, 37 ± 0.5 °C. Mean (n = 3), ±1s.d.

Table 2
The particle size distribution of the HPMC grades used in this work, from sieve analysis.

Sieve aperture (μm)	Percentage (%) retained		
	K100LV	K4M	K100M
<38	37.8	22.3	34.9
38	36.9	24.5	39.9
63	12.8	23.2	14.0
90	6.0	17.1	5.7
125	4.1	10.9	3.7
180	1.5	1.5	1.3
355	0.9	0.5	0.5
	100	100	100

Previous experiments had used the same polymer grade (Methocel™ K4M) throughout. In this study however, it was recognised that other differences between these polymer grades might potentially influence their dissolution performance in sucrose solutions. These include effects arising from differences in (a) polymer swelling, coalescence and dissolution rates of HPMC particles whilst forming the gel layer, (b) gel strength and viscosity of the hydrated polymer and (c) particle morphology. These aspects were investigated in more detail with confocal fluorescence imaging of early gel layer growth being used to elucidate the contribution of (a), basket rotation speed experiments to investigate gel layer susceptibility to erosion (b) and SEM imaging to investigate differences in particle morphology (c).

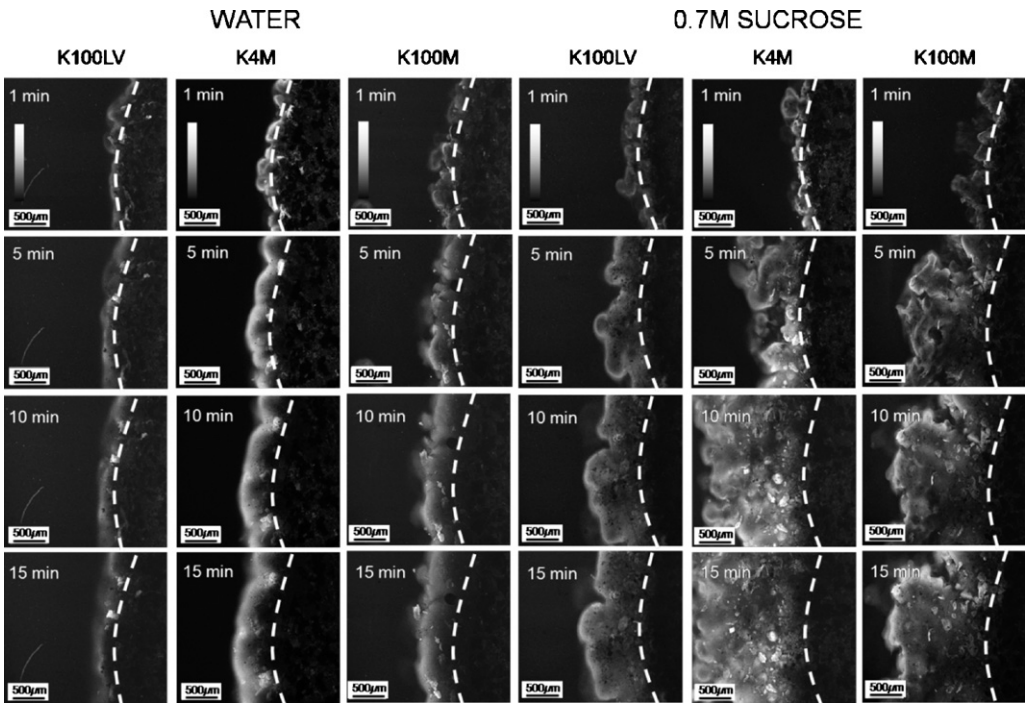

Fig. 5. Early gel layer formation in water and sucrose with respect to polymer viscosity grade. Images show the swelling of hydrated HPMC in the radial direction. Confocal fluorescence imaging at Ex 488 nm/Em > 510 nm, in hydration media at 37 ± 1 °C containing Congo red (0.008%, w/v) as a visualisation aid. Images are coded for fluorescent intensity using a continuous greyscale (white highest, black lowest). Dotted white lines denote the dry matrix boundary at $t = 0$ min. Scale bar 500 μm.

3.3.2. Early gel layer formation

Fig. 5 compares confocal microscopy images of early gel layer formation in matrices hydrating in water and 0.7 M sucrose. In water, all the viscosity grades of HPMC formed surface layers whose continuous morphology suggests a coherent gel barrier was formed after 15 min. A thinner gel layer was observed with the K100LV grade, and this can be attributed to the more rapid disentanglement and dissolution of this low viscosity HPMC into the surrounding medium (Reynolds et al., 1998). Other authors have suggested a reduced water uptake and swelling of these particles compared with higher viscosity polymer (Kavanagh and Corrigan, 2004; Wan et al., 1993), but as these grades have very similar levels of substitution, differences in molecular hydration in water seem unlikely.

In 0.7 M sucrose solutions, the low viscosity grade HPMC (K100LV) shows rapid hydration and significant particle coalescence after only 5 min, with only a small increase in thickness thereafter. This would imply the establishment of effective barrier properties that resists further ingress of surrounding medium. In contrast, the higher viscosity grades HPMC (K4M and K100M) exhibited irregular hydration and swelling, and after 5 and 10 min, they had formed expanded gels with an irregular internal and surface morphology. There was some evidence of poorly hydrated particles within the gel as reported in previous work (Williams et al., 2009). This pattern suggests that K4M and K100M particles exhibit more incomplete or slower particle hydration and coalescence in 0.7 M sucrose, which results in more liquid penetration. As a result, the gel layers formed at 15 min were significantly thicker than those formed in water.

Many papers have postulated how the hydration rate of different HPMC viscosity grades will affect swelling and drug release in a matrix: Campos-Aldrete and Villafuerte-Robles (1997) attributed the increased "initial burst" of high viscosity HPMC matrices containing metronidazole, to a slower rate of polymer particle hydration and gel layer formation. Wan et al. (1993) have observed faster release with higher viscosity grade HPMCs in ibuprofen matrices, and attributed this to the increased swelling capacity and disintegrant effect of these polymers. Pham and Lee (1994) used a flow-through cell to minimize polymer erosion, and showed that the gel layers of low viscosity grade HPMCs still had high rates of shrinkage. This was attributed to more rapid polymer hydration and dissolution at the gel layer surface. Johnson et al. (1993) have also showed that a low molecular weight hydroxypropyl cellulose can offer some protection to matrix tablets in high ionic strength media. More recently, Viriden et al. (2009) showed that lower viscosity HPMCs can in some cases, show slower polymer dissolution rates in comparison to higher viscosity HPMCs of the same USP 2208 substitution grade.

The confocal imaging provides visual evidence that appears to support these findings. Particles of K100LV are seen to hydrate rapidly at the matrix surface and form a continuous gel layer in both water and in 0.7 M sucrose. In contrast, the higher viscosity grades of HPMC exhibited irregular particle swelling and extensive water ingress, both indicators of poorer gel barrier formation. However, in dissolution tests (Fig. 4), the high viscosity K100M grade maintained extended release more effectively than K100LV at the highest sucrose concentration tested. This suggests that other properties of this polymer, for example the reported high gel strength of the gel layer, are important in maintaining extended release.

3.3.3. Erosion sensitivity

Methocel™ K100M has the highest viscosity and reported gel strength of the three HPMC polymers investigated in this study. It is possible that its high sucrose tolerance may arise not from early gel layer integrity, but from a greater robustness of the mature gel layer to surface erosion under the challenging conditions of high sucrose concentration. To explore this hypothesis, dissolution tests were undertaken at an increased basket rotation speed to test the sensitivity of the hydrated matrices to erosion. Fig. 6 shows that in water, increasing the basket speed had little effect on the drug release profile. However, in 0.7 M sucrose,

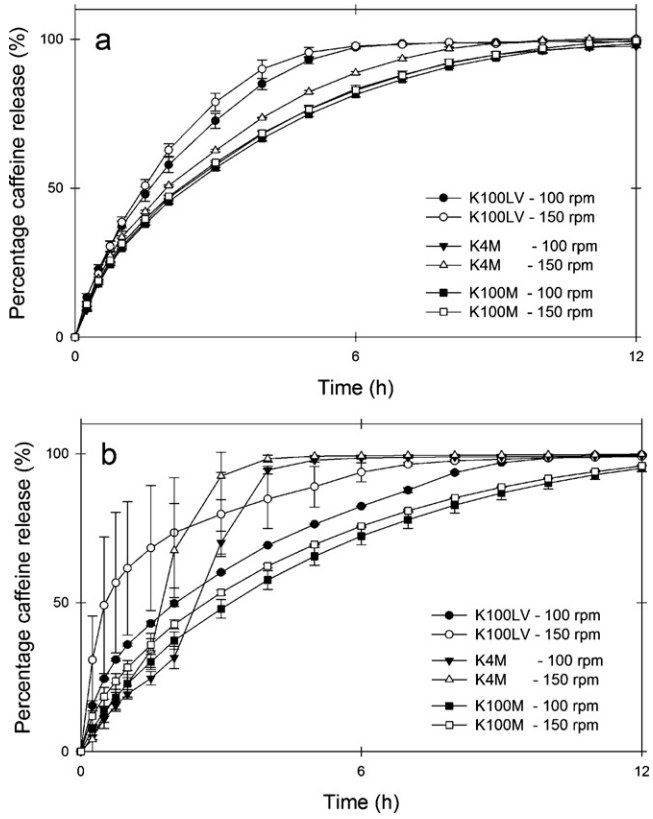

Fig. 6. Sensitivity of drug release to basket rotation speed, in water and sucrose, as a function of polymer viscosity grade. Dissolution medium (a) water (b) 0.7 M sucrose. Legend indicates the grade of Methocel™ HPMC used in the matrix. USP apparatus 1, 100 or 150 rpm, 900 ml, 37 ± 0.5 °C. Mean (n = 3), ±1s.d.

matrices containing K100LV and K4M were sensitive to rotation speed suggesting that the gel strength of the gel layer was reduced in the presence of sucrose. In contrast, K100M matrices under the same conditions showed little change. Hence, despite showing clear evidence of disruption during early gel layer formation, the gel formed by the K100M HPMC grade appears to offer good resistance to the erosion forces generated within the dissolution test, even in a challenging sucrose medium. Low viscosity HPMCs are often used at higher matrix loadings than the higher viscosity grades (Alderman, 1984). It is therefore possible that the sensitivity of a K100LV gel layers to sucrose induced erosion might be reduced at high polymer loadings, especially, given its faster rate of hydration However, at 30% it is clear that the K100M grade was the viscosity grade of choice for the "more resistant" formulation.

3.3.4. Comparative behaviour of unfractionated HPMC grades

Previous experiments in this study used a standardised 63–90 μm sieve fraction of HPMC to limit any variation resulting from particle size differences between the HPMC grades, but it could be argued that this may not reflect the extended release behaviour of the unfractionated polymer. Fig. 7 shows the drug release performance of matrices containing unfractionated HPMC in the presence of sucrose, and these graphs can be compared with the behaviour of matrices in which fractionated material was used (Fig. 4b and c). It can be seen that the behaviour of matrices containing the unfractionated HPMC, reflected those containing the fractionated polymer. Rank order sensitivity to sucrose was the same and any differences in the profiles were small. Matrices containing fractionated and unfractionated K4M

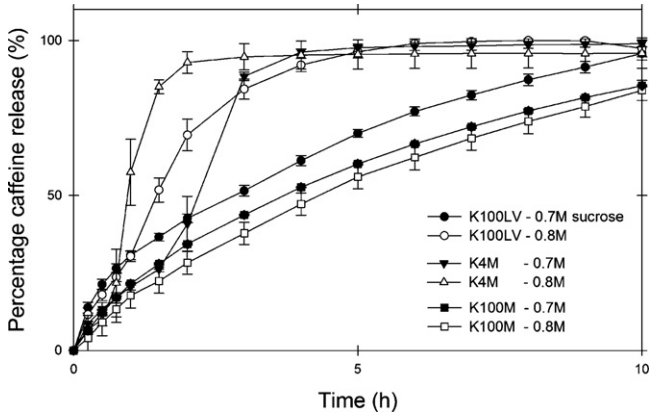

Fig. 7. Release of caffeine in 0.7 M and 0.8 M sucrose for matrices containing unfractionated polymers. Legend indicates the grade of Methocel™ HPMC used in the matrix. USP apparatus 1, 100 rpm, 900 ml, 37 ± 0.5 °C. Mean (n = 3), ±1s.d.

showed the same accelerated release in 0.7 M sucrose, and in 0.8 M sucrose, while only K100M matrices showed extended drug release. In these studies therefore, the 63–90 μm HPMC reflected the extended release behaviour of the native material. This can also be seen in Fig. 3 where different particle size fractions of K4M are compared.

3.3.5. Particle morphology of the different HPMC grades

There is some evidence that particle morphology may influence the behaviour of different HPMC grades in extended release matrices. Differences in matrix physical properties (Gustafsson et al., 1999) and drug release behaviour (Bonferoni et al., 1996) have been reported. Scanning electron micrographs of the different grades (in both fractionated and unfractionated form) show few obvious differences in particle morphology (Fig. 8). All grades comprised a mixture of fibrous and irregular-shaped flat particles, and sieve fractionation did not appear to isolate a particular morphology from the bulk powder.

3.4. Designing an HPMC matrix with greater resistance to dissolved sucrose

The investigations above show important matrix formulation variables such as diluent type, polymer particle size and viscosity grade can each influence sensitivity of an HPMC matrix to dissolved sucrose. To conclude this work, we investigate if knowledge of these variables can be used to increase the robustness of an HPMC matrix to dissolved sugar. In the previous experiments, the most robust matrix behaviour arose from using (i) MCC as the sole diluent (ii) a fine particle size fraction (<63 μm) of HPMC (iii) the highest viscosity grade of HPMC. These characteristics are brought together in the "more resistant" matrix formulation detailed in Table 3. The drug release performance of this matrix is shown in Fig. 9.

The original unmodified matrices were resistant to 0.6 M sucrose, but failed in 0.7 M sucrose solutions (Williams et al., 2009) whereas the new "more resistant" matrix provided extended release in 0.9 M sucrose, and only developed accelerated release characteristics when the sucrose concentration was increased to

Table 3
The composition of the HPMC matrix with increased resistance to dissolved sucrose.

Ingredients (%, w/w)	
Caffeine anhydrous	10.0
HPMC K100M (<63 μm sieve fraction)	30.0
Microcrystalline cellulose	59.0
Magnesium stearate	1.0

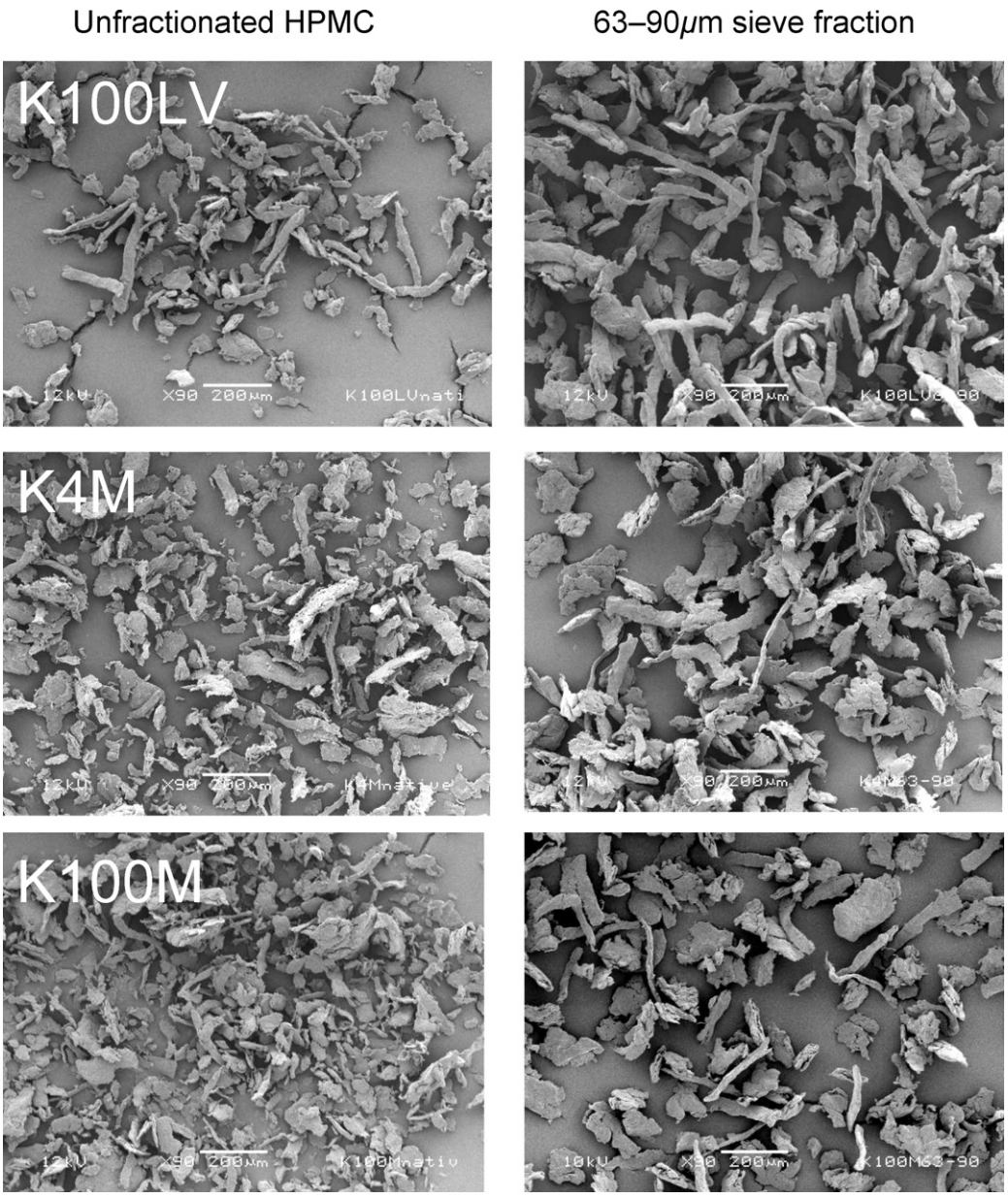

Fig. 8. Scanning electron micrographs comparing the particle morphologies of different HPMC viscosity grades and their 63–90 μm sieve fractions. Images show the unfractionated and a 63–90 μm sieve fraction of Methocel™ (a) K100LV (b) K4M (c) K100M. Scale bar = 200 μm.

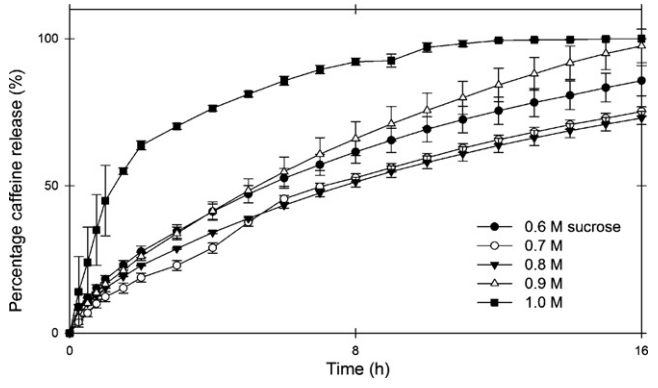

Fig. 9. Release of caffeine from the more resistant HPMC matrix formulation with respect to sucrose concentration in the dissolution medium. USP apparatus 1, 100 rpm, 900 ml, 37 ± 0.5 °C. Mean (n = 3), ±1s.d.

1.0 M. This represents an increase of over 40% in the concentration of sugar required for an effect on drug release behaviour and is clear evidence that the formulation variables investigated can be used to mitigate the effects of high sucrose concentration.

4. Conclusions

When designing a new HPMC matrix tablet formulation, building in a resistance to dissolved substances may be useful as it might potentially avoid a food effect. This investigation has identified several formulation factors that can reduce the sensitivity of HPMC matrices to high concentrations of dissolved sucrose. Whilst the effect of sugar on polymer hydration and swelling is an intrinsic response of the HPMC, the complexity of these formulations and the dynamic processes that develop and maintain the gel layer, allow formulation variables to modulate this behaviour. This study demonstrates that through the judicious choice of diluent and poly-

mer characteristics, HPMC matrices can be designed that show a greater resistance to sugar-laden environments.

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