European Journal of Pharmaceutics and Biopharmaceutics 76 (2010) 433–436

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

The effect of sucrose and salts in combination on the drug release behaviour of an HPMC matrix

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ARTICLE INFO

Article history:
Received 2 June 2010
Accepted in revised form 6 September 2010
Available online 15 September 2010

Keywords:
HPMC
Drug release
Sugar
Salt
Trisodium citrate

ABSTRACT

Previous work has shown how high concentrations of sugars can accelerate drug release from hydroxypropyl methylcellulose (HPMC) matrices by suppressing polymer hydration. This study investigates the effects of combining sugar and salts, using sucrose, sodium chloride and trisodium citrate, soluble ingredients commonly found in foods. A factorial study showed that each solute suppressed HPMC solution sol–gel transition temperature (a sensitive measure of molecular hydration) independently, and their effects reflected their rank order in the Hofmeister series. In mixtures, the effects were purely additive, with no evidence of antagonism or synergy. In dissolution tests, both salts significantly reduced the threshold sugar concentration required to elicit an acceleration of drug release, and when used in combination, 0.15 M sodium chloride with 0.015 M trisodium citrate reduced the threshold sucrose concentration from 0.7 M to 0.35–0.4 M, a reduction of almost 50%. The results show that food salts can significantly reduce the concentration required for sugar effects on HPMC matrices, and this may be a factor to consider when interpreting their in vivo behaviour in the fed state.

1. Introduction

Hydrophilic matrices are a robust extended-release technology in which the formation of a viscous hydrated polymer layer at the matrix surface provides a diffusion barrier, which retards drug release. Hydroxypropyl methylcellulose (HPMC) is the most widely used polymer in this application [1]. The hydration of HPMC is influenced by dissolved ionic salts in a Hofmeister rank order with higher valency ions being more potent [2]. However, very high concentrations of salts are usually required to significantly affect drug release from matrices. For example, in a typical HPMC matrix formulation, at least 0.6–0.75 M sodium chloride is required to precipitate immediate drug release by preventing formation of a coherent gel layer [3], or when incorporated into the tablet, at least 30% w/w trivalent sodium citrate is required to significantly change the drug release behaviour [4]. Recently, it has been shown that dissolved sugars can also influence matrix release behaviour. Sucrose, for example, increases gel layer thickness and slows drug release at concentrations below 0.5 M, whereas at higher concentrations (0.6–0.8 M), there is a disruption of gel layer formation and a marked acceleration of drug release (Fig. 1). These effects can be related to the progressive suppression of HPMC particle swelling and solubility, by sugars, during the formation of the gel layer [5]. At higher concentrations of sugars, particle swelling and coalescence is inhibited, a coherent diffusion barrier cannot form, and water penetrates the interior of the matrix. The threshold concentration of these effects appears to reflect the molecular ability of the sugar to disrupt water structure and destabilise the hydration sheath of the polymer [5].

These observations inevitably lead to questions about the combined effects of salts and sugars on HPMC matrices exposed to the fed state. Sucrose is present up to 10–14% w/v (~0.3–0.4 M) in soft drinks [6], sodium chloride is in high amounts in preserved foods [7], and sodium citrate is commonly used in ice creams, jams and wines, and up to 2% w/w in ripe cheese products [8]. In this short study, we show how combinations of these salts with sucrose can influence the properties of HPMC solutions and matrices.

2. Materials and methods

2.1. Materials

Sucrose and sodium chloride were from Fisher-Scientific, Leicestershire, UK; caffeine anhydrous, magnesium stearate and trisodium citrate were from Sigma–Aldrich, Poole, UK; lactose

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doi:10.1016/j.ejpb.2010.09.001

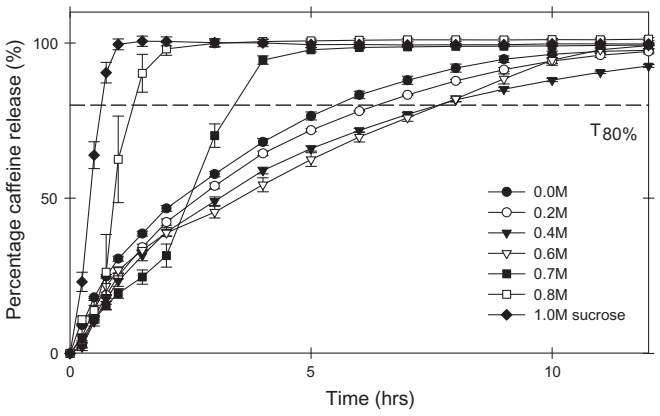

Fig. 1. Release of caffeine from HPMC matrices as a function of sucrose concentration in the dissolution medium. USP apparatus 1, 100 rpm, 900 ml, 37 ± 0.5 °C. Mean (n = 3) ± 1 sd. Reproduced from [5] without modification.

fast-flo USP was from Foremost Farms, Baraboo, USA; and microcrystalline cellulose (Avicel PH102) was from FMC Corporation, Philadelphia, USA. Hydroxypropyl methylcellulose (Methocel™ K4M-CR premium, 23.2% methoxyl, 8.2% hydroxypropyl, BN# UH22012N11) was a kind gift of Colorcon, Dartford, UK.

2.2. Manufacture of HPMC matrices

Matrices were prepared as previously described [5] by direct compression of powder blends containing 10% w/w caffeine, 30% w/w HPMC (63–90 μm sieve fraction), 38.3% w/w lactose, 19.7% w/w microcrystalline cellulose and 1% w/w magnesium stearate into 8-mm-diameter, round, flat-faced tablets (250 ± 5 mg) at ~240 MPa using an F3 tablet press (Manesty, Liverpool, UK).

2.3. Drug release from HPMC matrices

Drug release kinetics were determined in USP apparatus 1 (Dissolutest, Prolabo, France) at 100 rpm in 900 ml deaerated medium containing solutes, at 37 ± 0.5 °C connected to 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.

2.4. Manufacture of HPMC solutions

Using a hot dispersion method, 1% w/v HPMC solutions were manufactured, in which one third of the required volume of water was heated to 80–90 °C, HPMC powder was dispersed using a bench-top stirrer, and the remaining water was added. The solutions were stirred until satisfactory homogeneity was achieved and stored at 2–8 °C for >24 h prior to use. HPMC–solute mixtures were prepared by combining stock solutions of concentrated HPMC, sucrose, sodium chloride and trisodium citrate.

2.5. Turbidimetric determination of the sol–gel transition temperature of aqueous HPMC solutions

The sol–gel transition temperature of 1% w/v HPMC solutions with added solute(s) was determined as described previously, by cloud point measurements in a white light turbidimeter (Cloud Point Apparatus, Medical Physics, QMC, Nottingham, UK). The cloud point (CPT) was taken as the temperature for a 50% reduction in light transmission through the sample, and the gradient (Δ_{CPT}) was calculated from linear regression fitting of the CPT–solute concentration relationship using Instat Graphpad Software, San Diego, USA [5].

2.6. Experimental design

The effect of solute mixtures on the sol–gel transition temperature of HPMC solutions was investigated using a two-level, three-factor (2^3) factorial design (Stat-Ease, Design Expert v6.01, Minneapolis, USA). The factor levels and the full study design are shown in Table 1. Centre points were included to allow the determination of experimental error. Experimental data were fitted to the three-factor interaction equation:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3 \quad (1)$$

where Y is the response, b_0, b_1, ... are the regression coefficients calculated from the response, $X_1, X_2, \ldots$ are the factors studied, and $X_1X_2, X_1X_3 \ldots$ are interactive factors. Statistical analysis of the results was performed using the one-way analysis of variance (ANOVA) test in the Design Expert Software.

3. Results and discussion

3.1. The influence of individual salts on matrix drug release behaviour in sucrose

Fig. 2 shows matrix drug release behaviour in 0.5 M sucrose in the presence of sodium chloride or trisodium citrate. In sucrose alone, these matrices exhibited extended release (ER) over a 12- to 14-h period, but either salt when present above a threshold concentration accelerated drug release. Figs. 1 and 2 contrast the effects of increasing the concentration of sugar or salt, respectively. At low levels of salt, there is no apparent effect on dissolution profile. In contrast, low concentrations of sugars provide a moderate slowing of the dissolution profile, as discussed in [5]. Acceleration was often preceded by a period of extended release in which the matrices swelled extensively before disintegrating. This showed the gel diffusion barrier was unable to limit water penetration and suggested internal polymer swelling, dissolution of soluble ingredients with the eventual collapse of matrix structure. The lowest concentrations of salts to elicit this response (in the presence of 0.5 M sucrose) were 0.1 M sodium chloride or 0.015 M trisodium citrate. Studies had shown previously that an additional 0.2 M sucrose could cause the same response in this formulation (i.e. 0.7 M sucrose, Fig. 1) [5], and the potency of these solutes

Table 1
Factorial design: study design and outcomes.

Factor			Low level	High level
X_1: sucrose (M)			0	0.50
X_2: sodium chloride (M)			0	0.15
X_3: trisodium citrate (M)			0	0.05
Run	X_1	X_2	X_3	CPT (°C) (mean n = 3)
1	0.00	0.15	0.05	54.0
2	0.50	0.00	0.00	68.1
3	0.00	0.00	0.00	73.3
4[a]	0.25	0.075	0.025	59.5
5[a]	0.25	0.075	0.025	59.9
6	0.00	0.15	0.00	67.9
7	0.00	0.00	0.05	60.3
8	0.50	0.00	0.05	51.7
9	0.50	0.15	0.05	46.6
10	0.50	0.15	0.00	61.4

CPT is cloud point temperature.
[a] Denotes the centre points.

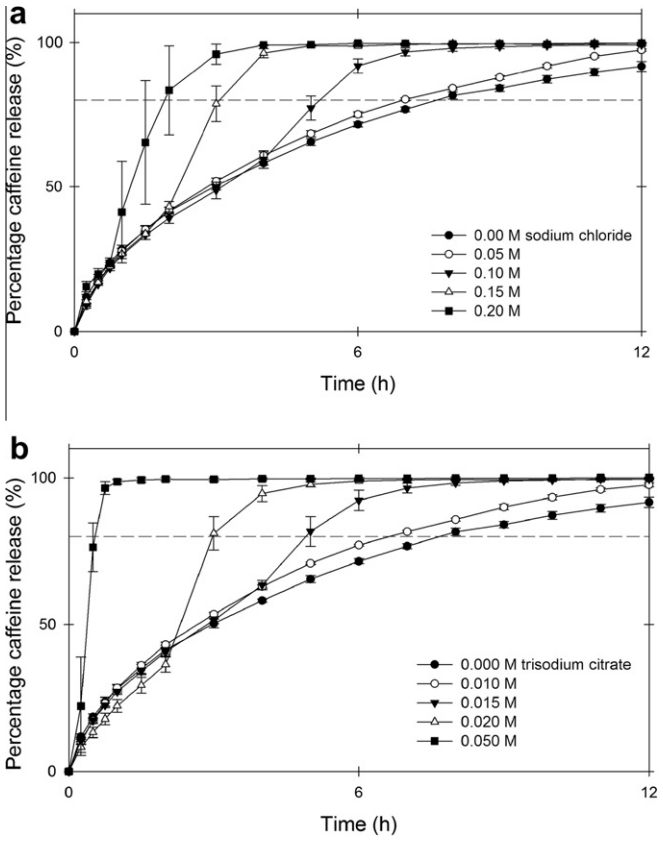

Fig. 2. Caffeine release from HPMC matrices in dissolution media containing 0.5 M sucrose and varying concentrations of (a) sodium chloride or (b) trisodium citrate. USP apparatus 1, 100 rpm, 900 ml, 37 ± 0.5 °C. Mean (n = 3) ± 1 sd.

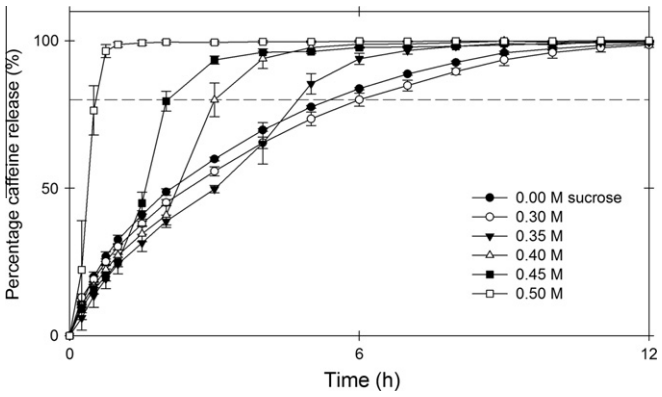

Fig. 3. Caffeine release in dissolution media containing a mixture of salts (0.15 M sodium chloride and 0.015 M trisodium citrate) and different sucrose concentrations. USP apparatus 1, 100 rpm, 900 ml, 37 ± 0.5 °C. Mean (n = 3) ± 1 sd.

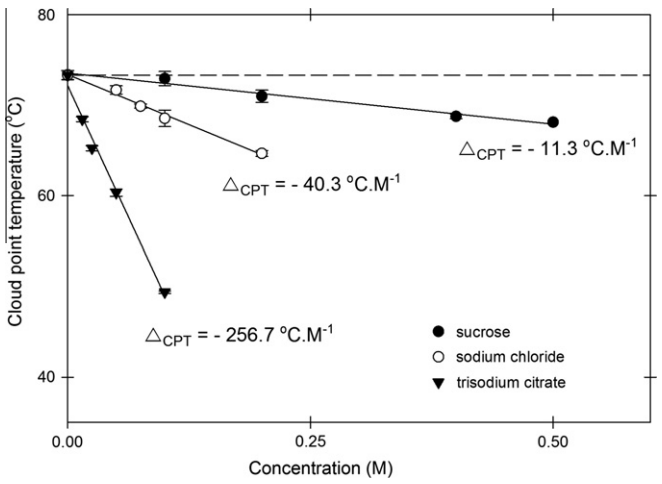

Fig. 4. The effect of individual sugar and salts on the cloud point temperature (CPT) of 1% HPMC solutions. The dotted line marks the CPT of 1% w/v HPMC in water. Δ_{CPT} is the gradient of the regression line. Mean ($n \geqslant 3$) ± 1 sd.

can be ranked as trisodium citrate (0.015 M) > sodium chloride (0.1 M) > sucrose (0.2 M). This is the same order as their suppression of HPMC sol–gel transition temperature, suggesting they dehydrate or restructure water in the polymer hydration sheath [2,4].

3.2. The influence of sugar and salt combinations on matrix drug release

For this study, 0.15 M sodium chloride and 0.015 M trisodium citrate concentrations were chosen because they (i) accelerated drug release in 0.5 M sucrose, (ii) had an equivalent effect (−4.9 °C to −5.9 °C) on the CPT of HPMC solutions and (iii) were within a range that may be reasonably found in foods. The influence of these salt concentrations on the sucrose concentration required to elicit an accelerated release response is shown in Fig. 3. In the presence of these salts, matrices maintained >12-h extended drug release in 0.3 M sucrose. In 0.35 M sucrose, there was evidence of accelered release after 4 h, and in 0.4 M sucrose, the extended-release phase was reduced to 2 h. In 0.5 M sucrose, they exhibited immediate release behaviour. These studies show how these salts, in combination, could significantly reduce the sucrose concentration required to accelerate drug release.

3.3. Effect of sugar and salt combinations on the cloud point temperature of HPMC solutions

The sol–gel transition temperature of HPMC solutions provides a sensitive measure of polymer molecular hydration, and the effect of sugar and salts was investigated by standard cloud point temperature determinations (CPT). Fig. 4 shows how each solute lowered the CPT from the original value of 73.3 °C, which is a typical value for Methocel K4M [9]. The calculated gradient, Δ_{CPT}, provides a convenient measure of solute potency.

Solute mixtures were studied using a 2^3 factorial design, with the aim of exploring whether the effects of sugar and salts were additive, synergistic or antagonistic. The maximum concentrations chosen reflect the amount of salt or sugar required for a significant acceleration of drug release in the previous experiments. The results of this study are shown in Table 1, and a statistical analysis is provided in Table 2. The results showed the following:

(i) Whilst the individual solutes (X_1 = sucrose, X_2 = sodium chloride, X_3 = trisodium citrate) exerted statistically significant effects on CPT, the interactive terms ($X_1X_2, X_1X_3, X_2X_3, X_1X_2X_3$) were not significant.
(ii) There was good agreement between predicted and actual values (Fig. 5a), and this was maintained when the interactive terms were removed (Fig. 5b).
(iii) There was no significant curvature (p = 0.173) that would indicate a mechanism more complex than simple additivity (Table 2).
(iv) The coefficients for "actual effect" for each solute calculated by the model from these solute mixtures were very close to the values of Δ_{CPT} calculated independently from the previous study (Fig. 4).

Table 2
Statistical analysis of the factorial design study.

Source	Sum of squares	*F* value	Probability	Coded effect	Actual effect	Δ_{CPT}[a] (°C M^{-1})
Model	588.33	1227.86	<0.05			
X_1	95.29	1392.10	<0.05	−3.45	−10.38	−11.3
X_2	69.21	1011.07	<0.05	−2.94	−36.20	−40.3
X_3	420.65	6145.29	<0.01	−7.25	−259.40	−256.7
X_1X_2	0.00012	0.0016	0.974			
X_1X_3	2.37	34.56	0.107			
X_2X_3	0.06	0.87	0.522			
$X_1X_2X_3$	0.76	11.14	0.185			
Curvature	0.88	12.84	0.173			
Error	0.068					

X_1 = sucrose, X_2 = sodium chloride, X_3 = trisodium citrate.
[a] Δ_{CPT} values were calculated using experimental data independent of this factorial design.

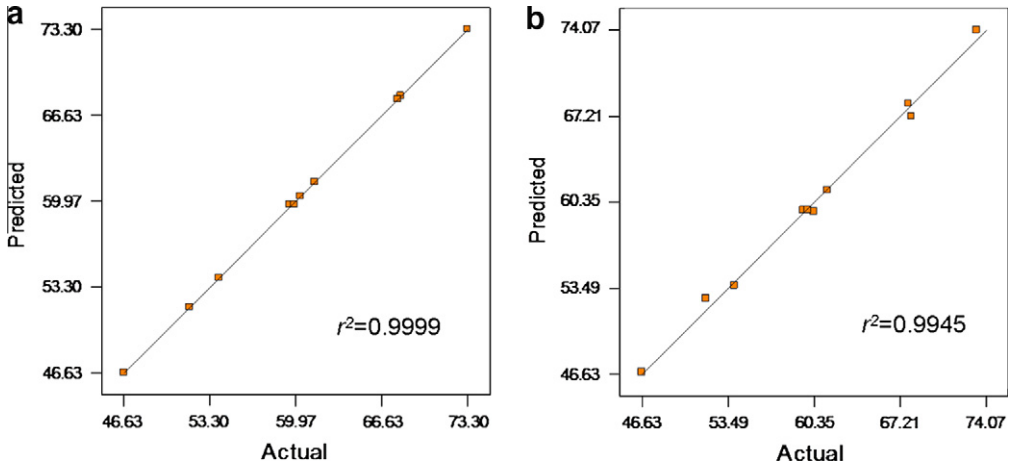

Fig. 5. Correlation between determined cloud points and values predicted by the statistical model from the factorial design study. Data points in (a) were fitted to a three-factor interaction equation (Eq. (1)), whilst in (b), interactive terms have been excluded from the model.

Overall, these results provide good evidence that individual solutes exert a cumulative but simple additive effect on the molecular hydration of the HPMC polymer. The high potency of the high-valency citrate ions, when used alone or in mixtures, is clearly evident, as would be predicted by a Hofmeister series and as shown in previous studies [2,4]. From the values of "actual effect", it appears that sodium citrate is 25 times more potent than sucrose on a molar basis.

In conclusion, this study demonstrates how the presence of dissolved salts that depress the sol–gel transition of HPMC can also lower the threshold concentration of sucrose at which HPMC matrices begin to lose extended-release properties and exhibit accelerated release. Accelerated release was a result of enhanced sensitivity of gel layers to erosion forces in the dissolution test [5], and we consider this finding to be of particular significance given that dosage forms taken with food will be exposed to the mechanical stresses of digestion [10]. In the matrix formulations studied, the presence of 0.15 M sodium chloride and 0.015 M trisodium citrate shifted this threshold from 0.7 M to 0.4 M sucrose. This is equivalent to ~14% w/v sugar, which is a concentration found in several high-sugar soft drinks [6]. Each component in the mixture was found to exert a simple additive effect on the sol–gel transition temperature (a measure of polymer molecular hydration), but the potency of each solute varied in accordance with previous studies. The study suggests that salts in combination can act cumulatively to increase the sensitivity of an HPMC matrix to the effects of dissolved sucrose.

Acknowledgments

This study was part of a collaborative PhD programme jointly sponsored by MSD and the University of Nottingham.

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